Washington State Health Care Authority

Health Technology Assessment

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Updated Final Evidence Report

October 31, 2012

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126

http://www.hta.hca.wa.gov
SHTAP@HCA.WA.GOV

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October 2012

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Center for Evidence-based Policy
Oregon Health & Science University
3455 SW US Veterans Hospital Road
Mailstop SN-4N, Portland, OR 97239-2941
Phone: 503.494.2182
Fax: 503.494.3807
http://www.ohsu.edu/ohsuedu/research/policycenter/med/index.cfm

About the Center for Evidence-based Policy

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring diverse and relevant perspectives are considered, and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

Nature and Purpose of Technology Assessments

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

Acknowledgements

This report was prepared by:

Martha Gerrity, MD, MPH, PhD
Aasta Thielke, MPH
Allison Werner Leof, PhD
Katharine Ryan, MPH
Alison Little, MD, MPH
Heidi Kriz, RD, MPH
Valerie King, MD, MPH

Center for Evidence-based Policy
Oregon Health and Science University

The tables of evidence were completed with assistance from:

Rachel Effros, MD, MPH
Janessa Graves, MPH
Heidi Gullett, MD, MPH
Catherine Pettenari, PhD
Sarah Present, MD, MPH
Hayes, Inc.

Suggested Citation:

Gerrity, M., Thielke, A., Leof, A.W., Ryan, K., Little, A., Kriz, H., & King, V. (2012). *Stereotactic radiosurgery and stereotactic body radiation therapy*. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.

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List of Abbreviations

bDFS – biochemical disease-free survival

CNS – central nervous system

CRT – conventional radiation therapy

CT – computed tomography

DFS – disease-free survival

EBRT – external beam radiation therapy

GI – gastrointestinal

GU – gastrourinary

HR – hazard risk

ICER – incremental cost-effectiveness ratio

IGRT – Image-guided radiation therapy

KPS - Karnofsky Performance Status

MA – meta-analysis

MRI – magnetic resonance imaging

NSCLC – non-small cell lung cancer

OR – odds ratio

OS – overall survival

PET – positron emission tomography

PFS – progression-free survival

QoL – quality of life

QALY – quality adjusted life year

RCT – randomized controlled trial

RFS – recurrence-free survival

RPA – recursive partitioning analysis

RR – relative risk

SBRT – stereotactic body radiation therapy

SCLC – small-cell lung cancer

SR – systematic review

SRS – stereotactic radiosurgery

TA – technology assessment

WBRT – whole brain radiation therapy

Executive Summary

Background

Clinical and epidemiological overview

Over the past ten years, significant advances have been made in the techniques available to deliver external beam radiation therapy (EBRT) as a treatment modality for certain cancers. The goal of these newer techniques is two-fold: to improve the targeting of radiation to the tumor to minimize damage to normal tissue and increase the dose of radiation delivered to the tumor.

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) have been rapidly accepted into clinical practice and are currently used for a number of cancers—most notably central nervous system (CNS), lung, colon, breast, head and neck, and prostate cancer. These are among the most prevalent cancers in the United States and have the following incidence rates:

- Brain and other nervous system cancers (6.5 per 100,000 men and women);
- Lung cancer (62.0 per 100,000 men and women);
- Colorectal cancer (47.2 per 100,000 men and women);
- Prostate cancer (156.0 per 100,000 men); and
- Oral cavity and pharynx (10.6 per 100,000 men and women) (National Cancer Institute [NCI] 2011).

Technology overview

Conventional EBRT, also called 2-dimensional (2DCRT) or 3-dimensional conventional radiation (3DCRT)[1], delivers photon beams of a uniform intensity and is usually given in 25 to 50 fractions (doses) delivered five days per week for 5 to 10 weeks. Stereotactic radiosurgery was initially developed in the 1950's to treat inoperable intracranial conditions. Stereotactic radiosurgery uses a single, or very limited number of, high dose(s) of radiation directed at a tumor within the CNS. When used outside the CNS, it is referred to as SBRT and is usually delivered in three to ten fractions. Multiple radiation beams are precisely targeted to the shape of the tumor from different directions instead of from a single direction or two directions. The full dose of radiation is limited to the areas of overlap of the beams and the surrounding normal tissue receives a much lower dose. Nine devices are currently approved by the Food and Drug Administration (FDA) for SRS/SBRT. These devices require a minimum staff including a certified radiation oncologist, qualified medical physicist, and licensed radiation therapist to safely deliver SRS/SBRT.

Stereotactic radiosurgery and SBRT require great precision in defining the tumor and delivering the radiation because the higher doses of radiation delivered in a fraction would cause significant damage to normal tissue. Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and other imaging techniques may be used to

[1] In this report 2DCRT and 3DCRT are grouped together as conventional radiation therapy (CRT) except where individual studies compare IMRT to either 2DCRT or 3DCRT. Current conventional EBRT is also referred to as CRT.

provide image guidance immediately prior to and/or during the course of radiation treatment. This approach is referred to as image guided radiation therapy (IRGT). In addition, SRS and SBRT require strategies and devices that minimize patient and organ movement. These include

1) Immobilization using body cases;
2) Implantation of radiopaque markers called fiducials;
3) Real-time CT imaging systems incorporated into linear accelerators; and
4) Techniques that manage respiratory movement (e.g. abdominal compression, breath holding when the beam is on, and gating where the beam is turned on and off with the respiratory cycle).

Policy context

Use of new radiation technologies has grown dramatically in the last decade. Despite this rapid adoption of SRS and SBRT, the FDA process for approving new radiation therapies does not require a review of safety and efficacy, which has resulted in limited information on the comparative effectiveness of SBRT and conventional EBRT, as well as potential harms. The purpose of this report is to provide a broader evidence analysis of SRS and SBRT than required by the FDA in granting approval for sale.

Methods

Key Questions

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for the following patients:

a. Patients with central nervous system (CNS) tumors
b. Patients with non-CNS cancers

KQ 2: What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations? Including consideration of:

a. Gender;
b. Age;
c. Site and type of cancer;
d. Stage and grade of cancer; and
e. Setting, provider characteristics, equipment, quality assurance standards and procedures.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Methods – Evidence

A search was conducted to identify published systematic reviews (SRs), meta-analyses (MAs), technology assessments (TAs) and individual studies (from April 2002 to April 2012) in MEDLINE® and Cochrane databases. References from a recently published Agency for Healthcare Research and Quality technology assessment of SBRT (Tipton 2011a, 2011b) were also reviewed to identify studies meeting our inclusion criteria.

General inclusion criteria:

- Published, peer reviewed, English-language articles;
- SRs, TAs, randomized controlled trials (RCTs), and observational comparative study designs (prospective, retrospective, and controlled clinical trials);
- Treatments generally delivered in 10 or fewer fractions;
- For KQ 2 (harms), *all* study designs with a minimum sample size of 50 participants; and
    - For pediatric populations and/or reports of serious harms (i.e., surgery, hospitalization, mortality), *all* study designs with a sample size of 20 participants.

Specific inclusion criteria by tumor location and malignancy:

Central Nervous System

- Minimum sample size of 20 participants;

Breast, Colon, Head and Neck, Lung, and Prostate

- Minimum sample size of 50 participants;

Other Malignancies

- Case series; and
- Minimum sample size of 20 participants.

Exclusions included studies published in a non-English language, commentaries, letters, editorials, narrative reviews, and news articles. Studies that focused on aspects of treatment planning, including different dosing regimens[2] were excluded.

The methodological quality of a body of evidence was rated in a two step process. First, the *methodological quality of each included study* was assessed using standard instruments developed and adapted by the Center for Evidence-based Policy and the MED Project. These instruments are modifications of systems used by National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) (NICE 2009; SIGN 2009). *Each study was assigned a rating of good, fair, or poor* based on its adherence to recommended research methods and potential for bias. The methodological quality of the economic studies was rated (good, fair, poor) using a standard instrument developed and adapted by the Center for Evidence-based Policy and the MED Project. This instrument is a

[2] Although dosimetric calculations are used in making treatment plans, the information on Dosimetry does not directly address any of the Key Questions and was excluded from this report.

modification of checklists in the British Medical Journal (Drummond 1996), the Consensus on Health Economic Criteria (Evers 2005), and NICE economic evaluation checklist (NICE 2009). Second, *the overall strength of a body of evidence, which usually includes more than one study,* was rated (high, moderate, low, very low) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Guyatt 2008).

A systematic review using best evidence methodology was used to search and summarize evidence for Key Questions #1 through #3 as outlined below:

- A complete search of the Medicaid Evidence-based Decisions (MED) Project primary evidence sources was conducted;
- Existing high quality SRs and TAs were summarized for each Key Question;
- If there were two or more comparable SRs or TAs identified and one was more recent, of better quality, or more comprehensive, the other review(s) were excluded;
- Additional search of the MEDLINE® and Cochrane databases was done to identify studies published after the search dates of the last high quality reviews. Individual studies published after the SR(s) were appraised and synthesized with the results of the high quality SRs; and
- If there were no high quality reviews identified, a search, appraisal, and summary of primary individual studies was completed for the last 10 years (April 20002 to April 2012).

For Key Question #4, all relevant economic evaluations were included, published between April 2002 and April 2012.

Methods – Guidelines

A search for relevant clinical practice guidelines was conducted using a list of predetermined high quality sources from the MED Project and additional relevant specialty organizations and associations. Guidelines included were limited to those published after 2007. The methodological quality of the guidelines was assessed using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration (AGREE Next Steps Consortium 2009). Each guideline was assigned a rating of good, fair, poor, based on the adherence to recommended methods and the potential for biases.

Methods – Policies

At the direction of the WA HTA program, select payer policies were searched and summarized. Aetna, Blue Cross Blue Shield, GroupHealth, and Medicare National and Local Coverage Determinations were searched using the payers' websites.

Methods – MAUDE Database

The Manufacturer and User Facility Device Experience (MAUDE) Database, hosted by the FDA, was searched using the terms "stereotactic radiation therapy", "stereotactic radiosurgery", "sbrt", "srs", "cyberknife", "cyber knife", "gamma knife", and "gammaknife". The search was limited to adverse events reports submitted between 2002 and 2012. Three reports of serious adverse events were identified and are summarized in Appendix M.

Public Comment and Peer Review

The topic nomination, draft key questions, and draft version of this report were open to public comment. All comments and references received from the public were reviewed and taken into account in the drafting of the final report. In addition, the draft report was reviewed by two peer reviewers and their comments were also taken into account in drafting the final report. The full disposition to peer review comments is available in Appendix J. The full disposition to public comments for the Key Questions is available in Appendix K. Full disposition to public comments on the draft report is available in Appendix L.

This report provides the best available evidence for multiple cancer types. The most completely evaluated cancers are those of the **central nervous system, liver, lung and spine**. For these cancers there are large TAs and several SRs. For many of the other cancers, there are as few as one case series. The evidence consists mostly of case series of which are non-comparative studies that may give estimates of outcomes or harms for SRS and SBRT without comparison with EBRT. Because of the absence of randomized trials and comparative studies, the strength of the evidence is low or very low for most of the findings.

Findings – Comparative Data

This section includes tumor types and locations where comparative data was available for SRS and SBRT compared with EBRT. This section includes a summary of the evidence on brain metastases, glioblastoma multiforme, gliomas, pituitary adenomas, head and neck cancer, and lung cancer.

Central Nervous System – Brain Metastases

Brain metastases are the most common intracranial tumor in adults. They occur in up to 40% of patients with cancer and are associated with poor prognosis (Bradley 2004) with an overall median survival estimated to be six months or less (Li 2000). The most likely cancers to have brain metastases include NSCLC, breast cancer, melanoma, and less commonly, colon and renal cell cancers (Patil 2008). Treatment options include whole brain radiation therapy (WBRT), surgery, SRS, chemotherapy and supportive care including corticosteroids. However, for the objectives of this review, we restricted our comparisons to SRS, or SRT, versus WBRT.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

For *SRS+WBRT compared to WBRT* alone, the overall strength of evidence is moderate for survival and tumor control. There is no statistically significant difference in OS for SRS+WBRT compared to WBRT alone (hazard ratio (HR) 0.82, 95% CI 0.65 to 1.01, I^2 = 0%) with differences in median survival of approximately 1 to 3 months. (See subgroup analyses in KQ3). Local tumor control was better with SRS+WBRT compared to WBRT alone (HR 0.27, 95% CI 0.14 to 0.52, I^2 = 0%).

For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is moderate for the outcome of OS and tumor control. There was no statistically significant difference in overall

survival (OS) (HR 0.98, 95% CI 0.71 to 1.35). Local and distant tumor control was significantly better for patients receiving SRS+WBRT compared to SRS alone (HR 2.61, 95% CI 1.68 to 4.06, I^2 = 60% and HR 2.15, 95% CI 1.55 to 2.99, I^2 = 54%, respectively). Low quality evidence suggests there is no difference in functional independence, time to worsened performance status or quality of life (QoL) for SRS+WBRT compared to SRS alone.

For *SRS alone compared to WBRT alone*, the overall strength of evidence is very low based on six cohort studies, two with historical controls, and two additional small poor quality cohort studies. These studies suggest that OS may be better for patients receiving SRS alone compared to WBRT alone, but the poor quality of the studies and the heterogeneity across studies limit any conclusions.

For *SRS for recurrent or progressive brain metastases*, the overall strength of evidence is very low for overall survival and local tumor control. It is uncertain if SRS+WBRT compared to WBRT alone or SRS alone, or SRS alone compared to WBRT alone improves overall survival or local tumor control.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

For *SRS+WBRT compared to WBRT* alone, the overall strength of evidence is moderate for harms based on one fair quality RCT. Acute and late toxicities were not significantly different for SRS+WBRT compared to WBRT alone. Information from cohort and case series generally corroborated the findings from the single RCT and indicated that approximately 2% to 5% of patients may experience severe (Grade 3 or 4) acute and late toxicities including symptomatic radionecrosis.

For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is low for harms based on an small RCT, cohort studies and case series. These studies may indicate that severe (Grade 3 or 4) acute and late toxicities are similar for SRS+WBRT compared to SRS alone and occur in approximately 2% to 5% of patients. Of note, some studies described a reduction in the SRS dose based on whether or not the patient would receive WBRT. There is low quality evidence, based on an interim analysis of one small fair quality RCT (n = 58), that patients receiving SRS+WBRT may be significantly more likely to have decline in total recall at four months than patients receiving SRS alone (52% vs. 24%, respectively), as well as delayed recall and delayed recognition.

SRS alone compared to WBRT alone, the overall strength of evidence is low for harms based on cohort studies and case series. Toxicity rates appear to be similar for SRS alone compared to WBRT alone.

For SRS for recurrent or progressive brain metastases, the overall strength of evidence is very low. It was not possible to determine whether the harms, when reported, were due to SRS with and without WBRT or to the initial treatment for brain metastases or the patients overall poor prognosis.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

The overall strength of evidence is low because it is based solely on subgroup analyses from a single fair quality RCT. Even though the authors stratified by subgroups and had a priori hypotheses, the number of patients in these subgroups was small, and there were multiple comparisons. Subgroup analyses suggested that median survival in patients with single metastases (6.5 vs. 4.9 months, SRS+WBRT vs. WBRT, respectively) and patients in recursive partitioning analysis (RPA) Class 1 (11.6 vs. 9.6 months) may be better with SRS+WBRT compared to WBRT alone. Local tumor control was better with SRS+WBRT compared to WBRT alone. Fewer patients receiving SRS+WBRT compared to WBRT alone may have worsened performance status at six months.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

One fair quality SR of seven economic evaluations identified two poor and one fair quality economic evaluations pertinent to this review. For *SRS+WBRT vs. WBRT alone*, the overall strength of evidence is very low that SRS+WBRT is more cost-effective than WBRT alone. Compared to WBRT, SRS+WBRT had an incremental cost-effectiveness ratio (ICER) of $12,289 per extra year of life gained and an incremental quality-adjusted life year (QALY) ratio of $10,753 per QALY. However, there is great uncertainty in these estimates. For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is low that SRS alone is more cost-effective than SRS+WBRT. The ICER for SRS alone (vs. SRS+WBRT) was $44,231 per year of life saved and $41,783 per QALY. For *SRS alone vs. WBRT alone*, one poor quality study, yielding very low strength of evidence, found the cost per QALY was significantly less for SRS alone than for WBRT alone ($10,381/QALY vs. $17,622/QALY, respectively, $p < 0.05$).

Central Nervous System – Primary Tumors

In this section, evidence on intracranial or central nervous system (CNS) tumors is summarized by each type of tumor. These are presented in alphabetical order: glioblastoma, high-grade (malignant) glioma, and pituitary adenoma.

Glioblastoma multiforme

Glioblastomas, also called glioblastoma multiforme, are high grade (undifferentiated, anaplastic) gliomas with poor prognosis. See the description under glioma for more background information.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

The overall strength of the evidence is low based on one fair quality RCT (n = 203) and two poor quality cohort studies, one with concurrent (n = 64) and one with historical controls (n = 114). For patients with *newly diagnosed* glioblastoma multiforme, the addition of SRS to EBRT and

chemotherapy may not affect survival. Results from the one RCT (no survival difference) conflicted with results from the cohort studies (survival better with addition of SRS) involving patients with *newly diagnosed* glioblastoma. Prognostic imbalances between groups in the cohort studies and use of historical controls likely created biased results, particularly given the small sample sizes in these studies. For patients with *recurrent* glioblastoma, the strength of the evidence is very low based on one fair quality case series and one poor quality cohort study. The effect of SRS on survival and other outcomes in patients with recurrent glioblastoma is uncertain.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on one fair quality RCT, one poor quality cohort studies, and three case series, the overall strength of evidence is low that adding SRS to other treatments for glioblastoma mutliforme may increase the risk of symptomatic radionecrosis, which may occur in 3% to 5% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Glioma

Gliomas are the most common primary tumors of the brain. Although various classification systems exist, gliomas are generally classified by their histology (cell type) and grade (pathologic appearance that is associated with prognosis).Gliomas have histologic features of glial, non-neuronal, cells including astrocytes, oligodendrocytes, ependymal cells, and Schwann cells. Some gliomas are benign, slow growing and miotitically inactive, but because of their location may be fatal or cause significant morbidity. Among gliomas that have malignant features, they can be classified as low-grade (well-differentiated histologically with a better prognosis) and high-grade (undifferentiated or anaplastic with a worse prognosis), the later includes glioblastomas (glioblastoma multiforme) and anaplastic astrocytomas.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Based on one poor quality cohort study, the overall strength of evidence is very low for prolonged survival with salvage SRS in patients with *recurrent* malignant gliomas. It is uncertain whether salvage SRS increases median survival in patients with recurrent malignant gliomas.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on one cohort study and eight case series, the overall strength of evidence is very low for harms in patients with malignant gliomas. Although there is uncertainty, these studies raise concerns about radiation necrosis leading to a mass effect requiring surgery.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

The overall strength of evidence is very low and the following conclusions are uncertain. Based on one poor quality case series, it is uncertain if SRS offers advantages for overall survival or progression free survival rates for pediatric patients treated for low grade gliomas. Patients may develop Moya Moya syndrome, and if they have progression of their tumor, it may be to anaplastic astrocytoma.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Pituitary Adenoma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Based on two fair quality cohort studies, there is a low overall quality of evidence suggesting there may be no difference in overall survival or local tumor control in patients treated with SRS instead of EBRT, but there is uncertainty regarding this conclusion. Because of the very low overall quality of evidence about hormonal normalization after treatment any conclusions are uncertain.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on two small fair quality cohort studies and 13 case series, the overall strength of evidence is very low. The most common permanent side effect from SRS treatment may be the development of pituitary hormone deficiencies, ranging from 9.3% to 30% of patients. Stereotactic radiotherapy may result in fewer patients having new hypopituitarism than EBRT, although this conclusion is uncertain. In the two cohort studies, differences between the groups favoring SRT over EBRT were noted but were not statistically significant. Acute complications from SRT treatment may be mild and include headache, nausea and fatigue. Other rare side effects may include edema, visual deficits, and cranial nerve palsies.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on costs or cost-effectiveness were identified.

Head and Neck Cancers

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Based on one poor quality cohort study, there is very low overall strength of evidence that there was no significant difference between SBRT and EBRT in local control of the tumor or in patient survival.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on one poor quality cohort study and six poor quality case series, the overall strength of evidence is very low. SBRT may be associated with less frequent harms than EBRT in patients with nasopharyngeal carcinoma and head and neck squamous cell carcinoma. Serious late complication rates may occur in 2% up to 20% of patients. One poor quality cohort study found that overall serious complication rate was lower for patients receiving SBRT than those receiving EBRT, but there is substantial uncertainty about this difference due to the overall strength of evidence being very low.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on costs or cost-effectiveness were identified.

Lung

The majority of studies assessing the outcomes of SBRT for lung cancer focus on patients with inoperable Stage 1 non-small cell lung cancer (NSCLC). Patients with Stage 1 NSCLC would normally undergo surgical resection with an estimated 5-year survival of up to 80% depending on the size of the tumor (Chi 2010). However, the location of the cancer or medical conditions (e.g., severe chronic obstructive pulmonary disease) may preclude surgery. For patients with inoperable Stage 1 (T1-2N0) NSCLC, treatment with conventional EBRT using 60 to 66 Gy

resulted in a 5-year OS of about 15% to 30% (Chi 2010; Rowell 2001; Sibley 1998). SBRT is being used in an attempt to improve survival in patients with inoperable stage 1 NSCLC. No randomized controlled trials have been done comparing SBRT with surgical resection in patient who are eligible for surgical resection for Stage 1 NSCLC.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Based on 68 case series consisting primarily of patients with *inoperable (based on location of the tumor, serious medical conditions and patient refusal) early stage non-small cell lung cancer (NSCLC)*, the overall strength of evidence is very low and any conclusions about outcomes are uncertain. Since there were no studies comparing SBRT to EBRT, it is uncertain whether SBRT improves survival or other patient-important outcomes compared to conventional EBRT. Stereotactic body radiation therapy for patients with inoperable early stage NSCLC may result in 3-year overall survival rates of 50% to 60% and local control rates of 80% to 100%. Survival rates were better for patients with Stage 1A compared to Stage 1B disease, as expected because of differing prognosis based on tumor size. Earlier studies of medically inoperable early stage NSCLC (Chi 2010; Rowell 2001; Sibley 1998) estimate that treatment with conventional EBRT using 60 to 66 Gy have a 5-year OS of about 15% to 30%; however, there have been no direct comparison with SBRT.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

The overall strength of evidence regarding harms is very low, based on 67 case series. There is uncertainty about the rate of acute and late toxicities, especially as they compared to EBRT. Acute toxicities from SBRT for lung cancer include fatigue, general malaise, pneumonitis, esophagitis, dermatitis, and chest wall pain. Few patients appear to have acute toxicities; and when they do, they are likely to be mild (Grade 1 and 2). Estimates of greater than or equal to Grade 3 acute toxicities may range from 2% to 5%. Late toxicities primarily involve the lungs (e.g., radiation pneumonitis) and chest wall (e.g., pain, dermatitis, and rib fractures). The rates of greater than or equal to Grade 3 late toxicities appear to range 0% to 28%, with most ranging 2% to 10%. In addition, the placement of fiducial markers, when used, may cause pneumothoraxes requiring chest tube placement or hospitalization in approximately 9% to 28% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

The overall strength of evidence is very low based on three poor quality economic analyses. There is uncertainty about the comparative costs and incremental cost-effectiveness of SBRT

versus conventional EBRT for inoperable early stage NSCLC. The costs (charges) for EBRT (35 factions) may be $50,000 to $61,000 and SBRT (four fractions) may be $41,000 to $57,000, and the incremental cost-effectiveness of SBRT compared to conventional EBRT may be $6,000 per QALY and range from $10,200/QALY to $40,300/QALY.

Findings – Non-Comparative Data

For tumor types and locations where there is not comparative data, summary information can be found in the full summary table (Appendix E).

Abdomen (Adrenal Metastases, Colorectal, Liver, Pancreas)

In this section, colorectal cancer (anus, rectum, colon), cancers of the liver and pancreas, and adrenal metastases are summarized. There is limited evidence for all four cancers. No other cancers were identified for this section.

Adrenal Metastases

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Based on two poor quality case series, the overall strength of the evidence is very low and any conclusions about outcomes are uncertain. Because of the study design and variations in patient characteristics and prior treatment, any conclusions based on the study results may not provide a reliable estimate of the true outcomes. One-year survival rates may be about 40%.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on two poor quality case series, the overall strength of the evidence is very low and any conclusions about harms are uncertain. Because of the study design and variations in patient characteristics and prior treatment, it is difficult to draw any conclusions, especially because neither study provides much information about toxicities.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Colorectal

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on two poor quality case series, there is very low overall strength of evidence that low grade complications (i.e., nausea, vomiting, pain) occur in 41% of patients and severe toxicities (i.e., hepatic failure, duodenal and colonic ulceration) in 3% to 7% of patients. These conclusions about harms are uncertain and may not provide a reliable indication of the true harms.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No cost or cost-effectiveness studies were identified.

Liver

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

The overall strength of evidence is very low. The following conclusions about outcomes are uncertain and may not be a reliable indicator of the true effects. Based on two poor quality systematic reviews of case series and seven additional case series, median overall survival for patients with liver metastases may range from 14.5 months to 32.5 months after SBRT and 13.4 months for patients with hepatocellular cancer.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on two SRs of case series and seven additional case series, the overall strength of evidence is very low and any conclusions about harms are uncertain. Grade 1 to 2 complications (e.g., fatigue, nausea, gastritis, liver enzyme abnormalities) may occur in 15% to 25% of patients; and greater than Grade 3 complications (e.g., liver toxicity, colonic perforation or small bowel obstruction) may occur in 0% to 15% of patients and may rarely include death.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Pancreas

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

The overall strength of evidence is very low and any conclusions about outcomes are uncertain. Based on one SR and four case series, median survival may range from 5.4 months to 18.6 months following SBRT treatment for pancreatic cancer. For patients with pain, almost half had complete relief of pain and the remainder had decreased pain after SBRT, based on 31 patients in one poor quality case series.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on one SR of case series and four case series, the overall strength of evidence is very low and any conclusions about harms are uncertain. Grade 1 to 2 complications occur in most patients and may be as high as 100%. Grade 3 or higher complication rates vary from about 3% to 22%.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

The overall strength of evidence is very low and any conclusions about cost-effectiveness are uncertain. One poor quality cost-effectiveness modeling study calculated that SBRT plus gemcitabine had an ICER of $69,500/QALY compared to gemcitabine alone.

Central Nervous System – Primary Tumors

In this section, evidence on intracranial or CNS tumors is summarized by each type of tumor. These are presented in alphabetical order: astrocytoma, meningioma, multiple brain tumors, neurocytoma, and schwannoma. Malignancies are discussed as they were reported in literature. For instance, although astrocytomas and glioblastoma multiforme are types of gliomas, they are discussed in separate sections as they were reported by individual studies.

For many primary and metastatic brain tumors, the treatment of choice may be surgical removal. However, the choice of treatment needs to balance the goal of removing the tumor with avoidance of neurologic damage and takes into account the location of the tumor in relation to critical structures; the type and histopathology of the tumor; and patient factors such as age, symptoms, and medical comorbidities. Thus, treatment options may include surgery alone, surgery plus radiation, radiation alone, and for benign slow growing primary tumors, observation. The objective of this report is to evaluate the evidence base for conventional EBRT, referred to as whole brain radiation therapy (WBRT), compared to the newer radiation techniques, SRS and SRT. The report objective is not intended to evaluate all treatments for a particular tumor. There are few studies comparing SRS/SRT and WBRT for many of the CNS tumors with the exception of brain metastases.

Astrocytoma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Based on three poor quality case series, the overall strength of the evidence is very low. Because of variations in patient characteristics and prior treatment, any conclusions about outcomes are uncertain. Based on two of the poor quality case series involving 143 patients with WHO Grade 2 astrocytomas, 5-year survival with SRS treatment may be about 58% and median survival at 32 months may be 92%. For WHO Grade 3 and 4 tumors, median survival may be 14 months.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on three poor quality case series, the overall strength of the evidence is very low for harms and any conclusions about harms are uncertain. Acute Grade 3 adverse events may occur in 3% and late adverse events in 6% of patients. Patients may experience neurologic adverse events.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Ependymoma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Overall strength of the evidence is very low based on two fair quality case series involving 60 children and adults. There is uncertainty in any estimate of survival, which was reported as an overall 1-year survival of about 50% to 60%.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Overall strength of the evidence is very low based on two poor quality case series involving 60 children and adults. There is uncertainty in any estimate of harms, which were reported as adverse radiation effects occurring in about 8% to 9% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified except for the one study that included only children (Kano 2010) described in KQ1.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies of cost or cost-effectiveness were identified.

Meningioma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on 28 case series, the overall strength of the evidence is very low for harms, and the following conclusions are uncertain. Erythema, alopecia and post-radiation edema are all common adverse effects. Patients treated with GKRS had an overall complication rate of 13%, with temporary morbidity of 6% and permanent morbidity of 7% in one large case series.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

Overall strength of the evidence is very low for differences in effectiveness and harms in different subpopulations. Based eight case series, the factors that may result in differences

include tumor volume, tumor margin dose greater than 14 Gy, male gender, supratentorial, hemispheric or parasagittal tumor location, higher radiation doses, marginal dose of less than or equal to 14 Gy and having fewer prior treatments. However, there is uncertainty in whether or not these factors are truly important.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Overall strength of the evidence is very low, and limited to a poor quality cost analysis with potential funding bias and poor applicability to the US setting. Conclusions regarding cost-effectiveness in the US setting cannot be drawn.

Multiple CNS Tumors

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Fourteen case series provide an overall very low strength of evidence. Because of the variability in tumors, dosing of SRS, and reporting of outcomes and harms, the studies are not summarized. The details of each study are provided in Appendix F.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Fourteen case series provide an overall very low strength of evidence. Because of the variability in tumors, dosing of SRS, and reporting of outcomes and harms, we did not attempt to summarize these studies. The details of each study are provided in Appendix F.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies of cost or cost-effectiveness were identified.

Neurocytoma

Neurocytomas are well-differentiated slow growing tumors with primarily a neuronal differentiation. They usually occur in the ventricles of the brain (central neurocytoma) and occasionally in the brain parenchyma or spinal cord (extraventricular neurocytoma). Patients present with symptoms of increased intracranial pressure from hydrpcephalus including headache, cognitive impairment, difficulty with balance, and visual impairment. The standard treatment is complete surgical resection. Adjuvant radiation therapy is often used for residual tumor if the resection is incomplete.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

The overall strength of the evidence is very low and based solely on a single comparison of cases and case series stratified by conventional EBRT and SRS. These cases suggest that in patients who do not have complete surgical resection, conventional EBRT and SRS may have similar overall 5-year survival and local tumor control and that 5-year survival is better than incomplete tumor resection alone. However, these conclusions are uncertain.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on one poor quality SR of case reports/case series and one addition case series, the overall strength of the evidence is very low. Very little data is available for harms. One case series of 13 patients suggests that parenchymal changes and secondary malignancies were not found on follow-up MRIs.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Schwannoma (Acoustic Neuroma)

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

The overall strength of the evidence is very low, consisting of two poor quality cohort studies that provide case series type of data for the purposes of this report. Local control may range from 86% to 100% and hearing preservation from 59% to 100% with hearing preservation likely being dependent on the tumor volume.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

The overall strength of evidence is very low, consisting of one SR of case series, two poor quality cohort studies and a large number of case series. Hearing loss may range 17% to 59%, hydrocephalus requiring a shunt 1% to 25%, new malignancies 2%, and new cranial nerve neuropathies 0% to 36%. Conclusions cannot be drawn concerning the relative harms of SRS and hypofractionated SRT, although hypofractionated SRT may be associated with less harm than SRS (new cranial neuropathy or malignancy, hydrocephalus). SRS doses less than 13 Gy

may be associated with a decreased likelihood of cranial neuropathy and hydrocephalus, but an increased likelihood of vertigo and tinnitus.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

Based on one poor quality cohort study and two poor quality case series, the overall strength of the evidence is very low, and too limited to draw conclusions, although patients with neurofibromatosis who develop schwannomas may have worse outcomes than patients without neurofibromatosis.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Head and Neck

In this section, cancer of the glomus jugulare and ocular melanoma are summarized. There is limited evidence for all three cancers. No other cancers were identified for this section.

Glomus jugulare

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on 13 case series summarized in one SR, there is very low strength of evidence overall, and any conclusions are uncertain. Transient (e.g., dysphagia, nausea or imbalance) toxicities may occur in 5% and severe toxicities (e.g., hearing loss, vertigo, facial palsy) may occur 9% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Ocular

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on seven case series, the overall strength of evidence is very low and any conclusions on harms are very uncertain. However, these studies suggest that high rates of significant toxicities including dry eye syndrome, retinopathy, optic neuropathy, neovascular glaucoma, and cataracts may occur. Most concerning is the possibility that between 4% and 13% of patients may require enucleation due to painful neovascular glaucoma and other complications.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Prostate

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on four poor quality case series, the overall strength of evidence is very low for harms. Reported QoL scores may decline and later returned to baseline, except for sexual QoL score which remained low in about 10% of men. Acute gastrourinary (GU) complications (i.e., urinary frequency, nocturia, dysuria, urinary retention) tend to be mild but Grade 1 GU toxicities may occur in up to 75% of men and Grade 2 toxicities in 2% to 4%. Similar mild severity and low rates of acute gastrointestinal (GI) complications (diarrhea, rectal pain) may occur. Late GU toxicities were mostly mild and occurred in 9% to 10% of patients but may be as high as 28%. Late GI toxicities may also be mild and occur in about 5% to 8% of men.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Spine

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

The overall strength of evidence is very low, based on one SR of 29 case series and eleven subsequent case series. The following estimates are uncertain. Some of the patients in these studies had received prior conventional EBRT and were treatment failures. Local tumor control rates may range from 76% to 96% and median survival from 11 months to 22.5 months. In addition, rates of pain control may range from 80% to 90% with improvement in QoL. However, there are no comparative data to compare these rates to those of conventional EBRT.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Based on one fair quality SR of case series and 13 case series (six fair and seven poor quality), overall strength of evidence is very low. Acute complications from SRS treatment of spinal tumors may be mild. Examples include fatigue, nausea, esophagitis, mucositis, and dysphagia. Severe complications may be rare and included spinal fractures, lumbar plexopathy, paraparesis and myelopathy. Due to the lack of comparative data, no conclusions can be drawn about harm from SRS compared to conventional EBRT.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

The overall strength of evidence on costs for SBRT for the spine compared to EBRT is very low. There is uncertainty in the cost estimates, but they may be $842,420/100 patients for SBRT, $676,309/100 patients for an EBRT protocol of 30 Gy in 10 fractions, and $499,911/100 patients for an EBRT protocol of 20 Gy in 5 fractions.

Multiple Tumor Sites

Four case series reported experience with SBRT across a variety of cancers. Since these reports did not analyze data by cancer type, they are summarized in this section.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

The overall strength of evidence is very low based on four poor quality case series that included patients with a variety of cancers. Local control rates are uncertain but reported as ranging from 51% at six months to 100% at one year.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

The overall strength of evidence is very low based on two fair and two poor quality case series that included patients with a variety of cancers. There is uncertainty about the rates of harms especially since they vary depending on the site of the cancer. As reported in these case series, 14 to 21% of patients may experience mild, transient acute toxicity such as nausea, fatigue or skin irritation. More severe toxicities may include pleural and pericardial effusion, gastric bleeding and vertebral fractures and may occur in 1% to 4% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on costs or cost-effectiveness were identified.

Maude Database

Three reports of serious adverse events were identified. Two patient deaths, one from metastatic lung cancer and one from metastatic stomach cancer were reported. The third adverse event identified reported a portal vein thrombosis and an occluded hepatic artery. Full summaries of the events are provided in Appendix J.

Guidelines

Based on fair to poor quality guidelines, SRS and SBRT are not recommended or considered appropriate by the ACR for the treatment of bone metastases, colon, low grade glioma, non-spine bone metastases, pancreatic, prostate, rectal, and operable stage I NSCLC cancer. For brain metastases, there are inconsistent recommendations for the use of SRS and SBRT from good to poor quality guidelines and the ACR ranging from usually not appropriate/not recommended to usually appropriate/recommended. For all other tumors discussed, SBRT is considered as a possible appropriate form of treatment by the ACR and included guidelines.

Policy Considerations

Federal and private payer policies vary across treatment modalities. Coverage for SBRT varies across Medicaid and private payer policies. The most strict criteria cover only spinal, vertebral, inoperable stage 1 NSCLC, and lung metastases. Other policies include treatment of lung, liver, kidney, pancreas, prostate tumors. Although covered tumor sites vary, all policies have requirements related to the appropriate use of SBRT over conventional therapies such as patient performance scales indicating good performance status, tumor proximity to critical structures, and repeated use of radiation. Coverage criteria are similar across policies for SRS. Conditions consistently covered include benign cranial lesions such as neuromas and meningioma and malignant brain lesions. Coverage criteria vary and include the use of performance scales, deep intracranial location, and life expectancy.

Only two policies address SRT. Both policies cover treatment of tumors in hard to reach places, or in close proximity to critical structures where high-dose single fractions of SRS would not be tolerated.

Overall Summary

Over the past ten years, important advances have been made in techniques to deliver EBRT for some cancers. This report presents the evidence regarding SRS/SRT and SBRT for cancers in the following anatomic locations: abdomen (anus/rectum/colon, liver, pancreas, and adrenal glands), CNS (astrocytoma, brain metastases, ependymoma, glioblastoma, glioma, meningioma, neurocytoma, pituitary adenoma, schwannoma), head and neck (glomus jugulare, head and neck, ocular melanoma), lung, prostate, and spine. A total of 3,034 citations were screened for inclusion (1,915 from a Medline search, 112 from Cochrane, 959 from public comments on the draft key questions, and 48 from public comments on the draft report). Two hundred and fifty-three studies met criteria for inclusion in this review. Except for six RCTs of SRS for brain metastases and one for glioblastoma, the evidence for SRS and SBRT is based on cohort and case series studies that have substantial methodological limitations. Almost all of these studies are non-comparative, and only two focus solely on children. Thus, the risk of bias is high and estimates of the relative benefits and harms of SRS/SBRT compared to conventional EBRT are highly uncertain for most of the tumors covered in this review.

The findings from comparative studies addressing outcomes (e.g., OS, QoL) and harms are summarized below by tumor. For the remainder of the tumors, the overall strength of evidence was very low and often heterogeneous. Therefore, no general conclusions can be drawn for these tumors. In addition, even though the overall strength of evidence is low or very low, harms for a few tumors will be described because of their frequency or severity. For the remaining tumors, in addition to fatigue and general malaise, harms were mostly regional toxicities based on the location of the malignancy (e.g., radiation pneumonitis for lung, headaches or radionecrosis with brain edema for brain, erectile dysfunction for prostate) and commonly included acute and late toxicities.

Brain Metastases

For *SRS+WBRT compared to WBRT* alone, the overall strength of evidence is moderate for survival and tumor control. Although local tumor control is probably better, SRS+WBRT compared to WBRT alone likely has *no significant difference in OS*. Subgroup analyses from one RCT, which provides low overall strength of evidence, suggest that median survival in patients with single metastases (6.5 vs. 4.9 months, SRS+WBRT vs. WBRT, respectively) and patients who are RPA Class 1 (11.6 vs. 9.6 months, SRS+WBRT vs. WBRT, respectively) may be better with SRS+WBRT compared to WBRT alone. Acute and late toxicities are probably not significantly different for SRS+WBRT compared to WBRT alone, base on moderate strength of evidence. Approximately, 2% to 5% of patients may experience severe (Grade 3 or 4) acute and late toxicities

For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is moderate for the outcome of OS and tumor control. Although local and distant tumor control is probably better, SRS+WBRT compared to SRS alone probably has *no significant difference in OS*. An overall low strength of evidence exists to suggest there is no difference in functional independence, time to worsened performance status or quality of life for SRS+WBRT compared to SRS alone. The overall strength of evidence is low for harms and indicates that severe (Grade 3 or 4) acute and late toxicities may be similar for SRS+WBRT compared to SRS alone and occur in approximately 2% to 5% of patients.

For *SRS alone compared to WBRT alone*, the overall strength of evidence is very low based on six cohort studies, two with historical controls, and two additional small poor quality cohort studies. These studies suggest that OS may be better for patients receiving SRS alone compared to WBRT alone, but the poor quality of the studies and the heterogeneity across studies limit any conclusions. For harms, severe (Grade 3 or 4) acute and late toxicities may be similar for SRS+WBRT compared to SRS alone and occur in approximately 2% to 5% of patients.

Glioblastoma

The overall strength of the evidence is low based on one fair quality RCT that conflicts with two poor quality cohort studies. The addition of SRS to EBRT and carmustine (chemotherapy) may not affect survival in patients with recurrent glioblastoma based on the results from the RCT. However, adding SRS to other treatments for glioblastoma may increase the risk of symptomatic radionecrosis requiring a second surgery, based on low overall strength of evidence.

Glioma

The overall strength of evidence is very low for prolonged survival with salvage SRS in patients with recurrent gliomas and for harms in patients with primary and recurrent malignant gliomas. Although there is uncertainty, these studies raise concerns about radiation necrosis leading to a mass effect requiring surgery or potentially stimulating recurrence.

Schwannoma

The overall strength of evidence for harms from SRS for schwannomas is very low. However, about 1% of patients may develop hydrocephalus requiring a shunt though one study suggests

this is as high as 12%, 1% to 2% may develop a new malignancy, and up to 36% may develop new facial nerve dysfunction. There were no studies that compared SRS to EBRT, so relative harms are uncertain.

Ocular melanoma

The overall strength of evidence for harms from SRS for choroidal and uveal melanoma is very low. However, enucleation due to treatment side effects such as painful neovascular glaucoma may occur in 4% to 13% of patients.

Early Stage Non-Small Cell Lung Cancer

The overall strength of evidence is very low for outcomes. SBRT for *non-operable* Stage I NSCLC may result in 3-year OS rates of 50% to 60% and local control rates of 80% to 100%. The overall strength of evidence regarding harms is very low. There is uncertainty about the rate of acute and late toxicities, especially as they compared to EBRT. However, rates of greater than or equal to Grade 3 late toxicities may range 2% to 10%. In addition, the placement of fiducial markers, when used, to help target the radiation to the tumor may cause a pneumothorax requiring chest tube placement or hospitalization in approximately 9% to 28% of patients.

Subgroups, Cost and Cost-effectiveness

Few, if any, studies addressed patient subgroups or costs of SRS/SBRT. Except as noted above for brain metastases, there was insufficient evidence to address outcomes and harms for any subgroup for any of the tumors in this report. The cost studies done for meningioma, NSCLC, and spine tumors were low quality with significant risk of bias in their estimates of effectiveness and costs. Study limitations make drawing any conclusions about cost or cost-effectiveness difficult.

Guidelines

Based on fair to poor quality guidelines, SRS and SBRT are not recommended or considered appropriate by the ACR for the treatment of bone metastases, colon, low grade glioma, non-spine bone metastases, pancreatic, prostate, rectal, and operable stage I NSCLC cancer. For brain metastases, there are inconsistent recommendations for the use of SRS and SBRT from good to poor quality guidelines and the ACR ranging from ranging from usually not appropriate/not recommended to usually appropriate/recommended. For all other cancers discussed, SBRT is considered as a possibly appropriate treatment by the ACR and included guidelines. In general, the guidelines recommend the use of SRS and SBRT as a potential alternative to other treatments appropriate for the tumor (e.g. for patients with one to three brain metastases that are less than 3 to 4 cm when their prognosis is good) or in specific situations (e.g., patients with medically non-operable Stage 1 NSCLC).

Policies

Federal and private payer policies addressing SRS/SBRT that are pertinent to this report include Medicare, Aetna, Regence Blue Cross Blue Shield (BCBS), and GroupHealth. Medicare has not issued a national coverage determination for SRS/SBRT. Two Medicare local coverage determinations (LCDs) cover Washington, one addressing SBRT, and another addressing SRS/SRT. SRS/SRT for intracranial lesions are covered when 1) the lesion has image-distinct

margins; 2) the patient's Karnofsky performance scale is greater than 50% or ECOG performance is less than or equal to 2; and 3) the tumors are in hard to reach locations, unusual shapes, or in close proximity to vital structures. SBRT is covered for primary and metastatic tumors of the lung, liver, kidney, pancreas, or low/intermediate risk prostate cancer when 1) aggressive treatment is justified; 2) other forms of radiotherapy or focal therapy cannot be as safely or effectively utilized; 3) the tumor can be targeted with acceptable risk to surrounding structures; or 4) the patient had previous radiotherapy to the same or adjacent sites.

Coverage criteria are similar across Medicaid and private payer policies for SRS/SRT. Conditions consistently covered include benign cranial lesions such as neuromas and meningioma and malignant brain lesions. Coverage criteria vary and include the use of performance scales/ good patient performance (e.g. Karnofsky score $\geq$ 70, RPA level 1), deep intracranial location, and life expectancy. Only two policies address SRT. Both policies cover treatment of tumors in hard to reach places, or in close proximity to critical structures where high-dose single fractions of SRS would not be tolerated. Coverage for SBRT varies across Medicaid and private payer policies. The strictest criteria cover only spinal, vertebral, stage 1 non-operable NSCLC, and lung metastases. Other policies include treatment of lung, liver, kidney, pancreas, prostate tumors. Although covered tumor sites vary, all policies have requirements such as good patient performance (e.g. Karnofsky score $\geq$ 70, RPA level 1), tumor proximity to critical structures, and repeated use of radiation.

Limitations of the Evidence

The evidence on SRS and SBRT is almost exclusively based on case series studies and a few RCT (i.e., brain metastases and glioblastomas) and comparative cohort studies. The case series and cohort studies included in this report have substantial methodological limitations creating high risk of bias, such as:

- All case series lacked a comparison group;
- Many of the studies did not adjust for confounding variables in analyses. Variables that may have a significant impact on outcomes include
    - Age;
    - Performance status and tumor staging prior to treatment;
    - Smoking status; and
    - Other medical comorbidities;
- Selection bias when consecutive patients meeting study inclusion/exclusion criteria are not included, especially problematic in retrospective studies;
- Many of the studies combined different types and stages of malignancies in their analyses; and

- Many of the studies have relatively small sample sizes making it difficult to infer findings to a broader population.

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Background

Over the past ten years, significant advances have been made in the techniques available to deliver external beam radiation therapy (EBRT) as a treatment modality for certain cancers. The goal of these newer techniques is two-fold: to improve the targeting of the radiation to the tumor to minimize damage of normal tissue and increase the dose of radiation (fraction) delivered in order to decrease the number of fractions and length of treatment. One of these newer techniques includes stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT).

Clinical and epidemiological overview

Cancers of the brain, breast, colon, head and neck, lung, and prostate are among the most common cancers in the United States (US) and are those where SRS and SBRT are utilized. Background information on the incidence, mortality, and median age at diagnosis for these seven common cancers is presented below with additional information for other cancers included in Table 1 (National Cancer Institute [NCI] 2011).

Central Nervous System (CNS): An estimated 22,340 men and women were diagnosed with cancer of the brain and nervous system in 2011. Approximately 13,110 died from the disease. The age-adjusted incidence from 2004-2008 was 6.5 per 100,000 men and women annually. The median age at diagnosis was 56 years.

Head and Neck: Head and neck cancer includes cancers arising in the oral cavity, salivary glands, larynx, hypopharynx, oropharynx, nasopharynx, nasal cavity, paranasal sinuses and occult primary cancers. They account for three to five percent of cancers in the US. Head and neck cancers are in close proximity to many dose limiting structures affecting basic functions including chewing, swallowing, breathing, taste, smell and hearing. An estimated 47,000 new cases of head and neck cancers were diagnosed in 2008 with an estimated 11,000 deaths from head and neck cancer.

Lung: For all types of cancer of the lung and bronchus, an estimated 221,130 men and women were diagnosed in 2011 and 156,940 died. The median age of diagnosis from 2004-2008 for all cancers of the lung and bronchus was 71 years old. The 2008 incidence of small cell lung cancer was 6.95 per 100,000 men and women while the incidence for non-small cell lung cancer (NSCLC) was 51.82 per 100,000. Small cell lung cancer accounts for approximately 20% of all cases of lung cancer.

Breast: In 2011, an estimated 230,480 women were diagnosed with and 39,520 women died from breast cancer. From 2004-2008 the age-adjusted incidence of breast cancer was estimated to be 124.0 per 100,000 women annually. In the same time period, the median age at diagnosis was 61 years of age.

Colon: It is estimated that in 2011, 141,210 men and women were diagnosed with colon cancer and 49,380 died from cancer of the colon and rectum. The 2004-2008 age-adjusted incidence of

colon and rectal cancer was estimated at 47.2 per 100,000 men and women annually. For the same time period, the median age at diagnosis was 70 years.

Prostate: An estimated 240,890 men were diagnosed with prostate cancer in 2011 and 33,720 died from the disease. From 2004-2208 the age-adjusted incidence of prostate cancer was 156.0 per 100,000 men annually. The median age of diagnosis was 67 years.

Table 1. Cancer Incidence and Prevalence by Site (NCI 2011)

Cancer/Tumor Site	Incidence	Prevalence[3] (2005 - 2009)	5-Year Relative Survival[4] (2002 – 2008)
Prostate	154.8 per 100,000 men	2,496,784	99.2%
Breast	124.3 per 100,000 women	2,747,459	89.0%
Lung	62.6 per 100,000 men and women	387,762	15.9%
Localized (confined to primary site)			52.2%
Regional (spread to regional lymph nodes)			25.1%
Distant (cancer has metastasized)			3.7%
Colorectal	46.3 per 100,000 men and women	1,140,161	63.4%
Pancreas	12.1 per 100,000 men and women	38,308	5.8%
Oral Cavity and Pharynx	10.8 per 100,00 men and women	264,442	61.5%
Liver and intraheptic bile duct	7.5 per 100,000 men and women	35,557	15.2%
Brain and other nervous system	6.5 per 100,000 men and women	135,402	33.5%
Larynx	3.4 per 100,000 men and women	89,142	60.5%
Eye and Orbit	0.8 per 100,000 men and women	-	83.1%

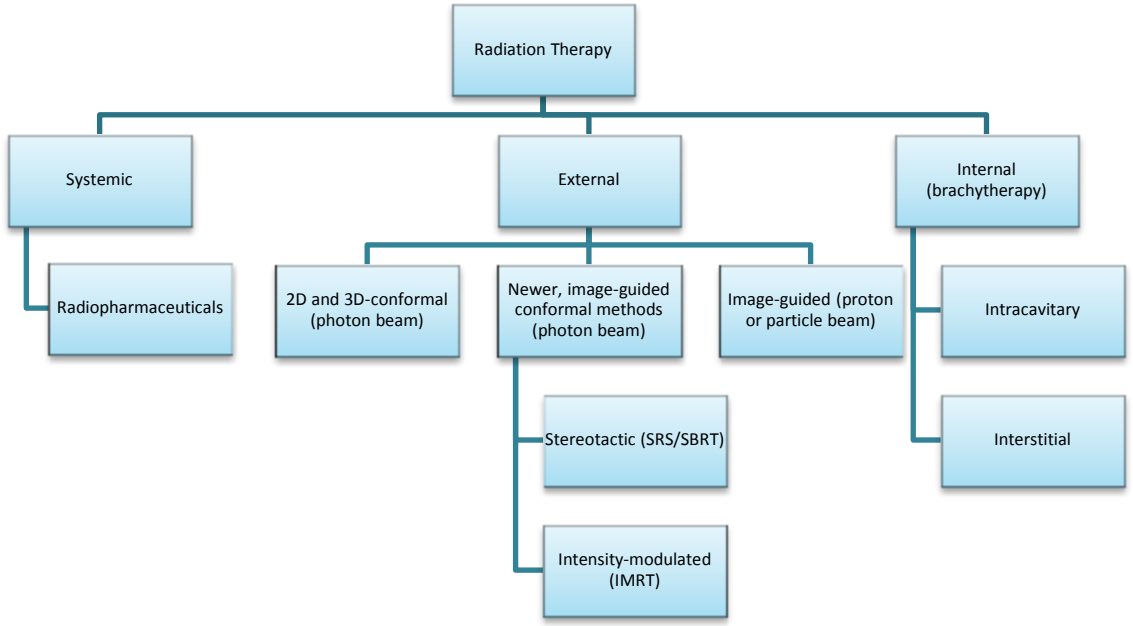
Approximately half of all cancer patients receive some form of radiation therapy (NCI 2010). Radiation utilizes high energy particles or waves to destroy or damage cancer cells. Patients may receive radiation therapy alone or in combination with other treatments including surgery, chemotherapy or other pharmaceuticals (American Cancer Society [ACS] 2010; Tipton 2011b). Radiation therapy may be given before, during, or after surgery or chemotherapy depending on the type and stage of the cancer and the goal of treatment (cure the cancer or palliate symptoms cause by the cancer). Radiation treatment causes acute and chronic side effects depending on the area of the body and dose of radiation. Fatigue is a common side effect no matter which body area is treated.

Technology overview

There are three main modalities for delivering radiation. Radiation can be delivered externally by a machine (EBRT), internally via radioactive material place in the body (brachytherapy), or systemically using radiopharmaceuticals that are swallowed or injected into the blood stream (NCI 2010) (Figure 1).

[3] Based on 2005-2009 Surveillance Epidemiology and End Results (SEER) data
[4] Based on 2002-2008 SEER data

Figure 1. Modalities used for the Delivery of Radiation Therapy[5]



Current conventional or standard EBRT (also called two-dimensional (2D) or three-dimensional (3D) conformal radiation therapy) uses imaging technology such as computed tomography (CT) for planning purposes and delivers photon beams of uniform intensity to the target tumor using a medical linear accelerator (linac) (Tipton 2011b). The imaging is done several days prior to the patient starting radiation treatment and markers are placed on the skin so the patient can be positioned and aligned each day for treatment. Typically, conventional EBRT (or 3DCRT) is delivered in 25 to 50 fractions (doses) delivered five days per week for 5 to 10 weeks. The newer photon (e.g., SRS/SBRT) and particle beam therapies rely on data directly from 3D imaging, such as CT, magnetic resonance imaging (MRI), and/or positron emission tomography (PET), done in the treatment room just prior to the patient receiving radiation treatment. When this type of planning process is used, it is referred to as image-guided therapy (IGRT). It provides greater precision in targeting the radiation to the tumor and is used with the newer photon and particle beam therapies. In addition, SRS and SBRT require strategies and devices that minimize patient and organ movement to minimize the risk of delivering high dose radiation to normal surrounding tissues. These include

1) Immobilization using body cases;

2) Implantation of radiopaque markers called fiducials;

3) Real-time CT imaging systems incorporated into linear accelerators; and

[5] Note: 2D and 3D indicates two and three-dimensional, respectively; SRS stereotactic radiosurgery; SBRT stereotactic body radiation therapy; and IMRT intensity-modulated radiation therapy.

4) Techniques that manage respiratory movement (e.g. abdominal compression, breath holding when the beam is on, and gating where the beam is turned on and off with the respiratory cycle).

Stereotactic radiation surgery (SRS) was initially developed in the 1950's to treat inoperable intracranial conditions through the use of targeted high dose photon radiation. Stereotactic radiation surgery uses a single high dose of radiation directed at a tumor within the central nervous system. The primary objective of SRS is to spare normal tissue surrounding the tumor while delivering high dose photon radiation to the tumor. The same type of radiation, photon beam, is used with SRS and conventional EBRT, but the amount of radiation delivered in a fraction (dose) is much higher with SRS. (When the total dose of radiation is hypofractionated, delivered in a small number of fractions, it is called stereotactic radiation therapy [SRT].) To achieve this objective, multiple radiation beams are precisely targeted to the shape of the tumor from different directions instead of from a single direction or two directions (Figures 2 and 3). The full dose of radiation is limited to the areas of overlap of the beams and the surrounding normal tissue receives a much lower dose. This technique requires precision in defining the tumor and delivering the radiation.

Figure 2. 3D-CRT Radiation Field

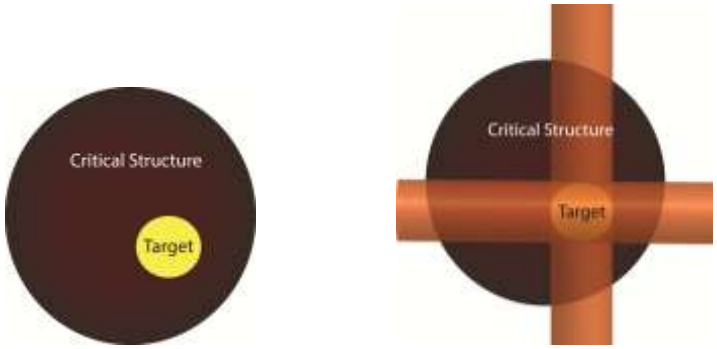


Figure 3. SRS Radiation Field

In the early 1990's, research began to explore the use of SRS for non-intracranial indications. When used outside the CNS, it is usually referred to as SBRT (Hayes 2011; Tipton 2011b). Stereotactic radiation therapy and SBRT have also been called "stereotactic radiotherapy," "fractionated stereotactic radiosurgery," "hypofractionated stereotactic radiosurgery," and

"staged radiosurgery" (Tipton 2011a). The intent of SBRT is to deliver higher doses of radiation therapy to a smaller area and in fewer fractions (doses). Usually, SBRT fractions (doses) are 20 to 60 gray (Gy), a unit of radiation, and given in one to five fractions (doses) on a daily basis. Typically, SBRT is used for 1) primary or metastatic tumors that are considered inoperable due to their location; 2) patients who would be high risk for surgery (e.g., patients with lung cancer who have severe underlying lung disease); or 3) patients who refuse surgery, when surgery would normally be indicated based on cancer type and stage. Nine devices are currently approved for SBRT by the Food and Drug Administration (FDA) (Table 2).

Table 2. Devices used for Stereotactic Body Radiation Therapy (adapted from Tipton 2011b)*

Device	Manufacturer	Indications presented on website
Axesse™	Elekta Inc.	Spinal metastases, lung, liver, prostate, head, neck
CyberKnife® robotic radiosurgery system	Accuray Incorporated	Spine, lung, liver, prostate, pancreas, kidney, head, neck
Leksell Gamma Knife® Perfexion™	Elekta Inc.	Cervical spine, head, neck, larynx
MHI-TM2000 Linear Accelerator System	Mitsubishi Heavy Industries (MHI)	Not reported
Novalis TX™	BrainLAB/Varian Medical Systems	Spine, lung, liver, prostate, head, neck
Oncor ARTISTE, Impression, Avant-Garde, Expression	Siemens	Head, neck, extracranial areas
Synergy®S	Elekta Inc.	Spine, lung, liver, prostate, pancreas, head, neck
TomoTherapy® Hi-Art®	TomoTherapy Inc.	Lung, liver, prostate, head, neck
Trilogy™	Varian Medical Systems	Whole body

* Since the publication of Tipton (2011b) the following devices manufactured by Varian Medical Systems, Inc have been approved by the FDA: TrueBeam, TrueBeam STx, and Clinac iX.

For optimal use of SBRT, the American College of Radiology (ACR) recommends the following minimum staffing levels and responsibilities for successful planning, implementation, and monitoring of treatment:

- Certified radiation oncologist: Manage overall disease-specific treatment regimen;
- Qualified medical physicist: Technical aspects including quality control; and
- Licensed radiation therapist: Implementation of treatment plan under supervision of a radiation oncologist.

Tipton (2011b) provides an outline of the staffing qualifications and responsibilities for optimal use of SBRT initially provided by the ACR (Table 3).

Table 3. Personnel Qualifications for SBRT (adapted from Tipton 2011b, p. D-1)

Personnel	Qualifications	Responsibilities
Radiation Oncologist	• Certified in radiology, radiation oncology, or therapeutic radiology **OR** • Satisfactory completion in an approved residency program • Specific training on extracranial SRS	• Manage overall disease-specific treatment regimen • Recommend most ideal patient-positioning method • Recommend procedure to account for inherent organ motion • Supervise patient simulation; contour the outline of the gross tumor volume (GTV) on the treatment planning computer • Coordinate design for proper planning target volume (PTV) • Convey case-specific expectations for prescribing radiation dose and setting limits on dose to adjacent normal issues • Attend and direct actual treatment process • Follow patient with attention to disease control • Monitoring and treating potential complications
Medical Physicist	• Certified in therapeutic radiological physics or radiological physics • Should be in accordance with the ACR Practice Guideline for Continuing Medical Education • Specific training in SRS should be obtained prior to performing any SBRT procedures	• Acceptance testing and commissioning of SBRT system • Implementing and managing a QC program • Establishing a comprehensive QC checklist • Directly supervising or checking the 3D and/or intensity-modulated treatment planning process • Consulting with radiation oncology to discuss optimal patient plan • Determine and check appropriate beam-delivery parameters (calculation of radiation beam parameters consistent with beam geometry) • Double-checking beam delivery process to assure accurate fulfillment of prescription
Radiation Therapist	• Fulfill state licensing requirements • Certified in radiation therapy	• Preparing treatment room • Assisting the treatment team with positioning/immobilization • Operating treatment unit after radiation oncologist & medical physicists approved clinical technical delivery aspects for beam delivery

Outcome and Toxicity Measures

Outcome measures for the multiple cancers include the primary outcomes of overall survival (OS) at 1-, 2- and 5-years and median survival, and secondary outcomes of tumor control, disease-free survival (DFS), and quality of life (QoL). Tumor control measures include tumor recurrence and development of local and distant metastases. Patient survival measures related to tumor control include DFS, progression-free survival (PFS), recurrence-free survival (RFS), biochemical disease-free survival (bDFS), and symptom-free survival. In addition, some studies of brain metastases stratify their analyses by Recursive Partitioning Analysis (RPA) class, a classification scheme related to patient prognosis (Gaspar 1997; Neider 2000). The RPA classes are

1) Class 1: Karnofsky Performance Status (KPS) greater than or equal to 70, age less than 65 years, and controlled primary disease with no extracranial metastases;

2) Class 2: not meeting criteria for Class 1 or 3; and

3) Class 3: KPS less than 70.

More importantly, many of the clinical trials restrict enrollment of patients to exclude Class 3 patients (KPS less than 70) who have the worst prognoses.

Adverse reactions to SRS of CNS tumors are classified as acute, occurring within 90 days of treatment, or late reactions, occurring after 90 days. Acute reactions are thought to be due to transient edema causing neurologic symptoms such as headache, nausea, dizziness, vertigo, and seizures. Some radiation oncologists routinely give short courses of steroids to decrease brain edema and the risk of acute reactions unless steroids are contraindicated. The Radiation Therapy Oncology Group (RTOG) developed scoring criteria for acute and chronic adverse reactions from CNS radiation. Because many of the studies of brain tumors focused on CNS toxicity, these criteria are listed below.

<u>RTOG Acute Radiation Morbidity Criteria</u>

- Grade 1 – Fully functional with mild neurologic symptoms, no need for medications;
- Grade 2 – Neurologic finding requiring home care and possibly requiring nursing care and/or medications (e.g., steroids, anti-seizure medications);
- Grade 3 – Neurologic findings requiring hospitalization for treatment;
- Grade 4 – Serious neurologic impairment including difficult to control seizures, coma, and paralysis; and
- Grade 5 – Death related to adverse events (RTOG 2012a).

<u>RTOG Late Radiation Morbidity Criteria</u>

- Grade 1 – Mild headache, mild lethargy;
- Grade 2 – Moderate headache, significant lethargy;
- Grade 3 – Severe headache, severe neurologic dysfunction (partial loss of power or dyskinesia);

- Grade 4 – Seizures, paralysis or coma; and
- Grade 5 – Death related to adverse events (RTOG 2012b).

For SBRT, adverse events are usually specific to the anatomical region of the tumor and are reported according to the newer Common Terminology Criteria for Adverse Events v3.0 (CTCAE). The CTCAE is divided into five grades related to the severity of adverse events, and is categorized by anatomy and/or pathophysiology. An overview of the grades includes:

- Grade 1 – Mild adverse events;
- Grade 2 – Moderate adverse events;
- Grade 3 – Severe adverse events;
- Grade 4 – Life-threatening or disabling adverse events; and
- Grade 5 – Death related to adverse events (Cancer Therapy Evaluation Program 2006).

Cost information

Medicare's national payment amount for SBRT (CPT 77373) is $1,590.44. Payments for CPT 77373 by Medicare local contractors range from $1,342.50 to $2,259.32 (Center for Medicare and Medicaid Services [CMS] 2011a). There is little available data on the costs associated with SRS and SBRT.

Policy context

Use of new radiation technologies has grown dramatically in the last decade. Despite this rapid adoption, the FDA process for approving new radiation therapies does not require a review of safety and efficacy of SRS/SBRT, which has resulted in limited information about efficacy and comparative effectiveness of these treatments (Konski 2011a).

A survey of radiation oncologists (Pan 2011) found that 64% were using SBRT in 2010 up from 30% in 2007. The most common reasons for using SBRT were

1) The ability to deliver higher doses of radiation (90%);
2) The ability to retreat selected patients (74%); and
3) To provide a competitive advantage or remain competitive (42% of private and 20% of academic radiation oncologists).

Most SBRT users (76%) planned to increase their use of SBRT, and 66% of non-users planned to use SBRT in the future. In 2009, an estimated 384 facilities had SBRT capacity (Tipton 2011b), and according to Gamma Knife® manufacturer, Elekta, the device has been used to treat 241,786 malignant tumors worldwide as of 2009 (Elekta 2009).

Comparative trials including randomized controlled trials (RCTs) have not been required by the FDA to clear the newer devices (e.g., Gamma Knife®) for sale. For moderate risk new devices, the FDA clears the device for sale under their 510(k) process that only requires manufacturers to demonstrate that new devices is substantially equivalent to a prior device that has been

cleared for sale (Institute of Medicine 2011). The purpose of this report is to provide a broader evidence analysis of SRS and SBRT than required by the FDA in granting approval for sale.

Washington State Data

Section 1: Agency usage, SBRT

Section 1 displays basic costs, counts and trends, using the paid amount for each claim, affording a summary of agency expenditures and number of patients served. Patient cost-sharing and coordination of benefits between other payers results in lower average payments compared to actual treatment costs (Section 2 – Allowed amount).

Figure 4.1a SBRT Payments by Agency –2008-2011

Agency/Year	2008	2009	2010	2011	4 Yr Overall Total[1]	Average % Change	
PEB[2]							
Agency Population	204,804	210,501	213,487	212,596		1.3%	
Patient Ct	49	55	60	70	205	11.3%	*
Amount Paid	$924,420	$1,473,980	$1,772,121	$1,135,340	$5,305,861	12.7%	*
Average Paid per Pt	$18,866	$26,800	$29,535	$16,219	$25,882	2.4%	
Per Pt 95% Upper Limit	$54,130	$80,915	$93,216	$75,486	$87,699		
Treatment Courses (courses/Pt)[3]	55 (1.1)	62 (1.1)	74 (1.2)	81 (1.2)	264 (1.3)	1.2%	*
Average SBRT Delivery CPTs only[4]	$9,342	$12,616	$13,368	$7,973	$10,630	0.2%	
Max/SBRT Delivery CPTs	$42,800	$47,536	$53,995	$108,142	$108,142		
%SBRT Delivery of per pt avg	49.5%	47.1%	45.3%	49.2%	41.1%		
Medicaid							
Agency Population	392,808	416,871	424,230	435,187		3.5%	
Patient Ct	59	74	92	108	291	18.3%	*
Amount Paid	$848,323	$1,091,784	$1,481,655	$1,816,629	$5,238,391	24.7%	*
Average Paid per Pt	$14,981	$16,021	$12,196	$11,033	$15,244	-8.8%	
Per Pt 95% Upper Limit	$71,826	$74,001	$56,370	$72,150	$98,798		
Treatment Courses (courses/Pt)[3]	92 (1.6)	103 (1.4)	176 (1.9)	165 (1.5)	536 (1.8)	21.6%	*
Average SBRT Delivery CPTs only[4]	$6,174	$6,522	$4,129	$5,645	$5,406	1.9%	
Max/SBRT Delivery CPTs	$14,802	$15,983	$15,788	$20,134	$20,134		
%SBRT Delivery of per pt avg	41.2%	40.7%	33.9%	51.2%	35.5%		

*Average % Change adjusted for population growth

[1] Patients who receive tests in multiple years are counted once in the "4 Yr Overall" total

[2] Public Employee Benefits

[3] Distinct SBRT treatments separated by more than 7 days

[4] See Related Medical codes table for SBRT Delivery CPT Codes and descriptions

Figure 4.2a: PEB SBRT Utilization - Age and Gender by Year

Patient Count					
Age Group	2008	2009	2010	2011	4 Yr Overall[1]
0-17	0	0	1	1	2
18-34	1	1	0	2	4
35-49	4	6	7	8	24
50-64	20	24	27	18	83
65-79	14	16	17	32	73
80+	6	3	2	9	19
Total Patients	45	50	54	70	205
% Female	2008	2009	2010	2011	4 Yr Overall
0-17				100.0%	50.0%
18-34				100.0%	50.0%
35-49	75.0%	83.3%	85.7%	62.5%	75.0%
50-64	65.0%	45.8%	59.3%	61.1%	55.4%
65-79	50.0%	31.3%	41.2%	56.3%	47.9%
80+	50.0%	66.7%	100.0%	77.8%	68.4%
Total % Female	57.8%	46.0%	57.4%	62.9%	56.1%

[1] Patients who receive tests in multiple years are counted once in the "4 Yr Overall" total

Figure 4.2b: PEB SBRT Patients by Age and Gender

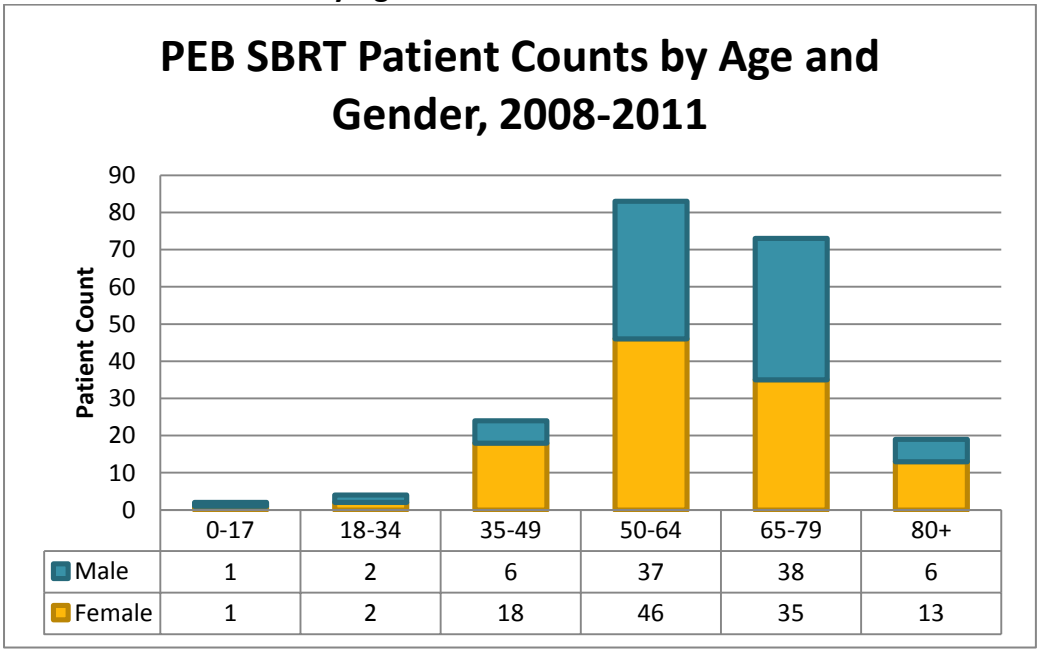


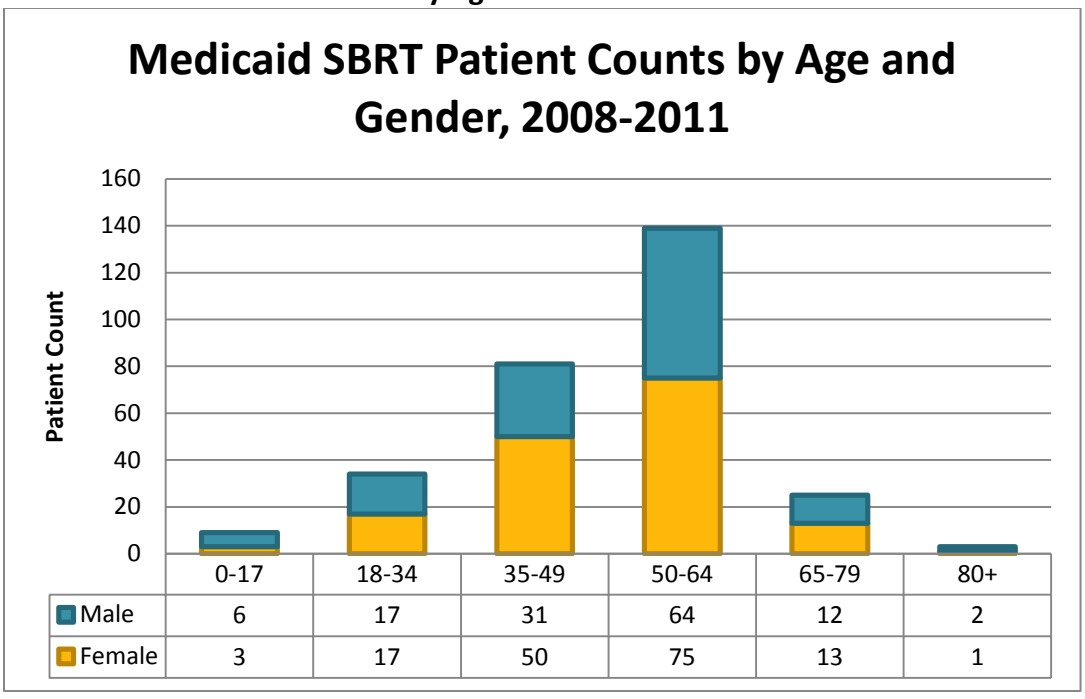
Figure 4.3a: Medicaid SBRT Utilization - Age and Gender by Year

Patient Count

Age Group	2008	2009	2010	2011	4 Yr Overall[1]
0-17	4	4	3	2	9
18-34	10	14	11	7	34
35-49	23	21	24	24	81
50-64	23	33	50	56	139
65-79	0	2	4	19	25
80+	0	1	0	2	3
Total Patients	60	75	92	110	291
% Female	2008	2009	2010	2011	4 Yr Overall
0-17	50.0%	25.0%	33.3%	50.0%	33.3%
18-34	40.0%	42.9%	36.4%	57.1%	50.0%
35-49	60.9%	61.9%	70.8%	54.2%	61.7%
50-64	56.5%	48.5%	62.0%	55.4%	54.0%
65-79		50.0%	25.0%	57.9%	52.0%
80+		100.0%			33.3%
Total % Female	55.0%	50.7%	58.7%	54.5%	54.6%

[1] Patients who receive tests in multiple years are counted once in the "4 Yr Overall" total

Figure 4.3b: Medicaid SBRT Patients by Age and Gender



Section II: Per procedure total cost

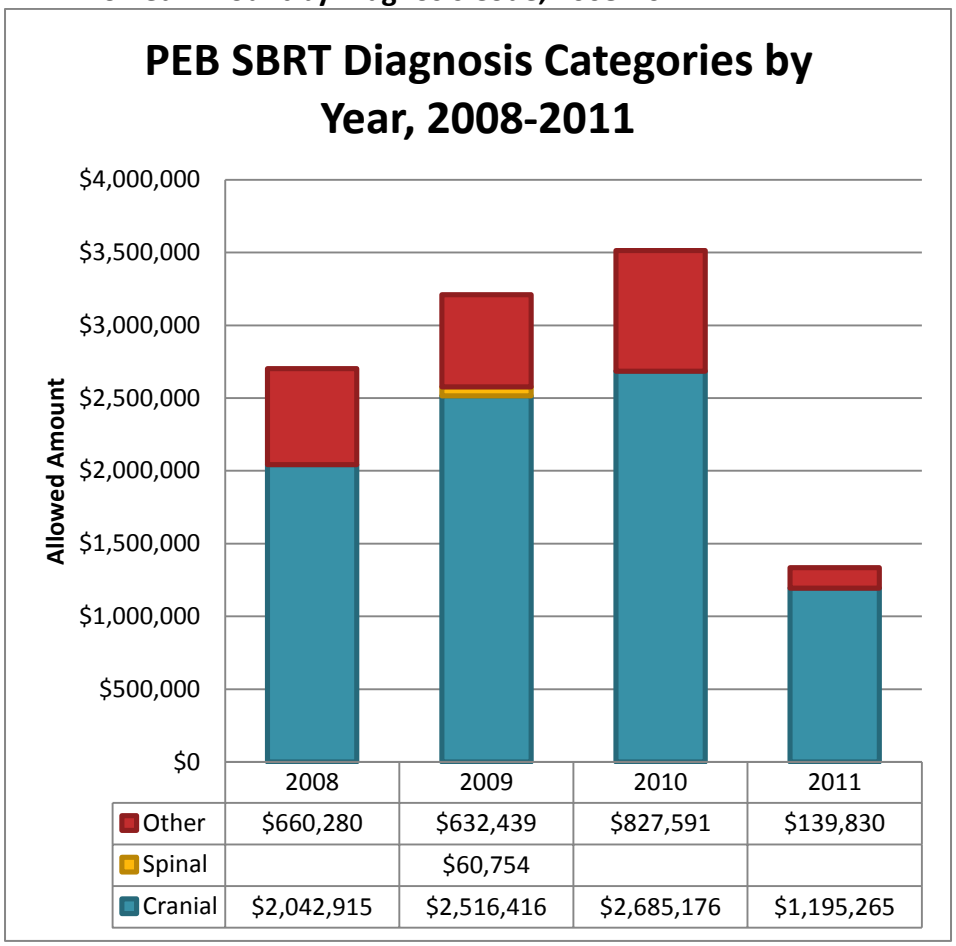
Investigation of per person charges use agency "Allowed" amounts so do not reflect patient cost-sharing or benefit coordination between payers.

Costs in the following tables are not comparable to Section I, which uses claim payments for estimation of future costs and decision impact.

Figure 5.1 Average Cost of Treatment, PEB, PEB Medicare, Medicaid, 2008-2011

Per Patient Average Charges	PEB Primary (w/o Mdcr)	Medicaid	PEB Medicare
Breakdown 1			
Professional Srvcs	$4,931	$2,587	$2,547
Facility	$40,920	$15,414	$58,084
Breakdown 2			
Planning charges	$6,811	$2,450	$11,332
Navigation/Imaging	$1,968	$350	$2,736
Delivery	$22,476	$12,919	$9,630
Other	$14,596	$2,283	$36,933
Average allowed amount per treatment course	**$45,851**	**$18,001**	**$60,630**

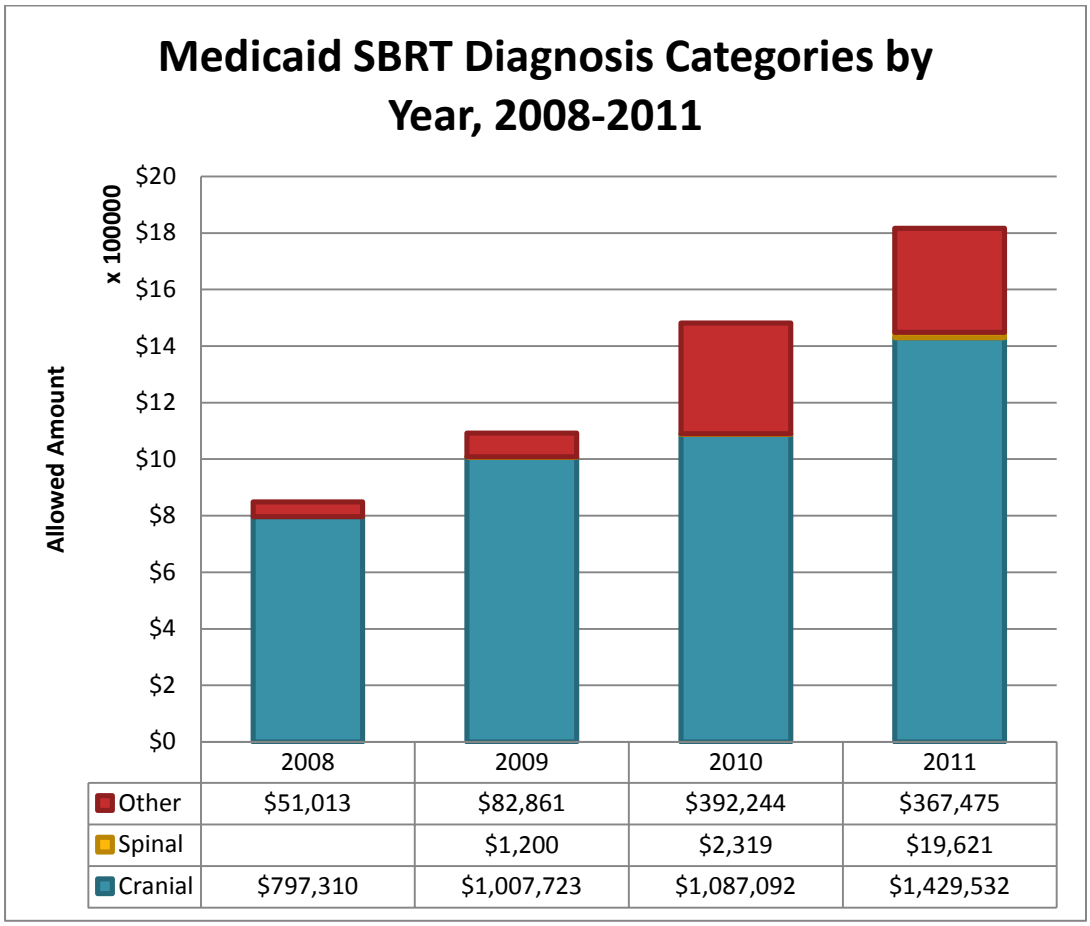
Figure 5.2a PEB Allowed Amount by Diagnosis Code, 2008-2011



"Other" category diagnoses consist mainly of malignancies of the respiratory system and GI tract, with some breast cancers and benign neoplasms.

Inconsistencies in the 2011 data are under investigation.

Figure 5.2b Medicaid SBRT Utilization by Diagnosis Categories and Year



	2008	2009	2010	2011
Other	$51,013	$82,861	$392,244	$367,475
Spinal		$1,200	$2,319	$19,621
Cranial	$797,310	$1,007,723	$1,087,092	$1,429,532

"Other" category diagnoses consist of malignancies of the lungs/bronchi, rectum and liver, and benign neoplasms of the cerebral meninges.

Related Medical Codes

Code	Description	Cranial/ Other	Progress	SBRT/ Other
61795	Stereotactic computer assisted volumetric (navigational) procedure, intracranial, extracranial, or spinal	Both	Navigation	SBRT
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion	Cranial	Delivery	SBRT
61797	Each additional cranial lesions, simple	Cranial	Delivery	SBRT
61798	Complex cranial lesion	Cranial	Delivery	SBRT
61799	Each additional cranial lesion, complex	Cranial	Delivery	SBRT
61800	Application of stereotactic headframe for stereotactic radiosurgery	Cranial	Delivery	SBRT
63620 /1	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion (63621 for each add'l spinal lesion)	Spinal	Delivery	SBRT
76830 /1 76856 /7	US (can be used for other therapy treatment planning	n/a	Alt Tx	Assoc
77011	Computed tomography guidance for stereotactic localization	Both	Navigation	Assoc
77371	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesions(s) consisting of 1 session; multi-source Cobalt 60 based	Cranial	Delivery	SBRT
77372	As 77371, but linear accelerator based	Cranial	Delivery	SBRT
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions	Other	Delivery	SBRT
77427 /31 /99	Radiation Treatment Management	Both	Alt Tx	Assoc
77432	Stereotactic radiation treatment management of cranial lesions(s) (complete course of treatment consisting of 1 session)	Cranial	Planning	SBRT
77435	Stereotactic body radiation therapy, tx management, per tx course, to 1 or more lesions, w/ image guidance, max 5 fractions	Other	Planning	SBRT
G0339	Image-guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session or first session of fractionated treatment	Both	Delivery	SBRT

Code	Description	Cranial/ Other	Progress	SBRT/ Other
G0340	Image-guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum 5 sessions/ course of treatment	Both	Delivery	SBRT
G0173	Linear accelerator based stereotactic radiosurgery, complete course of therapy in one session	Both	Delivery	SBRT
20665	Removal of fixation device	Cranial	Delivery	Assoc
77014	CT guidance for placement of radiation therapy fields	Both	Navigation	Assoc
77261 /2 /3	Radiation Therapy Planning, simple, intermediate, complex	Both	Planning	Assoc
77280 /85 77290 /95 /99	Set radiation therapy field, simple, intermediate, complex (0) or 3 dimensional (5)	Both	Planning	Assoc
77300	Radiation Therapy Dose Plan	Both	Planning	Assoc
77321	Special Teletx Port Plan	Both	Planning	Assoc
77332 /3 /4	Radiation treatment aids (simple, intermediate, complex)	Both	Planning	Assoc
77336	Continuing medical physics consultation	Both	Planning	Assoc
77370	Special medical radiation physics consultation	Both	Planning	Assoc
77470	Special Radiation Treatment management (extra planning for SRS)	Both	Planning	Assoc
70551 /2 /3	MRI Brain	Cranial	Planning	Assoc
70010-70559	Diagnostic Radiology Head and Neck	Cranial	Planning	Assoc
71010-71555	Diagnostic Radiology Head and Neck	Other	Planning	Assoc
72010-72295	Diagnostic Radiology Spine and Pelvic	Other	Planning	Assoc
74000-74190	Diagnostic Radiology Abdomen	Other	Planning	Assoc
74210-74363	Diagnostic Radiology Gastrointestinal Tract	Other	Planning	Assoc
74400-74485	Diagnostic Radiology Urinary Tract	Other	Planning	Assoc
74710-74775	Diagnostic Radiology Gynecological and Obstetrical	Other	Planning	Assoc
75557-75564	Diagnostic Radiology Spine and Pelvic Heart	Other	Planning	Assoc

Evidence Review

This section describes the report design, methods, and findings for the evidence review about SRS and SBRT.

PICO

Population: Adults and children with central nervous system (CNS) and non-CNS tumors where treatment by radiation therapy is appropriate.

Intervention: Stereotactic radiation surgery (SRS) or stereotactic body radiation therapy (SBRT) with devices such as Gamma Knife®, CyberKnife®, TomoTherapy®.

Comparator: Conventional (conformal) external beam therapy (EBRT).

Outcomes: Survival rate, duration of symptom-free remission, quality of life, harms including radiation exposure and complications, cost, cost-effectiveness.

Key Questions

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for the following patients:

a. Patients with central nervous system (CNS) tumors; and
b. Patients with non-central nervous system cancers?

KQ 2: What are the potential harms of SRS and SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations? Including consideration of:

a. Gender;
b. Age;
c. Psychological or psychosocial co-morbidities;
d. Other patient characteristics or evidence-based patient selection criteria, especially comorbidities of diabetes and high BMI;
e. Provider type, experience, or other characteristics and setting (including facility/team experience); and
f. Payer / beneficiary type including worker's compensation, Medicaid, state employees.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Methods

A systematic review using best evidence methodology for each procedure was used to summarize evidence for Key Questions 1 through 3 as outlined below.

- A complete a search of the Medicaid Evidence-based Decisions (MED) Project primary evidence sources was conducted;
- Existing high quality systematic reviews (SRs) and technology assessments (TAs) were summarized by procedure for each Key Question;
- If there were two or more comparable SRs or TAs identified and one was more recent, of better quality, or more comprehensive, the other review(s) were excluded;
- An additional search of the MEDLINE® and Cochrane databases was done to identify studies published after the search dates of the last high quality review(s). Individual studies published after the SR(s) were appraised and synthesized with the results of the high quality SRs (see Appendix A for search strategies and Appendix B for excluded references); and
- If there are no high quality reviews identified for a procedure, a search, appraisal, and summary of primary individual studies was completed for the last 10 years (April 2002 to April 2012).

Evidence

Search strategy

A search was conducted to identify published SRs, meta-analyses (MAs), TAs and individual studies (from April 2002 to April 2012) in the MEDLINE® and Cochrane databases. Tipton (2011b), an AHRQ TA of SBRT, found no comparative studies through their last search date (December 2010). Although Tipton (2011b) did not perform quality ratings of the studies, they did an extensive search of the literature to identify studies of SBRT. The 124 references from the Tipton (2011b) review were reviewed for possible inclusion in this report.

Inclusion criteria – General

- Published, peer reviewed, English-language articles;
- SRs, TAs, RCTs, and observational comparative study designs (prospective, retrospective, and controlled clinical trials);
- Treatments usually delivered in 10 or fewer fractions;
- For KQ 2 (harms), *all* study designs with a minimum sample size of 50 participants; and
    - For pediatric populations and/or reports of serious harms (i.e., surgery, hospitalization, mortality), *all* study designs with a sample size of 20 participants.

Specific inclusion criteria by tumor location and malignancy:

Central Nervous System

- Minimum sample size of 20 participants;

Breast, Colon, Head and Neck, Lung, and Prostate

- Minimum sample size of 50 participants;

Other Malignancies

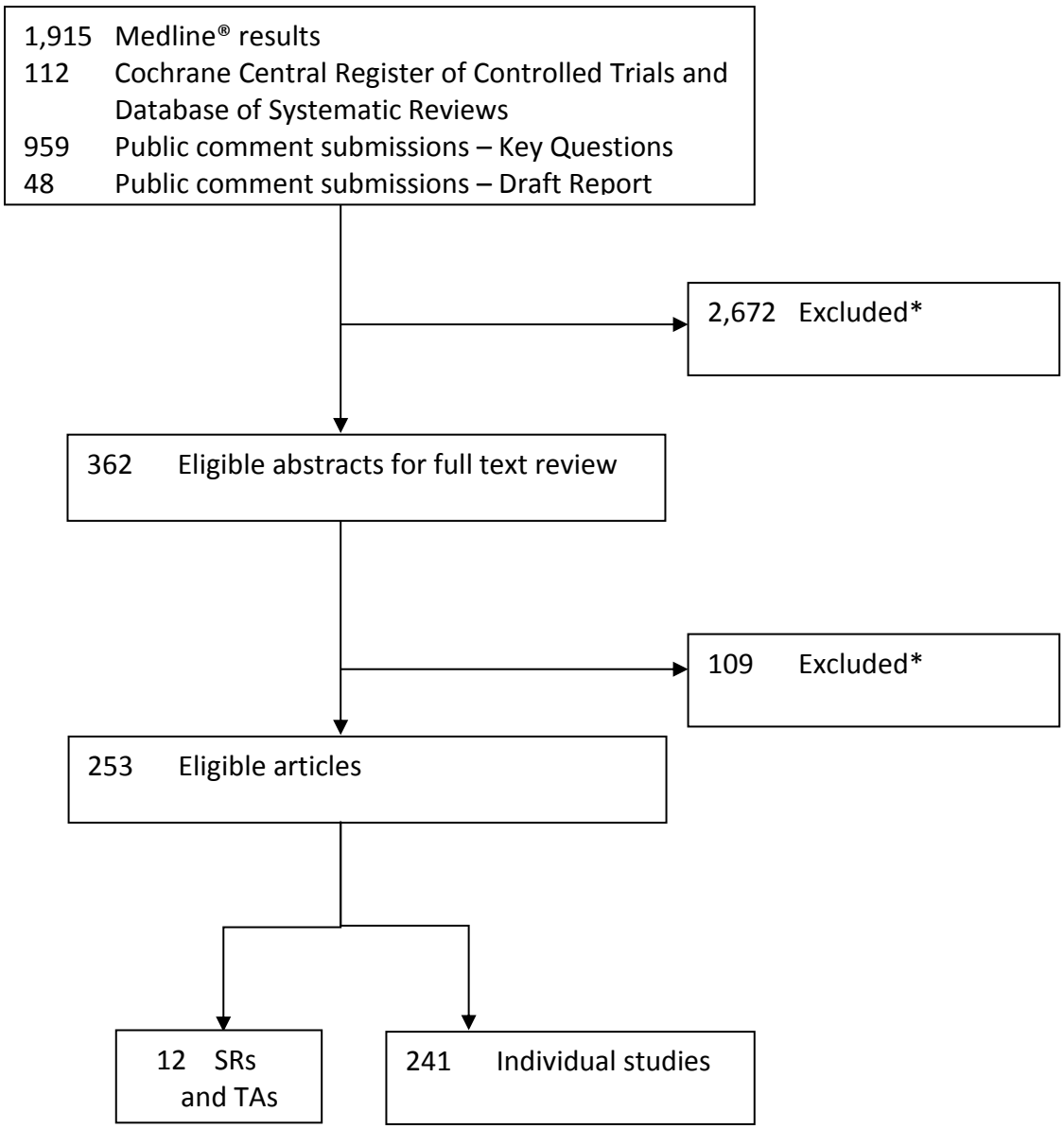
- Case series; and
- Minimum sample size of 20 participants.

Exclusion criteria – all malignancies

- Studies published in non-English language;
- Commentaries, letters, editorials, narrative reviews, and news articles;
- Studies that focused on aspects of treatment planning, including different dosing regimens[6]; and
- Studies that did not stratify results by SRS or SBRT when other treatments were included.

[6] Although dosimetric calculations are used in making treatment plans, the information on Dosimetry does not directly address any of the Key Questions and was excluded from this report.

Figure 6. Search Flow Chart for Inclusion



Quality Assessment – Evidence

The methodological quality of the included studies was assessed using standard instruments developed and adapted by the Center for Evidence-based Policy and the MED Project. These instruments are modifications of systems in use by NICE and SIGN (NICE 2009; SIGN 2009). All studies were assessed by two independent and experienced raters. In cases where there was not agreement about the quality of the study or guideline, the disagreement was resolved by conference or the use of a third rater. The evaluation checklists for individual studies and guidelines are provided in Appendix D.

Each study was assigned a rating of good, fair, or poor based on its adherence to recommended methods and potential for bias. In brief, good quality SRs included a clearly focused question, a literature search that was sufficiently rigorous to identify all relevant studies, criteria used to

select studies for inclusion (e.g., RCTs) and assess study quality, and assessments of heterogeneity to determine if a meta-analysis would be appropriate. Good quality RCTs clearly described the population, setting, intervention and comparison groups; randomly allocated patients to study groups; concealed allocation; had low dropout rates; and reported intention-to-treat analyses. Good quality SRs and RCTs also had low potential for bias from conflicts of interest and funding source. Fair quality SRs and RCTs had incomplete information about methods that might mask important methodological limitations. Poor quality SRs and RCTs had clear flaws that could introduce significant bias.

A summary judgment for the overall quality of evidence was assigned to each Key Question and outcome (Guyatt 2008). The GRADE system defines the quality of a body of evidence for an outcome in the following manner:

High: Further research is *very unlikely* to change the estimate of effect and our confidence in that estimate. Typical sets of studies would be large RCTs without serious limitations.

Moderate: Further research *may* change the estimate of effect and will *likely* have an important impact on our confidence in the estimate of effect. Typical sets of studies would be RCTs with some limitations or well-performed observational studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: Further research is *likely* to change the estimate and *very likely* to have an important impact on our confidence in the estimate. Typical sets of studies would be RCTs with serious limitations or observational studies without special strengths.

Very low: Any estimate of effect is *uncertain.* Typical sets of studies would be observational studies with serious limitations and outcomes for which there is very little evidence.

Evidence was not identified for every Key Question. In instances when no evidence was identified, it is clearly stated.

Quality Assessment – Economic studies

The methodological quality of the studies was assessed using a standard instrument developed and adapted by the Center for Evidence-based Policy and the MED Project. This instrument is a modification of checklists in the British Medical Journal (Drummond 1996), the Consensus on Health Economic Criteria (Evers 2005), and NICE economic evaluation checklist (NICE 2009). In brief, good quality economic evaluations include a well described research question with economic importance and detailed methods to estimate the effectiveness and costs of the intervention. A sensitivity analysis is provided for all important variables and the choice and values of variables are justified. Good quality economic evaluations also have low potential for bias from conflicts of interest and funding sources. Fair quality economic evaluations have incomplete information about methods to estimate the effectiveness and costs of the intervention. The sensitivity analysis may not consider one or more important variables, and

the choice and values of variables are not completely justified. All of these factors might mask important study limitations. Poor quality economic evaluations have clear flaws that could introduce significant bias. These could include significant conflict of interest, lack of sensitivity analysis, or lack of justification for choice of values and variables. All studies were assessed by two independent and experienced raters. In cases where there was not agreement about the quality of the study, the disagreement was resolved by conference or the use of a third rater. The economic evaluation checklist is provided in Appendix D.

Guidelines

Search Strategy

A search for relevant clinical practice guidelines was conducted, using the following sources: the National Guidelines Clearinghouse database, the Institute for Clinical Systems Improvement (ICSI), the Veterans Administration/Department of Defense (VA/DOD) guidelines, US Preventive Services Task Force (USPSTF), the National Comprehensive Cancer Network (NCCN) and the Center for Disease Control and Prevention (CDC). Guidelines from specialty organizations were also searched including the following: the American College of Radiology, the American Society of Clinical Oncology, and American Society for Radiation Oncology. Included guidelines were limited to those published after 2006.

Quality Assessment

The methodological quality of the guidelines was assessed using an instrument (Appendix D) adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration (AGREE Next Steps Consortium 2009). The guidelines were rated by two individuals. A third rater was used to obtain consensus if there were disagreements. Each guideline was assigned a rating of good, fair, poor, based on its adherence to recommended methods and potential for biases. A guideline rated as good quality fulfilled all or most of the criteria. A fair quality guideline fulfilled some of the criteria and those criteria not fulfilled were thought unlikely to alter the recommendations. If no or few of the criteria were met, the guideline was rated as poor quality.

Policies

At the direction of the WA HTA program, select payer policies were searched and summarized. Aetna, Regence Blue Cross Blue Shield, GroupHealth, and Medicare National and Local Coverage Determinations were searched using the payers' websites.

MAUDE Database

The Manufacturer and User Facility Device Experience Database, hosted by the US Food and Drug Administration (FDA), was searched using the terms "stereotactic radiation therapy", "stereotactic radiosurgery", "sbrt", "srs", "cyberknife", "cyber knife", "gamma knife", and "gammaknife." The search was limited to adverse events reports submitted between 2002 and 2012. Three reports of serious adverse events were identified and are summarized in Appendix M.

Public Comment and Peer Review

The topic nomination, draft key questions, and draft version of this report were open to public comment. All comments received from the public were reviewed and taken into account in the drafting of the final report. Submitted references that met inclusion criteria (as outlined in the methods section) were incorporated into the report. Studies were not reviewed for inclusion if there was not a request by the commenter to include them. In addition, the draft report was reviewed by two peer reviewers and their comments were also taken into account in drafting the final report. The full disposition to peer review comments is available in Appendix J. The full disposition to public comments on the key questions is available in Appendix K. Full disposition to public comments on the draft report is available in Appendix L.

Study Results

The MEDLINE search retrieved 1,915 citations, the Cochrane search retrieved 112 citations, and 1007 citations were submitted through public comment on the draft key questions and report. A total of 3,034 citations were reviewed and 253 articles met inclusion criteria. Appendix E contains detailed information for all studies cited in the Findings section. The data are presented by tumor location and type.

All relevant SR findings were integrated into this WA HTA report, regardless of the study inclusion criteria used by the SR authors. As a result, the inclusion criteria for subsequently published studies may differ from the inclusion criteria used in the SRs. Individual studies that were identified by the MEDLINE® and Cochrane database searches that are included in the included SRs that met inclusion criteria will not be summarized separately.

Study samples were generally heterogeneous and varied by tumor type and location and within malignancies. Therefore, it was not possible to generalize population information for every malignancy. For several cancers, other treatments (e.g., chemotherapy, surgery) combined with SRS and/or conventional EBRT were included because these treatments in combination with radiation treatment were the standard of care (e.g., glioblastoma). The findings from all included studies are reported in Appendix E.

Except for six RCTs of SRS for brain metastases (Andrews 2004; Aoyama 2006; Chang 2009; Chougle 2000; Kocher 2011; Kondziolka 1999) and once RCT for glioblastoma (Souhami 2004), the evidence for SRS and SBRT is largely based on cohort and case series studies. These studies had substantial methodological limitations. Many of the studies lacked a comparison group, and/or did not adjust for confounding variables in analyses. Variables that may have had a significant impact on outcomes include age, tumor stage prior to treatment, smoking status, and medical comorbidities. Many of the included studies have relatively small sample sizes making it difficult to infer findings to the broader population. Based on the general study designs included in this report, selection bias could be an issue. In addition, many of the studies combined different tumor stages and age groups in their analyses. Finally, several studies included patients receiving chemotherapy concurrent with SRS/SBRT.

For the pediatric population, only two studies were identified that focused on children (Kano 2010; Marcus 2005); Kano (2010) addressed pediatric ependymomas and Marcus (2005)

addressed gliomas. There are 51 additional studies that include children within the patient population. However, none of the studies report findings stratified by age (Astrocytoma – Hadjipanayis 2003, Szeifert 2007; Brain metastases – Liew 2011, Williams 2009; Ependymoma – Kano 2009b; Glioblastoma – Hsieh 2005, Nwokedi 2002; Glioma – Combs 2005, Fuchs 2002, Heppner 2005, Kano 2008a, Kong 2008, Roberge 2006; Meningioma – Bechker 2002, Chang 2003, DiBiase 2004, Han 2008, Kreil 2005, Lee 2002; Multiple CNS tumors – Adler 2006, Coppa 2009, Davidson 2009, Krishan 2005, Rowe 2007a, Rowe 2007b, Stafford 2003, Xu 2010; Neurocytoma – Rades 2006; Pituitary Adenoma – Colin 2005, Hayashi 2010, Iwata 2011, Kajiwara 2005, Kong 2007, Petrovich 2003, Puataweepong 2009, Pouratian 2006, Sheehan 2011, Vladyka 2003, Voges 2006; Schwannoma – Chung 2005, Lobata-Polo 2009, Mathieiu 2007, Sawamura 2003, Showalter 2008; Head and neck cancer – Ozyigit 2011, Hara 2008, Wu 2007; Lung – Hiraoka 2007; and Spine – Gagnon 2009, Nikolajek 2011, Sachdev 2011.

This report provides the best available evidence for multiple cancer types. The most completely evaluated cancers are those of the **central nervous system, liver, lung and spine**. For these cancers there are large TAs and several SRs. For many of the other cancers, there are as few as one case series. The evidence consists mostly of case series of which are non-comparative studies that may give estimates of outcomes or harms for SRS and SBRT without comparison with EBRT. Because of the absence of randomized trials and comparative studies, the strength of the evidence is low or very low for most of the findings.

Findings – Comparative Data

This section includes tumor types and locations where comparative data was available for SRS and SBRT compared with EBRT. This section includes a summary of the evidence on brain metastases, glioblastoma multiforme, gliomas, pituitary adenomas, head and neck cancer, and lung cancer.

Table 4 provides a detailed summary of the strength and direction of evidence per tumor type and location, comparator, and outcomes. Strength and direction of evidence is only provided for tumor types and locations where there is comparative data. For tumor types and locations where there is not comparative data, summary information can be found in the full summary table (Appendix E).

Figure 7. Symbol Key

Strength of Evidence

⊕⊕⊕⊕	**High**: Further research is *very unlikely* to change the estimate of effect and our confidence in that estimate. Typical sets of studies would be large RCTs without serious limitations.
⊕⊕⊕◯	**Moderate**: Further research *may* change the estimate of effect and will *likely* have an important impact on our confidence in the estimate of effect.
⊕⊕◯◯	**Low**: Further research is *likely* to change the estimate and *very likely* to have an important impact on our confidence in the estimate.
⊕◯◯◯	**Very Low**: Any estimate of effect is *very uncertain.*

Outcomes

↔	No Difference
↕	Inconsistent Evidence
↑	Increased
↓	Decreased

Table 4. Tumor Types and Locations with Comparative Evidence

Procedure		Strength of Evidence[7]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
CNS – Brain Metastases	7 SRs[8], 12 cohorts, 25 case series			
KQ # 1 Efficacy	6 SRs, 12 cohorts			
SRS+WBRT compared to WBRT		↔ OS ↑ Local tumor control		
SRS+WBRT compared to SRS		↔ OS ↑ Local tumor control ↑ Distant tumor control	↔ QoL ↔ Functional independence ↔ Time to worsened performance status	
SRS alone compared to WBRT alone				↑ OS
SRS for recurrent or progressive brain metastases				↕ OS ↕ Local tumor control
KQ # 2 Harms	6 SRs, 12 cohorts, 25 case series			
SRS+WBRT compared to WBRT		↔ Acute and late toxicities		
SRS+WBRT compared to SRS			↔ Acute and late toxicities	
SRS alone compared to WBRT alone			↔ Toxicities	
SRS for recurrent or progressive brain metastases				↕ Harms
KQ # 3 Subpopulations: *Single brain metastases and RPA Class 1*	3 SRs (1 RCT)			

[7] No procedure had a high strength of evidence, thus this column is not displayed in this table.
[8] Many overlapping individual between SRs, thus total number of individual studies across all SRs is not provided

Procedure		Strength of Evidence[7]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
SRS+WBRT compared to WBRT			↑ Median survival ↑ Local tumor control ↓Worsened performance status(at 6 months)	
KQ # 4 Cost and Cost-Effectiveness	1 SR (7 economic evaluations)			
WBRT alone				SRS is more cost-effective than WBRT alone or combined with SRS
CNS – Glioblastoma multiforme	1 RCT, 2 cohorts, 3 case series			
KQ # 1 Efficacy	1 RCT, 2 cohorts, 1 case series			
EBRT			↔ Survival	
KQ #2 Harms	1 RCT, 1 cohort, 3 case series			
EBRT			↑ Symptomatic radionecrosis	
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
CNS – Glioma	1 cohort, 8 case series			
KQ # 1 Efficacy	1 cohort			
EBRT				↕ Median survival
KQ #2 Harms	1 cohort, 8 case series			

Procedure		Strength of Evidence[7]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
No comparator				Radiation necrosis
KQ #3 Subgroups: *Pediatric patients*				
No comparator				OS, PFS, Moya Moya syndrome
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
CNS – Pituitary Adenoma	2 cohort studies, 13 case series			
KQ # 1 Efficacy	2 cohort studies			
EBRT			↔ OS ↔ Local tumor control	
KQ #2 Harms	2 cohort studies, 13 case series			
EBRT				↓ New hypopituitarism
No comparator				Headache, nausea, fatigue, edema, visual deficits, cranial nerve palsies
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
Head and Neck Cancers	1 cohort, 6 case series			
KQ # 1 Efficacy	1 cohort			
EBRT				↔ Patient survival ↔ Local tumor control
KQ #2 Harms	1 cohort, 6 case series			

Procedure		Strength of Evidence[7]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
EBRT				↓ Harms (nasopharyngeal carcinoma, head and neck squamous cell carcinoma) cranial neuropathy, carotid blow-out, brain necrosis, mortality, leucopenia, anemia, thrombocytopenia, mucositis, nausea, vomiting, weight loss, skin reactions, massive nasal bleeding, transient facial numbness, retinopathy, carotid aneurysm, xerostomia, pain, dysgeusia, dysphagia, fibrosis, trimus
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on cost or cost-effectiveness identified.				
Lung Cancer	1 SR (35 case series), 33 case series, 3 economic analyses			
KQ # 1 Efficacy	1 SR (35 case series), 33 case series			
No comparator				3-yr OS, local control
KQ #2 Harms	1 SR (35 case series), 33 case series			
No comparator				Fatigue, general malaise,

Procedure		Strength of Evidence[7]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
				pneumonitis, esophagitis, dermatitis, chest wall pain
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness	3 economic analyses			
EBRT				↕ cost, cost-effectiveness

Central Nervous System – Brain Metastases

In this section, the evidence on brain metastases is summarized. For many primary and metastatic brain and spine tumors, the treatment of choice may be surgical removal not radiation therapy. However, the objective of the report is to evaluate the evidence base for conventional EBRT, referred to as whole brain radiation therapy (WBRT) when used for brain metastases, compared to the newer radiation techniques, SRS and SRT. The report objective is not intended to evaluate all treatments for a particular tumor. There are few comparative studies for many of the CNS tumors with the exceptions of brain metastases.

Brain metastases are the most common intracranial tumor in adults. They occur in up to 40% of patients with cancer and are associated with poor prognosis (Bradley 2004) with an overall median survival estimated to be six months or less (Li 2000). The most likely cancers to have brain metastases include non-small cell lung cancer (NSCLC), breast cancer, melanoma, and less commonly, colon and renal cell cancers (Patil 2008). Treatment options include whole brain radiation therapy (WBRT), surgery, SRS, chemotherapy and supportive care including corticosteroids. Treatment decisions are based on prognostic factors including performance status, type of cancer, and number and size of the metastases (Eichler 2007). The Radiation Therapy Oncology Group developed a three-tiered prognostic measure using recursive partitioning analysis (RPA) to assist with the assessment of prognosis (Gaspar 2000).

Table 4. RTOG Assessment of Prognosis (Adapted from Gaspar 2000)

RPA class	Criteria	Median survival (months)
Class 1	KPS* score $\geq$ 70; and Age < 65 years; and Controlled primary tumor; and No extracranial metastases	7.1
Class 2	KPS score $\geq$ 70 and age $\geq$ 65 years; or Controlled primary tumor; or Extracranial metastases	4.2
Class 3	KPS score < 70	2.3

* Karnofsky Performance Status: KPS = 70 indicates that patients can take care of themselves, are out of bed more than 50% of the time, but are unable to do normal work and activities.

Over the past 50 years, corticosteroids and WBRT were the mainstays of palliative treatment for patients with brain metastases and is still the most common treatment option for patients with poor prognosis or multiple metastases (Eickler 2007). In selected patients with a single brain metastasis, good performance status (KPS greater than or equal to 70), and stable systemic disease; microsurgery was added to whole brain radiation therapy (WBRT) to improve survival as well as palliate neurologic symptoms (Muacevic 2008). Stereotactic radiosurgery as an alternative to surgery and WBRT was evaluated in a RCT involving 64 patients. Outcomes did not differ between patients receiving SRS compared to surgery and WBRT; however, patients

who had SRS had much shorter (if any) hospital stays and lower frequencies of Grades 1 and 2 toxicities (Muacevic 2008). Questions are now focused on the outcomes and harms of SRS compared to WBRT in various combinations for patients with single or oligometastases (fewer than 3 or 4 metastases): SRS+WBRT versus WBRT alone, SRS+WBRT versus SRS alone; and SRS alone compared to WBRT alone. The studies reviewed included all cancer types and did not do subgroup analyses by type of cancer.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

Six recent SRs compared various combinations of SRS and WBRT (Ammirati 2010; Elaimy 2011a; Linskey 2010; Muller-Rienmenschneider 2009; Patil 2010; Tsao 2011; Tsao 2012), with two publications of the SR by Tsao (2011, 2012). We excluded Müller-Rienmenschneider (2009) because it was poor quality and the last search date (August 2007) was prior to those in the other SRs. The RCTs included in Müller-Rienmenschneider (2009) were also included in the later SRs in this report. Elaimy (2011a), a poor quality SR, included two RCTs and 11 cohort studies. The RCTs were included in the better quality SRs in this review, so Elaimy (2011a) will not be described here but is listed in Appendix E. We reviewed the 11 cohort studies included in Elaimy (2011a) to determine if they met our inclusion criteria. All studies, except for one study by Rades (2008b), were included in the other SRs. The study not included in the other SRs (Rades 2008b) did not meet our inclusion criteria. The other 10 cohort studies are included in Appendix E or included the SRs by Patil (2010) and Linskey (2010).

Three SRs compare SRS and WBRT (SRS+WBRT) to WBRT alone (Patil 2010; Linskey 2010; Tsao 2012). *Two SRs compared SRS+WBRT to SRS alone* (Linskey 2010; Tsao 2012). *One SR compared SRS alone to WBRT alone* (Linskey 2010). One SR included only studies of patients with *recurrent or progressive brain metastas*es (Ammirati 2010). Although there was some variation in radiation doses used in the included studies, most used 15 to 24 Gy over one or two fractions for SRS (depending on tumor size and use of WBRT+SRS) and 30 to 37.5 Gy over 10 to 12 fractions for WBRT.

SRS+WBRT vs. WBRT alone. Linskey (2010), Patil (2010), and Tsao (2012), three good quality SRs, searched for RCTs that compared SRS+WBRT to WBRT alone through 2008, 2009 and 2010, respectively. These reviews identified three RCTs (Andrews 2004; Chougle 2000; Kondziolka 1999) that were all assessed to be low quality (high risk of bias) by Patil (2010). One of these RCTs (Andrews 2004), which included 333 patients, was assessed to be fair quality (moderate risk of bias) by Tsao (2012). We confirmed the fair quality rating for Andrews (2004), using the MED quality checklist, and the poor quality ratings of the other two RCTs (Chougle 2000; Kondziolka 1999). Chougle (2000) was excluded from the reviews because data were only reported in abstract form and did not include statistical tests. Patients entered into the RCTs were adults (greater than or equal to 18 years old) and generally had one to four metastases that were less than 4 cm and a good performance status (KPS greater than or equal to 70, WHO

performance status 0 to 2, or RTOG RPA class I or II). Included patients had to spend more than 50% of their time out of bed during the day and be able to care for themselves.

Patil (2010) and Tsao (2012) conducted meta-analyses of data from Andrews (2004) and Kondziolka (1999) involving 358 patients. Because Tsao (2012) set up the hazard ratios (HR) in the opposite direction from Patil (2010), we will report only the HRs from Patil (2010). Both SRs found *no statistically significant difference in overall survival* between patients receiving SRS+WBRT compared to WBRT alone (HR 0.82, 95% CI 0.65 to 1.01, I^2 = 0%) with differences in median survival of approximately 1 to 3 months. *Local tumor control was better* (less chance of local failure) with SRS+WBRT compared to WBRT alone (HR 0.27, 95% CI 0.14 to 0.52, I^2 = 0%). Andrews (2004) also reported that among the 154 patients still alive at 6 months, *fewer patients receiving SRS+WBRT compared to WBRT alone had a worsened KPS score* (RR 0.78, 95% CI 0.61 to 1.00). The SR by Linskey (2010) reported individual study results for the included RCTs above and came to similar conclusions.

SRS+WBRT vs. SRS alone. Two good quality SRs, (Linskey 2010; Tsao 2012) searched for studies through 2008 (Linskey 2010) and 2010 (Tsao 2012) and identified one good quality (Aoyama 2006) and two fair quality (Chang 2009b; Kocher 2011) RCTs that compared SRS+WBRT to SRS alone. The RCTs had similar entry criteria as those described for SRS+WBRT versus WBRT alone. The pooled analysis of 190 patients from Aoyama (2006) and Chang (2009b) *did not find a significant difference in overall survival* for patients receiving SRS+WBRT compared to SRS alone (HR 0.98, 95% CI 0.71 to 1.35). There was substantial heterogeneity across these studies (I^2 = 91%). *Local tumor control was better for patients receiving SRS+WBRT* compared to SRS alone, based on a pooled analysis of all three RCTs, (HR 2.61, 95% CI 1.68 to 4.06, I^2 = 60%). *Distant tumor control was also significantly better with SRS+WBR*T compared to SRS alone (HR 2.15, 95% CI 1.55 to 2.99, I^2 = 54%). The results from Kocher (2011) were not included in the pooled analysis by Tsao (2012) because Kocher (2011) combined patients who had surgery (160 patients) and SRS (199 patients) prior to randomization to WBRT or observation and did not provide stratified analyses of survival for the SRS subgroup. Kocher (2011) reported there was no significant difference in overall (HR 0.98, 95% CI 0.78 to 1.24) or median survival between patients who were randomized to WBRT, in addition to SRS or surgery, compared to those who were randomized to observation, in addition to SRS or surgery, (median survival 10.7 months vs. 10.9 months, respectively).

The primary outcome in the Kocher (2011) RCT was *duration of functional independence* (time to decline to a WHO performance status (PS) of 2 (symptomatic but spends less than 50% of the day in bed and is capable of all self care but not work activities) or worse. The *median time to a decline in functional status (WHO PS greater than or equal to 2) was similar in both groups* (HR 0.96, 95% CI 0.76 to 1.20) and approximately 10 months. Aoyama (2006) found that preservation of functional status (KPS greater than or equal to 70) at 12 months was 33.9% versus 26.9% (p = 0.53) for patients receiving SRS+WBRT compared to SRS alone. *Quality of life* outcomes were not reported in two RCTs (Aoyama 2006; Kocher 2011), and found to be similar between patients receiving SRS+WBRT compared to SRS alone (FACT-BR mean difference at 4 months = 2.8; 95% CI, -26 to 21, p=0.76) in Chang (2009b).

SRS alone vs. WBRT alone. One good quality SR (Linskey 2010) compared SRS alone with WBRT alone for patients with newly diagnosed single and multiple brain metastases. Linskey (2010) did not identify any RCTs, but found six observational studies: one prospective cohort (Li 2000); three retrospective cohort studies with concurrent control groups (Lee 2008; Rades 2007; Wang 2002); and two retrospective cohort studies with historical controls that included 251 (Kocher 2004) and 108 patients (Datta 2004) with various cancers. Linskey (2010) reported that the four better quality studies (Lee 2008; Li 2000; Rades 2007; Wang 2002) found a "statistically significant survival advantage for single-dose SRS alone compared to WBRT alone for patients with single or multiple brain tumors" (p. 64). Li (2000) reported the median survival of 10.6 versus 5.7 months ($p = 0.0001$) for SRS compared to WBRT for 42 patients with lung cancer. Lee (2008) studied 15 patients with ovarian cancer and found median survivals of 29 versus 6 months ($p = 0.006$) for patients receiving SRS compared to WBRT, respectively. Rades (2007) reported median survivals of 13 versus 7 months ($p = 0.045$) for SRS compared to WBRT for 186 patients with various metastatic cancers. Finally, Wang (2002) found median survivals of 67 weeks (approximately 16 months) versus 37 weeks (approximately 9 months) ($p < 0.00001$) for SRS compared to WBRT for 203 patients with various metastatic cancers.

SRS for recurrent or progressive metastases. One good quality SR (Ammirati 2009) searched for studies through 2008 that examined the use of SRS for treatment of patients with recurrent or progressive brain metastases who were previously treated with surgery, WBRT or SRS. They identified 12 small (sample size ranged 12 to 54) non-comparative studies that examined SRS as the intervention. Of the 12 studies, eight used SRS for tumor recurrence following WBRT and four used SRS for tumor recurrence following SRS. The studies included patients with NSCLC, small cell lung cancer, and breast cancer. Not all studies provided survival data. Of those that did, *median survival* ranged from four to 19 months after SRS. Local control rates were provided in four studies and were approximately 80% to 93% at six months to a year.

Subsequently Published Studies

No additional RCTs were published after the last search dates for the SRs (2008 to 2010) although two RCTs were noted to be ongoing during this period (Linskey 2010).

Twelve cohort studies met the inclusion and exclusion criteria (Basina 2010; Bernad 2010; Elaimy 2011b; Fokas 2010; Fokas 2011; Frazier 2010; Kased 2009; Kong 2010; Marko 2011; Park 2009; Park 2011; Rades 2008a). One study compared SRS+WBRT to WBRT alone, four compared SRS+WBRT to SRS alone, one compared SRS alone to WBRT alone, and six studies made multiple comparisons of which four studies included surgery in the comparisons. Samples varied in size from 23 to 275 patients and included patients with a variety of cancers. eight studies were rated poor quality (Bernad 2010; Elaimy 2011b; Fokas 2010; Fokas 2011; Marko 2011; Park 2009; Park 2011; Rades 2008a), three were rated fair (Basina 2010; Frazier 2010; Kong 2010) and one rated good quality (Kased 2009). Most of studies found no statistically significant differences in *overall survival* among any of the comparison groups while a few studies found some improvement in *local control of the tumor*.

The good quality study by Kased (2009) compared SRS+WBRT to SRS alone for a subgroup of 81 patients with metastatic breast cancer and recurrent brain metastases and found no

statistically significant difference in OS, progression free survival (PFS), local or distant control of metastases. The detailed results from the other cohort studies are outlined in Appendix E.

Overall Summary

For *SRS+WBRT compared to WBRT* alone, the overall strength of evidence is moderate for survival and tumor control. There is no statistically significant difference in OS for SRS+WBRT compared to WBRT alone (hazard ratio (HR) 0.82, 95% CI 0.65 to 1.01, I^2 = 0%) with differences in median survival of approximately 1 to 3 months. (See subgroup analyses in KQ3). Local tumor control was better with SRS+WBRT compared to WBRT alone (HR 0.27, 95% CI 0.14 to 0.52, I^2 = 0%).

For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is moderate for the outcome of OS and tumor control. There was no statistically significant difference in overall survival (OS) (HR 0.98, 95% CI 0.71 to 1.35). Local and distant tumor control was significantly better for patients receiving SRS+WBRT compared to SRS alone (HR 2.61, 95% CI 1.68 to 4.06, I^2 = 60% and HR 2.15, 95% CI 1.55 to 2.99, I^2 = 54%, respectively). Low quality evidence suggests there is no difference in functional independence, time to worsened performance status or quality of life (QoL) for SRS+WBRT compared to SRS alone.

For *SRS alone compared to WBRT alone*, the overall strength of evidence is very low based on six cohort studies, two with historical controls, and two additional small poor quality cohort studies. These studies suggest that OS may be better for patients receiving SRS alone compared to WBRT alone, but the poor quality of the studies and the heterogeneity across studies limit any conclusions.

For *SRS for recurrent or progressive brain metastases*, the overall strength of evidence is very low for overall survival and local tumor control. It is uncertain if SRS+WBRT compared to WBRT alone or SRS alone, or SRS alone compared to WBRT alone improves overall survival or local tumor control.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

SRS+WBRT vs. WBRT alone. Two good quality SRs addressed harms (Patil 2010; Tsao 2012), but based their results on a single RCT involving 333 patients (Andrews 2004). The other two RCTs (Chougule 2000; Kondziolka 1999) did not report harms. Acute toxicities (occurring within 90 days) did not differ significantly for SRS+WBRT compared to WBRT alone. Nausea or vomiting, skin changes, and CNS toxicities were the most common toxicities. The percentage of patients having *acute toxicities* with SRS+WBRT compared to WBRT were 43% vs. 36%, respectively, for Grade 1; 18% vs. 26% for Grade 2; 2% vs. 0% for Grade 3; and 1% vs. 0% for Grade 4, with higher Grades indicating worse toxicity. The percent of patients having *late toxicities* were not significantly different: 14% vs. 14% for Grade 1; 6% vs. 7% Grade 2; 3% vs. 2% Grade 3; and 3% vs. 1% Grade 4 for SRS+WBRT compared to WBRT.

SRS+WBRT vs. SRS alone. Two good quality SRs (Linskey 2010; Tsao 2012) addressed harms and reported results separately for the three included RCTs (Aoyama 2006; Chang 2009b; Kocher 2011). Chang (2009b) stopped their RCT involving 58 patients early based on results from the Revised Hopkins Verbal Learning Test. Using Bayesian probability, they estimated, based on a subgroup of 11 patients receiving SRS+WBRT and 20 patients receiving SRS alone, that there was a 96% probability of patients receiving SRS+SBRT being significantly more likely to have decline in total recall at four months than patients receiving SRS alone (52% of SRS+WBRT patients vs. 24% of SRS alone patients). Similar differences were noted for delayed recall and delayed recognition. Acute and late toxicities did not differ significantly for SRS+WBRT compared to SRS alone. Of note, Kocher (2011) reported that 13% of patients receiving SRS+WBRT and 8% of patients receiving SRS alone had symptomatic radionecrosis.

SRS alone vs. WBRT alone. One good quality SR (Linskey 2010) did not identify any RCTs, but found six observational studies (see KQ 1 for details). Linskey (2010) reported on harms from only one cohort study. Rades (2007) is a retrospective cohort study that included 186 patients and found that toxicity rates were similar for SRS alone compared to WBRT alone.

SRS for recurrent or progressive metastases. Because the cohort studies and case series included patients with a wide variety of initial treatments for their brain metastases and had overall poor prognosis, it was not possible to determine the extent that SRS with or without WBRT was responsible for harms when they were reported.

Subsequently Published Studies

We found no RCT subsequent to the last search dates of the SRs. Because many of the cohort and case series studies included multiple radiation treatment comparisons (e.g., SRS alone, WBRT alone, SRS+WBRT) and occasionally included patients who had surgery as part of their treatment, we will describe their general characteristics and findings across these treatment groups unless specific treatment results from good and fair quality studies have been reported specifically by treatment group.

Only 5 of the 12 cohort studies, published since the last search dates in the SRs, reported data on harms. Four were poor quality (Fokas 2010 [n = 88], Fokas 2011 [n = 78], Park 2011 [n = 56], Rades 2008a [n = 144]) and one was good quality (Kased 2009 [n = 176]). The patients in these studies were adults (mean and median ages between 50 and 60 years old) with characteristics and cancers that varied across studies. The mean and median doses of SRS were mostly 18 to 22 Gy (range, 18 to 27) and for WBRT were 30 Gy. In general, acute Grade 3 or 4 toxicities occurred in 2% to 5% of patients and did not differ substantially across any of the treatment groups (SRS alone, WBRT alone, SRS+WBRT) and late toxicities occurred in approximately 4% to 5%, though all of these analyses are limited by small subgroup sizes. Among the 95 newly treated patients with brain metastases from breast cancer, in the good quality cohort study by Kased (2009), symptomatic radionecrosis occurred in 10.5% of patients overall (9% of patients receiving SRS alone and 3% of those receiving SRS+WBRT). Among the 144 newly treated patients in the poor quality cohort study by Rades (2008), Grade 3 or 4 acute toxicities occurred in 2% of patients and were similar for those receiving SRS+WBRT compared to SRS alone. Grade

3 or 4 late toxicities occurred in 4% of patients and were similar for SRS+WBRT compared to SRS alone.

All of the *25 case series* identified since the last search dates of the SRs reported information on harms (Appendix E). These types of studies provide very low quality evidence; and within this study type, two were rated as good (Dea 2010; Rush 2011), 12 rated as fair (Blonigen 2010; Choi 2009; Elliott 2011b; Franzin 2009; Giubilei 2009; Ishikawa 2009; Kano 2011; Liew 2011; Molenaar 2009; Motta 2011; Nath 2010a; Williams 2009), and eleven rated as poor quality (Breneman 2009; Clarke 2010; Gu 2009; Kelly 2011; Kondziolka 2011; Koyfman 2010; Meisner 2010; Nath 2010b; Skeie 2011; Wegner 2011; Wei 2010). Patients included in these studies were adults (median ages ranged 50 to 63 years old) who had a wide variety of cancers (mostly NSCLC, breast, colorectal, renal cell, and melanoma) with some patients having failed prior treatments or received concurrent WBRT (Blonigen 2010; Breneman 2009; Dea 2010; Kano 2011; Koyfman 2010; Liew 2011; Meisner 2010). Median SRS doses ranged from 15 to 24 Gy. Across these studies, acute neurologic toxicities (Grade 3 or 4) occurred in 2% to 14% of patients. The two good quality case series (Dea 2010; Rush 2011) involving approximately 404 patients reported 5% to 6% of patients had symptomatic adverse neurologic effects, 1% had radiation necrosis, and 3% had permanent worsening in their neurologic status. The heterogeneity across studies, particularly related to prior and concurrent treatments, make it difficult to interpret results from these 25 case series.

Overall Summary

For *SRS+WBRT compared to WBRT* alone, the overall strength of evidence is moderate for harms based on one fair quality RCT. Acute and late toxicities were not significantly different for SRS+WBRT compared to WBRT alone. Information from cohort and case series generally corroborated the findings from the single RCT and indicated that approximately 2% to 5% of patients may experience severe (Grade 3 or 4) acute and late toxicities including symptomatic radionecrosis.

For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is low for harms based on cohort studies and case series. These studies may indicate that severe (Grade 3 or 4) acute and late toxicities are similar for SRS+WBRT compared to SRS alone and occur in approximately 2% to 5% of patients. Of note, some studies described a reduction in the SRS dose based on whether or not the patient would receive WBRT.

SRS alone compared to WBRT alone, the overall strength of evidence is low for harms based on cohort studies and case series. Toxicity rates appear to be similar for SRS alone compared to WBRT alone.

For SRS for recurrent or progressive brain metastases, the overall strength of evidence is very low. It was not possible to determine whether the harms, when reported, were due to SRS with and without WBRT or to the initial treatment for brain metastases or the patients overall poor prognosis.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

Systematic Reviews

No SRs reported subgroup analyses, but three (Linskey 2010; Patil 2010; Tsao 2012) described the subgroup analyses reported in one RCT (Andrews 2004). Andrews (2004) reported longer survival with SRS+WBRT compared to WBRT alone for the subgroup of 186 patients with a single brain metastasis (median survival 6.5 months vs. 4.9 months, respectively, p = 0.039) and the subgroup of 90 patients in the best prognostic group, Recursive Partitioning Analysis (RPA) Class 1 (median survival 11.6 months vs. 9.6 months, respectively, p = 0.045).

Subsequently Published Studies

None of the subsequently published cohort or case series reported subgroup information.

Overall Summary

The overall strength of evidence is low because it is based solely on subgroup analyses from a single fair quality RCT. Even though the authors stratified by subgroups and had a priori hypotheses, the number of patients in these subgroups was small, and there were multiple comparisons. Subgroup analyses suggested that median survival in patients with single metastases (6.5 vs. 4.9 months, SRS+WBRT vs. WBRT, respectively) and patients in recursive partitioning analysis (RPA) Class 1 (11.6 vs. 9.6 months) may be better with SRS+WBRT compared to WBRT alone. Local tumor control was better with SRS+WBRT compared to WBRT alone. Fewer patients receiving SRS+WBRT compared to WBRT alone may have worsened performance status at six months.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Systematic Reviews

One fair quality SR of seven economic evaluations (Chang 2011b) identified two poor and one fair quality economic evaluations pertinent to this review. For *SRS+WBRT vs. WBRT alone*, the overall strength of evidence is very low that SRS+WBRT is more cost-effective than WBRT alone. Compared to WBRT, SRS+WBRT had an incremental cost-effectiveness ratio (ICER) of $12,289 per extra year of life gained and an incremental quality-adjusted life year (QALY) ratio of $10,753 per QALY. However, there is great uncertainty in these estimates. For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is low that SRS alone is more cost-effective than SRS+WBRT. The ICER for SRS alone (vs. SRS+WBRT) was $44,231 per year of life saved and $41,783 per QALY. For *SRS alone vs. WBRT alone*, one poor quality study, yielding very low strength of evidence, found the cost per QALY was significantly less for SRS alone than for WBRT alone ($10,381/QALY vs. $17,622/QALY, respectively, p < 0.05).

Subsequently Published Studies

No studies were identified.

Overall Summary

Based on one fair quality SR qualitatively summarizing seven economic evaluations of which only three were pertinent to this report, the overall strength of evidence is very low that SRS

alone is more cost-effective than WBRT alone or SRS+WBRT. Overall, the included studies, which based model assumptions on very poor quality evidence of effectiveness and varying estimates of costs, were of poor methodological quality and any conclusions about cost-effectiveness are uncertain.

Central Nervous System – Primary Tumors

In this section, the evidence on intracranial or central nervous system (CNS) tumors is summarized by each type of tumor. These are presented in alphabetical order: glioblastoma, high-grade (malignant) glioma, and pituitary adenoma. *Malignancies are discussed as they were reported in literature. For instance, although astrocytomas and glioblastoma multiforme are types of gliomas, they are discussed in separate sections as reported by individual studies.* For many primary and metastatic brain and spine tumors, the treatment of choice may be surgical removal not radiation therapy. However, the objective of the report is to evaluate the evidence base for conventional EBRT, referred to as whole brain radiation therapy (WBRT) when used for brain metastases, compared to the newer radiation techniques, SRS and SRT. The report objective is not intended to evaluate all treatments for a particular tumor. There are few comparative studies for many of the CNS tumors with the exceptions of brain metastases.

Glioblastoma multiforme

Glioblastomas, also called glioblastoma multiforme, are high grade (undifferentiated, anaplastic) gliomas with poor prognosis. See the description under glioma for more background information.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One fair quality RCT (Souhami 2004), two poor quality cohort studies (Nwokedi 2002; Kong 2008), and one fair quality case series (Hsieh 2005) were identified.

One fair quality RCT (Souhami 2004) randomly assigned 203 adult patients with *newly diagnosed* supratentorial glioblastoma mutliforme (tumor less than or equal to 4 cm) to receive either SRS (15 Gy to 24 GY depending on tumor size) followed by EBRT and carmustine (BCNU) or EBRT+BCNU alone. Patients' mean age was 55.7 (range, 18 to 79), 60% were men and 95% had a KPS greater than or equal to 70. Median survival did not differ between groups (13.6 vs. 13.5 months, SRS+EBRT+BCNU vs. EBRT+BCNU alone, p = 0.57), nor did quality of life (questionnaire not described) differ between groups (p = 0.7).

One poor quality cohort study (Nwokedi 2002) analyzed data from 64 patients *newly diagnosed* with glioblastoma multiforme who had at least one month of follow-up (median age 50 years,

39% with KPS less than 70). Although the patient population included children and adolescents, results were not stratified by age. Thirty-three received EBRT alone (median dose 60 Gy; range, 28 to 70) and 31 received EBRT and SRS (median dose 17 Gy; range, 10 to 28). Seventy percent had surgical resection and 53% received chemotherapy. Median survival was 13 compared to 25 months for patients receiving EBRT alone vs. EBRT+SRS (p = 0.34).

Kong (2008), a poor quality cohort study, examined 114 patients with *recurrent* malignant glioma, 65 of whom were diagnosed with glioblastoma. Median follow-up was 11.2 months. The patients had previously been treated with EBRT but were offered SRS upon recurrence. Kong (2008) compared these patients to a historical control group that had not received SRS and found that SRS significantly prolonged survival as a salvage treatment for patients with recurrent glioblastomas (23 months vs. 12 months, p< 0.0001.)

Hsieh (2005), a fair quality case series, enrolled 51 consecutive patients with *newly diagnosed* glioblastoma. They had a median age of 59 years and 55% male. While the patient population included adolescents, results were not stratified by age. Patients received SRS as adjuvant *upfront* therapy with surgery (49%) or received SRS for *recurrent* (51%) glioblastoma mutliforme after surgery. All patients received EBRT (median dose 60 Gy) as part of their initial treatment. Seventy-one percent received chemotherapy. The median dose of SRS was 24 Gy (range, 15 to 32). Overall median survival was 14.3 months (95% CI, 14.0 to 20.4), and 1-year survival rate was 43%. Median overall survival for patients receiving SRS as upfront adjuvant therapy was 10 months compared to 16.7 months for patients were SRS was used for recurrence or progression, but this difference was not statistically significant (p = 0.09) nor were baseline differences between these groups controlled for in statistical analyses.

Overall Summary

The overall strength of the evidence is low based on one fair quality RCT (n = 203) and two poor quality cohort studies, one with concurrent (n = 64) and one with historical controls (n = 114). For patients with *newly diagnosed* glioblastoma multiforme, the addition of SRS to EBRT and chemotherapy may not affect survival. Results from the one RCT (no survival difference) conflicted with results from the cohort studies (survival better with addition of SRS) involving patients with *newly diagnosed* glioblastoma. Prognostic imbalances between groups in the cohort studies and use of historical controls likely created biased results, particularly given the small sample sizes in these studies. For patients with *recurrent* glioblastoma, the strength of the evidence is very low based on one fair quality case series and one poor quality cohort study. The effect of SRS on survival and other outcomes in patients with recurrent glioblastoma is uncertain.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One fair quality RCT (Souhami 2004), one poor quality cohort study (Nwokedi 2002), one fair quality case series (Hsieh 2005) and two poor quality case series (Biswas 2009; Smith 2008) were identified. See KQ1 for the description of Souhami (2004), Nwokedi (2002), and Hsieh (2005).

Souhami (2004) reported that Grade 3 late toxicities occurred in 5% of patients receiving SRS+EBRT+BCNU and 0% in those receiving EBRT+BCNU; Grade 1 and 2 toxicities were 26% and 24%, respectively. These differences were not statistically different.

Nwokedi (2002), a poor quality cohort study described in KQ1, reported that no acute Grade 3 or 4 toxicities occurred, but 7% of patients in the EBRT+SRS group had radiation necrosis.

Hsieh (2005), a fair quality case series including 51 patients (described in KQ1), reported that radionecrosis developed in 33% of patients, but no one had acute toxicities.

The two poor quality case series (Biswas 2009; Smith 2008) involving 58 patients reported no acute toxicities. Smith (2008) reported that 47% of patients had symptomatic radionecrosis, and Biswas (2009) reported 3% had symptomatic necrotic tumor requiring a second surgery.

Overall Summary

Based on one fair quality RCT, one poor quality cohort studies, and three case series, the overall strength of evidence is low that adding SRS to other treatments for glioblastoma mutliforme may increase the risk of symptomatic radionecrosis, which may occur in 3% to 5% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Glioma

Gliomas are the most common primary tumors of the brain. Although various classification systems exist, gliomas are generally classified by their histology (cell type) and grade (pathologic appearance that is associated with prognosis).Gliomas have histologic features of glial, non-neuronal, cells including astrocytes, oligodendrocytes, ependymal cells, and Schwann cells. Some gliomas are benign, slow growing and miotitically inactive, but because of their location may be fatal or cause significant morbidity. Among gliomas that have malignant features, they can be classified as low-grade (well-differentiated histologically with a better prognosis) and high-grade (undifferentiated or anaplastic with a worse prognosis), the later includes glioblastomas (glioblastoma multiforme) and anaplastic astrocytomas.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One poor quality cohort study (Kong 2008) compared 114 consecutive patients with recurrent malignant gliomas treated with salvage SRS (2000 to 2006) with 360 historical controls with malignant gliomas (1995 to 1999) treated at the same institution (details of treatment not provided). Median age for the SRS group was 49 years (range, 5 to 75) and 60% were men. All patients had standard EBRT (median dose 60 Gy; range, 54 to 70); 57% had a complete resection of the tumor and 28% received chemotherapy. Median peripheral SRS dose was 16 Gy (range, 12 to 50). Median OS from diagnosis was 37.5 months (95% CI, 11.7 to 63.2) for patients with WHO Grade 3 gliomas and 23 months (95% CI, 16.2 to 29.3) for patients with glioblastomas. Stereotactic radiosurgery prolonged survival for patients with recurrent glioblastomas compared to historical controls (23 months vs. 12 months, respectively, $p < 0.0001$), but did not affect survival in patients with recurrent Grade 3 gliomas (37.5 months vs. 26 months, $p = 0.789$).

Overall Summary

Based on one poor quality cohort study, the overall strength of evidence is very low for prolonged survival with salvage SRS in patients with *recurrent* malignant gliomas. It is uncertain whether salvage SRS increases median survival in patients with recurrent malignant gliomas.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One cohort study (Kong 2008) and eight case series (Combs 2005; Elliott 2011a; Fuchs 2007; Heppner 2005; Kano 2009a; Marcus 2005; Roberge 2006; Ulm 2005) were identified. The cohort study (Kong 2008) was poor quality, one case series was fair quality (Elliott 2011a) and the remaining seven case series were poor quality (Combs 2005; Fuchs 2007; Heppner 2005; Kano 2009a; Marcus 2005; Roberge 2006; Ulm 2005).

One poor quality cohort study (Kong 2008) compared 114 consecutive patients with recurrent malignant gliomas treated with salvage SRS (2000 to 2006) with 360 historical controls (1995 to 1999). While the patient population included children and adolescents (range, 5 to 76 years), results were not stratified by age. This study reported that “common adverse effects of SRS include nausea, vomiting, and headache, which were usually controlled with steroid medications” (Kong 2008, p. 2048). Radiation necrosis occurred in 22 (24.4%) patients and four of these patients had surgical resection for the mass effect.

One fair quality (Elliott 2011a) and seven poor quality (Combs 2005; Fuchs 2007; Heppner 2005; Kano 2009a; Marcus 2005; Roberge 2006; Ulm 2005) case series were identified.

Elliott (2011a), in a fair quality retrospective case series, studied 26 patients with recurrent high grade glioma. Median age was 60.4 years (range, 36.5 to 70). Median SRS dose was 15 Gy (range, 10 to 18). Radiation necrosis occurred in two (7%) patients with one requiring resection to relieve the mass effect, and transient worsening in hemiparesis occurred in one patient.

Seven additional poor quality case series involving 344 patients were identified (Combs 2005; Fuchs 2007; Heppner 2005; Kano 2009a; Marcus 2005; Roberge 2006; Ulm 2005). All of the studies with the exception of Ulm (2005) included children and adolescents in their patient populations; however results were not stratified by age. Three studies included patients with primary and recurrent low grade gliomas (Heppner 2005; Marcus 2005; Roberge 2006), one included patients with gliomas of the brainstem (Fuchs 2002), one involved patients with high grade gliomas (Combs 2005), one mixed low and high grade gliomas (Kano 2009a), and one study included patients with glioblastomas and analyplastic astrocytomas (Ulm 2005). These studies are summarized in Appendix E. The adverse events described in these studies are similar to those already noted.

Overall Summary

Based on one cohort study and eight case series, the overall strength of evidence is very low for harms in patients with malignant gliomas. Although there is uncertainty, these studies raise concerns about radiation necrosis leading to a mass effect requiring surgery.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Few studies include children, so we include the following poor quality case series by Marcus (2005) for its outcomes. It is a prospective case series of *50 pediatric patients* with low grade gliomas. Median age was nine years (range, 2 to 26), 52% were male. The indication for SRS was *progression of the glioma* during or after chemotherapy. Mean total SRS dose was 52.2 Gy. Overall survival was 98% at five years and 82% at eight years. Progression free survival rates were 82.5% at five years and 65% at eight years. Six patients (7.4%) had local progression. Of the six children who developed progression during follow-up after SRS, two had progression to anaplastic astrocytoma and died. No significant acute toxicities were reported. Four children with optic gliomas developed Moya Moya syndrome after SRS. This syndrome is a constriction of cerebral arteries in the Circle of Willis with development of collateral arteries, and it may cause strokes and epilepsy.

Overall Summary

The overall strength of evidence is very low and the following conclusions are uncertain. Based on one poor quality case series, it is uncertain if SRS offers advantages for overall survival or

progression free survival rates for pediatric patients treated for low grade gliomas. Patients may develop Moya Moya syndrome, and if they have progression of their tumor, it may be to anaplastic astrocytoma.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Pituitary Adenoma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One fair quality (Kong 2007) and one poor quality (Puataweepong 2009) cohort studies were identified. Kong (2007), a fair quality cohort study, reported on 125 patients with primary pituitary ademonas. The patient population included adolescents; however results were not stratified by age. Sixty-four patients were treated with EBRT and 61 patients received GKS treatment. Mean follow-up was 36.7 months. No difference was reported in tumor control between the groups. Based on the endocrinologic results in patients with hormone secreting tumors, overall hormone complete remission rate was 26.2% at two years and 76.3% at four years. For hormone secreting tumors, the median time to remission was 26 months in the GKS group and 63 months in the FRT group (p=0.0068).

Puataweepong (2009), a poor quality cohort study, examined 72 patients with primary and recurrent pituitary ademona. The patient population included adolescents; however results were not stratified by age. Twenty-two patients received EBRT treatment and 59 patients were treated with SRS. Median follow-up for the EBRT group was 4.6 years and for the SRS group 4.7 years. Five-year OS rates were 91% for EBRT and 100% for SRS (p=0.10). Five-year tumor control rates were 95% for EBRT and 96% for SRS (p=0.33). Hormonal normalization at three years was 72% for EBRT and 61% for SRS (no p-value reported). For growth hormone secreting tumors, serum growth hormone level returned to normal within one year after SRS (71% of patients) but it took three years to achieve normal levels after EBRT.

Overall Summary

Based on one fair quality and one poor quality cohort studies, there is a low overall quality of evidence suggesting there may be no difference in overall survival or local tumor control in patients treated with SRS instead of EBRT, but there is uncertainty regarding this conclusion. Because of the very low overall quality of evidence about hormonal normalization after treatment any conclusions are uncertain.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews
No SRs were identified.

Subsequently Published Studies
One fair quality cohort study (Kong 2007), one poor quality cohort study (Puataweepong 2009), four fair quality case series (Colin 2005; Pouratian 2005; Sheehan 2011; Vladyka 2003), and nine poor quality case series were identified (Hayashi 2010; Iwata 2011; Kajiwara 2005; Losa 2004; Mingione 2006; Petrovich 2003; Pollock 2007; Sheehan 2007; Voges 2006).

Kong (2007), a fair quality cohort study, included 64 patients treated with fractionated radiotherapy and 61 patients with GKS. Mean follow-up was 36.8 months. Median age was 41.3 years (range, 14 to 73 years). While this study included adolescents, results are not stratified by age. New onset of hypopituitarism occurred in eleven patients (out of the 95 patients who did not have hypopituitarism before treatment). Only one of the eleven patients belonged to the GKS group.

Puataweepong (2009), a poor quality cohort study, looked at 72 patients treated with either EBRT (n=22) or SRS (n=59) for pituitary adenoma. Median follow-up was 4.6 years for the EBRT group and 4.7 years for the SBRT group. Median age was 37.5 years (range, 16 to 66) for the EBRT group and 47 years (range, 17 to 65) for the SBRT group. While this study included adolescents, results are not stratified by age. The study found that the incidence of newly developed hypopituitarism was higher in the EBRT group than in the SRS group, but the difference was not statistically significant. The 5-year freedom from newly initiated hormonal replacement was 50% in the EBRT group and 75% in the SRS group. Severe toxicities were not reported.

Colin (2005), a fair quality case series, examined 100 patients treated with fractionated SRT for primary and recurrent pituitary adenoma. Median follow-up was 82 months. Median age was 50 years (range, 6 to 80). While this study included children and adolescents, results were not stratified by age. Acute complications included transient headache (5.5%). Radiation induced pituitary deficiencies occurred at the following rates: the adrenocorticotropic hormone axis (25.5%); the thyroid stimulating axis (28.2%); and the follicular stimulating hormone-leutenizing hormone axis (10.9%). Newly initiated hormone replacement was required in 36 patients (32.7%).

Pouratian (2006), a fair quality case series, reported on 37 patients treated with GKS for primary and recurrent prolactinomas. Median follow-up was 55 months. Median age was 42.9 years (range, 17 to 71). While this study included adolescents, results are not stratified by age. New pituitary hormone deficiencies occurred in eight patients (29%): four with thyroid stimulating hormone deficiencies, two with growth hormone deficiencies, one with adrenocorticotropic hormone deficiency and one patient with both thyroid and adrenocorticotropic hormone deficiencies. Two patients (5.4%) developed new onset extraocular movement difficulty.

Sheehan (2011), a fair quality case series, looked at 418 patients treated with GKS for primary or recurrent pituitary adenomas. Median follow-up was 31 months. Median age was 44 years

(range, 12 to 91). While this study included children and adolescents, results were not stratified by age. New pituitary hormone deficiencies developed in 102 patients (24.4%), diabetes insipidus occurred in one patient (0.24%), cranial nerve defects developed in five patients (1.2%) and new visual acuity or field deficits occurred in eight patients (1.9%.) No cases of radiosurgically induced neoplasia or carotid artery injury were observed.

Vladyka (2003), a fair quality case series, reported on 63 patients treated with GKS for primary and recurrent pituitary adenomas. Median follow-up was 58-66 months. Median age was 46 years (range, 17 to 69). While this study included adolescents, results were not stratified by age. Gonadal hypofunction occurred in eleven patients (17.5%), adrenocorical hypofunction in thirteen patients (20.6%) and thyroidal hypofunction in nineteen patients (30.2%).

Hayashi (2010), a poor quality case series, examined 89 patients treated with GKS for primary and recurrent pituitary ademona. Mean follow-up was 36 months. Patient ages ranged from 10 to 83 years. The patient population included children and adolescents; however results were not stratified by age. Transitory cranial nerve palsy developed in two patients (2.2%), but no patients experienced pituitary hormone deficits or visual impairment.

Iwata (2011), a poor quality case series, reported on 100 patients treated with hypofractionated SRT for primary and recurrent pituitary adenoma. Median follow-up was 33 months. Median age was 59 years (range, 16 to 82). While this study included adolescents, results were not stratified by age. Grade 2 visual disorder at 36 months occurred in 1.7% of patients. Hypopituitarism developed in 4.1%, and transient cyst enlargement occurred in 3%. No patient developed brain necrosis, oculomotor nerve paralysis or abducens nerve paralysis.

Kajiwara (2005), a poor quality case series, looked at 21 patients treated with Cyberknife fractionated SRS or single dose treatment for pituitary adenoma. Mean follow-up was 35.3 months. Median age was 60 years (range, 11 to 72). While this study included children and adolescents, results were not stratified by age. Visual acuity deterioration occurred in one patient (4.8%) out of 10 with visual dysfunction prior to treatment. No patients developed new visual dysfunction. Panhypopituitarisim occurred in 9.5% of patients.

Losa (2004), a poor quality case series, reported on 54 patients treated with GKS for primary pituitary adenoma. Mean follow-up was 41.1 months. Mean age was 51.1 years (SD 1.7). Two patients experienced a moderate headache at 2 to 4 months (3.7%). New hypogonadism developed in three patients (12.5% of 24 patients at risk,) new hypothroidism occurred in three patients (8.6% of 35 patients at risk,) and new hypoadrenalism developed in one patient (2.3% of 43 patients at risk.) In total, five patients (9.3% of sample) developed a loss of pituitary function including one patient who had normal function before treatment.

Mingione (2006), a poor quality case series, looked at 100 patients treated with GKS for primary and recurrent nonsecretory pituitary macroadenoma. New hormone deficits developed in twelve patients (19.7%) 8 to 107 months after treatment (mean 26 months). Nine patients (14.8%) required thyroid hormone replacement at a mean of 27.7 months after GKS (range, 8 to 107), four patients (6.6%) required glucoricoid replacement at a mean of 15.5 months after

treatment (range, 11 to25), and two patients (3.2%) developed new onset growth hormone deficit requiring hormone replacement at 13 and 39 months post treatment.

Petrovich (2003), a poor quality case series, reported on 78 patients treated with GKS for primary and recurrent pituitary adenoma. Mean follow-up was 41 months. Median age was 53 years (range, 17 to 82). While this study included adolescents, results were not stratified by age. Acute toxicity was mild and included mild nausea (1.2%), headache (2.4%) and fatigue (1.2%). One patient (1.2%) developed new onset cranial nerve palsy two years post GKS. Of the 15 patients with cranial nerve palsy prior to treatment, 53% had resolution of their symptoms, 28% had decreased nerve function and 27% had no change. Diplopia developed in three patients (3.8%) and hypopituitarism in two (4% of 52 patients with normal function prior to treatment.)

Pollock (2007), a poor quality case series, examined 176 patients treated with GKS for primary and recurrent pituitary adenoma. Median follow-up and age were not reported. New anterior pituitary deficits occurred in 20% of patients with hormone producing tumors and over 40% of patients with nonfunctional tumors. Other harms included temporal lobe necrosis and asymptomatic internal carotid artery stenosis (statistics not reported) and one case of unilateral blindness.

Sheehan (2007), a poor quality case series, looked at 434 patients treated with GKS for pituitary adenomas. Most patients were followed for more than twelve months. Median age was not reported. On post treatment imaging, no incidence of radiation induced neoplasia was identified and in the four patients who underwent post GKS resection, no different tumor pathology was noted.

Voges (2006), a poor quality case series, looked at 142 patients treated with LINAC RS for primary and recurrent pituitary macroadenomas. Mean follow-up was 81.9 months. Median age was 47.3 years (range, 17 to 75). While this study included adolescents, results were not stratified by age. One patient developed quadrant anopsis (0.7%) and one patient had decreased visual acuity (0.7%). Four patients (2.8%) had CT images displaying ring-like contrast enhancement and edema in the temporal lobe next to treatment site. Two of these patients had resolved seizures, but two patients had long term complications involving seizures and memory loss. Of the 114 patients evaluated for pituitary function, 30 patients (26.3%) had one affected axis and 24 patients (21.1%) had two affected axes. Fourteen patients (12.3%) developed treatment related hypothalamopituitary dysfunction.

Overall Summary

Based on two small fair quality cohort studies and 13 case series, the overall strength of evidence is very low. The most common permanent side effect from SRS treatment may be the development of pituitary hormone deficiencies, ranging from 9.3% to 30% of patients. Stereotactic radiotherapy may result in fewer patients having new hypopituitarism than EBRT, although this conclusion is uncertain. In the two cohort studies, differences between the groups favoring SRT over EBRT were noted but were not statistically significant. Acute complications

from SRT treatment may be mild and include headache, nausea and fatigue. Other rare side effects may include edema, visual deficits, and cranial nerve palsies.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on costs or cost-effectiveness were identified.

Head and Neck Cancers

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One poor quality cohort study, Ozyigit (2011) was identified that examined 51 patients with primary or recurrent nasopharyngeal carcinoma. The median age was 46 years and median follow-up was 24 months. The patient population included adolescents; however results were not stratified by age. Twenty-four patients received SBRT with CyberKnife and 27 patients were treated with EBRT. The 2-year cancer-specific survival [DSS] rate was 45% for all patients, 64% for the SBRT group and 47% for the EBRT group. The difference was not statistically significant. Two-year local control rates were 82% for all patients, 82% for SBRT and 80% for EBRT, also not statistically significant. Univariate and multivariate analysis found that T-stage at recurrence was the only significant predictor for cancer specific survival and local control rates, but type of radiation therapy was not included in univariate and multivariate analysis.

Overall Summary

Based on one poor quality cohort study, there is very low overall strength of evidence that there was no significant difference between SBRT and EBRT in local control of the tumor or in patient survival.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One poor quality cohort study (Ozyigit 2011) and six poor quality case series (Chen 2006; Hara 2008; Rwigema 2010; Rwigema 2011a; Unger 2010; Wu 2007) were identified.

In Ozyigit (2011), a poor quality cohort study, overall serious (greater than or equal to Grade 3) late complication rates were 20.8% (5 patients) in the SBRT and 48.1% (13 patients) in the EBRT group, p=0.04. One SBRT patient (4.2%) and three EBRT patients (14.3%) developed cranial neuropathy. Four SBRT patients (16.7%) and one EBRT patient (4.8%) experienced carotid blow-out. Brain necrosis developed in one SBRT patient (4.8%) and in five EBRT patients (18.5%). No SBRT and five EBRT patients (18.5%) developed trismus. Fatal complications occurred in three SBRT patients (12.5%) and four EBRT patients (14.8%). No relationship was found between serious late toxicities and use of brachytherapy or chemotherapy, tumor volume or cumulative nasopharyngeal dose.

Chen (2006), a poor quality case series, looked at 64 patients who received EBRT followed by a SBRT boost for newly diagnosed nasopharyngeal carcinoma. Acute toxicities included leucopenia, with 30 patients (47%) experiencing Grade 1 to 2 and 10 patients (16%) with Grade 3. Anemia Grade 1 to 2 occurred in 49 patients (77%) and thrombocytopenia Grade 1 to 2 developed in 19 patients (30%.) Mucositis Grades 1 and 2 occurred in 41 patients (64%) with 23 patients (36%) developing Grade 3. Thus, 100% of patients experienced Grades 1 to 3 mucositis. Grades 1 to 2 nausea and vomiting occurred in 39 patients (61%) and 12 patients (19%) developed Grade 3. Grade 1 to 2 weight loss occurred in 50 patients (78%), and Grade 1 to 2 skin reactions developed in 58 patients (91%) while 6 patients (9%) experienced Grade 3 skin reactions. Late stage toxicity occurred in two patients (3%), both of whom developed massive nasal bleeding six to seven months after treatment and died shortly thereafter.

Hara (2008), a poor quality case series, reported on 82 patients newly diagnosed with nasopharyngeal carcinoma who received a SBRT boost two to six weeks after EBRT treatment. Patient ages ranged from 14 to 80 years. While the patient population included adolescents, results were not stratified by age. Transient facial numbness developed in four patients (5%) and retinopathy in three patients (4%). One patient (1%) had a carotid aneurysm develop in the EBRT neck field 24 months after treatment. Ten patients (12%) showed temporal lobe necrosis on radiography, two of whom had seizures.

Rwigema (2010), a poor quality case series, examined SBRT treatment of squamous cell carcinoma of the head and neck in 85 patients. Most toxicities were Grade 1 or 2 and not detailed, but four patients (4.7%) developed Grade 3 complications. Two patients (2.4%) developed Grade 3 xerostomia, one patient (1.2%) had Grade 3 level pain, and one patient (1.2%) experienced Grade 3 dysgeusia.

Rwigema (2011a), a poor quality case series, reported on 96 patients with squamous cell carcinoma of the head and neck who received fractionated SBRT (n=92) or single-dose SBRT (n=4). Median follow time was 14 months (range, 2 to 39). Median age was 67 years (range, 39 to 88). Acute Grade 1 (37.6%), Grade 2 (17.7%), and Grade 3 (5.2%) toxicities were reported. Acute Grade 3 toxicities included dysgeusia (1.0%), dysphagia (2.1%), and xerostomia (2.1%). Late Grade 1 (16.7%), Grade 2 (9.3%), and Grade 3 (3.1%) were reported. Late Grade 3 toxicities included dysphagia (2.1%) and fibrosis (1.0%).

Unger (2010), a poor quality case series, looked at 65 patients with recurrent, second primary or persistent malignancies of the head and neck that were previously treated with RT. Cyberknife SRS was applied. Median follow-up was 16 months. Acute Grade 1 to 3 toxicity occurred in 19 patients (29%) including mucositis, dermatitis and nausea. One patient (1%) died of unknown causes two weeks after completion of irradiation; death was considered treatment related. Severe late radiation induced toxicity in six patients (9%). One patient (1%) had Grade 4 soft tissue necrosis, one patient (1%) had Grade 4 pharynocutaneous fistula, and one patient (1%) had Grade 4 dysphagia. Two patients (2%) experienced Grade 4 arterial bleeding requiring embolization and one patient (1%) had dysphagia, cranial neuropathy and trismus.

Wu (2007), a poor quality case series, reported on 90 patients with primary and recurrent nasopharyngeal carcinoma who were treated with fractionated SRT. Median follow-up was 20.3 months (range, 3.1-77.5). Median age was 43 years (range, 13 to 70). While the patient population included adolescents, results were not stratified by age. Severe late complications included temporal lobe necrosis in three patients, nasopharyngeal mucosal necrosis in six patients, massive hemorrhage in the nasopharynx in two patients, and brain stem necrosis in three patients.

Overall Summary

Based on one poor quality cohort study and six poor quality case series, the overall strength of evidence is very low. SBRT may be associated with less frequent harms than EBRT in patients with nasopharyngeal carcinoma and head and neck squamous cell carcinoma. Serious late complication rates may occur in 2% up to 20% of patients. One poor quality cohort study found that overall serious complication rate was lower for patients receiving SBRT than those receiving EBRT, but there is substantial uncertainty about this difference due to the overall strength of evidence being very low.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on costs or cost-effectiveness were identified.

Lung Cancer

The majority of studies assessing the outcomes of SBRT for lung cancer focus on patients with inoperable Stage 1 non-small cell lung cancer (NSCLC). Patients with Stage 1 NSCLC would normally undergo surgical resection with an estimated 5-year survival of up to 80% depending on the size of the tumor (Chi 2010). However, the location of the cancer or medical conditions (e.g., severe chronic obstructive pulmonary disease) may preclude surgery. For patients with inoperable Stage 1 (T1-2N0) NSCLC, treatment with conventional EBRT using 60 to 66 Gy resulted in a 5-year OS of about 15% to 30% (Chi 2010; Rowell 2001; Sibley 1998). SBRT is being

used in an attempt to improve survival in patients with inoperable stage 1 NSCLC. No randomized controlled trials have been done comparing SBRT with surgical resection in patients who are eligible for surgical resection for Stage 1 NSCLC.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

One poor quality SR was identified (Chi 2010). Chi (2010) looked at 35 case series (total n = 1804) of SBRT for early stage NSCLC. A majority of the studies were single institution experiences with a few phase I trials, small case series designed to assess the appropriate dose of a therapy (Rubenstein 2003), and phase II trials, studies that test whether a therapy has an anticancer effect and works against a certain type of cancer (NCI n.d.). Median age ranged from 60 to 78 years and the median follow-up was between 11 to 90 months. Median doses for SBRT ranged from 15 Gy in 1 fraction to 70 Gy in 10 fractions. For Stage I NSCLC, reported local control rates of 80% to 100% were commonly reported although rates of less than 70% were observed in two small studies. Three and 5-year OS rates were 58% ± 16% and 45% ± 20%, respectively. Three and 5-year DSS rates were 72% ± 12% and 57% ± 16%, respectively. The regional recurrence rate ranged from 0% to 23% and was mostly below or slightly above 10%. Distant recurrence rates ranged from none to over 50%, with the higher rates mostly due to the results reported in two retrospective studies.

Subsequently Published Studies

We identified two studies that could be classified as cohort studies since they compared outcomes and harms for 1) SBRT for primary lung cancer versus metastatic cancer to the lung (Takeda 2011); and 2) NSCLC diagnosed clinically or pathologically by biopsy (Verstegen 2011). However, for the purposes of this review, a comparison of SBRT with conventional EBRT, these studies only provide outcomes for one group of patients, those treated with SBRT. They will be included as a single group study (case series) of SBRT for this review.

Takeda (2011), a fair quality case series, reported on 217 patients treated with SBRT for lung cancer. The study compared patients with a primary diagnosis of lung cancer (n = 183) to patients with metastases from colorectal cancer (n = 15) or metastases from other primary sites (n = 19.) Median follow-up ranged from 15 months to 29 months for various patient groups. Survival rates were not reported. The study found that 1-year tumor control rates were 86% for patients with lung metastases and 97% for patients with primary lung cancer. Two-year tumor control rates were 82% and 93% respectively.

Verstegen (2011), a fair quality case series, reported on 591 patients with Stage I NSCLC treated with stereotactic ablative radiotherapy (SBRT). The study compared patients who were clinically diagnosed (n = 382) to those who were diagnosed based on tissue pathology (n = 209.) Median follow-up was not reported. Median three-year OS was 54% in the clinical group and 55% in the pathological group. Median 3-year local control, regional control and distant control rates for

the clinically versus pathologically diagnosed groups were 91% and 90%, 88% and 90% and 73% and 80%, respectively. None of these differences were statistically significant.

We identified an additional 31 case series; 12 included only patients with Stage 1 NSCLC (Andratschke 2011; Baba 2010; Barriger 2012; Baumann 2008; Bradley 2010; Hoppe 2008; Matsuo 2011; Onishi 2011; Stephans 2009; Taremi 2012; Timmerman 2010) and 17 included patients with primary lung cancer at different stages and/or primary lung cancer and metastatic cancer treated with SBRT (Appendix E). Nineteen (59%) studies had 100 or fewer patients, and 22 were poor quality.

Nine (total n = 814 patients) of the 12 case series that included only patients with Stage 1 NSCLC (localized to lung, without spread to lymph nodes or other organs) provided data on survival (Andratschke 2011; Baba 2010; Bradley 2010; Matsuo 2011; Onishi 2011; Stephans 2009; Taremi 2012; Timmerman 2010). For these studies, median doses for SBRT generally ranged from 44 to 60 Gy. Across these nine studies, overall 1-year survival ranged 79% to 90% and 3-year survival ranged 38% to 59%, similar to survivals reported in Chi (2010). As expected, several studies noted that survival for Stage 1A NSCLC (tumor size less than or equal to 3 cm) was better than survival for Stage 1B (tumor size greater than 3 cm) disease. For example, Stephans (2009) reported 1-year survival as 83% and 77% for Stage 1A versus Stage 1B NSCLC, respectively; Baba (2010) reported 3-year survival as 79% and 56% (Stage 1A vs. Stage 1B, respectively); and Onishi (2011) reported 5-year survival as 72% and 62% (Stage 1A vs. Stage 1B, respectively).

For the remaining 17 studies that included patients with mixed stages of NSCLC and/or NSCLC and metastases to the lung, we could not summarize survival data since many of the studies did not report results by cancer type or stage. These studies primarily contributed information on harms. Details of the studies can be found in Appendix F.

Overall Summary

Based on 68 case series consisting primarily of patients with *inoperable (based on location of the tumor, serious medical conditions and patient refusal) early stage non-small cell lung cancer (NSCLC)*, the overall strength of evidence is very low and any conclusions about outcomes are uncertain. Since there were no studies comparing SBRT to EBRT, it is uncertain whether SBRT improves survival or other patient-important outcomes compared to conventional EBRT. Stereotactic body radiation therapy for patients with inoperable early stage NSCLC may result in 3-year overall survival rates of 50% to 60% and local control rates of 80% to 100%. Survival rates were better for patients with Stage 1A compared to Stage 1B disease, as expected because of differing prognosis based on tumor size. Earlier studies of medically inoperable early stage NSCLC (Chi 2010; Rowell 2001; Sibley 1998) estimate that treatment with conventional EBRT using 60 to 66 Gy have a 5-year OS of about 15% to 30%; however, there have been no direct comparison with SBRT.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

Chi (2010), a poor quality SR, included 35 case series (total n = 1804) with the goal of describing the patterns of failure following SBRT for early stage (Stage 1) NSCLC. Reported acute toxicity was mostly mild with a significant number of patients without any adverse affects during treatment. Common acute toxicities reported included radiation pneumonitis, esophagitis, skin reaction, chest wall pain and general malaise. Rates of Grade 3 and 4 late toxicities ranged from 0 to 28%, but were 0 to 10% in most studies. Grade 3 and 4 toxicities were mostly pulmonary and chest wall including radiation pneumonitis, chest pain, rib fracture and dermatitis. Grade 5 toxicities were reported in six studies (Fakiris 2009; Le 2006; 2006; Timmerman 2006; Uematsu 2008), but most came from the Indiana phase 2 study (Fakiris 2009; Timmerman 2006). Grade 5 toxicities included broncho-pulmonary vein fistulas, tracheoesophgeal fistulas, pneumonitis, pleural effusion and massive bleeding. Grade 3 to 5 toxicities occurred most often in patients with centrally located tumors or prior pulmonary disease.

Chi (2010), citing three case series (Collins 2009; Le 2006; Pennathur 2007), and an additional small poor quality case series (Brown 2007b) noted high rates of complications from the placement of fiducial markers to guide SBRT (e.g., pneumothorax requiring chest tube placement). Pennathur (2007) reported that nine (28%) patients required a chest tube for a pneumothorax after fiducial placement. Based on 24 patients, Collins (2007) reported that 30% developed a pneumothorax, and 17% of all patients required a chest tube for the pneumothorax. Le (2006) noted that out of 32 patients six (19%) developed a pneumothorax with three (9%) requiring a chest tube. Brown (2007b) reported that five (16%) patients developed a pneumothorax requiring a chest tube and/or hospitalization and one had a cardiac arrest during fiducial placement. All four studies used CyberKnife to deliver SBRT.

Subsequently Published Studies

We identified three studies (Olsen 2011; Takeda 2011; Verstegen 2011) that could be classified as cohort studies since they compared outcomes and harms for different SBRT doses or types of lung cancer or methods used to diagnose the cancer. However, for the purposes of this review, a comparison of SBRT with conventional EBRT, these studies only provide outcomes for one group of patients, those treated with SBRT. They will be included as a single group study (case series) of SBRT for this review.

Takeda (2011), a fair quality case series, observed no acute toxicity from SBRT in 217 patients. Late Grade 2 radiation pneumonitis developed in two patients (6%) with lung metastases and 24 patients (13%) with primary lung cancer. Grade 3 radiation pneumonitis occurred in one metastatic cancer patient (3%) and six primary lung cancer patients (3%). No Grade 4 or 5 radiation pneumonitis occurred and no other Grade 3 or higher toxicities developed.

Verstegen (2011), a fair quality case series, found low rates of toxicity in 591 patients. Eighteen patients (3%) developed Grade 3 to 5 radiation pneumonitis, ten patients (2%) had rib fractures on follow-up scans, and three patients (less than 1%) experienced Grade 3 to 5 chest wall pain.

Olsen (2011), a poor quality case series with 130 patients, also found low levels of toxicity. Twenty-one patients (16%) experienced chest wall pain and four patients (3%) developed Grade 2 radiation pneumonitis.

Twenty-nine additional case series were identified; 12 included only patients with Stage 1 NSCLC (Andratschke 2011; Baba 2010; Barriger 2012; Baumann 2008; Bradley 2010; Brown 2007a; Hoppe 2008; Matsuo 2011; Onishi 2011; Stephans 2009; Taremi 2012; Timmerman 2010) and 17 included patients with primary lung cancer at different stages and/or primary lung cancer and metastatic cancer treated with SBRT (Appendix E). Approximately half the studies had 100 or fewer patients and 23 were poor quality. There was variability across studies in reported toxicities; but in general, they reported similar types of acute (i.e., fatigue, malaise, skin reactions, chest wall pain, nausea/vomiting, cough, shortness of breath, bronchitis) and late toxicities (i.e., pneumonitis, chest wall pain/rib fractures, dermatitis, pneumonia). The rates of acute and late toxicities were also similar to those reported by Chi (2010). Most acute toxicities were Grade 1 and 2. The estimates of Grade 2 to 4 acute toxicities ranged 2% to 5%. For late toxicities, Grade 2 to 3 pneumonitis occurred in approximately 5% to 15%, rib fracture in approximately 2% to 4% depending on location of tumor (central or peripheral). Timmerman (2010) in a *fair quality prospective case series* (n=55) reported on protocol-specified adverse pulmonary events related to SBRT. Grade 3 events occurred in 12.7% (95% CI, 9.6% to 15.8%), Grade 4 events occurred in 3.6% (95% CI, 2.7% to 4.5%), and no Grade 5 events occurred. An additional 10.9% (95% CI, 8.2% to 13.6%) had SBRT-related adverse events not specified in the protocol with half being dermatitis or rib fractures.

Overall Summary

The overall strength of evidence regarding harms is very low, based on 67 case series. There is uncertainty about the rate of acute and late toxicities, especially as they compared to EBRT. Acute toxicities from SBRT for lung cancer include fatigue, general malaise, pneumonitis, esophagitis, dermatitis, and chest wall pain. Few patients appear to have acute toxicities; and when they do, they are likely to be mild (Grade 1 and 2). Estimates of greater than or equal to Grade 3 acute toxicities may range from 2% to 5%. Late toxicities primarily involve the lungs (e.g., radiation pneumonitis) and chest wall (e.g., pain, dermatitis, and rib fractures). The rates of greater than or equal to Grade 3 late toxicities appear to range 0% to 28%, with most ranging 2% to 10%. In addition, the placement of fiducial markers, when used, may cause pneumothoraxes requiring chest tube placement or hospitalization in approximately 9% to 28% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

We identified three poor quality economic analyses that include SBRT for non-operable early stage NSCLC (Grutters 2010b; Lanni 2011; Sher 2011). Grutters (2010b), a poor quality economic evaluation, uses a Markov model to represent changing health states and risk over time to estimate the costs and incremental cost effectiveness ratios (ICER) of particle beam therapy, SBRT and conventional EBRT for inoperable Stage 1 NSCLC. There was no comparative outcomes data on which to estimate their model, so they based their estimates on a SR and

meta-analysis of case series for SBRT (Grutters 2010a). Costs are estimated from the health system perspective and based on the Dutch manual for cost research (Oostenbrink 2004). SBRT yielded 3.2 quality adjusted life years (QALYS) at a total health-care cost per patient of €13,871, and conventional EBRT yielded 2.05 QALYs at a cost per patient of €19,561. The authors acknowledge there is "considerable uncertainty" in their model.

Lanni (2011), a poor quality cost evaluation, estimated the effectiveness and costs of SBRT and conventional EBRT based on a poor quality cohort study of 86 patients with inoperable Stage 1 NSCLC treated at their hospital between 2002 and 2008. Overall 3-year survival was 71% for patients receiving SBRT and 42% for those receiving EBRT. Costs were based on average number of fractions used and billed charges based on current procedural terminology (CPT) codes. Expected reimbursement was estimated using the 2010 Medicare hospital-based Ambulatory Payment Classification and physician fee reimbursement rates for technical and professional components. The authors estimate the costs (charges) for EBRT (35 factions) to be $50,000 to $61,000 and SBRT (four fractions) to be $41,000 to $57,000.

Sher (2011), a poor quality economic analysis, uses a Markov model to represent changing health states and risk over time to estimate the costs and incremental cost-effectiveness ratios (ICER) of SBRT, radiofrequency ablation (RFA) and conventional EBRT for inoperable Stage 1 NSCLC. There was no comparative outcomes data on which to base probability estimates in their model, so they based their estimates on data from single case series. Costs are estimated from the 2009 Medicare payment schedules. No data were available that evaluated patient utilities after treatment with SBRT, EBRT, or RFA, so Sher (2011) used utility data for several health states associated with NSCLC in their model. The incremental cost-effectiveness of SBRT compared to conventional EBRT was $6,000 per QALY and was reported to range $10,200/QALY to $40,300/QALY in the one-way sensitivity analyses.

Overall Summary

The overall strength of evidence is very low based on three poor quality economic analyses. There is uncertainty about the comparative costs and incremental cost-effectiveness of SBRT versus conventional EBRT for inoperable early stage NSCLC. The costs (charges) for EBRT (35 factions) may be $50,000 to $61,000 and SBRT (four fractions) may be $41,000 to $57,000, and the incremental cost-effectiveness of SBRT compared to conventional EBRT may be $6,000 per QALY.

Findings – Non-Comparative Data

Abdomen (Adrenal Metastases, Colorectal, Liver, Pancreas)

In this section, colorectal cancer (anus, rectum, colon), cancers of the liver and pancreas, and adrenal metastases are summarized. Although the most appropriate comparator for these cancers may be surgery, we restricted our review to SBRT in comparison to conventional EBRT based on the overall objective of the review. There is limited evidence for all four cancers. No other cancers were identified for this section.

Adrenal Metastases

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Two poor quality case series (Casamassima 2012; Chawla 2009) reported on 78 patients with adrenal metastases from a variety of cancers including lung, liver, breast, melanoma and pancreas. Approximately 45% of patients had received chemotherapy and many had other treatments prior to SBRT.

Casamassima (2012) reported on 48 patients with a median age of 63 years who received 36 Gy in three fractions. Median follow-up was 16 months (range, 3 to 63 months) and median age was 62.7 years (range, 43 to 77). One- and 2-year actuarial survival rates were 40% and 14%, respectively. Casamassima (2012) states SBRT was "generally well tolerated."

Chawla (2009) reported on 30 patients with a mean age of 62 years who received Gy in four fractions to 50 Gy in 10 fractions with a median dose of 40 Gy. Median age was 61.8 years (range, 39.4 to 77.6). Twenty-four patients (80%) had at least a three month follow-up. One-year survival was 44%, and local control was 55%.

Overall Summary

Based on two poor quality case series, the overall strength of the evidence is very low and any conclusions about outcomes are uncertain. Because of the study design and variations in patient characteristics and prior treatment, any conclusions based on the study results may not provide a reliable estimate of the true outcomes. One-year survival rates may be about 40%.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

See KQ 1 for study descriptions of the two included poor quality case series (Casamassima 2012; Chawla 2009). No acute harms greater than Grade 2 were reported by either study. Casamassima (2012) reported one patient had Grade 2 adrenal insufficiency. Chawla (2009)

reported that mild fatigue and Grade 1 nausea was common among patients and that no patient developed Grade 2 acute toxicity. No late toxicities were reported.

Overall Summary

Based on two poor quality case series, the overall strength of the evidence is very low and any conclusions about harms are uncertain. Because of the study design and variations in patient characteristics and prior treatment, it is difficult to draw any conclusions, especially because neither study provides much information about toxicities.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Colorectal

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Two poor quality case series studies were identified (Hoyer 2006; Kang 2010). Hoyer (2006) reported on 64 patients with metastatic colorectal cancer. Median follow-up was 4.3 years (range, 0.2 to 6.3) and median age was 67 years (range, 62 to 81). Grade 3 or greater complications (7%) were reported in four patients. Grade 4 hepaticfailure (1.6%), Grade 3 duodenal ulceration (3.2%), Grade 3 colonic ulceration (1.6%), and Grade 2 or higher pain (28%), nausea (16%), diarrhea (6.6%) and skin effects 6.6%) were reported.

Kang (2010), a poor quality case series, reported on 59 patients with metastatic colon cancer. Median follow-up was 32 months (range, 9 to 80) and median age was 57 years (range, 57 to 83). Twenty-four 24 patients (41%) experienced Grade 1 to 2 toxicities of nausea, vomiting and musculoskeletal discomfort. Two (3%) Grade 4 complications were also reported.

Overall Summary

Based on two poor quality case series, there is very low overall strength of evidence that low grade complications (i.e., nausea, vomiting, pain) occur in 41% of patients and severe toxicities

(i.e., hepatic failure, duodenal and colonic ulceration) in 3% to 7% of patients. These conclusions about harms are uncertain and may not provide a reliable indication of the true harms.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on sub-populations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Liver

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

Two poor quality SRs (Tao 2012; Zamboglou 2012) were identified. Tao (2012) reported on 15 prospective clinical trials (n=499) where SBRT was used to treat primary and metastatic liver cancer. Most of the clinical trials were Phase I and II. The studies had no comparator. Median follow-up for all studies was 16 months (range 0.5 to 85). Patients had primary (n=158) and metastatic (n=341) tumors. Tao (2012) reported 1-year local control rates of 50% to 100% and 1-year OS rates of 33% to 100%.

Zamboglou (2012), a poor quality SR, included two pilot trials (n=40) that investigated SBRT for extrahepatic cholangiocarcinoma in the liver hilum. Follow-up time was not reported. One pilot study, Freiburg (2010), reported a median OS of 32.5 months, while Aarhus (2010) reported a median OS of greater than 10 months.

Subsequently Published Studies

Two fair quality (Andolino 2011; Shun 2008) and five poor quality (Chang 2011a; Katz 2007; Lee 2009; Rusthoven 2009; Tse 2008) case series studies were identified.

Andolino (2011), a fair quality case series, examined the records of 60 patients with hepatocellular carcinoma treated with SBRT. Median follow-up was 27 months. Actuarial 2-year local control, PFS and OS rates were 90%, 48%, and 67%, respectively.

Shun (2008), a fair quality case series, looked at QoL scores for 99 patients treated with SRS for liver cancer. Patients were followed weekly for six weeks following SRT. Mean age was 62.42 (standard deviation [SD] 12.6). Quality of life scores increased from 113.80 (SD 21.98) to 114.48 (SD 25.84) following treatment (p=0.746).

Chang (2011a), a poor quality case series, reported on SBRT treatment of 65 patients with liver metastases from colorectal cancer. Median follow-up was 1.2 years. Median age was 67 years (range, 39 to 87). Twelve-, 18- and 24-month OS rates were 72%, 55% and 38%.

Katz (2007), a poor quality case series, reported on SBRT treatment of 69 patients with liver metastases. Median follow-up was 14.5 months. Median age was 59.8 years (range, 35.6 to 87.7). Actuarial overall local control at 10 and 20 months was 76% and 57%. Median OS was 14.5 months, and actuarial OS at 10- and 20-months was 78% and 37%. Progression free survival was 46% at 6 months and 24% at 12 months.

Lee (2009), a poor quality case series, reported on 68 patients treated with SBRT for liver metastases. Median survival was 17.6 months (95% CI, 10.4-38.1 months). Eighteen-month survival rate was 47% (95% CI, 32%-61%). Median PFS was 3.9 months (95% CI, 3.4-7 months). Thirty-three patients had sustained objective tumor response: four patients (6%) had complete response, 29 patients (43%) had partial response, and 20 patients (30%) had stable disease. The 12-month local control rate was 71% (95% CI, 58-85%). Fifty-six patients (83.9%) developed recurrence.

Rusthoven (2009), a poor quality case series, looked at 47 patients treated with SBRT for liver metastases with a median follow-up of 16 months. Median age was 58 years (range, 0 to 236). Distant progression occurred in 39 patients (83%) at a median time interval of 6 months after SBRT (range, 2 to 53). Median distance PFS and median PFS were both 6.1 months. Median OS was 20.5 months. The 2-year OS rate was 30% (95% CI, 15.1% to 47.2%).

Tse (2008), a poor quality case series, reported on 41 patients treated with SBRT for liver cancer. Median follow-up was 17.6 months. Mean age was 62 years (range, 41 to 85).Median survival was 13.4 months (96% CI, 11.0-21.1 months). Overall tumor response rate was 49 % with 5% of patients achieving complete response and 44% partial response.

Overall Summary

The overall strength of evidence is very low. The following conclusions about outcomes are uncertain and may not be a reliable indicator of the true effects. Based on two poor quality systematic reviews of case series and seven additional case series, median overall survival for patients with liver metastases may range from 14.5 months to 32.5 months after SBRT and 13.4 months for patients with hepatocellular cancer.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

Two poor quality SRs (Tao 2012; Zamboglou 2012) were identified. Neither SR included studies with a comparator. See KQ1 for study summaries.

Tao (2012) reported a complications rate of 17% (73 events for 499 patients) including three deaths.

Zamboglou (2012) reported that in one of the two studies reviewed, six patients developed severe gastrointestinal ulcerations while three had duodenal stenosis. More details on the harms reported are available in Appendix E.

Subsequently Published Studies

Two fair quality (Andolino 2011; Shun 2008) and five poor quality (Chang 2011a; Katz 2007; Lee 2009; Rusthoven 2009; Tse 2008) case series reported on harms data.

Andolino (2011), a fair quality case series, found that 14 patients (23.3%) developed Grade 1 or 2 nonhematologic toxicities such as fatigue, nausea, right upper quadrant or chest wall pain. Grade 3 toxicities included liver enzymes or hyperbilirubinemia (15%), thrombocytopenia (3.3%), elevated INR (11.7%) and hypoalbuminemia (1.7%). One patient (1.7%) experienced Grade 4 thrombocytopenia and hyperbilirubinemia.

Shun (2008), a fair quality case series, reported on changes in liver function tests for 99 patients but reported no other toxicity rates. See Appendix E for details.

Chang (2011a), a poor quality case series, examined 65 patients. Short term complications included Grade 2 or greater GI toxicity in 11 patients (17%) and Grade 3 or greater elevated liver enzymes in two patients (3%). Late toxicities included Grade 2 small bowel ulcers in two patients (3%), Grade 3 gastritis in two patients (3%), Grade 3 elevated liver enzymes in two patients (3%) and persistent chest wall pain in two patients (3%). One patient (1.5%) experienced both gastritis and chest wall pain and one patient had both gastritis and elevated liver enzymes.

Katz (2007), a poor quality case series, reported on 69 patients with a median follow-up of 14.5 months. The study found 17 patients (25%) developed Grade 1 or 2 elevation of liver function tests. No Grade 3 or higher complications were reported.

Lee (2009), a poor quality case series, reported on 68 patients. Acute toxicities reported included Grade 3 transient thrombocytopenia (3%), thrombocytopenia requiring splenectomy (1%), Grade 3 liver enzymes (3%), and Grade 1 or 2 liver or chest wall pain (12%). Ten patients (15%) experienced Grade 1 or 2 gastritis and two patients (3%) reached Grade 3. Grade 1 to 2 lethargy occurred in 27 patients (40%) rising to Grade 3 in one patient (1%). Other acute toxicities included Grade 2 colitis in one patient, Grade 1 to 2 nausea (18%) and Grade 3 nausea (3%). Reported late toxicities included Grade 4 duodenal bleed (1%) and a Grade 4 (1%) and a Grade 5 small bowel obstruction (1%). Grade 2 non-traumatic rib fractures (3%), Grade 2 chest wall pain (1%) and Grade 2 dyspepsia (1%) were reported.

Rusthoven (2009), a poor quality case series, found very low toxicity rates in a population of 47 patients with a median follow-up of 16 months. At last follow-up, only one patient (2%) experienced Grade 3 toxicity. None of the patients who died before six months experienced treatment complications.

Tse (2008), a poor quality case series, looked at 41 patients. Acute toxicities included Grade 3 liver enzymes in 10 patients (24%), thrombocytopenia in one patient (2.4%) and nausea in three

patients (7.3%). Grade 1 pleural effusion occurred in three patients (7.3%), seven patients (17%) saw a decline in liver function from Child-Pugh A to B, and two patients (5%) experienced transient biliary obstruction. Late complications (not specified) occurred in two patients (5%).

Overall Summary

Based on two SRs of case series and seven additional case series, the overall strength of evidence is very low and any conclusions about harms are uncertain. Grade 1 to 2 complications (e.g., fatigue, nausea, gastritis, liver enzyme abnormalities) may occur in 15% to 25% of patients; and greater than Grade 3 complications (e.g., liver toxicity, colonic perforation or small bowel obstruction) may occur in 0% to 15% of patients and may rarely include death.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on sub-populations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Pancreas

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

One poor quality SR was identified (Zamboglou 2012). Zamboglou (2012a) reported on six studies (n=244) of SBRT treatment for pancreatic cancer. Two of the studies were pilots, two Phase I trials and two Phase II trials. Five of the studies showed promising results for local tumor control while one study did not. Results ranged from a median OS of 5.4 months and local control rate after 6 months of 57% (Aarhus 2005) to 6.4 months and 90% (Stanford 2004).

Subsequently Published Studies

One fair quality (Seo 2009) and three poor quality (Chang 2009a; Didolkar 2010; Rwigema 2011b) case series were identified. Seo (2009), a fair quality case series, reported on 30 pancreatic cancer patients treated with EBRT followed by a SBRT boost. Median OS was 14 months and the 1-year OS rate was 60%. Median time to progression was 10 months.

Chang (2009a), a poor quality case series, reported 6- and 12-month PFS rates of 26% and 9% in a sample of 77 patients. Six- and 12-month OS rates were 56% and 21%. Median survival duration from SBRT for entire group was 6.4 months, for locally advanced group 6.7 months and for metastatic group 4.7 months. Median follow-up was 6 months.

Didolkar (2010), a poor quality case series, reported on 85 patients treated with SRS for pancreatic cancer. Local tumor controlled was achieved in 78 patients (91.7%), a complete response in 10 patients (11.8%), partial response in 27 (31.7%) and stable disease in 41 (48.2%).

Distant disease progression occurred in 65 patients (76.5%). Overall median survival from time of diagnosis was 18.6 months and from SRS treatment 8.65 months. Of 31 patients with pain scores greater than or equal to four, 15 patients (48.4%) had complete pain relief lasting more than six months. Remaining 16 patients (51.6%) had relief of pain to lower scores following SRS.

Rwigema (2011b), a poor quality case series, reported on 71 patients treated with SBRT for pancreatic cancer. Median follow-up was 6 months. Median OS was 10.3 months. Six-month OS rates for adjuvant and locally advanced groups were 100% and 57.4%. One-year OS rates for the two groups were 81.8% and 30.2%, respectively. Of the 16 patients who reported pain, 13 patients (81.3%) reported complete pain relief after SBRT.

Overall Summary

The overall strength of evidence is very low and any conclusions about outcomes are uncertain. Based on one SR and four case series, median survival may range from 5.4 months to 18.6 months following SBRT treatment for pancreatic cancer. For patients with pain, almost half had complete relief of pain and the remainder had decreased pain after SBRT, based on 31 patients in one poor quality case series.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

Zamboglou (2012), a poor quality SR, reported varying levels of toxicity in six studies. One study found unacceptable levels of toxicity (Aarhus 2005) with 100% of patients experiencing Grade 2 nausea. Other five studies found comparatively mild side effects. Serious harms included small bowel perforation, serious mucositis, and stomach and bowel ulcerations.

Subsequently Published Studies

One fair quality (Seo 2009) and three poor quality case series (Chang 2009a; Didolkar 2010; Rwigema 2011b) were identified. Seo (2009), a fair quality case series, reported on 30 patients treated with EBRT followed by a SBRT boost for pancreatic cancer. Twenty out of 30 patients (67%) developed acute nausea, vomiting and/or pain and one patient (3%) developed a Grade 4 duodenal obstruction three months after the SBRT boost.

Chang (2009a), a poor quality case series, reported on toxicity in 77 patients. Acute complications included Grade 2 small bowel ulcer (3%), Grade 3 gastric ulcer (1%), and Grade 1 pain (1%). Late toxicities included Grade 2 small bowel ulcers (4%), Grade 3 gastric (4%), a Grade three duodenal stricture (1%), Grade 3 biliary stricture (3%) and Grade 4 small bowel perforation (1%).

Didolkar (2010), a poor quality case series, evaluated 85 patients. Multiple Grades 3 or 4 GI toxicities were reported in 22.3% of patients, including duodenitis (14.1%), gastritis (12.9%) and diarrhea (3.5%).

Rwigema (2011b), a poor quality case series, evaluated 71 patients. Thirty-one patients (43.7%) reported that they experienced some toxicity from treatment. Grade 1 acute toxicities occurred

in 26% of patients including diarrhea (6%), fatigue, abdominal pain and vomiting (4%), and weight loss and nausea (3%). Grade 2 acute toxicity was experienced by 11.3% of patients, including fatigue and nausea (4%) and abdominal pain and weight loss (1%). Acute Grade 3 toxicity occurred in 4.2% of patients, including nausea (1%), abdominal pain (1%) and gastroparesis (1%). Late toxicities were all Grade 1. Abdominal pain occurred in one patient (1%) and weight loss in two patients (3%).

Rates of harms of Grade 3 or higher ranged from Seo (2009) at 3.3% to Didolkar (2010) with 22.3%.

Overall Summary

Based on one SR of case series and four case series, the overall strength of evidence is very low and any conclusions about harms are uncertain. Grade 1 to 2 complications occur in most patients and may be as high as 100%. Grade 3 or higher complication rates vary from about 3% to 22%.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

A fair quality cost-effectiveness study (Murphy 2012) used a Markov model to estimate incremental cost effectiveness ratios (ICER) for various forms of radiation therapy along with gemcitabine chemotherapy for treatment of locally advanced pancreatic cancer. In the model, all patients received gemcitabine; comparisons were made between gemcitabine plus EBRT, IMRT or SBRT compared to gemcitabine alone and compared to one another. Costs were calculated using regional Medicare fee schedules for Santa Clara County, California in 2009 US dollars. Clinical effectiveness was estimated using expert opinion. The ICER for SBRT plus gemcitabine compared to gemcitabine alone was $69,500/QALY. The ICER for EBRT plus gemcitabine compared to gemcitabine alone was $126,800. Murphy (2012) concludes that the ICER for SBRT plus gemcitabine is within what society currently considers cost effective.

Overall Summary

The overall strength of evidence is very low and any conclusions about cost-effectiveness are uncertain. One poor quality cost-effectiveness modeling study calculated that SBRT plus gemcitabine had an ICER of $69,500/QALY compared to gemcitabine alone.

Central Nervous System – Primary Tumors

In this section, evidence on intracranial or central nervous system (CNS) tumors is summarized by each type of tumor. These are presented in alphabetical order: astrocytoma, ependymoma,

meningioma, multiple brain tumors, neurocytoma, and schwannoma. *Malignancies are discussed as they were reported in literature. For instance, although astrocytomas and glioblastoma multiforme are types of gliomas, they are discussed in separate sections as reported by individual studies.* For many primary and metastatic brain and spine tumors, the treatment of choice may be surgical removal not radiation therapy. However, the objective of the report is to evaluate the evidence base for conventional EBRT, referred to as WBRT when used for brain metastases, compared to the newer radiation techniques, SRS and SRT. The report objective is not intended to evaluate all treatments for a particular tumor. There are few comparative studies for many of the CNS tumors with the exceptions of brain metastases.

Astrocytoma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Three poor quality case series were published since 2002 (Hadjipanayis 2003; Plathow 2003; Szeifert 2007) including 266 patients with supratentorial astrocytomas.

Plathow (2003), a poor quality case series, reported on 143 patients with World Health Organization (WHO) Grade 2 astrocytomas who were treated with fractionated stereotactic radiation therapy (FRST). Median age was 40.5 years (range, 18 to 86), 34% had KPS scores greater than 80, 39% had recurrent tumor, 28% had a subtotal resection of the tumor, and 60% received a total SRS dose great than 55 Gy. Overall survival was 58% at five years and 50% at eight years.

Hadjipanayis (2003), a poor quality case series, reported on 49 patients with recurrent or unresectable low-grade astrocytomas: 37 (median age 14 years) with pilocytic astrocytomas and 12 (median age 25 years) with WHO Grade 2 fibrillary astrocytomas. Results were not stratified by age. Stereotactic radiosurgery was used as part of a multimodal treatment plan. At a median of 32 months, 92% of patients were alive.

Szeifert (2007), a poor quality case series, reported on 74 patients with supratentorial astrocytoma or oligoastrocytoma. Mean age was 34.4 years (range, 4 to 84) and KPS was 60 to 100. Results were not stratified by age. Tumors were Grade 1 (n=15), Grade 2 (n=17), Grades 3 and 4 (n=42) with some patients having had prior surgical resection. Median survival was 14 months (range, 2 to 58 months) for patients with Grade 3 and 4 tumors and not stated for Grade 1 and 2 tumors.

Overall Summary

Based on three poor quality case series, the overall strength of the evidence is very low. Because of variations in patient characteristics and prior treatment, any conclusions about

outcomes are uncertain. Based on two of the poor quality case series involving 143 patients with WHO Grade 2 astrocytomas, 5-year survival with SRS treatment may be about 58% and median survival at 32 months may be 92%. For WHO Grade 3 and 4 tumors, median survival may be 14 months.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews
No SRs were identified.

Subsequently Published Studies
See KQ 1 for descriptions of the three included poor quality case series (Hadjipanayis 2003; Plathow 2003; Szeifert 2007). Toxicities were mild with Grade 3 acute side effects occurring in about 3% of patients (Plathow 2003). Hadjipanayis (2003) reported two patients had transient neurologic worsening, and there were no patients with permanent procedure related morbidity or mortality. Sziefert (2007) reported at least five patients experienced neurologic adverse events. For all three case series, late side effects (greater than 6 months) were predominately hearing loss (4%) and tiredness (2%) and these were all less than Grade 3.

Overall Summary
Based on three poor quality case series, the overall strength of the evidence is very low for harms and any conclusions about harms are uncertain. Acute Grade 3 adverse events may occur in 3% and late adverse events in 6% of patients. Patients may experience neurologic adverse events.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Ependymoma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews
No SRs were identified.

Subsequently Published Studies
Two fair quality case series reported on 60 patients with ependymomas (Kano 2009b; Kano 2010). Kano (2009b) reported on 39 patients with a median age of 23 years (range, 3 to 71). Results were not stratified by age. All patients had prior surgical resection of their

ependymoma, and 36% had received chemotherapy. Patients received a median margin dose of 15.0 Gy (range, 10 to 22). Overall survival rates after SRS were 60% at one year, 36% at three years, and 32% at five years.

Kano (2010) published a fair quality retrospective case series of *21 children*, mean age 7 years (range, 3 to 17), with ependymomas. All had resection and radiation treatment and 11 had adjuvant chemotherapy prior to SRS. The median dose of SRS to the tumor margin was 15 Gy (range, 9 to 22). Median survival after SRS was 27.6 months (95% CI, 12 to 36), and OS was 85% at one year, 53% at two years, and 23% at three years.

Overall Summary

Overall strength of the evidence is very low based on two fair quality case series involving 60 children and adults. There is uncertainty in any estimate of survival, which was reported as an overall 1-year survival of about 50% to 60%.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

See KQ 1 for a description of the two included poor quality case series (Kano 2009b; Kano 2010). Kano (2009b) reported that adverse radiation toxicity occurred in 3 (8%) patients including two patients with tumor necrosis and one with facial paresis. Kano (2010) reported that two patients (9.5%) had adverse radiation effects including radiation necrosis and facial paresis.

Overall Summary

Overall strength of the evidence is very low based on two poor quality case series involving 60 children and adults. There is uncertainty in any estimate of harms, which were reported as adverse radiation effects occurring in about 8% to 9% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified except for the one study that included only children (Kano 2010) described in KQ1.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies of cost or cost-effectiveness were identified.

Meningioma

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Four fair quality (Bledsoe 2010; Hasegawa 2011; Iwai 2008; Kondziolka 2008) and 24 poor quality (see Appendix E) case series were identified. The case series ranged in size from 30 to 4565 patients, and reported adverse effects of SRS. Six of the studies included children and adolescents in their patient populations (Becker 2002; Chang 2003; DiBiase 2004; Han 2008; Kreil 2005; Lee 2002); however results were not stratified by age. The largest study (Santacroce 2012), a poor quality case, series reported on 4565 patients from 15 centers treated with GKRS and having a minimum of five years follow-up. They report an overall complication rate of 13%, with temporary morbidity of 6% and permanent morbidity of 7%. Four treatment related deaths were reported.

Adverse effects reported by the case series ranged in type and frequency. Highest reported adverse effects included erythema/radiodermatitis (21 to 33%), alopecia (73 to 87%), new endocrine deficits (8 to 14%), nausea (13%), asymptomatic post-radiosurgery edema (1 to 22%), and symptomatic post-radiosurgery edema (2 to 17%). Reported instances of headache, vertigo, and motor weakness ranged from 1 to 12 %. Asymptomatic cysts, internal carotid artery “issues”, cerebral infarction, seizure, hemiparesis, cranial nerve dysfunction, diplopia/visual field defected, ataxia, hearing loss, facial numbness, increased intracranial pressure requiring shunting, radiation necrosis, cerebellar symptoms, conjunctivitis, cataract, memory disturbance, and hyperlacrimation were reported in 1 to 6% of patients.

Overall Summary

Based on 28 case series, the overall strength of the evidence is very low for harms, and the following conclusions are uncertain. Erythema, alopecia and post-radiation edema are all common adverse effects. Patients treated with GKRS had an overall complication rate of 13%, with temporary morbidity of 6% and permanent morbidity of 7% in one large case series.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Three fair quality case series (Bledsoe 2010; Hasegawa 2011; Kondziolka 2008) and five poor quality case series (Chang 2003; Flickinger 2003; Lee 2002; Metellus 2005; Patil 2008) were identified.

Bledsoe (2010), a fair quality case series (n=116) of large volume meningiomas treated with GKRS found that the only factors significantly associated with higher complication rates were male gender and supratentorial location of tumor.

Hasegawa (2011), a fair quality case series (n=112) of convexity, parasagittal and falcine meningiomas treated with GKRS found that those factors that significantly increased the likelihood of radiation-induced edema were a marginal dose of ≤ 14 Gy and having fewer prior treatments (primary treatment with GKRS has higher risk than adjuvant treatment). The authors speculate that patients who received a lower marginal dose had larger tumors, which in turn have a higher risk of edema.

Kondziolka (2008), a fair quality case series (n=972) of primary and recurrent meningiomas treated with GKRS reported that the only independent predictor of complications was tumor volume.

Chang (2003), a poor quality case series (n=179) of benign meningiomas treated with GKRS found that the only factor associated with a higher rate of peritumorous imaging changes was cerebral hemispheric tumor location compared to any other location.

Flickinger (2003), a poor quality case series (n=219) of meningioma treated with GKRS found that the only factor that was significantly associated with a higher rate of post-RS sequelae was the use of CT targeting with the associated higher radiation doses, compared to stereotactic MRI and the associated lower radiation doses.

Lee (2002), a poor quality case series (n=159) of cavernous sinus meningiomas treated with GKRS reported that the rate of adverse radiation effects is lower in patients treated after 1995 than those treated from 1987-1995 (2.5% vs. 10%).

Metellus (2005), a poor quality case series, reported radiologic response was not affected by patient age, gender, or tumor volume, type or grade.

Patil (2008), a poor quality case series (n=102) of supratentorial meningiomas treated with SRS reported that a parasagittal tumor location increases the likelihood of symptomatic edema by four times compared to non-midline locations.

Overall Summary

Overall strength of the evidence is very low for differences in effectiveness and harms in different subpopulations. Based eight case series, the factors that may result in differences include tumor volume, tumor margin dose greater than 14 Gy, male gender, supratentorial, hemispheric or parasagittal tumor location, higher radiation doses, marginal dose of less than

or equal to 14 Gy and having fewer prior treatments. However, there is uncertainty in whether or not these factors are truly important.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Systematic Reviews
No SRs were identified.

Subsequently Published Studies
One good quality cost analysis (Tan 2011) compared initial treatment costs as well as first year follow-up costs of microsurgery, linear accelerator (LINAC) radiosurgery, and GKRS in meningioma patients treated in the Netherlands. A total of 59 patients were included (microsurgery (n=18), LINAC radiosurgery (n=15), GKRS (n=26)). Initial treatment costs were €12,288 for microsurgery, €1,547 for LINAC radiosurgery, and €2,412 for GKRS. Higher initial treatment costs for microsurgery were predominantly due to inpatient stay (€5,321) and indirect costs (€4,350). LINAC and gamma knife radiosurgery were equally expensive when equipment was valued per treatment (€2,198 and €2,412, respectively). Follow-up costs were slightly, but not significantly, higher for microsurgery compared with LINAC and GKRS. This study was funded by the GKRS manufacturer, and has limited applicability to the US setting.

Overall Summary
Overall strength of the evidence is very low, and limited to a poor quality cost analysis with potential funding bias and poor applicability to the US setting. Conclusions regarding cost-effectiveness in the US setting cannot be drawn.

Multiple CNS Tumors

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews
No SRs were identified.

Subsequently Published Studies
Between 2002 and 2012, 14 case series were published that described, within a single report, patients with a wide variety of tumors including pituitary adenomas, mixed germ cell tumors, brain metastases, schwannomas, neurofibromas, hemangioblastomas and other rare tumors. Four case series were fair quality (Davidson 2009; Koytko 2006; Rowe 2007b; Stafford 2003) and the remainder were poor quality (Adler 2006; Chao 2012; Cheshier 2007; Coppa 2009; Ganz 2009a; Krishnan 2006; Lunsford 2007; Roos 2006; Rowe 2007b; Xu 2010). Eight of the studies included children and adolescents in their patient population (Adler 2006; Coppa 2009; Davidson 2009; Krishan 2005; Rowe 2007a; Rowe 2007b; Stafford 2003; Xu 2010); however results were not stratified by age. For some of the studies, patients treated with SRS may have been pooled across various tumors because of the location of the tumor: adjacent to the optic apparatus (Adler 2006; Stafford 2003), base of the skull (Coppa 2009; Krishnan 2005; Lundsford

2007), or in the brain stem (Davidson 2009). Because of the variability in tumors, dosing of SRS, and reporting of outcomes and harms, these studies are not summarized. The details of each study are provided in Appendix F.

Overall Summary

Fourteen case series provide an overall very low strength of evidence. Because of the variability in tumors, dosing of SRS, and reporting of outcomes and harms, the studies are not summarized. The details of each study are provided in Appendix F.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Fourteen case series were identified. See KQ 1 for descriptions and quality ratings of included studies. Details of each study are provided in Appendix F.

Overall Summary

Fourteen case series provide an overall very low strength of evidence. Because of the variability in tumors, dosing of SRS, and reporting of outcomes and harms, we did not attempt to summarize these studies. The details of each study are provided in Appendix F.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies of cost or cost-effectiveness were identified.

Neurocytoma

Neurocytomas are well-differentiated slow growing tumors with primarily a neuronal differentiation. They usually occur in the ventricles of the brain (central neurocytoma) and occasionally in the brain parenchyma or spinal cord (extraventricular neurocytoma). Patients present with symptoms of increased intracranial pressure from hydrpcephalus including headache, cognitive impairment, difficulty with balance, and visual impairment. The standard treatment is complete surgical resection. Adjuvant radiation therapy is often used for residual tumor if the resection is incomplete.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

Rades (2006), a poor quality comparative SR of case reports/case series, reported on patients with typical neurocytomas who did not have complete resection of their tumor and were followed for at least 12 months. Rades (2006) grouped the 121 cases by treatment following incomplete resection: incomplete resection alone (ITR) (n=59), ITR and conventional radiation therapy (CRT) (n=41), or ITR and SRS (n=21). Median follow-up was 42 months (range, 12 to 158), and 56% were male. The mean age of patient cases was 27 years (range, 3 to 76) and results were not stratified by age. Median CRT dose was 54 Gy (range, 43 to 60) and median total SRS dose was 15 Gy (range, 10 to 24). Overall 5-year survival did not differ significantly between any of the treatment groups (93% for ICT alone, 100% for ITR+CRT, and 100% for ITR+SRS, p values were $\geq$ 0.13 for pair-wise comparisons). The rates of 5-year local tumor control differed significantly between ITR alone (51%) and ITR+CRT (87%, p =0.001) and ITR alone and ITR+SRS (100%, p = 0.004). However, there was no statistically significant difference between ITR+CRT compared to ITR+SRS (87% vs. 100%, respectively, p = 0.45).

Subsequently Published Studies

No studies were identified.

Overall Summary

The overall strength of the evidence is very low and based solely on a single comparison of cases and case series stratified by conventional EBRT and SRS. These cases suggest that in patients who do not have complete surgical resection, conventional EBRT and SRS may have similar overall 5-year survival and local tumor control and that 5-year survival is better than incomplete tumor resection alone. However, these conclusions are uncertain.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

Rades (2006) is a poor quality comparative SR of case reports/case series of patients with typical neurocytomas who did not have complete resection of their tumor and were followed for at least 12 months. See KQ1 for study description. No data were provided on harms.

Subsequently Published Studies

Kim (2007), a poor quality case series, retrospectively reviewed 13 patients with neurocytoma who were treated with SRS, six received SRS as the primary treatment and seven as secondary treatment after incomplete resection. Follow-up MRIs over a median of 61 months (range, 6 to 96) did not demonstrate parenchymal changes or secondary malignancies.

Overall Summary

Based on one poor quality SR of case reports/case series and one addition case series, the overall strength of the evidence is very low. Very little data is available for harms. One case series of 13 patients suggests that parenchymal changes and secondary malignancies were not found on follow-up MRIs.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Schwannoma (Acoustic Neuroma)

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Two cohort studies (Collen 2011; Coombs 2010) were identified, both comparing SRS with fractionated SRT. For the purposes of this report these studies provide case series type of data on SRS and SRT. Collen (2011), a poor quality study, examined 119 patients, 78 treated with SRS (median dose 12.5 Gy) and 41 treated with fractionated SRT (10 fractions of 3 to 4 Gy or 25 fractions of 2 Gy). There was no significant difference between treatment types in local control, with the overall local control rate being 95%. For hearing preservation, although there was no statically significant difference between groups, the rate for SRS was 82% and the rate for fractionated SRT was 59%. The mean tumor volume was significantly smaller in the SRS group (1.7 ml vs. 6.3 ml), and the analysis did not take this into account.

Combs (2010) was a poor quality study of 202 patients with vestibular schwannoma treated with either fractionated SRT (n=172) or SRS (n=30). Local control was not statistically different for both groups. The radiation dose for the SRS group significantly influenced hearing preservation rates, with those treated with less than or equal to 13 Gy having a higher probability of hearing preservation than those treated with greater than 13 Gy, and the same probability as those treated with fractionated SRT.

Overall Summary

The overall strength of the evidence is very low, consisting of two poor quality cohort studies that provide case series type of data for the purposes of this report. Local control may range from 86% to 100% and hearing preservation from 59% to 100% with hearing preservation likely being dependent on the tumor volume.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

One poor quality SR was identified (Sughrue 2009). Sughrue (2009) included 63 studies and 5631 patients with vestibular schwannoma who were treated with GKRS. There was no comparison group, and the purpose of the review was to report harms. Results were examined by doses less than 13 Gy and greater than 13 y. Complication including new cranial nerve neuropathy (non-VII or VIII) (2.4% - primarily cranial nerve V), hydrocephalus (0.85% - 75% requiring shunt placement), vertigo (1.5%), and tinnitus (0.4%) were reported.

Doses less than 13 Gy were associated with a significantly decreased likelihood of non-VII/VIII cranial neuropathy and requiring a shunt for treatment of hydrocephalus, but an increased likelihood of vertigo and tinnitus.

Subsequently Published Studies

Two poor quality cohort study (Collen 2011; Combs 2010), and 34 case series were identified.

Collen (2011), a poor quality cohort study as described above, reported on treatment-related cranial nerve toxicity. The rate of radiation-induced facial nerve damage was 16% for SRS and 3% for fractionated SRT. The 5-year facial nerve function preservation was 83% in SRS group and 97% in fractionated SRT group, which was statistically significant. Other factors that predicted facial nerve damage included prior surgery, tumor volume and Koos tumor grading classification. However, mean tumor volume was significantly smaller in the SRS group (1.7 ml vs. 6.3 ml), making it difficult to draw conclusions about differences in harms.

Combs (2010), a poor quality cohort study as described above, reported that patients treated with SRS doses of less than or equal to 13 Gy had cranial nerve toxicity that was comparable to that of the fractionated SRT group, while those treated with greater than 13 Gy had higher rates of cranial nerve dysfunction (number of patients and percentages not provided).

Thirty-four subsequent case series described harms associated with treatment of schwannomas. Twenty-nine studies reported on SRS while four reported on SRT, and one included both treatments. Follow up ranged from six months to 16 years. Five of the studies included adolescents in their patient populations (Chung 2005; Lobato-Polo 2009; Mathieiu 2007; Sawamura 2003; Showalter 2008); however results were not stratified by age. For SRS, outcomes of hearing loss ranged from 18% to 59%, vertigo ranged from 7% to 13%, tinnitus ranged from 4% to 58%, new facial nerve dysfunction ranged from 0% to 36%, tumor progression ranged from 2% to 7%, new trigeminal nerve dysfunction ranged from 0% to 11%, hydrocephalus requiring shunt ranged from 1% to 25%, additional surgery required ranged from 0% to 15%, tumor or treatment related to mortality ranged from 0% to 1%, and new malignancy was reported by one study in 2% of patients.

For SRT, outcomes of hearing loss after surgery was reported by one study as 17%, tinnitus ranged from 4% to 26%, new facial nerve dysfunction ranged from 2% to 4%, new trigeminal nerve dysfunction ranged from 2 to 13%, hydrocephalus requiring shunt ranged from 0% to 12%, and new malignancy was reported by one study in 2% of patients.

Other miscellaneous adverse effects include anxiety, syncope, dysequilibrium, loosening of stereotactic frame, groin hematoma, acute coronary episode, headache, seizures, fatigue, nausea, vomiting.

Acute toxicities of SRT were reported to include fatigue (6% to 45%), nausea (8% to 43%), headache (2% to 20%), and vomiting (5%).

Overall Summary

The overall strength of evidence is very low, consisting of one SR of case series, two poor quality cohort studies and a large number of case series. Hearing loss may range 17% to 59%, hydrocephalus requiring a shunt 1% to 25%, new malignancies 2%, and new cranial nerve neuropathies 0% to 36%. Conclusions cannot be drawn concerning the relative harms of SRS and hypofractionated SRT, although hypofractionated SRT may be associated with less harm than SRS (new cranial neuropathy or malignancy, hydrocephalus). SRS doses less than 13 Gy may be associated with a decreased likelihood of cranial neuropathy and hydrocephalus, but an increased likelihood of vertigo and tinnitus.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

One poor quality cohort study (Combs 2010) and two poor quality case series (Mandl 2010; Rowe 2008) were identified.

Combs (2010), a poor quality cohort study as described above, reported that hearing preservation was significantly less likely in patients who also had neurofibromatosis (numbers of patients or percentages not provided).

Mandl (2010), a poor quality case series, addressed patients with large (greater than 3.0 cm) vestibular schwannoma. Twenty-nine patients were treated with either fractionated SRT (n=21) or SRS (n=8). The overall (transient and permanent) cranial nerve neuropathy percentages were 36% for the trigeminal nerve, 44% for the facial nerve, and 63% for the cochlear nerve.

Rowe (2008), a poor quality case series, reported exclusively on schwannomas in patients with neurofibromatosis who were treated with radiosurgery (n=118). They report outcomes significantly worse than for spontaneously developing schwannomas, with only 50% of patients being well controlled after eight years follow up, and only 40% maintaining functional hearing after three years follow-up. Two malignancies were reported in this series of 122 tumors (n=92).

Overall Summary

Based on one poor quality cohort study and two poor quality case series, the overall strength of the evidence is very low, and too limited to draw conclusions, although patients with

neurofibromatosis who develop schwannomas may have worse outcomes than patients without neurofibromatosis.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Head and Neck

In this section, cancer of the glomus jugulare and ocular melanoma are summarized. There is limited evidence for all three cancers. No other cancers were identified for this section.

Glomus jugulare

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

One fair quality SR, Guss (2011), was identified that evaluated 19 case series with a total of 355 participants who received either Gamma Knife or linear accelerator-based radiosurgery. Follow-up ranged from 10 to 60 months. Thirteen studies reported on harms. Seventeen patients experienced transient toxicities such as dysphagia, low grade nausea or imbalance. Thirty-three patients experienced more severe toxicities such as hearing loss, vertigo and facial palsy. Grades for these toxicities were not reported. A complete list of reported toxicities is in Appendix E.

Subsequently Published Studies

No subsequently published studies were identified.

Overall Summary

Based on 13 case series summarized in one SR, there is very low strength of evidence overall, and any conclusions are uncertain. Transient (e.g., dysphagia, nausea or imbalance) toxicities may occur in 5% and severe toxicities (e.g., hearing loss, vertigo, facial palsy) may occur 9% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Ocular

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Four poor quality (Dieckmann 2007; Emara 2004; Krema 2009; Somani 2009) and three fair quality (Al-Wassia 2011; Modorati 2009; Muller 2009) case series were identified.

Al-Wassia (2011), a fair quality case series, reported on 50 patients treated with SRT for choroidal melanoma. Median follow-up time was 29 months. Actuarial complication rate at two years and five years was 9.3% and 46.9%. Complications included dry eye, neovascular glaucoma, optic neuropathy, radiation retinopathy, optic neuritis and cataract. Two patients (4%) required enucleation due to treatment complications.

Modorati (2009), a fair quality case series, examined 78 patients with uveal melanoma treated with SRT. The median age was 64 and the median follow-up time was 31.3 months. Modorati (2009) reported few acute complications with the most frequent being minor cutaneous bleeding and subconjunctival hemorrhage due to sutures. Subsequent complications included exudative retinopathy, neovascular glaucoma, vitreous hemorrhage and cataract. Four patients required enucleation due to complications.

Muller (2009), a fair quality case series, looked at 72 uveal melanoma patients treated with SRT to determine if a dose-volume relationship existed between a radiated lacrimal gland and the development of dry-eye syndrome. 17 patients (24%) developed Schirmer test results of less than 10mm at six months following treatment and nine patients (13%) developed DES.

Dieckmann (2007), a poor quality case series, reported on 158 patients treated with SRT for uveal melanoma. Median follow-up time was 33.4 months. Acute side effects recorded included bleopharoconjunctivitis in eight patients (5%), cornea-epithel-defects in five patients (3%), epitheliolysis in eight patients (5%), and madarosis in nine patients (6%.) Long-term side effects included opticopathy in 65 patients (41%), retinopathy in 70 patients (44%), and neovascular glaucoma in 23 patients (15%). 30 of 127 patients (23%) had newly developed cataracts. Twenty-one patients (13%) required enucleation due to treatment side effects.

Emara (2004), a poor quality case series, reported on 28 patients treated with SRT for choroidal melanoma. Median age was 62 years and the median follow-up time was 18 months. Harms incidence at 18-months included cataracts in 29% of patients, tumor vasculopathy in 45%, radiation retinopathy in 30%, optic neuropathy in 37%, and neovascular glaucoma in 20%. Two patients (7%) required enucleation due to complications from treatment.

Krema (2009), a poor quality case series, looked at 64 patients with choroidal melanoma treated with SRT. The median follow-up time was 37 months. Actuarial rates of complications at 37 months included neovascular glaucoma in 27 patients (42%), radiation cataract in 34 patients (53%), retinopathy in 52 patients (81%), optic neuropathy in 41 patients (64%), tumor vasculopathy in 51 patients (80%), vitreous hemorrhage in 21 patients (33%), and worsening of retinal detachment in nine patients (14%). Six patients (9%) required enucleation due to the development of neovascular glaucoma.

Somani (2009), a poor quality case series, reported on 64 patients treated with SRT for choroidal melanoma. Median follow-up time was 26 months. Somani (2009) found complication rates at 26 months ranged from 14% for worsening of retinal detachment to 83% for tumor vasculopathy. Visual acuity significantly declined after radiation therapy ($p < 0.0001$). Four patients required enucleation for painful neovascular glaucoma. Details on this and other studies can be found in Appendix E.

Overall Summary

Based on seven case series, the overall strength of evidence is very low and any conclusions on harms are very uncertain. However, these studies suggest that high rates of significant toxicities including dry eye syndrome, retinopathy, optic neuropathy, neovascular glaucoma, and cataracts may occur. Most concerning is the possibility that between 4% and 13% of patients may require enucleation due to painful neovascular glaucoma and other complications.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Prostate

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

No comparative studies were identified.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews
No SRs were identified.

Subsequently Published Studies
Four poor quality case series were identified (Friedland 2009; Katz 2010; King 2012; Townsend 2011). Friedland (2009) (n=112) reported that mean urinary obstruction, rectal assessment and sexual health inventory scores all worsened during treatment but returned to baseline within one to four months post SBRT. Seven patients (6.3%) experienced urinary obstruction during first month after SBRT, with one patient (0.9%) requiring a transurethral resection of the prostate immediately after treatment. One patient (0.9%) experienced Grade 3 rectal bleeding. Maintenance of erectile function occurred in 82%, 81% and 82% of patients at one, two and three years post treatment. Median follow-up was 24 months.

Katz (2010), a poor quality case series, found that among 304 patients (mean age 69) with a median follow-up of 17 months, bowel and urinary QOL scores decreased after treatment and then returned to baseline values. Sexual QOL scores showed overall reduction of 10% at median of 18 month follow-up. Eighty seven percent of patients maintained potency with or without medication. Acute Grade 1 GU toxicity was reported in 226 patients (74.6%) and Grade 2 in 14 patients (4.6%). Two hundred and twenty-seven patients (74.9%) experienced acute Grade 1 GI toxicity and 11 patients (3.6%) had Grade 2. No Grade 3 or 4 acute toxicities were reported. Late Grade 1 GU toxicity was experienced by 12 patients (4.7%) and Grade 2 by 13 (5.1%). Thirteen patients (5.1%) experienced late Grade 1 GI toxicity and 6 patients (2.4%) Grade 2. Patients receiving higher treatment doses were slightly more likely to experience Grade 2 late toxicities.

King (2012), a poor quality case series of 67 patients with a median follow-up of 2.7 years, reported late Grade 1 GU toxicity in 13 patients (23%), Grade 2 in three patients (5%) and Grade 3 in two patients (3.5%). Late Grade 1 GI toxicity occurred in eight patients (14%) and Grade 2 in one patient (2%). Every other day treatment resulted in lower frequency of Grade 1 to 2 GU toxicity than daily treatment (17% vs. 56%, p=0.007) as well as less frequent Grade 1 to 2 GI toxicity (5% vs. 44%, p=0.001.)

Townsend (2011), a poor quality case series, examined 48 patients with a median follow-up of 11.5 weeks and reported 26 patients (54%) experienced acute Grade 1 GU toxicities. Five patients (10%) had Grade 2 and four patients (8%) had Grade 3. Grade 3 toxicities included frequency/nocturia, retention and dysuria. Only five patients (10%) experienced Grade 1 GI toxicity of diarrhea. No late toxicities were reported.

Overall Summary
Based on four poor quality case series, the overall strength of evidence is very low for harms. Reported QoL scores may decline and later returned to baseline, except for sexual QoL score which remained low in about 10% of men. Acute gastrourinary (GU) complications (i.e., urinary frequency, nocturia, dysuria, urinary retention) tend to be mild but Grade 1 GU toxicities may occur in up to 75% of men and Grade 2 toxicities in 2% to 4%. Similar mild severity and low rates of acute gastrointestinal (GI) complications (diarrhea, rectal pain) may occur. Late GU

toxicities were mostly mild and occurred in 9% to 10% of patients but may be as high as 28%. Late GI toxicities may also be mild and occur in about 5% to 8% of men.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on cost or cost-effectiveness were identified.

Spine

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

One fair quality SR was identified (Gerszten 2009). Gerszten (2009) reported on 29 case series of SBRT treatment of spinal tumors. Although many of the 29 studies were labeled as cohort studies by Gerszten (2009), most of these appear to be small feasibility studies and did not provide comparative data. Therefore, they will be classified as case series using study design criteria that we applied to subsequent studies. These studies found that radiosurgery was highly effective at decreasing pain associated with symptomatic spinal metastasis regardless of prior treatment with EBRT. Overall the reported improvement rates averaged 85%. Local control rates averaged 90% and 42 to 90% of patients demonstrated improvement in progressive neurologic defects.

Subsequently Published Studies

Six fair quality (Garg 2011; Nelson 2009; Nikolajek 2011; Tsai 2009; Wang 2012; Wowra 2008) and five poor quality (Ahmed 2012; Gagnon 2009; Gerszten 2006; Gibbs 2007; Mahadevan 2011) case series were identified.

Garg (2011), a fair quality case series, reported on 59 patients treated with SBRT after previous EBRT for spinal tumors. Mean follow-up was 17.6 months. Actuarial 1-year local PFS was 76% and actuarial 1- year OS was also 76%. Median survival time was 22.5 months. Pain reduction in patients from levels greater than or equal to level 4 to less than or equal to level 3 was significant at one month (p=0.07), three months (p=0.04) and six months (p=0.03.)

Nelson (2009), a fair quality case series, looked at 32 patients treated with SBRT for spinal months. Median follow up was seven months for all patients and 8.2 months for survivors. Actuarial 1-year overall survival was 13.5 months.

Nikolajek (2011), a fair quality case series, examined 54 patients treated with Cyberknife radiosurgery. Thirteen patients had primary spinal tumors previously treated with radiotherapy and 41 patients had spinal metastases. Patient ages ranged from 17 to 82 years; results were

not stratified by age. Median follow-up was not reported. Local failure occurred in nine patients (12.9%). Actuarial rate of freedom from local failure at 6, 12 and 18 months was 93%, 88% and 85% respectively. Median survival after SRS was 16.2 months and after initial radiotherapy 42 months.

Tsai (2009), a fair quality case series, reported on 69 patients treated with Cyberknife radiosurgery for spinal metastases. Three patients (4.3%) experienced local treatment failure.

Wang (2012), a fair quality case series, reported on 149 patients with spinal metastases that received treatment of SBRT. Median follow-up was 15.9 months and median age was 58 years (range, 20 to 88). Median OS was 23 months (SD 17.1). Reported rates of 1- and 2-year actuarial survival were 68.5% (95% CI, 60.1 to 75.4) and 46.4% (95% CI, 37.8 to 54.7), respectively. Reported rates of actuarial PFS based on MRI scans were 86.1% (95% CI, 79.4 to 90.7) at 6 months, 80.5% (95% CI, 72.9 to 86.1) at one year, and 72.2% (95% CI, 63.1 to 79.7) at two years.

Wowra (2008), a fair quality case series, looked at 102 patients treated with Cyberknife radiosurgery for spinal metastases. Median follow-up was not reported. Median survival was 1.4 years (95% CI, 1.2 to 1.6). Five-year survival after diagnosis of primary cancer ranged from 33% (GI cancers) to 95% (breast cancer).

Ahmed (2012), a poor quality case series, reported at 66 patients treated with SBRT for malignant spinal tumors. Median follow-up was not reported. Survival at 1-year for patients with prior radiation therapy was 28% and 59% in patients without prior radiation treatment (p=0.002). Overall local control in patients with prior RT was 83.3% and 91.2% in patients without prior RT (p=0.050). Quality of life scores improved from a baseline of 15.7 (SD 6.1) to 18.2 (SD 5.2) at three months (p=0.04).

Gagnon (2009), a poor quality case series, looked at 200 patients with primary and metastatic spinal tumors. Median follow-up was not reported. Patient ages ranged from 3 to 91 years; results were not stratified by age. Median survival in patients with malignancy was 14.5 months and 10.5 months in patients with primary spinal cancer treated with Cyberknife radiosurgery after previous radiation therapy.

Gerszten (2006), a poor quality case series, reported on 77 patients treated with Cyberknife radiosurgery for spinal metastases from lung cancer. Median follow-up was twelve months. Sixty-five of 73 patients (89%) treated for significant pain reported long-term improvements in pain measured on a ten-point pain scale.

Gibbs (2007), a poor quality case series, examined records of 74 patients treated with Cyberknife radiosurgery for spinal metastases. Mean follow-up was nine months. One year actuarial survival rate was 46.3% and the median time to death was 11 months.

Mahadevan (2011), a poor quality case series, looked at 60 patients treated with SBRT for spinal metastases with a median follow-up of 12 months. Median OS was 11 months (range, 3 to 39).

Overall Summary

The overall strength of evidence is very low, based on one SR of 29 case series and eleven subsequent case series. The following estimates are uncertain. Some of the patients in these studies had received prior conventional EBRT and were treatment failures. Local tumor control rates may range from 76% to 96% and median survival from 11 months to 22.5 months. In addition, rates of pain control may range from 80% to 90% with improvement in QoL. However, there are no comparative data to compare these rates to those of conventional EBRT.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

One fair quality SR was identified (Gerszten 2009). Gerszten (2009) examined 29 studies of radiosurgery treatment of spinal metastases. The study found that complications were generally self limited and mild including esophagitis, mucositis, paresthesia, transient laryngitis, transient ridiculitis, dysphagia and diarrhea. No spinal cord toxicity was reported in two studies. On study reported a single case of radiation-induced cord injury thirteen months after radiosurgery and a multi-center study of 1075 patients reported only six patients with delayed radiation-induced myelopathy. Authors noted limitations of collecting radiation related harms data due to multiple confounding variables, relatively short follow-up and nonprospective datasets.

Subsequently Published Studies

Six fair quality (Garg 2011; Nelson 2009; Nikolajek 2011; Tsai 2009; Wang 2012; Wowra 2008) and seven poor quality (Ahmed 2012; Gagnon 2009; Gerszten 2006; Gibbs 2007; Mahadevan 2011; Ryu 2010; Sachdev 2011) case series were identified.

Garg (2011), a fair quality case series, looked at 59 patients with spinal tumors treated with SBRT after previous EBRT therapy. Mean follow-up was 17.6 months. Grade 1 and 2 neurotoxicity occurred in 11 patients (19%) including transient numbness and tingling, headache and anxiety. Two patients (3%) reached Grade 3 neurotoxicity, with one patient experiencing persistent neuropathic pain, paresthesia and ipsilateral foot drop due to lumbar plexopathy and one patient suffering from lumbar plexopathy limited to ipsilateral foot drop. Grade 1 and 2 GI toxicity occurred in 12 patients (20%) including transient nausea and vomiting, radiation esophagitis, anorexia and diarrhea. Other Grade 1 and 2 toxicities were reported in 35 patients (59%). No other Grade 3 or higher toxicity was reported.

Nelson (2009), a fair quality case series, reported on 32 patients treated for spinal metastases. The study noted that seven patients (22%) experienced Grade 1 nausea. No other toxicities were noted.

Nikolajek (2011), a fair quality case series, examined 54 previously irradiated primary spinal cancer and spinal metastases patients. The study reported only that one patient with multiple treatments and tumor progression developed progressive paraparesis one year after treatment.

Tsai (2009), a fair quality case series, reported on 69 patients treated with Cyberknife radiosurgery for spinal metastases. Rates of Grade 1to 2 complications included fatigue (50%),

nausea (27%), vomiting (16%), diarrhea (3%), sore throat (5%), anemia (1%), thrombocytopenia (2%) and neutropenia (4%).

Wang (2012), a fair quality case series, reported on 149 patients with mechanically stable, non-cord-compressing spinal metastases. Median follow-up was 15.9 months. Median age was 58 years (range, 20 to 88). Grade 1 and 2 transient numbness and tingling, nausea and vomiting were reported. Grade 3 toxicities included nausea, vomiting, diarrhea, fatigue, non-cardiac chest pain, dysphagia, neck pain, diaphoresis, and paint associated with severe tongue edema and trismus). Grade 4 toxicities and radiation-related spinal cord myelopathy did not occur during the study.

Wowra (2008), a fair quality case series, reported on 102 patients treated with Cyberknife radiosurgery for spinal metastases. Acute complications were limited to nausea (9%). Two patients (2%) experienced late complications. One patient developed segmental neuropathy due to a circumscribed hemorrhage into a metastases and one patient developed spinal instability due to a pathological fracture.

Ahmed (2012), a poor quality case series, looked at 66 patients treated with SBRT for oligometastatic disease of the spine. Twelve patients (18%) had acute Grade 1 toxicity, six patients (9%) Grade 2 and two patients (3%) had Grade 3. Of the latter patients, one had a T-12 spinal fracture three months after SBRT and one developed severe low back pain radiating down the left leg to the knee.

Gagnon (2009), a poor quality case series, examined 200 patients treated with GK SRS for various spinal tumors. The study found acute complications were self-limited and mild including fatigue, nausea, esophagitis, dysphagia and transient diarrhea. Three patients (1.5%) experienced significant complications. One patient with a history of EBRT treatment and prior surgery had breakdown at the surgical site requiring debridement and wound reclosure. Two patients developed vertebral fractures in the irradiated spine.

Gerszten (2006), a poor quality case series, looked at 77 lung cancer patients with metastases to the spine treated with Cyberknife radiosurgery. Median follow-up was 12 months (range, 6 to 40). No radiation toxicity was reported for any patients.

Gibbs (2007), a poor quality case series, reported on 74 patients treated with Cyberknife radiosurgery for spinal metastases. Mean follow-up was nine months (range, 0 to 33). Three patients (4%) developed severe myelopathy, of which two survived with severely limited mobility and one patient died of progressive disease. Two of the affected patients had been previously treated with EBRT and two had received anti-angiogenic or epidural growth factor inhibitor.

Mahadevan (2011), a poor quality case series, looked at 60 patients treated with SBRT for spinal metastases who had previous RT. Median follow-up was 12 months. In the first month following reirradiation, 24 patients (40%) developed Grade 1 fatigue and 12 patients (20%) experienced Grade 2 nausea. Four patients (7%) had persistent or worsening neurological

symptoms with three patients experiencing persistent radicular pain and one patient developing a new onset of lower extremity weakness.

Ryu (2010), a poor quality case series, examined 62 patients treated with SBRT for spinal metastases. Median follow-up was 11.5 months. The study noted transient Grade 1 esophageal mucositis in patients who received RS to thoracic spine. No acute Grades 2 to 4 toxicities were reported. Nine patients (16%) showed neurological progression after treatment, two of whom were neurologically intact before starting SBRT.

Sachdev (2011), a poor quality case series, reported on 87 patients treated with RS for benign spinal tumors. Patient ages ranged from 12 to 86 years; results were not stratified by age. One patient (1%) had treatment failure 73 months after RS and one patient developed transient myelitis nine months after treatment which was successfully treated with coriticosteroids.

Overall Summary

Based on one fair quality SR of case series and 13 case series (six fair and seven poor quality), overall strength of evidence is very low. Acute complications from SRS treatment of spinal tumors may be mild. Examples include fatigue, nausea, esophagitis, mucositis, and dysphagia. Severe complications may be rare and included spinal fractures, lumbar plexopathy, paraparesis and myelopathy. Due to the lack of comparative data, no conclusions can be drawn about harm from SRS compared to conventional EBRT.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Haley (2011), a poor quality economic study, compared the cost of Cyberknife to EBRT for the treatment of spinal metastases in 44 patients. The author estimated costs (charges) using the Medicare 2010 Hospital Setting fee schedule for charge data. Analysis found that 23% of EBRT patients had subsequent SBRT but only 9% of SBRT patients had a second SBRT course. Taking these assumptions into consideration, cost modeling found that *for 100 patients*, the cost of SBRT would be $842,420. For an EBRT treatment protocol of 30 Gy in 10 fractions, the estimated cost would be $676,309, or 80% of the cost of SBRT. For an EBRT protocol of 20 Gy in 5 fractions, the estimated cost for 100 patients was $499,911 or 59% of the cost of SBRT.

Overall Summary

The overall strength of evidence on costs for SBRT for the spine compared to EBRT is very low. There is uncertainty in the cost estimates, but they may be $842,420/100 patients for SBRT, $676,309/100 patients for an EBRT protocol of 30 Gy in 10 fractions, and $499,911/100 patients for an EBRT protocol of 20 Gy in 5 fractions.

Multiple Tumor Sites

Four case series reported experience with SBRT across a variety of cancers. Since these reports did not analyze data by cancer type, they are summarized in this section.

KQ 1: What is the evidence of effectiveness for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT) compared to conventional external beam radiation therapy (EBRT) for patients with CNS tumors and patients with non-CNS cancers?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Two fair quality (McCammon 2009; Milano 2008) and two poor quality (Milano 2010; Scorsetti 2011) case series were identified.

McCammon (2009), a fair quality case series, looked at 141 patients treated with SBRT for a variety of cancers including adenocarcinoma, squamous cell carcinoma, sarcoma, melanoma, renal cell carcinoma, neuroendocrine carcinoma and other unspecified cancers. Median follow-up was 8.2 months. One and 3-year local control rates were provided by dose: for 50 to 60 Gy the rates were 100% and 89.3%. For doses between 36.1 and 53.9 Gy, the rates were 89% and 59% and for any dose less than 36.1 Gy, the rates were 40.5% and 8.1%.

Milano (2008), a fair quality case series, reported on 121 patients with multiple metastatic cancers. All patients were treated with SBRT and median follow-up was not reported. The study reported local control rates at two and four years as 77% and 73%.

Milano (2010), a poor quality case series, examined 77 patients treated with SBRT for oligometastases at various sites. Of the patients with liver metastases, 30 (71%) had died by a median follow-up of 20 months, 12 (29%) were alive at a median follow-up of 43 months and four patients (10%) had not developed new metastases at a median follow-up of 43 months. Of patients with lung metastases, 14 (67%) were deceased at a median of 17 months, seven (33%) were alive at 40 months and four patients (19%) had developed new metastases at a median of 34 months. Of patients with thoracic lymph node metastases, three (60%) were alive at 72 to 82 months and two patients (40%) had developed local reoccurrence. Of patients with thorax-confined metastases, 11 were deceased (85%) at median follow-up of 16 months, two patients (15%) were alive and both had developed new metastases.

Scorsetti (2011), a poor quality case series, looked at 37 patients treated with SBRT for primary or metastatic cancer in the abdominal cavity. Median follow-up was 12 months. Local control at six months reported to be 51%.

Overall Summary

The overall strength of evidence is very low based on four poor quality case series that included patients with a variety of cancers. Local control rates are uncertain but reported as ranging from 51% at six months to 100% at one year.

KQ 2: What are the potential harms of SRS and SBRTS compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms?

Systematic Reviews

No SRs were identified.

Subsequently Published Studies

Two fair quality (McCammon 2009; Milano 2008) and two poor quality (Levine 2009; Scorsetti 2011) case series were identified.

McCammon (2009), a fair quality case series, reported that 28 patients (19.9%) experienced Grade 2 to 4 complications related to SBRT treatment. Grade 2 to 4 pneumonitis occurred in nine patients (6.4%), Grade 2 to 3 dermatitis in six patients (4.3%), Grade 2 to 3 soft tissue or muscle inflammation or fibrosis in six patients (4.3%), unspecified Grade 2 to 3 effects in five patients (3.5%) and vertebral fractures in two patients (1.4%).

Milano (2008), a fair quality case series, found that 21 out of 121 patients (17%) experienced Grade 1 to 2 toxicities such as fatigue, skin irritation, diarrhea, nausea, vaginal bleeding, flank pain, dysphagia and alopecia. One patient (1%) experienced Grade 3 nonmalignant pleural and pericardial effusion.

Levine (2009), a poor quality case series, found that five out of 24 patients (21%) developed adverse effects not requiring treatment including nausea, malaise, skin irritation, transient radiculopathy with dysesthesias and partial motor loss. One patient (4%) developed a rectal tumor cavity fistula requiring diverting colostomy and drainage.

Scorsetti (2011), a poor quality case series, reported that five out of 37 patients (14%) experienced acute toxicity. Three patients (8.1%) developed enteritis and two patients (5.4%) had transient liver damage. Late toxicities reported were one patient (2.7%) with diarrhea and abdominal pain and one patient (2.7%) with Grade 3 gastric bleeding.

Overall Summary

The overall strength of evidence is very low based on two fair and two poor quality case series that included patients with a variety of cancers. There is uncertainty about the rates of harms especially since they vary depending on the site of the cancer. As reported in these case series, 14 to 21% of patients may experience mild, transient acute toxicity such as nausea, fatigue or skin irritation. More severe toxicities may include pleural and pericardial effusion, gastric bleeding and vertebral fractures and may occur in 1% to 4% of patients.

KQ 3: What is the evidence that SRS and SBRT have differential efficacy or safety issues in subpopulations?

No studies on subpopulations were identified.

KQ 4: What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

No studies on costs or cost-effectiveness were identified.

MAUDE Database

Three reports of serious adverse events were identified. Two patient deaths, one from metastatic lung cancer and one from metastatic stomach cancer were reported. The third adverse event reported on a patient who developed a portal vein thrombosis and an occluded hepatic artery. Full summaries of the events are provided in Appendix M.

Guidelines

A total of 16 guidelines and 11 ACR Appropriateness Criteria ®[9] were identified that address the use of SRS and SBRT. Appropriateness Criteria® issued by ACR are considered to be a clinical decision making aid rather than a broadly applied guideline. The included guidelines cover CNS (meningioma, brain metastases, spine metastases, glioma), liver/hepatobiliary, lung, pancreas, and soft tissue. ACR Appropriateness Criteria® are included for bone metastases, non-spine bone metastases, brain metastases, rectal cancer, head and neck cancer, NSCLC, and prostate cancer. The guidelines and Appropriateness Criteria® are summarized below and described in more detail in Appendix G. Appendix H describes each guideline's quality assessment rating. Appendix D includes the guideline quality assessment tool used for performing these guideline assessments.

All of the National Comprehensive Cancer Network (NCCN) guidelines were rated as poor quality. While the NCCN guidelines have a transparent guideline development process and are explicit about guideline panel members and NCCN staff conflicts of interest, the methods for identifying and selecting evidence are unclear. After several email and phone conversations with NCCN staff about their methodology, it is still unclear how evidence is identified (e.g., search strategy and databases searched), what the inclusion/exclusion criteria are, and if individual studies are assessed for quality. Based on the dearth of information in these areas, all of the NCCN guidelines were rated as poor. See Appendix H for the full quality assessment of individual guidelines.

The ACR Appropriateness Criteria® are developed through an expert panel process and focus on diagnostic imaging, interventional radiology, and radiation oncology. Technologies are given an appropriateness rating between 1 and 9; the appropriateness rating can vary depending on treatment situation and patient characteristics. Ratings of 1, 2 or 3 are considered usually not appropriate, ratings of 4, 5 or 6 are considered as may be appropriate, and ratings of 7, 8, or 9 are considered usually appropriate. All of the ACR Appropriateness Criteria® included in this report were fair quality.

Central Nervous System

Meningioma: The NCCN (2012a) provides recommendations for WHO Grade 1 meningiomas. Stereotactic radiosurgery doses of 12 to 14 Gy in a single fraction are recommended when appropriate.

[9] The ACR uses a scale of Appropriateness Criteria®. A score of 1 to 3 is considered "usually not appropriate", 4 to 6 is considered "may be appropriate", and 7 to 9 is considered "usually appropriate."

Brain Metastases: For the initial management of single brain metastases, Tsao ([ASTRO] 2012) recommends that when prognosis is good and complete resection is possible metastases less than or equal to 3 to 4 cm could be treated with surgery and WBRT, radiosurgery and WBRT, or radiosurgery alone, all with level I evidence. Level I evidence is obtained from at least one properly designed RCT. Surgery with a radiosurgery/radiation boost with or without WBRT has level III evidence. Level III evidence is drawn from opinions of respected authorities, clinical, experience, and descriptive studies or reports of expert committees. For metastases greater than 3 to 4 cm surgery with radiosurgery/radiation boost with or without WBRT has level III evidence. In cases with good prognosis that are not resectable, for metastases less than or equal to 3 to 4 cm radiosurgery and WBRT or radiosurgery alone are recommended with level I evidence. For metastases greater than 3 to 4 cm, WBRT is recommended with level III evidence.

For patients with multiple brain metastases with good prognosis and all metastases less than or equal to 3 to 4 cm, Tsao ([ASTRO] 2012) recommends radiosurgery and WBRT, radiosurgery alone, or WBRT with level I evidence. For other cases of multiple brain metastases radiosurgery is not recommended.

The International RadioSurgery Association (IRSA) (2008) recommends SRS for newly diagnosed single or multiple brain metastases or as a boost after WBRT. It is also recommended for treatment of recurrent brain metastases after WBRT or if there is residual tumor following resection.

Ammirati (2010) recommends the treatment of recurrent or progressive brain metastases be based on functional status, extent of disease, volume/number of metastases, recurrence or progression at original versus non-original site, previous treatment and type of primary cancer. SRS can be recommended depending on the patient's specific condition.

NCCN (2012a) recommends SRS for the treatment of brain metastases.

For patients with solitary brain metastasis from renal cell carcinoma whose disease is well controlled extracranially, NCCN (2012d) SRT is recommended as an alternative to surgery based with a Category 2A recommendation (based upon lower-level evidence with uniform NCCN consensus that the intervention is appropriate.

One guideline from the Australian Cancer Network (ACN) (2008) recommends that melanoma patients with limited or no extracranial disease and favorable prognosis, SRS can be considered for the treatment of brain metastases.

Two guidelines address the use of SRS for brain metastases from thyroid cancer. NCCN (2012j) recommends neurosurgical resection or SRS for solitary brain or CNS lesions. Kloos [American Thyroid Association] (2009) specifies that for isolated or limited brain metastases that are not amenable to surgery, EBRT, including SRS, may be indicated.

Spine metastases: The NCCN (2012a) states that SRT is appropriate in selected cases or in recurrence after previous radiation.

Glioma: For grade I/II gliomas, NCCN (2012a) does not recommend using SRS in the management of low grade gliomas, particularly as an initial treatment.

Hepatobiliary: One guideline from NCCN (2012c) determines that all tumors irrespective of location may be amenable to SBRT. Most commonly, it is recommended for us in cases with one to three tumors with a cumulative diameter under 6 cm although it could be considered for larger lesions if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected. This is a Category 2A recommendation.

Two guidelines from NCCN (2012b, 2012h) indicate that for limited liver metastases from rectal or colon cancer, radiotherapy can be considered in highly selected cases or clinical trials but should not be used in the place of surgical resection. This recommendation is based on Category 3 evidence, meaning there is major NCCN disagreement that the intervention is at all appropriate.

Lung Cancer

NSCLC: For patients who are medically inoperable, Scott ([ACCP] 2007) suggests SRT may be appropriate but should not be used in patients who are surgical candidates outside the context of a clinical research study.

In stage I NSCLC, NCCN (2012f) recommends SBRT for patients who are medically inoperable, older patients (e.g., greater than 75 years old), and for potentially operable patients who refuse surgery. Treatment of tumors within 2 cm of proximal bronchial tree using the most intensive regiments is considered unsafe, but modified regimens are effective and safe. All recommendations are Category 2A.

Lung metastases: Two guidelines from NCCN (2012b, 2012f) indicate that for limited lung metastases from rectal or colon cancer, radiotherapy can be considered in highly selected cases or clinical trials but should not be used in the place of surgical resection. This recommendation is based on Category 3 evidence, meaning there is major NCCN disagreement that the intervention is appropriate.

Pancreas

A guideline from NCCN (2012g) on pancreatic cancer includes the use of SBRT concurrently with chemotherapy as a general principle. Because no standard dose has been established it is not recommended in cases of unresectable/locally advanced cancers. Recommendations are category 2A.

Soft tissue sarcoma

One guideline from NCCN (2012i) recommends SRS as a method for the control of metastatic lesions generally. For symptomatic patients with disseminated metastases SRS may be an option but guidelines are intentionally nonspecific because many factors are included in the decision and should be left to clinical judgment.

ACR Appropriateness Criteria®

Appropriateness Criteria® issued by ACR is considered to be a clinical decision-making aid rather than broadly applied guideline. The use of SRS, alone or in combination with other therapies, is recommended in some cases for the following conditions: bone metastases (Janjan 2008), follow-up and retreatment of brain metastases (Patel 2011; Videtic 2009; Suh 2010), recurrent of head and neck cancer (McDonald 2010), NSCLC (Gewanter 2010; Rosenzweig 2008). The use of SRS is not recommended in any variants for non-spine bone metastases (Lutz 2011) or recurrent rectal cancer (Konski 2011b). For stage T1 and T2 prostate cancer, SRS is noted as promising but more studies are needed.

Table 5. Summary of Guidelines and ACR Appropriateness Criteria® by Tumor Location

Malignancy	Guideline (Year) Quality	Usually Not Appropriate / Not Recommended	May be Appropriate	Usually Appropriate / Recommended
Abdomen				
Recurrent rectal cancer	Konski [ACR] 2011b Fair	In four case variants of recurrent rectal cancer presented, SBRT therapy was considered "usually not appropriate" in all cases.		
Hepatocellular carcinoma	NCCN 2012c Poor		All tumors irrespective of location may be amenable to SBRT or external-beam conformal radiation. SBRT is often used for 1-3 tumors with a cumulative diameter under 6 cm. SBRT could be considered for larger lesions, if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected.	
Rectal cancer	NCCN 2012h Poor	In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection.		
Colon cancer	NCCN 2012b Poor	In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly		

Malignancy	Guideline (Year) Quality	Usually Not Appropriate / Not Recommended	May be Appropriate	Usually Appropriate / Recommended
		selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection.		
Pancreatic adenocarcinoma	NCCN 2012g Poor	No standard dose or dose per fraction has been established for SBRT; therefore, it should preferably be utilized as part of a clinical trial.		
Brain and CNS				
Melanoma	ACN 2008 Good		To improve survival, patients with limited or no extracranial disease and with favorable prognosis brain metastases can be considered for surgical resection and if unresectable, for stereotactic radiosurgery	
Brain metastases	Patel [ACR] 2011 Fair		Radiosurgery for recurrent brain metastases is a viable option if size and number permit.	
Brain metastases	Videtic [ACR] 2009 Fair	Given the finding that SRS does not increase survival of patients with two or more brain metastases, clinicians need to practice careful selection of patients for this intervention.		
Brain metastases	Suh [ACR] 2010 Fair		Since much controversy exists regarding optimal treatment for a patient with a single brain metastasis, patient participation in clinical trials is important to evaluate best treatment. For those patients who do not participate in clinical trials, the roles of surgery and SRS in improving outcomes for patients with a single lesion are evident.	
Brain	American		EBRT (including stereotactic	

Malignancy	Guideline (Year) Quality	Usually Not Appropriate / Not Recommended	May be Appropriate	Usually Appropriate / Recommended
metastases from thyroid cancer	Thyroid Association 2009 Poor		radiosurgery) may be indicated for brain metastases not amenable to surgery	
Brain metastases	Ammirati 2010 Poor		Re-irradiation (either WBRT and/or SRS), surgical excision or, to a lesser extent, chemotherapy, can be recommended depending on a patient's specific condition and based on the judgment of the patient's treating physician.	
Brain metastases	Tsao [ASTRO] 2012 Fair		If patient has good prognosis and brain metastasis $\leq$ 3-4 cm. For multiple brain metastases, patients with good prognosis and all metastases $\leq$ 3-4cm.	
Brain metastases	IRSA 2008 Poor			The available data indicate that SRS and open surgical resection (where feasible) are both excellent treatment options for patients with solitary brain metastases. Stereotactic radiosurgery is an effective treatment for patients with multiple brain metastases
Low grade glioma	NCCN 2012a Poor	SRS has not been established to have a role in the management of low grade gliomas. Phase I trials using SRS do not support its role as initial treatment.		
Meningioma	NCCN 2012a		WHO grade 1 meningiomas may also be treated with stereotactic radiosurgery doses of 12-14 Gy in a	

Malignancy	Guideline (Year) Quality	Usually Not Appropriate / Not Recommended	May be Appropriate	Usually Appropriate / Recommended
	Poor		single fraction when appropriate.	
Brain metastases	NCCN 2012a Poor			Recommended maximum marginal doses of 24, 18, or 15 Gy according to tumor volume is recommended.
Metastatic Spine	NCCN 2012a Poor		Doses to vertebral body metastases will depend on patient's performance status and primary histology. In selected cases, or recurrences after previous radiation, stereotactic radiotherapy is appropriate.	
Brain metastases from thyroid cancer	NCCN 2012j Poor			For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred.
Head and Neck				
Recurrent head and neck	McDonald [ACR] 2010 Fair		SBRT therapy "may be appropriate" in one of five cases. SBRT was not considered in the treatment for the remaining four cases.	
Lung				
Stage I/II NSCLC	Scott [ACCP] 2007 Fair		Other local therapies such as **stereotactic radiation** or radiofrequency ablation may be appropriate for **patients who are medically inoperable**. The use of these techniques in patients who are surgical candidates should not occur outside of the context of a clinical research study.	
Stage I NSCLC	Gewanter [ACR] 2010 Fair		Emerging institutional data suggest that central early-stage lung lesions can be treated safely with lower doses per fraction	

Malignancy	Guideline (Year) Quality	Usually Not Appropriate / Not Recommended	May be Appropriate	Usually Appropriate / Recommended
Stage I NSLCL	Rosenzweig [ACR] 2008 Fair	Currently **extracranial stereotactic body radiotherapy (SBRT)** is being examined as an alternative to conventionally fractionated radiotherapy in patients with inoperable stage I disease		
Stage I	NCCN 2012f Poor		Recommended for patients who are medically inoperable and is also an appropriate option for many older patients	
Prostate				
	Morgan [ACR] 2011 Fair	The use of hypofractionation in general and a stereotactic approach looks very promising, but more robust studies with longer follow-up clearly are needed.		
Other Cancers/Multiple Sites				
Bone metastases	Janjan [ACR] 2008 Fair	SBRT therapy was considered to be "usually not appropriate" in seven of 8 cases. SBRT was not considered in the treatment for the remaining case.		
Non-spine bone metastases	Lutz [ACR] 2011 Fair	SBRT therapy was considered to be "usually not appropriate" in four of five cases. SBRT was not considered in the treatment for the remaining case.		
Soft tissue sarcoma	NCCN 2012i Poor		Patients can also receive stereotactic radiosurgery or chemotherapy as an alternate method for control of metastatic lesions. Many different issues are factored into this decision (e.g., patient performance status, patient preferences, specific clinical problems from the metastases,	

Malignancy	Guideline (Year) Quality	Usually Not Appropriate / Not Recommended	May be Appropriate	Usually Appropriate / Recommended
			treatment availability), and specific details are best left to clinical judgment.	

Summary of Guidelines

Based on fair to poor quality guidelines, SRS and SBRT are not recommended or considered appropriate by the ACR for the treatment of bone metastases, colon, low grade glioma, non-spine bone metastases, pancreatic, prostate, rectal, and stage I NSCLC cancer. For brain metastases, there are inconsistent recommendations for the use of SRS and SBRT. These recommendations arise from good to poor quality guidelines and the ACR criteria with ratings ranging from ranging from usually not appropriate/not recommended to usually appropriate/recommended. For all other cancers discussed, SBRT is considered as a possible form of treatment by the ACR and included guidelines.

Policy Considerations

This section summarizes coverage policies by Medicare, Aetna, Regence Blue Cross Blue Shield (BCBS), and GroupHealth addressing SRS/SBRT. Appendix H provides further detail and direct web links to each policy reviewed.

Medicare

Medicare has not issued a national coverage determination for SRS/SBRT. Coverage decisions are therefore issued by regional Medicare contractors through Local Coverage Determinations (LCDs). This review identified two Medicare LCDs that cover Washington: one addressing SBRT (L28366 [2011]), and another addressing SRS and SRT (L30318 [2011]) (CMS 2011b, 2011c). The Medicare LCDs identify coverage of SBRT for the following indications.

SBRT: LCD 28366 (2011) states that SBRT is covered for primary and metastatic tumors of the lung, liver, kidney or pancreas when the following criteria are met:

- Patient's medical condition justified aggressive treatment;
- Other forms of radiotherapy or focal therapy (including but not limited to EBRT and IMRT) cannot be as safely or effectively utilized;
- The tumor can be completely targeted with acceptable risk to surrounding critical structures;
- For germ cell or lymphoma, effective chemotherapy regimens have been exhausted or are not otherwise feasible; and
- When other forms of focal therapy cannot be as safely or effectively used.

Coverage is possible for other lesions with documented necessity. Coverage for SBRT is not covered for the following conditions and circumstances:

- Treatment is unlikely to result in clinical cancer control and/or functional improvement;
- When there is wide-spread cerebral or extra-cranial metastases; or
- Patient has poor performance status.

For prostate cancer, SBRT is covered as monotherpay for low and intermediate risk prostate cancer when:

- Patient's medical condition justified aggressive treatment;
- Other forms of radiotherapy or focal therapy (including but not limited to EBRT and IMRT) cannot be as safely or effectively utilized; and
- The tumor can be completely targeted with acceptable risk to surrounding critical structures;

Lesions of other sites (bone, breast, uterus, ovary, and other internal organs) are generally not covered, but may be in cases of recurrence after conventional radiation modalities.

SRS: LCD 30318 (2011) states that intracranial lesions are covered under the following conditions:

- The lesion(s) has an image-distinct margin; and
- Karnofsky performance scale > 50% or ECOG $\leq$ 2.

Specific indications include neuromas of the cranial nerves, and unresectable/residual meningioma where surgery is not appropriate. Metastatic brain lesions are covered when patients should have otherwise stable disease, margins are distinct, and treatment is for less than five lesions. SRS is also covered as a boost treatment for larger lesions treated with EBRT or surgery, acoustic neuromas, pituitary adenomas, craniopharyngiomas, and glomus jugulare tumors.

SRT: LCD 30318 (2011) states that SRT is considered medically necessary for the treatment of tumors in hard to reach locations, unusual shapes, and close proximity to vital structure. Specific indications include:

- Benign lesions (e.g., pituitary adenoma, vestibular schwannoma, meningioma);
- Benign neoplasms previously treated with conventional radiotherapy; and
- Malignant lesions (lesions less than 5mm of the optic nerves or chiasms, recurrent malignant gliomas, brain metastasis, base of skull, recurring malignancies in head and neck cancers, such as cancer of the tonsil, larynx, tongue, sinus, and mouth).

Aetna

Coverage for SBRT is limited to localized malignant conditions where highly precise application is required. This includes lung or liver metastases not amenable to surgery, medically inoperable early stage lung cancer, primary liver cancer not amenable to surgery, spinal and para-spinous tumors, though this is not an exhaustive list. The use of SRS is considered medically necessary for the treatment of benign tumors considered unresectable due to deep intracranial location or if the patient cannot tolerate surgery. Brain malignancies are also

covered, both primary and metastatic. When the coverage criteria for SRS is met, SRT is considered medically necessary for tumors with such proximity to vital structures that even very accurate high-dose single fraction SRS could not be tolerated (Aetna 2011).

GroupHealth

Coverage criteria for SBRT is identical to that contained in the related LCD. Coverage for SRS is identical to the coverage criteria contained in the Aetna policy for SRS (GroupHealth 2011).

Regence BCBS Washington

Coverage of SRS or SBRT is considered medically necessary for the treatment of acoustic neuromas, pituitary adenomas, and meningiomas. Patients with brain metastases with a Karnofsky performance greater than 70 and life expectancy greater than 6 months are also covered. Additional conditions include primary malignancies of the CNS, spinal or vertebral body tumors in patients who have received prior radiation therapy, and stage 1 NSCLC. Treatment for lung metastases are covered when life expectancy greater than 6 months, Karnofsky greater than 70, there is adequate lung function, locally controlled primary tumor, oligometastases, diameter greater than 5 cm, no other metastatic disease, and records documenting tumor is not resectable or not good surgical candidate. The use of SRS or SBRT is considered investigational for other extracranial sites except those included (Regence BCBS 2010).

Overall Summary

Over the past ten years, important advances have been made in techniques to deliver external beam radiation therapy for some cancers. This report presents the evidence regarding SRS/SRT and SBRT for cancers in the following anatomic locations: abdomen (anus/rectum/colon, liver, pancreas, and adrenal glands), CNS (astrocytoma, brain metastases, ependymoma, glioblastoma, glioma, meningioma, neurocytoma, pituitary adenoma, schwannoma), head and neck (glomus jugulare, head and neck, ocular melanoma), lung, prostate, and spine. A total of 3,034 citations were screened for inclusion (1,915 from a Medline search, 112 from Cochrane, and 1007 from public comments). Two hundred and fifty-three studies met criteria for inclusion in this review. Except for six RCTs of SRS for brain metastases and one for glioblastoma, the evidence for SRS and SBRT is based on cohort and case series studies that have substantial methodological limitations. Almost all of these studies are non-comparative, and only two focus on children. Thus, the risk of bias is high and estimates of the relative benefits and harms of SRS/SBRT compared to conventional EBRT are highly uncertain for most of the tumors covered in this review.

The findings from comparative studies addressing outcomes (e.g., OS, QoL) and harms are summarized below by tumor. For the remainder of the tumors, the overall strength of evidence was very low and often heterogeneous. Therefore, no general conclusions can be drawn for these tumors. In addition, even though the overall strength of evidence is low or very low, harms for a few tumors will be described because of their frequency or severity. For the remaining tumors, in addition to fatigue and general malaise, harms were mostly regional toxicities based on the location of the malignancy (e.g., radiation pneumonitis for lung,

headaches or radionecrosis with brain edema for brain, erectile dysfunction for prostate) and commonly included acute and late toxicities.

Brain Metastases

For *SRS+WBRT compared to WBRT* alone, the overall strength of evidence is moderate for survival and tumor control. Although local tumor control is probably better, SRS+WBRT compared to WBRT alone likely has *no significant difference in OS*. Subgroup analyses from one RCT, which provides low overall strength of evidence, suggest that median survival in patients with single metastases (6.5 vs. 4.9 months, SRS+WBRT vs. WBRT, respectively) and patients who are RPA Class 1 (11.6 vs. 9.6 months, SRS+WBRT vs. WBRT, respectively) may be better with SRS+WBRT compared to WBRT alone. Acute and late toxicities are probably not significantly different for SRS+WBRT compared to WBRT alone, base on moderate strength of evidence. Approximately, 2% to 5% of patients may experience severe (Grade 3 or 4) acute and late toxicities.

For *SRS+WBRT compared to SRS* alone, the overall strength of evidence is moderate for the outcome of OS and tumor control. Although local and distant tumor control is probably better, SRS+WBRT compared to SRS alone probably has *no significant difference in OS*. Based on an interim analysis of one small fair quality RCT, patients receiving SRS+WBRT may be more likely to have cognitive decline at four months compared to patients receiving SRS alone. An overall low strength of evidence exists to suggest there is no difference in functional independence, time to worsened performance status or quality of life for SRS+WBRT compared to SRS alone. The overall strength of evidence is low for harms and indicates that severe (Grade 3 or 4) acute and late toxicities may be similar for SRS+WBRT compared to SRS alone and occur in approximately 2% to 5% of patients.

For *SRS alone compared to WBRT alone*, the overall strength of evidence is very low based on six cohort studies, two with historical controls, and two additional small poor quality cohort studies. These studies suggest that OS may be better for patients receiving SRS alone compared to WBRT alone, but the poor quality of the studies and the heterogeneity across studies limit any conclusions. For harms, severe (Grade 3 or 4) acute and late toxicities may be similar for SRS+WBRT compared to SRS alone and occur in approximately 2% to 5% of patients.

Glioblastoma

The overall strength of the evidence is low based on one fair quality RCT that conflicts with two poor quality cohort studies. The addition of SRS to EBRT and carmustine (chemotherapy) may not affect survival in patients with recurrent glioblastoma based on the results from the RCT. However, adding SRS to other treatments for glioblastoma may increase the risk of symptomatic radionecrosis requiring a second surgery, based on low overall strength of evidence.

Glioma

The overall strength of evidence is very low for prolonged survival with salvage SRS in patients with recurrent gliomas and for harms in patients with primary and recurrent malignant gliomas. Although there is uncertainty, these studies raise concerns about radiation necrosis leading to a

mass effect requiring surgery or potentially stimulating recurrence and progression to a more aggressive tumor type.

Schwannoma

The overall strength of evidence for harms from SRS for schwannomas is very low. However, about 1% of patients may develop hydrocephalus requiring a shunt though one study suggests this is as high as 12%, 1% to 2% may develop a new malignancy, and up to 36% may develop new facial nerve dysfunction. There were no studies that compared SRS to EBRT, so relative harms are uncertain.

Ocular melanoma

The overall strength of evidence for harms from SRS for choroidal and uveal melanoma is very low. However, enucleation due to treatment side effects such as painful neovascular glaucoma may occur in 4% to 13% of patients.

Early Stage Non-Small Cell Lung Cancer

The overall strength of evidence is very low for outcomes. SBRT for *non-operable* Stage I NSCLC may result in 3-year OS rates of 50% to 60% and local control rates of 80% to 100%. The overall strength of evidence regarding harms is very low. There is uncertainty about the rate of acute and late toxicities, especially as they compared to EBRT. However, rates of greater than or equal to Grade 3 late toxicities may range 2% to 10%. In addition, for the devices that require fiducial markers to help target the radiation to the tumor, the placement of these markers, may cause a pneumothorax requiring chest tube placement or hospitalization in approximately 9% to 28% of patients.

Subgroups, Cost and Cost-effectiveness

Few, if any, studies addressed patient subgroups or costs of SRS/SBRT. Except as noted above for brain metastases, there was insufficient evidence to address outcomes and harms for any subgroup for any of the tumors in this report. The cost studies done for meningioma, NSCLC, and spine tumors were low quality with significant risk of bias in their estimates of effectiveness, when done, and costs. Study limitations make drawing any conclusions about cost or cost-effectiveness difficult.

Guidelines

Based on fair to poor quality guidelines, SRS and SBRT are not recommended or considered appropriate by the ACR for the treatment of bone metastases, colon, low grade glioma, non-spine bone metastases, pancreatic, prostate, rectal, and operable stage I NSCLC cancer. For brain metastases, there are inconsistent recommendations for the use of SRS and SRT from good to poor quality guidelines and the ACR ranging from ranging from usually not appropriate/not recommended to usually appropriate/recommended. For all other cancers discussed, SBRT is considered as a possibly appropriate treatment by the ACR and included guidelines. In general, the guidelines recommend the use of SRS and SBRT as a potential alternative to other treatments appropriate for the tumor (e.g. for patients with one to three brain metastases that are less than 3 to 4 cm when their prognosis is good) or in specific situations (e.g., patients with medically non-operable Stage 1 NSCLC).

Policies

Federal and private payer policies addressing SRS/SBRT that are pertinent to this report include Medicare, Aetna, Regence Blue Cross Blue Shield (BCBS), and GroupHealth. Medicare has not issued a national coverage determination for SRS/SBRT. Two Medicare LCDs cover Washington, one addressing SBRT, and another addressing SRS/SRT. SRS/SRT for intracranial lesions are covered when the lesion has image-distinct margins and Karnofsky performance scale > 50% (50% indicates that a patient requires help often and requires frequent medical care) or ECOG $\leq$ 2 (2 indicates that a patient is symptomatic, but able to do all self-care and spends less than 50% of the time in bed) and for treatment of tumors in hard to reach locations, unusual shapes, and close proximity to vital structure. SBRT is covered for primary and metastatic tumors of the lung, liver, kidney, pancreas, or low/intermediate risk prostate cancer when 1) aggressive treatment is justified; 2) other forms of radiotherapy or focal therapy cannot be as safely or effectively utilized; 3) the tumor can be targeted with acceptable risk to surrounding structures; or 4) the patient had previous radiotherapy to the same or adjacent sites.

Coverage criteria are similar across Medicaid and private payer policies for SRS/SRT. Conditions consistently covered include benign cranial lesions such as neuromas and meningioma and malignant brain lesions. Coverage criteria vary and include the use of performance scales/ good patient performance (e.g. Karnofsky score $\geq$ 70, RPA level 1), deep intracranial location, and life expectancy. Only two policies address SRT. Both policies cover treatment of tumors in hard to reach places, or in close proximity to critical structures where high-dose single fractions of SRS would not be tolerated. Coverage for SBRT varies across Medicaid and private payer policies. The strictest criteria cover only spinal, vertebral, stage 1 non-operable NSCLC, and lung metastases. Other policies include treatment of lung, liver, kidney, pancreas, prostate tumors. Although covered tumor sites vary, all policies have requirements such as good patient performance (e.g. Karnofsky score $\geq$ 70, RPA level 1), tumor proximity to critical structures, and repeated use of radiation.

Limitations of the Evidence

The evidence on SRS and SBRT is almost exclusively based on case series studies and a few RCT (brain metastases and glioblastomas) and comparative cohort studies. The case series and cohort studies included in this report have substantial methodological limitations creating high risk of bias, such as:

- All case series lacked a comparison group;
- Many of the studies did not adjust for confounding variables in analyses. Variables that may have a significant impact on outcomes include
    - Age;
    - Performance status and tumor staging prior to treatment;
    - Smoking status; and
    - Other medical comorbidities;

- Selection bias when consecutive patients meeting study inclusion/exclusion criteria are not included, especially problematic in retrospective studies;
- Many of the studies combined different types and stages of malignancies in their analyses; and
- Many of the studies have relatively small sample sizes making it difficult to infer findings to a broader population.

Appendix A. Database Search Strategies

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to April Week 1 2012>

Search Strategy:

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1 exp Radiosurgery/ (7221)

2 limit 1 to (controlled clinical trial or meta analysis or practice guideline or randomized controlled trial) (127)

3 exp Cohort Studies/ (1162156)

4 exp case-control studies/ (545054)

5 1 and 3 (2372)

6 limit 5 to yr="2002 -Current" (1648)

7 1 and 4 (1255)

8 limit 7 to yr="2002 -Current" (968)

9 limit 1 to systematic reviews (183)

10 2 or 9 (269)

11 6 or 8 or 10 (1856)

12 limit 11 to yr="2002 -Current" (1805)

13 limit 12 to english language (1692)

14 Comparative Study/ (1568492)

15 1 and 14 (752)

16 limit 15 to (english language and humans and yr="2002 -Current") (455)

17 16 not 13 (223)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2012>

Search Strategy:

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1 radiosurg$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (138)

2 gamma knif$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (38)

3 (stereotac$ adj3 radiother$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (33)

4 1 or 2 or 3 (157)

5 limit 4 to yr="2002 -Current" (99)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 2012>

Search Strategy:

---

1 radiosurg$.mp. [mp=title, abstract, full text, keywords, caption text] (13)

2 gamma knif$.mp. [mp=title, abstract, full text, keywords, caption text] (8)

3 (stereotac$ adj3 radiother$).mp. [mp=title, abstract, full text, keywords, caption text] (6)

4 1 or 2 or 3 (13)

5 limit 4 to yr="2002 -Current" (13)

Appendix C. MEDLINE® Search Dates by Malignancy

Procedures and Key Questions with searches of the full date range (April 2002 to April 2012) are highlighted in green. Malignancies and Key Questions highlighted in orange represent those with a SR or TA where subsequent search dates were limited.

Malignancy	Review	MEDLINE Beginning Search Dates			
		Key Question 1	Key Question 2	Key Question 3	Key Question 4
Abdomen					
Adrenal gland metastases		April 2002	April 2002	April 2002	April 2002
Colorectal		April 2002	April 2002	April 2002	April 2002
Liver	Tao (2012) Zamboglou (2012)	April 2002	April 2002	April 2002	April 2002
Pancreas		April 2002	April 2002	April 2002	April 2002
Brain					
Astrocytoma		April 2002	April 2002	April 2002	April 2002
Brain metastases	Elaimy (2011a) Linskey (2010) Patil (2010) Tsao (2011) Tsao (2012)	September 2009	September 2009	September 2009	September 2009
Ependymoma		April 2002	April 2002	April 2002	April 2002
Glioblastoma		April 2002	April 2002	April 2002	April 2002
Glioma		April 2002	April 2002	April 2002	April 2002
Meningioma		April 2002	April 2002	April 2002	April 2002
Neurocytoma	Rades (2006)	April 2002	April 2002	April 2002	April 2002
Pituitary		April 2002	April 2002	April 2002	April 2002
Schwannoma		April 2002	April 2002	April 2002	April 2002

Malignancy	Review	MEDLINE Beginning Search Dates			
		Key Question 1	Key Question 2	Key Question 3	Key Question 4
Head and Neck					
Glomus jugulare	Guss (2011)	April 2002	April 2002	April 2002	April 2002
Head and neck cancer		April 2002	April 2002	April 2002	April 2002
Ocular		April 2002	April 2002	April 2002	April 2002
Lung	Chi (2010)	April 2002	April 2002	April 2002	April 2002
Prostate		April 2002	April 2002	April 2002	April 2002
Spine	Gerszten (2009)	April 2002	April 2002	April 2002	April 2002
Other cancers / Multiple sites		April 2002	April 2002	April 2002	April 2002

Appendix D. Quality Assessment Tools

MED PROJECT	Methodology Checklist: Systematic Reviews and Meta-analyses

Study citation (*Include last name of first author, title, year of publication, journal title, pages*)	
MED Topic:	Key Question No.(s):
Checklist completed by:	Date:

SECTION 1: INTERNAL VALIDITY					
In a well conducted systematic review		***In this study the criterion is met:***			
1.1	The study addresses an appropriate and clearly focused question.	YES	NO	UNCLEAR	N/A
1.2	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	YES	NO	UNCLEAR	N/A
1.3	The literature search is sufficiently rigorous to identify all the relevant studies.	YES	NO	UNCLEAR	N/A
1.4	The criteria used to select articles for inclusion is appropriate.	YES	NO	UNCLEAR	N/A
1.5	Study quality is assessed and taken into account.	YES	NO	UNCLEAR	N/A
1.6	There are enough similarities between the studies selected to make combining them reasonable.	YES	NO	UNCLEAR	N/A
1.7	Competing interests of members have been recorded and addressed.	YES	NO	UNCLEAR	N/A
1.8	Views of funding body have not influenced the content of the study.	YES	NO	UNCLEAR	N/A
SECTION 2: OVERALL ASSESSMENT OF THE STUDY					
2.1	How well was the study done to minimize bias? *Code: Good, Fair or Poor*	GOOD	FAIR	POOR	
2.2	If coded as fair or poor, what is the likely direction in				

	which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this Key Question?	YES NO UNCLEAR N/A
2.4	Other reviewer comments:	

MED Project 2009. Adapted from NICE and SIGN materials.

MED PROJECT	Methodology Checklist: Randomized Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

MED topic:	Key Question No(s):

Checklist completed by:	Date:

SECTION 1: INTERNAL VALIDITY

	In a well conducted RCT study…	***In this study this criterion is met:***
RANDOM ALLOCATION OF SUBJECTS		
1.1	An appropriate method of randomization was used to allocate participants to intervention groups.	YES NO UNCLEAR N/A
1.2	An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	YES NO UNCLEAR N/A
1.3	The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	YES NO UNCLEAR N/A
ASSESSMENT AND FOLLOW-UP		
1.4	Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	YES NO UNCLEAR N/A
1.5	The intervention and control groups received the same care apart from the intervention(s) studied.	YES NO UNCLEAR N/A
1.6	The study had an appropriate length of follow-up.	YES NO UNCLEAR N/A
1.7	All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES NO UNCLEAR N/A
1.8	What percentage of the individuals or clusters	

	recruited into each group of the study dropped out before the study was completed? What percentage did not complete the intervention(s)?	
1.9	All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)	YES NO UNCLEAR N/A
ASSESSMENT AND FOLLOW-UP, Cont.		
1.10	All relevant outcomes are measured in a standard, valid and reliable way.	YES NO UNCLEAR N/A
1.11	The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	YES NO UNCLEAR N/A
1.12	The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	YES NO UNCLEAR N/A
CONFLICT OF INTEREST		
1.13	Competing interests of members have been recorded and addressed.	YES NO UNCLEAR N/A
1.14	Views of funding body have not influenced the content of the study.	YES NO UNCLEAR N/A
Section 2: Overall Study Assessment		
2.1	How well was the study done to minimize bias? *Code Good, Fair, or Poor*	GOOD FAIR POOR
2.2	If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO UNCLEAR N/A
2.4	Other reviewer comments:	

MED Project 2009. Adapted from NICE and SIGN materials.

MED PROJECT	Methodology Checklist: Cohort Studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Review topic:	Key Question No.(s), if applicable:
Checklist completed by:	Date:

SECTION 1: INTERNAL VALIDITY

	In a well conducted cohort study:	***In this study the criterion is:***
1.1	The study addresses an appropriate and clearly focused question.	YES NO N/A
	SELECTION OF SUBJECTS	
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	YES NO N/A
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	YES NO N/A
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	YES NO N/A
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	
1.6	Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.	YES NO N/A
	ASSESSMENT AND FOLLOW-UP	
1.7	The study employed a precise definition of outcome(s) appropriate to the Key Question(s).	YES NO N/A
1.8	The assessment of outcome(s) is made blind to exposure status.	YES NO N/A
1.9	Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	YES NO N/A
1.10	The measure of assessment of exposure is reliable.	YES NO N/A

1.11	Exposure level or prognostic factor is assessed more than once.	YES NO N/A
1.12	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	YES NO N/A
1.13	The study had an appropriate length of follow-up.	YES NO N/A
1.14	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	YES NO N/A
CONFOUNDING		
1.15	The main potential confounders are identified and taken into account in the design and analysis.	YES NO N/A
STATISTICAL ANALYSIS		
1.16	Have confidence intervals been provided?	YES NO N/A
CONFLICT OF INTEREST		
1.17	Competing interests of members have been recorded and addressed.	YES NO N/A
1.18	Views of funding body have not influenced the content of the study.	YES NO N/A
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code Good, Fair, or Poor*	GOOD FAIR POOR
2.2	If coded as Fair, or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO N/A
2.4	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	YES NO N/A
2.5	Other reviewer comments:	

MED Project 2009. Adapted from NICE and SIGN materials.

MED PROJECT	Methodology Checklist: Economic Evaluation

Study citation (*Include last name of first author, title, year of publication, journal title, pages*)

MED Topic:	Key Question No.(s):
Checklist completed by:	Date:

Cost
Cost analysis (no measure of benefits)

Economic Evaluations (please circle):

Study Type	*Measurement of Benefits*
Cost minimization	Benefits found to be equivalent
Cost effectiveness analysis	Natural units (e.g., life years gained)
Cost utility analysis	Healthy years (e.g. quality adjusted life years, health years equivalent)
Cost-benefit analysis	Monetary terms

Section 1: applicability

In a well conducted economic study…		*In this study the criterion is met:*
1.1	The results of this study are directly applicable to the patient group targeted by this Key Question.	YES NO UNCLEAR N/A
If criterion 1.1 is rated no, the study should be excluded.		
1.2	The healthcare system in which the study was conducted is sufficiently similar to the system of interest in the topic Key Question(s).	YES NO UNCLEAR N/A

SECTION 2: Study Design, Data Collection, and Analysis

In a well conducted economic study…		*In this study the criterion is met:*
2.1	The research question is well described.	YES NO UNCLEAR N/A
2.2	The economic importance of the research question is stated.	YES NO UNCLEAR N/A
2.3	The perspective(s) of the analysis are clearly stated and justified (e.g. healthcare system, society, provider institution, professional organization, patient group).	YES NO UNCLEAR N/A

2.4	The form of economic evaluation is stated and justified in relation to the questions addressed.	YES	NO	UNCLEAR	N/A
Methods to estimate the effectiveness of the intervention					
2.5	*Circle one* a. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies). b. Details of the design and results of effectiveness study are given (if based on a single study).	YES	NO	UNCLEAR	N/A
2.6	Estimates of effectiveness are used appropriately.	YES	NO	UNCLEAR	N/A
2.7	Methods to value health states and other benefits are stated.	YES	NO	UNCLEAR	N/A
2.8	Outcomes are used appropriately.	YES	NO	UNCLEAR	N/A
2.9	The primary outcome measure for the economic evaluation is clearly stated.	YES	NO	UNCLEAR	N/A
2.10	Details of the subjects from whom valuations were obtained are given.	YES	NO	UNCLEAR	N/A
2.11	Competing alternatives are clearly described.	YES	NO	UNCLEAR	N/A
Methods to estimate the costs of the intervention					
2.12	All important and relevant costs for each alternative are identified.	YES	NO	UNCLEAR	N/A
2.13	Methods for the estimation of quantities and unit costs are described.	YES	NO	UNCLEAR	N/A
2.14	Quantities of resource use are reported separately from their unit costs.	YES	NO	UNCLEAR	N/A
2.15	Productivity changes (if included) are reported separately.	YES	NO	UNCLEAR	N/A
2.16	The choice of model used and the key parameters on which it is based are justified.	YES	NO	UNCLEAR	N/A
2.17	All costs are measured appropriately in physical units.	YES	NO	UNCLEAR	N/A

2.18	Costs are valued appropriately.	YES	NO	UNCLEAR	N/A
2.19	Outcomes are valued appropriately.	YES	NO	UNCLEAR	N/A
2.20	The time horizon is sufficiently long enough to reflect all important differences in costs and outcomes.	YES	NO	UNCLEAR	N/A
2.21	The discount rate(s) is stated.	YES	NO	UNCLEAR	N/A
2.22	An explanation is given if costs and benefits are not discounted.	YES	NO	UNCLEAR	N/A
2.23	The choice of discount rate(s) is justified.	YES	NO	UNCLEAR	N/A
2.24	All future costs and outcomes are discounted appropriately.	YES	NO	UNCLEAR	N/A
2.25	Details of currency of price adjustments for inflation or currency conversion are given.	YES	NO	UNCLEAR	N/A
2.26	Incremental analysis is reported or it can be calculated from the data.	YES	NO	UNCLEAR	N/A
2.27	Details of the statistical tests and confidence intervals are given for stochastic data.	YES	NO	UNCLEAR	N/A
2.28	Major outcomes are presented in a disaggregated as well as aggregated form.	YES	NO	UNCLEAR	N/A
2.29	Conclusions follow from the data reported.	YES	NO	UNCLEAR	N/A
2.30	Conclusions are accompanied by the appropriate caveats.	YES	NO	UNCLEAR	N/A
SECTION 3: sensitivity Analysis					
In a well conducted economic study…		*In this study the criterion is met:*			
3.1	The approach to sensitivity analysis is given.	YES	NO	UNCLEAR	N/A
3.2	All important and relevant costs for each alternative are identified.	YES	NO	UNCLEAR	N/A

3.3	An incremental analysis of costs and outcomes of alternatives is performed.	YES	NO	UNCLEAR	N/A
3.4	The choice of variables for sensitivity analysis is justified.	YES	NO	UNCLEAR	N/A
3.5	All important variables, whose values are uncertain, are appropriately subjected to sensitivity analysis.	YES	NO	UNCLEAR	N/A
3.6	The ranges over which the variables are varied are justified.	YES	NO	UNCLEAR	N/A
SECTION 4: CONFLICT OF INTEREST					
In a well conducted economic study…		*In this study the criterion is met:*			
4.1	Competing interests of members have been recorded and addressed.	YES	NO	UNCLEAR	N/A
4.2	Views of funding body have not influenced the content of the study.	YES	NO	UNCLEAR	N/A
SECTION 5: OVERALL ASSESSMENT					
5.1	**How well was the study done to minimize bias?** ***Code: Good, Fair or Poor***	GOOD		FAIR	POOR
5.2	If coded as fair or poor, what is the likely direction in which bias might affect the study results?				
5.3	Other reviewer comments:				

MED Project 2011. Adapted from BMJ, NICE, and the Consensus on Health Economic Criteria (CHEC).

MED PROJECT	Methodology Checklist: Guidelines

Guideline citation *(Include name of organization, title, year of publication, journal title, pages)*

MED Topic:	Key Question No.(s), if applicable:
Checklist completed by:	Date:

SECTION 1: PRIMARY CRITERIA

To what extent is there		*Assessment/Comments:*
1.1	**RIGOR OF DEVELOPMENT: Evidence** • Systematic literature search • Study selection criteria clearly described • Quality of individual studies and overall strength of the evidence assessed • Explicit link between evidence & recommendations *(If any of the above are missing, rate as poor)*	GOOD FAIR POOR
1.2	**RIGOR OF DEVELOPMENT: Recommendations** • Methods for developing recommendations clearly described • Strengths and limitations of evidence clearly described • Benefits/side effects/risks considered • External review	GOOD FAIR POOR
1.3	**EDITORIAL INDEPENDENCE**[10] • Views of funding body have not influenced the content of the guideline • Competing interests of members have been recorded and addressed	GOOD FAIR POOR

If any of three primary criteria are rated poor, the entire guideline should be rated poor.

SECTION 2: SECONDARY CRITERIA

2.1	**SCOPE AND PURPOSE** • Objectives described • Health question(s) specifically described • Population (patients, public, etc.) specified	GOOD FAIR POOR

SECTION 2: SECONDARY CRITERIA, CONT.

10 Editorial Independence is a critical domain. However, it is often very poorly reported in guidelines. The assessor should not rate the domain, but write "unable to assess" in the comment section. If the editorial independence is rated as "poor", indicating a high likelihood of bias, the entire guideline should be assessed as poor.

2.2	**STAKEHOLDER INVOLVEMENT** • Relevant professional groups represented • Views and preferences of target population sought • Target users defined	GOOD	FAIR	POOR
2.3	**CLARITY AND PRESENTATION** • Recommendations specific, unambiguous • Management options clearly presented • Key recommendations identifiable • Application tools available Updating procedure specified	GOOD	FAIR	POOR
2.4	**APPLICABILITY** • Provides advice and/or tools on how the recommendation(s) can be put into practice • Description of facilitators and barriers to its application • Potential resource implications considered Monitoring/audit/review criteria presented	GOOD	FAIR	POOR
SECTION 3: OVERALL ASSESSMENT OF THE GUIDELINE				
3.1	How well done is this guideline?	GOOD	FAIR	POOR
3.2	Other reviewer comments:			

[This tool is adapted from the Appraisal of Guidelines Research & Evaluation (AGREE) II tool. The full AGREE II tool is available from http://www.agreetrust.org/resource-centre/agree-ii/]

Description of Ratings: Methodology Checklist for Guidelines

The checklist for rating guidelines is organized to emphasize the use of evidence in developing guidelines and the philosophy that "evidence is global, guidelines are local." This philosophy recognizes the unique situations (e.g., differences in resources, populations) that different organizations may face in developing guidelines for their constituents. The second area of emphasis is transparency. Guideline developers should be clear about how they arrived at a recommendation and to what extent there was potential for bias in their recommendations. For these reasons, rating descriptions are only provided for the primary criteria in section one. There may be variation in how individuals might apply the good, fair, and poor ratings in section two based on their needs, resources, organizations, etc.

Section 1. Primary Criteria (rigor of development and editorial independence) ratings:

Good: All items listed are present, well described, and well executed (e.g., key research references are included for each recommendation).
Fair: All items are present, but may not be well described or well executed.
Poor: One or more items are absent or are poorly conducted

Appendix E. Summary of Findings Table by Tumor Location and Type

Introduction

This summary of findings provides an overview of the strength of evidence for the use of SRS and SBRT compared to EBRT. This summary of findings is intended to *supplement* the Washington Health Technology Assessment Program's *Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy* report. The findings presented in this document are in aggregate. For specific details and findings per tumor type and location, please refer to the full report on the WA HTA website.

Strength of Evidence

⊕⊕⊕⊕	**High**: Further research is *very unlikely* to change the estimate of effect and our confidence in that estimate. Typical sets of studies would be large RCTs without serious limitations.
⊕⊕⊕◯	**Moderate**: Further research *may* change the estimate of effect and will *likely* have an important impact on our confidence in the estimate of effect.
⊕⊕◯◯	**Low**: Further research is *likely* to change the estimate and *very likely* to have an important impact on our confidence in the estimate.
⊕◯◯◯	**Very Low**: Any estimate of effect is *very uncertain.*

Outcomes

↔	No Difference
↕	Inconsistent Evidence
↑	Increased
↓	Decreased

Overview

The summary tables provide a detailed summary of the strength and direction of evidence per tumor type and location, comparator, and outcomes. Strength and direction of evidence is only provided for tumor types and locations where there is comparative data (Table 1). For non-comparative data, outcomes are listed without strength or direction of the evidence (Table 2).

Table 1. Tumor Types and Locations with Comparative Evidence

Procedure		Strength of Evidence[11]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
CNS – Brain Metastases	7 SRs[12], 12 cohorts, 25 case series			
KQ # 1 Efficacy	6 SRs, 12 cohorts			
SRS+WBRT compared to WBRT		↔ OS ↑ Local tumor control		
SRS+WBRT compared to SRS		↔ OS ↑ Local tumor control ↑ Distant tumor control	↔ QoL ↔ Functional independence ↔ Time to worsened performance status	
SRS alone compared to WBRT alone				↑ OS
SRS for recurrent or progressive brain metastases				↕ OS ↕ Local tumor control
KQ # 2 Harms	6 SRs, 12 cohorts, 25 case series			
SRS+WBRT compared to WBRT		↔ Acute and late toxicities		
SRS+WBRT compared to SRS			↔ Acute and late toxicities	
SRS alone compared to WBRT alone			↔ Toxicities	
SRS for recurrent or progressive brain metastases				↕ Harms
KQ # 3 Subpopulations: *Single brain metastases*	3 SRs (1 RCT)			

[11] No procedure had a high strength of evidence, thus this column is not displayed in this table.
[12] Many overlapping individual between SRs, thus total number of individual studies across all SRs is not provided
Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[11]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
and RPA Class 1				
SRS+WBRT compared to WBRT			↑ Median survival ↑ Local tumor control ↓Worsened performance status(at 6 months)	
KQ # 4 Cost and Cost-Effectiveness	1 SR (7 economic evaluations)			
WBRT alone				SRS is more cost-effective than WBRT alone or combined with SRS
CNS – Glioblastoma multiforme	1 RCT, 2 cohorts, 3 case series			
KQ # 1 Efficacy	1 RCT, 2 cohorts, 1 case series			
EBRT			↔ Survival	
KQ #2 Harms	1 RCT, 1 cohort, 3 case series			
EBRT			↑ Symptomatic radionecrosis	
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
CNS – Glioma	1 cohort, 8 case series			
KQ # 1 Efficacy	1 cohort			
EBRT				↕ Median survival

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[11]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
KQ #2 Harms	1 cohort, 8 case series			
No comparator				Radiation necrosis
KQ #3 Subgroups: *Pediatric patients*				
No comparator				OS, PFS, Moya Moya syndrome
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
CNS – Pituitary Adenoma	2 cohort studies, 13 case series			
KQ # 1 Efficacy	2 cohort studies			
EBRT			↔ OS ↔ Local tumor control	
KQ #2 Harms	2 cohort studies, 13 case series			
EBRT				↓ New hypopituitarism
No comparator				Headache, nausea, fatigue, edema, visual deficits, cranial nerve palsies
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
Head and Neck Cancers	1 cohort, 6 case series			
KQ # 1 Efficacy	1 cohort			
EBRT				↔ Patient survival ↔ Local tumor control

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased

Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[11]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
KQ #2 Harms	1 cohort, 6 case series			
EBRT				↓ Harms (nasopharyngeal carcinoma, head and neck squamous cell carcinoma) cranial neuropathy, carotid blow-out, brain necrosis, mortality, leucopenia, anemia, thrombocytopenia, mucositis, nausea, vomiting, weight loss, skin reactions, massive nasal bleeding, transient facial numbness, retinopathy, carotid aneurysm, xerostomia, pain, dysgeusia, dysphagia, fibrosis, trimus
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on cost or cost-effectiveness identified.				
Lung Cancer	1 SR (35 case series), 33 case series, 3 economic analyses			
KQ # 1 Efficacy	1 SR (35 case series), 33 case series			
No comparator				3-yr OS, local control
KQ #2 Harms	1 SR (35 case series), 33 case series			

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[11]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
No comparator				Fatigue, general malaise, pneumonitis, esophagitis, dermatitis, chest wall pain
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness	3 economic analyses			
EBRT				↕ cost, cost-effectiveness

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Table 2. Tumor Types and Locations with Non-Comparative Evidence

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
Abdomen – Adrenal Metastases	2 case series			
KQ # 1 Efficacy	2 case series			
No comparator[14]				1-yr actuarial survival, 2-yr actuarial survival, local control
KQ # 2 Harms	2 case series			
No comparator				Fatigue, nausea, adrenal insufficiency
KQ # 3 Subpopulations				
No studies on subpopulations identified.				
KQ # 4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
Abdomen – Colorectal Cancer	2 case series			
KQ # 1 Efficacy				
No studies on efficacy identified.				
KQ # 2 Harms	2 case series			
No comparator				hepaticfailure, duodenal ulceration, colonic ulceration, pain , nausea, diarrhea, skin effects

[13] No procedure had a high strength of evidence, thus this column is not displayed in this table.
[14] Due to lack of comparative data, no directionality can be given for outcomes
Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
KQ # 3 Subpopulations				
No studies on subpopulations identified.				
KQ # 4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
Abdomen – Liver Cancer	2 SRs (17 case series), 7 case series			
KQ # 1 Efficacy	2 SRs (17 case series), 7 case series			
No comparator				OS, local control, PFS, QoL
KQ # 2 Harms	2 SRs (17 case series), 7 case series			
No comparator				fatigue, nausea, gastritis, liver enzyme abnormalities, liver toxicity, colonic perforation, small bowel obstruction, death
KQ # 3 Subpopulations				
No studies on subpopulations identified.				
KQ # 4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
Abdomen – Pancreatic Cancer	1 SR (6 trials[15]), 4 case series			
KQ # 1 Efficacy	1 SR (6 trials), 4 case series			
No comparator				OS, pain
KQ # 2 Harms	1 SR (6 trials), 4 case series			
No comparator				bowel perforation, mucositis, stomach and bowel ulcerations,

[15] Trials included two pilot trials, two Phase I trials, and two Phase II trials

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased

Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
				nausea, vomiting, ulcers, gastritis, duodenitis, diarrhea, fatigue
KQ # 3 Subpopulations				
No studies on subpopulations identified.				
KQ # 4 Cost and Cost-Effectiveness 1 cost-effectiveness study				
EBRT				SBRT + gemcitabine is more cost-effective than EBRT + gemcitabine
CNS – Astrocytoma	3 case series			
KQ # 1 Efficacy	3 case series			
No comparator				OS, 5-yr survival, median survival
KQ # 2 Harms				
No comparator				neurologic adverse events, hearing loss, tiredness
KQ # 3 Subpopulations				
No studies on subpopulations identified.				
KQ # 4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
CNS – Ependymoma	2 case series			
KQ # 1 Efficacy	2 case series			
No comparator				OS
KQ # 2 Harms	2 case series			

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased

Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
No comparator				radiation toxicity, facial paresis
KQ # 3 Subpopulations				
No studies on subpopulations identified.				
KQ # 4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
CNS – Meningioma	28 case series, 1 cost analysis			
KQ # 1 Efficacy				
No studies on efficacy identified.				
KQ #2 Harms	28 case series			
No comparator				Erthema/radiodermatitis, alopecia, nausea, post-radiosurgery edema
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness	1 cost analysis			
LINAC radiosurgery versus GammaKnife® Radiosurgery				Costs were slightly higher for LINAC radiosurgery than GKRS
CNS – Multiple CNS Tumors	14 case series			
KQ # 1 Efficacy	14 case series			
No comparator				*Unable to draw any conclusions due to study heterogeneity in tumors, dosing, and reported*

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
				outcomes and harms.
KQ #2 Harms	14 case series			
No comparator				*Unable to draw any conclusions due to study heterogeneity in tumors, dosing, and reported outcomes and harms.*
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
CNS – Neurocytoma	1 SR (121 case reports/case series), 1 case series			
KQ # 1 Efficacy	1 SR (121 case reports/case series)			
No comparator				5-yr OS, 5-yr Local tumor control
KQ #2 Harms	1 SR (121 case reports/case series), 1 case series			
No comparator				*SR did not report harms.* *Case series reported no harms found.*
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
CNS – Schwannoma	1 SR, 36 case series			
KQ # 1 Efficacy	2 case series			
No comparator				Local control, hearing preservation
KQ #2 Harms	1 SR, 36 case series			
No comparator				Hearing loss, hydrocephalus requiring a shunt, new malignancies, new cranial nerve neuropathies
KQ #3 Subgroups – *Neurofibromatosis, Large Vestibular Schwannoma*	3 case series			
No Comparator				Pts with neurofibromatosis may have worse outcomes than pts without neurofibromatosis
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
Head and Neck – Glomus Jugulare	1 SR (19 case series)			
KQ # 1 Efficacy				
No studies on efficacy identified.				
KQ #2 Harms	1 SR (19 case series)			
No comparator				Transient (e.g., dysphagia,nausea, imbalance) toxicities, servere toxicities

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
				(hearing loss, vertigo, facial palsy)
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on cost or cost-effectiveness identified.				
Head and Neck – Ocular Cancer	7 case series			
KQ # 1 Efficacy				
No studies on efficacy identified.				
KQ #2 Harms	7 case series			
No comparator				Dry eye syndrome, retinopathy, optic neuropathy, neovascular glaucoma, cataracts
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on costs or cost-effectiveness identified.				
Prostate Cancer	4 case series			
KQ # 1 Efficacy				
No studies on efficacy identified.				
KQ #2 Harms	4 case series			
No comparator				QoL, sexual QoL, GU toxicities, GI toxicities
KQ #3 Subgroups				

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
No studies on subpopulations identified.				
KQ #4 Cost and Cost-Effectiveness				
No studies on cost or cost-effectiveness identified.				
Spine	1 SR (29 case series), 13 case series, 1 economic study			
KQ # 1 Efficacy	1 SR (29 case series), 11 case series			
No comparator				Local tumor control, median survival, pain control, QoL
KQ #2 Harms	1 SR (29 case series), 13 case series			
No comparator				Fatigue, nausea, esophagitis, mucositis, dysphagia, spinal fractures, lumbar plexopathy, paraparesis, myelopathy
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost Effectiveness	1 economic study			
EBRT				SBRT costs > EBRT costs
Multiple Tumor Sites	4 case series			
KQ # 1 Efficacy	4 case series			
No comparator				Local control
KQ #2 Harms	4 case series			
No comparator				Nausea, fatigue, skin irritation, pleural and pericardial effusion,

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased

Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Procedure		Strength of Evidence[13]		
Malignancy Comparator	**# of SRs (# included studies in SRs), # of subsequently published studies**	⊕⊕⊕◯ **Moderate**	⊕⊕◯◯ **Low**	⊕◯◯◯ **Very Low**
				gastric bleeding, vertebral fractures
KQ #3 Subgroups				
No studies on subpopulations identified.				
KQ #4 Cost and Cost Effectiveness				
No studies on costs or cost-effectiveness identified.				

Outcomes: ↔ No Difference; ↕ Inconsistent Evidence; ↑ Increased; ↓ Decreased
Abbreviations: OS – overall survival; PFS – progression free survival; QoL – quality of life; EBRT – external beam radiation therapy; WBRT – whole brain radiation therapy; GI – gastrointestinal; GU – gastrourinary

Appendix F. Summary of Findings Tables by Tumor Location

Abdominal Cancer (Colorectal/Rectal, Liver, Pancreas)

Adrenal Metastases

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Casamassima (2012) Case Series **Adrenal metastases** Primary: lung, colon, melanoma, breast, kidney, uterus, unknown	n = 48 Median age 62.7 y (range 43-77y); 18 previously received chemo for metastatic disease; unilateral adrenal mets = 79.2%; bilateral = 20.8%; median interval primary dx to adrenal mets = 37.2mo	Not overtly defined in text; retrospectively reviewed all pts treated at Uni Florence w/adrenal mets w/SBRT (2002-2009)	Hypofractionated SBRT; no comparator F/U: Median f/u 16.2 mo (range 3-63 mo); followed from treatment to disease progression; measured by RECIST on CT/PET	Most dosed w/ 36Gy in 3 fractions (17.14 Gy per fraction); 8 pts single-fraction, 40 pts multi-fraction; BED10 = 137.3 (>100 recommended for LC)	n/a (no control or comparison group)	"Generally well-tolerated," but limited length of f/u so no report on late toxicity (common w/SBRT); 1 case Grade II adrenal insufficiency	Poor No conflict of interest reported
Chawla (2009) Case Series **Adrenal metastases** Primary: lung, liver, breast, melanoma, pancreas, head/neck, unknown	n = 30 Mean age 61.8 (range 39.4-77.6); 17 previously received chemo for met dz; 9 received previous SBRT; unilateral adrenal mets = 83.3%; bilateral =	Not overtly defined in text; retrospectively reviewed all pts treated at Uni Rochester w/adrenal mets w/SBRT (2001-2008); Selected for "adverse risk factors (i.e., bulky	Hypofractionated SBRT; Goal of SBRT: curative intent n= 14 (6 underwent additional SBRT other lesions), palliation n = 16; no comparator F/U: n = 24 w/ >3	Median dose = 40Gy; Range: 16Gy in 4 fractions to 50Gy in 10 fractions	n/a (no control or comparison group)	Mild fatigue and Grade 1 nausea were common; No Grade 2-4 toxicity; 16 followed >6 mo and no late toxicity observed	Poor No conflict of interest reported

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	16.7%; median interval primary dx to adrenal mets = 8.4 mo (range 0-101.4mo); Histologic conf of adrenal met n = 2; radiographic dx of adrenal mets n = 28	dz)"	mo f/u w/serial CT; followed from treatment of adrenal mets w/SBRT until disease progression; evaluation done using RECIST on CT/PET imaging; 16 followed >6 mo				

Colorectal

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Hoyer (2006) Case Series **Colorectal cancer**	n = 64 (141 CRC metastases) colorectal cancer, metastatic 44 men, 20 women; median age 67 yrs (62-81); 41% had rectal and 59% had colon cancer as primary tumor for median of 1.5 yrs (0-	Inclusion criteria: Histologically proven CRC, radical resection of primary tumor, judged inoperable and not amendable for other local tx; maximum diameter of largest metastasis ≤6 cm; tumors visible on CT scan; 1-4 metastases, but more could be	SBRT delivered using Siemens Primus or Varian Clinac 2100/2300 F/U: median 4.3 yrs (0.2-6.3)	central dose of 45 Gy, delivered in 3 fractions of 15 Gy, w/in 5-8 days	n/a (no control or comparison group)	Toxicity (in 61 pts): 1 pt (1.6%), Grade 4 hepatic failure; 3 pts (4.9%), Grade 3 intestinal toxicity (2 pts duodenal ulceration, 1 pts colonic ulceration); 18 pts (28%), Grade ≥2 pain; 16 pts (25%), Grade ≥2 analgesic score; 10 pts (16%), Grade ≥2 nausea; 5 pts (8.2%), deteriorated to WHO performance status Grade ≥2; 4 pts (6.6%), Grade ≥2 diarrhea; 4 pts (6.6%), Grade ≥2 skin reaction.	Poor Potential conflict of interest, small sample size

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	12.8) before SBRT; median of 2 metastases (1-6); median diameter of largest metastasis 35 mm (10-88)	permitted; WHO-ECOG performance status 0-2; no chemotherapy w/in 1 mo before inclusion; Exclusion criteria: sx related to brain or bone metastases					
Kang (2010) Case Series **Colorectal Cancer**	59 pts (78 lesions) Colon cancer, metastatic (confined to one organ) Males (34), female (25). Age (yrs) 57-83 (median 57). 21 pts had undergone curative-intent tx prior to SBRT – resection (4), radiation therapy (16), RFA (1). 10 pts did not receive systemic therapy for metastatic disease prior to enrollment. 49 pts received chemotherapy after dx of metastatic CRC prior to enrollment	Histologicaly proven colorectal adenocarcinoma, radical resection of the primary tumor, inoperable as assessed by a trained surgeon, not amenable to another local treatment, progression or stable disease after chemotherapy for recurrence, 1-4 lesions confined one organ as determined by PET/CT, and max diameter of the largest lesions of 7 cm by CT Excluded: tumors attached to the esophagus, stomach, or bowl; pts with PS	CyberKnife SBRT F/U: 9 to 80 mos (median 32 mos)	Lung mets: 39-51 Gy Liver mets: 36-51 Gy Lymph node mets: 36-51 Gy; 16 + 40-45 (EBRT) Others: 14/1 fx - 40/3 fx	n/a (no control or comparison group)	Acute Grade 1-2 toxicities (24 pts, 41%) – nausea, vomiting, musculoskeletal discomfort Grade 4 complications (2 pts, 3%)	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
		>2					

Liver

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Tao (2012) Systematic Review **Liver**	N = 499 15 prospective clinical trials Patient characteristics: primary (158 pts), metastatic (341 pts)	SBRT (equipment or techniques used in 15 studies not described), no comparator F/U: Median among all studies, 16 months, or 1.3 years (range, 0.5-85 months, or 0.4-7.1 years; mean, 17.8 months, or 1.48 years) Dose: 18-60 Gy in 1-10 fractions of 4-30 Gy (median or mean not reported)	1-yr local control rate of 50-100%; 1-yr overall survival rate of 33-100%	Tx-related adverse events rate 17% (73 events for 499 pts) Radiation-induced liver disease: classic, 8 patients; non-classic, 5 patients. Grade 3-5 treatment-related adverse events: grade 3, 66; grade 4, 4; grade 5, 3 (after elimination of events not related to treatment or occurring as a result of disease progression). No grade 3-5 events in 8 studies.	Poor
Zamboglou (2012) Systematic Review **Extrahepatic cholangiocarcinoma / Pancreatic Cancer**	N = 284 8 studies (4 pilot, 2 phase I, 2 phase II) Patient characteristics: NR, very heterogeneous	Stereotactic radiotherapy, no comparator F/U: NR Dose: 15 to 45 Gy	Not summarized.	"Acceptable" toxicity in 6 studies, "considerable" in 1 study, and "not acceptable". In one study, Grade 3 to 4 toxicity 10% of patients. Most serious was a small bowel perforation. Late 6- and 12- months Grade 2 toxicity in 11% and 25% of patients. In one study, 8% of pts had acute Grade 3 toxicity. Late toxicity in 5.5% of patients (gastrointestinal bleeding requiring transfusion)/ No treatment-related deaths./ In one study, all patients experienced Grade 2 nausea, other serious side effects were: serious	Poor The poor quality is mostly related to the limited number of studies available for this topic. Most studies are pilot, phase 1 and 2 studies. There were significant difference among centers in terms of outcomes and harms. The authors recommend that highest precision

				mucositis (7.4%), stomach/bowel ulcerations (7.4%), perforation of a stomach ulcer (3.7%), severe gastrointestinal ulcerations (22.2%), duodenal stenosis (11.%).	for diagnostics, positioning, and irradiation are observed to keep irradiated volume as small as possible.

Individual studies (published after review)

Reference Study Design	Sample size and Pt Characteristics	Patient Selection Criteria	Intervention Comparator Follow-up	Dose	Outcomes Assessed Main Findings	Harms	Quality Comments
Andolino (2011) Case Series **Liver**	n = 60 36 Child-Turcotte-Pugh (CTP) class A and 24 CTB class B liver cirrhosis Hepatocellular carcinoma (HCC), primary Males 49, females 11. Median age 59 (24-85). Median KPS: 90 (60-100). Hep C: 30 (50%), Hep B: 8 (13.3%), other: 22 (36.7%). Of 36 CTP class A, CTP score: 5: 15 (41.7%), 6: 21 (58.3%). Of 24 CTP class B, CTP score: 7: 15 (62.5%), 8: 6 (25%), 9: 3 (12.5%). AJCC T stage: T1: 47 (78.3%), T2: 12	Pts tx at clinic between 2005-2009 with SBRT for hepatocellular carcinoma (CTP class A or B) with no metastases	stereotactic body radiation therapy F/U: at 1 month, every 3 months first two years and then every 6 months. Median follow-up 27 months (2-52)	Median dose for CTP class A: 3 fractions of 14 Gy (8-16 Gy) median total dose 44 Gy (30-48 Gy). For CTP class B: 5 fractions of 8 Gy (8-16) with median total dose 40 Gy (24-48 Gy)	Overall actuarial 2 year local control (LC), progression free survival (PFS) and overall survival (OS) rates were 90%, 48% and 67%. Median time to progression (TTP) was 47.8 months. Larger tumor volume, CTP class B and absence of OLT were associated with worse PFS (p=0.029, 0.013 and 0.018 respectively) and OS (p<0.001, 0.018, <0.001 respectively) and lower total dose was associated with worse OS (p=0.006) but not PFS. No significant prognostic factors for LC or TTP.	13 pts (21.7%) developed grade 1/2 nonhematologic toxicity (fatigue, nausea, right upper quadrant pain.) 1 pt (1.7%) grade 2 chronic chest wall toxicity. 9 pts (15%) grade 3 liver enzymes and/or hyperbilirubinemia. 9 pts (15%) grade 3 thrombocytopenia. 2 pts (3.3%) elevated INR. 7 pts (11.7%) grade 3 hypoalbuminemia. 1pt (1.7%) grade 4 thrombocytopenia and hyperbilirubinemia. data shows a relationship between prior CTP score and development of toxicity	Fair Small sample size, case series design

	(20%), T3: 1 (1.7%). # lesions: 1: 51 (85%), 2: 7 (11.7%), 3: 2 (3.3%). Tumor diameter in cm: <1: 1 (1.7%), 1-2: 9 (15%), 2-3: 17 (28.3%), 3-4: 19 (31.7%), >4: 14 (23.3%). Median gross tumor volume: 29 cc (2-112 cc). Median uninvolved liver: 1644 cc (788-3,083 cc). 6 pts (10%) received prior transarterial chemoembolization. 23 pts (38.3%) proceeded to orthotopic liver transplant (OLT)						
Chang (2011a) Case Series **Liver**	n = 65 (102 lesions) Colorectal liver metastases median age 67 yrs (39-87); 63% Princess Margaret, 25% University of Colorado, 12% Stanford University; 72% had ≥1 chemotherapy regimen after dx,	1-4 lesions, received 1-6 fractions of SBRT, radiologic imaging ≥3 mos post-tx; pts enrolled at Stanford or Princess Margaret Hospital required to have unresectable disease or be medically inoperable	SBRT from conventional linear accelerator (n=57) or by CyberKnife (n=8) F/U: Follow-up ≥3 mos after SBRT, repeat imaging every 3 mos	Dose and fractionation schedule varied by institution; total median dose 41.7 Gy (22-60), median of 8 Gy/fractio	12-, 18-, 24-month OS: 72%, 55%, 38%	Acute toxicities: 11 pts (17%), grade ≥2 acute gastrointestinal (GI) toxicity; 2 pts (3%) had grade ≥3 elevated liver enzymes, no symptomatic liver toxicity. Late toxicities: 4 pts (6%), grade ≥2 late toxicities (2 pts w/ grade 3 gastritis, 2 w/ grade 2 small bowel ulcers); 2 pts (3%), grade 3 elevated liver enzymes; 2 pts (3%) persistent chest wall pain; 1 pt (1.5%), gastritis and chest wall pain; 1 pt (1.5%), gastritis and elevated liver enzymes; no rib fractures noted.	Poor Potential conflict of interest, small sample size

	42% had ≥2 prior regimens; 34% had active nonhepatic disease		for first yr, then every 3-6 mos; median 1.2 yrs (0.3-5.2)	n (5-30), median of 6 fractions (1-6)			
Katz (2007) Case Series **Liver**	n = 69 69. 60 pts (87%) had follow-up CT scans making them available for analysis Males 34, females 35. Median age: 59.8 (35.6-87.7). Mean # mets: 2.5 (1-6). Primary cancer: colorectal: 20 (29%), breast: 16 (23.2%), pancreas: 9 (13%), lung: 5 (7.2%), hepatocellular: 5 (7.2%), GI: 5 (7.2%), carcinoid: 5 (7.2%), other: 4 (5.8%). Extrahepatic mets: 35 (51%). Concurrent chemo: 28 (41%)	Pts tx at clinic between April 2001-Oct. 2004 with SBRT for metastases to the liver. Pts included if mets were confined to liver. Pts with extrahepatic disease included if liver disease considered most life limiting component of disease. Adequate liver function, life expectancy ≥6 months. Pts with less than 1,000 cm3 of uninvolved liver excluded.	Stereotactic body radiation therapy (SBRT) F/U: at 1 month then every 3 months for first 2 years, then every 3-6 months afterward. Median follow-up 14.5 months (3.6-37.0)	most common 10 fractions of 5 Gy over two weeks for total dose 50 Gy	Actuarial overall local control at 10 and 20 months was 76% and 57%. Median overall survival (OS) was 14.5 months. Actuarial OS at 10 and 20 months was 78% and 37%. Progression free survival was 46% at 6 months and 24% at 12 months.	Grade 1 or 2 elevation of liver function tests: 17 (28%). No grade 3 or higher toxicity	Poor No comparison, no prognostic modeling with control variables
Lee (2009) Case Series Liver	n = 68 Liver, metastatic and recurrent Males 32, females	Pts with inoperable liver mets. Extrahepatic disease allowed if largest disease	stereotactic body radiation therapy (SBRT)	median prescription dose: 41.4 Gy in 6 fractions (27.7 - 60	Median survival 17.6 months (95% CI, 10.4-38.1 months). 18-month survival rate: 47% (95% CI: 32% - 61%). Median progression free survival 3.9 months (95% CI: 3.4 - 7 months). In 67 pts with	Acute toxicity: thrombocytopenia transient grade 3: 2 (3%), thrombocytopenia leading to thrombocytopenic purpura requiring splenectomy: 1 (1%), grade 3 liver enzymes: 2 (3%). Decline in liver	Poor Small sample size, case series design, did

	36. Mean age 63 (30-90). KPS: 70-80: 9 (14%), 90: 31 (49%), 100: 23 (36%), unknown: 5 (8%). Extrahepatic disease: 36 (53%). Median time from diagnosis to hepatic mets: 2.5 yrs (0.4-10.9), # prior liver recurrences: 0: 32 (47%), 1: 16 (24%), 2: 10 (15%), ≥3: 9 (13%), unknown: 1 (1%). previous tx: surgery: 7 (10%), radio frequency ablation (RFA): 8 (12%). previous lines of chemo: 0: 9 (13%), 1: 15 (22%), 2: 29 (43%), ≥3: 15 (22%). median # tumors: 1 (1-8). median gross tumor volume: 75.2 cm3 (1.2-3,090). primary cancer: Colorectal cancer (CRC): 40 (59%), breast: 12 (18%), other: 16 (24%0	burden was hepatic. KPS ≥60, life expectancy > 3 months. >800 mL of uninvolved liver. Child's A liver score, hemoglobin ≥90 g/L, neutrophils ≥1.5 billion/L, platelets ≥ 80,000 billion/L, bilirubin < 3x upper limit of normal range, international normalized ratio < 1.3 or correctable with vitamin K, AST or ALT < 6x the ULN, creatine < 200 umol/L.	F/U: at 1 month, every 3 months for 1st year, every 6 months to year 3 and then annually to year 5	Gy)	follow-up, 33 (49%) had sustained objective tumor response: 4 (6%) complete response, 29 (43%) partial response. Stable disease in 20 pts (30%). 12-month local control (LC) rate 71% (95% CI: 58% - 85%). On univariate analysis, LC improved in smaller volume tumors (<75.2 mL, p=0.001) and with higher delivered dose (p-0.01). 56 pts (83.9%) developed recurrence.	function to Child's score B: 3 (4%), or score C: 1 (1%). liver pain grade 1: 3 (4%), grade 2: 3 (4%). Chest wall pain grade 1: 2 (3%). skin grade 2: 1 (1%). Gastritis/esophagitis: grade 1: 5 (7%), grade 2; 5 (7%), grade 3: 2 (3%). Colitis: grade 2: 1 (1%) Lethargy grade 1: 15 (22%), grade 2: 12 (18%), grade 3: 1 (1%). Nausea grade 1: 8 (12%), grade 2: 4 (6%), grade 3: 2 (3%). Late toxicity: duodenal bleed grade 4: 1 (1%), small bowel obstruction grade 4: 1 (1%), grade 5: 1 (1%). Non-traumatic rib fracture grade 2: 2 (3%). Chest wall pain grade 2: 1 (1%). Dyspepsia grade 2: 1 (1%)	not report all variables tested only significant ones
Rusthoven (2009) Case Series **Liver**	n = 47 Liver metastasis, metastatic	Adult patients with 1 to 3 liver metastases; any primary tumor	SBRT F/U: For patients	Phase 1: 36 to 60 Gy; Phase 2: 60 Gy in	Distant progression occurred in 39 pts (83%) at median 6-months after SBRT (range, 2 to 53)	Grade 4 or 5: none; Grade 3: soft tissue injury in 1 patient; actuarial rate of any Grade 3 toxicity was 2% at last follow-up. RILD: none. None of the 7 patients	Poor Possible underreporti

	47 patients with 63 lesions; median age 58 years, range 27 to 92; median time since diagnosis 22.7 months, range 0 to 236; median number of prior systemic treatments 3.4, range 0 to 55; presence of extrahepatic disease in 45% of patients; maximum lesion diameter median 2.7 cm, range 0.4-6.8	except germ cell tumor, leukemia, or lymphomia; individual tumor size <6 cm; no prior radiotherapy to the upper abdomen; total bilirubin < 3mg/mL; albumin>2.5g/dL; normal prothrombin, partial thromboplastin times unless on anticoagulants; serum liver enzymes <3x upper limit of normal; no chemotherapy 14 days before and after SBRT; KPS at least 70	assessable for local control (defined as minimum 6 months follow-up; 36 patients): median 16 months (range, 6 to 54)	3 fractions	Median distant progression-free survival: 6.1 mos Median progression-free survival: 6.1 mos Median OS rate: 20.5 mos 2-yr OS: 30% (95% CI, 15.1% to 47.2%)	who died before 6 months experienced toxicity.	ng of toxicity, especially mild
Shun (2008) Case Series **Liver**	n = 99 Liver cancer, primary and recurrent 68 men (31.3%) and 31 women (31.3%); Mean age (±SD), 62.42±12.6; Mean years of education, 8.87±4.77;	Inclusion criteria: Adult (≥18 years-old) liver cancer patients who were aware of their cancer diagnosis; Receiving SRT; Able to verbally communicate; Willing to participate in the	SRS F/U: Once weekly for 6 weeks following SRT	Mean dose of SBRT, 4,260.57 cGy (SD ± 1,253.56; range 1,080-7,200); Fraction numbers: 20, 22	QoL scores increased from 113.80 (SD=21.98) to 114.48 (SD=25.84) (p=0.746) GEE analysis indicates that functional status (p=0.003), depression (p=0.0001), level of albumin (p=0.001), and overall symptom severity (p=0.0001) are important factors associated with changes of QoL during tx.	Group differences and symptoms were analyzed with generalized estimating equations; Radiation dosage was unrelated to overall symptom severity (p=0.728 at week 3 and p=0.552 at week 6) (not consistent with other studies); Hemoglobin (mean ± SD g/dL at 0, 3, and 6 weeks: 12.43±1.94, 12.04±1.83, and 11.94±1.84, respectively) and Serum albumin (mean ± SD g/dL at 0, 3, and 6 weeks: 3.74±0.53, 3.62±0.50, and 3.59±0.48,	Fair Original group was 116 patients, but 17 (14.7%) did not complete study because they

	Employment: Currently employed. 18 (18.2%); Unemployed, 80 (80.8%); Able to carry out normal activity without restriction, 51.5%; Eastern Cooperative Oncology Score at Baseline: Fully active, 51 (51.5); Restricted, 36 (36.4); Ambulatory, 10 (10.1%); Missing, 2 (2.0); Received transcatheter arterial chemoembolization before SRT: Yes, 50 (50.5%); No, 47 (47.5%);	study and sign a consent form; Treated between April 2002 and December 2005; Exclusion criteria not reported		(22.2%); 21-25, 54 (54.5%); 26-30, 23 (23.3%); Mean Irradiated volume ± SD, 220.39±343.33 cm3;		respectively) decreased over time and Alanine aminotransferase (mean ± SD, U/l at 0, 3, and 6 weeks: 56.54±43.29, 79.57±94.45, and 96.27±142.83, respectively) increased over time; (authors termed this an "imperceptible side effect); NOTE: Fatigue; nausea; sleep disturbance; pain; abdominal distension; diarrhea; and lack of appetite occurred in patients, as they were analyzed for effects on quality of life, however, no information on patient numbers of severity of side effects was reported.	withdrew from SRT; those who withdrew did not differ from the remaining patients in clinical characteristics
Tse (2008) Case Series **Liver**	n = 41 hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (IHC), primary, metastatic Mean age 62 years, range 41 to 85; 31 men, 10 women; 41% of patients had prior therapy;	Inclusion: unresectable HCC or IHC; age >18 years; life expectancy >12 weeks; Child-Pugh A liver function; >800 mm3 uninvolved liver; Karnofsky performance status ≥60; E:xclusion: bilirubin ≥3x	SBRT F/U: Median 17.6 months (range, 10.8 to 39.2)	Median 36 Gy (range, 24 to 54)	Median survival: 13.4 mos (96% CI, 11.0 to 21.1) 1-yr survival rate 51% (95% CI, 34%, to 65%) Overall RECIST response rate: 49% (complete response 5%; partial response 44%)	Within 3 months: Grade 4/5: None for up to 3 months. Grade 3 liver enzymes (24%), thrombocytopenia (2.4%), and nausea (7.3%); Grade 1 pleural effusion (7.3%); decline in liver function from Child-Pugh A to B (17%), transient biliary obstruction (5%); Late Toxicity in 5% of patients (disease progression with possible relationship to treatment)	Poor Discrepancy in numbers for harms in abstract and text. Small sample size, especially for subgroup analysis. 7 of 49 enrolled patients

	Karnofsky performance score 100 (24%), 90 (32%), 80 (29%), 70 (14%), unknown (10%). T1N0, T2N0, or T3N0 (875). 10% of HCC and 100% of IHC patients had extrahepatic/metastatic disease. 525 of HCC and 40% of IHC patients had vascular involvement. Median tumor volume of largest single lesions, 173 mL	upper limit of normal; AST or ALT ≥6x upper limit of normal; creatinine >200 mol/L; international normalized ration 1.3; hemoglobin <90 g/L; platelets < 80,000/mL; clinical ascites, and previous irradiation to the right upper abdomen; no chemotherapy at least 2 weeks before and 4 weeks after SBRT					(14%) were not eligible and were removed from treatment.

Pancreas

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Zamboglou (2012) Systematic Review **Extrahepatic cholangiocarcinoma / Pancreatic Cancer**	N = 284 8 studies (4 pilot, 2 phase I, 2 phase II) Patient characteristics: NR, very heterogeneous	Stereotactic radiotherapy, no comparator F/U: NR Dose: 15 to 45 Gy	Not summarized.	"Acceptable" toxicity in 6 studies, "considerable" in 1 study, and "not acceptable". In one study, Grade 3 to 4 toxicity 10% of patients. Most serious was a small bowel perforation. Late 6- and 12- months Grade 2 toxicity in 11% and 25% of patients. In one study, 8% of pts had acute Grade 3 toxicity. Late toxicity in 5.5% of patients (gastrointestinal bleeding requiring transfusion)/ No treatment-related deaths./ In one study, all patients experienced Grade 2 nausea, other serious side effects were: serious mucositis (7.4%), stomach/bowel ulcerations (7.4%), perforation of a stomach ulcer (3.7%), severe gastrointestinal ulcerations (22.2%), duodenal stenosis (11.%).	Poor The poor quality is mostly related to the limited number of studies available for this topic. Most studies are pilot, phase 1 and 2 studies. There were significant difference among centers in terms of outcomes and harms. The authors recommend that highest precision for diagnostics, positioning, and irradiation are observed to keep irradiated volume as small as possible.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Chang (2009a) Case Series **Pancreas**	n = 77 Adenocarcinoma of the pancreas,	Inclusion criteria: Confirmed histologic evidence of	SBRT alone, 61 (79%); SBRT with fEBRT, 16	25 Gy in a single fraction to the isodose line covering >95% of	6- and 12-mos progression free survival: 26%, 9% 6- and 12-mos overall	Acute: Small bowel ulcer, 2 (3%) (Grade 2); gastric ulcer, 1 (1%) (Grade 3); pain, 1 (1%) (Grade 1). Late: Small bowel ulcer, 3 (4%)	Poor Retrospectiv e study with

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Primary, metastatic, and recurrent 49 (64%) men and 28 (36%) women, median age 64 (range 39 to >90); Cancer stage: Locally unresectable, 56 (73%), medically inoperable, 4 (5%), marginally resectable, 2 (3), metastatic, 15 (19%). Initial diagnosis, 69 (90%); recurrent 8 (10%). Prior radiation therapy: 9 (12%); Prior chemotherapy: 15 (19%). Current chemotherapy: 59 (77%).	adenocarcinoma of the pancreas; treated in a single fraction of Gy; no previous Whipple procedure or other resection; unresectable disease (e.g., presence of metastatic disease, radiographic findings of major vessel involvement, comorbid illnesses that make patient high risk); Exclusion criteria: tumors >7.5 cm in any 1 dimension or single-fraction SBRT	(21%); CyberKnife; gemcitabine therapy starting 2 wks after SBRT F/U: Follow-up pancreatic protocol CT scans and PET/CT scans at 4 to 12 weeks after SBRT and every 2 to 4 months thereafter until disease progression; the overall median follow-up was 6 months (range 3-31 months)	planning target volume	survival: 56%, 21% Median survival durations from time of SBRT for entire group (6.4 mos), locally adv group (6.7 mos), metastatic group (4.7 mos)	(Grade 2); gastric ulcer, 3 (4%) (Grade 3); duodenal stricture, 1 (1%), (grade 3); biliary stricture, 2 (3%) (Grade 3); small bowel perforation, 1 (1%) (Grade 4). Total: 14 (18%) (6 grade 2, 7 grade 3, 1 grade 4)	very heterogeneous population
Didolkar (2010) Case series **Pancreas**	n = 85 Pancreas, primary, recurrent Males 50, females 35. Median age 66	Pts seen at clinic between Feb 2004-Nov 2009 with inoperable primary or recurrent pancreatic cancer	stereotactic radiosurgery (SRS) F/U: every 2-3 months. 2pts (2.4%)	median total dose 25.5 Gy (15-30 Gy) in 1-4 fractions (mean 3 fractions)	Local tumor control obtained in 78 (91.7%) pts. Complete response: 10 (11.8%), partial response: 27 (31.7%) and stable disease: 41 (48.2%). Distant disease progression in 65	19 pts (22.3%) developed multiple grades III or IV gastrointestinal toxicities. Duodenitis: 12 (14.1%), gastritis: 11 (12.9%), diarrhea: 3 (3.5%)	Poor Didn't report full statistical analysis

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(36-88). Tumor location in pancreas: head: 57 (67%), body/tail: 28 (33%). Histology: adenocarcinoma: 80 (94.1%), neuroendocrine/islet cell carcinoma: 3 (3.5%), other: 2 (2.4%). Prior tx: surgery: 14 (16.5%), radiation therapy: 29 (24.1%), chemo: 48 (56.5%). Pre SRS pain: mild 0-3: 54 (63.5%), mod. 4-7: 18 (21.2%), severe 8-10: 13 (15.3%). KPS <80: 14 (16.5%), >80: 71 (83.5%) stet. Pre SRS tumor staging: T3: 18 (21.2%), T4: 67 (78.8%), N0: 12 (14.1%), N1: 16 (18.8%), NX: 57 (67.1%), M0: 64 (75.3%), M1: 21 (24.7%). Gross tumor volume (GTV): median 59..7 cm3, mean 70.4 cm3		lost to follow-up		pts (76.5%). Of 31 pts with pain scores ≥4, 15 (48.4%) had complete relief lasting >6 months. Remaining 16 pts (51.6%) had relief of pain to lower scores following SRS. Overall median survival from diagnosis 18.6 months and from SRS 8.65 months		

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(9.8-223.3 cm3)						
Rwigema (2011b) Case Series **Pancreas**	n = 71 advanced adenocarcinoma of the pancreas, primary, metastatic, recurrent Median age 71 yrs, range 33 to 91: 37 men, 34 women; primary in (56%), recurrent (16%), metastatic disease (11%), positive margins (17%); prior radiotherapy (14 patients); median tumor volume, 17 cm3 (range 5.1-249)	Histologcially confirmed pancreatic cancer. Patients with metastatic disease were selected based on expected palliation.	SBRT. 55% patients had chemotherapy post-SBRT. F/U: Whole patient group: Median 6 months (range, 0.3 to 26); Surviving patients: Median 12.7 months (range, 4 to 26)	Median 24 Gy (range, 18 to 25) as a single fraction in 67 patients and fractionated in 4 patients	Median overall survival from time of SBRT: 10.3 mos Time recurrence for recurrent disease or time of diagnosis for primary disease: 12.8 mos 6-mos overall survival rate (adjuvant vs locally-advanced groups): 100% vs 57.4% (p=0.001) 1-yr overall survival rate (adjuvant vs locally-advanced groups): 81.8%% vs 30.2%% (p=0.001) OF the 16 pts who reported pain symptoms at time of SBRT, 13 pts (81.3%) reported complete pain relief shortly after SBRT	Any toxicity: 43.7% patients. Acute toxicities (% patients): Grade 3 (4.2%) including nausea (1 patient), abdominal pain (1 patient), gastroparesis (1 patient); Grade 2 (11.3%) including fatigue (3 patients), nausea (3 patients), abdominal pain (1 patient), weight loss (1 patient); Grade 1 (24%) including diarrhea (4 patients), fatigue (3 patients), nausea (2 patients), abdominal pain (3 patients), vomiting (3 patients), weight loss (2 patients); Late toxicities (% patients): Grade 1 (4.2%) including abdominal pain (1 patient) and weight loss (2 patients)	Poor
Seo (2009) Case Series **Pancreas**	n = 30 pancreatic cancer, primary 13 men and 17 women; Median patient age, 63 years	Inclusion criteria: Patients with pathologically confirmed, locally advanced, nonmetastatic, inoperable pancreatic cancer;	EBRT to 40 Gy followed by SBRT boost; SBRT delivered with CyberKnife (Accuracy,	EBRT delivered at a total dose of 40 Gy in 20 fractions using a linear accelerator (10-MV or 15-MV); After EBRT cessation, a single fraction of 14 to 17	1-yr overall survival: 60.0% Median overall survival: 14 mos In pts with distant metastases, 1-yr progression free survival was 35.5%.	Acute toxicities defined as adverse events occurring within 3 months after SBRT and late ones were defined as those occurring after 3 months; Acute: Nausea, vomiting, and/or pain, grade 1 or 2, 20 (66.7%); Duodenal obstruction, grade 4, 1 (3%); Patient developed	Fair NOTE: Severe toxicity was encountered at 17 Gy so dose

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(range, 40-74); Median gross tumor volume, 41 mL (range 21-96); Primary tumor location: pancreatic head, 17; body or tail, 13; All 30 patients had a T4 lesion and 9 patients had positive lymph nodes; High carbohydrate antigen 19-9 serum levels PRE-EBRT, 24 of 30 patients; these 24 patients had 8 week post-SBRT re-evaluation: 16 (66.7%) had reduced carbohydrate antigen 19-9 level of more than 30% compared to their initial levels; The other 8 patients (33.3%) showed either carbohydrate antigen 19-9 increase or reduction of less than 30% of their initial levels	Eastern Cooperative Oncology Group score from 0-2; Adequate bone marrow function for radiotherapy (leukocytes >3,000 /μL, absolute neutrophil count >1,500 /μL); Treated between May 2004 and November 2006; Exclusion criteria: Invasion of the duodenum; Previous abdominal RT; Involvement of more than 3 regional lymph nodes by CT or PET scan;	Inc., Sunnyvale, CA) F/U: Follow-up included CT scan 8 weeks after SBRT; then abdominal CT or PET/CT or CA19-9 every 2 or 3 months after SBRT	Gy SBRT was administered as a boost without a break; Delivered radiation doses*: 14 Gy, 3; 15 Gy, 6; 16 Gy, 6; 17 Gy, 15; Radiation doses were prescribed at the isodose line (75-80% of maximum dose) to cover at least 97% of planning target volume; *Information about dose cohorts: Starting dose of 14 Gy administered as single fraction based on calculations of normalized total dose (28 Gy in 2-Gy fractions, $\alpha/\beta = 10$ Gy); At least 3 patients were included in each SBRT dose cohort; If none of the first 3 patients showed grade 3 or 4 toxicity after 3-4 months of	Median time to progression: 10 mos	3 months after SBRT; had largest gross tumor volume and received a 17 Gy SBRT boost; required bypass surgery; No late complications developed among the 25 patients with adequate follow-up	increases were stopped there

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				follow-up, the dose was escalated by 1 Gy/fraction for the next cohort; Accrual to cohort did not close for toxicity assessment before the dose was escalated; NOTE: Total irradiation times maintained at 40-50 minutes			
Murphy (2012) Cost effectiveness **Pancreatic cancer**	Markov model cost effectiveness analysis		Chemotherapy alone vs. Chemo plus EBRT vs. Chemo plus IMRT vs. Chemo plus SBRT		**Chemo** / **Chemo & EBRT** / **Chemo & IBRT** / **Chemo & SBRT** 1.Rad costs: $0 / $13412 / $25366 / $7146 2.Chemo costs: $13400 / $13400 / $13400 / $13400 3.End of life costs: $13040 / $13040 / $13040 / $13040 4.Cost of Rad Toxicity event: $15248 / $15248 / $15248 / $15248 5.Prob of Rad Toxicity event: 0 / 0.016 / 0.0061 / 0.009 **Incremental cost effectiveness ratio (ICER)** Chemo & SBRT vs. Chemo alone: ICER = $69,500/QALY EBRT & chemo vs. chemo alone : ICER = $126,800/QALY IBRT & chemo vs. EBRT & chemo: ICER = $1,584,100/QALY		Fair Values used for clinical effectiveness based on expert opinion

Central Nervous System

Astrocytoma

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Hadjipanayis (2003) Case Series **Astrocytoma**	n = 49 (37 w/pilocytic astrocytoma and 12 w/Grade II fibrillary astrocytoma) Median age = 14 for pilocytic astrocytoma; median age = 25 for fibrillary astrocytoma; Age </= 18 = 59% (n=29); Age > 18 41% (n=20); both infratentorial and supratentorial tumor locations, multiple prior treatment modalities; Radiosurgery adjuvant in 49% (n=24), recurrent tumor 51% (n=25)	13 year interval (actual dates of radiosurgery not ID)l; underwent stereotactic radiosurgery as part of multimodal treatment after evaluation of initial bx sample or attempted resection	Gamma Knife Surgery; no comparator F/U: serial neuroimaging (3, 6, 12, 24 mo); Median f/u 32 mo after radiosurgery (range 3-159 mo) and 63 mo(range 2-186 mo) after diagnosis; 16 patients followed > 60 mo	15 Gy (9.6-22.5 Gy)	n/a (no control or comparison group)	No permanent procedure-related morbidity or mortality; 1 patient with aphasia 6 mo after radiosurgery and 12 mo after fractionated radiation therapy with later resolution; 1 patient worsening of hemiparesis 7 mo after radiosurgery with later improvement; no age stratification given	Poor Unclear if conflict of interest potential
Plathow (2003) Case Series **Astrocytoma**	n = 143 Median age 40.5 y (18-86y);	(1984-2000) Histologically proven Grade 2 Astrocytoma treated w/fractionated	Fractionated stereotactic radiotherapy (FSRT); harms comparators among dosing	Two groups for dose response comparison (</= 55Gy, and > 55Gy);	n/a (no control or comparison group)	"Mild"; Acute (<6mo) and late effects (>6mo) evaluated by Group - 1 Low-dose (<54Gy); 2 moderate dose (54-60Gy); 3 high-dose (>60Gy); Severe effects= acute Grade 3 toxicity n=4 (2.8%) - 3 from high-dose group, 1	Poor Unclear if conflict of interest potential

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
		stereotactic RT w/inoperable, incompletely resected, or radiographically/clinically progressive disease	groups reported F/U: Median 44 mo (11-146 mo); 125 (87.4%) monitored for min 3y	Median target dose 57Gy w/conventional daily fraction 1.8-2Gy + weekly fraction of 5X 1.8 or 2Gy; typical prescribed dose 50-60Gy; dose escalation/boost tech in select pts		from mod-dose group; No Grade 4 toxicity; most common acute effects = erythema and epilation/alopecia = 80.4% all cases; subacute/late toxicity greater than Grade 2 not observed; no cases of radionecrosis; 1 pt w/tinnitus 3mo after high-dose RT, 1pt w/persistent nausea after high-dose RT; 2 pts each w/motor, sensory, and hearing deficits and 3 pts w/tiredness - late side effects/high-dose; EORTC/RTOB scores reported Table 2 (summarized above)	
Szeifert (2007) Case Series **Astrocytoma**	n = 74 Supratentorial Grade 2 Astrocytoma or Oligoastrocytoma Mean age 34.4 (4-84); KPS between 60-100; Included Grade 1 (n=15) , 2 (n=17), and 3/4 (n=42) via histologic dx	(1989-1997) All patients w/astrocytoma treated with GKS at UVA during specified time period for whom f/u info was available	GKS; comparison among various multimodal treatment course groups (surg resection + RT + GKS, surgery + GKS, RT + GKS, GKS); primary tx in critical locations after bx, secondary tx following partial resection or to	Grade 1 mean max dose(MMD) 33.3 Gy; Grade 2 MMD 36.3 Gy, Grade 3/4 MMD 24.3 Gy	n/a (no control or comparison group)	No acute morbidity after GKS; Grade 1: n=6 (40%) w/enlargement cystic/tumor vol, n=1 radiation-induced edema and hemorrhage; n=1 hemiparesis, ptosis; Grade 2: n=5 (31.1%) increased tumor mass; n=3 transient neuro deficits; Grade 3/4: 45% failure of tumor control; psychologic impact not assessed, but future recommendation	Poor Unclear if conflict of interest potential

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			escalate dose previous RT F/U: Mean Grade 1 = 28.8 mo (8-96mo); Grade 2 = 33.4mo (6-81mo); Grade 3/4 = 17.7 mo (2-58mo); F/U imaging 3-6 mo intervals				

Brain Metastases

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Ammirati (2010) Systematic Review **Brain Metastases**	Total n = 503 13 observational studies (12 case series and 1 comparative case series for split dose vs. single dose SRS) SR (September 2008 last search date) Recurrent or progressive metastases after WBRT, surgical resection or SRS	Intervention: SRS Comparator: None, except one study used historical controls for SRS vs. 2 fraction SRS F/U: NR Dose: NR	Median survival: 4 months to 22.4 months; Median time to recurrence/progression: 5.8 to 24.5 mos, "conflicting results with regard to neurologic improvement and quality of life"	NR	Good Included 13 case series, no statement regarding role of funders
Chang (2011b) Systematic Review (costs) **Brain Metastases**	7 - 6 original papers, 1 meta-analysis; 3 cost analyses, 1 w/ a cost-effectiveness analysis (CEA), cost-utility analysis (CUA), incremental cost-effectiveness ratio (ICER) and incremental cost-utility ration (ICUA); 1 w/ CEA, CUA and ICER, 1 w/ CEA and CUA, and 1 w/ CEA and ICEA	Studies were grouped in 3 categories: (1) stereotactic radiosurgery (SRS) vs other interventions; (2) SRS systems comparison, Fractionated SRS vs hypofractionated SRS F/U: see evidence table in article for each study Dose: NR	The paper is not a meta-analysis, so rather than synthesizing the 7 economic evaluations, each is summarized individually. Key points from commentary provided by economic experts include: (1) substantial uncertainty exists surrounding the cost-effectiveness of SRS tx in treating brain mets due to a lack of RCTs that use standard trt comparisons, (2) currently most evidence is individual studies rather than head-to-head comparisons and cost analysis-	Only summarized from one study (manning et al 2000), which compares survival and toxicity for HSRT pts in the study w/ those obtained from the literature and found that survival and long-term toxicity were similar.	Fair Summary of individual articles and commentary on the state of the evidence upon which to base health economics studies; the paper is

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	N = NR		only studies; (3) Many methodological issues exist including differences in time horizons, types of trt comparators, types of cancers and mets, and sources of costs that mitigate the ability to directly compare studies and reach a robust conclusion (4) 2 studies (Lal et al (2011) and Lee et al 2009) have the methodological strength details provided in article) to suggest that SRS is a cost-effective option in comparison w/ traditional RT interventions, thus SRS is a favorable option in mgmt of brain mets. (5) An alternative to CEA or CUA would be a cost-benefit analysis (systematic process to calculate and compare benefits and costs of a project over time, generally for policy purposes) , which would calculate the difference between the present value of benefits and costs, and could help determine annual budget allocations - however to do so would require further research on efficacy, effectiveness, pt preferences and willingness-to-pay thresholds for these interventions.		limited by the nature of the evidence it has to review

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Elaimy (2011a) Systematic review **Brain Metastases**	Total n = NR 2 RCTs, 11 cohort studies SR (June 2010 last search date)	Intervention: SRS Comparator: SRS+WBRT F/U: NR Dose: NR	SRS + WBRT and SRS alone offer improved survival compared to WBRT alone	Described in general terms. Notes that the stereotactic head frame attached to the skull produces headaches.	Poor Mixed RCT and observational studies
Linskey (2010) Systematic review **Brain Metastases**	Total n = NR Metastatic, newly diagnosed SR (September 2008 last search date) SRS+WBRT vs WBRT: 2 RCTs, 3 cohort studies SRS vs WBRT: 5 cohort studies	Intervention: SRS Comparator: SRS+ WBRT, WBRT F/U: NR Dose: NR	There is a suggestion of equivalent OS with SRS alone vs. SRS+WBRT and conflicting results for local tumor control. Single dose SRS appears to be superior to WBRT for patients with up to 3 metastases.	NR	Poor Mixed RCT and observational studies
Patil (2010) Systematic review **Brain Metastases**	Total n = 358 SR + MA (November 2009 last search date) Metastatic, newly diagnosed > 18 years old, newly diagnosed metastases (single or multiple), KPS > 70, no prior cranial radiation	Intervention: SRS + WBRT Comparator: WBRT alone F/U: NR Dose: NR	OS: HR 0.82 (95% CI, 0.65 to 1.01); Local tumor control: HR 0.27 (95% CI, 0.14 to 0.52),favoring SRS+WBRT	Based on Andrews (2004), acute (SRS+WBRT: 43% Grade 1, 18% Grade 2, 2% Grade 3, 1% Grade 4; WBRT alone: 36% Grade 1, 26% Grade 2) and late toxicities did not differ:	Good Cochrane SR that included 2 poor quality RCTs, 1 RCT excluded since no statistics reported

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Tsao (2011) Systematic review **Brain Metastases**	SR + MA (November 2010 last search date) SRS vs. SRS+WBRT: 3 RCTs Total n = 190 [2 RCTs w/ OS data) and 399 (3 RCTs for local control, harms) SRS + WBRT vs WBRT: 2 RCTs, total n = 172 > 18 years old; newly diagnosed metastases (single or < 4); RTOG RPA class I or II, KPS > 70 and/or WHO PS 0 - 2; < 4cm in size Metastatic, newly diagnosed	Intervention: SRS+WBRT Comparator: SRS F/U: NR Dose: NR	SRS vs SRS+WBRT: OS: HR 0.98 (95% CI, 0.71 to 1.35),favoring SRS+WBRT; Local tumor control: HR 2.61 (95% CI, 1.68 to 4.06),favoring SRS+WBRT; Distant brain control: HR 2.15 (95% CI, 1.55 to 2.99),favoring SRS+WBRT SRS + WBRT vs WBRT: OS: HR 1.63 (95% CI, 0.72 to 3.69); Local tumor control: HR 2.88 (95% CI, 1.63 to 5.08),favoring SRS+WBRT; Andrews (2004) single metastasis: median survival 6.5 mos vs. 4.9 mos, SRS+WBRT vs. WBRT, p = 0.053 (multivariate)	SRS+WBRT vs WBRT: Based on Andrews (2004), acute (SRS+WBRT: 43% Grade 1, 18% Grade 2, 2% Grade 3, 1% Grade 4; WBRT alone: 36% Grade 1, 26% Grade 2) and late toxicities did not differ (2% to 3% Grade 3 and 1% to 3% Grade 4)	Good Secondary publication of a good quality Cochrane SR that included 3 RCTs that were poor to fair quality
Tsao (2012) Systematic Review **Brain Metastases**	SRS + WBRT vs WBRT: 2 RCTs SRS + WBRT vs WBRT: total n = 172 SRS vs SRS+WBRT: 3 RCTs (See Patil 2010. These are the same RCTs with 1 published in abstract form.)	Intervention: SRS+WBRT Comparator: SRS F/U: NR Dose: NR	SRS vs SRS+WBRT: Overall survival: HR 0.98 (95% CI, 0.71 to 1.35); Local tumor control: HR 2.61 (95% CI, 1.68 to 4.06),favoring SRS+WBRT; Distant tumor control: HR 2.15, (95% CI, 1.55 to 2.99) SRS + WBRT vs WBRT: (NOTE: HR reversed compared to 2011 Cancer article) Overall survival:	SRS+WBRT vs WBRT: Based on Andrews (2004), acute (SRS+WBRT: 43% Grade 1, 18% Grade 2, 2% Grade 3, 1% Grade 4; WBRT alone: 36% Grade 1, 26% Grade 2) and late toxicities did not differ (2% to 3% Grade 3 and 1% to 3% Grade 4)	Good Included 2 published RCTs, one fair and the other poor quality. See Patil (2010)

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	SRS vs SRS+WBRT: Total n = 190 (2 RCTs with OS data) and 389 (3 RCTs for local control, harms) SR + MA (July 2011 last search date) Metastatic, newly diagnosed > 18 years old; newly diagnosed metastases (single or < 4); RTOG RPA class I or II, KPS > 70 and/or WHO PS 0 - 2; < 4cm in size		HR 0.61 (95% CI, 0.27 to 1.39); Local brain control: HR 0.35 (95% CI, 0.2 to 0.61) favoring SRS+WBRT		

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Andrews (2004) RCT – Included in Tsao (2011, 2012) SR **Brain Metastases**	total n = 333 Brain metastases RCT (multiple centers in US) Mean age 59.3 (19-90),	> 18 years old, 1 to 3 metastases, < 4 cm diameter, RPA class 1 or 2 or KPS > 70, no prior SRS/WBRT, no active cancer (last	Intervention: SRS+WBRT; Comparator: WBRT alone F/U: Clinical evaluation	SRS: 24 Gy (< 2 cm), 18 Gy (> 2 and < 3 cm), 15 Gy (> 3 and <4 cm); WBRT: 37.5 Gy in daily	OS: no difference between SRS+WBRT vs. WBRT in multivariate analysis (p = .13) except for trend in pts with single metastases (SRS+WBRT better than WBRT, p = 0.053); Mean survival (all): 6.5 mos vs.	Acute neuro toxicity: 19% (2.5% with Grade 3-4) vs. 15% (0% with Grade 3-4) for SRS+WBRT vs. WBRT alone, respectively; Late neuro toxicity: 12.5% (1.2% with Grade 3-4) vs. 4.2% (1.2%	Fair Unclear blinding, 19% not get SRS in SRS+WBRT vs. vs. 0% in

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	52.5% men, 56% single metastasis, 63.5% lung primary, 36.5% with no neuro symptoms; 84.5% with MMSE 25-30 (normal)	treatment > 1 mo prior to enrollment)	and MRI every 3 mos	2.5 Gy fractions over 3 weeks	5.7 mos, p = 0.14, SRS+WBRT vs. WBRT alone; Mean survival (single metastasis): 6.5 mos vs. 4.9 mos, p = 0.039, SRS+WBRT vs. WBRT alone; Local recurrence was 43% greater with WBRT alone vs. SRS+WBRT, p = .0021; KPS improved in 13% (SRS+WBRT) vs 4% (WBRT alone), p = 0.033; OS by treatment unit (Gamma Knife vs. LINAC) did not differ (p = 0.94).	with Grade 3-4), for SRS+WBRT vs. WBRT alone, respectively; Worst reported acute toxicity grade (all toxicities): SRS+WBRT 43%, 18%, 2%, 1% (Grades 1 - 4, respectively) and WBRT alone: 36%, 26%, 0%, 0% (Grades 1-4, respectively); Worst reported late toxicity grade (all toxicities): SRS+WBRT 14%, 6%, 3%, 3% (Grades 1 - 4, respectively) and WBRT alone: 14%, 7%, 2%, 1% (Grades 1-4, respectively);	WBRT
Aoyama (2006) RCT – Included in Tsao (2011, 2012) SR **Brain Metastases**	n = 132 Brain metastases RCT (multiple centers in Japan) Mean age 63.3 (33-86), 75% men, 48.5% single metastasis, 66.5% lung primary, 64% with no neuro symptoms	> 18 years old, 1 to 4 metastases, < 3 cm diameter, KPS > 70	Intervention: SRS alone; Comparator: SRS+WBRT F/U: Clinical evaluation and MRI at 1 mo, 3 mos, then every 3 mos thereafter	SRS alone: mean dose 21.9 (SD, 2.7) Gy; SRS+WBRT: SRS mean dose 16.6 (SD, 3.6) Gy and WBRT 30 Gy in 10 fractions over 2-2.5 weeks	OS: HR 1.37 (95% CI, 0.93 to 1.98) for SRS+WBRT; 1-year survival: 38.5% vs. 28.4%, P = .42 and median survival: 7.5 mos vs. 8.0 mos, p NS, SRS+WBRT vs. SRS; Local and distant recurrence at 12 mos: 46.8% vs, 76.4%, p < 0.001, SRS+WBRT vs. SRS; KPS score > 70 at 12 mos: 33.9% vs. 26.9%, p = .53, SRS+WBRT vs. SRS	Acute neuro toxicity: 6.2% (1 pt with Grade 3) vs. 12% (2 pt with Grade 3), p = .36, SRS+WBRT vs. SRS respectively; Late neuro toxicity: 11% (2 pt with Grade 3) vs. 4% (2 pt with Grade 4), p = .2, SRS+WBRT vs. SRS	Good Unclear if allocation concealed, 12% vs. 3% not adherent to protocol (SRS+WBRT vs. SRS)
Chang (2009b) RCT – Included in Tsao (2011, 2012) SR **Brain**	n = 58 SRS alone: 30 (51.7%), SRS + WBRT: 28 (48.3%)	Pts tx at MD Anderson cancer center between Jan. 2, 2001 - Sept. 14, 2007 for	SRS and SRS +WBRT F/U: at 1, 2, 4,6,9,12,15	Mean dose in SRS alone group 19 Gy (15-20). For SRS + WBRT,	Study examined cognitive effects of different txs. Study halted when total recall at 4 months for SRS + WBRT was inferior to total recall for SRS	in SRS+WBRT group, one case grade 3 toxicity (3.6%) for seizures, motor neuropathy, depressed level of consciousness. In SRS alone	Fair Cohorts similar, measures

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Metastases	Male/Female ratio: SRS: 12/18, WBRT: 17/11. Median age: SRS: 63 (35-82), WBRT: 64 (40-78). # Metastases: SRS: 1: 18 (60%), 2: 7 (23%), 3: 5 (17%); WBRT: 1: 15 (54%), 2: 8 (28%), 3: 5 (18%). RPA: SRS class I: 7 (23%), class II: 23 (77%). WBRT: class I: 3 (11%), class II: 25 (89%). GPA group: SRS: group 1: 3 (10%), group 2: 19 (63.3%), group 3: 5 (16.7%), group 4: 3 (10%). WBRT: group 1: 3 (10.7%), group 2: 19 (67.9%), group 3: 5 (17.9%), group 4: 1 (3.5%). Primary cancer: breast: SRS: 4 (13%), WBRT: 4 (14%). Lung: SRS: 16 (53%), WBRT: 16 (57%). RCC: SRS: 2 (7%), WBRT: 2 (7%). Melanoma: SRS: 4 (13%), WBRT: 3 (11%). Other: SRS: 4 (13%), WBRT: 3 (11%). median tumor volume: SRS: 1.4 cm3 (0.1-20.0 cm3, SD 4.6), WBRT: 2.3 cm3 (0.05-27.6 cm3, SD 6.3)	brain metastases. Pts > 18 years, RPA class I or II, KPS ≥ 70, 1-3 newly diagnosed brain metastases, brain MRI w/ one month of enrollment, signed consent. Pts excluded for prior brain surgery, SRS or WBRT, leukemia, lymphoma, germ-cell tumor, small-cell lung cancer, leptomeningeal disease, or unknown primary tumor	and 18 months post treatment and then every 6 months. Median follow-up 9.5 months (0.2-66)	20 Gy (15-20) WBRT total dose 30 Gy in 12 daily fractions of 2-5 Gy per day	alone. 7 pts deteriorated out of 11 assessed (64%) for SRS + WBRT vs. 4 out of 20 (20%) for SRS alone (96% confidence level). Total recall difference persisted at 6 months. At 4 months, the HVLT-R delayed recognition tests also differed, 11% for SRS + WBRT vs. 0% for SRS alone at the 86% confidence level. 73% of pts in SRS +WBRT group were free from CNS recurrence at 1 yr compared to 27% SRS alone (p.0.0003)	group, 1 grade 3 aphasia (3.3%), 2 grade 4 radiation necrosis (6.7%)	robust
Chougle (2000) RCT [published	n = 68 Brain metastases	1 to 3 metastases, tumor volume < 30 cc, minimum 3	Intervention: SRS+WBRT; Comparator:	SRS: 16 Gy to tumor margin;	Median survival: no difference in SRS+WBRT vs. WBRT alone groups; Local control: 91% in	NR	Poor Published in

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
abstract only] **Brain Metastases**		mos life expectancy	WBRT alone F/U: (30 Gy in 10 fractions over 2-2.5 weeks)	WBRT: 30 Gy in 10 fractions	SRS+WBRT vs. 62% WBRT groups; no statistical analyses provided		abstract form only, no statistical tests reported
Kocher (2010) RCT **Brain Metastases**	n = 359 Brain metastases Mean age 60 (26-81), 65% men, 89% WHO PS < 1; 81% single metastasis, 53% lung primary, 54% with no neuro symptoms	> 18 years old, 1 to 3 metastases, < 3.5 cm diameter, WHO PS < 2; stable cancer for > 3 mos	Intervention: SRS (99 pts) or surgery (81 pts) + WBRT; Comparator: SRS (100) or surgery (79) + observation F/U: Clinical evaluation and MRI every 3 mos	SRS: 25 Gy to center; WBRT: 30 Gy in 10 fractions of 3 Gy	OS: no difference between SRS alone vs. SRS+WBRT; Local recurrence at 24 mos: 19 % vs. 31%, p < 0.04 (SRS vs. SRS+WBRT); Distant brain metastases at 24 mos: 33% vs. 48%, p < 0.023, (SRS vs. SRS+WBRT)	Harms were not reported by SRS and surgery subgroups. One patient in the SRS+WBRT group probably died due to radionecrosis	Fair Harm results were not separated for SRS and surgery
Kondziolka (1999) RCT – included in Linskey (2010), Patil (2010) and Tsao (2012) SRs **Brain Metastases**	n = 27 Brain metastases RCT (single center) Mean age 58.5 (33-77), 59.5% men, 44% lung primary, median KPS 100	2 to 4 metastases, < 2.5 cm diameter, KPS > 70	Intervention: SRS+WBRT; Comparator: WBRT alone F/U: Clinical evaluation and MRI at 6 weeks, 3 mos, then every 3 mos	Dose: SRS: 20 Gy to tumor margin; WBRT: 30 Gy in 12 fractions of 2.5 Gy	OS: no difference between SRS+WBRT vs. WBRT; Median survival: 11 mos vs. 7.5 mos, p = 0.22, SRS+WBRT vs. WBRT alone; Median time to local recurrence: 36 mos vs. 6 mos, p < 0.0005 (SRS+WBRT vs. WBRT); Median time to any recurrence: 34 mos vs. 5 mos, p < 0.002 (SRS+WBRT vs. WBRT);	"No neurologica or systemic morbidity related to stereotactic radiosurgery." Mild scalp erythema and hair loss after WBRT.	Poor Coin toss used to randomize patients, no allocation concealment, 71% vs. 62% had active cancer in WBRT alone vs. SRS+WBRT groups,

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
							respectively, and this was a predictor of survival and not controlled in the primary analyses
Basina (2010) Cohort **Brain Metastases**	n = 100 (50 pts GKS alone, 50 GKS + WBRT) Male/Female ratio: GKS: 19/31, WBRT: 24/26. Mean age: GKS: 62 (36-78), WBRT: 59 (34-82). Primary cancer: lung: GKS: 18 (36%), WBRT: 29 (58%); melanoma: GKS: 16 (32%), WBRT: 8 (16%); breast: GKS 8 (16%), WBRT: 8 (16%); RCC: GKS: 4 (8%), WBRT: 2 (4%) other: GKS: 4 (8%), WBRT: 3 (6%). Extracranial metastases: Yes: GKS 23 (46%), WBRT: 24 (48%); No: GKS: 27 (54%), WBRT: 26 (52%). Mean # metastases: GKS: 2.6 (1-7), WBRT: 3.3 (1-7) Mean tumor volume: GKS: 12 cm^3, WBRT: 15 cm^3.	Pts tx at clinic between April 2004 - Mar. 2008 with GKS for brain metastases. Excluded pts whose KPS < 70, prior fractionated radiation therapy or chemotherapy, > 7 lesions at time of GKS and no follow-up > 3 months	GKS alone or GKS + subsequent WBRT F/U: every 3 months	GKS 18-24 Gy, mean prescription dose GKS: 21.1Gy, maximum dose GKS: 37.4 Gy. Mean prescription dose GKS+WBRT: 20.2 Gy, maximum dose: 35.6 Gy. WBRT 3000-3400 rads in 10-15 fractions	Development of new metastases in anterior temporal lobe was comparable as a function of time for both groups at 6 and 12 months post GKS (p>0.05.)	NR	Fair Groups not randomized to tx but groups similar in most pt characteristics

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Bernad (2010) Cohort **Brain Metastases**	n = 23 By tx: SRS alone: 7 (30%), Surgery + SRS: 6 (26%), SRS + WBRT: 1 (4%), Surgery + WBRT + SRS: 1 (4%), surgery alone: 2 (8%), WBRT + surgery: 3 (13%), WBRT alone: 3 (13%) 12 males, 11 females, median age 63 (20-81). Pathology of primary thyroid cancer for 12 pts: papillary: 9 (39%), hurthle cell: 2 (8.7%) and medullary: 1 (4.3%). Median KPS = 90 (50-100). Graded Prognostic Assessment (GPA) group 1: 3 (13%), group 2: 15 (65%),group 3: 4 (18%), group 4: 1 (4%). RPA class I: 1 (4.5%), class II: 21 (91%), class III: 1 (4.5%). median # lesions 1.5 (1-9)	Pts tx at one of 11 institutions between 1985-2007 for brain metastases from thyroid cancer. Pts excluded if incomplete information regarding method of tx or follow-up	SRS, WBRT and Surgery in all combinations F/U: schedule not noted, median follow-up for living pts (40%) was 35.2 months	NR	Pts tx with SRS had overall median survival of 37.4 months in comparison to 12.3 months for those treated without SRS. Difference was not statistically significant (p=0.29).	NR	Poor Data not well reported, no dose information, no follow-up information, small sample size, diverse tx modalities
Elaimy (2011b) Cohort **Brain Metastases**	n = 275 Brain metastases WBRT alone: 117 (42.5%), SRS alone: 65 (23.6%), WBRT+SRS: 48 (7.5%),	Pts tx at clinic between 1998-2008 for newly diagnosed brain metastases	combinations of WBRT, SRS and surgery F/U: median follow-up 7.2 months	med SRS dose 18 Gy (13-22 Gy). Median WBRT dose: 30 Gy (5-54 Gy)	pt survival favored SRS alone compared to WBRT alone (p<0.001, 95% CI: 1.37-2.53) and surgery + SRS compared to SRS alone (P=0.020).	NR	Poor Small sample size of some tx groups, didn't have values for several

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Surgery + WBRT: 11 (4%), Surgery + SRS: 15 (5.5%), Surgery + WBRT+SRS: 19 (6.9%) Median age 60 (29-86), ECOG performance score: 0: 9 (3.3%), 1: 66 (24%), 2: 29 (10.5%), 3: 7 (2.5%), 4: 2 (<1%), unk: 162 (58.9%). Primary cancer: NSCLC: 112 (40.7%), SCLC: 27 (9.8%), breast: 42 (15.3%), melanoma: 25 (9.1%), RCC: 9 (3.3%0, other: 45 (16.4%), Unk.: 15 (5.5%). #mets: 1: 117 (42.5%), 2-4: 71 (25.8%), >4: 19 (6.9%), unk: 68: (24.7%). tumor volume cm3: <2: 30 (10.9%), 2-3.9: 29 (10.5%), 4-5.9: 15 (5.5%), 6-7.9: 17 (6.2%), ≥8: 33 (12%), unknown: 151 (54.9%)		(0.20-117)				variables for large segments of population
Fokas (2010) Cohort **Brain Metastases**	n = 88 #pts receiving different txs: SRS: 51 (58%), SRS+WBRT: 17 (19.3%) or WBRT: 20 (22.7%) males 59, females 29. Age < 63 years: SRS: 21 (41%),	pts tx at clinic between 1996-2006 for brain metastases from renal cell carcinoma. No prior brain tx	Stereotactic radiosurgery (SRS) alone, whole brain radiotherapy (WBRT), and WBRT+SRS F/U: at 3	SRS median dose 19 Gy (15-22 Gy). WBRT: if KPS < 70, 10 x 3 Gy over 2 weeks. If KPS ≥ 70 then 20 X 2 Gy over 4	improved overall survival associated with absence of extracerebral metastases (p<0.001) and RPA class (p=0.04) and intercerebral control with tx (p=0.019). No association between local control and any prognostic factors	Grade 3 acute toxicities (nausea, vomiting, headaches) occurred in 2% of SRS pts, 3% of WBRT pts and 3% of WBRT+SRS pts. Grade 3 late toxicities (headache, neurocognitive deficits, visual/hearing impairments) occurred in 4% of SRS pts, 4%	Poor Pts in WBRT alone group significantly sicker than other groups (higher RPA class, more

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	WBRT: 4 (20%), WBRT+SRS: 9 (52%), ≥63 years: SRS: 30 (59%), WBRT: 16 (80%), WBRT +SRS: 8 (48%). #mets: single: SRS: 42 (82%), both WBRT and WBRT+SRS=0. Multiple mets: SRS 9 (18%), WBRT: 20 (100%), WBRT+SRS: 17 (100%). Extracerebral mets: yes: SRS: 14 (28%), WBRT: 12 (60%), WBRT+SRS: 8 (48%), No: SRS: 37(72%), WBRT: 8 (40%), WBRT+SRS: 9(52%). RPA class I: SRS: 17 (33%), WBRT: 1 (5%), WBRT+SRS: 3 (17%). class II: SRS: 34 (77%), WBRT: 11 (55%), WBRT+SRS: 13 (77%), class III: SRS: 0, WBRT: 8 (40%), WBRT+SRS: 1 (6%). Interval from diagnosis to tx: ≥ 20 months: SRS 17 (33%), WBRT: 8 (40%), WBRT+SRS: 5 (29%), <20 months: SRS: 34 (77%), WBRT: 12 (60%), WBRT+SRS: 12 (71%)		months after tx then every 6 months. Followed till death. Range of follow-up for surviving pts 9-95 months	weeks		of WBRT pts and 5% of WBRT+SRS pts	likely to have extracerebral mets, higher # mets, older), small sample size
Fokas (2011) Cohort **Brain Metastases**	n = 78 # pts receiving different txs: WBRT only: 21 (27%), SRS only: 33 (42%), OP	Pts tx at clinic between 1996-2007 for colorectal cancer and metastases to	various combinations of stereotactic radiosurgery	SRS: median dose 20 Gy in single fraction (18-24 Gy). For	surgical tx resulted in significant improvement in overall survival (OS) (p=0.036). OS and intracerebral control (ICC) were significantly correlated with lack	of groups of tx (SRS only, WBRT only, OP+WBRT and WBRT+SRS respectively) acute toxicity rates were 2%, 3%, 5% and 4%. Late toxicity	Poor Small sample size, did not compare tx

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	only: 0, OP + WBRT: 17 (22%), WBRT + SRS: 5 (6%), OP + SRS: 2 (3%) Not broken out by tx group. Males 30, females 48. Age < 62 yrs: 29 (37%), ≥ 62: 49 (63%), # metastases: 1-3: 36 (47%), > 3: 42 (53%). Extracerebral mets: yes: 50 (64%), no: 28 (36%). RPA class I-II: 39 (50%), class III: 39 (50%). Interval from tumor diagnosis to radiotherapy: < 12 months: 43 (55%), ≥ 12 months: 35 (45%)	the brain. No prior brain tx	(SRS), surgical resection (OP) and whole brain radiotherapy (WBRT). F/U: at 3 months after tx then every 6 months. All pts followed to death, range 1-53 months	WBRT, if KPS < 70 then 10 x 3 Gy over 2 wks. If KPS ≥ 70 then 20 x 2 Gy over 4 wks	of extracerebral mets (p=.024, p=.041) lower # of lesions (p < .001, p=.007) and interval from primary diagnosis (p<.001, p=.005). RPA class I-II significant only for OS (p=.045).	rates were 4%, 4%, 7%, and 5%. No details provided	group characteristics, pts with fewer lesions placed in SRS group
Frazier (2010) Cohort **Brain Metastases**	n = 237 Group A-GK alone=192 (81%) Group B: GK + WBRT=45 (19%) males 124, females 113. Mean age: group A: 57.3 ± 13, B: 52.9 ± 11.5. Primary cancer: NSCLC: A: 63 (32.8%), B: 18 (40%), Breast: A: 27 (14.1%), B: 6 (13.3%), Melanoma: A; 22 (11.5%), B: 7(15.6%), RCC: A:12 (6.2%), B:1 (2.2%), Other: A:68 (35.4%), B:13	pts tx at clinic between 2003-2007 with gamma knife radiosurgery for brain metastases	Gamma knife radiosurgery alone ((GK) vs. whole brain radiotherapy (WBRT) +GK F/U: at 1 month after tx then every 3 months.	mean prescription dose for first tx 18 Gy and for pts undergoing second tx 21 Gy	no significant increase in risk of death to GK alone compared to WBRT+GK (risk ratio 0.77, 95% CI 0.49-1.23, p.0.27)	NR	Fair Analysis accounted for age, RPA class, KPS, tumor volume and histology. pts in WBRT + GK group slightly younger, in a better RPA class and had more lesions than those tx with GK alone,

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(28.9%). # lesions: 1: A: 87 (46%), B:11 (25%), 2-3: A: 66 (34.9%), B:17 (38.6%), ≥4: A: 36 (19%), B:16 (36.4%). KPS 30-70: A: 47 (24.5%), B:8 (17.8%), KPS 80-100: A:145 (75.5%), B: 37 (82.2%). RPA class I: A: 14 (11.1%), B: 11 (27.5%), class II: A: 105 (83.3%), B: 28 (70%), class III: A: 7 (5.6%), B: 1 (2.5%)						small sample size for WBRT+SRS group
Kased (2009) Cohort **Brain Metastases**	n = 176 Brain metastases from breast cancer, metastatic and recurrent Group A: SRS alone: 64 (36.4%), Group B: SRS + WBRT: 31 (17.6%), Group C: SRS for recurrence: 81 (46%) Age < 50: group A: 27 (42%), B: 14 (45%0, C: 41 (51%). KPS ≥70: A: 61 (95%), B: 29 (94%), C: 78 (96%). Primary tumor controlled: A: 56 (88%), B: 23 (74%), C: 74 (91%). No extracranial mets: A: 8 (13%), B: 14 (45%), C: 19:	Pts tx at clinic between 1991-2005 for brain metastases from breast cancer with SRS with or without WBRT	gamma knife SRS with WBRT and gamma knife SRS without WBRT F/U: every three months. 134 pts (76.1%) with imaging follow-up. Median follow-up for pts with initial mets: 31.6 months (0-76.8) and median follow-up for	median prescribed dose and range: Group A: 19 Gy (15.2-20.0 Gy). Group B: 18.5 Gy (12.0-20.6 Gy). Group C: 18.5 Gy (7.5-21.0)	no significant difference in survival between pts tx with SRS alone initially and those tx with SRS plus upfront WBRT (p=0.20). No significant difference in freedom from progression (FFP) endpoints in groups A and B. 1 year local FFP: p-0.68, median freedom from new brain metastases: p-0.83 and median brain FFP: p=0.75	symptomatic necrosis in 10 pts (5.7%). 6 pts in group A (9.4%), 1 pt Group B (3.2%), 3 group C (3.7%)	Good Variables analyzed: age, primary tumor control, extracranial metastases, ER status, progesterone receptor status, Her2/neu status, # brain metastases, total target volume and tx

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(23%). Estrogen receptor status: Negative: A: 29 (45%), B: 15 (48%), C: 34 (42%), Positive: A: 26 (41%), B: 12 (39%), C: 28 (35%). Unknown: A: 9 (14%), B: 4 (13%), C: 19 (23%). Her2/neu status: Negative: A: 24 (38%), B: 4 (13%), C: 11 (14%), Over expressed: A: 20 (31%), B: 8 (26%), C: 26 (32%), Unknown: A: 20 (31%), B: 19 (61%), C: 44 (54%). # brain metastases: 1: A: 16 (25%), B: 6 (19%), C: 11 (14%), 2: A: 20 (31%), B: 8 (26%), C: 17 (21%). 3: A: 12 (19%), B: 1 (3%), C: 12 (15%). 4-6: A: 7 (11%), B: 9 (29%), C: 17 (21%). >6: A: 9 (14%), B: 7 (23%), C: 24 (30%). Total target volume <3cm3: A: 35 (55%), B: 13 (42%), C: 27 (33%)		pts with metastatic recurrence: 9.0 (0-59.8 months)				
Kong (2010) Cohort **Brain Metastases**	n = 245 Brain metastases Group A: SRS alone: 168 (68.6%). Group B: SRS+WBRT: 77 (31.4%)	Pts tx at clinic between Jan. 2002-Dec. 2007 for brain metastases with SRS alone or SRS+WBRT as an initial tx. Pts	SRS alone or SRS+WBRT F/U: all pts followed till death at intervals of between 3	mean marginal dose for SRS alone: 20 Gy (13-26 Gy. For SRS+WBRT: 18.5 Gy (12-	for pts in RPA class 1, SRS+WBRT was associated with a longer survival time than SRS alone (854 days vs. 426 days, p=0.042) and better local control (p.0.021) but not better distance control (p=0.079). For RPA classes 2 and 3, no	NR	Fair Small sample size in subgroup of RPA class I (N=43), accounted for

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	mean age: group A: 58.3, B: 57.5. Primary cancer: Lung: A: 81 (48.2%), B: 35 (45.4%), GI: A: 25 (14.9%), B: 12 (15.6%), Breast: A: 21 (12.5%), B: 10 (13.0%), Other: A: 41 (24.4%), B: 20 (26%). # mets: 1: A: 76 (45.2%), B: 27 (35.1%), 2-3: A: 66 (39.3%), B: 33 (42.9%), 4-6: A: 17 (10.1%), B: 11 (14.2%), 7-10: A: 9 (5.4%), B: 6 (7.8%). Total tumor volume: ≤5 cm3: A: 71 (42.3%), B: 33 (42.9%), 5-10 cm3: A: 91 (54.2%), B: 41 (53.2%), ≥10 cm3: A: 6 (3.5%), B: 3 (3.9%). Controlled primary cancer: A: 97 (57.7%), B: 53 (68.8%). Extracranial mets: A: 59 (35.1%), B: 26 (33.8%). KPS ≥70: A: 119 (70.8%), B: 55 (71.4%), <70: A: 49 (29.2%), B: 22 (28.6%), RPA class I: A: 28 (16.7%), B: 15 (19.5%), class II: A: 91 (54.2%), B: 40 (51.9%), class III: A: 49 (29.1%), B: 22 (28.6%)	excluded for previous history of surgery, >10 lesions, or SRS as a salvage tx	months and a year. Mean follow-up 414 days (19-2,196 days)	19 Gy) median WBRT dose 30 Gy in 10 fractions	significant difference in overall survival, local control or distance control between the two groups.		age, KPS, extracranial mets, histology, control of primary cancer, tumor volume, # mets
Marko (2011) Cohort **Brain**	n = 207 Brain metastases from	Pts tx at clinic between 1997-2006 with	Four tx modalities: SRS alone,	Pts tx with SRS alone had a median	No statistically significant difference when mean survival time of SRS was compared with	NR	Poor Small sample

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Metastases	NSCLC 26 pts (12.6%) tx with SRS alone. 121 pts (58.5%) tx with WBRT alone. 45 pts (21.7%) tx with WBRT + surgery, and 15 pts (7.2%) with WBRT + SRS Pt characteristics given only for SRS group: males 17, females 9. Mean age 63.4 ± 6.5. Median KPS = 90. mean # lesions: 1.60 ± 0.81. mean tumor volume: 1.86 cm3. RPA class I: 4 (15%), class II: 22 (85%). Extracranial metastases: 6 (23%)	stereotactic radiosurgery (SRS) as initial, solitary treatment for brain metastases from NSCLC. Pts also identified who were treated with WBRT, WBRT+ surgery, or WBRT+SRS. Pt >18 years old and KPS ≥90. Pts excluded if they had more than one malignancy or had insufficient clinical information	WBRT alone, WBRT + surgery or WBRT + SRS F/U: at least every 3 months, total f/u time NR	prescription dose of 24 Gy. Pts with WBRT alone had median total dose (MTD) 30 Gy and median fractionated dose (MFD) of 3 Gy. WBRT + surgery pts had a MTD of 37.5 Gy and MFD of 2.5 Gy. Pts receiving WBRT + SRS had WBRT MTD of 36.5 and MFD of 2.6 Gy and SRS median prescription dose of 21 Gy.	WBRT (p=0.98), WBRT + surgery (p=0.07) and WBRT + SRS(p=0.62) Subgroup analysis of RPA class II pts had same outcome.		size, did not report characteristics of all tx groups
Park (2009) Cohort **Brain Metastases**	n = 33 Brain metastases from lung cancer Group A: GKS: 14 (42.4%),	pts tx at clinic between Jan. 2005-Dec. 2006 for brain metastases from lung cancer. Pt	Gamma knife radiosurgery (GKS) vs. whole brain radiotherapy (WBRT)	GKS: mean prescription dose 19.2 Gy (18-21 Gy). WBRT: 30 Gy in 15	no significant difference in baseline characteristics between tx groups. Overall survival significantly better in GKS group than WBRT group (p=0.04) and qualitative survival	NR	Poor Small sample size

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	group B: WBRT: 19 (57.6%) M/F ratio: A: 9/5, B: 15/4. Age <65: A: 10 (71.4%) B: 9 (47.4%), ≥65: A: 4 (28.6%), B: 10 (52.6%). KPS <70: A: 0, B: 2 (10.5%), ≥70: A: 14 (100%), B: 17 (89.5%). Controlled primary site: A: 8 (57.1%), B: 7 (36.8%). Extracranial metastases: A: 6 (42.9%), B: 10 (52.6%). RPA class I: A: 6 (42.9%), B: 3 (15.8%), class II: A: 8 (57.1%), B: 14 (73.7%), class III: A: 0, B: 2 (10.5%). # mets: <10: A: 12 (85.7%), B: 15 (78.9%), ≥10: A: 2 (14.3%), B: 4 (21.1%). diameter of maximal lesion <20mm: A: 4 (28.6%), B: 8 (42.1%), ≥20mm: A: 10 (71.4%), B: 11 (57.9%). Chemotherapy: A: 10 (71.4%), B: 14 (73.7%)	have 2-20 lesions, life expectancy > 2 months, no previous GKS or WBRT tx, lesions with maximum diameter 3 cm	F/U: at 1 and 3 months after tx and then every 3 months. Mean follow-up for GKS group: 55 weeks (10-124) and for WBRT group: 31 weeks (8-104)	fractions over 3 weeks or 10 fractions over 2 weeks	(interval between initial diagnosis to date of impaired quality of life) also better in GKS group (p=0.04). Significant factors for a poor prognosis were uncontrolled primary site (p=0,03) and tx with WBRT (p=0.04)		
Park (2011) Cohort **Brain Metastases**	n = 56 Brain metastases from advanced gastric cancer (AGC) Group A: tx with GKS only: 11 (19.6%)), Group B: tx	pts tx at clinic between Jan. 1991 - May 2008 for brain metastases for AGC. Pts with gastric lymphoma excluded	Gamma knife radiosurgery (GKS) vs. whole brain radiotherapy (WBRT) F/U: at 1	marginal dose 17.0 Gy (14.0-23.6 Gy)	no statistically significant difference between two tx groups, although WBRT group more likely to have high number of lesions and a lower KPS score. In univariate and multivariate analysis, variables showing a better prognosis	in GKS tx group: 1 pt (6.7%) severe brain swelling due to radionecrosis, 1 pt (6.7%) temporary aggravation of diplopia, and 1 pt (6.7%) uncontrolled seizure at 3 months	Poor Small sample size

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	with WBRT: 41 (73.2%). 4 pts (7.1%) tx with both GKS and WBRT and so not included in comparative analysis M/F ration: group A: 8/3, B: 34/7. Median age: A: 54 (42-67), B: 57 (30-77). Primary cancer: adenocarcinoma: A: 9 (81.8%), B: 38 (92.7%), signet ring carcinoma: A: 2 (18.2%), B: 3 (7.3%). KPS ≥70: A: 9 (81.8%), B: 31 (75.6%), <70: A: 2 (18.2%), B: 10 (24.4%). RPA class II: A: 9 (81.8%), B: 3 (75.6%), class III: A: 2 (18.2%), B: 10 (24.4%) # mets: 1: A: 4 (36.4%), B: 21 (51.2%), 2-3: A: 5 (45.5%), B: 5 (12.2%), 4-6: A: 1 (9.1%), B: 1 (2.4%), >6: A: 1 (9.1%), B: 14 (34.1%). tumor size: <3 cm: A: 11 (100%), B: 36 (87.8%), ≥3 cm: A: 0, B: 5 (12.2%). extracranial mets: yes: A: 10 (90,9%), B: 37 (90.2%). interval between diagnosis and brain mets: A: 6 months (0-78), B: 11 months (0-119)		month and then every 3 months. All 15 GKS pts had MRI scans to review but only 14/41 pts (34.1%) of WBRT pts.		were RPA class II ($p<0.001$) and GKS tx ($p<0.001$)		

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Rades (2008a) Cohort **Brain Metastases**	n = 144 Brain metastases Group A: tx with SRS alone: 93 (64.6%). Group B: tx with WBRT + SRS: 51 (35.4%) M/F ration: A: 42/51, B: 20/31. Age ≤61: A: 46 (49%), B: 26 (51%). ≥62: A: 47 (51%), B: 25 (49%). ECOG Performance 0-1: A: 60 (65%), B: 31 (61%). 2: A: 33 (35%), B: 20 (39%). Primary: breast: A: 15 (16%), B: 10 (20%) lung: A: 36 (39%), B: 27 (53%), other: A: 42 (45%), B: 14 (27%). # mets: 1: A: 51 (55%), B: 29 (57%), 2-3: A: 42 (45%), B: 22 (43%). Extracerebral mets: A: 45 (48%), B: 22 (43%). RPA class I: A: 35 (38%), B: 24 (47%). class II: A: 58 (62%), B: 27 (53%). Interval from diag. to tx: ≤20 months: A: 47 (51%), B: 27 (53%). ≥21 months: A: 46 (49%), B: 24 (47%)	pts tx at clinic between 1999-2007 with SRS or SRS+WBRT for brain metastases. Only RPA classes I and II, 1-3 metastases with diameter ≤4 cm, no prior tx to brain	stereotactic radiosurgery (SRS) alone or whole brain radiotherapy (WBRT) with SRS boost F/U: mean follow up 9 months (1-52 months). Schedule not specified	in SRS group, median marginal dose 25 Gy (18-25 Gy). In WBRT+SRS group, median marginal dose for SRS 20 Gy (18-25 Gy). WBRT: either 5 x 4 Gy in 1 wk: 10 pts (20%), 10 x 3 Gy in 2 wks: 22 pts (43%) or 20 x 2 Gy in 4 wks: 19 pts (37%)	no statistically significant difference in overall survival between tx modalities. WBRT + SRS had statistically significant better outcomes for intercerebral control (RR: 1.51; 95% CI: 0.93-2.51, p=0.09) and local control (RR: 2.15; 95% CI: 1.09-4.63, p=0.026). Subgroup analysis by RPA class showed local control improving for both classes with WBRT, but for intercerebral control, the addition of WBRT only improved outcomes for RPA class I.	Grade ≥3 acute toxicity in 2 SRS pts (2%) and 1 WBRT pt (2%). Grade ≥ 3 late toxicity in 4 SRS pts (4%) and 2 WBRT pts (4%)	Poor Accounted for age, tx, ECOG performance score, Primary cancer, # mets, extracerebral mets, RPA class, interval from diagnosis to tx
Blonigen	n = 63 (173 lesions)	Pts tx at clinic	stereotactic	mean dose	n/a (no control or comparison	asymptomatic necrosis in 7	Fair

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
(2010) Case Series **Brain Metastases**	mean age 54 (32-79), male/female ratio 1.17. Avg. heterogeneity index 1.22 (1,01-2.03). Avg. conformality index 2.45 (1.00-16.0). 40 pts (63%) received previous whole brain irradiation	between Sept. 2004 - Dec. 2006 w/single fraction SRS for brain metastases who developed radionecrosis or had at least 6 months of follow-up	radiosurgery (SRS) F/U: minimum at 3 month intervals, median follow-up 13.7 months (3.5-51)	18 Gy in single fraction (12-22 Gy)	group)	lesions (4%) and symptomatic necrosis in 17 lesions (10%). No other harms	Included all pts with radionecrosis even if they hadn't reached 6 months follow-up cut off which tilted sample, controlled for many confounders
Breneman (2009) Case Series **Brain Metastases**	n = 53 (158 lesions) males 21, females 32. median age 54 (27-86). Previous whole brain radiotherapy (WBRT): 32 (60.4%), primary cancer lung: 28 (52.8%), melanoma: 11 (20.8%), breast: 9 (17%), other: 5 (9.4%). Recursive partitioning class (RPS) class I: 13 (24.5%), class II: 39 (73.6%), class III: 1 (1.9%). median lesions per pt: 2 (1-15). median lesion size: 0.20 cm3 (0.01-19.9 cm3)	Pts tx at clinic between Aug. 2005-Oct. 2006 with brain metastases treated with frameless SRS	frameless stereotactic radiosurgery (SRS) F/U: at 2-3 month intervals, median 38 weeks (14-112 wks)	median dose 18 Gy in single fraction (12-22 Gy)	n/a (no control or comparison group)	radiation necrosis: 2 (3.8%0. hemorrhage of treated lesions: 3 (5.7%)	Poor Controlled for histology, previous WBRT and tumor size. Other variables not noted
Choi (2009)	n = 62	Pts tx at clinic	5 treatments:	GKS: mean	# of brain lesions, liver function	NR	Fair

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Case Series **Brain Metastases**	(5 treatments: steroids alone: 25 (40.3%), resection alone: 6 (9.7%), whole brain radiotherapy (WBRT): 16 (25.8%), gamma knife surgery (GKS): 10 (16.1%) and resection + WBRT: 5 (8.1%) Males 47, females 15. Median age 54 (30-76) 53 pts had hepatitis B (85.5%), Recursive partitioning analysis (RPA) class: class I: 2 (3.2%), class II: 36 (58.1%), class III: 24 (38.7%). ECOG performance status: ≤ 2: 22 (35.5%), ≥ 3: 40 (64.5%)	between 1995 - 2006 for hepatocellular carcinoma with brain metastases	steroids alone, resection alone, whole brain radiotherapy (WBRT), gamma knife surgery (GKS), and resection + WBRT. F/U: NR	maximal dose 27 Gy (20-30), mean marginal dose 13.5 Gy (10-15)	and treatment modality all independently related to survival. Median survival 33.6 wks for pts receiving surgery + WBRT, 10.0 wks for pts receiving surgery, GKS or WBRT alone and 2.0 wks for steroids alone		Controlled for lots of variables in analysis but small sample size and analysis of 5 txs. Not directly relatable to study as included little information on GKS
Clarke (2010) Case Series **Brain Metastases**	n = 27 (22 pts SRS alone (81%) and 5 pts SRS + WBRT (19%)) Males 15, females 12. Mean age 56 (39-81), 9 pts (33.3%) renal cell carcinoma, 18 melanoma (66.6%). RPA class I: 1 (4%), II: 25 (92%), III: 1 (4%)	Pts tx from 2000-2007 with radioresistant brain metastases from primary renal cell carcinoma or melanoma. Only pts with single metastasis	SRS alone or SRS + whole brain radiotherapy (WBRT) F/U: follow-up ranged from 1.8 to 23.2 months, usually terminated by pt death.	mean prescription dose 19 Gy (15-22 Gy)	Adding WBRT did not appear to affect local control, progression-free survival or overall survival in analysis (p= 0.32, 087 and 0.69, logrank test.) 15 pts (56%) developed distant brain failures	5 pts developed worsening of neurologic symptoms within 6 mos of SRS – only 1 incident was attributable to post-SRS effects No late toxicities were observed	Poor Compared SRS to SRS+WBRT but small sample size (N=5) of WBRT group hinders analysis. Did not note whether analysis controlled for

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			No loss to follow-up except death				age, RPA class or other variables
Dea (2010) Case Series **Brain Metastases**	n = 95 (164 metastases) males 40, females 55. median age 59 (27-83), median KPS score 80% (50-100%). RPA class I: 21 (22.1%), class II: 67 (70.5%) and class III: 7 (7.4%). Tx with GKS alone 68 (72%). Tx with GKS + WBRT: 27 (28%). Primary cancer: NSCLC: 60 (63.2%), small cell lung: 8 (8.4%), breast 7 (7.4%), colorectal: 5 (5.3%), renal cell: 4 (4.2%), melanoma: 4 (4.2%), other: 7 (7.4%).	Pts tx at clinic between Aug. 2004-April 2008 with brain metastases in eloquent locations (primary motor, somatosensory, speech and visual cortices; the basal ganglia; the thalamus; and the brainstem.) pts with prior surgery excluded	Gamma knife surgery (GKS) F/U: at 2,4,6 months after tx and then every 3 months	median dose to tumor margin 18 Gy (14-24 Gy), median maximal dose 36 Gy (22.5-48 Gy)	n/a (no control or comparison group)	radiation necrosis: 1 (1.4%). Temporary post tx seizures 4 of 70 pts (5.7%) and transient neurological deficits in 4 of 70 pts (5.7%)	Good Controlled for sex, age, primary cancer origin, KPS score, RPA class, symptoms at presentation, presence of brain edema, use of coricosteroid medications, type of tx, dosage and irradiated volume
Elliott (2011b) Case Series **Brain Metastases**	n = 109 (114 consecutive pts, 5 lost to follow-up and excluded) males 34, females 75; median age 61.2 (28-94), primary tumor: NSCLC: 55 (50.5%), breast: 21 (19.3%), melanoma: 20 (18.4%), renal: 7 (6.4%), colon: 2	adults w/1-3 cerebral metastases, tumor diameter ≤ 2 cm, Karnofsky performance score ≥ 60, estimated life expectancy ≥ 4 months, no prior WBRT, no	Gamma knife radiotherapy (GKR) F/U: at 6 wks after tx and then every 3 months. Median follow-up 29.9 months	20 Gy to the 50% isodose line	n/a (no control or comparison group)	grade 1 headache: 10 (9.2%), grade 1 nausea: 7 (6.4%), grade 1 dizziness: 6 (5.5%). Transient neurological deficits requiring steroids grade 2: 3 (2.8%), grade 3: 1 (0.9%). Grade 2 seizures: 3 (2.8%). Grade 4 pathologically diagnosed radiation necrosis: 2 (1.8%). Grade 4 radiographically	Fair Analysis examined variables related to tumor size and tx but not pt characteristics. All pts received same

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(1.8%), esophageal: 1 (0.9%), hepatocellular: 1 (0.9%), bladder: 1 (0.9%), ovarian: 1 (0.9%), unknown: 1 (0.9%). Primary tumor controlled: yes: 67 (61.5%), no: 41 (37.6%), unknown: 1 (0.9%). extracerebral metastases: yes: 80 (73.4%), no: 29 (26.6%). median Karnofsky performance score: 80 (60-100). RPA class I: 17 (15.6%), class II: 80 (78,9%), class III: 6 (5.5%)	brainstem lesions	(6.6 months-7.8 years)			suspected radiation necrosis: 1 (0.9%). Grade 4 hemorrhage of tx lesion: 1 (0.9%)	radiation dose
Franzin (2009) Case Series **Brain Metastases**	n = 185 Males 123, females 62. Age < 65 yrs: 106 (54%), ≥ 65: 79 (46%). Karnofsky performance status < 70: 10 (5%), ≥70: 175 (95%). Primary tumor: NSCLC: 106 (57%), breast: 20 (11%), melanoma: 10 (5%), kidney: 16 (9%), colon: 13 (7%), other known: 13 (7%), unknown: 4 (2%). Primary tumor controlled: yes: 76 (41%), no: 102 (55%), unknown: 7 (4%). Presence of extracranial	Pts tx at clinic between Jan 2003-Apr. 2005 who had ≤ 4 lesions, Karnofsky performance status ≥ 60, no WBRT or surgical resection and minimum follow-up of 6 months	Gamma knife surgery (GKS) F/U: every three months. Median follow-up 11 months (0-46 months) follow-up terminated upon pt death	mean prescription dose to tumor margin 22.6 ± 3.4 Gy (9-25 Gy)	n/a (no control or comparison group)	1 pt (.54%) died following hematoma of brain metastasis 24 hrs after GKS. 16 pts (8.6%) radionecrosis. 2 pts (1.1%) carcinomatous meningitis	Fair Analysis included variables for age, gender, tumor size, tx, Karnofsky score, RPA class, SIR class, tumor location, number of lesions, histology. Radiation dose varied

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	metastases: yes: 84 (45%), no: 88 (48%), unknown: 13 (7%). Recursive Partitioning Analysis (RPA) class I: 31 (17%), class II: 144 (78%), class III: 10 (5%). Score Index for Radiosurgery (SIR) class I: 15 (8%), II: 140 (76%), III: 30 (16%)						
Giubilei (2009) Case Series **Brain Metastases**	n = 30 males 14, females 16, median age 63, < 65: 21 (70%), ≥ 65: 9 (30%). Karnofsky performance status ≤ 80: 13 (43.3%), > 80: 17 (56.7%). Primary tumor controlled: yes: 17 (56.7%), no: 13 (43.3%). Extracranial metastases: yes: 11 (36.7%), no: 19 (63.3%). Number of metastases: 1: 21 (70%), 2: 6 (20%), 3: 1 (3.3%), 4: 2 (6.4%). Primary tumor: lung: 17 (57%), breast: 4 (13%), colon: 2 (6.6%), melanoma: 2 (6.6%), kidney: 2 (6.6%), other: 3 (10%).	Pts tx at clinic between Apr. 2001 - Jan. 2006 with ≤ 4 brain lesions tx with both HSRT and WBRT	hypofractionated stereotactic radiotherapy (HSRT) with whole brain radiotherapy (WBRT) F/U: every three months. Range: 3.5 - 54.7 months	HSRT: median total dose 18 Gy (16-32 Gy). WBRT: 30 Gy in 10 sessions	n/a (no control or comparison group)	no acute or late complications reported	Fair Controlled for variables age, KPS, primary cancer and status, presence of extracranial metastases, # brain metastases, stereotactic dose. Small sample size
Gu (2009) Case Series **Brain**	n = 106 159 treatments, 640	Pts tx at clinic between Nov. 2000 and Apr.	Novalis shaped beam radiosurgery.	Avg total dose in single session: 19.7	n/a (no control or comparison group)	14 pts (13.2%) worsening neurologic symptoms, 2 pts (1.9%) cerebral edema	Poor Mistakes in

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Metastases	tumors males 58, females 48. median age 56.5 (26-87). Mean tumor volume 3.253 ± 8,994 mm3 (1.28-158.110 mm3), median Karnofsky performance score 80 (40-100), number of lesions: 1: 38 (35.8%), 2-3: 26 (24.5%), > 3: 42 (39.7%). Primary cancer: lung: 72 (45.3%), breast: 29 (18.2%), GI tract: 21 (13.2%), hepatobiliary: 9 (5.7%), productive: 9 (5.7%), nasopharyngeal: 5 (3.1%), renal cell: 2 (1.3%), unknown: 8 (5.0%), other: 4 (2.5%).	2008 with stereotactic radiosurgery for brain metastases	620 tumors tx in single session, 20 in fractionated session F/U: every 1-3 months for 6 months after radiosurgery. Avg follow-up 11.6 months (0.3-84.2)	Gy (2-37.5 Gy). For fractionated tx, Avg total dose 35.5 Gy (20-51 Gy) in Avg 7.5 fractions		related with radiation necrosis, 2 pts (1.9%) seizure after tx	charts: table 1, primary pathologies lists number of tx, not lesions. Number of metastases listed in chart does not match numbers given in text. Analysis accounted for age, sex, KPS, # metastases, pathology, interval from primary diagnosis to metastases, dissemination, RPA class
Ishikawa (2009) Case Series **Brain Metastases**	n = 80 mean age at tx 61.4 yrs (19-79), mean lesion number 3 , median 1, range 1-31. Cumulative tumor volume median 2.82 mL (0.08-30.30 mL) and mean median tumor volume 1.53 mL (0.02-30.30 mL).	Pts tx at clinic between Nov. 1991 - Dec. 2004 with GKRS for brain metastases who survived 3 years or more after tx	Gamma knife radiosurgery (GKRS) F/U: every 2-6 months until death	Dose levels given for pts w and w/o development of DCF. Minimal dose per lesion for non-DCF group (n=72): 20.3 ± 3.9 Gy,	n/a (no control or comparison group)	delayed cyst formation(DCF): 8 (10%), no others noted	Fair Study to determine prognostic factors for development of DCF in pts tx with GKRS for brain

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Primary cancer: lung: 50 (62.5%), urogenital: 13 (63%), breast: 9 (11.3%), alimentary track: 5 (6.3%), others: 2 (2.5%), unknown: 1 (1.3%). Karnofsky performance status ≥ 80: 76 (95%) and 70 in 4 (5%). Prior tx, 22 pts (27.5%) surgery, 7 pts (8.8%) radiotherapy.			for DCF group: 22.3 ± 2.9 Gy. Maximal dose per lesion for non-DCF group: 38.1 ± 6.0 Gy, for DCF group: 41.2 ± 6.6 Gy			metastases
Kano (2011) Case Series **Brain Metastases**	n = 158 (231 procedures, 531 metastases) Brain metastases from renal cell carcinoma (RCC) males 47, females 111. median age 61 (38-83), # metastases: 1: 80 (50.6%), 2-4: 62 (39.2%), ≥5: 16 (10.1%. Previous tx: chemotherapy: 94 (59.5%), immunotherapy: 56 (35%), surgery: 18 (11.4%), biopsy: 4 (2.5%), WBRT: 57 (36.1%). KPS: 90-100: 131 (82.9%), ≤80: 27 (17.1%) range 50-100. Score index for radiosurgery (SIR): 0-3: 8 (5.1%), 4: 16 (10.1%), 5-6: 84 (53.2%), 7-8: 47 (29.7%), 9-10: 3 (1.9%). Graded	Pts tx at clinic between June 1989-Oct. 2009 for brain metastases from RCC with gamma knife radiosurgery	gamma knife radiosurgery F/U: at 2 months after procedure then every 3 months first 2 years, every six months to through 5th year and then annually	median prescription dose 18.0 Gy (10-22 Gy), median maximal dose: 35.0 Gy (20-44 Gy)	n/a (no control or comparison group)	clinical follow-up available in 108 pts who did not die before follow-up. 8 pts (7%) developed symptomatic adverse radiation effects (ARE) and 3 (3%) developed asymptomatic AREs. 6 pts (5.5%) intratumoral hemorrhage	Fair Accounted for age, sex, RPA, SIR, GPA, KPS, # mets, prior tx, extracranial disease, tx dose, histology

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Prognostic Assessment (GPA): 3.5-4.0: 11 (7.0%), 3.0: 87 (55.1%), 1.5-2.5: 37 (23.4%), 0-1.0: 23 (14.6%). median total tumor volume 3.0 cm3 (0.06-35 cm3)						
Kelly (2011) Case Series **Brain Metastases**	n = 24 males 10, females 14. median age 57 (42-92). 21 pts (87.5%) other brain metastases, 23 pts (95.8%) also tx with WBRT. Median Karnofsky performance status 80 (60-100). Primary cancer: NSCLC: 8 (33.3%), breast: 8 (33.3%), melanoma: 3 (12.5%), RCC: 3 (12.5%), other: 2 (8.3%).	Pts tx at clinic between 2001-2009 with LINAC SRS to single brainstem metastases	Novalis LINAC SRS F/U: at 4-8 weeks after SRS then every 3-4 months. Median follow-up 6.6 months (0-21.1). 2 pts (8.3%) lost to follow-up	median dose 13 Gy (8-16) in one fraction. One pt fractionated tx 5 Gy in 5 fractions	n/a (no control or comparison group)	grade 3 ataxia: 1 pt (4.2%), grade 3 confusion: 1 pt (4.2%).	Poor Did not report full analysis only statistically significant outcomes. Small sample size. Authors noted that absence of late stage toxicity might be due to high pt mortality rate
Kondziolka (2011) Case Series **Brain Metastases**	n = 350 Brain metastases from breast cancer median age 54 (29-84). # mets: 1: 117 (33.4%), 2-4: 155 (44.3%), ≥5: 78 (22.3%). Previous tx: chemo: 339 (96.9%),	Pts tx at clinic between May 1990 - March 2009 with SRS for brain metastases from breast cancer	stereotactic radiosurgery SRS F/U: at 8 weeks, every 3 months for 2 years, every 6 months to year 5 and	median prescription dose 17 Gy (8-23 Gy), median maximum dose 32.0 Gy (18-42.5 Gy)	n/a (no control or comparison group)	of 275 pts with clinical follow-up, 16 pts (6%) symptomatic adverse radiation effects: 10 pts (3.6%) grade 3 hemiparesis with headache, 2 pts (0.7%) grade 4 radiation necrosis, 1 pt (0.4%) grade 4 mixed necrosis and persistent tumor. 14 pts (5%) asymptomatic adverse	Poor Analysis accounted for age, # mets, chemo, WBRT, interval between primary diagnosis and

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	cranial resection: 31 (8.9%), WBRT 227 (64.9%). Extracranial mets: 317 (90.6%). Systemic disease status: active: 233 (66.6%), controlled: 117 (33.4%). KPS 90-100: 278 (79.4%), ≤80: 72 (20.6%). RPA class I: 24 (6.9%), II: 310 (88.6%), III: 16 (4.6%). median tumor volume per tumor: 0.7 cm3 (0.01-48.9 cm3). median total tumor volume 4.9 cm3 (0.09-74.1 cm3)		then annually. Median follow-up 9.5 months (0.2-145 months)			radiation effects	mets, status of systemic disease, tumor location, radiation dose, estrogen receptor, HER2/neu
Koyfman (2010) Case Series **Brain Metastases**	n = 43 Brain metastases in the brainstem (metastatic and recurrent) males 16, females 27. median age 59 (27-79). Med KPS = 80 (50-100), Primary cancer: NSCLC: 19 (44%), RCC: 8 (19%), breast: 7 (16%), other: 9 (21%). SRS as first tx: 21 (48%), as salvage tx after WBRT: 22 (52%). Median tumor volume 0.37 cm3 (0.01-8.8 cm3)	Pts tx at clinic between 1997-2007 with SRS for single brainstem metastasis	stereotactic radiosurgery SRS F/U: at one month, some every 3-6 months unless death or decision to follow-up closer to home. Median follow-up 4.3 months (0.2-53.4)	median prescription dose 15 Gy (9.6-24 Gy)	n/a (no control or comparison group)	of 33 pts with follow-up, radiographic evidence of radionecrosis in 2 (6%). Grade 1 or 2 weakness, ataxia and bleeding from a pin site in 3 pts (9.1%). No grade 3 or 4 toxicity	Poor Small sample size, short follow-up, didn't report all variables in analysis
Liew (2011) Case Series	n = 333	Pts tx at clinic between Aug.	Gamma knife radiosurgery	median marginal	n/a (no control or comparison group)	17 (6%) had asymptomatic evidence of peritumoral	Fair

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Brain Metastases	Brain metastases from melanoma males 224, females 109. median age 53 (16-87). # mets: 1: 122 (36.6%), 2-3: 104 (31.2%), 4-6: 65 (19.5%), ≥7: 42 (12.6%). Previous tx: chemo: 163 (48.9%), immunotherapy: 173 (52%), extracranial radiation: 46 (13.8%), vaccine: 38 (11.4%), cranial resection: 50 (15%), WBRT: 118 (35.4%), cyst aspiration: 3 (0.9%), stereotactic biopsy: 10 (3%). systemic disease status: active: 263 (79%), controlled: 70 (21%). KPS 90-100: 221 (66.4%), ≤80: 112 (33.6%). RPA class I: 33 (9.9%), II: 277 (83.2%), III: 23 (6.9%). SIR: 0-3: 40 (12%), 4: 63 (18.9%), 5-6: 129 (38.7%), 7-8: 85 (25.5%), 9-10: 16 (4.8%)	1987-Dec. 2008 with GKS for brain metastases from melanoma	(GKS) F/U: at 8 weeks then every 3 months for first year and then on a case by case basis	dose 18 Gy (10-22 Gy), median maximal dose: 33.3 Gy (20-50 Gy)		radiation effect. 21 (7%) developed symptoms related to imaging evidence of peritumoral radiation effect. 64 pts of 259 with follow-up imaging (25%) had evidence of tumoral hemorrhage	Wide variety of tx regimens makes comparison difficult
Meisner (2010) Case Series **Brain Metastases**	n = 93 (142 lesions) Brain metastases Of pts, 59 (63%) were newly diagnosed with brain	Pts tx at clinic between May 1998 - Oct. 2006 for 1-4 brain metastases with stereotactic	SRS given alone or with WBRT F/U: at 6 wks post tx then	median dose 16 Gy (10-20), WBRT dose 15 x 2.5 Gy	n/a (no control or comparison group)	20 pts (22%) progressive neurologic symptoms requiring steroids. 10 pts (11%) seizures. 2 pts (2.2%) radionecrosis	Poor Didn't break out pt characteristics by tx group,

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	metastases. Of these 46 (49%) had SRS alone, 13 (14%) had SRS with up-front WBRT. 34 pts (37%) tx with SRS for recurrent brain mets after failure of previous WBRT. Analysis not done on different tx groups. Characteristics not broken out by tx group. Median age 57 (34-83), Primary cancer: NSCLC: 35 (37.6%), breast: 18 (19.4%), melanoma: 14 (15.1%), RCC: 9 (9.7%), colorectal: 4 (4.3%), other: 13 (14%). RPA class I: 33 (35.5%), II: 55 (59.1%), III: 5 (5.4%). # metastases: 1: 59 (63.4%), 2: 22 (23.7%), 3-4: 12 (12.9%). Gross tumor volume: 1.8 mL (0.1-22.5ml)	radiosurgery (SRS)	every 3 months for year. Median follow-up 7.5 months (0.1-81.6 months). 2 pts (2.2%) lost to follow-up				didn't compare tx doses
Molenaar (2009) Case Series **Brain Metastases**	n = 86 Brain metastases Males 40, females 46. Median age: 60 (33-87). # mets: 1: 44 (51%), ≥2: 42 (49%). KPS 50:1 (1%), 60: 2	Pts tx at clinic between July 2004 - Jan 2007 for brain metastases with 1-4 mets, max diameter 40 mm or less per lesion,	stereotactic radiosurgery (SRS) F/U: mean follow-up 6.3 months (0.1-30.2). 11 pts	median dose 21 Gy (12-25 Gy)	n/a (no control or comparison group)	5 pts (6%) radionecrosis	Fair Controlled for age, sex, # mets, control of primary disease, histology, KPS,

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(2%), 70: 11 (13%), 80:20 (23%), 90: 32 (37%), 100:20 (23%). RPA class I: 24 (28%), class II: 59 (69%), class III: 3 (4%). Primary cancer: lung: 49 (57%), breast: 16 (19%), melanoma: 11 (13%), colorectal: 5 (6%), unknown: 2 (2%), other: 2 (2%). extracranial disease controlled: 44 (51%), progressive: 42 (49%). median tumor diameter: 19 mm (0.3-5.8) mean # lesions: 1.7.	KPS ≥70, contraindications for surgery because of location of tumor in deep or eloquent regions	(12.8%) lost to follow-up				RPA, tumor diameter, other tx, presenting symptoms, tx dose
Motta (2011) Case Series **Brain Metastases**	n = 373 Brain metastases from NSCLC males 298, females 75. mean age 64.9 (38.2-89.2). Mean # mets: 2.16 (1-8). Mean lesional volume: 3.55 cc (0.01-34.6 cc). RPA class I: 35 (9.4), II: 297 (79.6%), III: 16 (4.3%), unknown: 25 (6.7%). Previous tx (surgery, WBRT, stereotactic drainage of cystic metastasis): 113 (30.3%)	Pts tx at clinic between 2001-2006 with brain metastases from non-small cell lung cancer (NSCLC). # mets <8, KPS >70, RPA class I and II, clinical exam within 3 months, life expectancy > 6 months	Gamma knife radiosurgery (GKS) F/U: mean follow-up 51 months (6-91 months)	mean prescription dose 22.45 Gy (12-28 Gy)	n/a (no control or comparison group)	radiation necrosis 30 pts (8%)	Fair Accounted for age, gender, surgery, WBRT, # mets, tumor volume, RPA class, tx dose

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Nath (2010a) Case Series **Brain Metastases**	n = 65 (204 lesions) Brain metastases males 27 females 38. Median age 58 (20-83), primary cancer: lung: 28 (44%), breast: 20 (31%), melanoma: 12 (18%), ovarian: 2 (3%), other: 2 (4%). Median lesions per pt: 2 (1-13). Med tumor diameter: 9 mm (1-35 mm). Tx: SRS alone: 53 (81.5%), SRS+WBRT: 9 (14%). Surgery + SRS: 1 (1.5%). Brachytherapy (BR)+SRS: 1 (1.5%), BR+SRS+WBRT: 1 (1.5%)	Pts tx at clinic between Dec. 2005 -June 2008 for brain metastases with frameless SRS	frameless stereotactic radiosurgery (SRS) F/U: at 1 week then every 3 months to 18 months then on case by case basis. Median follow-up 6.2 months (0.13-32.4)	median dose 18 Gy (14-22 Gy)	n/a (no control or comparison group)	9 pts (14%) grade 2 harms: 1 seizure (1.5%), 1 transient mild ataxia (1.5%), 7 edema (10.8%). 1 pt grade 3 aphasia (1.5%), 1 pt grade 3 hemorrhage (1.5%), 1 pt grade 3 hemiparesis secondary to radionecrosis (1.5%)	Fair Reported survival and local control rates for frameless SRS, small sample, no comparison population
Nath (2010b) Case Series **Brain Metastases**	n = 26 males 10, females 16. median age 53 (24-83). RPA class I: 5 (19%), class II: 12 (46%), class III: 9 (35%). Primary cancer: breast: 11 (42%), lung: 8 (31%), melanoma: 7 (27%).	Pts tx at clinic between March 2005 - May 2008 with single-center, frameless intensity-modulated SRS for brain metastases	single-center frameless intensity-modulated SRS F/U: at 1 wk following tx, then every 3 months for 18 months, then schedule determined	median 18 Gy (14-25 Gy)	n/a (no control or comparison group)	grade 2 seizure: 1 pt (3.8%), grade 2 worsening of visual symptoms: 1 (3.8%), grade 3 hemiparesis after hemorrhage of tx lesion: 1 (3.8%), grade 3 radionecrosis: 1 (3.8%)	Poor Accounted for age, sex, histology, tumor size, # metastases, RPA class, dose

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			on case by case basis. Median follow-up 3.3 months (0.2-21.3) with 20 of 26 pts followed to death. Of remaining six pts alive at analysis, median follow-up 14.6 months (9.3-18.0)				
Rush (2011) Case Series **Brain Metastases**	n = 109 (114 pts identified, 5 lost to follow-up, 109 analyzed) males 34, females 75, median age 61.2 (28-94). Primary cancer: NSCLC: 55 (50.5%), breast: 21 (19.3%), melanoma: 20 (18.3%), renal: 7 (6.4%), colon: 2 (1.8%), esophageal: 1 (0.9%), hepatocellular: 1 (0.9%), bladder: 1 (0.9%), ovarian: 1 (0.9%), unknown: 1 (0.9%). primary cancer controlled:	Pts tx at clinic between 2001-2009 for brain metastases. Adults with 1-3 metastases, maximum tumor diameter 2 cm, KPS score ≥ 60, estimated life expectancy ≥ 4 months, no prior WBRT	Gamma knife radiosurgery (GKS) F/U: at 6 wks then every 3 months.	20 Gy	n/a (no control or comparison group)	transient neurological worsening: 4 pts (3.7%), in one pt (0.9%) due to hemorrhage. Permanent neurological worsening: 3 pts (2.8%). Radiation necrosis: 3 pts (2.8%)	Good Analysis accounted for sex, age, histology, RPA, KPS, active primary disease, extracranial metastases, # metastases, tumor volume. Well defined selection criteria, consecutive

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	yes: 67 (61.5%), no: 41 (37.6%), unknown primary: 1 (0.9%). extracerebral metastases: yes: 80 (73.4%), no: 29 (29.6%). Median KPS score: 90 (60-100). RPA class I: 17 (15.6%), class II: 86 (78.9%), class III: 6 (5.5%). # metastases: 1: 69 (63.3%), 2: 25 (22.9%), 3: 15 (13.8%). median tumor volume: 0.35 cm3 (0.004-4 cm3)						series and identical radiosurgical tx plan
Skeie (2011) Case Series **Brain Metastases**	n = 80 (140 metastases) males 31, females 34. mean age 63.5 ± 12.4 (23-84), mean KPS score 75 ± 14, RPA class I: 8 (10%), class II: 61 (76.2%), class III: 11 (13.8%). Primary cancer: rectum: 50 (35.7%), colon: 90 (64.3%). # metastases: 1: 52 (65%), 2: 15 (18.8%), 3: 4 (5%), >3: 9 (11%). extracranial metastases: yes: 69 (86.2%), no: 11 (13.8%). Tx: GKS: 59 (73.8%), GKS + WBRT: 3 (3.8%), GKS + resection: 6 (7.5%), GKS + WBRT + Resection: 12 (15%)	Pts tx at clinic between May 1996-Dec 2008 with colorectal cancer. ≤ 3 metastases at time of referral, maximum diameter 3.5 cm (22 pts (27.5%) had developed more metastases or had tumor diameter > 3.5 cm at time of tx)	Gamma knife surgery (GKS) F/U: at 1 month and then every 3 months. Mean follow-up 5.4 months (0.5-75 months.) 12 pts (15%) lost to follow-up due to poor medical status	20-25 Gy in 103 (73.6%) of tumors. 37 tumors (26.4%) received ≤ 18 Gy	n/a (no control or comparison group)	radiation edema: 16 pts (23.5%)	Poor High loss to follow-up, chart error in pt characteristics (re: extracranial mets), analysis accounted for age, sex, KPS, RPA, neurological deficits, # mets, tumor volume, extracranial mets,

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
							histology, latency, radiation dose, prior WBRT and other tx parameters. large variation in tx protocols
Wegner (2011) Case Series **Brain Metastases**	n = 44 Brain metastases from small cell lung cancer (SCLC) (metastatic and recurrent) Males 14, females 30. Median age 63 (38-84). Median KPS 80 (50-100). Active systemic disease: 24 (55%). Previous WBRT or PCI: 30 (68%)	Pts tx at clinic from July 1991-June 2008 for brain metastases from SCLC	Pts underwent various combinations of WBRT, SRS and prophylactic cranial irradiation (PCI). PCI-> SRS: 9 (20.%), PCI -> WBRT -> SRS: 3 (6.8%), WBRT -> SRS: 18 (40.9%), WBRT + SRS (combined): 6 (13.6%), SRS: 8 (182%) F/U: at 2 months post tx, every 3 months for		n/a (no control or comparison group)	1 pt (2.2%) transient peritumoral steroid responsive edema after SRS alone	Poor Small sample size, variety of tx protocols

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			first year and then every 4-6 months afterward. Median follow-up 9 months (1-49 months)				
Wei (2010) Case Series **Brain Metastases**	n = 78 Brain metastases Males 46, females 32. Median age 55 (28-75), # mets: 1: 49 (62.8%), ≥2: 29 (37.2%). Primary cancer: lung: 50 (64.1%), breast: 10 (12.8%), colorectal: 5 (6.4%), esophageal: 2 (2.6%), gastric: 2 (2.6%), other: 9 (11.5%). KPS ≥ 70: 61 (78.2%, <70: 17 (21.8%). Controlled extracranial tumor: 29 (37.2%), not controlled: 49 (62.8%)	Pts tx at clinic between July 1999-Dec. 2004 for brain metastases	SRS 39 pts (50%) also given WBRT F/U: schedule not given. Mean follow-up 14.8 months (1.7-77.4). 4 pts (5.1%) lost to follow-up	38 lesions tx with single SRS with median dose 15 Gy (11-24 Gy). 84 lesions tx with 2-6 times SRS with median dose 24 Gy (11-40 Gy)	n/a (no control or comparison group)	no serious toxicity reported	Poor
Williams (2009) Case Series **Brain Metastases**	n = 273 (316 tumors) males 162, females 111. Median age 57 (12-93). Median KPS 90 (40-100). Primary cancer: lung: 97 (36%) melanoma: 69 (25%), RCC: 47 (17%), breast: 35	Pts tx at clinic between June 1993 - Dec. 2004 for 1-2 brain metastases with SRS. Excluded if received previous tx (resection,	stereotactic radiosurgery (SRS) F/U: at 1 month and then every 3 months.	median dose 18 Gy (10-24 Gy)	n/a (no control or comparison group)	complications associated with 127 (40%) of 316 lesions (numbers below from lesions.) Severe complications (≥ grade 3) occurred in 44 (14%) of lesions. Seizure: grade 2: 22 (7%), grade 3: 16 (5%), grade	Fair Pt pop did not include pts with prior WBRT, analysis accounted for

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
	(13%), other: 25 (9.2%). Median tumor volume: 1.26 cm3 (0.01 - 22 cm3).	WBRT or SRS) for a lesion, underwent adjuvant WBRT following SRS or no post SRS follow-up	Median follow-up of all pts 6.9 months (0.2-90.8) median follow-up of pts alive at end of study: 11.6 months (0.2-90.8)			4: 3 (1%). Visual deficit: grade 1: 7 (2%), grade 2: 3 (1%), grade 3: 2 (0.6%); motor deficit: grade 1: 5 (1.6%), grade2: 11 (3.5%), grade3: 8 (2.5%). Sensory deficit: grade 1: 7 (2%), grade 2: 3 (1%). Cognitive deficit: grade 1: 6 (1.9%), grade2: 17 (5.4%), grade3: 1 (0.3%), grade4: 4 (1.3%). Speech deficit: grade1: 1 (0.3%), grade2: 3 (1%), grade 3: 2 (0.6%). Headache grade 1: 17 (5.4%), grade 2: 6 (1.9%). Nausea grade 1: 9 (2.8%), grade 2: 4 (1.3%). hemorrhage: 10 (3%), Hydrocephalus: 4 (1.3%), Deep vein thrombosis: 9 (2.8%), Steroid dependency: 86/275 (31%). Cushing syndrome: 7 (2%)	many confounds. Higher rate of complications could be from a sample with higher rates of eloquent brain stem metastases. Severity of complications was assessed retrospectively, introducing possible pro-complication bias to analysis. Heterogeneous population

Ependymoma

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Kano (2009b) Case Series **Ependymoma**	n = 39 Intracranial ependymoma - SRS for recurrence, residual primary tumor, and distant intracranial mets Median age 22.8 y (Range 2.9-71.1 y); 14 pts also underwent previous chemo; low-grade ependymoma n=34, anaplastic n=22; 36 patients underwent SRS for recurrence, 3 received SRS as boost for residual tumors after RT; 11 received SRS for distant intracranial mets	(1989-2006) All w/prior surgical resection followed by radiotherapy for histologically confirmed ependymoma	Stereotactic radiosurgery (SRS); no comparator F/U: Median 23.5 mo (range 6.1-155.2 mo); MRI at 3-6 mo after radiosurgery	Median 15 Gy (10-22.5Gy)	n/a (no control or comparison group)	Overall adverse radiation effects (AREs) n = 3 (7.7%); 20 y/o w/ central necrosis of tumor at 1y MRI f/u, managed successfully w/ po steroids; 3 y/o w/ipsilaterial facial paresis 3 mo after SRS, success managed w/po steroids; 52 y/o w/ tumor necrosis, asymptomatic at 13 mos, but death at 28m after SRS when tumor progressed + hemorrhage after reoperation	Fair Potential conflict of interest potential w/multiple authors
Kano (2010) Case Series **Ependymoma**	n = 21 Median age 6.9 y (2.9-17.2 y); 11 pts received adjuvant chemo; 12 w/low-grade, 9 2/anaplastic	(1989-2008) Recurrent or residual intracranial ependymoma after resection and fractionated RT (cranial -12 or neuraxis if spinal mets - 9) - median dose 52.2Gy	SRS; no comparator F/U: Median 21.6 mo (6 -> 24 mo)	15 Gy (9.6-22 Gy)	n/a (no control or comparison group)	ARE in 2 patients (9.5%); 3 y/o w/ipsilaterial facial paresis 3 mo after SRS 12Gy dose, success managed w/po steroids; 8yo w/ e/o necrosis via increased contrast enhancement on MR, SRS dose 15 Gy	Fair Potential conflict of interest potential w/multiple authors

Glioblastoma multiforme

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Souhami (2004) Prospective RCT **Glioblastoma**	n = 168 Primary Stratified by age and KPS. mean age 55.5 (28-79) vs 56.4 (18-79). Subjects also matched as to KPS, gender, race, neurologic fxn, MMSE, tumor size, recursive partitioning analysis class, Spitzer QOL index, education level.	≥18 y/o, histo proven dx of supratentorial GBM; no prior cranial radiation or chemo, KPS≥60, life expectancy ≥3 mos, adequate bone marrow reserve, acceptable renal and hepatic function, nml chest xray, lesion ≤40mm before or after resection.	external beam radiation therapy (EBRT) + stereotactic radiosurgery (SRS) 1 week prior vs EBRT alone. All pts received surgery prior and carmustine (BCNU) chemotherapy F/U: median f/u time 61 mos. Imaging at 3-4 month intervals or with clinical change. MMSE, QOL Index, neuro exam at each visit.	SRS dose size dependent: ≤20mm=24 Gy, 21-30mm= 18Gy, 31-40mm=15Gy; EBRT 2gy daily 5 days/week for total of 60 Gy.	No difference in survival, quality of life or cognitive functioning.	no difference between treatment arms	Fair
Nwokedi (2002) Cohort **Glioblastoma**	n = 64 Primary median age 50.4 (6-85); median tumor volume 29 vs 25 cm3; KPS <70 in39% pts;	path confirmed dx, no prior brain irradiation or antineoplastic therapy, receipt of EBRT in dept	planned gamma knife SRS boost w/in 4wk s/p EBRT (after 1997) vs none planned (<1997) F/U: followed every 3 months, median f/u 17.5 mos	median EBRT dose 59.7 Gy (45-70.2), GK-SRS median dose 17.1 Gy (10-28)	Actuarial survival for entire cohort 1-yr (67%), 2-yr (40%), 3-yr (26%)/ Median OS 16 mos (range, 2-65 mos). <u>OS</u> GK-SRS Boose – 25 mos EBRT 13 mos	2/31 EBRT+GK-SRS pts with radiation necrosis.	Poor Undisclosed COI, no info on comorbidities. 10/33 EBRT alone later got GK-SRS as salvage tx-not factored in.
Biswas (2009) Case Series	n = 33	Enhancing lesions < 4 cm, at the	SRS with Novalis linear accelerator, 6 MV	Median dose 60 Gy	n/a (no control or comparison group)	0 patients, grade 1 or 2; 1 patient (3%), grade 4 toxicity	Poor

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Glioblastoma	Primary and recurrent Karnofsky performance status > 70, median age 57.8 (33-81)	discretion of treating physician	photons F/U: Followed at 6 weeks then every 2-3 months	(50-64 Gy) with 1.8-2 Gy per fraction		(enlarging tumor, decreased blood perfusion)	Potential conflict of interest
Hsieh (2005) Case Series **Glioblastoma**	n = 51 Primary, recurrent male: Female::28:23, median age 59 (17-81), KPS 60-100, 6 with multifocal; GK-SRS given upfront to 25, at recurrence to 26	path confirmed dx, tumor <64 cm3, KPS>60, life expectancy >3 mos.	GK-SRS given as upfront adjuvant therapy vs at time of tumor recurrence. F/U: every 8-12 wks until death. Median f/u 21 mos (5-56)	median EBRT dose 60 Gy; median maximal GK-SRS dose (24 Gy (15-32)	n/a (no control or comparison group)	no acute neurological toxicity, 15pts required multiple operations, 16 cases radionecrosis.	Fair Undisclosed COI
Smith (2008) Case Series **Glioblastoma**	n = 25 8 pts later found with multifocal disease or large put into 'high-risk' cohort, (HRG) male:fem::13:6, median age 52(19-79), HRG median age 67.5 (61-77), KPS>60	radiographic evidence or biopsy-proven GBM, no definitive resection or other tx, age 18-80, anticipated surgical cavity ≤60cm	gross-total resection and Gliadel wafer implantation. GK-SRS w/in 2 wks. Standard fractionated RT, temozolomide at recurrence. Tumor tissue PCR analysis for MGMT gene promoter methylation. F/U: MRI, neuro exam, quality of life evaluation every 2 mos.	GK-SRS 12Gy at 50%; EBFRT 60 Gy over 6 wks), average 5 wafers 93-8)	n/a (no control or comparison group)	no acute early toxicity or complications. Delayed symptomatic radionecrosis in 47%, delayed hydrocephalus requiring VP shunt in 47%, steroid dependence in 16 pts.	Poor

Glioma

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Kong (2008) Cohort **Glioma**	n = 474 Recurrent malignant gliomas SRS group: 114 pts; median age at presentation 49 (5-75), M/F 69 (60.5%)/45(39.5%); median pre-op KPS 100(50-100)*(error in article text says median is 80 table says 100); hx control: 360 pts; median age 53(4-89), M/F 217(60.3%)/143(39.7%) , median pre-op KPS 100(40-100)	SRS group: pts treated w/ SRS using linear accelerator or GK (Gamma knife) as salvage tx; grade 3 or GBM at time of initial surgical resection or biopsy, and who underwent subsequent fractionated brain irradiation and demonstrated new or recurrent lesions <3cm between Jan 2000 and Dec 2006. hx control group: pts w/ malignant gliomas tx from Jan 1995 to Dec 1999	SRS group: 5 pts tx w/ Varian linear accelerator, other 109 tx w/Elektra GK - (is this an issue?) Hx control: no specific description of tx provided F/U: SRS group median after SRS 11.2 mo (1.5-99.5 mo) Hx control - no information	SRS group: median dose 60 Gy (range, 54-70 Gy) in conventional fractionations of 2 Gy/day; hx control - no info provided on tx	comparison with historical control group - increased 12 mo OS for GBM for SRS (23 mo vs 12 mo p=<.0001) 23.0 (95% CI, 16.2-29.3 mo) vs 12 mo (95% CI, 10.4-13.6 mo); no significant difference in 12 mo OS for Grade 3 gliomas (37.5 mo vs 26 mo p=.789) (37.5 mo (95% CI, 11.7-63.2 mo) vs 26 mo (95% CI, 1.0-62.0 mo)	SRS Common adverse effects were nausea, vomiting and headache, usually controlled w/ steroid meds. F/U MRI scans show radiation-induced necrosis in 22 (24.4%) pts, but most weren't histologically confirmed; 4 w/ suspicious radiation-induced necrosis had surgical resection for the mass effect. Repeated MRI f/u images, MRS or PET scans were used to differentiate tumor recurrence and radiation-induced necrosis. The findings showed necrosis intermingled with tumor infiltration. No other NIC grade 3 or 4 toxicities obtained. Hx control - no info	Poor Error in text, no info on tx provided to control group, nothing re competing interests, potential confounders
Combs (2005) Case Series **Glioma**	n = 172 glioma (Grades 2 & 3) , glioblastoma multiforme (GBM) male/female 93:79;	pts w/ recurrent gliomas treated w/ fractionated stereotactic reirradiation (FSRT) from Jan 1990 to Dec 2004	FSRT F/U: pts seen 6 wks after FSRT, then every 3 mo or as needed clinically	target doses prescribed to the isocenter at a median of 36 Gy (range, 15 -	n/a (no control or comparison group)	No toxicity tables in article. Article states 1 pt had radiographically diagnosed and histologically confirmed radiation-induced necrosis after irradiation. Minor temporary side effect of FSRT included alopecia headaches, nausea/vomiting, skin erythema. No	Poor No controlling for prior treatment

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	median age at primary dx 41 (5 to 76 yrs) rest listed here as in article according to WHO grades 2/3/4 as in article: median age at primary dx of tumor 35 (13-64)/ 39 (21-74)/ 54 (18-76); median age at recurrence: 42 (16-66)/ 43 (24-75)/ 55 (19-77); presence of neurologic sx at recurrence (pts, %) 55 (77%)/ 32 (76%); 37 (63%); KPS > at recurrence (pts, %) 65 (92%); 39 (93%); 37 (63%)			62 Gy) delivered in a median fractionation of 5x3 Gy/wk. Defined target volume was encompassed by the 90% isodose.		severe early or late side effects more than NCI common toxicity criteria Grade 2 could be documented.	
Elliott (2011a) Case Series **Glioma**	n = 26 high-grade gliomas (HGGs), recurrent median age at dx of HGC 59 years (36-70) and at time of GKR for recurrence 60.4 (36.5-70); male/female 17(65.4%):9(34.6%). Median KPS 90; 100 in 6 pts (23.1%), 90 in 11(42.3%), 80 in	Adults who underwent gamma knife radiosurgery (GKR) for HGGs; criteria for GKR was KPS >70, HGG pathology types anaplastic astrocytoma (AA) WHO III/IV, anaplastic mixed oligoastrocytoma (AMOA) WHO	gamma knife radiation (GKR) F/U: At 6 weeks, and then at 8 to 12 week intervals thereafter	median dose 15 Gy to the 50% isodose line (IDL; range 10-18 Gy) and the median maximal dose was to 30 Gy (range 20-36 Gy)	n/a (no control or comparison group)	no toxicity tables in article. 2(7.7%) pts had transient headaches (RTOG Grade 2) after GKR that resolved within 3-4 wks; 1(3.6%) pt had transient worsening of pre-existing hemiparesis that returned to baseline with a course of steroids (RTOG grade 4); 2 pts (7.7%) with seizures before GKR had recurrent seizures at time of progression 6 mo and 10 mo after GKR. Two pts (7.7%) had radiation necrosis. 1 pt developed significant radiation necrosis (pathologically diagnosed) 3 mo after GKR and required resection for	Poor

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	8(30.8%), 70 in 1(3.8%).	II/II, and GBM WHO IV/IV between 2004-2009				resolution of mass effect. Another had excellent tx response of a left parietal tumor with extension into the spenium of the corpus callosum but developed radiation necrosis (radiologically dxed) 9 mo after GKR and died as a result of further neurologic progression shortly after.	
Fuchs (2002) Case Series **Glioma**	n = 21 brainstem Gliomas, benign WHO grade I or 2 (12 pts) malignant grade 3 or 4 (9 pts) median age 23 (8 - 56) male/female 2:1; tumor location: 7 midbrain (benign:malignant 5:2), 12 pons (6:6), 2 medulla oblongata (1:1)	pts w/ gliomas located in the brainstem (midbrain, pons and medulla oblongata) and had stereotactic radiosurgery using the 201-source Cobalt-60 Gamma Knife Model B between Aug 1992 and Dec 1999	gamma knife radiosurgery (GKRS) F/U: median 29 mo (3-99)	median dose of 12 Gy (9-20 Gy) applied to the tumor margin by the median isodose of 45%	n/a (no control or comparison group)	(reported as in article - grouped into benign and malignant) Benign: 3 pts died after 3.5-27.6 mo (median 20.7) due to their general condition, not GKRS; 2 pts required shunting procedure post GKRS; Malignant: 3 pts w/ multiloculated glioblastoma died within 3-5.8 mo (median 5.5); 3 pts w/ anaplastic astrocytoma died within 23.7-45 mo (median 28), tumor growth outside the radiosurgical (RS) tx volume and poor clinical condition in these 6 pts; 1 pt who had implantation of "a drainage" into a tumor cyst prior to craniotomy and RS developed malfunction of the drainage and tumor cyst regrowth; microsurgical cyst fenestration was performed 18 mo post RS. 74 mo post RS he is in satisfactory condition; no therapy related mortality or serious morbidity post GKRS in malignant. Within first 12 hrs post RS, 3 (33%) of malignant pts had nausea, vomiting and/or transient headache	Poor No controlling for prior treatments

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
						responsive to symptomatic tx.	
Heppner (2005) Case Series **Glioma**	n = 49 low-grade glioma, Grade 1 and 2, Primary and recurrent median age 27 (2-70), male/female 23:26, 25 had previous biopsy 24, had previous debunking , 5 had previous radiotherapy: 5	pts who had GKS for low grade gliomas between 1989 and 2003; RS was reserved for pts w/ focal tumors in eloquent regions of brain, for residual tumor post surgery or for late tumor recurrence following surgery	GKRS provided early - (immediately after dx and surgery) 28 pts, or late (performed on evidence of disease progression on serial neuroimaging studies before Gamma surgery) (21 pts) F/U: MRI scanning at 6-month intervals with additional scanning if there was neurological deterioration, this study reports on outcomes for a median of 63 mo clinically and 59 mo radiologically	median maximum dose was 36 Gy (range, 10 to 50 Gy); median dose to tumor periphery was 15 Gy (range, 2 - 26 Gy)	n/a (no control or comparison group)	Complications: 4 (8%) pts suffered clinical complications after GKS. 3(6%) pts had temporary neurological decline; 1 (2%) had surgery for radiation induced changes; 1(2%) had significant long-term neurological defect. 7 (14%) had radiological evidence of radiation-induced changes;	Poor
Kano (2009a) Case Series	n = 30	Pts who had primary or	stereotactic radiosurgery	median prescription	n/a (no control or comparison	Complications: 2 pts (6.7%) developed adverse radiation effects; both had	Poor

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Glioma	oligodendroglioma (ODG), Grade 2 and 3, newly diagnosed and progressive median age 43.2 (10.8-75.4), male/female 18:12,prior tumor resection 24, prior op (in grades 2:3) 4:11, prior FRT 5:17, prior biopsy 8:7.	adjuvant stereotactic radiosurgery (SRS) for histologically confirmed ODG between Dec 1992 and June 2006	(SRS) using gamma knife F/U: average 39.2 mo (12-133 mo); all had minimum of 12 mo	dose to the tumor margins was 14.5 Gy (range, 11-20 Gy), prescription isodose was 50% in 29 cases, maximum dose varied from 22 to 40 Gy (median 30 Gy).	group)	received doses of >15 Gy at the margin and developed increased peritumoral T2 signal changes on MR imaging. Effects in both cases were successfully managed initially with corticosteroids. 1 pt (3.3%) died of tumor progression 16 mo after SRS. In 1 pt (3.3%), an asymptomatic cavernous malformation was noted at 75 mo after SRS (newly diagnosed, possibly related to SRS or FRT or both)	Prior treatments not controlled for, relationship to gamma knife technology company
Marcus (2005) Case Series **Glioma**	n = 50 pediatric low-grade Gliomas, primary median age 9 (2-26), male/female 26:24; indication for SRT, progression after chemo/resection 12:38	pts between 18 mo - 25 yrs w/ biopsy-proven localized brain tumor or presumed optic glioma in the setting of neurofibromatosis; no prior RT. Histologic subtypes were also specified	stereotactic radiotherapy (SRT) F/U: median 6.9 yrs (2-26)	mean tumor dose 52.2 Gy (range, 50.4-58 Gy); maximum dose to optic chiasm 54 Gy	n/a (no control or comparison group)	Pediatric: no significant acute toxicity attributable to SRT; rarely minimal thinning of hair occurred temporarily. 1 (2%) pt developed a primitive neuroectodermal tumor, possibly radiation induced, 6 yrs after RT within the irradiated volume and died of the second tumor. 4 (8%) pts w/ optic glioma developed Moya Moya syndrome at 23, 40, 57, and 83 mo after SRT. 1 of these pts also had neurofibromatosis.	Poor Prior surgery and chemotherapy apparently not controlled for, nothing re competing interests
Roberge (2006) Case Series	n = 21 low-grade Gliomas,	patients treated for low-grade glioma using	hypofractionated stereotactic radiotherapy	13.3 years for living pts (minimum 8	n/a (no control or comparison group)	1 (4.7%) pt had minor pin site cellulites; 1 pt (4.7%) had focal transient alopecia. 3 (14.2%) pts had late complications: 1	Poor No competing

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Glioma	primary and recurrent median age23 (9-94), male/female 9:12; most common presenting sx seizure (29%), tumors predominately WHO grade 2 (71%)	hypofractionated SRS between July 1987 to Nov 1992.		yrs)		had sx of peri-lesional edema requiring steroid therapy; made a full recovery and remains well 10+ yrs pot-tx. 1 pt had persistent worsening of his hemiparesis 4 mo post-tx which failed to resolve w/ conservative mgmt and was present at last f/u (8.8 yrs); 1 pt had edema refractory to steroid tx 10 mo post-tx and was operated - both tumor and necrosis were seen.	interest statement, nothing stated re prior surgical or chemotherapy
Ulm (2005) Case Series **Glioma**	n = 100 Grade 3 (anaplastic astrocytoma) and Grade 4 (glioblastoma astrocytic tumors median age 55 (21-80), 10 pts alive at time of study, one lost to follow-up, 80 had died. 56 had lesion in an eloquent location; 74 dx w/ glioblastoma, 26 anaplastic astrocytoma. Median KPS 90 (60-100)	patients treated with LINAC-based radiosurgery for anaplastic astrocytoma and GBM from 1 May 1989 to June 12 2002.l	linear-accelerator-based radiosurgery F/U: minimum was 18 months or until death	dose of radiation after biopsy only (<54.4 Gy or > 54.4 Gy)	n/a (no control or comparison group)	22 (22%) pts underwent further surgery after RS tx; 1 required a ventriculoperotoneal shunt, 1 needed aspiration of a thalmic cyst; remaining 20 had aggressive debulking of recurrent mass. In 16 of the 20, recurrent tumor and radiation necrosis both were identified, in 2, tumor alone was seen, and in the other 2, pure radiation necrosis was seen; this suggests RS contributes to need for surgical debulking of recurrent mass in some pts.	Poor Would give a rating of good if there were a competing interest statement

Meningioma

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Becker (2002) Case Series **Meningioma**	n = 39 Optic nerve sheath meningioma, primary and metastatic Primary optic nerve sheath meningioma was considered as arising from the orbital or canalicular portion of the optic nerve); Secondary optic nerve sheath meningioma was considered as arising from the intracranial meninges and subsequently involving visual pathways); Median age at first diagnosis: primary, 44 (range 13-67) and secondary, 52.5 (range 28-83); Median time from first symptoms to first diagnosis: primary, 12 months (range 5-120) and secondary, 5 months (range 1-240) and time from first diagnosis to radiotherapy: primary, 12 (range 2-115) and secondary, 4 (range 1-115); No surgical intervention in 12 of the primary and 8 of	Histologically proven or clinically and radiographically documented or suspected optic nerve sheath meningioma.	SRS with Phillips linear accelerator, 6 MV; no systematic therapy prior to radiation therapy in patients with secondary tumor; prophylactic steroids as needed. F/U: Ophthalmologic and radio-oncologic evaluations and MRI every 3 months, first year; every 3-6 months, second year; every 6 month after second year and yearly after the end of the fifth year. Endocrinologic testing every 6 months, first 2 years and yearly	Initial: 50.40 Gy in 26 daily fractions (safety margin of 5 mm); Boost: 3.60 Gy in 2 daily fractions (safety margin of 2 mm); Total prescribed tumor dose: 54 Gy in 28 fractions within 5.5 weeks of using 6-MV photons form linear accelerators; Primary cancer dose to planning target volume median: 104% (range 101%-07%); Secondary cancer dose to planning target volume median: 105% (range 101%-12%); Primary cancer minimal dose to planning target	n/a (no control or comparison group)	Erythema in the RT field, primary: 5 (33%) and secondary: 5 (21%); Alopecia within the RT field, primary: 11 (73%) and secondary: 18 (75%); New endocrinologic deficits after stereotactic fractionated radiotherapy, primary: 2 (14%) and secondary: 2 (8%), NOTE: These patients had large tumor masses extending to the pituitary gland and the radiotherapy dose had to include the sella turcica; NO radiotherapy-induced late brain or optic nerve injury during the follow-up period.	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	the secondary patients, biopsies in 3 primary and no secondary patients, subtotal removal in 1 primary and 13 secondary patients, and no primary and total removal in 3 secondary patients; Histologic findings for primary: none, 11; grade I, 3; grade II, 1 and for secondary: none, 8; grade I, 16; and grade II, 0; Systemic therapy pre-radiotherapy for primary: none, 7; steroids, 7; others, 2 and for secondary: none, 24; steroids, 0; others, 0; Endocrinologic disturbances before radiotherapy: functional hyperprolactinemia, primary: 2 (15%) and for secondary: 3 (12.5%); partial insufficiency of the pituitary gland, primary: 1 (7%) and secondary, 8 (33%)		thereafter, unless otherwise indicated by sign and symptoms of disease. Median follow-up for primary cancer, 39 months (range 10-73); for secondary cancer, 32.5 (range 10-56).	volume median: 85% (range 70%-97%); Primary cancer minimal dose to planning target volume median: 86.5% (range 65%-93%).			
Bledsoe (2010) Case Series **Meningioma**	n = 116 Large-volume (>10cm3) benign Meningiomas, primary and recurrent	Inclusion criteria: Radiosurgery for Intracranial meningioma.	Leksell Gamma Knife (Elekta Instruments) F/U: MRI at 6, 12,	Multiple-shot dose plans were typically used for conformational irradiation of the	n/a (no control or comparison group)	Postradiosurgical edema: 16 (14%), 7 (6%) of these were symptomatic and received corticosteroid therapy; Asymptomatic cysts, 3; ICA issues in patients treated for cavernous sinus	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	35 men and 81 women. Average patient age was 60 years (range 20-84); Prior surgery: 74 patients (64%); Average time from resection to stereotactic radiosurgery: 53.7 months (range 1-240 months); Tumor locations: Skull base: 91 (78%), more specifically, cavernous sinus 52 (45%), petroclival 11 (10%), cerebellopontine angle 8 (7%), sphenoid wing 8 (7%), foramen magnum 5 (4%), tentorium 5 (4%), anterior fossa 2 (2%); Supratentorial: 25 (22%), more specifically, parasagittal 13 (11%), falx 7 (6%), convexity 5 (4%)	Exclusion criteria: Tumors <10cm3, atypical meningiomas, malignant meningiomas, prior radiation therapy, neurofibromatosis, or follow-up of <12 months	and 24 months from the date of the operation; if the tumor remained stable at 24 months, MRI was recommended every 24-36 months; Mean follow-up duration after stereotactic radiosurgery: 70.1 months (range 12-199)	enhancing tumor; Mean number of isocenters: 12.9 (range 5-27); Radiation dose was prescribed to the 50% isodose line for 102 tumors (88%); Mean PIV: 17.5 cm3 (range 10.1-48.6cm3); Mean tumor margin dose: 15.1 Gy (range 12-18 Gy); Mean maximal radiation dose: 31.1 Gy (range 24-26 Gy)		meningiomas, 3: stenosis in 1 and occlusion in 2; Cerebral infarction 30 months after stereotactic radiosurgery, 1, also 2 were reported to be asymptomatic; Pontine infarction 8 months after stereotactic radiosurgery of a petroclival meningioma, 1; Median time to the following complications was 7 months (range 1 day -99 months): Seizure, 7 (6%); Hemiparesis, 6 (5%); Trigeminal dysfunction, 5 (4%); Headache, 4 (3%); Diplopia, 3 (3%); Cerebral infarction, 2 (2%); Ataxia, 2 (2%); Hearing loss, 1 (1%); Complication rates by tumor locations: Skull base: 16 (18%), more specifically, cavernous sinus 11 (21%) petroclival, 2 (18%), cerebellopontine angle 1 (13%), sphenoid wing 0, foramen magnum 0, tentorium 1 (20%), anterior fossa 1 (50%); Supratentorial: 11 (44%), more specifically, parasagittal 7 (54%), falx 3 (43%), convexity 1 (20%). Patient factors association with complications: sex, HR 2.44 (CI 1.15-5.26; P=0.02); location, HR 3.57 (CI 1.64-7.81; P<0.001); age, prior operation, prescription isodose volume, margin dose, maximum dose, number of isocenters, and ratio of prescription isodose volume to number of isocenters were all nonsignificant.	
Chang (2003)	n = 179 (194 lesions)	Inclusion	KULA dose	Tumor covered	n/a (no control or	OVERALL COMPLICATIONS found in 35	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Case Series **Meningioma**	Benign Meningiomas, primary and recurrent 40 men and 139 women; Mean age at time of radiosurgery: 50.4 years (range 7.4-82.2); Most common presenting symptoms: headache, 55 (30.7); trigeminal neuralgia, 18 (10.1%); visual disturbance, 13 (7.3); Meningiomas were incidentally detected in 49 (27.4); Gamma knife surgery as primary treatment: 109 (60.9%) and as adjuvant treatment: 70 (39.1%); Tumor location: skull base, 112 (57.7%); cerebral hemispheres, 72 (37.1%); ventricles, pineal region or sylvan fissure, 10 (5.2%); Cerebral hemispheric meningioma locations: frontal region, 42 (58.3%); parietal region, 18 (25.0%); occipital region,4 (5.6%); temporal region, 3 (4.2%); cerebellar convexity, 5 (6.9%); Relation of tumor to major	criteria: None reported; Exclusion criteria: atypical meningioma, malignant meningioma	planning system (version 5.4, Elekta, Sweden) and GammaPlan (version 5.30, Elekta, Sweden) F/U: 140 (72.2%) of the 194 lesions were followed-up with MRI for >6 months; mean follow-up duration: 37.3 months (range 6.4-86.3)	within 40%-90% (mean 50.5%) of the isodose curve; Mean tumor margin dose: 15.1 Gy (range 9.5-24.5); Mean maximum tumor dose: 30.0 Gy (range 19-45 Gy); Mean number of isocenters: 6.3 (range 1-15)	comparison group)	(25%) of the 140 lesions followed-up with MRI; these included: transient cranial nerve dysfunction, 2 (1.4%) and peritumorous imaging changes, 33 (23.6%); Of the 33 peritumorous lesions, 13 (39.4%) produced transient symptoms including: headaches caused by increased intracranial pressure, 6 lesions; seizures, 4 lesions; other neurological deficits, 3 lesions; Overall rate of symptomatic edema, 9.3%; Imaging changes developed at a mean of 7.8 months (range 2.8-48.9) after gamma knife surgery; Imaging changes were sustained for 13.5 months (range 3.0-28.0); Imaging changes were evident in 4 (5.1%) of the 79 skull base meningiomas and 26 (50.0%) of the 52 hemispheric meningiomas. FACTORS ASSOCIATED WITH PERITUMOROUS IMAGING CHANGES: Univariate analyses: tumor location (P<0.001), maximum tumor dose (P=0.0002), tumor margin dose (P=0.037). Multivariate analysis (Cox regression): Only tumor location was significant. Other factors in model included lobar location and size, patient age, sex, presenting symptom, relation to major venous sinus, pre-GKS degree of edema, treatment modality, and various radiosurgical parameters. Cerebral hemispheric	The model of the gamma knife was not reported

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	venous sinus due to tumor invasion: complete occlusion, 2 (1.0%); partial occlusion, 21 (10.8%); no venous sinus invasion, 171 (88.1%); Peritumorous edema pre-gamm+F4a knife surgery, grade 1 to 6: 26 (13.4%); Mean tumor volume: 10.1 cc (range 0.6-45cc)					meningiomas had higher rate of peritumors imaging changes that tumors in other locations.	
Deinsberger (2004) Case Series **Meningioma**	n = 37 Benign skull base Meningiomas, primary and recurrent men, 13 and women, 17; Median age, 62 years (range 35-88)Tumor location: cavernous sinus, 17; petroclival, 13; tentorial edge, 5; olfactory groove, 2; Treatment paradigms: Received microsurgery as first treatment modality with LINAC radiosurgery planned to tumor remnants, 8; Treatment for tumor recurrence after surgery, 2; LINAC radiosurgery as sole treatment (no pathological	Inclusion criteria: Patients with skull base meningiomas treated from January 1996-August 2003 with LINAC radiosurgery; Exclusion criteria not reported	Treatment planning: X Knife planning system (Radionics); Surgery: A combination of the commercially available X Knife Radiosurgery System (Radionics) and the University of Florida System (see Friedman and Bova, 1989); F/U: MRI and/or CT and neurological examination were scheduled 1 month after	Treatment volume, 5.9 mL (range 0.7-22 mL); Median dose at tumor margin, 1460 cGy (1100-1800 cGy), prescribed to the 80% isodose line in 1 or 2 isocenters; Median diameter of collimators, 18 mm (rang 5-25 mm); Due to irregular shape of skull base meningiomas, multiple isocenters were used in 32 out of	n/a (no control or comparison group)	Hemiparesis, 1 (2.7%), 8 months after LINAC for petroclival meningioma and received 16 Gy to tumor margin, a dose also given to brain stem, symptoms resolved almost completely after corticosteroid treatment; 27 patients developed no new neurological deficits; Facial numbness, 1 (2.7%), 6 months after treatment for cavernous sinus meningioma; Radiographic changes: hypodensity of temporal lobe, 1, without any clinical symptoms and resolved spontaneously without any treatment 4 months thereafter	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	verification), 29;		procedure, every 6 months for 2 years, and once a year thereafter; Median follow-up period, 66 months (range 9-96); NOTE: range in abstract is reported as 12-96 months for follow-up.	37 patients			
DiBiase (2004) Case Series **Meningioma**	n = 137 Benign intracranial meningioma 137 patients; 139 tumors (results appear to be reported for 121 patients for whom serial MRI was available) Median age, 57 years (range, 8-83 years); males, 34 (24.8%); females, 103 (75.2%); prior surgery, 38%; median gross tumor volume, 4.5 cc (range, 0.32-80.0 cc); cavernous sinus, 20.9%; petroclival, 12.9%; posterior fossa, 11.5%; sphenoid wing, 10.1%,	NR	SRS with 201-source 60Cobalt gamMedian, 4.5 years (range, 0.33-10.5 years)ma knife unit (Elekta Instruments) F/U: median f/u time for entire cohort 4.5 yrs (range, 0.33-10.5 yrs)	Median, 14 Gy (range, 4-25 Gy) to the 50% isodose line; number of treatments or fractions not reported	n/a (no control or comparison group)	New neurological deficits: 10 patients, (8.3%), including edema with consequent headache (9 patients; time of occurrence not reported) and/or seizures at 3-4 months (2 patients); intracranial pressure requiring shunt placement (1 patient; time of occurrence not reported); corticosteroid-refractory radiation necrosis requiring surgical resection (1 patient; time of occurrence not reported); severe positional vertigo developing 1 month after SRS and resolving slowly after unspecified conservative management (1 patient)	Poor Overall adverse event rate as reported by authors suggests that it was based on the 121 patients with serial MRI

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	frontal, 7.9%; central-pontine angle, 5.8%; tentorial, 5.8%; occipital, 5.8%; parafalcine, 5.0%; parasagittal, 5.0%; parietal, 2.9%; orbital, 2.2%; olfactory, 1.4%; temporal, 1.4%; parasellar, 1.4%						
Flannery (2010) Case Series **Meningioma**	n = 168 Intracranial meningioma Primary, 129 patients, or 76.8%; recurrent, 39 patients, or 23.2% Mean age, 57 years (range not reported); males, 44 (26%); females, 124 (74%); mean tumor volume, 7.7 cm3 (range not reported); atypical meningioma (WHO Grade II) at prior surgery, 1.8%; anaplastic meningioma (WHO Grade III) at prior surgery, 1.2%; multiple intracranial tumors (not necessarily meningioma), 2.9%; meningioma related to prior fractionated radiotherapy, 2.9%	Petroclival (between petrous apex and upper 2/3 of clivus) meningioma and complete follow-up	SRS with Leksell Gamma Knife Unit model U, B, C, or 4C (Elekta Instruments) F/U: f/u imaging studies requested at 6 mos, 1,2,4,8, and 12 yrs after radiosurgery, and 4-yr intervals thereafter. Median imaging f/u 64 mos (range, 3-204).	Median dose to tumor margin, 13 Gy to 50% isodose line (range not reported)	n/a (no control or comparison group)	Clinical or neurological deterioration in absence of tumor growth: 14 patients, (8.3%), including new or worsening cranial neuropathy (1.8%), worsening cerebellar symptoms (1.2%), new seizures and headaches (0.5%), edema alone (2.4%), or unspecified effects (2.4%)	Poor
Flickinger	n = 219	Diagnosis of	SRS with Leksell	Median marginal	n/a (no control or	Post-SRS sequelae: 12 patients (5.5%),	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
(2003) Case Series **Meningioma**	Intracranial meningioma, 2 pts (0.9%) reported to have history of biopsy-proven meningioma in different location than current tumor Median age, 62 years (range, 18-86 years); males, 58 (26.5%); females, 141 (73.5%); Karnofsky performance status ≥90, 95.4%; cavernous sinus, 34.2%; petroclival, 21.9%; frontal, 11.9%; paragagittal, 10.0%; occipital, 5.9%; pons or midbrain involvement, 5.5%; cerebellar, 4.6%; temporal, 4.6%; intraventricular, 0.9%; corpus callosum involvement, 0.5%	meningioma based on imaging alone (homogenously enhancing, dural-based tumor with no evidence of rapid growth or metastasis); no prior surgery	Gamma Knife Unit model U, B, or C (Elekta Instruments) F/U: Up to 10 years; range, mean, or median not reported	dose, 14 Gy (range, 8.9-20 Gy); median maximum dose, 38 Gy (range, 22-50 Gy); number of treatments or fractions not reported. Dose greater before 1991, when planned by computed tomography, than after 1991, when planned by magnetic resonance imaging (median marginal dose, 17 Gy versus 14 Gy)	comparison group)	including edema and consequent headache (1.8%), worsening hemiparesis (0.9%), mental status changes requiring steroids or shunt placement (0.9%), trigeminal nerve numbness or tic (1.4%), and temporary visual field deficits (0.45%). Actuarial rate of post-SRS symptomatic sequelae greater in 28 patients treated before 1991 than in 191 patients treated later (22.9% versus 5.3%). Univariate analysis of harms and treatment/patient factors: Harms correlated with CT versus MRI (P=0.0104); marginally correlated with treatment volume (P=0.054) and volume of tissue receiving ≥12 Gy (P=0.063); not correlated with marginal dose, sex, age, treatment isodose, maximum dose, or isocenters.	
Franzin (2007) Case Series **Meningioma**	n = 123 Intracranial meningioma Mean age, 62.6 years (range, 31-86 years); males, 25 (20.3%); females, 98 (79.7%); prior microsurgery, 33.3%; cranial nerve deficits,	Cavernous sinus meningioma	SRS with Leksell Gamma Knife Unit model C (Elekta Instruments) F/U: Median, 36 months (range, 7-71 months)	Mean dose to tumor margin, 13.8 Gy (range, 10-20 Gy) to the 50% isodose line for multiple small isocenters (for more conformal treatment);	n/a (no control or comparison group)	New neurological deficits: 5 patients (4.1%), including abducen nerve palsy developing at 8 months (0.8%), facial pain developing at 3-4 months and resolving thereafter (1.6%), and edema with consequent generalized convulsion and focal seizure developing at 3-6 months and resolving thereafter (1.6%). No deterioration in visual acuity or visual	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	60.2% overall (58.5% in patients with prior microsurgery); mean tumor volume, 7.99 cm3 (range, 0.7-30.5 cm3)			number of treatments or fractions not reported		field	
Ganz (2009b) Case Series **Meningioma**	n = 97 Intracranial meningioma Mean age, 48.1 years (range, 20.4-87.2 years); males, 27 (27.8%); females, 70 (72.2%); mean tumor volume, 15.9 cm3 (range, 10.0-43.2 cm3); parasellar, 29.9%; petroclival, 24.7%; sphenoidal ridge, 19.6%; non-basal supratentorial, 11.3%; anterior fossa, 9.3%; tentorial, 3.1%; cerebellopontine angle, 1.0%	Consecutive patients with meningioma measured ≥10 cm3 by treatment planning software. Excluded: Patients with atypical, malignant, multiple, or en plaque tumors.	SRS with Leksell Gamma Knife unit (model not specified; Elekta Instruments F/U: Mean, 53 months, or 4.4 years (range, 25-86 months, or 2.1-7.2 years)	12 Gy to the tumor margin in 75 patients (77%); dose lowered to 6.0 Gy due to prior radiotherapy and proximity of optic nerve (1 patient), 9.0 Gy due to poor vision and inability to visualize optic pathways (1 patient), 10-11.5 Gy to protect optic pathway (19 patients), and 11 Gy to protect brainstem (2 patients); number of treatments or fractions not reported	n/a (no control or comparison group)	Adverse radiation effects: 3 patients (3.0%) either without clinical symptoms (1.0%) or with consequent headache (1.0%) or headache and visual field loss (1.0%) developing at 3-12 months and resolving 2-6 months later. Dose of 12 Gy in all 3 patients with edema	Poor
Hamm (2008)	n = 224	Inclusion	SRT planning	SRT: 1.8-2.0 Gy	n/a (no control or	Acute toxicity was temporarily	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Case Series **Meningioma**	Skull base Meningiomas, primary and recurrent 53 men and 171 women; Median age, 59 years (range 22-85); Treatment: SRT, 183; hypofractionated SRT, 30; SRS, 11; Single prior resection, 95 of 224 (42.4%); Multiple prior resections, 34 of 224 (15.2%); WHO grades: Previously resected meningiomas that were benign (WHO grade 1), 113 of 129 (87.6%); atypical (WHO grade II), 10 of 129 (7.8%); malignant (WHO grade III), 6 of 129 (4.7%); Patients treated with SRT or SRS alone, 95 (42.4%); Median tumor volume, 9.1 mL (range 0.2-90.2); Neurological deficits before treatment were suffered by 92.3%, 7.7% were asymptomatic; Neuropathies included: reduction/loss of vision, 68.1%; headache, 41.8%; trigeminal neuralgia, 40.7%; diplopia, 36.4%;	criteria: Patients treated with stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS), or hypofractionated SRT between 1997 and 2003 with an indication for tumor growth at MRI follow-up; No exclusion criteria reported	target volume consisted of target volume for SRS plus safety margin of 2 mm for WHO grades I-II and 5 mm for WHO grade III; 3D-dose-distribution calculated with stereotactic treatment planning systems "Voxelplan" and "BrainScan of the Novalis system;" SRS and SRT were performed with 6MV photons, delivered by a linear accelerator (Siemens KD2 and Novalis) F/U: Follow-up was for at least 6 months and yearly thereafter; included clinical exam (and neurological	to the isocenter daily = 100%, up to a cumulative median dose of 55.8 Gy (50.4-67.5 Gy); the daily dose to parts of the optical structures was not more than 1.6-1.8 Gy to the 90%-95% isodose level; dose inhomogeneity of not more than 12% above perscribed dose level; Hypofractionated SRT: Isocenter dose of 10x4 Gy or 6-7x5 Gy; prescription isodose set to a level between 90%-95% of the isocenter dose; SRS: Single prescribed dose of 12.8-18 Gy (80% of	comparison group)	observed and included: alopecia:36.6% grade I, 50.9% grade II (depending on the number of non-coplanar beams or dynamic arcs); radiodermatitis: 18.8% grade I, 2.7% grade II; vertigo: 8.0% grade I, 4.5% grade II; nausea: 8.0% grade I, 5.4% grade II; headache: 8% grade I, 4.5% grade II; Clinically significant grade III severe acute toxicity: ataxia and headache, 2.7%; No grade IV toxicities observed at any time; Totally asymptomatic patients: 50.9%; No differences between the three therapies were found; Low grade late toxicity: grade 1, 8.8% and grade II 4.4%, included: conjunctivitis: 4.4% grade 1, 1.1% grade II; vertigo: 2.2% grade I, 1.1% grade II; headache: 2.2% grade 1, 1.1% grade II; reduced vision: 1.1% grade II; loss of visual fields: 1.1% grade I; trigeminal neuralgia: 1.1% grade I; grade III reduction in visual fields: 1.1%; No grade IV late toxicities observed; 85.7% of patients did not develop any late toxicity during follow-up	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	vertigo, 35.2%; reduction/loss of hearing, 35.2%; loss of visual fields, 28.6%; ptosis, 24.2%; facial nerve palsy, 22.0%; ataxia, 20.9%; exophthalmus, 17.6%; depression, 15.4%; occulomotor nerve palsy, 14.3%; In cases with optic nerve sheath meningioma or olfaction nerve meningioma, patients suffered from conjunctivitis, 12.1% and reduction/loss of olfaction, 11.0%		status exam) and MRI under same conditions as used for treatment planning; Median follow-up, 36 months (range 12-72)	isocenter dose, encompassing the entire tumor volume), with not more than 6 Gy to the optical system; NOTE: In general, patients were treated with a single isocenter			
Han (2008) Case Series **Meningioma**	n = 63 Skull base Meningiomas, primary and recurrent Patients who underwent surgical resection before radiosurgery (with histologically confirmed diagnosis of meningioma), 35; Mean age, 50 years (range 15-73); Women, 48 (76.2%); Radiosurgery: primary treatment, 43 (68.3%); adjuvant therapy after surgical resection, 19 (30.1%); salvage treatment	Inclusion criteria: Patients with skull base meningiomas treated with Gamma Knife radiosurgery, between 1998 and 2002; Exclusion criteria: neurofibromatosis type 2, atypical and anaplastic meningiomas, multiple	Treatment plan generated with Leksell GammaPlan (Elekta Instrument) system; Radiosurgery performed with Leksell Gamma Knife (Elekta Instrument, Stockholm, Sweden) model B. F/U: Patients	Mean marginal dose, 12.7 Gy (range 7.0-20.0); Mean maximal dose, 25.5 Gy (range 14.2-40.1); Mean number of shots, 13.7 (range 7-20); Conformity index*, 1.09 (range 0.88-1.56); NOTE: radiosurgery isodose, maximum dose, and marginal	n/a (no control or comparison group)	Complications: Peritumoral edema, 12 (19.0%) (edema developed after 6-7 months and persisted for 1-2 year thereafter in 9 patients; of these: 1 had no related symptoms, 3 experienced transient aggravation of a cranial neuropathy, 5 took medications for headaches, which disappeared later; also, 2 patients had edema related to delayed cyst formation near the tumor after radiosurgery at 90 and 102 months after radiosurgery, but had no symptoms); Delayed cyst formation or enlargement, 4 (6.3%) (one of these patients developed a cyst that replaced the tumor at 36 months after radiosurgery; it persisted but caused	Fair NOTE: Conformity index = (prescription dose)/(gross tumor volume), as in DiBiase, et al., 2004

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	after surgery and radiotherapy, 1 (1.6%); Mean tumor volume, 6.3 cm3 (range 0.5-18.4); Tumor locations: Petroclival, 17 (30.0%); Cerebello-pontine angle, 15 (23.8%); Cavernous sinus, 12 (19.0%); Middle fossa, 6 (9.5%); Parasellar, 4 (6.3%); Retrobulbar, 3 (4.8%); Foramen magnum, 2 (3.2%); Tentorial incisura, 2 (3.2%); Posterior fossa convexity, 2 (3.2%)	meningiomas, lost during follow-up period, followed for <48 months	followed-up at 1, 3, 6, and 12 months after radiosurgery and then annually for clinical evaluations; Mean follow-up duration: 77 months (range 48-116)	dose were initially decided on the basis of tumor volume calculated during dose planning with the best-fit isodose method; dose was optimized by reducing dose or excluding some portion of the tumor from treatment according to the proximity of critical neural structures; ~12-14 Gy was prescribed to the margin of the target; highest dose to optic apparatus, <8 Gy when the patient had vision; Treatments were designed to deliver 50% of the maximum dose to the margins of the		no symptoms); Recurrent seizure attacks, well-controlled with neuroleptic drugs, 2, one of these patients had history of surgical resection for meningioma of the cavernous sinus by a combined approach in the middle fossa and posterior fossa: the other patient who had radiosurgery for a tuberculum sella meningioma with peritumoral edema at the right frontal base experienced a brief loss of consciousness and spells of staring from 5 months after radiosurgery; Cataract, 1: woman had surgery for cataract 8 years after radiosurgery; dose to bilateral lens at time of radiosurgery was 0.2 Gy at the highest dose determined by the computerized dose plan	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				target			
Hasegawa (2011) Case Series **Meningioma**	N = 112 (125 tumors) Convexity, parasagittal, and falcine Meningiomas, primary and recurrent Men, 31 (28%) and women, 81 (72%); Median age at time of gamma knife surgery, 57 years (range 23-80); Gamma knife surgery as initial treatment, 46 (41%); 1 prior surgery, 47 (42%); 2 prior surgeries, 15 (13%); 3 prior surgeries, 3 (3%); 4 prior surgeries, 1 (1%); Resection prior to gamma knife surgery, 66 (59%); Lesion location: parasagittal, 54 (43%); falx, 41 (33%); convexity, 23 (18%); cerebellar convexity, 7 (6%); Peritumoral edema before surgery, (of the 46 patients who underwent gamma knife surgery as initial treatment), 6 (13%); Median tumor diameter, 24.7 mm (range 7.7-49.2); Median tumor volume, 7.9 cm3 (range 0.2-62.7)	Inclusion criteria: Patients with convexity, parasagittal, or falcine meningiomas who underwent gamma knife surgery between 1991-2008; Exclusion criteria: atypical and anaplastic meningioma	Leksell stereotactic frame (Model G; Elekta Instruments); Treatment planning: KULA system (Elekta Instruments) until 1996; GammaPlan software (Elekta Instruments) after 1996; Gamma knife surgery: Leksell Model B or C Gamma Knife (Leksell Instruments) F/U: Radiological studies and clinical and neurological data: at 3 month intervals during the first year after surgery, at 6 month intervals for the next 2 years, and	Median maximum dose, 30.0 Gy (range 20.0-50.0); Median margin dose, 16 Gy (range 10.0-20.4); Median number of isocenters, 5 (range 1-23); NOTE: in an earlier era at the institution, patients with meningiomas <10 cm3 received 15 Gy or greater to the tumor margin, regardless of tumor location and patients with meningiomas ≥10 cm3 were treated with a reduced margin dose of <15 Gy; therefore, many patients in this study may have	n/a (no control or comparison group)	Radiation-induced edema: 29 (28%) of 103 patients who had serial MRI during the first 3 years post-surgery; of these 29 patients, 11 had parasagittal, 10 had falx, 4 had cerebellar convexity, and 4 had convexity lesions; Of these 29 patients, 7 were symptomatic (6 had gamma knife surgery as initial treatment, 1 as adjuvant treatment), 5 of whom had falx or parasagittal lesions, 2 had convexity and cerebellar convexity lesions; Actuarial symptomatic radiation-induced edema rate (time point not specified), 7%; GKS as initial treatment in the 29 patients, 21 (72%); Motor weakness requiring resection of the lesion, 2 (both with parasagittal lesions); Seizure that required resection, caused by severe edema, 1 (parasagittal meningioma); Severe edema, 1 at 3 months post-surgery (falx meningioma, died of pneumonia at 29 months); Transient headache without neurological symptoms, 1 (falx meningioma); Ataxic gait, transient, 1 (cerebellar convexity meningioma); Memory disturbance that required resection, 1 (radiation-induced left temporal convexity meningioma suspected); Severe panhemispheric edema resulting in neurological deterioration, 4 (2	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			annually thereafter; Median follow-up time, 72 months (range 4-184); ≥5 years, 71 (66%); ≥10 years, 18 (17%); lost to follow-up, 4; NOTE: Clinical follow-up data were obtained from patients or their referring physicians if they lived too far away for a follow-up visit	received a dose higher than the current optimal dose of 12-14 Gy; In recent cases, patients received 14 Gy or less to the tumor margin depending on meningioma volume, for gamma knife as an initial treatment whereas in cases of recurrent meningiomas with a predicated low rate of radiation-induced meningioma, 15 Gy or greater was administered		parasagittal, 1 falx, 1 convexity; all had gamma knife surgery as initial treatment and all had peritumoral edema before surgery); Radiosurgery in 27 patients with a dose of ≤14 Gy: Radiation-induced edema, 9 (33%), 3 were symptomatic; Gamma knife surgery as initial treatment in 11 patients with mean tumor size 3 cm diameter: Radiation-induced edema, 7 (64%); Of 3 patients with pre-surgery peritumoral edema, all were symptomatic and 2 required craniotomy (not clear if these 3 patients are part of the previous group discussed); Factors associated with radiation-induced edema: Univariate analysis: fewer prior treatments (=0.0021), low margin dose (P=0.0103), female sex (P=0.0317). Multivariate analysis: fewer prior treatments (P=0.0021) and low margin dose (=0.0098) were significant. age, maximum dose, tumor volume, tumor location, were not significant in either analysis.	
Hayashi (2011) Case Series **Meningioma**	n = 66 Benign skull base meningioma, primary and recurrent 13 men and 53 women;	Inclusion criteria: Patients who had radiosurgical procedure with Leksell Gamma Knife between	Leksell G stereotactic frame (Elekta Instruments AB); Treatment planning: Leksell Gamma Plan	Mean marginal dose, 12 Gy (range 10-14); Mean maximal dose, 24 Gy (range 20-28); Mean radiation	n/a (no control or comparison group)	No early complications or adverse effects after radiosurgery were noted in any case in this series*; No retreatment with radiosurgery or fractionated radiation therapy was done in any case; Treatment-related morbidity, 1 (1%) with cavernous sinus	Poor NOTE: Authors note that extremely low rate of

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Mean age, 61 years (range 26-86); Initial microsurgical tumor resection w/histological confirmation of diagnosis of WHO grade 1 meningioma, 16; Of these 16 cases, 8 had indications for subsequent radiosurgery for the presence of residual tumor and 8 for regrowth/recurrence of the neoplasm during postoperative follow-up; Diagnosis based on typical radiographic findings, 50 (not including 16 with resection); Mean tumor volume at time of radiosurgery, 6.6 cm3 (range 0.3-50.6); Karnofsky Performance Scale score ≥80; Tumor locations included petrous, cavernous sinus, tentorial, petroclival, tuberculum sellae, anterior clinoid, and clival; NOTE: Figure 1 is a table that shows tumor location, but it is a bar graph so numbers not reported here	January 2003-September 2008 for the management of intracranial meningiomas located on the skull base; followed for at least 2 years after the procedure; Exclusion criteria: nonbenign histopathology of the tumor, additional application of fractionated radiation therapy before radiosurgery	version 5.34 (Elekta Instruments AB); Radiosurgery: Leksell Gamma Knife model C with APS F/U: Regular clinical examination and serial neuroimaging once every 6 months for the first 2 years after treatment and yearly thereafter; Mean length of follow-up, 46 months (range 26-80)	energy delivered to tumor, 96.7 mL (range 5.9-687.4); Mean radiation energy delivered per tumor volume, 15.9 mL/cm3 (range 12.5-22.6); Dose to anterior visual pathways, <10 Gy; Dose to brainstem, <14 Gy; NOTE: Complete coverage of neoplasm with 50% prescription isodose line using multi-center technique; 50% isodose line was kept within the capsule of the tumor		meningioma; this patient had transient abducans nerve palsy, which developed at 6 months and resolved completely after 2 months of steroid therapy; *See note in comments section	complications in their patients may result from 3-D evaluation of MRI distortion artifacts in each individual case and adjustment of the isocenter positioning based on the fused images of high-resolution MRI and 'bone window' CT.
Iwai (2008)	n = 108	Consecutive	SRS with Leksell	Median dose to	n/a (no control or	Transient neurological injury (2	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Case Series **Meningioma**	Benign skull base (cranial base) meningioma Median age, 57 years (range, 18-81 years; males, 17 (15.7%); females, 91 (84.3%); median tumor volume, 8.1 cm3 (range, 1.7-55.3 cm3); cavernous sinus, 29.6%; petroclival,18.5%; cerebellopontine angle, 14.8%; petrocavernous segment of internal carotid artery, 12.0%; sphenoid wing, 8.3%; tuberculum sella, 5.6%; clivus, 4.6%; foramen magnum, 2.8%; jugular foramen, 1.9%; frontal base, 1.9%; prior resection, 57%; prior radiosurgery, 43%	patients with benign skull base meningioma, SRS at a dose no greater than 12 Gy, and complete follow-up	Gamma Knife Unit (model not specified; Elekta Instruments) F/U: Mean, 86.1 months, or 7.2 yrs (range, 20-144 months, or 1.7-12 years)	tumor margin, 12 Gy (range, 8-12 Gy) to 50% (range, 30%-80%) isodose line ; median dose to tumor center, 24 Gy (range, 15-24 Gy). Single – stage SRS in most patients; 2-stage SRS in 10 patients with large-volume tumors (median, 38.5 cm3; range, 25.1-55.3 cm3)	comparison group)	patients, or 1.9%); 1 patient had edema developing at 1 month; another had or convulsive attack at 4 months and worsening optic nerve function at 16 months; permanent neurological deterioration in the absence of tumor growth (7 patients, or 6.5%; mean time to clinical deterioration, 22 months), including 1 patient each with temporal lobe edema at 24 months, slight worsening of oculomotor nerve palsy at 42 months, worsening of a preexisting facial palsy at 7 months, perifocal edema at 3 months with worsening of trigeminal sensory disturbance at 66 months, hemiparesis due to occlusion of middle cerebral artery perforating vessel at 32 months (patient had sphenoid wing meningioma), worsening of tinnitus and vertigo at 30 months (cerebellopontine angle meningioma), and worsening of previously improved trigeminal neuropathy at 36 months.	
Kondziolka (2008) Case Series **Meningioma**	n = 972 (1045 tumors) Intracranial meningioma, primary and recurrent Mean age, 57 years (maximum, 90 years; range not reported); males, 299 (30%); females, 683 (70%);	Residual or recurrent small-volume meningioma after prior resection; Symptomatic primary meningioma in	SRS with Leksell Gamma Knife Unit (model not reported; Elekta Instruments) F/U: Median, 4 years (range not reported); 5, 7,	Mean dose to tumor margin, 14 Gy (up to 28 Gy, range not reported); dose to tumor margin delivered to 50% isodose line in 25% of tumors	n/a (no control or comparison group)	Immediate symptoms: Nausea and other symptoms rare; 1 patient developed peneumonia at 1 week and died. SRS-attributed adverse effects: Simple rates: Overall, 76 patients (7.7%) at mean of 11 months. Cavernous sinus location: 6.3% (including cranial nerve deficits in 12 patients, decreased visual acuity in 4).	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	mean tumor volume, 7.4 mL (range not reported); Grade II or III tumors, 15.5% in males and 5.2% in females; multiple tumors, 16.6%; no prior treatment, 51%; prior resection, 84%; prior radiotherapy, 5.6%; prior chemotherapy, 0.8%; tumors developing after fractionated radiotherapy, 2.4% (of tumors); petroclival, 11.7%; petrous ridge, 6.3%; foramen magnum, 2.1%; other posterior fossa locations, 4.0%; cavernous sinus, 29.3%, sphenoid wing, 3.0%; other middle fossa locations, 1.2%; olfactory groove, 2.8%; planum sphenoidale, 2.8%; anterior clinoid, 1.6%; parasellar, 1.2%; convexity, 12%; parasagittal, 10.8%; tentorial notch, 3.8%; torcular, 0.6%; falcine, 4.5%; intraorbital, 1.2%; intraventricular, 0.9%	location at high risk for resection; meningioma in patients with concomitant illness or advance age; meningioma in younger patients who chose SRS over other treatment options, who have minimal symptoms, or who have no symptoms but choose SRS over observation.	10, or 12 years in 34%, 19.5%, 9.3%, or 4.2%, respectively	(otherwise not reported)		Parasagittal location: 9.7%. Cumulative rates (Kaplan-Meier) for entire study group: 10 years, 9.1%; 15 years, 9.1%. Hydrocephalus, 0.4%; cranial nerve deficits (e.g., diplopia, trigeminal neuropathy with neuralgic pain, decreased visual acuity), 3.4%; headache, 2.2%; seizures, 2.4%; motor deficit, 1.4%; sensory deficit, 0.3%. Complications completely resolved in 35% of patients. Multivariate analysis: Tumor volume was an independent predictor of complications after adjustment for 12-Gy volume, WHO grade, age, sex, isocenters, marginal dose, maximum dose, and isodose; none of the other variables were independent predictors.	
Kreil (2005) Case Series **Meningioma**	n = 200 Intracranial meningioma	Benign skull-base meningioma and follow-up of	SRS with Leksell Gamma Knife Unit model B (Elekta	Median dose to tumor margin, 12 Gy (range, 10-20 Gy); median	n/a (no control or comparison group)	Treatment-related adverse events: 5 patients (2.5%), including transient edema with consequent worsening seizure activity and headache (0.1%)),	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Median age, 57 years (range, 10-81 years); males, 40 (20%); females, 160 (80%); median tumor volume, 6.5 cm3 (range, 0.38-89.9 cm3); prior resection, 49.5%; prior external bean radiotherapy, 0%; cavernous sinus, 34.5%; petroclival, 22%; sphenoid wing, 16%; cerebellopontine angle, 10.5%; frontobasal, 6.5%; orbita, 0.5%; craniocervical, 3.5%; sella, 0.2%;	≥5 years	Instruments) F/U: Median, 7.9 years (range, 5-12 years)	dose to tumor center, 26.7 Gy (range, 15-56.7 Gy); median number of isocenters, 6.0 (range, 1-21) . Single-stage SRS, 96%; 2-stage SRS, 3.5%; 3-stage SRS, 0.5%		new but transient trigeminal neuralgia developing at 12-16 months (0.1%), and permanent visual deterioration (0.5%)	
Lee (2002) Case Series **Meningioma**	n = 159 164 SRS procedures, Intracranial meningioma, adjuvant SRS (48%), primary SRS (52%) Median age, 56 years (range, 10-87 years); males, 47 (29.6%); females, 112 (70.4%); prior resection, 48%; prior radiation therapy, 3.8%; prior chemotherapy or hormonal therapy, 1.6%); median tumor volume, 6.5 cm3 (range, 0.5-52.4 cm3);	Symptomatic cavernous sinus meningioma and complete follow-up	SRS with Leksell 201-source 60Cobalt Gamma Knife Unit model U or B (Elekta Instruments) F/U: Mean clinical follow-up, 35 months (range, 2-138 months); mean imaging follow-up, 39 months, (range, 2-145 months)	Median dose to tumor margin, 13 Gy (range, 8-25 Gy) to the 50% (range, 40%-80%) isodose line; median maximum dose to tumor center, 26 Gy (range, 16-50 Gy); multiple isocenters used in 158 patients (99%) ; number of treatments or fractions not	n/a (no control or comparison group)	Any neurological deterioration in the absence of tumor growth: 11 patients (6.9%) at mean of 25 months. Transient: 3 patients (1.9%), including parethesias (1, 0.6%) and temporal lobe seizures (2, 1.3%).Permanent: 8 patients (5.0%); including permanent visual acuity or visual field loss (1.9%), trigeminal nerve dysfunction (3.1%) involving transient paresthesias (0.6%) or permanent neuralgia or keratitis (2.5%); partial complex seizures developing at 16 months and responding to medical treatment (1.3%), cognitive deterioration developing at 7 months and requiring shunt placement (0.6%). Temporal	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	histologically proven malignant or atypical meningioma, 2.5%.			reported		trend: rate of adverse radiation effects lower in patients treated after 1995 than in those treated in 1987-1995 (2.5% versus 10%).	
Lo (2002) Case Series **Meningioma**	n = 53 (63 tumors) Intracranial meningioma Median age, 66 years (range, 22-85 years); males, 15 (28%); females, 38 (72%); single tumor, 84.9%; two tumors, 11.3%; 3 tumors, 3.8%; prior radiotherapy, 11.1%; petroclival, 15.8%; sphenoid and cavernous sinus, 30.1%; optic nerve sheath, 1.5%; convexity, 30.1%; cerebellar, 6.3%; parasagittal, 6.3%; tentorial, 9.5%. SRS group: 35 patients; median age, 69 years (range, 22-85 years); median Karnofsky score, 80 (range, 50-90); median tumor volume, 6.8 mL (range, 0.5-34 mL). Fractionated SRS group: 18 patients; median age, 58.5 years (range, 37-80 years); median Karnofsky score, 80 (range, 60-90); median	Included: Meningioma without symptoms or located near critical structures (e.g., brainstem, optic apparatus) and unresectable disease, residual disease after subtotal resection, failed previous treatment, or patient preference for stereotactic radiotherapy. Tumors located <5 mm from critical structure or sized ≥4 cm selected for fractionated SRS. Excluded: Patients treated with	SRS or fractionated SRS with Philips SRS 200 stereotactic system (Philips Medical System) until 1994 and with X-Knife SRS System (Radionics Software Applications) thereafter F/U: Median follow-up, 38 months (range, 4.1-97 months) for SRS and 30.5 months (range, 6.0-63 months) for fractionated SRS	Median dose, 14 Gy (range, 5-45 Gy) for SRS and 54 Gy (range, 40-60 Gy) in fractions of 1.8 Gy (range, 1.8-2.5 Gy) for fractionated SRS. Intratumoral boost (single SRS dose of 6.0 Gy) in 5 patients, each with one tumor, in fractioned SRS group	n/a (no control or comparison group)	Early adverse events:K8 None requiring treatment. Late adverse events, SRS group: Adverse effects (2 patients, 5.7%), including progressive visual deterioration developing at 36 months in 1 patient with optic nerve sheath tumor treated with dose of 8 Gy, and symptomatic brain necrosis with edema developing at 6 months in 1 patient with cavernous sinus tumor treated with dose of 12 Gy. Late adverse events, fractionated SRS: Progressive deterioration in visual acuity beginning at 14 months In 1 patient (5.5%) with tumor close to optic nerve treated with 54 Gy delivered over 30 fractions+K6	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	tumor volume, 8.8 mL (range, 2.4-58.6 mL)	conventional fractionated radiation therapy with SRS as a boost					
Malik (2005) Case Series **Meningioma**	n = 277 (309 tumors) Intracranial meningioma, primary and recurrent Mean age, 52 years (range not reported); males, 72 (26%); females, 205 (74%); multiple tumors, 15.2%; mean tumor volume, 7.3 cm3 (range not reported); prior surgery, 56% of tumors; atypical or chordoid tumors, 5.2%; malignant tumors, 2.3%; skull base tumors, 70% (46.6% involving cavernous sinus); convexity, 14%)	Meningiomas treated with SRS at participating center between 1994 and 2000	SRS with Leksell Gamma Knife Unit (model not reported; Elekta Instruments) F/U: Mean clinical follow-up, 44 months (range not reported)	Mean dose to tumor margin, 19.7 Gy (range, 10-30 Gy) to 50.3% (range, 28%-75%) isodose line; mean number of isocenters per tumor, 6.5 (range, 1-14)	n/a (no control or comparison group)	Adverse neurological events attributable to radiation: Overall: 10 patients (2.8% of patients; 3% of tumors). Cranial nerve involvement: 7 of 144 (4.9%) patients. Worsening of facial numbness (1 patient), new but transient trigeminal symptoms (3 patients), new or altered diplopia (3 patients).Involvement of other structures: Weakness related to treatment of falcine meningiomas close to motor strip (2 patients) and weakness at 7 years related to treatment of petroclival tumor (1 patient).	Poor Time of occurrence not clear for all adverse events
Metellus (2005) Case Series **Meningioma**	n=74 cavernous sinus meningioma (CSM), primary and recurrent 38 FR, 36 GKRS FR: mean age 53 (33-77), male: female 7:31, f/u	selection criteria was not explicitly stated	fractionated radiotherapy (FR); gamma knife radiosurgery (GKRS) F/U: follow-up schedule not reported; see pt	FR median total dose 53 Gy (range, 50-55 Gy), median dose/fraction of 1.9 Gy; GKRS dose not specified; it was adjusted according to	n/a (no control or comparison group)	(Note: numbers of pts not provided, only percentages.) FR: No severe complications; 28% had transient tinnitus, dizziness, headache, or general weakness, mostly disappeared after end of RT procedure. 6% needed short-term course of corticotherapy (<3mo). RT had to be stopped in 1 pt due to poor tolerance, but was completed a few mo later; 1 82 y/o pt	Poor Could not discern blinding of outcomes, selection criteria, whether analyses

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	mean 88.6 mo (42-168), >60 mo 66%; GKRS: mean age 51.2 (48-92), male: female 7:29, f/u mean 63.6 mo (48-92), >60mo 55.5%		characteristics for mean and range f/u, for FR. All pts had at least a 3-yr f/u, for GKRS at least a 4-yr f/u	tumor volume, location, risk to adjacent structures		had a moderate progressive, short-term memory loss 8 mo after FR; GKRT: 1 pt tx in 1994 for Grade 4 CSM had a transient ischemic stroke during f/u; 1 yr later, had a transient contralateral central facial palsy, MRI and Magnetic resonance antiography showed intracavernous occlusion of the ICA but no change in tumor volume. No other complications during f/u period.	were adjusted to allow for differences in length of f/u, competing interests
Milker-Zabel (2006) Case Series **Meningioma**	n = 57 Cavernous sinus Meningiomas, primary and recurrent Cases 1990-2003; Histologic grades 1 and unknown (no bx or surgery); pt characteristics not defined (no age, demographics, etc.)	All pts tx w/FSRT for cavernous sinus meningioma at institution included	Fractionated stereotactic radiotherapy (primary tx n=29, adjuvant p surgery n=10, recurrent n=18); no comparator F/U: Median 6.5 y (no range given); 50/57 followed >36 mo; min f/u 12mo; clinical/neuro exam 6 wks, 3 and 6 mo p RT, Ophtho exam 6 mo, 1y, then yearly	Median 57.6Gy (52.2-61.4Gy) w/1.8 Gy/fraction	n/a (no control or comparison group)	Acute CTC grade 1: hair loss, skin erythema; No late toxicity reported (but limited f/u and no reported range prohibits accurate report of late onset morbidity); Recurrent hyperlacrimation unilateral side of irradiation n=1; subjective visual deterioration w/o objective ophtho findings n=3; 2 deaths from cardiac failure (unrelated to RT)	Poor Did not address potential conflict of interest
Patil (2008)	n = 102	Min f/u period 3	Stereotactic	Median marginal	n/a (no control or	N=15 (14.7%) w/symptomatic edema p	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Case Series **Meningioma**	Supratentorial Meningiomas, primary and recurrent Cases 2001-2006; Mean age 59.8 y (24-86y); 41 men, 61 women; no symptomatic edema before SRS; both high and low grade histology; Previous conventional RT n=8	mo, SRS for supratentorial meningioma; SRS indications: symptomatic presentation, interval tumor growth, mass effect, residual tumor, pt tx preference	radiosurgery (SRS); no comparator F/U: Mean 20.9 mo (6-77 mo)	dose 18 Gy (11.3-25 Gy) delivered in 1-5 fractions; max dose 22.2 Gy (14-38.7 Gy)	comparison group)	SRS; location parasagittal location >4X more likely than nonmidline supratentorial location to develop symptomatic edema (OR 4.1 (1.5-11.5); Median time to edema onset = 7mo (4-20mo); 11/15 pts required prolonged corticosteroids (2-9mo); Symptoms assoc w/edema = motor deficits (8), HA (8), seizure (4), memory deficit (3), visual deficit (2); 1/15 w/o resolution of edema and sx - remains on steroids	Did not address potential conflict of interest
Santacroce (2012) Case Series **Meningioma**	n = 4565 (15 centers, detailed data 3768) Meningiomas, primary and recurrent Cases 1987-2003; Median tumor vol 4.8 cubic cm; Median age 57y +/- 13.4; 1161 men, 3404 women; Grade 1 histologic or dx by imaging	Pts w/meningioma who underwent RS >5y before study w/ avail data; min 50 cases/center	GK; no comparator F/U: All GK at least 5 y before study; min f/u 24mo; median imaging f/u 63 mo; Avg clinical f/u 61 mo +/- 38; Patients lost to f/u 11.5%	Median dose to tumor margin 14 Gy +/- 3; max dose 28 +/- 7.2; isocenters 9+/- 8	n/a (no control or comparison group)	Overall complications p RS n=497 (12.9%) = Table 6 detailed breakdown each complication/classification; temporary morbidity 6.3%, permanent morbidity rate 6.6% (perm mild 1.8%, perm cont not disabling 3.6%, perm cont disabling 1.2%); Deaths: 3 edema p RS, 1 radionecrosis p RS. No radiation-induced tumors identified, but atypical histology or frank malignancy on reoperation seen in 8 pts	Poor Conflicts of interest reported
Shuto (2005) Case Series **Meningioma**	n = 160 Intracranial Meningiomas, recurrent Cases 1992-2001; All w/prior surgery and histologic confirmation, mean tumor vol 10.5 cubic	Medical record availability for more than 2 years p GKS for meningioma; not o/w well-defined	GKS, cyst assessments on MR imaging; no comparator F/U: Min 2 yrs after GKS in text; Range 12-118.3mo on	Mean margin dose 13.4 Gy (median 14 Gy), mean max dose 27.5 Gy (median 24.1 Gy)	n/a (no control or comparison group)	Cyst formation/enlargement following GKS n=5 in multiple intracranial locations; 2 cyst enlargement p RS, 2 cysts developed de novo p GKS (1.7%); multiple histologic findings p excision of cyst in 3/5 pts	Poor Did not address potential conflict of interest

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	cm; Mean age cyst formation 61.2 yrs (34-65y); 5 women, 1 man		Table 1				
Spiegelmann (2002) Case Series **Meningioma**	n = 42 Cavernous sinus Meningiomas, primary and recurrent LINAC RS b/w 1993-2001; mean tumor vol 8.2 cubic cm; 11 w/prior surgery	Pts w/CSM tx at center w/RS and min 12 mo f/u	LINAC radiosurgery; no comparator F/U: Median 36mo (mean 38mo); 1 y intervals clinical, MRI, neuro-ophtho evals, serum hormone levels HPA	Mean radiation dose 14Gy to margin (12-17.5Gy)	n/a (no control or comparison group)	Trigeminal neuropathy 4.7%, new visual field deficit 2.8%; n=2 hydrocephalus development req VP shunt; n=1 symptomatic temporal lobe edema resulting in partial tumor excision; Acute SE: "rare and mild"; 2 pts w/HA, emesis X24h p RS; n=3 (7.1%) w/lasting neuro deficit; no pituitary dysfunction; no mortality related to RS	Poor Did not address potential conflict of interest **Patients in this series are also included in study by Spiegelmann 2010 below**
Spiegelmann (2010) Case Series **Meningioma**	n = 102 Cavernous sinus Meningiomas, primary and recurrent LINAC RS b/w 1993-2007; Mean age 57y (31-86); Mean tumor vol 7 cubic cm; previous microsurgery n=33; n=35 w/histologic dx	Pts w/CSM tx at center w/RS and min 12 mo f/u	LINAC radiosurgery; no comparator F/U: 1 y intervals clinical, MRI, neuro-ophtho evals, serum hormone levels HPA; Mean 67 mo (12-180 mo)	Mean min dose margin 13.5 (12-17.5Gy)	n/a (no control or comparison group)	Permanent complications n=5 (1 w/deafferentation pain, 1 w/facial hypesthesia, 1 w/visual loss, 2 w/partial VI neuropathy); Acute: "few" pts w/HA, emesis X24h p RS; Transient complications: n=1 HA>2y, n=2 transient oculomotor neuropathies X sev wks, n=1 transient facial hypesthesia; n=2 hydrocephalus req VP shunt	Poor Did not address potential conflict of interest
Torres (2003) Case Series **Meningioma**	n = 128 Intracranial Meningiomas,	All pts reviewed w/meningioma tx w/either SRS	Stereotactic RS (SRS) used in 79 lesions, and	Mean dose SRS 1567 cGy (1200-2285); mean	n/a (no control or comparison group)	SRS symptomatic complication n=4 (5%) - 2 w/slight decrease visual acuity, 2 w/decrease in facial sensation, 3	Poor Did not

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	primary and recurrent Tx w/various forms LINAC stereotactic RS b/w 1991-2002; 88 women, 40 men; mean age 57.2y (18-87y); RT first line n=44, adjuvant p surgery in 84	or SRT; however only analyzed if complete clinical and radiologic data available	fractionated stereotactic radiotherapy (SRT) used in 77; no comparator - separate case series data reported, but no comparison F/U: Overall mean 32.5mo (6-125mo); SRS mean f/u 40mo; SRT mean f/u 24mo	dose SRT 4859 cGy (2380-5400)		w/radiation-induced changes w/o clinical symptoms; SRT n=4 (5.2%) - 3 w/mild reduction facial sensation, 1 w/worsened diplopia; overall symptomatic complication incidence 5.1%; no surgical intervention necessary related to RT, no affect on ADLs	address potential conflict of interest

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
Tan (2011) Cost Analysis **Meningioma**	n = 59 Meningioma 18 microsurgery, 15 LINAC, 26 GKS; all pts w/radiologically confirmed Grade I meningioma less than/= 3cm; many characteristics rev Table 3 Comparison of initial treatment cost, f/u costs 1st year	microsurgery, LINAC RS, GKS; utilized microcosting methodology; retrospective enrollment F/U: N/A - retrospective review of initial costs and costs up to 1 yr	Initial tx costs: microsurgery (Euro 12,288) - presumed diff inpatient stay; LINAC (Euro 1547); GKS (Euro 2412); comparable f/u costs	NR	NR	NR	Good Potential conflict of interest w/study support from Elekta BV; Concern for limited translation to US given differences highlighted about practice patterns and health system in The Netherlands

Multiple CNS Sites

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Adler (2006) Case Series **Multiple CNS Sites**	n = 49 "perioptic tumors": meningioma, pituitary adenoma, craniopharyngioma, mixed germ cell tumor mean age 49 (17-86); male: female 23(47%): 26(53%); 39(80%)pts had previous open surgical resection in a total of 53 operations; 35 (71%) had visual field deficits	pts w/ a "perioptic" tumor located w/in 2 mm of a "short segment" of the optic apparatus as determined by MRI and who were > 3 yr post RS tx	Cyberknife radiosurgery (CKRS) F/U: mean visual field f/u 49 mo (range, 6-96 mo), there was less than 24 mo in only 2 cases, 1 of whom died, the other was 82 y/o w/ unchanged visual field at 18 mo	delivered in 2 to 5 sessions using a total marginal dose of 20.3 Gy (range, 15.0-30.0 Gy); dose was prescribed to a mean isodose line of 80% (range, 70-95%) normalized to an average maximum dose of 25.5 Gy (range, 18-43 Gy) in 5 (n=19), 4 (n=2), 3 (n=17) or 2 (n=11) sessions	n/a (no control or comparison group)	short term treatment-related morbidity except for "rare and fleeting headaches and an occasional complaint of transient diplopia lasting for < 6 wks" no acute or subacute morbidity. Long term treatment morbidity: in 2 pts w/ histologically benign radiation-induced cavernous sinus meningiomas, varying degrees of blindness developed over time and correlated w/ massive tumor re-growth after an initial period of tumor shrinkage. 1 pt had visual loss attributed to radiosurgery, had been tx w/ standard RT and RS on 3 previous occasions before experiencing injury to his optic nerve in this series (see article for more detail on this)	Poor Eligibility criteria not clear, potential confounders and competing interests
Chao (2012) Case Series **Multiple CNS Sites**	n = 76 66% had benign disease, brain metastases as a dx is also included median age 62 (18-90); brain metastases 26(34%), trigeminal neuralgia 15(20%), schwannoma 12(16%), meningioma	no previous SRS, life expectancy > 3 mo, no physical or mental limitations that would prevent answering questions, willing to participate in phone interviews, GKRS tx	gamma knife radiosurgery (GKRS) F/U: repeat questionnaires obtained as 1-2 wks, 1 mo, and 2 mo following GKRS	NR	n/a (no control or comparison group)	(no table of findings)scalp numbness: 1 wk after GKRS, 24% of pts reported minimal scalp numbness, not interfering w/ function and 1 % reported mild scalp numbness, interfering w/ function, but not activities of daily living (p=0.0004 baseline compared to 1 wk). At 1 and 2 mo, 13% and 2% reported minimal scalp numbness, respectively (p=NS compared to baseline for both intervals). pin site pain 13% developed it at 1 wk w/ a	Poor Reasons for drop-out not quantified, no table of complications, potential competing interests

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	10(13%), arteriovenous malformation 7(9%), pituitary adenoma 3(4%), other 3(4%)					median intensity level of 2 out of 10. By 1 mo, only 3% had pin site pain w/ a median intensity level of 3 out of 10. 4% reported pin-site infection at 1 wk and none at 1 and 2 mo. nausea difference from baseline NS, but worsening nausea at 1 mo (p=0.0114). other by 1 mo, 10% reported new local hair loss; 23%, 16%, and 15% reported new/worsening fatigue at 1 wk, 1 mo, and 2 mo, but 40% reported fatigue at baseline (p=NS for all 3 comparisons). Balance improved following GKRS over all periods (for all comparisons, p<0.009,) 1%, 6%, and 3% developed new tinnitus at 1 wk, 1 mo, 2 mo, sig when comparing baseline to non-baseline (p=0.0269). 3 (9%) of 32 employed persons did not return to work; 27 (84%) returned to work a median of 4 days after GKRS. NS difference in scalp tingling, face swelling, headache, eye pain vomiting, seizures or syncopal episode at any intervals compared to baseline.	
Cheshier (2007) Case Series **Multiple CNS Sites**	n = 35 foramen magnum (FM)lesions, benign and malignant (see pt characteristics column for tumors), primary, metastatic	pts tx for FM lesions w/ CKRS from 1999 to 2004 for FM lesions	CKRS F/U: No follow-up schedule was reported in the paper. However, radiographic	Fractionation schedule (mean of 2 sessions, range 1-5) was based on size of treated lesion; see tables 3-4. Range of prescribed	n/a (no control or comparison group)	complications directly related to CKRS in 4 (11%) of the 35 pts. These included 2 cases of temporary emesis immediately following tx, 1 case of cystic enlargement 2 mo post tx, and 2 cases of radiation necrosis 1.5 and 2.5 yrs from tx. Surgical treatment was carried out for the cystic enlargement and radiation necrosis cases. The radiographic and clinical	Poor No routine follow-up schedule, confounders, eligibility criteria not well-

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	mean age 51 (18-83); male: female 17:18; 25 benign tumors 9 meningioma, 5 schwannoma, 4 neurofibroma, 3 hemangioblastoma, 2 ependymoma, 1 chordoma, 1 pilocytic astrocytoma; 10 malignant growths 9 metastases, 1 chondrosarcoma		f/u was obtained for 23 (66%) pts; mean imaging f/u was 15.4 mo (2-48 mo); to determine pt sx, a f/u survey was collected for 24 (69%) of pts at an average of 32.4 mo post tx (range, 9 to 76 mo)	doses was 15 to 30, range of maximal doses provided was from 19.7 to 39; mean dose utilized was 19 Gy		follow-up table notes signs and symptoms 11/24 (45.8%) stable (29.2%), and deteriorated 6/24 (25%).	reported
Coppa (2009) Case Series **Multiple CNS Sites**	n = 31 skull base lesions, malignant, metastatic. Primary tumors were not included unless they had the potential to metastasize and were thus considered malignant (e.g. hemagiopericytoma). Malignant orbital, sinus and head and neck tumors included only if there was intracranial extension. median age 57 (11-81),	pt w/ malignant skull base tumors who were tx w/ CKRS between Jan 2002 and Dec 2007 who had f/u of > 4 wks	CKRS F/U: median f/u 37 wk (range, 6-238 wk) ; f/u schedule - 1 mo post conclusion of radiology and every 3 mo thereafter	dependent on several factors; median tx dose of 2500 cGy delivered to tumor margins (range, 1260-3500 cGY) during a median number of 5 sessions (range, 2-7) on a median isodose line of 75% (range, 68-88%) as defined	n/a (no control or comparison group)	Reduced visual acuity: in 10 pts of which 4 improved, 6 remained stable, 0 got worse post CKRS; diplopia: in 13 pts - 3 improved, 10 stable; proptosis in 1 pt who remained stable; facial weakness in 10 pts: 1 improved, 8 stable, 1 worse; facial pain in 7 pts: 6 stable, 1 worse; swallowing difficulty in 4 pts; 3 stable, 1 worse; hearing loss in 3 pts who remained stable post CKRS. Paper states that each case of neurological deterioration was accompanied by local tumor progression. Neurological sx remained stable or improved in 94% of pts (no N provided, although there is a table that lists tx outcomes for each pt).	Poor Questionable apriori exclusion of 6 pts w/ < 4 wks f/u

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	male: female 21:10; most frequent tumors: squamous cell CA (6 lesions), adenoid cystic CA (5 lesions), rhabdomysarcoma (2 lesions) and metastases of melanoma and renal cell CA (3 lesions each)			at the margin of the treated tumor		No neurological deficits were attributable to toxicity of CKRS.	
Davidson (2009) Case Series **Multiple CNS Sites**	n = 107 (114 lesions) lesions in and adjacent to the brainstem, primary, benign, metastatic - see pt characteristics for most frequent, see also Table 1 in paper for all of them median age 55 (8-96), male: female 49 (46%):58 (54%); most frequent lesions meningiomas, metastases, and vestibular schwannomas (VS) in 48 *42.1%), 27 (23.7%), and 18 (15.8%) respectively 69 (611%) tx previously including 49 (43%) w/ open surgical procedure and 8 (7%) w/ EBRT alone and 12 (11%) w/ surgery and EBRT	pts between Sept 1994 and Sept 2003 w/ lesions in the brainstem or, if extra-axial, lesions whose 25% isodose line covered at least 10% of the area of the adjacent brainstem	GKRS F/U: total mean f/u 40 mo (median 26 mo; range 6-141 mo), for benign primary intracranial tumors, mean f/u 51 mo (median 47 mo; range, 6-141 mo); for primary malignant intracranial tumors mean f/u 24 mo (median 10 mo; range, 6-86 mo); for metastases mean f/u 15	median dose to the tumor margin was 16 Gy (range, 6-20 Gy); tumors, many of which were irregularly shaped, were tx w/ a median of 6 isocenters (range, 1-12 isocenters) (for more info see Table 2 in article)	n/a (no control or comparison group)	13 (12%) developed clinical evidence of toxicity; median age was 55 (30-79); median latency from GKRS to clinical evidence of delayed toxicity was 6 mo (3-24 Mo). For these 13 pts, most common dx were VS in 6, meningiomas in 3, the rest had 1 each of pineocytoma, ependymoma, metastatic adenocarcinoma, and cavernoma. 6 pts had had a resection prior to GKRS, but only the pt w/ ependymoma had prior conventional RT. Of the 13 pts, 7 had no change in tumor size, 5 had decrease; 1 pt w/ adenocarcinoma had initial decrease in tumor size, but then radiation necrosis and it showed growth, was resected, no viable tumor found and no subsequent recurrence. New cranial neuropathy developed in 7 pts: 5 had multiple cranial neuropathies. 6 pts presented w/ non-specific signs of brainstem edema and/or hydrocephalus, including headache, imbalance, dysarthria, memory impairment, papilledema and ambulatory difficulty.	Fair No info on competing interests

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			mo (median 9 mo; range, 6-91 mo)			Brainstem edema was shown on MRI in 7 pts, radiation necrosis w/in the tumor in 2 pts, hydrocephalus in 3 pts including 1 w/ brainstem edema and another w/ radiation necrosis. 3 pts w/ cranial nerve palsies following tx for VS had no x-ray findings showing toxicity. (see article for recovery of these pts following tx, and also for Kaplan-Meier stats on actuarial incidence of toxicity at 1,2,5 yrs, and incidence of toxicity variance according to tumor size.) The only factors that contributed to toxicity were tumor volume (p=0.02) and tx volume (p=0.04); gender, age, tumor histology, prior surgery, prior radiation, and dose did not contribute to rate of toxicity.	
Ganz (2009a) Case Series **Multiple CNS Sites**	n = 514 meningiomas (MEN) (275), vestibular schwannomas (VSs) (132), arteriovenous malformations (AVMs) (107) MEN mean age 49 (18.9-87.2), VS mean age 48.2 (21.1-72.7) AVM mean age 28.7 (9-57)	consecutive pts w/ MEN, VS, and AVM all w/ > 24 mo of f/u;	GKRS F/U: ALL: every 6 months during period relating to this study. MEN mean f/u 51 mo (range, 26 to 84 mo); VS 48 mo (range, 28 to 83 mo), AVM 28.7 (range, 25 -	MEN: 228 pts had 12 Gy as prescription dose; mean tumor volume for entire series was 8.6 cm (range, 0.3 to 43.2 cm); 43 had a mean prescription dose of 10.5 Gy, see article for more info; VS all had 12 Gy, mean	n/a (no control or comparison group)	MEN 7(2.6%) had an adverse radiation effect, in 4 (1.5%) of the pts w/ clinical change had a temporary problem that resolved over a few mo (see article): 2 (0.07%) had a permanent disturbance; in 1 a small left-sided posterior temporal tumor developed a sensory aphasia associated w/ an expansive peritumoral edema. In the other, the tumor was large (volume 34.9 cm); had an actively growing tumor, (see article, complex course) resulted in marked reduction in tumor volume 1 yr post tx, but also peritumoral edema in brain stem w/ deterioration of hearing, ataxia, facial numbness. VS 8 (6%)pts had an adverse	Poor Several items are difficult to determine, if pts from more than 1 center, if entered study at similar point, if sample is representati ve, drop-out rate,

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			78 mo)	tumor V 4.7 com (range, 0.07-17.8 cm) AVM mean and median target doses were 23.1 and 25 Gy respectively (range, 14 - 25 Gy), dose was reduced in 33 pts, see table		radiation effect (ARE); 3 had permanent trigeminal numbness that did not resolve, 4 had temporary trigeminal numbness, and 1 had Brackmann-House Grade 2 facial palsy; AVM radiation-induced increases in T2 signal in 65 (60%) of pts, in 47 edema was present but no tendency to expansion, distortion or secondary brain shifts. In 17, edema was expansive. In 9,there were sx - 2 (1.8%) had permanent severe hemipareses, 7 (6.5%) had temporary neurological deficits (hemiparesis) 2 (1.8%) further had temporary increase in headache. there was a highly significant relationship between target volume and adverse radiation effects ($p<0.0005$), and between target volume and development of any form of edema ($p<0.0001$) development of ARE-induce sx was related to the anatomical location of the lesion	confounders
Korytko (2006) Case Series **Multiple CNS Sites**	n = 129 (198 lesions) non-arteriovenous malformation (non-AVM) intracranial tumors, primary, metastatic mean age 60(no range provided); Male: female 1:1.56, mean lesions/pt 1.56, total metastases 106,	consecutive pts tx w/ GKRS from Jan 2001 to Mar 2003 >18 yrs, tx for CNS tumor, f/u > 3 mo, no repeat radiosurgery to same lesion	GKRS F/U: Every 3 mo after tx for malignant lesion (no endpoint specified in paper) or every 6 mo, 1.5 yrs, 3 yrs	dependent on tumor volume; median peripheral dose 17.3 Gy (range, 11-25 Gy, median prescribed maximum dose 34.6 Gy (range, 22-50)	n/a (no control or comparison group)	the following factors are associated w/ development of symptomatic radiation necrosis (S-NEC): 12-GyV ($p<0.01$), occipital and temporal lesions ($p<0.01$) previous whole-brain radiotherapy ($p=0.03$), male sex ($p=0.03$)There was no significant association between 12-GyV and development of asymptomatic radiation necrosis.	Fair Unexplained discrepancy between number of pts in abstract and body of paper (129) and in pt

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	total CNS primary 92		and 5 yrs for benign lesions				characteristics table (127); will use 129; no competing interests
Krishnan (2005) Case Series **Multiple CNS Sites**	n = 29 Cranial base chordomas and chondrosarcomas, primary and recurrent 10 males and 19 females; Median patient age, 45 years (range 10-81); Cancer type: Chordomas, 25; Chondrosarcomas, 4; Chordomas that were histologically consistent with chondroid variant, 6; Number of patients with radiosurgery as primary management, 18; Treated for tumor recurrence or progression, 11; Median years of after initial treatment for treatment of recurrence/progression, 6.2 (range 0.8-22.5); Previously underwent tumor resections, 25; Resection type, according to surgeon's impression: Gross total	Inclusion criteria: Patients with cranial base chordoma or chondrosarcoma who underwent radiosurgery between September 1990 and December 2002; No exclusion criteria reported	Leksell gamma knife (Elekta Instruments, Norcross, GA); MRI was imaging modality for dose planning; F/U: Follow-up at 6 and 12 months, and yearly thereafter; Median clinical follow-up after radiosurgery, 4.8 years (range 0.8-11.4); Median imaging follow-up, 4.5	Median dose, 50.4 Gy (range 45-54); Median number of radiation isocenters per patient, 10 (range 3-17); Median prescription isodose volume, 14.4 cm3 (range 0.6-65.1 cm3); Median tumor margin dose, 15 Gy (range 10-20); Median maximum dose, 30 Gy (range 20-40); Radiosurgical dose < 15, 11; Radiosurgical dose ≥15, 18; NOTE: Complete	n/a (no control or comparison group)	Radiation-related complications, 10 (34%); NOTE: Some patients had more than one complication; Cranial nerve dysfunction, 6 (21%); Specific types of cranial nerve dysfunction: Diplopia, 3; Ocular neuromyotonia, 1; Hearing loss, 1; Dysarthria, 1; Dysphagia, 1; Other complications: Brain necrosis, 5 (17%); 3 of these patients were symptomatic and 1 requires a temporal lobectomy to relieve mass effect; All five patients with radiation necrosis received EBRT in addition to radiosurgery; Anterior pituitary dysfunction, 3 (10%);	Poor NOTE: One patient died from tumor progression despite an attempt at surgical salvage;

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	resection, 6; Subtotal tumor resection, 19; Patients undergoing repeat surgery: After gross total resection, 1; After subtotal tumor resection, 3; Other disease conformation methods: Only biopsies, 3; No tissue confirmation before radiosurgery and treated on the basis of imaging alone, 1; EBRT used in conjunction with radiosurgery, 19; Histology: Typical chordoma, 19; Chondroid chordoma, 6; Chondrosarcoma, 4		years (range 0-9.4); NOTE: All toxicity information was based on a composite of clinical and imaging follow-up studies	coverage of MRI-defined tumor was obtained in all patients			
Lunsford (2007) Case Series **Multiple CNS Sites**	n = 238 Miscellaneous skull base tumors, primary and recurrent Skull base tumors, total 238: Nonacoustic schwannoma: Trigeminal, 35; Facial, 4; 9-10 cranial nerve, 26; Craniopharyngioma, 43; Glomus tumor, 16; Chordoma, 26; Chondrosarcoma, 17; Hemangioblastoma, 36;	Inclusion criteria: Treated with Gamma Knife radiosurgery for skull base tumors from September 1987 through December 2004; No exclusion criteria reported	Leksell Model G stereotactic head frame; GammaPlan (e.g., 5.34 or 4C); A mixture of surgical approaches including: Gamma Knife (including Perfexion model); Cyberknife;	Hemangioma, for 4 patients: range 14-19 Gy at the margin;	n/a (no control or comparison group)	Nonacoustic schwannomas: New neurological complaints: Facial weakness, 1; Worsening of preradiosurgical facial numbness, 1; NOTE: Authors comment that trigeminal nerve sheath tumors have much higher likelihood of developing transient, but occasionally impressive, short-term swelling in the 1st year after radiosurgery - and is distinct from patients who have undergone acoustic tumor surgery; In trigeminal neuroma patients, transient swelling is followed by delayed shrinkage, often profound in degree; This tumor enlargement phase may be accompanied by temporary concomitant	Poor NOTE: text confusing regarding which groups overlap; table is poorly written and also unclear about where overlaps occur; follow-up

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Hemangioma, 7; Invasive skull base tumors, 28; Adenocarcinoma, 14; Squamous cell carcinoma, 13; Neuroendocrine carcinoma, 1; Patient characteristics by tumor type: Nonacoustic schwannomas: 35 patients; All 35 patients received radiosurgery for trigeminal nerve sheath tumors that were defined by clinical examination, high-resolution intraoperative imaging, and in selected cases prior to surgery; Tumors of 9th and 10th cranial nerve - jugular bulb schwannomas, 26; Previous treatment: Gross total resection with tumor recurrence, 12; Prior partial resection, 4; Gamma Knife radiosurgery for facial schwannomas, 3 (identified at time of prior microsurgery and associated with recurrence or subtotal partial resection); Craniopharyngioma, 43; All underwent Gamma Knife		Synergy; LINAC-based radiosurgery F/U: Nonacoustic schwannomas: 23 patients with median follow-up of 40 months; Tumors of 9th and 10th cranial nerve - jugular bulb schwannomas, 38.7 months (whether mean or median not identified); Craniopharyngioma, at least 8.5 months;			neurological symptoms, most of which will resolve as tumor regresses during the following 3-6 months; Hemangioma: Persistent diplopia,1 ; In the text, there is a table that summarizes the publications from this group associated with benign skull base tumors and it includes the rate of complications, but not the actual complication. Table summarized here, reported as: Technique, diagnosis, number of patients, mean follow-up, percentage of complications: FSRT, glomus tumor, n=22, 67 months, 18%; Gamma knife radiosurgery, glomus tumor, n-13, 60 months, 0%; Gamma knife radiosurgery, jugular foramen schwannomas, n=27, 38.7 months, 0%; LINAC SR, 5, 7, 9, 10, 11 schwannomas, n=18, 32 months, 22%; Gamma knife radiosurgery, trigeminal schwannomas, n=23, 40 months, 8%; Gamma knife radiosurgery, nonvestibular schwannomas, n=23, 43 months, 17%; Gamma knife radiosurgery, trigeminal schwannomas, n=46, 68 months, 8%; From here down, table is summarized as: Technique, diagnosis, number of patients, mean follow-up, number of patients with complications (percentage): LINAC-SRT, chordomas and chondromas, n=45, 27 months, 2; Proton beam RT, chordomas and chondromas, n=58, 60 months, 6 (12.5%); Proton beam RT,	from table is included in harms section because it is unclear how it relates to group as whole and may be useful in evaluating incidence over time.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	radiosurgery as part of a primary or adjuvant management strategy; Glomus tumor, 16; Glomus tympanicum tumor, 1; Hemangioma, 7; All received radiosurgery; Hemangioblastoma, 36; Usually treated in conjunction with von Hippel-Lindau disease;					chordomas, n=13, 69 months, 6 (43%); Gamma knife radiosurgery, , chordomas and chondromas, n=15, 40 months, 0; LINAC-SR, carcinomas and sarcomas, n=13, follow-up time not reported, 30%; LINAC-SR, carcinomas and metastases, n=47, 18 months, 8.40%; Gamma knife radiosurgery, carcinomas and sarcomas, n=32, 27 months, 3%	
Roos (2006) Case Series **Multiple CNS Sites**	n = 165 (168 lesions) Intracranial lesions, primary, metastatic, and recurrent Acoustic neuroma, 65; 38 men and 27 women; Median age, 61 years (range 19-81); Median largest tumor diameter, 22 mm (range 11-40); Tumor site: Left, 39; Right, 22 (sporadic unilateral cases, not counting neurofibromatosis); Arteriovenous malformation, 56; 24 men and 32 women; Median age, 36.5 years (range 5-69); Median largest tumor diameter, 23 mm (range 5-	No inclusion or exclusion criteria were reported	Radiosurgery: Siemens KD2 linac (Siemens Medical Systems, Concord, CA, USA) before 1998; Varian 6/100 linac (Varian Medical Systems, Palo Alto, CA, USA) after 1998 F/U: Follow-up carried out at 12 months, yearly for 2-3	Median marginal dose for radiosurgery patients, by tumor type: Acoustic neuroma, 12 (range 12-14); Arteriovenous malformation, 18 (range 12-23); Metastasis, 19 (15-23); Meningioma, 15 (14-18); Isocenters by tumor type (1:2:3): Acoustic neuroma, 51:11:0;	n/a (no control or comparison group)	Nonspecific acute side-effects (none in most patients); Vomiting, 6 (3.6%) (analgesia or anesthesia may have contributed to this effect); Minor toxicity relating to head ring pins: Hematoma, Infection, Transient focal scalp tingling or numbness; Temporary 1-1.5 cm patches of alopecia at posterior pin sites; Reversible circular or ellipsoidal alopecia in the case of subcranial lesions; Lethargy for a week or two after radiosurgery; Facial flushing and fever (38-39°), 1; No obvious infection; Symptoms settled conservatively; NOTE: Authors note that low incidence of side-effects may be due to routine premedication with dexamethasone and metoclopramide . Serious side effects by tumor type: Acoustic neuroma, Death at 5 months due to unrelated cause; Hearing loss, 2 (neurofibromatosis 2 patients; lost at 2 months, dose of 14 Gy and lost at 8	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	70); Metastasis, 22; 12 men and 10 women; Median age, 64 years (range 36-83); Median largest tumor diameter, 19 mm (range 3-34); Classification by Radiation Therapy Oncology Group recursive partitioning analysis: Class 1, 4; Class 2, 16; Class 3, 2; Prior treatments: 2 patients had previous excision; Meningioma, 14; 5 men and 9 women; Median age, 24.5 years (range 17-35); Median largest tumor diameter, 24.5 mm (range 17-35); Prior treatments: None , 10; Surgical debulking, 2; Surgery followed by progression at 5-6 yrs; Miscellaneous, 7; 3 men and 4 women; Age 43-65 years; Prior treatment: 2 patients		years and then every 2 years thereafter, unless clinical indications dictated otherwise	Arteriovenous malformation, 55:9:0; Metastasis, 22:2:0; Meningioma, 11:2:1; Prescription isodose curve by tumor type: Acoustic neuroma, 85% (range 70-90); Arteriovenous malformation, 80% (range 70-90); Metastasis, 75% (range 60-90); Meningioma, 80%)range 70-90); NOTE: 7 of the biggest arteriovenous malformation lesions were treated with stereotactic radiotherapy of 30 Gy in 5-6 fractions; 1 patient with 70 mm		months, dose of 12 Gy); Loss of useful hearing by 8-77 months (median 24), 18 of 34 patients with useful hearing before treatment (53%; median 24 months); Nausea lasting 1.5-4 weeks after radiosurgery, 5; Worsened disequilibrium at 1-7 months,5; Mild, partial trigeminal neuropathies,7 (4 new cases at 4-20 months; 3 in a distribution of pre-existing numbness at 2-41 months; Mild facial neuropathies, 4 (3 new at 4-7 months);De novo hydrocephalus, 1 of 63 patients without previous hydrocephalus(1.6%); Development of distant neoplasms, none that would satisfy the criteria for radiation-induced tumors; Arteriovenous malformation: Persistent diffuse vascular abnormality, 1 (at 6.5 years; poorly compliant patient); Hemorrhage, 1 and Radionecrosis, 1; Complications of angiography: 3; each resolved conservatively without sequelae; arRecurrent, more frequent, or more severe partial seizures within a few days of radiosurgery, 3; De novo seizures, 0.Symptomatic edema at median 6.5 months, 6 ; Progressive hemiparesis, 2; Hydrocephalus, 1; Patient was pediatric; Required shunting; Symptom occurred at 21 months; Unclear if this was a complication of radiosurgery; Nonfatal hemorrhageal 36 months and 9 years, 2 (4%); Occurred at the site of	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				arteriovenous malformation was offered volume fractionation but failed to attend after 2 of 3 components had been treated; 6 equally dose-weighted non-coplanar arcs per isocenter using 140° gantry rotation per arc and equal angular separation (30°) between the arcs; Available collimators have 80% isodose curve diameters at isocenter ranging from 4-55mm;		arteriovenous malformation; Metastasis: None reported; Meningioma: Side effects attributable to treatment, 5 (36%): Transient worsening of ipsilateral facial paresthesia from cavernous sinus meningioma at 18 months; Partial ipsilateral VI nerve palsy at 14 months, 1 (petroclival meningioma); Transient contralateral hemisensory loss at 6 months, 1 (parietal meningioma); Decreased visual acuity during stereotactic radiotherapy,1 (optic nerve sheath meningioma), resolved with steroids; subsequent intermittent steroids for episodes of visual blurring and orbital pain, 1; Worsening ipsilateral trigeminal neuralgia from a cerebellopontine angle meningioma at 3 months,1 resolving with steroids; Miscellaneous: No adverse events reported.	
Rowe (2007b) Case Series **Multiple CNS Sites**	n = 4877 Cranial tumors, primary and recurrent	Inclusion criteria: Treated from 1985 to 2005; Exclusion criteria:	Gamma knife stereotactic radiosurgery (comparison	Radiosurgery plans by pathology (mean±SD):	n/a (no control or comparison group)	New primary intracranial tumor, 1; An astrocytoma reported 8 years after radiosurgery for cavernoma; Patient was still alive after a further interval of 9	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	2405 males and 2472 females; Mean age at treatment, 45±17 years; Previous cranial radiation treatments: Arteriovenous malformations, 22%; Carcinoma or other metastases, 19%; Pituitary adenomas, 14%; Meningiomas, 13%; Other tumors, 30%; Underwent >1 radiosurgical treatment, 382 (83% of those were for arteriovenous malformations that had been incompletely obliterated after the 1st treatment); Patient details by pathology (±SEM where indicated): Arteriovenous malformations, 2615; Age at treatment, 37 years±15 (range 1-75); Vestibular schwannoma, 856; Age at treatment, 57 years±13 (range 18-86); Meningioma, 460; Age at treatment, 54 years±13 (range 6-88); Cerebral metastasis, 111; Age at treatment, 56 years±12 (range 21-75); Other tumor, 494; Age at	Patients with neurofibromatosis-2 or von Hippel-Lindau disease;	between pathologies) F/U: Follow-up in mean years ± SD (range): Arteriovenous malformations, 7.9±5.0 (0-19); Vestibular schwannoma, 3.8±3.0 (0-18); Meningioma, 4.3±3.1 (0-14); Cerebral metastasis, 1.3±1.6 (0-9); Other tumor, 4.7±4.0 (0-18); Other pathology, 3.9±3.9 (0-19); Overall follow-up mean per patient, 6.1±4.8 years (median, 5.2; range 0-19);	Vestibular Schwannoma, Target volume, 2.8±2.3 cm3; Treatment volume, 2.8±2.2 cm3; Prescription isodose, 50.5±1.6%; Marginal dose, 13±0 Gy; Integral dose, 1.2±0.5 Joules; Arteriovenous malformation, Target volume, 2.8±3.4 cm3; Treatment volume, 2.3±2.6 cm3; Prescription isodose, 50±0%; Marginal dose, 23.5±1.3 Gy; Integral dose, 1.8±1.0 Joules; Pituitary adenoma, Target volume, 2.2±1.8 cm3; Treatment		years; Corrected data would predict 2.47 cases of central nervous system malignancy to occur spontaneously (95% CI, 0.01 and 2.25); Summary of observed incidence: Central nervous system, intracranial, 1; Nose, sinuses, 0; Oropharyngeal, 3; Larynx, bronchus, lung, 18; GI tract, 13; Thyroid/endocrine, 1; Melanoma of skin, 2; Other skin, 31; Breast, 23; Gynecological, 10; Urinary tract, 11; Hemopoietic, 10; Primary site unknown, 4; Total, 127	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	treatment, 49 years±17 (range 1-87); Other pathology, 347; Age at treatment, 52 years±20 (range 0-97);		862 patients completed 10-15 years of follow-up; 364 patients had longer than 15 years follow-up	volume, 2.1±1.6 cm3; Prescription isodose, 50±0%; Marginal dose, 28±4.8 Gy; Integral dose, 2.5±1.2 Joules; Radiotherapy plans by pathology: Pituitary adenoma, Target volume, 66.7±17.0 cm3; Treatment volume, 110.4±28.3 cm3; Prescription isodose, 100±0%; Marginal dose, 45 Gy in 25 fractions; Integral dose, 23.9±1.9 Joules;			
Rowe (2007a) Case Series **Multiple CNS Sites**	n = 137 (of the 118 neurofibromatosis-2 patients, 173 tumors) Cranial tumors, primary and	Inclusion criteria: Treated with gamma knife radiosurgery between 1985	Gamma knife radiosurgery F/U: Mean years ± SD of	NR	n/a (no control or comparison group)	New malignant intracranial tumors, 2 of 118 neurofibromatosis patients; Patient details: Patient 1 had multiple intracranial tumors, including left-side vestibular schwannoma that grew from	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	recurrent n=117 with Neurofibromatosis-2 and n=19 with von Hippel-Lindau disease; Tumor and patient details by condition: Neurofibromatosis-2, 63 men and 55 women; Tumor type: Vestibular schwannoma, 146; Meningioma, 23; Other type of tumor, 4; Number of treatment occasions, 144; Mean age ± SD at time of diagnosis, 25±12 years; Mean age ± SD at time of 1st radiosurgical treatment, 32±14 years; von Hippel-Lindau disease, 12 men and 7 women; Tumor type: Hemangioblastoma, 65; Number of treatment occasions, 20; Mean age ± SD at time of diagnosis, 25±11 years; Mean age ± SD at time of 1st radiosurgical treatment, 36±13 years;	and 2004; No exclusion criteria reported	follow-up: Neurofibromatosis-2, 7.7±4.6 years; von Hippel-Lindau disease, 3.3±3.0 years			0.2-3.9 cm3 in less than 2 years; Radiosurgery dose, 15 Gy to margin of lesion; Tumor continued to grow and measured 13.6 cm3 and was resected 3 years later; Histology interpreted as malignant transformation in schwannoma; Tumor rapidly recurred, patient declined further treatment and died within 1 year of surgery; Patient 2 was treated for 1.8 cm3 vestibular schwannoma with marginal dose of 14 Gy; Developed glioblastoma within 3 years of treatment; Resulted in death within 6 months; Estimated from treatment plan that: 24 cm3 of the brain received more than 2 Gy and 54 cm3 of the brain received 1-2 Gy; No malignant tumors developed in the von Hippel-Lindau patients	
Stafford (2003) Case Series **Multiple CNS Sites**	n = 215 (218 procedures) Benign tumors adjacent to the optic apparatus, primary and recurrent	Inclusion criteria: Patients undergoing radiosurgery between March	Radiosurgery with the Leksell Gamma Knife (Elekta	Median prescription isodose volume, 6.3 cc (range 0.1-30.4	n/a (no control or comparison group)	Radiation optic neuropathy, 4 (1.9%); Characteristics for these patients: Patient #1: Meningioma, 3 prior surgeries and EBRT at 58.8 Gy, Optic nerve dose, 7.0 Gy; Visual complication, Decreased visual	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Tumor pathology: Meningioma, 122; Pituitary adenoma, 86 (89 procedures); Craniopharyngioma, 7; Median age at radiosurgery, 52 years (range 6-86); Previous treatment: Prior surgery, 141 (66%); Of those 141, 23 underwent 2 or more operations; Prior external beam therapy (EBRT), 23 (11%); EBRT in conjunction with radiosurgery, 1; Median EBRT dose, 50.2 Gy (range 39-58.8); EBRT dose unknown for 1 patients;	1990 and December 1998 for benign tumors adjacent to the anterior optic apparatus; Exclusion criteria: Malignant tumors were excluded to delineate potential radiation injury from tumor progression in order to determine the risk of developing radiation optic neuropathy after skull base radiosurgery;	Instruments, Norcross, GA): model U until January 1997; model B after January 1997; For patients treated before April 1997: Maximal optic apparatus dose was determined by interpolation of the isodose curves in the axial and coronal planes (n=96) generated by earlier versions of GammaPlan ; For patients treated after April 1997: Leksell Gamma Plan	cc); Median number of isocenters, 9 (range 1-21); Median tumor margin dose, 18 Gy (range 12-30); The majority of patients (n=193) were treated to the isodose line; Maximum dose to the optic nerve or chiasm for a single procedure, range 0.4-16 Gy; More specifically: Maximum doses: <8 Gy, 58 (27%); 8.0-10.0 Gy, 58 (27%); 10.1-12.0 Gy, 70 (33%); >12 Gy, 29 (13%); Median maximum dose, 10 Gy; Patients exposed to 8 Gy		acuity, time to onset was 93 months; Patient #2: Pituitary (ACTH), prior surgery and pre-existing visual field loss, decreased visual acuity, and right eye atrophy; Optic nerve dose, 12.8 Gy; Visual complication, Complete right eye field visual loss; time to onset was 18 months; Patient #3: Pituitary (ACTH), 2 prior surgeries and EBRT at 50.4 Gy, Optic nerve dose, 9.0 and 12.0 Gy; Visual complication, Complete left eye visual loss; time to onset was 36 and 61 months; Patient #4: Pituitary (ACTH), prior surgery and EBRT at 45 Gy, Optic nerve dose, 9.0 Gy; Visual complication, Bilateral decreased visual acuity, time to onset was 24 months; General summary characteristics of these patients: Median dose of EBRT for the 3 patients who received it, 50.4 Gy (range 45-58.8); NOTE: Of the 23 patients who had prior EBRT, 2 (87%) developed radiation optic neuropathy; The 1 patient having EBRT after radiosurgery developed a radiation optic neuropathy; 3 patients underwent a single radiosurgery procedure with a median maximum dose to optic apparatus, 9 Gy (range 7-12.8); The risk of developing radiation optic neuropathy for the 212 patients having single radiosurgery per dose range: <8 Gy (1 of 58): 1.7%; 8-10.0 Gy (1 of 58), 1.8%; 10.0-12.0 Gy (0 of 67), 0%; >12 Gy (2 of 29),	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			(Elekta Instruments, Norcross, GA) software was used to determine maximum dose for some patients (n=101); Maximum dose for others (n=18) was reconstructed from the archived or reconstructed plan; F/U: MRI and clinical examinations at 6, 12, and 24 months and yearly thereafter; Median follow-up, 40 months (range 4-115);	or more, 157 (73%); For the 3 patients who underwent repeat radiosurgery for hormone-producing pituitary adenomas: Maximum dose at 1st and 2nd procedures: 9 and 12 Gy; 12.4 and 11.2 Gy; and 10.8 and 9.2 Gy, respectively;		6.9%; The risk of developing a clinically significant radiation optic neuropathy in this series was 1.1% for patients receiving <12 Gy to a short segment of the anterior optic apparatus; Patients receiving prior or concurrent EBRT had greater risk of developing radiation optic neuropathy after radiosurgery (p=0.004); Univariate analysis did not find maximum dose (<10 Gy vs. ≥10 Gy (p=0.56) or prior surgery (p=0.19) to be associated with radiation optic neuropathy after radiosurgery; Repeat radiosurgery was not a significant risk for radiation optic neuropathy (p=0.054);	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Xu (2010) Case Series **Multiple CNS Sites**	n = 202 Orbital tumors, primary, metastatic, and recurrent 84 males and 118 females; Mean age ± SE, 39.5±14.6 years (range 5-85 years); Diagnosis determination: Based on pathological analysis, 113; Presumed based on characteristic clinical and neuroimaging findings, 89; Tumor type: Meningioma, 84 (41.6%); Lacrimal gland tumor, 38 (18.8); Schwannoma, 23 (11.4%); Malignant choroidal melanoma, 18 (8.9%); Optic nerve glioma, 12 (5.9%); Orbital metastasis, 11 (5.4%); Pseudotumor of the orbit, 10 (5.0%); Retinoblastoma, 3 (1.5%); Fibromatosis, 3 (1.5%); Tumor volume by tumor type (mean): Meningioma, 1.4-35.6 cm3 (5.1); Lacrimal gland tumor, 1.2-22.4 cm3 (9.3); Schwannoma, 1.9-11.7 cm3 (5.3); Malignant choroidal melanoma, 0.04-1.0 cm3	Inclusion criteria: Patients with presumed or pathologically proven orbital tumors between 1998 and 2008; Detailed treatment records available; Criteria for undergoing gamma knife surgery: Small to moderate- sized tumor; Recurrent or residual tumor after prior resection or coexisting morbidity precluding surgery; No exclusion criteria reported	Stereotactic radiosurgery with the Leksell Gamma Knife model B (before February 2005) or Leksell Gamma Knife model C (after February 2005) (Elekta Instruments AB, Stockholm, Sweden); Dose planning with the Leksell GammaPlan workstation F/U: Examinations scheduled at 6 month intervals for the first 2 years after gamma knife	Prescribed peripheral radiation dose, range 10-40 Gy; Dose by tumor type (median): Meningioma, 10-15 Gy (13); Lacrimal gland tumor, 15-22 Gy (18); Schwannoma, 12-17 Gy (14); Malignant choroidal melanoma, 40 Gy (median not reported); Optic nerve glioma, 14-20 Gy (16); Orbital metastasis, 16-20 Gy (18); Pseudotumor of the orbit, 15-16 Gy (16); Retinoblastoma, 18-20 (18); Fibromatosis, 13-18 Gy (14); Number of treatment sessions: One,	n/a (no control or comparison group)	Visual acuity changes after surgery: Improvement, 72; Preservation, 129; Severe deterioration (decline from normal to count fingers or light perception), 18 (of 147 patients with useful vision before treatment; Transient conjunctival edema, 19 (9.4%); Authors report that no other acute side effects were observed; NOTE: Authors note in the discussion section regarding complications that 23 patients suffered from impairment of visual acuity	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(0.5); Optic nerve glioma, 2.3-7.8 cm3 (4.4); Orbital metastasis, 0.3-5.4 cm3 (2.8); Pseudotumor of the orbit, 2.2-11.4 cm3 (6.6); Retinoblastoma, 0.03-2.7 cm3 (1.1); Fibromatosis, 3.4-7.8 cm3 (5.5); Median lesion volume, pre gamma knife surgery, 5.4 cm3 (range 0.04-35.6); Other medication: Patients with preoperative visual function who received a single 40-80 mg dose of methylprednisolone intravenously 1 hour before gamma knife surgery and a 40 mg dose every 12 hour for the next 3 days, 111; Clinical characteristics, symptoms or signs: Proptosis, 124; Loss of visual acuity, 117; Headache or orbit pain, 59; Diplopia, 36; Conjunctival chemosis & injection, 41; Lid retraction, 21; Enophthalmos, 7; Visual acuity: 1.0 or better, 31; 0.4-1.0, 57; 0.1-0.4, 59; Count fingers to 0.1, 39; Blind, 16; All patients had been examined by an		surgery and at 2 year intervals thereafter; Median follow-up period (SE), 34.5±14.7 months (range 12-114);	187;Two, 15; Median number of isocenters, 10 (range 5-16); An attempt was made to deliver no more than 10 Gy of radiation per session to any portion of the anterior visual pathway; NOTE: Similar dose plans were used for single and double session treatments; NOTE: Treatments over 2 sessions were separated by 24 hours; Tumors enveloped optic apparatus and visual acuity was 0.5 or better;		

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	ophthalmologist who made the clinical diagnosis based on ophthalmological and neurological findings or prior treatment history						

Neurocytoma

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Rades (2006) Systematic Review **Neurocytoma**	n = 121 Primary Patients with typical neurocytoma with incomplete resection 53 females, 68 males, median age 27 (3-76 yrs). 59 treated with ITR, 41 ITR+cRT, and 21 ITR+ SRS	Incomplete resection alone (ITR), ITR and conventional radiotherapy (ITR+cRT) or ITR plus Stereotactic radiosurgery (ITR+SRS) F/U: Minimum follow-up allowed in study 12 months. Range 12-158 months, median 42 months IRT+cRT median dose 54 Gy (range 43-60 Gy); IRT+SRS median total dose 15 Gy (range 10-24 Gy)	Tumor control improved with radiotherapy after incomplete tumor resection. 5 year local control (LC) after ITR was 51%, after ITR+cRT 87% (p=0.001) and after ITR+SRS 100% (p=0.004). The difference between ITR+cRT and ITR+SRS was not significant (p=0.45). 5 year overall survival (OS) was 93% ITR, and 100% for both ITR+cRT and ITR+SRS. Differences between groups were not significant.	No harms noted but authors speculated that SRS may have fewer long term harms than CRT because of lower dosing and because SRS is more precise allowing for a smaller treatment volume and thus less potential toxicity.	Poor Did not provide details of literature search, did not account for differences in tumor severity or pt prognosis, small sample size in tx groups with small incidence reports

Pituitary adenoma

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Kong (2007) Cohort **Pituitary Adenoma**	n = 125 Pituitary Adenoma, primary Mean age, 41.3 years, range 14-73 years; Tumor size, ≤3 cm, 119 patients; >3 cm, 6 patients	Pituitary adenoma; surgical and medical treatment failed to remove tumor or normalize hormone levels; stereotactic radiosurgery criteria (tumor ≤30 mm, ≥2 mm between tumor and optic apparatus)	Fractionated radiotherapy (64 patients) or stereotactic radiosurgery (61 patients) F/U: Mean follow-up was 36.8 months (range 2-140)	Fractionated radiotherapy: mean dose 50.4 Gy (range 48-54); Stereotactic radiosurgery: median dose 25.1 Gy (range 9-30)	n/a (no control or comparison group)	New-onset hypopituitarism, 11 patients (11.6% of 95 patients without hypopituitarism before treatment) at median 84 mos, only 1 patient in stereotactic radiosurgery group. Factors associated with development of hypopituitarism: no association with secretory versus nonsecretory adenoma, type of treatment, age, or sex (type of analysis not reported; univariate assumed).	Fair
Puataweepong (2009) Cohort **Pituitary Adenoma**	n = 72 Pituitary Adenoma, primary and recurrent EBRT group: n=22; 8 (36%) men and 14 (64%) women; Median age, 37.5 years (range 16-66); Type of tumor: Nonfunctional adenoma, 11 (50%); Growth hormone-secreting, 2 (9%); Prolactin-secreting, 6 (27%); Adrenocorticotropic hormone, 3 (14%); Presenting symptom: Visual	Inclusion criteria: Treated between September 1990 and October 2003; No exclusion criteria reported	EBRT: Linac system (6 or 10 MV CLINAC 2100C, Varian Medical system, Palo Alto, CA, USA) or Cobalt 60 system (Theratron 780C, Atomic Energy of Canada Limited, Ottawa, Canada); SRS/SRT: LINAC system (6 MV dedicated LINAC,	EBRT: 1.8-2 Gy daily fractions; Median tumor dose, 54 (range 46-60) in 30 fractions (range 23-33); In 1 patient treated with radiotherapy alone, dose was 60 Gy; SRS/SRT:	Overall survival: EBRT, 2 deaths from cerebrovascular accident and pancreatic cancer; No patient died from tumor progression; 5-year OS: EBRT, 91%; SRS/SRT, 100% (p=0.10); 5-year overall tumor control rate: EBRT, 95%; SRS/SRT, 96%	Late radiation complications: Authors note that incidence of newly developed hypopituitarism tend to be higher in EBRT group then SRS/SRT group, but differences were not statistically significant; 5 year freedom from newly initiated hormonal replacement: EBRT, 50%; SRS/SRT, 75%; NOTE: Severe late radiation toxicity such as brain necrosis, visual impairment, or radiation-induced tumor was not reported in present study	Poor NOTE: This manuscript has an informative discussion section that details differences between EBRT and SRS/SRT in regard to pituitary adenoma

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	disturbance, 15 (53%); Headache, 7 (24%); Hormone disturbance, 5 (17%); Any mass effect, 1 (3%); Incidental finding, 1 (3%); Surgery: Postoperative RT, 21 (95%); RT alone, 1 (5%); Previous radiation, 0; Median tumor volume, No record; SRS/SRT group: n=51; 29 (57%) men and 22 (43%) women; Median age, 47 years (range 17-65); Type of tumor: Nonfunctional adenoma, 30 (59%); Growth hormone-secreting, 14 (27%); Prolactin-secreting, 2 (4%); Adrenocorticotropic hormone, 5 (10%); Presenting symptom: Visual disturbance, 29 (57%); Headache, 2 (4%); Hormone disturbance, 17 (35%); Any mass effect, 2 (4%); Incidental finding, 0; Surgery: Postoperative RT, 46 (90%); RT alone, 5 (10%); Previous radiation, 6 (12%); Median tumor volume, 10 mL (range 0.46-37.7); Breakdown of SRS/SRT group: SRS: n=12; 7 (58%)		Varian, Palo Alto, CA; XKNIFE planning system version 3&4, Radionics, Boston, MA) F/U: Clinical evaluation every 1-6 months; Median follow-up: EBRT, 4.6 years (range 0.6-9.7); SRS/SRT, 4.7 years (range 1.5-7.4);		(p=0.33); Hormonal response: Hormonal normalization at 3 years: EBRT, 72%; SRS/SRT, 61% (SRS, 75% and SRT, 50%) ; Growth hormone-secreting tumors with serum growth hormone level returned to normal within 1 year after SRS, 5 (71%) of 7; It took 3 years to achieve normal levels after EBRT;		treatment.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	men and 5 (42%) women; Median age, 43.5 years (range 17-65); Type of tumor: Nonfunctional adenoma, 2 (18%); Growth hormone-secreting, 7 (64%); Prolactin-secreting, 0 (0%); Adrenocorticotropic hormone, 2 (18%); Presenting symptom: Any mass effect, 0; Visual disturbance, 2 (18%); Headache, 0; Hormone disturbance, 9 (82%); Surgery: Postoperative RT, 8 (73%); RT alone, 3 (27%); Previous RT therapy, 1 (16%); Median tumor volume, 1.6 mL (range 0.7-10.8); SRT: n=39; 22 (56%) men and 18 (44%) women; Median age, 47 years (range 23-67); Type of tumor: Nonfunctional adenoma, 28 (70%); Growth hormone-secreting, 7 (17%); Prolactin-secreting, 2 (5%); Adrenocorticotropic hormone, 3 (8%); Presenting symptom: Any mass effect, 2 (5%); Visual disturbance, 27 (67%); Headache, 2, 5%; Hormone						

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	disturbance, 9 (23%); Surgery: Postoperative RT, 38 (95%); RT alone, 2 (5%); Previous RT therapy, 5 (84%); Median tumor volume, 11.9 mL (range 0.5-37.7);						
Colin (2005) Case Series **Pituitary Adenoma**	n = 110 Pituitary Adenoma, primary and recurrent Median age, 50 years, range 6-83; performance status, 0-1, 83.6%; 2-3, 16.4%; Tumor status, macroadenoma, 93.6%; microadenoma, 6.4%; suprasellar extension, 75.4%; cavernous sinus involvement, 46.3%	Pituitary adenoma	fractionated stereotactic radiotherapy with (n=89) or without (n=21) surgery F/U: Median follow-up was 82 months (range 48-150)	50.4 Gy in five fractions of 1.8 Gy weekly within 5-6 weeks	n/a (no control or comparison group)	Transient headache, 6 patients (5.5%); radiation-induced pituitary deficiency, adrenocorticotropic hormone axis, 28 patients (25.5%); thyroid-stimulating hormone axis, 31 patients (28.2%); follicular stimulating hormone-leutenizing hormone axis, 12 patients (10.9%); newly initiated hormonal replacement, 36 patients (32.7%); visual toxicity attributable to radiation, 0	Fair
Hayashi (2010) Case Series **Pituitary Adenoma**	n = 89 Pituitary Adenoma, primary and recurrent Mean age, 50 years, range 10-83; Tumor status: Residual, 77 patients; Recurrent, 12 patients	Residual or recurrent pituitary adenomas invading the cavernous sinus; initial microsurgical endoscope-assisted tumor removal	Gamma knife robotic microradiosurgery F/U: every 6 months for first 2 years, then yearly thereafter; mean follow-up was 36 months (range	Marginal dose varied from 12-25 Gy in non-functional tumors and 12-35 in hormone-secreting tumors	n/a (no control or comparison group)	Transitory cranial nerve palsy, 2 patients (2.2%); pituitary hormone deficit, 0; visual impairment, 0	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			24-76)				
Iwata (2011) Case Series **Pituitary Adenoma**	n = 100 Pituitary Adenoma, primary and recurrent Median age, 59 years, range 16-82; Karnofsky Performance Score: 100, 86 patients; 90, 6 patients; 80, 7 patients; 70, 1 patient;	Confirmed pituitary adenoma; nonfunctional adenoma; no prior radiotherapy or chemotherapy	Hypofractionated stereotactic radiotherapy with CyberKnife F/U: Median 33 months (range 12-118)	21 Gy in 3 fractions or 25 Gy in 5 fractions; once daily, 3-5 days per week	n/a (no control or comparison group)	Grade 2 visual disorder at 36 months, 1.7%; hypopituitarism, 4.1%; transient cyst enlargement, 3%; Brain necrosis, oculomotor nerve paralysis, or abducens nerve paralysis, 0.	Poor
Kajiwara (2005) Case Series **Pituitary Adenoma**	n = 21 Pituitary Adenoma Median age, 60 years, range 11-72; Tumor size, functional, 7.5 cm3; non-functional, 13.3 cm3	pituitary adenoma; transsphenoidal or craniotomy surgical approach	CyberKnife stereotactic fractionated or single radiosurgery F/U: Assessed at 3, 6, and 12 months, then every 6 months thereafter; mean follow-up, 35.3±10.7 months	Mean dose 14.3±4.5 Gy in 2-5 fractions	n/a (no control or comparison group)	Visual acuity deterioration: 1 patient at 2 years out of 10 with visual dysfunction before treatment; none in patients with no pretreatment dysfunction; Panhypopituitarism, 2 pts (9.5%)	Poor
Losa (2004) Case Series **Pituitary Adenoma**	n = 54 Pituitary Adenoma, primary Mean age, 51.1±1.7 years; mean maximal tumor diameter, 32.2±0.9 mm	Residual non-functioning pituitary adenoma	Gamma Knife surgery F/U: Follow-up at 6, 12, 24, 36, and 48 months then 2-year intervals	Prescription dose, 16.60.4 Gy; maximum dose, 33.2±0.7 Gy	n/a (no control or comparison group)	Moderate headache at 2-4 months, 2 patients (3.7%); new hypogonadism, 3 patients (12.5% of 24 at risk); new hypothyroidism, 3 patients (8.6% of 35 at risk); new hypoadrenalism, 1 patient (2.3% of 43 at risk); loss of pituitary function, 5 patients (9.3% of study	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			thereafter; mean follow-up was 41.1 months (range 8-90)			sample), including 1 patient normal before treatment; diabetes insipidus, 0	
Mingione (2006) Case Series **Pituitary Adenoma**	n = 100 Nonsecretory pituitary macroadenoma, primary or recurrent 60 men and 40 women; Mean age, 51.1 (range 21-82); Previous treatments: Patients who had transcranial or transsphenoidal operations before gamma surgery, 92; Single, 45; Multiple (2-4), 47 (2, 37; 3, 9; 4,1); Patients who had radiotherapy procedures before gamma surgery, 10; Immunoreactivity results: Positive for hormone immunoreactivity: 33; Null cell, 31; Gonadotroph, 21; Adrenocorticotropic hormone, 11; Growth hormone, 1; Number of tumors with parasellar space involvement, 68; Mean tumor volume, 4.8 cm3 (range 0.6-27);	Inclusion criteria: Patients with pituitary adenoma treated between June 1989 and March 2004; patients with nonsecretory adenoma; No exclusion criteria reported	Gamma surgery: Leksell Gamma Unit, model U until July 2001 and model C after July 2001 (Elekta Instruments, Inc., Norcross, GA); Treatment planning: KULA software from 1989 to July 1994 and Gamma Plan software (versions 1.045.12) from June 1994 to present; F/U: MR or CT scans at 4-12 month intervals;	Mean peripheral dose, 18.5 Gy (range 5-25); Mean maximal dose, 41.5 (10-70); Mean isodose configuration, 44.5% (range 30-53); Mean number of isocenters per patient, 6.6 (range 1-24); Dose to visual pathways limited to 1 to 4 Gy (mean 2.5 Gy); NOTE: In a few cases of tumors close to optic pathway, <2% of nerve received doses >8 Gy; NOTE: The dose rate varied: 3.66 Gy/minute in	n/a (no control or comparison group)	No adverse effects due to gamma surgery were observed; No patient with normal vision experiences a visual deficit following treatment ; 8 deaths unrelated to the tumor or gamma surgery occurred at least 1 year after treatment; Endocrinologic findings: New hormone deficits 8-107 months (mean 26) after treatment, 12 (19.7%); Patients requiring thyroid hormone replacement from 8-107 months (mean 27.7) after surgery, 9 (14.8%); Glucocorticoid replacement 11-25 months after surgery (mean 16.5), 4 (6.6%); New onset growth hormone deficit requiring hormone replacement, 2 (13 and 39 months after surgery);	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				1989 to 1.59 Gy/minute in October 1995; 3.56 Gy/minute in November 1995 to 2.31 Gy/minute in July 2001; 3.67/minute in July 2001 to 2.58 Gy /minute in March 2004;			
Petrovich (2003) Case Series **Pituitary Adenoma**	n = 78 Pituitary adenoma, primary or recurrent 46 (59%) men and 32 (41%) women; Median age at time of diagnosis, 53 years (range 17-82); Histological confirmation at time of diagnosis, 74 (95%); Diagnosis by MRI finding, 4 (5%); Tumor type: Hormonally inactive adenoma, 56 (72%); Hormone secreting, 22 (28%); Hormone secreting tumor types: Prolactinoma, 12; Growth hormone-secreting tumors, 6;	Inclusion criteria: Treated between September 1994 and January 2002; Patients with a diagnosis of pituitary adenoma; Inclusion criteria specific to patients with pituitary adenomas: Histological or MRI diagnosis of adenoma; Recurrent or residual lesion	GammaKnife radiosurgery F/U: Median follow-up after GKRS ± SD, 36±24.5 months (Mean 41; range 9-100); Follow-up schedule included examinations and MRI at 3, 6, and 9-month intervals for the 1st 18 months; Ophthalmological and endocrinological evaluations	Median prescription dose ± SD, 15±0.2 Gy (mean, 15; range 14-16); Median maximum dose ± SD, 30±1.6 Gy (mean, 30; range 20-32); Median prescribed isodose line ± SD, 50±4% (mean, 51%; range 50-75); Median tumor volume treated ± SD, 100±6%	n/a (no control or comparison group)	Acute toxicity was uncommon and of no clinical significance; Acute toxicity: Mild nausea, 1 (lasted for several days); Headache, 2 (moderate); Severe fatigue, 1 (for a period of a few days); None of these problems required specific therapy; Late toxicity, 3 (4%); VIth cranial nerve palsy 2 years after GKRS, 1; Diplopia, 3 (two cases spontaneously resolved at 1 year; one case developed at 3 months and persisted for 3 years and this patient was treated with a simple surgery that resolved the problem); Hypopituitarism, 2 (4%) (out of 52 patients with pre-surgery normal pituitary function; required replacement therapy); Other symptom issues: Of 15	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Adrenocorticotropic hormone-secreting tumor, 4; Tumor location: Cavernous sinus, 75 (86%); Pituitary fossa, 3 (4%); Tumor location sites in detail: Right cavernous sinus, 32 (41%); Left cavernous sinus, 26 (33%); Cavernous sinus and sella, 12 (15%); Bilateral cavernous sinus, 5 (6%); Sella alone, 3 (4%); Tumor: Recurrent, 65 (83%); Residual, 13 (17%); Treatments: Surgery alone, 90%; Surgery followed by external beam radiotherapy, 5%; Radiotherapy alone, 5%; Number of patients who underwent ≥2 surgical procedures, 23; Number of surgical procedures before gamma knife radiosurgery: One, 51 (65%); Two, 20 (26%); Three, 2 (3%); Four, 1 (1%); EBRT experience: Administered to treat recurrent adenomas, 4 (5%) at 45-50 Gy; Patents with contraindications to surgery who received EBRT as only	after prior definitive therapy; No chiasm or IInd cranial nerve compression Tumor more than 3 mm from the chiasm or the IInd cranial nerve; No increased intracranial pressure; No exclusion criteria reported	occurred before treatment, at 6-month intervals for the 1st 18 months, and annually thereafter; 2 patients were lost to follow-up	(mean, 96%; range 71-100); Median total volume treated ± SD, 3.8±5.5 cm3 (mean, 5.3; range 0.4-33.8); Median conformity index ± SD, 1.56±0.50 (mean, 1.71; range 0.83-3.79); Median number of isocenters ± SD, 6±2.3 (mean, 6%; range 1-10); Radiation dose delivered to critical structures with limits: chiasm, <8 Gy; Optic nerve, <9 Gy; Pons, <14 Gy; Median volume of pituitary gland that received prescribed minimum tumor dose of		patients with cranial nerve palsy before gamma knife surgery: Palsy resolved, 8 (53%); Decreased neurological dysfunction, 3 (20%); No change, 4 (27%);	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	definitive treatment, 4 (5%); Grade distribution in 75 patients with cavernous involvement: I, 2 (2.7%); II, 8 (10.7%); III, 27 (36%); IV, 33 (44%); V, 5 (6.7%); Interval from diagnosis to treatments: Median time from 1st surgery to gamma knife radiosurgery ± SD, 65±60.2 months (mean 82; range 8-355); Median time from 1st to last surgery ± SD, 61±75.4 months (mean 81; range 5-308); Median time from EBRT to gamma knife radiosurgery ± SD, 36±108.7 months (mean 74; range 4-336); Median time from recurrence to gamma knife radiosurgery ± SD, 2±8.0 months (mean 41; range 9-100); Median tumor volume ± SD, 2.3±4.7 cm3 (mean, 3.7; range 0.1-27.4);			15 Gy, 10%; Median dose to critical structure ± SD: Optic nerve, 7.0±2.3 Gy (mean, 6.3; range 1.0-12.0); Chiasm, 5.0±1.9 Gy (mean, 4.7; range 0.5-8.0); Pituitary gland, 15.0±8.0 Gy (mean, 18.0; range 3.0-32.0); Pituitary volume receiving tumor dose, 10±31.0% (mean 26.3%; range 0.0-100%) Pituitary stalk, 6.0±3.2 Gy (mean, 6.6; range 0.5-15.0); Hypothalamus, 1.8±2.5 Gy (mean, 2.2; range 0.0-16.0); Pons, 7.0±4.4 Gy (mean, 7.4; range 1.0-19.1); NOTE: Median			

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				conformity index in the text cited as 0.64;			
Pollock (2007) Case Series **Pituitary Adenoma**	n = 176 Pituitary adenoma, primary and recurrent 90% undergone prior surgery, 75% had tumors extending into cavernous sinus; Pts with hormone producing tumors: 112 (64%), pts with nonfunctional tumors 64 (36%)	patients undergoing stereotactic radiosurgery at Mayo Clinic from Jan. 1990 to Dec. 2004	Radiosurgery with Leksell Gamma Knife F/U: 6-month intervals for first two years then yearly. Still on follow-up, up to fifteen years at this point	hormone producing tumors > 20 Gy; non-functional tumors 14-16 Gy	n/a (no control or comparison group)	new anterior pituitary deficits in 20% of pts with hormone producing tumors and over 40% of pts with nonfunctional tumors. Other harms: temporal lobe necrosis, asymptomatic internal carotid artery stenosis (numbers not reported) and 1 case unilateral blindness	Poor
Pouratian (2006) Case Series **Pituitary Adenoma**	n = 37 Prolactinomas, primary and recurrent Endocrine outcomes analysis: n=23 patients; 11 (48%) men and 12 (52%) women; Mean age, 42.9 (range 17-71); Pre-gamma knife radiosurgery tumor volume, 3.0 cm3 (range 0.2-10.6); Pre-gamma knife radiosurgery prolactin, 928 ng/mL (range 49-5154); Dopamine agonist therapy	Inclusion criteria: Patients with prolactinoma, treated with gamma knife radiosurgery between 1990-2003; Presenting with serum prolactin level >200 ng/mL OR had previous surgery with immunohistolo	Gamma knife radiosurgery F/U: Endocrine outcomes analysis: Median follow-up, 55 months; Mean follow-up, 58 months (range15-117); Imaging analysis: Median follow-up, 48 months; Mean follow-up, 52 months	Endocrine outcomes analysis: Mean maximum gamma knife radiosurgery dose, 42.2 Gy (range 10-62.5); Mean margin gamma knife radiosurgery dose, 18.6 Gy (range 0.3-25); Mean number of collimators, 4.7 (range 2-	n/a (no control or comparison group)	23 patients were assessed for endocrine remission and all patients with at least 12 months follow-up were assessed for long-term complications; New pituitary hormone deficiency, 8 (29%); Specifically: Thyroid stimulating hormone deficiency, 4; Growth hormone deficiency, 2; Adrenocorticotropic hormone deficiency, 1; Combined thyroid stimulating hormone and adrenocorticotropic hormone deficiencies, 1; All deficiencies required replacement therapy; Average time to onset of new	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	at time of Pre-gamma knife radiosurgery, 15 (57%); Previous operation, 19 (83%); Previous radiation, 4 (17%); included in endocrine outcomes analysis and n=28 patients included in imaging outcomes; Imaging outcomes patients medications: Took dopamine agonist therapy for duration of follow-up period, 18 (64%); Discontinued agonist therapy, 10 (36%); Imaging outcomes analysis: n=28 patients; 12 (43%) men and 16 (57%) women; Mean age, 43.1 (range 17-71); Pre-gamma knife radiosurgery tumor volume, 3.4 cm3 (range 0.2-21); Pre-gamma knife radiosurgery prolactin, 799 ng/mL (range 10-5154); Dopamine agonist therapy at time of Pre-gamma knife radiosurgery, 16 (57%); Previous operation, 24 (85%); Previous radiation, 4 (14%);	gical confirmation of prolactin-staining pituitary adenoma; Inclusion criteria used for endocrine outcomes: Elevated pre-gamma knife radiosurgery serum prolactin level; at least 1 year of endocrine follow-up; Exclusion criteria for this group: Normal prolactin level at last follow-up but receiving dopamine agonist therapy; Inclusion criteria used for imaging outcomes: At least 1 year of imaging follow-	(range 15-122)	11); Imaging analysis: Mean maximum gamma knife radiosurgery dose, 42.2 Gy (range 10-62.5); Mean margin gamma knife radiosurgery dose, 18.6 Gy (range 0.3-25); Mean number of collimators, 4.7 (range 2-11); General information: Dose to optic apparatus limited to ≤8 Gy (Average 3.6 Gy; range, 1-8);		deficiencies, 44 months (range 33-51); For those with new pituitary deficiencies: Average tumor size, 4.6 cm3; Average maximum and margin gamma knife radiosurgery doses, 39.9 Gy and 18.3 Gy, respectively; Average follow-up, 70.2 months; New onset extraocular movement difficulty, 2; Of these: IIIrd cranial nerve palsy, 1 and VIth cranial nerve palsy, 1; Tumor volumes, 7.1 cm3 and 3.0 cm3, respectively; Both tumors had cavernous sinus extension and treated areas involved cavernous sinus; Both cases treated with maximal and marginal doses of 50 Gy and 25 Gy respectively; No cerebrospinal fluid leaks occurred after gamma knife radiosurgery, even in patients with extensive tumor shrinkage;	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
		up					
Sheehan (2007) Case Series **Pituitary Adenoma**	n = 434 Pituitary adenomas Underwent surgical resection following radiosurgery, 0.92%; Patients who had histological results after gamma surgery, 4; Tumor types: Nonsecretory, 1 and Adrenocorticotropic releasing hormone-secreting, 3; 2 of the 3 adrenocorticotropic releasing hormone-secreting adenomas had increased cellular pleomorphism, prominent mitotic activity, and moderate to high proliferative index compared to surgical specimen collected before surgery; In 1 of 2 of these tumors, tumor necrosis was evident;	Inclusion criteria: Treated with Gamma Knife between 1989 and 2004; Minimum of 6 months of endocrine and neuroimaging follow-up; Treated for persistent functioning adenoma or radiological evidence of growth of a nonfunctioning adenoma; Exclusion criteria not reported	Radiosurgery F/U: Postoperative neuroimaging at 6 month intervals whenever possible; Most followed for >12 months	NR	n/a (no control or comparison group)	Patients with recurrent or residual pituitary adenomas followed for more than 12 months had NO demonstrable radiation-induced neoplasia on follow-up neuroimaging; In the fraction who underwent surgical resection following radiosurgery (n=4), no cases of a different tumor pathology (malignant degeneration following radiosurgery) were observed;	Poor
Sheehan (2011) Case Series **Pituitary Adenoma**	n = 418 Pituitary adenomas, primary and recurrent	Inclusion criteria: Treated with Gamma Knife between 1989 and 2006;	Radiosurgery with Gamma Knife: Model U from 1989 to 2001; Model C	Median treatment volume, 1.9 cm3 (range 0.1-27); Median	n/a (no control or comparison group)	New pituitary hormone deficiency, 102 (24.4%); Typically observed in the first 2-5 years post-surgery; Factors related to development of new pituitary hormone deficiency:	Fair NOTE: Authors note that

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	193 (46%) men and 225 (54%) women; Median age, 44 years (range 12-91); Cushing's disease, 82 (20%); Acromegaly, 130 (31%); Prolactinoma, 32 (7.7%); Nelson's syndrome, 22 (5.3%); Nonsecretory pituitary adenoma, 152 (36%); Adenoma with suprasellar extension, 148 (35%); Cavernous sinus extension, 182 (44%); Gamma knife radiosurgery to entire sella turcica, 38 (9%); Endocrine suppression at time of gamma knife radiosurgery, 74 (18%); Prior radiation therapy, 35 (8.3%); Number of prior transsphenoidal resections: 0, 31; 1, 268; 2, 102; 3, 15; 4, 2; Prior craniotomy, 19 (4.5%); In 2000, patients with acromegaly or prolactinoma were instructed to discontinue pituitary suppressive medication before radiosurgery: Time period for cessation of antisecretory medications: Dopamine agonist, 4 weeks;	Minimum of 6 months of endocrine and neuroimaging follow-up; Treated for persistent functioning adenoma or radiological evidence of growth of a nonfunctioning adenoma	from 2001-2007; Perfexion from 2007 to present; F/U: Median follow-up, 31 months (range 6-124); MRI at 6 month intervals for the 1st 2 years; MRI for the next 3 years; Follow-up scans at 2-year intervals thereafter	margin dose, 24 Gy (range 9-30); Median isodose, 50% (range 20-70); Median number of isocenters, 8 (range 1-19); Tumor margin doses: Patients with functioning adenoma, 18-30 Gy; Nonfunctioning adenoma, 12-18 Gy; Radiation limited to dose of ≤8 Gy to 1% of optic apparatus volume in patients who had no prior radiation or preexisting optic neuropathy;		Treatment with somatostatin analog (acromegaly) or dopamine agonist (prolactinoma) at tie of gamma knife treatment (p<0.001; OR 1.85 [95% CI 1.28-2.58]); Prior craniotomy (p=0.27; OR 2.03 [95% CI 1.11-3.12]); Larger tumor volume (p=0.007; OR 1.10 [95% CI 1.03-1.19); Prior radiation therapy was not related in a statistically significant fashion to development of new pituitary hormone deficiency; Diabetes insipidus, 1 (0.24%); Panhypopituitarism was not observed; Other complications: Partial III cranial nerve deficit, 3; Partial IV cranial nerve deficit, 1; Partial VI cranial nerve deficit, 1; Two of these cranial nerve deficits were permanent; New visual acuity or field deficits, 8 patients; (75% of these patients received prior fractionated radiation therapy); Ophthalmological complications showed no correlation with radiation dose, tumor volume, adenoma type, or adenoma location; No cases of radiosurgically induced neoplasia or carotid artery injury were observed	given the short follow-up in some patients, it is possible that the rate of pituitary of hormone deficiency underestimates the true rate of this latent radiosurgery-induced effect; Also noted: Study limitations dictate longer follow-up and larger population size to better define true risk-to-benefit profile of stereotactic radiosurgery for patients with

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Somatostatin analog, 6-8 weeks;						recurrent or residual pituitary adenomas;
Vladyka (2003) Case Series **Pituitary Adenoma**	n = 63 Pituitary adenomas, primary and recurrent Worsening pituitary function, n=30; 11 (37%) men and 19 (63%) women; Median age, 46 (range 17-69); Previous surgery, 23 (77%); Acromegaly, 23 (77%); Cushing's disease, 5; Nelson's syndrome, 1; Prolactinoma, 1; Nonfunctioning adenoma, 0; Adenoma well-demarcated, 29; Hypophysis visible, 11 (37%); Dynamic study, 2 (7%); Diffuse hyperplasia, 1 (3%); Whole-sellar irradiation, 5; Median volume of adenoma, 1265 mm3 (range 109-8500); Continuously eupituitary, n=33; 8 (24%) men and 25 (76%) women; Median age, 40 (range 15-73); Previous surgery, 11 (33%);	Inclusion criteria: Pituitary adenoma treated over a period between 1993-1997; Exclusion criteria: Patients who had panhypopituitarism before gamma knife radiosurgery, had been irradiated previously by conventional fractionated radiotherapy, or those who could not be followed-up endocrinologically	3-dimensional conformal planning, GammaPlan 5.11 software (Elekta Instruments, Atlanta, GA), 88% of patients; KULA system (Elekta Instruments) in 12% of patients; All patients treated with gamma knife Model B (Elekta Instruments) F/U: Worsening pituitary function group, median follow-up: 58 months (range 36-92); Continuously eupituitary group, median follow-up: 66 months (range	Antiproliferative minimum dose: 50% isodose, Median 20 Gy (range 12-25); Antisecretory minimum dose: 50% isodose, Median 35 Gy (range 10-49); Median isocenters for dose delivered, 5 (range 1-14); Collimator: 8mm, 70.6% of patients; 4mm, 11.2% of patients; Dose information by group: Worsening pituitary function group, Median volume of irradiation, 2200 mm3 (range 360-	n/a (no control or comparison group)	Hypopituitarism after gamma knife surgery: Gonadal hypofunction, 11; Median latency of hypofunction after gamma knife surgery, 50.5 months (range 19-84); Statistically higher risk observed in patients who had undergone previous operations (B, P=0.035; T-W, P=0.042) of whose hypophysis was not well-imaged (LR, P=0.010; B, P=0.003; T-W, P=0.004); Other factors increasing the risk: Nonselective radiation (LR, P=0.027; B, P=0.005; T-W, P=0.008), Mean dose to the hypophysis >17 Gy (LR, P=0.049; T-W, P=0.043; authors note that this is probably the most important influencing factor), Integral dose to hypophysis >7.5 mL (LR, P=0.005; T-W, P=0.028), and Dose to infundibulum (spot 2) > 15 Gy (B, P=0.049); NOTE: Hypopituitarism occurred in ~60% of patients after 90 months of follow-up when mean dose to hypophysis was ≤ 17 Gy; No gonadotropic hypofunction was observed in patients with mean	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Acromegaly, 13 (40%); Cushing's disease, 5; Nelson's syndrome, 2; Prolactinoma, 0; Nonfunctioning adenoma, 4; Adenoma well-demarcated, 33; Hypophysis visible, 27 (82%); Dynamic study, 7 (21%); Diffuse hyperplasia, 0; Whole-sellar irradiation, 3; Median volume of adenoma, 1300 mm3 (range 34-1270);		48-96); Median overall follow-up, 2 years; Checked for endocrine function every 6 months; MRI at 1, 2, 3, and 5 years after irradiation;	8700); Median treatment isodose, 50% (range 50-80); Collimator: 4mm (0-8), 0; 8mm (0-8), 3.5; 14 mm (0-3), 0; Hypophysis: Maximum dose, 52 Gy (range 31-96); Mean dose, 31.4 Gy (range 15.7-63); Integral dose, 4.3 Gy (range 0.6-27.6); Infundibulum: Distal spot 1 dose, 28.5 Gy (range 9.3-78.3); Center spot 2, 12.5 Gy (range 1.6-29); Proximal spot 3, 3.5 Gy (range 0.6-13.3); Internal carotid artery maximum dose, 27.5 Gy (range 7.5-80); Oculomotor		dose to hypophysis ≤ 15 Gy; Adrenocortical hypofunction, 13; Median latency of hypofunction after gamma knife surgery, 60 months (range 12-87); Statistically higher risk observed in patients who had undergone previous operations (B, P=0.036; T-W, P=0.037; C, P=0.028) and in patient with these variables: Nonselective irradiation (C, P=0.025), Total number of isocenters >5 (C, P=0.014), Mean dose to hypophysis was > 20 Gy (B, P=0.026; T-W, P=0.012; C, P=0.001; authors note that this is probably the most important influencing factor), and When dose to distal infundibulum (Spot 1) was > 20 Gy (LR, P=0.044)); NOTE: Risk of hypocorticotropic function occurs in ~85% of patients after 90 months of follow-up with the mean dose to hypophysis was > 20 Gy; Risk occurs in 10% of patients after 90 months when the mean dose to hypophysis is ≤20 Gy; No hypocorticotropic function was observed in patients with mean dose to hypophysis ≤ 18 Gy; Thyroidal hypofunction, 19; Median latency of hypofunction	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				nerve maximum dose, 14 Gy (range 3.3-38); Abducens nerve, 13.4 Gy (range 3.3-32.4); Continuously eupituitary group, Median volume of irradiation, 1300 mm3 (range 92-1430); Median treatment isodose, 50% (range 50-80); Collimator: 4mm (0-8), 0; 8mm (0-8), 3.; 14 mm (0-6), 0; Hypophysis: Maximum dose, 45 Gy (range 7-70); Mean dose, 18.4 Gy (range 5-41.5); Integral dose, 2.5 Gy (range 0.2-12.4); Infundibulum:		after gamma knife surgery, 46 months (range 12-57; note 12-57 appears in table; 12-87 appears in text); Statistically higher risk observed in patients with the following pretreatment variables: male sex (LR, P=0.041; B, P=0.005; T-W, P=0.012; C, P=0.030), Patient who had undergone previous operations (B, P=0.043; C, P=0.011), and Those with partial pituitary hypofunction (LR, B, T-W, P<0.01; C, P=0.001); Treatment variables showed higher risk for thyrotropic hypofunction when hypophysis was not well-imaged (LR, P=0.013; B, P=0.002; T-W, P=0.003; C, P=0.026), When selective irradiation could not be performed (LR, P=0.011; B, P=0.001; T-W, P=0.002), When tumor volume was >1900 mm3 (C, P=0.005); Radiation doses increasing risk were: Dose to tumor margin >20 Gy (C, P=0.005), Maximum dose to hypophysis > 50 Gy (LR, P=0.044; B, P=0.041; T-W, P=0.040; C, P=0.005), Mean dose to hypophysis >17 Gy (LR, P=0.006; B, P=0.020; T-W, P=0.011; Probably most important influencing factor), Integral dose to hypophysis >7.5 mL (B, P=0.027;	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				Distal spot 1 dose, 19.2 Gy (range 5.1-45.3); Center spot 2, 6.7 Gy (range 0.6-18.9); Proximal spot 3, 1.9 Gy (range 0.2-6.8); Internal carotid artery maximum dose, 30.6 Gy (range 5.3-61.6); Oculomotor nerve maximum dose, 12.6 Gy (range 3.4-30.7); Abducens nerve, 9.2 Gy (range 1.1-27.5);		T-W, P=0.043), Dose to distal infundibulum (Spot 1) >20 Gy (LR, P=0.006; B, P=0.027; T-W, P=0.013), Dose to center of infundibulum (Spot 2) >15 Gy (LR, P<0.001; B, P<0.001; T-W, P<0.001; C, P=0.002), and Dose to proximal infundibulum (Spot 3) >5 Gy (LR, P=0.014; B, P=0.024; T-W, P=0.017; C, P=0.001), Two other risk factors contributed to higher level of risk: Lower value of prescribed marginal isodose (C, P=0.007) and Total number of isocenters >5 (C, P<0.001); NOTE: Risk of hypothyroidism occurs in ~85% of patients after 90 months of follow-up with the mean dose to hypophysis was > 17 Gy; Risk occurs in 15% of patients after 90 months when the mean dose to hypophysis is ≤17 Gy; No hypothyroidism was observed in patients with mean dose to hypophysis ≤ 15 Gy;	
Voges (2006) Case Series **Pituitary Adenoma**	n = 142 Pituitary macroadenomas, primary and recurrent 57 men and 85 women; Adenoma: Nonfunctioning, 53; Hormone-secreting,	Inclusion criteria: Pituitary adenoma with radiologically confirmed progression and/or	Treatment planning: Software, STP 3.3 and 3.5, Stryker-Leibinger, Freiburg, Germany);	Upper limit, prescribed at 20 Gy; Dose delivered to anterior visual pathway, <9 Gy; Since 1994, volume of	n/a (no control or comparison group)	Quadrant anopsia, 1 (0.7%); Decreased visual acuity, 1 (0.7%) (3 years after therapy); CT images that display ring-like contrast enhancement and edema in the temporal lobe next to treated site, 4 (2.8%) (7-12 months after LINAC-RS); Of these 4 patients:	Poor NOTE: There is some information in the discussion about

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	122; NOTE: after this point, data are reported on 142 patients (33 were excluded for follow-up < 12 months); All characteristics are reported at ± SD; Mean age, 47.3±13.9 (range 17-75); Tumor volume, 4.3±3.9 mL (range 0.2-26.9); Adenoma type (number of patients and volume±SD): Nonsecreting, 37, 5.3±4.6cc; Growth hormone-secreting, 64, 3.0±2.9 cc; Adrenocorticotropic hormone-secreting, 17, 2.9±2.5 cc; Nelson tumor, 9, 3.1±1.7 cc; Prolactin-secreting, 13, 6.5±6.3 cc; Thyroid stimulating hormone-secreting, 2, 3.1cc and 5.7cc for the two patients; Intra/extrasellar involvement: Intrasellar tumor extension combined with extrasellar and/or parasellar tumor extension, 80 (56.3%); Intrasellar adenoma, 15 (10.6%); Isolated extrasellar/parasellar tumor growth, 47 (33.1%);	medically intractable hormone secretion; Surgically inaccessible adenoma; Clear-cut tumor borders on CT or MRI scans; Greatest tumor dimension ≤35mm; Minimum distance of 1-2 mm between tumor and optic nerves and/or chiasm and/or optic tract; No compression of normal brain tissue by tumor; Data collected between August 1990 and January 2004; Exclusion criteria: Follow-up <12 months	Standard linear accelerator (8-MeV or 6-MeV photons; Philips SL20 or Elekta Sli25; Philips, Best, the Netherlands); F/U: Every 6 months for the 1st 3 years and yearly thereafter; Mean follow-up, 81.9±37.2 months (range 17.7-160.2); 50% f these patients had minimum follow-up of 77 months	healthy brain tissue exposed minimum dose of 10 Gy was <10 cc; Mean therapeutic dose ± SD, 15.3±3.1 (range 8.0-20.0); Mean maximum dose ± SD, 33.7±9.1 (range 12.6-57.4); Mean isocenter level ± SD, 66±5.8 (range 50-80); Mean number of isocenters ± SD, 3.0±1.5 (range 1-9); Dose by tumor type: Non-secreting adenomas, 13.4±2.1 Gy; Prolactin-secreting, 13.5±3.3; Adrenocorticotropic-secreting adenomas, 16.4±3.2 Gy; Growth		Symptomatic single seizure episode, 2 (treated with steroid for several weeks until CT images and clinical status had normalized), Repeated seizures, transient memory disturbances, and transient motor aphasia, 1 (patient treated with anti-convulsive medication or 2 years) and Permanent deficit syndrome characterized by memory disturbances and imperative sleeping attacks, 1; Of 114 patients evaluated for pituitary function: 1 affected axis of anterior pituitary, 30; 2 affected axes of anterior pituitary,24; Treatment-related hypothalamopituitary dysfunction, 14 (12.3%); (12 of 14 events occurred within 1st 5 years post-surgery; the other two were 86 and 92 months post-surgery); Cumulative risk for developing hypopituitarism after LINAC-RS of a macroadenoma, 13.2% at 3 years, 18.3% at 5 years; No patients were observed who had radiosurgery-related diabetes insipidus; None of these factors showed significant association with treatment-related hypopituitarism (univariate	neurotoxicity and radiation-induced brain damage, it seems to be discussing some previous results from this current study but also from others.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Adenoma infiltration of cavernous sinus, 127 (89.4%) and 23 of those were bilateral; Prior therapy: 1 operation, 73; 2-4 operations, 64; Local irradiation with iodine-125 seeds, 4; XRT adjuvant to surgery, 4; XRT as only treatment, 5;			hormone-secreting adenomas, 16.5±3.0 Gy		analysis): Tumor margin dose (0-16 Gy vs. > 16 Gy; P=0.41), Maximum dose (0-35 Gy vs. >35 Gy; P=0.22), Tumor volume (0-3.5 cc vs. >3.5 cc; P=0.43), Bilateral invasion of the cavernous sinus (yes vs. no, P=0.92); DI Other related symptom issues: Improvement of cranial nerve function (in nerves III, IV, or VI), 4;	

Schwannoma

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Sughrue (2009) Systematic Review **Schwannoma**	63 studies including 5631 patients. 3248 patients received < 13 Gy and 2383 patients received >13 Gy. Vestibular schwannoma Inclusion criteria did not include specific patient criteria. Studies had to include morbidity/complication rates for GKS without other modalities of radiotherapy. Studies including patients with NF2 included. Excluded studies of patients that underwent microsurgery as definitive treatment or who had other forms of radiation. Not described other than all tumors included in this study < 25 mm in largest diameter	Gamma Knife Radiosurgery; No comparison group. F/U: Median f/u time for < 13 Gy cohort 39.5 months and for >13 Gy group 36.5 months Dose: subdivided studies by dose: < 13 Gy versus > 13 Gy	No comparator group. Outcomes assessed were all harms- see next column.	Cranial Nerve Neuropathy: new non-CN VII or VIII neruopathy in 135 patients (2.4%) with trigeminal neuropathy (facial paresthesias or tingling) 28 times more likely than next most common. Higher in higher dose patients: 3.15% in >13 Gy vs 1.63 in < 13 Gy ($p<0.001$); Hydrocephalus: 48 patients (0.85 %) with 36 of these (75%) requiring shunt placement. NS difference based on dose but patients who received high dose radiation who developed hydrocephalus were more likely to require shunt than those receiving low dose (96% vs 56% $p<0.001$); Vertigo : 84 patients (1.5%) with those receiving low dose more likely to have than high dose (1.8 vs 1.1% p =0.001) Tinnitus: 25 patients (0.4%) with low dose having higher rates than high dose (0.7% vs 0.1% p =0.001) (Facial Nerve and Hearing morbidities reported in a separate study)	Poor No baseline characteristics of patients, outcomes may be caused by progression of tumor. No quality assessment of included studies and no assessment of similarity of treated populations and treatments to determine if results can be combined.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Collen (2011) Cohort **Schwannoma**	n = 119 Vestibular schwannoma SRS: Median age 59 (25-88); mean tumor vol=1.7mL (0.1-9.5) SRT: Median age 57 (22-84); mean tumor vol=6.3mL (0.2-18.6) Other characteristics not reported.	Progressive residual disease after surgical resection or RT complementary with surgery (N=27); for others, decreased hearing and/or tumor progression on successive MRI for 19 mo before RT. Consultation with neurosurgeon & radiation oncologist	SRS (N=78) or SRT (N=41) with Novalis linear accelerator, 6-MV photons F/U: Followed at 6 weeks, 6 mo, 12 mo, then yearly up to 5 years; median follow-up=62 mo (6-136 mo)	SRS: Median single dose 12.5 Gy (11-14 Gy) to 80% isodose line SRT: 95% isodose line, different fractionation schedules used (25x2 Gy[n=10], 10x4 Gy[n=11], 10x3 Gy[n=20]).	No survival data reported 4-year probability of preservation of useful hearing (Gardner-Robertson score 1 or 2)=59% for SRS and 82% for SRT (no significant difference) 5-yr local control rate = 95% 5-yr trigeminal nerve preservation probability=97% (no difference by SRT or SRS)	5 patients (4%) vertigo; 12 (10%) facial nerve disorder; 9 (8%) facial nerve palsy; 3 (3%) facial spasms; 5 patients (4%) required surgery after tx; 5-yr facial nerve neuropathy=96% (SRT) and 83% (SRS).	Poor Comparisons are not always clear; Not clear which confounders taken into account in multivariable analyses.
Combs (2010) Cohort **Schwannoma**	n = 202 Vestibular schwannoma Age not reported Gender: 84 male (42%) Prior surgical resection: 37 (18%) Neurofibromatosis type 2: 16 (8%) Tumor location: 98 (49%) right, 102 (50%)	Consecutive patients with vestibular schwannoma; selected for tx based on tumor progression and/or progression of clinical symptoms.	Fractionated stereotactic radiotherapy (FSRT) (N=172); stereotactic radiosurgery (SRS) (N=30) F/U: Median follow-up time 75 mo	Fractionated stereotactic radiotherapy Median planning target volume 2.8ml (range 0.2-33ml) Median total dose 57.6 Gy prescribed to isocenter in	After median follow-up of 75 mo, local tumor control was 98% at 3 yrs and 96% at 5 & 10 yrs. Local tumor control not significantly influenced by neurofibromatosis type 2, age,	No acute toxicity greater than Grade II observed. Minor (Grade I) acute reactions after tx included alopecia, headaches, ski erythema, or nausea. 5 (3%) pts in FSRT grp developed new tinnitus symptoms (tinnitus decreased in 9 pts) 1 (3%) pt in SRS grp developed new tinnitus (preexisting tinnitus evolved after SRS in 1 pt) 20 (12%) pts in FSRT grp had decline	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	left, 2 (1%) bilateral) 94 (47%) had useful or serviceable hearing at baseline (Gardner-Robertson Grade I & II) 174 (86%) had normal nerve fxn at baseline (House-Brackmann Grade I) 28 pts (14%) with facial nerve weakness at baseline 172 tumors (85%) treated with fractionated stereotactic radiotherapy (FSRT); 30 (15%) treated with stereotactic radiosurgery (SRS) Baseline tinnitus documented in 88 FSRT pts and 12 SRS pts.		(range 2mo-19yr) No patient was lost to follow-up All patients seen 6 weeks after tx, at 3 mo intervals for 1 yr, then at 6 mo intervals (duration not specified), and annual thereafter	median fractionation of 5 x 1.8 Gy/week. 90% isodose line encompassed the planning target volume. Stereotactic radiosurgery Median single dose 13 Gy (range 10-20 Gy) prescribed to 80% isodose.	prior surgical intervention, or tumor size.	in dizziness after tx No pts in SRS had decline in dizziness after tx Of pts at risk for trigeminal neuralgia dysfunction (N=175), 8 (4.6) developed persistent radiation-induced damage to trigeminal nerve (mild trigeminal dysesthesia, CTCAE Grades I & II); of these pts, 2 had been treated with SRS and 6 with FSRT No new severe damage to trigeminal nerve observed. Rate of radiation-induced trigeminal nerve fxn: 7% for SRS and 3% for FSRT After tx, 8 (4%) of all pts developed new treatment-induced facial nerve dysfunction in the 176 VSs at risk. Of these, 5 were SRS and 3 were FSRT. Rate of radiation-induced facial nerve damage was 17% for SRS and 2% for FSRT. Probability of preserving Gardner-Robertson hearing grade was 83% at 1 yr, 79% at 3 yrs, 76% at 5 yrs, and 69% at 10 yrs after tx. Preservation of useful hearing was significantly more likely for FSRT group than SRS	
Chang (2005) Case Series **Schwannoma**	n = 61 Vestibular schwannoma	Unilateral acoustic neuromas	Staged approach radiostereotactic	21 Gy for the first 14 patients; 18 Gy for remaining	n/a (no control or comparison group)	1 patient (2% of sample) had increase tumor size 4 years after tx (subsequently underwent resection); 2 patients (3%) had transient facial	Poor Potential conflict of

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Mean age 54 (range 27-79); 49% male; 51% of tumors on right side; Mean pretreatment maximal tumor dimension 18.5 mm (range 5-32); no neurofibromatosis Type II; possible recurrence in N=8 (previous surgical resection). 13 (21%) of patients had no measureable hearing (Gardner-Robertson Grade 5) at baseline.		radiosurgery (all patients) using CyberKnife F/U: Radiography (MRI) follow-up every 6 mo for 2 years; clinical (i.e. hearing) follow-up every 6 mo for 2 years, then annually. Mean radiological and clinical follow-up 48 mo (range 36-62).	47 patients. For all patients, total dose was divided into 3 equal doses delivered in consecutive daily stages separated by approx. 24 hr.		twitching during first 12 mo after tx (resolved within 3 mo and 5 mo). Symptomatic brainstem or cerebellar edema in 1 patient (2%) during first 12 mo of tx (tumor was recurrence apparent from MRI, treated with 18Gy radiation; pt had left lower extremity sensory loss 5 mo after radiosurgery, which resolved over 3 mo; pt's abnormalities resolved fully on subsequent imaging studies).	interest (one author, JRA is Chief Medical Officer of the manufacturer of CyberKnife); Inclusion criteria not clearly predefined.
Chihara (2007) Case Series **Schwannoma**	n = 125 Vestibular schwannoma Median age 53 Gender: 64 male (51%) Tumor location: 66 (53%) right, 59 (47%) left Neurofibromatosis in 6 (4.8%) of patients,	Acoustic neuroma (vestibular schwannoma); treated unilaterally only (6 (4.8%) had neurofibromatosis that was treated unilaterally)	Radiosurgery using 201-source 60-Co gamma. No comparison as this was a case series F/U: Median	Mean max dose = 29.8Gy (range 20-40) Mean peripheral dose= 15.4Gy (range 10-25.2) Median number of isocenters=4 (range 1-12)	n/a (no control or comparison group)	12 (14%) of 84 pts with measurable hearing at baseline became "totally deaf" after radiosurgery. Neurofibromatosis was only risk factor. Pure tone threshold of 20 dB or more occurred in 37 (45%) of 83 pts. Neurofibromatosis was only risk factor. Facial nerve dysfunction (including	Poor Authors report outcomes for varying sample sizes but it is not immediately clear why this is done.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	although these were only treated unilaterally. Prior surgical resection: 31 (25%) Mean tumor diameter: 13.9mm (range 6.7-25.4mm)		follow-up 60 mo (range 6-191 mo)	Dose < 16 Gy: 84 pts (67%) Dose > 16Gy: 41 (33%)		transient spasm) in 44 (36%) of 123 pts (median onset 6 mo, peripheral tumor dose only risk factor). Facial palsy occurred in 20 (16%) of 123 pts (prior surgery, peripheral tumor dose, and tumor diameter significantly associated). Severe facial palsy (House-Brackmann Grade 5 or more) in 8 (6.5%) of 123 pts (median onset 4.5 mo, peripheral tumor dose only risk factor). Delayed trigeminal nerve dysfunction in 32 (26%) of 124 pts (median onset 5 mo, peripheral tumor dose only risk factor).	Standardized outcome measures not used for some outcomes (hearing). Patient age range reported in Table 1 is 13-17, which must be a mistake, as the median age is 53 yrs.
Chopra (2007) Case Series **Schwannoma**	n = 216 Vestibular schwannoma Mean age 56.5 yrs (range 22-88) 116 male pts (53.7%) Serviceable hearing (Gardner-Robertson Class 1-2) in 106 pts (49.1%) at baseline 18 pts (8.3%) had trigeminal nerve symptoms at baseline Median tumor volume 1.3 cm3 (range 0.08-37.5 cm3)	Untreated unilateral VS seen at Uni of Pittsburg	Gamma knife radiosurgery using Model B, C, or U Leksell Gamma Knife (Elekta) F/U: Median 68 mo (max 143 mo) 41 pts (19.0%) followed for >96 mo Follow-up MRIs every 6 mo for 2 yrs,	Marginal tumor doses 12Gy (n=21), 12.5Gy (n=11) or 13Gy (median dose, n=184) Median maximum dose 26 Gy (range 20-26) Marginal tumor dose prescribed to the 50% isodose volume in 199 pts, 55% in 12, 60% in 4, and 65% in 1 pt. Median number	n/a (no control or comparison group)	3 pts (1.4%) required tumor resection after tx (2 complete resection, 1 partial) No new facial neuropathy observed 3 pts (1.4%) experienced transient facial twitching on ipsilateral side after tx 1 pt (0.5%) developed slight palsy on follow-up, but might have been present before tx	Poor Multivariable analyses are not clear, nor are useful results reported from multivariable analyses (analyses do not evaluate outcomes adjusting for confounders)

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			then annually	of isocenters=6 (range 1-6)			
Chung (2005) Case Series **Schwannoma**	n = 187 Vestibular schwannoma Mean age 51 (range 11-82); mean tumor vol 4.1 cm3; previous tx in N=76 (3 VP shunt surgeries, 8 craniotomies with total resection, 61 craniotomies with partial resection, 3 partial resections with VP shunt insertion)	None indicated; discretion of treating facility	Gamma knife surgery (all pts) F/U: Follow-up at 6 month intervals after tx; mean follow-up=36 mo (median 31 mo, range 1-110)	Prescription dose = median isodose of 57% (50-94%); median mean tumor dose=17.2 Gy (14.7-20.7 Gy)	n/a (no control or comparison group)	3 deaths during follow-up (unrelated to tx); 12 patients (6.4%) increased tumor volume; 7 patients (3.6%) had general symptoms such as headache, dizziness, tinnitus, and unsteadiness; 2 (1%) had temporary facial palsy; 2 (1%) trigeminal neuralgia; 27 patients (14.4%), "adverse radiation effects"; 6 patients required second GKS or craniotomy; 4 patients (2%) developed hydrocephalus that required VP shunt placement.	Poor Not all patients followed for the same period of time (biases results); Confounders not taken into account in analyses.
Flickinger (2004) Case Series **Schwannoma**	n = 313 Vestibular schwannoma Median age 56 years (range 18-88 yrs); 164 (52.4%) male; Baseline hearing useful or serviceable in 246 pts (78.6%) (Gardner Robertson Class 1-2), 21 (6.1%) pts with Class 3-4 hearing, 46 pts (14.7%) with Class 5 at baseline. Median baseline tumor volume=1.1 mL (range 0.4-21.4 mL).	Consecutive patients with unilateral vestibular schwannoma at University of Pittsburg from Feb 1991 to Feb 2001	Gamma knife radiosurgery performed with Model B, C, or U Leksell Gamma Knife (no comparison group) F/U: MR imaging every 6 mo for 2 yrs, then yearly. Median	Marginal tumor dose=12Gy (n=25), 12.5Gy (n=18), or 13Gy (median dose, n=270). Marginal tumor dose prescribed to the 50% isodose volume in 286 pts (91.4%), 55% in 21 pts (6.7%), 60% in 5 pts (1.6%), and 65% in 1 pt (0.3%). Median number	n/a (no control or comparison group)	New facial neuropathy (not observed in any patients. 2 pts had transient episodes of facial twitching on side of tumor after tx. 8 pts (2.5%) new trigeminal neuropathy 5-48 mo after radiosurgery. (6 developed numbness and 2 developed typical trigeminal neuralgia). Repeat radiosurgery in 1 pts with baseline trigeminal neuropathy symptoms before initial tx. 225 pts (84.3%) of 267 with serviceable hearing at baseline experienced hearing preservation (by Gardner Robinson hearing class) for 5-yr actuarial hearing-level preservation	Poor Multivariable analyses are not clear, nor are useful results reported from multivariable analyses.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	2 pts (0.6%%) had typical trigeminal neuralgia before tx.		follow-up 24 mo (max 115 mo); 36 pts (11.5%) had follow-up over 60 mo.	of isocenters=6 (range 1-15)		rate of 70.3 +/- 5.8%.	
Fukuoka (2009) Case Series **Schwannoma**	n = 152 Vestibular schwannoma Mean age 54 (median 54, range 22-83) Gender: 61 male (40%) Prior surgical resection: 45 (30%) Mean tumor size: 2.8cm3 (median 24 cm3, range 0.1-18.6 cm3) 59 (39%) had useful or serviceable hearing at baseline (Gardner-Robertson Grade I & II) 135 (89%) had normal nerve fxn at baseline (House-Brackmann Grade I)	Consecutive patients between 5/91 and 5/98 with unilateral vestibular schwannoma at Nakamura memorial hospital	All patients received gamma knife surgery (KULA or GammaPlan) No comparison group (case series) F/U: "At least 5 years"	Mean max dose = 25.5 Gy (median 24; range 17.1-30.0) Mean marginal dose= 12.8 Gy (median 12.0, range 9-15) Median number of isocenters= 9.1 (median 9, range 2-18)	n/a (no control or comparison group)	1 case underwent extirpation 8 years after GKRS due to chronic intratumoral hemorrhage 1 case (with history of 3 surgeries) developed ataxia with tumor expansion 6 mo after GKRS (necessitating partial removal at 18 mo)	Poor
Hasegawa (2005a) Case Series **Schwannoma**	n = 73 Vestibular schwannoma Mean age 52 yrs (range 18-79) Gender: 25 male (34%)	Vestibular schwannoma excluding neurofibromatosis Type 2	Gamma knife surgery (GKS) with Leksell stereotactic frame (model G, Elekta) No	Mean max dose = 28.4Gy (range 16.3-36.0) Mean tumor margin dose = 14.6Gy (range 10.0-18.0)	n/a (no control or comparison group)	11 (15%) had additional tx following GKS: 7 had craniotomy, 4 had section GKS tx 9 pts (12%) had hydrocephalus requiring placement of ventriculoperitoneal shunt (mean tumor vol 12.7cm3, range 1.5-41.2	Poor Tumor volume reported In study is the same as that reported in

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	19 pts (26%) had previous surgery for VS; 54 pts (74%) had GKS as initial tx Tumor location: 36 (49%) right, 37 (51%) left Mean tumor volume 6.3 cm3 (range 0.2-36.7) Useful hearing at baseline (House-Brackmann grade I or II): 66 pts (89%) Normal facial function at baseline (Gardner-Robertson Class I or II): 19 pts (26%)		comparison as this was a case series F/U: Median follow-up 135 mo Neuroimaging studies requested at 3 mo intervals for 1st yr after GKS, at 6 mo intervals for 2 yrs, then annually	Mean number of isocenters=4.8 (range 1-12) Mean isodose % = 52% (range 40-80%)		cm3) 8 pts (11%) had persistent or transient facial palsy 6-15 mo after tx. 6 pts (8%) had facial numbness 6-13 mo after tx.	Hasegawa 2005 (in Neurosurgery); this may not be of concern, however, in this article, authors report hydrocephalus in pts with tumor volume range that exceeds that range reported for all patients. Multivariable analyses not used to adjust for confounders in outcomes - they were used to identify factors significantly associated with PFS only.
Hasegawa (2005b) Case Series **Schwannoma**	n = 317 Vestibular schwannoma Mean age 54 (range 18-79) Gender: 118 (37%) male	Pts with vestibular schwannoma (excluding neurofibromatosis type 2)	Gamma knife surgery with Leksell Model G stereotactic frame (Elekta Instruments)	Mean maximum dose 26.2Gy (range 15-36 Gy) Mean marginal dose 13.2 Gy (range 10-18	n/a (no control or comparison group)	16 deaths (4 due to tumor progression or radiation-induced edema 10-79 mo after tx) 22 pts (7%) treatment failure (tumor enlargement, 17; peritumoral edema, 5). (20 pts (6.3%) developed tx failure within 3 yrs, additional 2 developed tx	Fair Study design appears to be a case series, although authors do

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Tumor location: 151 (48%) right, 166 (52%) left Prior surgical resection: 72 pts (23%); 245 (77%) underwent GKS as initial tx Useful/serviceable hearing at baseline: 97 (31%) Normal facial fxn at baseline: 260 (83%) Mean tumor volume 5.6 cm3 (range 0.2-36.7 cm3)		No comparison (case series), although patients were either given marginal dose of <=13 Gy (N=178) or >13 Gy (N=123) and authors make some comparisons between these dose groups. F/U: Median follow-up 93 mo 77 pts (24%) were followed for >10 yr Radiographic and audiometry follow-up every 3 mo for 1 yr, every 6 mo	Gy) 178 pts (56%) received low dose (<=13Gy), 123 (39%) received high dose (>13 Gy) Mean isodose line for tumor margin 51% (range 40-80%) Mean number of isocenters: 4 (range 1-12)		failure >3 yrs.) 8 pts (6%) reported facial weakness in high dose group, compared to 2 pts (1%) in low dose group (no statistical test). 5 pts (4%) reported facial numbness in high dose group, compared to 4 pts (2%) in low dose group (no statistical test). 27 (9%) of patients underwent additional tx after GKS (21 received craniotomy, 6 underwent second GKS) 21 (7%) developed hydrocephalus requiring ventriculoperitoneal shunt (mean tumor vol of these pts, 10. 1cm3, range 0.7-36.7 cm3, of whom 8 pts developed hydrocephalus with tx failure Among pts assessed for tumor expansion (N=254), 42 (17%) experienced expansion between 2 & 69 mo after tx. Of these, 17 underwent further tx (incl surgery or GKS).	make some post hoc comparisons between high (>13 Gy) and low (<=13 Gy) dose groups.

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			for next 2 yrs, then annually thereafter				
Hempel (2006) Case Series **Schwannoma**	n = 123 Vestibular schwannoma Median age 59 yrs (range 19-85) Gender: 60 (48.8%) male Tumor location: 59 (47.2%) right, 65 (52.8%) left Median tumor volume 1.6 cm3 (range 0.1-9.9 cm3) Among those with pre-tx audiogram (N=63), 42% had pre-surgical slight to moderate hearing loss	Unilateral VS treated at Gamma Knife Center in Munich and the Dept of ENT, Head and Neck Surgery, Ludwig Maximilians Uni (Munich); Bilateral VS excluded (e.g. Recklinghausen's neurofibromatosis)	Leksell Gamma Knife (model B) and Leksell GammaPlann (versions 2.01 to 5.12) No comparison (case series) F/U: Mean follow-up 98 mo (range 63-129 mo) Clinical exam and repeated imaging studies every 6 mo for 1 yr, then yearly	Median central tumor dose 22.7Gy (range 15.6-32.5) Median tumor marginal dose 13Gy (range 10-14.5) Median number of target points=6 (range 1-23) Median Isodose=55% (range 40-85%)	n/a (no control or comparison group)	Tumor increased in 5 pts (4%) 4 pts (3%) required retreatment with GKS 49 pts (42.2%) post-radiation swelling 3 pts (2.4%) hydrocephalus (requiring temporary shunt placement) 52 of 112 pts (46.4%) questioned about hearing changes reported impairment Among those with pre-tx audiogram (N=63), 11 (18%) experienced hearing loss 5 pts (4%) reported new tinnitus (after tx) 16 pts (13%) reported new onset of vertigo after tx 7 pts (6%) reported loss of trigeminal nerve sensation after tx	Poor Baseline audiometry obtained greater than 5 mo before tx in 73% of patients for whom data was obtained (46 of 63)
Iwai (2003) Case Series **Schwannoma**	n = 51 Acoustic neuroma, primary mean age 55 yrs (32-76). 19 males, 32 female. , 9 pts (17.6%) previous surgery. Mean tumor	Patients treated between Jan. 1994 and Dec. 1996 with gamma knife radiosurgery with a dose ≤ 12 Gy	Gamma knife radiosurgery (GKS), no comparator F/U: 18-96 months, (median 60 months.)	8-12 Gy, median 12 Gy. Smaller doses given to larger tumors	n/a (no control or comparison group)	facial spasms: 3 (6%). Intratumoral bleeding: 2 pts (4%). Hydrocephalus: 4 pts (8%).	Poor

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	diameter 5.2 to 32.7 mm (median, 18.8mm). Tumor volume from 0.7 to 24.9 cm3 (median 3.6 cm3). Hearing evaluations before GKS by Gardner-Robertson classification: 9 pts class 1 (18%), 11 class 2 (22%), 14 class 3 (27%), 4 class 4 (8%) and 13 class 5 (25%). 7 pts (14%) had facial palsy before GKS, by House-Brackman scale 1 pt grade 2, 1 grade 3, 4 grade 4, 1 grade 5.		Frequency not reported.				
Kalogeridi (2009) Case Series **Schwannoma**	n = 20 Acoustic neuroma, primary and recurrent median age 66 (57-80), 5 males, 15 females; 13 pts (65%) had tumors with both intracanalicular and cerebellopontine angle components. 4 pts (25%) previous surgery. Tumor diameter range 10-32mm, median tumor volume 5.95 cm3 (0.44-	Pts tx at clinic between May 2000 and June 2004 with unilateral tumors with a maximum diameter of 35 mm. Pts had documented tumor progression, progression of symptoms or both	LINAC based SRS, no comparator F/U: every 6 months first year and then annually. Median follow-up 55 months (36-84 months)	11-12 Gy	n/a (no control or comparison group)	No pts developed new trigeminal nerve neuropathy and 1 of 2 patients with prior symptoms showed improvement. No pts developed long term facial nerve neuropathy.	Poor Small sample size, no negative outcomes to analyze

Individual studies (published after review)							
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	15.7 cm3)						
Koh (2007) Case Series **Schwannoma**	n = 60 Acoustic neuroma, primary and recurrent 31 males, 29 females. Median age 58 (18-80). Average tumor size 4.9 cm3 (0.3-49.0 cm3)	Pts tx at clinic between Oct. 1996 and Feb. 2005, pts with tumor or symptom progression or pt choice absent progression, tumor diameter ≤ 4cm; 2 pts withdrew from tx, 1 chose single dose RT and 3 pts with neurofibromatosis and bilateral tumors excluded	Fractionated stereotactic radiotherapy (FSRT) F/U: every 6 months first year and then annually. Median follow-up 31.9 months (6.1-107.4 months)	total dose 50 Gy in 25 daily fractions over 5 wks	n/a (no control or comparison group)	Acute toxicities including grade I:II fatigue (45%:5%), nausea (43.3%:6.7%), headache (20%:6.7%), and vomiting (5%:3.3%). No grade 3 reactions. One pt with history of metastatic breast cancer developed a radiation-induced glioblastoma 5.8 yrs post FSRT	Poor Didn't account for age, sex, tumor size
Liu (2006) Case Series **Schwannoma**	n = 74 Acoustic neuroma, primary 33 males, 41 females. Mean age 45 yrs (19-76). 19 pts (25.7%) surgery prior to GKS. House-Brackman grading system, before GKS, 63 pts (85.1%) grade I, 2 (2.7%) grade II, 3 (4.1%) grade III, 2 (2.7%) grade	Pts tx at clinic between Oct. 1995-Oct. 2003 with unilateral tumor. Pts with neurofibromatosis type 2 excluded	Gamma knife radiosurgery (GKS), no comparator F/U: every 6 months first two years then every 2 years. Median follow-up 68.3 ± 32.9 months (30-	peripheral dose 10-14 Gy (mean dose 12.27 ± 0.96 Gy). Central dose 21-30 Gy (mean dose 24.9 ± 2.18 Gy)	n/a (no control or comparison group)	Deterioration of hearing 13 of 62 pts (21%), 17.6% of total sample. Facial nerve neuropathy, 3/63 (4.8%) 2 transient. Risk of post GKS facial nerve neuropathy 1.5%. 5 pts (6.8%) trigeminal dysfunction, 3 transient. 2.7% risk of post GSK trigeminal neuropathy in all pts. 2 pts (2.7%) clinical signs and symptoms (imbalance, dysphagia, paresthesia, vertigo) and 4 pts (5.4%) developed hydrocephalus.	Poor

Individual studies (published after review)							
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	IV and 1 (1.4%) both grade V and grade VI. Gardner-Robertson classification system: pretreatment, 12 pts (16.2%) Class I, 35 (47.3%) Class II, 15 (20.3%) Class III, 7 (9.5%) Class IV, and 5 (6.8%) Class IV. Mean intercranial tumor diameter 21.2 ± 10.8 mm (range 6-48 mm)		122 months)				
Lobato-Polo (2009) Case Series **Schwannoma**	n = 55 Acoustic neuroma, primary 31 males, 24 females. Median age 35 (13-40). 14 (26%) had previous surgery. Median tumor volume 1.7mm3	40 yrs or younger, underwent GKS between 1987-2003, minimum 4 yrs follow-up. Excluded pts with neurofibromatosis type 2	Gamma knife radiosurgery (GKS), no comparator F/U: follow-up schedule not specified. Follow-up MRI scans obtained at 6 months, 1 yr, 2 yrs, 4 yrs and 8 yrs	median tumor margin dose 13.0 Gy (11-20 Gy)	n/a (no control or comparison group)	Of 40 pts with Gardner-Robertson (GR) hearing scores class i-IV prior to GKS, 10 (25%) experienced hearing loss of at least one GR class, 3 of 26 pts receiving < 13 Gy experienced hearing loss and 7 of 14 pts receiving ≥ 13 Gy had hearing loss. 1 pt (1.8 %) developed permanent facial neuropathy (pt. received dose of 20 Gy). 4 pts (7.3%) developed trigeminal neuropathy, for 2 pts it was transient. No pt with a dose lower than 13 Gy developed trigeminal neuropathy.	Fair
Mandl (2010) Case series **Schwannoma**	n = 29 21 pts tx with SRT (72.4%) , 8 with SRS (27.6%) 29 pts identified, 4 lost to	Pts tx at clinic between Jan. 1992 and March 2007 with large tumors (tumor diameter ≥ 3.0 cm	stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS)	SRT: five fractions of 5 Gy in one week. SRS: single dose of 12.5 Gy	Local tumor control achieved in 21 of 25 pts (84%). Didn't distinguish between pts tx	percentages are figured as number of pts developing complication divided by number of pts at risk for outcome. New trigeminal neuropathy 2/15 (13%), progressive trigeminal neuropathy 1/10 (0%), sixth nerve	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	follow-up. 25 pts included in full analysis Acoustic neuroma, primary and recurrent Mean age 54.1 (12-80). Mean tumor diameter 3.3 cm (3.0-4.0 cm). Mean tumor volume 15.3 cm3 (6.7-22.8 cm^3.) 9 of 29 pts (31%) had prior microsurgery. 3 pts had neurofibromatosis type 2.		F/U: followed at least yearly. Mean follow-up 3 yrs (range 1-10 years)		with SRT and SRS.	neuropathy 2/25 (8%), new facial neuropathy 5/17 (29%), progressive facial neuropathy 3/8 (38%), facial spasm 1/25 (4%), hearing loss 5/8 (63%), swallowing difficulties 1/25 (4%) and accessory nerve neuropathy 1/25 (4%).	
Mathieu (2007) Case Series **Schwannoma**	n = 62 (74 tumors) Acoustic neuroma, primary and recurrent 29 males, 33 females, mean age at time of first procedure 36 yrs (11-79), mean tumor volume 5.7 cm3 (0.2-21.1 cm3). 21 tumors (8%) in 17 pts (27%) had at least one prior surgery before GKS	Pts treated at clinic between 1987 - 2005 with diagnosis of neurofibromatosis type 2	Gamma knife radiosurgery (GKS), no comparator F/U: every 6 months first year and then annually, median follow-up 53 months (4-196 months), 2 pts lost to follow-up	mean margin dose 14 Gy (11-20 Gy), mean maximum dose 27.5 Gy (21.8-40 Gy)	n/a (no control or comparison group)	Measurable hearing preservation rate 42%. Facial weakness occurred in 12 tumors (17%). According to House-Brackman scale, scored as following: 1 (1.3%) Grade 2 (permanent), 6 (8.1%) Grade 3 (3 permanent), 1 (1.3%) Grade 4 (permanent), 2 (2.7%) Grade 5 (1 permanent), and 2 (2.7%) Grade 6 (both permanent.) Trigeminal neuropathy occurred in 8 tumors (11%). Ataxia and vertigo, 5 pts (7%). Hemifacial spasm, trigeminal neuralgia and abducens palsy each 1 case (1.3%).	Fair
Okunaga (2005) Case Series	n = 46 (53 pts, 7 loss to f/u, so 46 included in the analysis)	Unilateral Vestibular Schwannoma,	LINAC stereotactic radiosurgery	Mean radiation dose to tumor margin 14 Gy	n/a (no control or comparison group)	procedural complications: Hearing loss: only 37 patients had data on hearing function and 17 patients	Poor 7/53 patients

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Schwannoma	vestibular schwannoma 14 men and 32 women, mean age 60 years (range 21-78 years); number with previous resection 12 (26%); median tumor volume 2.29 ml (range 0.4-7.01 ml)		directed at 1-4 isocenters (median 2). No comparator. F/U: Followed every 3-4 months with MR imaging. Median duration of follow up MR imaging 56.5 months (range 12-120 months).	(range 10-16) and median maximal dose 23.2 Gy (range 17-36.13. Radiation to brainstem limited to 10 Gy.		totally deaf and 11 with nonuseful hearing levels at the time of the procedure. Of the 9 with useful hearing levels, 3 had a deterioration in hearing. Facial palsy:9 patients with preexisting facial palsy- 1 got better. 2 patients/42 (4.8%) developed new facial palsy, 1 patient(2.4%) temporary facial palsy. trigeminal neuropathy: 4 patients had before radiosurgery and none of these changed; 1 patient developed new (2.4%) **all percentages based on 42 patients on whom had follow up for more than a year	lost to f/u and not included in analysis, another 4 only observed for 1 year only (this is 20% of total group treated), cannot establish what net effect was. Authors state that need 2 year f/u. Do not delineate difference between pts with prior txs vs those in whom this is first tx. All outcomes including harms can occur with underlying condition and/or related to tx
Ottaviani (2002) Case Series **Schwannoma**	n = 30 Acoustic neurinoma 13 men and 17 women; mean age +/- SD, 54.6	Unilateral acoustic neurinoma	Gamma knife stereotactic radiosurgery-201-source Cobalt 60 gamma unit.	peripheral tumor doses of 1200-1400 rad (mean +/-SD 1340 +/-80 rad), max	n/a (no control or comparison group)	Hearing loss is main outcome. Other harms:1 patient with transient facial spasm (resolved within 1 year), 5 patients with mild trigeminal disturbances-none severe or painful. (percentages not provided by	Poor Hearing loss as outcome-can be d/t underlying

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	+/-13.3 years; 4 patients deaf on affected side prior to therapy so excluded from analysis.		No comparator F/U: Followed at 6 months, 12 months and 24 months	tumor doses 1750-2800 rad (mean +/- SD, 2500 +/- 260 rad)		authors)	condition and/or tx and this study does not help differentiate. No info on previous txs or baseline characteristics other than age and sex; no COI or funding statement provided.
Pollock (2002) Case Series **Schwannoma**	n = 55 vestibular schwannoma (recurrent or residual) 18 males, 37 females; mean age 51 years (range 18-79). 50/55 (91%)had 1 previous surgery, remainder had 2-3 previous surgeries. At BASELINE 37/55 (67%) palsy or weakness of facial muscles, 14/44 (27%) had trigeminal deficit, 52/55 (94%) deaf, 15/55 (27%) ataxia	Recurrent or residual tumors, previously treated with microsurgery or radiosurgery	Leksell Gamma Knife, median number of isocenters 8 (range 2-14). No comparator group F/U: clinical and MRI follow up at 6, 12, 24 months and then biyearly after that	Median tumor margin dose 14 Gy (range 12-20); median maximum radiation dose 28 Gy (range 24-40)	n/a (no control or comparison group)	7 patients (14 %) with complications after radiosurgery: trigeminal deficits (n=2), facial weakness (n=4), ataxia (n=3), diplopia (n=1)	Poor
Powell (2011) Case Series	n = 72	Progressive dz without	Fractionated stereotactic	33 pts received 45 Gy in 25	n/a (no control or comparison	8 patients (11%) developed hydrocephalus after treatment	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Schwannoma	vestibular schwannoma, primary or recurrent 37 males, 35 females. Median age 58 years (range 20-78). 13/72 patients with previous surgery. No patients had hydrocephalus at before treatment.	treatment or recurrent disease after prior surgery. Excluded patients who received low dose radiotherapy (<30 Gy)and non-acoustic neuroma tumors	radiotherapy. No comparator group F/U: Weekly during treatment for assessment of acute toxicity. Baseline MRI scan at 3 months following treatment, then annual scans- more frequent as needed.	fractions, 39 patients received 50 Gy in 30 fractions.	group)	(median time to hydrocephalus 8.5 months, range 1-19 months) and these all had a VP shunt placed. Development of hydrocephalus in more likely if larger tumor or tumor closer to or crossing midline or partial effacement of 4th ventricle at baseline.	Better than average description of study methodology, patient population, reviewers blinded to outcomes. Tumor itself can cause hydrocephalus and so lack of a comparison group does not allow any conclusion about the relationship
Roche (2008) Case Series **Schwannoma**	n = 44 vestibular schwannoma, Primary or recurrent Group A: mean age 62.7 years, 4 patients with NF2, Group B: mean age 62.9 years, 1 patient with NF2	Group A: 32 patients with VS who had preexisting hydrocephalus; Group B: 11 patients with VS who developed hydrocephalus after procedure	Gamma Knife Radiosurgery. No comparator group in terms of treatment F/U: Mean f/u 43 months in Group A and 50 months in	NR	n/a (no control or comparison group)	Only 20/32 pts with preexisting hydrocephalus got follow up and 25% of these required a shunt for the condition. All 11 pts who developed hydrocephalus after the procedure required a shunt.	Poor Hydrocephalus can occur as a result of tumor itself so unclear what this study says about the relationship of this treatment to the outcome. 33% of patients in

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			group B				Group A lost to follow up. Little study info on how charts reviewed or exactly what the tx was.
Rowe (2003) Case Series **Schwannoma**	n = 234 acoustic neuroma, Primary or recurrent/residual 129 women/105 men; mean age at treatment 53 years (range 23-85). 59 patients (25%) previously had undergone surgery. 108 (47%) totally deaf at tie of surgery, 50 (22%) with useful hearing.	sporadic unilateral acoustic neuromas	Gamma Knife Radiosurgery; No comparison group F/U: Annual f/u: median 24-59 months	Median peripheral dose 15 Gy; Median number of isocenters 6	n/a (no control or comparison group)	Hearing preservation: of 119 patients with discernable hearing 75% unchanged after treatment; facial nerve function: of 225 patients with complete data 10 patients (4.5%) facial nerve function adversely affected but persisted in only 2 patients (less than 1%); trigeminal nerve function 4% of patients transient disturbance, 1.5% persistent dysfunction); other: nonspecific vestibulocochlear symptoms, earache, dizziness, nausea, tinnitus reported in 28 patients (13%)	Poor Authors make an attempt to account for baseline patient characteristics in outcomes seen but because no comparison group, cannot directly associate outcomes with tx. Some outcomes may be a result of underlying disease.
Rowe (2008) Case Series **Schwannoma**	n = 118 vestibular schwannoma primarily though several patients with other types of tumors as well	vestibular schwannoma in patients with established diagnosis of NF2 treated with	Radiosurgery; no comparator group F/U: ~9 years	Only stated for 92 of initial series of 96-mean marginal dose of 13.4 Gy	n/a (no control or comparison group)	Adverse effects on hearing (26 of 61 (42%) patients with hearing before treatment had decreased hearing after treatment with 12 patients becoming totally deaf, 5% of patients had persisting facial nerve weakness,	Poor Inadequate info on tx itself, methodology for reviewing

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	96 patients in first series [1986-2000] with 122 VS (i.e. sometimes bilateral); Additional 22 patients [2001-2004] treated for VS (22), meningioma (23), trigeminal neuroma(4) 27 of 96 patients in initial series had multiple intracranial tumors in addition to VS.	radiosurgery				2% of patients excluding those with trigeminal neuromas developed a trigeminal neuropathy; intracranial malignancies developed in 2 of 118 patients	charts not clearly described, minimal data provided on outcomes. One strength is that just pts with NF-2 i.e. may be same histologic tumor but different patterns of growth than when unilateral sporadic
Sawamura (2003) Case Series **Schwannoma**	n = 101 vestibular schwannoma, Primary or recurrent/residual Median age 53 years (range 14-82), 38 males, 63 females. One patient had NF1. 12 patients had undergone previous resection, 17 patients had symptoms or tumors that had progressed between initial diagnosis and start	Patients with solitary VS treated with fractionated radiotherapy. Excluded patients with NF2	Fractionated SRT; no comparator. Authors do provide indications for SRT (in contrast to other studies) F/U: every 6 months for 5 years, then every 12 months.	40-50 Gy (median 48) in 20-25 fractions	n/a (no control or comparison group)	Transient facial nerve palsy 4 patients (4%), trigeminal neuropathy in 14 patients (13.9%), dysequilibrium in 17 patients (16.8%). Hydrocephalus developed in 23% - 12% required a shunt, 11 had communicating hydrocephalus which may have been related to the primary tumor versus tumor necrosis related to SRT.	Poor Unclear why authors chose to say that hydrocephalus was not a consequence of SRT. Not clear whether the pts w/ preexisting CSF malabsorption were the ones who required a shunt. Unclear

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	of treatment; 7 patients with large tumors had resection prior to SRT. Median of calculated mean of diameter of tumor 15.5 mm (range 3-40 mm). 82 patients (81%) had measurable hearing prior to treatment		Median f/u period 45 months				if prospective or retrospective.
Selch (2004) Case Series **Schwannoma**	n = 50 acoustic neuroma, primary and recurrent/residual 30 men, 18 women; median patient age 59 (range 20-76); 42/48 with primary tumor, 6 patients with residual tumor growth after primary resection; no patients with NF or cystic acoustic neuroma Hearing levels not formally tested but 42/48 with useful hearing, though 40/42 with decreased acuity; Tinnitus in 23/48. Ataxia or vertigo in 15/48. Facial weakness 2/48	Patients with AN treated with stereotactic radiotherapy	6-MV Novalis LINAC SRT delivered to a single isocenter; no comparator F/U: median f/u 36 months (range 6-74 months)	54 Gy in 30 fractions of 1.8 Gy prescribed to the 90% isodose line	n/a (no control or comparison group)	acute morbidity: 4/48 (8.3%) with nausea controlled with medication; 3/48 (6.2%) with transient fatigue; 1/48 (2%) with headaches. Hearing loss: hearing subjectively declined in 4/42 (9.5%) patients with useful hearing prior to treatment but remained useful; 3/42(7%) patients lost useful hearing. New facial nerve dysfunction in 1/48 (2.1%). New trigeminal nerve dysfunction in 1/48 (2%). Tinnitus worsened in 6/23 (26%) patients, improved in 2/23 (4.1%) patients. No new balance dysfunction and 1 patient with pretreatment ataxia improved(denominator unclear since ataxia/vertigo not divided out). No hydrocephalus.	Poor Pt preference was why treated with the therapy in 32/42 pts with primary tumor (may cause additional bias);hearing not tested objectively; f/u period may not be long enough to see all of effects. Can't distinguish between tumor progression vs tx as cause of effects.

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Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	and facial numbness in 4/48. Tumor diameter median 2.2 cm (range 0.6-4cm)						
Showalter (2008) Case Series **Schwannoma**	n = 39 Nonacoustic cranial nerve schwannomas (NACNS), primary and recurrent/residual Mean age 45 years (range 16-93); 21 female and 18 male patients; Median Karnofsky Performance Scale 90% (range 80-100%); mean tumor volume 6.49 +/- 1.01 ccm (median 4.2 ccm); CNIII n=2, V n=19, VI n=3, VII n=5, IX n=2, X n=5, XII n=2, cavernous Sinus n=1. 16/39 patients (41%) had previous surgery	Patients who were treated with FSR or SRS for NACNS. Excluded patients with neurofibromatosis, schwannoma of CN II. Patients were generally offered FSR if intact cranial nerve function but selected SRS because of convenient treatment schedule	Gamma Knife Model U for SRS, LINAC for SRS and FSR; 24 patients got FSR, 15 patients single fraction SRS F/U: Only longer than 12 months for 26/39 patients (67%).	FSR: 1.8-2.0 Gy fractions to median dose 50.4 Gy (range 45-54 Gy): SRS Median dose 12.0 Gy (range 12-15 Gy)	n/a (no control or comparison group)	Acute toxicity assessed in 35 patients: headache/dizziness in 23% of patients. Cranial nerve function only reassessed in 26 patients who had longer than 12 month f/u: 1/26 patients had worse CN deficits.	Poor No comparison group so difficult to ascertain effect of tx. In addition. Per authors, objective measurements of CN not made, no data on time to changes in CN function, relatively short f/u time.
Timmer (2009) Case Series **Schwannoma**	n = 69 Vestibular Schwannoma 38 male/ 31 female; Mean age at SRS 53 years (24-76 years); Tumor location: 66	Tumor <3 cm at first scan with referral for GKRS because of MRI-proven MRI growth of >2mm maximal diameter or because of	GKRS using Leksell titanium stereotactic frame F/U: Mean f/u 14.2	If patients able to use their affected ear on the telephone, dose of 12.5 Gy, if patients said affected ear useless dose	n/a (no control or comparison group)	Only 32/69 patients had serviceable hearing prior to treatment; and among these 32, only 13 patients (41%) had serviceable hearing after GKRS. PTA: no significant correlation between maximal dose at tumor and worsening of hearing or tumor size/volume and PTA difference.	Poor MRI done only at beginning of study so unclear if change in hearing had to

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	extrameatal (96%), 3 intrameatal (4%); Mean tumor size (based on Tokyo 2003 guidelines) 17 mm (6-32 mm)	personal preference. Excluded patients with NF or with a pure tone average (PTA) > 90 dB	months (range 3-56 months)	13.0 Gy. Doses actually delivered: mean marginal dose 11 Gy (9.3-12.5 Gy SD 0.46), Mean Maximal dose 19.7 Gy (range 16-25.5 Gy, SD 1.73). Doses in the cochlea: min. 2.6 Gy (range 0.9-7.4 SD 1), max 10.3 Gy (range 3.1-16.1 SD 2.9)		+Correlation between maximal cochlear dose and difference in PTA before and after GKRS (Spearman correlation, r=0.3, p<.05, two tailed test).	do with changes in the tumor size versus radiation. Also hearing can worsen with the tumor itself.
Unger (2002) Case Series **Schwannoma**	n = 86 Vestibular schwannoma, residual/recurrent	VS who underwent previous resection.	Radiosurgery with Gamma Knife Model B; no comparator group F/U: Mean 75 months (range 42-114 months)	Marginal dose (30-80%) of 10-18 Gy in a single treatment. In early years of series, marginal tumor dose 18 Gy, later years 12-14 Gy.	n/a (no control or comparison group)	20% of patients with transient nausea/vomiting, 12 % transient headache. Hydrocephalus-3 cases, 1 required shunting, two treated medically with steroids, trigeminal/facial nerve- no permanent additional facial or trigeminal deficits though 5 patients (10%) had delayed transient trigeminal neuropathy and 4 patients(8%) had delayed transitional incomplete facial nerve palsy	Poor 36 patients not included in analysis which may bias results; Harms/side effects noted may be from tumor or treatment. Ambiguities in outcomes section.
Vachhrajani	n = 973	All patients who	Leksell	NR	n/a (no control	Acute: anxiety/syncopal episode 19	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
(2008) Case Series **Schwannoma**	Acoustic neuroma, trigeminal neuralgia, AVM, Brain mets, meningioma, Glioma (primary and recurrent/mets) 146 patients(15%) with acoustic neuroma; 270 patients (28%) trigeminal neuralgia, 64 patients (6%) AVM; 292 patients (30%)brain mets; 87 patients (9%) meningioma; 19 patients (2%) glioma	underwent gamma knife surgery at 2 centers between 2004-2007	Gamma Knife 4 C machine, no comparison group F/U: median f/u 11.5 months		or comparison group)	(2%), loosening of stereotactic frame without abortion of tx 3 (0.3%), loosening of frame with abortion of tx 3(0.3%), groin hematoma 1 patient (0.1%), acute coronary episode 2 (0.2%); abortion of procedure for reason other than frame loosening 9 (0.9%); Delayed: severe headache 8 (0.8%), severe facial pain 9 (0.9%), motor deficit 11 (1.1%), hydrocephalus4 (0.4%), seizures 16 (01.6%), severe fatigue 6 (0.6%).	Incomplete f/u on many patients, hard to know if sx related to treatment or disease progression, many different tumor types and no differentiation of dose, symptoms are often subjective
van de Langenberg (2011) Case Series **Schwannoma**	n = 33 Vestibular schwannoma 15 men, 18 women with mean age of 54.8 years (30-83), all patients with baseline hearing loss, 12 (36%) with serviceable hearing; 23 (70%) with tinnitus, 17 (51%) with vertigo, 12 (36%) with trigeminal hypesthesia, 1 (3%)patient with HB grade II facial paresis. 2 patients (6%) with	All patients who underwent gamma knife surgery for VS larger than 6 ccm between 2002 and 2009. Excluded patents who had undergone microsurgery, patients with NF2, patients with maximum extracanalicular diameter >4 cm	Leksell Gamma Knife Radiosurgery and dexamethasone 10mg prior to GKS and then for 12 day taper; No comparison group F/U: median f/u 30 months (12-	isodose 12.5-13 Gy (mean 12.6) covering 90% of tumor volume. Max dose 18.1-25.5 (mean 20.79 Gy), tumor margin dose 10.3-13 Gy (mean 11.6); number of isocenters 3-23 (mean 9).	n/a (no control or comparison group)	Transient facial paresis 2/33 patients (6%), transient facial hypesthesia 2/21 patients (14%), hydrocephalus requiring shunt 2/31 patients (6%), ataxia 1/33 patients (3%) Hearing loss: 5/12 patients with serviceable hearing (41%) lost this hearing.	Poor Choice to do GKS (as opposed to microsurgery) was somewhat based on pt preference or comorbid conditions in more than half pts. Median f/u 30 months but authors report that mean time

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	baseline hydrocephalus requiring shunting.	(mass effect present).	12-72 months				to clinical failure 35 months. 3/33 pts lost to f/u (>10), questionable effect of dexamethasone given to all pts. Cannot establish causality of tx vs natural progression of tumor.
Wackym (2004) Case Series **Schwannoma**	n = 32 Only analyzed 29 patients since 3 had less than 6 mo f/u acoustic neuroma, Primary and recurrent/residual 24 patients primary tumor, 5 patients with recidivistic tumor(had previous microsurgery). Facial nerve function normal in 23/24 patients (96 %) in primary tumor patients, 2/5 (40%) with recivistic. Trigeminal	Study included all patients treated with gamma knife radiosurgery for unilateral sporadic acoustic neuromas. Excluded patients with NF2 and those patients with less than 6 months f/u (3 patients)	Leksell Gamma Knife model B. no comparator. F/U: Serial MRI or CT images, audiometry at 6 month intervals; f/u range between 6-36 months.	In 20/24 primary and 4/5 recidivist tumor the 50% isodose line used to irradiate tumor margin. Remainder of patients 45-60% isodose line used. Tumor margin dose 12-14 Gy (mean 13.45 Gy) and maximal dose 20.3-32.1 Gy	n/a (no control or comparison group)	Headache in 2/24 primary (8%) and 1/5 recidvistic (20%); Disequilibrium in 17/24 (71%) primary and 3/5 recidivistic patients; Tinnitus in 14/24 (58%) primary and 2/5 (40%) recedivistic- resolved in 3 of primary patients. Facial nerve function: no change in any of primary patients, one recidvistic tumor patient improved from facial nerve paralysis at 6 month visit. Trigeminal nerve dysfunction transient in 1/29 patients- resolved 12 months post treatment. Hearing presented in graph form, not as summary results	Poor Excluded 3/32 patients (>10%)because inadequate follow up. Cannot differentiate primary tumor effects from treatment effects, including harmful effects. Unclear what criteria were to qualify for

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	nerve function normal in all 29 patients (100%). Tinnntus in 13/24 (54%)with primary and 2/5 (40%) recidvistic. Hearing with Gardner-Robertson Grade 1 or 2 in 9/24 primary patients (38%) and 0/5 recidivistic patients. Disequilibrium in 9/24 (38%) primary and 3/5 (60%)recidivistic. Vertigo in 3/24 (13%) primary patients/ 0/5 recidivistic. Degree of vestibular paresis: in primary 1/24 (4%) and recidivistic 5/5 (100%)			(mean 27.47 Gy).			primary radiosurgery vs microsurgery.
Wackym (2008) Case Series **Schwannoma**	n = 55 (appears to include the 32 patients in Wackym (2004) -1 patient excluded for less than 6 mo f/u vestibular schwannoma, primary and recurrent/residual 28 men, 26 women. 7/55 patients had	Unilateral Vestibular Schwannoma treated with gamma knife radiosurgery	Leksell Gamma Knife model B-single session. no comparator. F/U: every 6 month interval MRI, audiometric testing, vestibular function	43/54 patients-50% isodose line for the tumor margin. Remainder had 45-60% isodose line used. Mean tumor margin dose 12.9 Gy (range 11.7-14) and maximal mean dose 25.68 Gy (range 23.5-31.11)	n/a (no control or comparison group)	Vestibular function:Disequilibrium27/47(57%) of primary patients and 4/7 secondary (57%)- in 13 patients this was a new symptom. Onset between 6 months and 12 months after treatment, generally resolved by 18 month though severe in several patients. Dizziness(DHI: reported by 35 patients at some point before or after procedure- got worse in 10 (28%), better in 18 (51%). Additional analyses done to relate changes in DHI to sex, age, size of tumor and	Poor Main outcome measure unreliable Dizziness Handicap Inventory (DHI) was performed retrospectively-patients supposed to remember how dizzy they were

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	recidivistic (aka secondary) VS after prior microsurgical removal. Facial nerve function: normal in 46/47 (98%)with primary and 2/7 (28.6%)with secondary. Trigeminal nerve function: normal in 41/47 (87%) primary, 4/7 (57%) secondary. Tinnitus: in 26/47 primary (55%), 3/7 (43%) secondary. Headaches: 11/47 (23%) primary and 1/7 (14%) secondary. Complete unilateral vestibular paralysis 1/47 primary (2%) and 7/7 secondary (100%). Disequilibrium in 18/47 primary (38%) and 4/7 secondary (57%). Vertigo 4/47 (8.5%)primary and 0/7 (0%) secondary.		testing, facial nerve electromyography. until 2.5 years out then testing done annually. Mean f/u 54.7 months. 43/54 patient had more than 24 months of f/u.			time since procedure- no significant correlation	in some cases more than 5 years earlier. No way to know if symptoms related to treatment or tumor itself.
Wowra (2005) Case Series **Schwannoma**	n = 111 vestibular schwannoma 37 patients (33%) had undergone surgery prior to GKS, 74 (66.7%) GKS	presence of VS with documented growth or clearly progressive symptoms, tumor volume less than 10 ccm. Do not	Leksell Gamma Knife model B. no comparator. F/U: 3-6 months, 18-	Margin tumor dose 13 Gy (range 10-16 Gy) placed in a median peripheral isodose of 55%	n/a (no control or comparison group)	Facial neuropathy-"mild and transient in 3 patients after GKS", trigeminal neuropathy-13 patients, hearing loss-Median hearing loss -10dB.	Poor 174 pts treated but only included 111 (63.8%) in this analysis and not

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	was primary treatment. 10 patients (9%) had NF2. Mean tumor volume 1.6ccm. Baseline facial neuropathy in 75% of those with prior surgery.	explicitly say exclusion criteria	24 months, and 30-36 months after GKS, then every 2 years. Median f/u 7 years (range 5-9.6 years)	(range 45-85%). Median number of isocenters/patient 8 (1-25)			really clear why others excluded; unclear difference between "tumor swelling" and growth. No comparator group and so cannot determine whether growth pattern or side effects related to tumor or intervention. Inadequate description of baseline characteristics of group. Authors present "reference case" results for volumetry but do not describe methodology or define this at all.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Yang (2011) Case Series **Schwannoma**	n = 65 Vestibular schwannoma, Primary and recurrent residual tumor volume range 5-22 ml (median 9 ml); 37 men and 28 women with mean age 51 years (range 19-89). 17/65 (26%) patients had previously undergone resection (8 of these had progression of residual tumor and 9 had recurrent tumors). All tumors indented brainstem: Koos grade 3 in 37 cases, Koos grade 4 in 28 cases. 5 patients (8%) with clinically significant hydrocephalus and had VP shunt prior to treatment. Hearing: 22 patients (34%) with serviceable hearing (class I and II Gardener-Robertson), 15 patients (23%) with facial weakness	Tumors between 3-4 cm in one extracanalicular maximum diameter; excluded NF2 , tumors >4 cm	No comparator. Model 4-C or Perfexion Leksell Gamma Knife F/U: 6 months 12 months, 2 years, 4 years, 6-8 years with clinical and imaging f/u. Median f/u 36 months 9range 1-146 months)	Median prescription dose delivered to margin 12 Gy (range 11-15 Gy), prescription isodose 50%, minimum tumor dose >10 Gy	n/a (no control or comparison group)	Hearing loss: 4/22 patients with serviceable hearing prior to SRS lost it following treatment(hearing preservation correlated with smaller tumor volume (<10 ml). 7 patients (11%) underwent tumor resection between 1 and 50 months after SRS-2 with increased ICP, 5 with persistence of preexisting symptoms. 1 patient with multiple medical problems had a stroke 17 months after SRS. 4 patients (5%) developed increased ICP and required VP shunt. 4 patients (5%) with trigeminal sensory loss, 1 patient (1.5%) with facial weakness	Fair Unclear if outcomes including harms are from primary tumor or treatment and study type does not allow to differentiate. Potential conflict of interest since several authors are consultants for GKS manufacturer and one is a stockholder.

Head and Neck

Glomus jugulare

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Guss (2011) Systematic Review **Glomus jugulare**	19 studies N = 335 Type of therapy: Gamma knife therapy, 278; Linear accelerator-based radiosurgery or Cyberknife, 57; No other patient characteristics reported	Intervention: Gamma knife therapy (14 studies), Linear accelerator-based radiosurgery (LINAC or Cyberknife), 5 studies) Comparator: NR F/U: Follow-up range, 10-60 months; 8 studies had follow-up >36 months; 11 studies had mean follow-up time <36 months; NOTE: In the text, it was reported in two different places that 10 and 8 studies had follow-up >36 months Dose: Average marginal dose range, 12-20.4 Gy; 1 study used fractionated dosing (Gy not reported);	n/a (no control or comparison group)	Documented complications/toxicities , number of studies (number of patients): None, 6; Transient facial palsy, 2 (1); Trigeminal neuraliga, 1 (1); Transient tongue weakness, 1 (2); Decreased facial sensation, 1 (1); Tinnitus, 1 (1); Partial hearing loss, 1 (5); Hearing loss, 3 (5); Inner ear inflammation, 1 (2); Transient vocal cord paresis, 1 (1); Vocal cord paralysis, 1 (1); Transient dysphagia, 1 (1); Transient low grade nausea, 1 (6); Nausea and vomiting, 1 (1); Transient balance disturbance with vertigo, 1 (1); Imbalance and vertigo, 1 (1); Vertigo, 4 (6); Transient headache, 1 (1); Headache, 1 (2); Mucositis, 1 (4); Transient neuropathy of cranial nerves IX, X, XII, 1 (1); Transient facial spasm, 1 (1); Transient incomplete facial palsy, 1 (1); Facial palsy, 2 (3); Transient hoarseness, 1 (1);	Fair

Head and Neck Cancer

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Ozyigit (2011) Cohort **Head and Neck Cancer**	n = 51 Nasopharyngeal carcinoma, primary and recurrent 36 men, 15 women; median age 46 yrs (13-70); median tumor volume for SBRT group was 63.4 cm3 (26.3-170.4) and for CRT was 70 cm3 (20.4-189)	Inclusion: Locally recurrent nasopharyngeal cancer reirradiated with conformal radiation therapy or SBRT; Exclusion: 2D conventional radiotherapy, receiving a third course of irradiation with SBRT	SBRT using CyberKnife (n=24); CRT using 6 MV linear accelerator with or without brachytherapy (n=27) F/U: Follow-up every 3 mos during first year, then every 3-4 mos; median follow-up for all patients of 24 mos (3-76), for SBRT group 23 mos (3-33), and for conformal radiation therapy 24 mos (4-76)	SBRT (30 Gy over 5 days); CRT delivered 2 Gy/day, median dose of 57 Gy (30-61)	2-yr cancer-specific survival rate: 45% for all patients, 64% for SBRT group, 47% for CRT group (not statistically significant); 2-yr local control rates: 82% for all patients, 82% for SBRT group, 80% for CRT group (not statistically significant); univariate analysis showed that T stage at recurrence was significant predictor of 2-yr cancer specific survival (85% for stage T1-2 at recurrence vs 46% for stage T3-4 at recurrence, P=0.005) and for 2-yr local control rates (75% for stage T1-2 at	Overall serious (grade ≥3) late complications (SBRT group, conformal radiation therapy group): 5 patients (20.8%), 13 patients (48.1%) (P=0.04); cranial neuropathy: 1 patient (4.2%), 3 patients (14.3%); carotid blow-out syndrome: 4 patients (16.7%), 1 patient (4.8%); brain necrosis: 1 patient (4.2%), 5 patients (18.5%); trismus: 0 patients, 5 patients (18.5%); use of brachytherapy and chemotherapy regimen at recurrence were not related to serious late effects; fatal complications: 3 patients (12.5%), 4 patients (14.8%); no significant correlation between tumor volume or cumulative nasopharyngeal dose and rate of serious late side effects.	Poor Retrospective, not blinded, historical comparison group, initial experience in single institution

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
					recurrence vs 54% for stage T3-4 at recurrence, P=0.02); multivariate analyses found that T stage at recurrence was only significant independent predictor for cancer-specific survival and local control rates (but type of RT was not included in univariate or multivariate analysis)		
Chen (2006) Case Series **Head and Neck Cancer**	n = 64 Newly Diagnosed Nasopharyngeal Carcinoma, Primary and metastatic Median age, 48 years (range 23-83); 51 (79.7%) men; WHO classification pathology: Type I, 1 (1.6%); Type II, 22 (34.4%); Type III, 41 (64.1%); T	Inclusion criteria: Patients with previously untreated, biopsy-proven nasopharyngeal carcinoma who underwent a planned SBRT boost after previously receiving EBRT Exclusion criteria:	Initial treatment: 2D RT technique with linear accelerator of 6 MV photons; Boost: Frameless SBRT system (Cyberknife Robotic Radiosurgery system) within 1 week of initial treatment	All patients received a planned SBRT boost dose of 12-15 Gy in 3 Gy fractions over 4-5 consecutive days; Prescribed dose of radiation administered to periphery of original lesion, mostly corresponding to	n/a (no control or comparison group)	Acute toxicities during conventional radiotherapy + SBRT boost: Leukopenia, grade 0, 24 (37.5%); grade 1, 6 (9.4%); grade 2, 24 (37.5%); grade 3, 10 (15.6%); grade 4, 0; Anemia, grade 0, 15 (23.4%); grade 1, 41 (61.4%); grade 2, 8 (12.5%); grade 3, 0; grade 4, 0; Thrombocytopenia, grade 0, 45 (70.3%); grade 1, 17 (26.6%); grade 2, 2 (3.1%); grade 3, 0; grade 4, 0; Mucositis, grade 0, 0; grade 1, 2 (3.1%); grade 2, 39	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	stage: T1, 15 (23.4%); T2, 19 (29.7%); T3, 15 (23.4%); T4, 15 (23.4%); N stage: N0, 9 (14.1%); N1, 22 (34.4%); N2, 22 (34.4%); N3, 11 (17.2%); Overall stage: I, 1 (1.6%); IIA, 3 (4.7%); IIB, 14 (21.9%); III, 22 (34.4%); IVA, 13 (20.3%); IVB, 11 (17.2%); Nonkeratinizing squamous cell carcinoma or undifferentiated carcinoma, 63 of 64; Advanced primary tumors, 30; T3, 15; T4, 15; Nodal metastases, 55 (86%); Stage III/IV disease, 72%; Chemotherapy: Neoadjuvant, 14 (21.9%); Concurrent, 38 (59.4%); None, 12 (18.8%); tumor volume, 62.6 cm3 (range 21.1-145.3)	none reported; NOTE: Chest CT and bone marrow biopsy were not routine, but were selectively performed when there was a suspicion of lung metastasis after chest radiography or an abnormal blood count was noted	F/U: Follow-up after treatment: monthly for the first 3 months; every 2-3 months to the end of the 2nd year, and every 6 months thereafter. Median follow-up 31 months (range 22-54).	the 85% isodose contour (range 75-90%); Mean prescribed dose, 12.8 Gy (range 12.0-15.0); Mean maximal dose, 15.0 Gy (range 13.3-18.3); Mean minimal dose, 11.1 Gy (range 9.1-14.0); Mean treatment isodose, 83.5% (range 75.0-90.0); For SBRT boost specifically: Mean target volume, 62.6 cm3; Percentage of target receiving 95% of the prescribed dose, 98.4% (range 88.4-100);		(60.9%); grade 3, 23 (35.9%); grade 4, 0; Nausea/vomiting, grade 0, 13 (20.3%); grade 1, 20 (31.2%); grade 2, 19 (29.7%); grade 3, 12 (18.7%); grade 4, 0; Weight loss, grade 0, 14 (21.9%); grade 1, 35 (54.7%); grade 2, 15 (23.4%); grade 3, 0; grade 4, 0; Skin reaction, grade 0, 0; grade 1, 26 (40.6%); grade 2, 32 (50.0%); grade 3, 6 (9.4%); grade 4, 0. Late toxicities: 3 patients with initial large T3 or T4 tumors developed sudden onset of massive nasal bleeding 6-7 months after therapy and died soon after; exact cause of massive bleeding was difficult to determine; authors deduced that tumor invasion into the wall of great vessels and caused a wall rupture after tumor cell regression coupled with poor regeneration of the supporting tissue; except for the afore mentioned bleeding fatalities, there were no severe radiation-related late complications.	
Hara (2008) Case Series **Head and Neck Cancer**	n = 82 Nasopharyngeal carcinoma, metastatic 61 men, 21 women;	Newly diagnosed nasopharyngeal cancer treated with definitive radiation therapy and planned SRT	SRT boost 2-6 wks after EBRT; 33 patients treated by frame-based approach with	Median dose 11 Gy (7-15); median of 1 isocenter (1-4); median of 27 days to SRT after EBRT (5-128)	n/a (no control or comparison group)	4 patients (4.9%), transient facial numbness; 0 patients, permanent cranial nerve deficits; 3 patients (3.7%), retinopathy (1 patient had diabetes); 1 patient (1.2%), carotid aneurysm in EBRT neck field 24	Poor Potential conflict of interest, small

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	median age 44 yrs (14-80); median Karnofsky performance status of 90 (60-100); 4% Stage IIA, 16% Stage IIB, 24% Stage III, 35% Stage IVa, 21% Stage IVb; median tumor volume in frameless patients of 34.2 cm3 (6.4-102.2)	boosts	conventional linear accelerator, 49 patients underwent frameless SRS using CyberKnife F/U: Clinical exam every 2 mos for first 2 yrs, then at longer intervals; MRI scans 3 mos after SRT boost, then 1-2 times per year for at least 2 yrs; annual chest radiographs, blood chemistry panels, thyroid function tests; median follow-up for living patients 40.7 mos (6.5-144)			mos after treatment; 10 patients (12.2%), temporal lobe necrosis by radiography, 8 patients asymptomatic, 2 had seizures	number of patients, study conducted over long time frame (1992-2006) so technology used may have changed over time
Rwigema (2010) Case Series **Head and Neck Cancer**	n = 85 Squamous cell carcinoma of head and neck, Primary, metastatic, recurrent	Inclusion: Recurrent, unresectable head and neck cancer; previously irradiated; age ≥	SBRT with Cyberknife-SRS and Dynamic Tracking System or Varian Trilogy IMRS for 30-120	Median SBRT dose 35 Gy (15-44); median fraction size 8 Gy (4-18)	n/a (no control or comparison group)	Most toxicities were grade 1 or 2; 4 patients (4.7%), grade 3 toxicities consisting of 2 patients (2.4%) with xerostomia, 1 patient (1.2%) with grade 3 pain, and 1 patients (1.2%) with dysgeusia; 0	Poor Retrospective study

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	64 men, 21 women; median age 65 yrs (39-88); median tumor volume 25.1 cm3 (2.5-162 cm3); mix of local, regional, locoregional, and distant recurrence	18 yrs; Karnofsky performance score ≥50; previously treated with standard therapies; Exclusion: Cyberknife-SRS as planned boost after radiation therapy; no prior radiation therapy; nonsquamous cell histologies	mins per fraction, fractions every other day (except for weekends and holidays) F/U: Follow-up at 1 mo, then every 3 mos; median follow-up for all patients of 6 mos (1.3-39)			patients, grade 4 or 5 toxicities; late complications: all late toxicities were grade 1 or 2; overall rate of acute and late grades 1 to 3 toxicity did not differ by low dose (<35 Gy) or high dose (≥35 Gy).	
Rwigema (2011a) Case Series **Head and Neck Cancer**	n = 96 Squamous cell carcinoma of head and neck, Primary, metastatic, recurrent 70 men, 26 women; mean age 66.0 yrs, median age 67 yrs (39-88); median gross tumor volume 24.3 cm3 (2.5-162 cm3)	Inclusion: Recurrent, unresectable, previously irradiated cancer; age ≥ 18 yrs; Karnofsky performance score ≥50; previously treated with standard therapies; Exclusion: Cyberknife-SRS as planned boost after radiation therapy; no prior radiation therapy;	SBRT with Cyberknife-SRS and Dynamic Tracking System (n=85) or Varian Trilogy IMRS (n=11) for 30-120 mins per fraction, 2-3 times per week F/U: Follow-up at 1 mo, then every 3 mos; median follow-up for all patients 14 mos (2-39)	92 patients received fractionated SBRT (2-5 fractions); 4 patients receive single-dose SBRT; Group I (15-28 Gy), Group II (30-36 Gy), Group III (40 Gy), Group IV (44-50 Gy); median SBRT dose 35 Gy (15-50); for fractionated SBRT median fraction size 8 Gy (4-10)	n/a (no control or comparison group)	Acute toxicities: 36 patients (37.5%), grade 1; 17 patients (17.7%), grade 2; 5 patients (5.2%), grade 3; grade 3 toxicities consisted of 1 patient (1.0%) with dysgeusia, 2 patients (2.1%) with dysphagia, and 2 patients (2.1%) with xerostomia; Late complications: 16 patients (16.7%), grade 1; 9 patients (9.3%), grade 2; 3 patients (3.1%), grade 3; grade 3 toxicities consisted of 2 patients (2.1%) with dysphagia, 1 patient (1.0%) with fibrosis	Poor Retrospective study

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
		failure to complete prescribed treatment; nonsquamous cell histologies					
Unger (2010) Case Series **Head and Neck Cancer**	n = 65 Head-and-Neck Cancer, Secondary primary (9) or recurrent (47) 43 (66%) men; Median age, 63 years (range 22-91); Histology: Squamous cell carcinoma, 54 (83%); Adenoid cyctic carcinoma, 4 (6%); Adenocarcinoma, 2 (3%); Acinic cell carcinoma, 2 (3%); Sarcoma, 1 (2%); Pleomorphic adenoma, 1 (2%); Esthesioneuroblastoma, 1 (2%); Initial treatment: Surgery, 37 (57%); Chemotherapy, 36 (55%); Disease presentation: Recurrence, 47 (72%); Second primary, 9 (14%); Persistent, 9 (14%); Median interval between initial radiation and SRS, 26 months (range 2-318);	Inclusion criteria: Recurrent, second primary, or persistent cancers of the head and neck after previous RT; all patients had histologically proven disease within previous radiation fields; Exclusion criteria, none reported	CyberKnife SRS system with a 6-MV X-band linear accelerator mounted on a fully articulated robotic arm; no comparator F/U: Post-treatment surveillance FDG-PET/CT scan and/or MRI scan, clinical examination with laryngoscopy (with biopsy as indicated) 2-3 months after SRS completion and every 6 months thereafter; median follow-up 16 months.	Standard dose, 30 Gy in 5 fractions, individualized by treating physician (37 patients received this scheme); Median radiation dose, 67 Gy (range 32-120); Dosimetric parameters: SRS dose, 30 Gy (range 21-35): BED10, 48 Gy (range 22-60); BED8, 53 Gy (range 24-66); BED 6, 60 Gy (range 27-76); BED3, 90 Gy (37-120); SRS dose per fraction, 6 Gy (range 4-12); Number of SRS fractions, 5 (range 2-5); Cumulative BED3, 189 (127-298); SRS treatment	n/a (no control or comparison group)	RTOG grade 1-3 acute toxicity: 19 patients (29%); mucositis/dermatitis/nausea(transient and resolved with conservative management). RTOG grade 4 acute toxicity; 0. Death: 1 patient (unknown causes, 2 weeks after completion of reirradiation; considered treatment-related; initial radiotherapy dose: 67 Gy, SRS dose: 25 Gy in 5 fractions plus concurrent chemotherapy; time interval between initial radiation therapy and reirradiation, 7 months). Severe late radiation-induced toxicity: 6 (9%); soft tissue necrosis requiring debridement 1 patient (oropharynx), grade 4, 6 months after SRS, initial radiotherapy dose: 67 Gy, SRS dose: 30 Gy in 5 fractions; time interval between initial radiation therapy and reirradiation, 106 months; pharyngocutaneous fistula, 1 patient (oropharynx), grade 4, 6 months after SRS, initial radiotherapy dose: 119 Gy, SRS	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Two groups: Definitive treatment, 38 patients whose known locoregional disease was within the reirradiated volume and who did not have evidence of metastatic disease; Palliative treatment, 27 patients who had metastatic disease and/or untreated locoregional disease at the time of retreatment; Patients in this group were treated for palliation of symptoms or to reduce future morbidity associated with disease progression; Surgery before reirradiation: Complete resection, 4; Positive margins, 5; Tumor debulking or regrowth, 10; Chemotherapy with reirradiation: Concurrent, 21; Induction + concurrent, 6; Concurrent + adjuvant, 8; Reirradiated sites: Oral cavity, 3; Oropharynx, 13; Nasopharynx, 7; Paranasal sinus, 7; Infratemporal fossa/base of skull, 6; Hypopharynx, 8; Parapharyngeal space, 6;			duration, 7 days (range 3-29); Target volume, 75 cm3 (range 7-276); Prescribed isodose line, 75% (range 60-90); Conformality index, 1.66 (range 1.12-2.74); Dmax:Dmin ratio, 1.61 (range 1.16-4.31); Gradient index, 3.40 (range 2.45-9.23); Maximum dose to critical structures: Spinal cord, 9 Gy (range 3-21); Brainstem, 16 Gy (range 4-37); Optic nerve, 15 (range2-58)		dose: 30 Gy in 5 fractions plus concurrent chemotherapy; time interval between initial radiation therapy and reirradiation, 16 months; Dysphagia requiring long-term feeding tube and hospitalization, 1 patient (oropharynx), grade 4, 3 months after SRS, initial radiotherapy dose: 56 Gy, SRS dose: 30 Gy in 5 fractions plus concurrent chemotherapy; time interval between initial radiation therapy and reirradiation, 24 months; Arterial bleeding requiring embolization, 1 patient (oropharynx), grade 4, 12 months after SRS, initial radiotherapy dose: 70 Gy, SRS dose: 30 Gy in 5 fractions; time interval between initial radiation therapy and reirradiation, 130 months; Dysphagia, cranial neuropathy, and trismus, 1 patient (nasopharynx), grade 4, 5 months after SRS, initial radiotherapy dose: 70 Gy, SRS dose: 30 Gy in 5 fractions; time interval between initial radiation therapy and reirradiation, 16 months; Arterial bleeding requiring embolization, 1 patient (oropharynx), grade 4, 10 months after SRS, initial	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Neck, 7; Parotid, 7; Dermal, 1.					radiotherapy dose: 60 Gy, SRS dose: 30 Gy in 5 fractions plus concurrent chemotherapy; time interval between initial radiation therapy and reirradiation, 18 months	
Wu (2007) Case Series **Head and Neck Cancer**	n = 90 pts (94 lesions) Nasopharyngeal Carcinoma, Primary (34) and recurrent (56); Also, 3 patients had distant metastases at the time of local relapse Disease spread: Confined to nasopharynx, 46; Extended beyond nasopharynx, 44; Lesion numbers: Single lesion in primary site at time of relapse, 87; Multiple lesions, 3; Median tumor volume, 5.7 mL (range 0.8-24.7); Median maximal diameter, 3.4 (range 1.8-6.2 cm); More than one site of disease: 9 patients. Persistent disease (local relapse at < 6 months of primary RT), 34 (38%): 27 men (79%) and 7 women; Median age, 43 (range 13-	Inclusion criteria: Patients with locally persistent or recurring nasopharyngeal carcinoma treated with fSRT; histologic proof of local failure before fSBRT, except those with lesion located in inaccessible sites such as pharyngeal space, base of skull, or cavernous sinus and were treated based on radiologic evidence of relapse; reported; institutional practice was to use fSRT for nasopharyngeal carcinoma where	fSRT (Creat, China) with a modified 8-MV linear accelerator (Elekta, Sweden) NOTE: Axial contract-enhanced CT scans with a slice thickness of 3 mm was used for treatment planning; MRI and PET scans were not routinely used because of limited resources F/U: Patients were regularly followed every 3 months after fractionated stereotactic	Median primary radiation dose: Persistent disease, 70 Gy (range 50-86); Recurrent disease, 70 Gy (range 60-80); Fractions: 1 fraction per day, 2-3 fractions per week, with an interfractional interval of at least 1 day; Target volume defined as abnormal contrast-enhanced mass plus a margin od ~2-3 mm; Target volume covered by 1 (92%) or 2 (8%) isocenters using 4-6 arcs with a degree of 30-150; Collimator size range: 20-50 mm; Dose prescribed to	n/a (no control or comparison group)	All patients were able to complete the scheduled fSRT; Acute complications: Treatment was well-tolerated with no significant acute complications; Severe late complications: 17 (19%); 8.8% (3/34) in persistent disease; 25% (14/56) in recurrent disease; Severe late complications in persistent disease group: Temporal lobe necrosis, 3; Severe late complications in recurrent disease group: Temporal lobe necrosis, 3; Nasopharyngeal mucosal necrosis, 6 (7%); developed 2-12 months after treatment; Massive hemorrhage in the nasopharynx, 2 (2%); developed at 9 months after treatment; both patients died of this complication; Brainstem necrosis, 3 (3%); confirmed by MRI a 5, 10, and 21 months after treatment (In one of these patients, fSRT was used to treat a tumor abutting the brain stem and the complication was considered	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	70); WHO histologic type: I, 0; II, 5; III, 29; rT stage: rT1-2, 13; rT3-4, 21; Main site of local relapse: Nasopharynx, 20; Parapharyngeal space, 7; Skull base, 4; Sphenoid sinus, 2; Cavernous sinus, 1; Intracranial, 1; Other, 4; Previous treatments: Primary radiotherapy of 60-74 Gy, 25; Primary radiotherapy of 70-74 Gy followed by boost dose of 6-12 Gy using 2-dimensional technique, 7 (T4 disease); Primary radiotherapy of 50-60 Gy followed by boost dose of 15-18 Gy in 3 fractions using intracavitary brachytherapy of fractionated stereotactic radiotherapy, 2 (T2 disease); Median tumor diameter, 3.6 cm (range 1.8-5.7); Median tumor volume, 6.2 cc (0.8-17.3); ; Recurrent disease (local relapse beyond 6 months after primary RT), 56 (62%): 45 men (80%) and 11 women; Median age,	tumor size was ≤4 cm in longest diameter.	radiotherapy; CT or MRI of the nasopharynx was performed at 3 months after fractionated stereotactic radiotherapy, then annually for 3 years; Nasopharyngoscopy was routinely performed during follow-up visits; Chest X-rays and ultrasounds of abdomen were performed annually; Median follow-up times after fSRT: For all patients: 20.3 months (range 3.1-77.5); For survivors, 25.3 months (range 4.9-77.5)	90% of isodose line (range 55-90%) in 90% of patients; Group-specific treatment parameters: Persistent disease: Median total prescribed dose, 18 Gy (10-24); Median fractional dose, 6 Gy (range 4-8); Median fraction number, 3 (2-4); Median biologically effective dose, 23 Gy (range 15-43) ; Recurrent disease: Median total prescribed dose, 48 Gy (12-49); Median fractional dose, 8 Gy (range 5-10); Median fraction number, 6 (2-8); Median biologically effective dose, 79 Gy (range 19-86);		to be related to the treatment; the other 2 patients had 2 courses of RT before fSRT at the time of analysis). Time range of development of temporal lobe necrosis after treatment for both disease groups, 5-63 months	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	48 (range 29-69); WHO histologic type: I, 1; II, 7; III, 48; rT stage: rT1-2, 38; rT3-4, 18; Main site of local relapse: Nasopharynx, 35; Parapharyngeal space, 7; Skull base, 10; Sphenoid sinus, 1; Cavernous sinus, 8; Intracranial, 4; Other, 0; Previous treatments: Treated for 1st local recurrence, 51; Treated for 2nd local recurrence, 5; Median time interval between completion of 1st or 2nd course of RT and start of fSRT: 23 months (range 6-109); fSRT as definitive treatment for local failure, 49; 36-64 Gy of reirradiation by conventional radiotherapy followed by fSRT as a boost, 7; Also received chemotherapy (Cisplatin + 5-FU ± paclitaxel before or after or concurrent with fSRT), 17; Median tumor diameter, 3.4 cm (range 2.0-6.2); Median tumor volume, 5.1 cc (1.3-24.7)						

Ocular

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Al-Wassia (2011) Case Series **Ocular Melanoma**	n = 50 Choroidal melanoma 18 men, 32 women; median age 69 yrs (30-92); 4% AJCC Stage T1, 96% Stage T2; median tumor height 4 mm (1-9.70; median tumor volume 270 mm3 (19-721); 84% had medium-size lesions, 16% had small-size lesions	Juxtapapillary choroidal melanoma tx'd by SRT; small or medium lesions (by COMS classification); lesion localized ≤2 mm from optic disc; Exclusion: echographic extrascleral extension or metastasis	LINAC-based fractionated SRT F/U: median 29 mos (1-77)	54-60 Gy in 9-10 daily fractions	n/a (no control or comparison group)	Complications: 12 patients (24%), dry eye; 10 patients (20%), neovascular glaucoma; 12 patients (24%), optic neuropathy; 25 patients (50%), radiation retinopathy; 8 patients (16%), cataract; 1 patient (2%), optic neuritis; Actuarial complication rate (2 yr, 5 yr): 9.3% and 46.9%, dry eye; 18% and 38%, neovascular glaucoma; 11% and 54%, optic neuropathy; 33% and 88%, radiation retinopathy; 12% and 53%, cataract. Enucleation performed in 3 patients (6%) due to local progression in 1 patient and symptomatic complications (ocular hemorrhage, neovascular glaucoma) in the other 2 patients.	Fair Retrospective
Dieckmann (2007) Case Series **Ocular Melanoma**	n = 158 Uveal melanoma mean age 59.5 yrs (range 21-89); 92 men, 66 women; initial tumor volume 329 mm (34-1950); 93% tumors >3 mm thickness	1) Tumors thicker than 7 mm OR 2) posterior pole tumor smaller in thickness (but >2.5 mm) but with central margin w/in 3 mm to optic disc rim or macula	arc beam SRT with 4-7 arcs per isocenter or static conformal SRT with 8-12 beams using linac with 6 M Follow-up at 1 mo after SRT, event 3 mos for 2 yrs, then every 6 mos;	5 fractions of 12 or 14 Gy	n/a (no control or comparison group)	Acute side effects: 8 patients (5%), bleopharo-conjunctivitis; 5 patients (3%), cornea-epithel-defects; 8 patients (5%), epitheliolysis; 9 patients (6%), madarosis; side effects more common if tumor was anterior; Long-term side effects: 65 patients (41%), opticopathy with median time to occurrence of 27 mos; 70 patients (44%), retinopathy with median time to occurrence of 23 mos; 23 patients (7%), neovascular glaucoma after median time 24 mos; 30 of 127 patients (23%) had newly developed	Poor Unclear whether retrospective or prospective

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			median 33.4 mos (3-85)			cataract 2-4 yrs after SRT and in 19 of 61 patients (31%) a cataract operation has been performed; Enucleation performed in 23 patients (14%) after median of 24 mos (5-87) for tumor progression (2 patients) or neovascular glaucoma, secondary glaucoma, or total retinal detachment (21 patients).	
Emara (2004) Case Series **Ocular Melanoma**	n = 28 Choroidal melanoma 19 men, 9 women; median age 62 yrs, mean age 61 yrs; median tumor height 4.6 mm (2.2-9.1); median maximum tumor diameter 9.4 mm (4.7-17.0)	Inclusion criteria: juxtapapillary choroidal melanoma; located ≤2 mm of optic nerve; tx'd with SRT; Exclusion criteria: metastasis	SRT using Varian linear accelerator and 6 MV photons F/U: Follow-up at approximately 3-6 mo intervals; median f/u 18.5 mos (5-37)	70 Gy as 5 fractions, every other day, over 10 days; median total dose delivered to tumor apex 73.78 Gy (58.71-76.65)	n/a (no control or comparison group)	Harms incidence at 18 mos in 28 patients: 29%, cataract w/ onset at 8-37 mos; higher frequency of cataracts associated with higher radiation dose to lens (P=0.02); 45%, tumor vasculopathy; 30%, radiation retinopathy; 37%, optic neuropathy w/ onset at 2-26 mos; 20%, neovascular glaucoma w/ onset at 9-15 mos; trend toward higher rate of neovascular glaucoma when V70 was greater (P=0.055); cumulative number (and percentage) of complications was 4 patients (14%) for neovascular glaucoma; 9 patients (32%) for cataracts; 11 patients (39%) for optic neuropathy; 13 patients (46%) for retinopathy; 6 patients (21%), vitreous hemorrhage w/ onset at 3-20 mos post-tx; 6 patients (21%), developed or had worsening of retinal detachment at 3-9 mos; 2 patients (7%), corneal ulceration at 6 or 23 mos; 2 patients (7%), localized alopecia; 1 patient	Poor Retrospective, small sample size

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
						(3.6%), punctal canalicular stenosis; enucleation required in 4 patients (14.3%) due to tumor recurrence (2 patients) or neovascular glaucoma (2 patients), median time to enucleation 15 mos.	
Krema (2009) Case Series **Ocular Melanoma**	n = 64 Choroidal melanoma 36 men, 28 women; median age 63 yrs; median tumor height 4.2 mm (1.5-11); median largest basal diameter 9.8 mm (4.7-17); 3 patients had pre-existing primary open-angle glaucoma	Inclusion criteria: Juxtapapillary choroidal melanoma, tx'd with SRT; Exclusion criteria: metastases	SRT using Varian linear accelerator and 6 MV photons or Elekta Synergy S linear accelerator and 6 MV photons F/U: median 37 mos (6-106)	70 Gy in 5 fractions, every other day, over 10 days; median of maximum tumor doses 74.6 Gy (47.2-78.6); median of minimum tumor doses 70.2 Gy (40.7-74.7)	n/a (no control or comparison group)	Actuarial rates of complications at 37 mos: 27 patients (42%), neovascular glaucoma; 34 patients (53%), radiation cataract; 52 patients (81%), retinopathy; 41 patients (64%), optic neuropathy; 51 patients (80%), tumor vasculopathy; 21 patients (33%), vitreous hemorrhage; 9 patients (14%), worsening of retinal detachment; 10 patients (16%) had to undergo enucleation due to tumor recurrence (4/10) or neovascular glaucoma (6/10). A higher rate of neovascular glaucoma was associated with greater lens minimum dose (P=0.001); no other BL factors were significantly predictive of higher complication rates.	Poor Retrospective study, small sample size
Modorati (2009) Case Series **Ocular Melanoma**	n = 78 Uveal melanoma 37 men, 41 women; median age 64 yrs (IQR 58-71); median tumor thickness 6.1 mm (IQR 4.7-8.8)	Previously untreated uveal melanoma, tumor thickness ≥3 mm, eligible for brain MRI	SRS with Leksell Gamma Knife Follow-up 1 day after SRS, then at 1, 3, 6 mos, then every 6 mos;	Median margin dose 35 Gy (IQR 35-40) delivered in single session	n/a (no control or comparison group)	Acute complications: Few acute ocular complications; most frequent were minor cutaneous bleeding and subconjunctival hemorrhage due to sutures (no frequency data provided). Early side effects due to SRS were transient retinal hemorrhages on tumor surface. Subsequent complications (not defined): exudative	Fair Retrospective review, small sample size

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			median 31.3 mos (IQR 17.6-60.6)			retinopathy (33.3%); neovascular glaucoma (18.7%); radiogenic retinopathy (13.5%); vitreous hemorrhages (10.4%); radiogenic optic neuropathy (15.5%); cataract (6.2%); bulbar phthisis (2.0%). Enucleation conducted for 8 patients (10%) due to tumor recurrence in 4 patients and subsequent ocular complications (recalcitrant pain, neovascular glaucoma, phthisis bulbi) in 4 patients. (Note: only reported frequency rates b/c number of patients wasn't adding up correctly).	
Muller (2009) Case Series **Ocular Melanoma**	n = 72 Uveal melanoma mean age 62 (28-82)	Patients with Uveal melanoma treated at clinic between 1999-2006 who gave consent for study Patients with Uveal melanoma treated at clinic between 1999-2006 who gave consent for study	all treated with fractionated stereotactic radiotherapy; attempting to determine whether a dose-volume relationship exists between a radiated lacrimal gland and the development of dry eye syndrome (DES) and	total dose 50 Gy in 5 fractions on 5 consecutive days	n/a (no control or comparison group)	17 patients (23.6%) developed Shirmer test results <10mm at six months following treatment or later. 9 patients (12.5%) developed DES	Fair

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			whether a dose constraint can be established F/U: Followed at 3, 6 and 12 weeks, then every 3 months for a year and every 4 months after that. Median follow-up 32 months (6-74)				
Somani (2009) Case Series **Ocular Melanoma**	n = 64 Choroidal melanoma 36 men, 28 women; median age 63 yrs; median tumor height 4.2 mm (1.5-11.0); median maximum tumor diameter 9.8 mm (4.7-17.0)	Inclusion criteria: Juxtapapillary choroidal melanoma, located ≤2 mm of optic nerve; tx'd with SRT; Exclusion: metastases	SRT using Varian linear accelerator and 6 MV photons or Elekta Synergy S linear accelerator and 6 MV photons F/U: median 26 mos (6-72)	70 Gy in 5 fractions, every other day, over 10 days	n/a (no control or comparison group)	Harms incidence at 26 mos in 64 patients: 29 patients (45%), cataract, developed at median of 18 mos; higher rate of cataract formation associated with greater lens minimum dose (P=0.02); 53 patients (83%), tumor vasculopathy; 51 patients (80%), radiation retinopathy developed at median of 15 mos; higher rate of radiation retinopathy associated with greater V70 (P=0.01); 33 patients (52%), optic neuropathy, median onset 29 mos; 18 patients (28%), neovascular glaucoma at median 20 mos; higher frequency of neovasuclar glaucoma associated w/ greater lens minimum dose (P=0.001); 17 patients (27%),	Poor Retrospective, small sample size

Individual studies (published after review)							
Reference Study Design Malignancy	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
						vitreous hemorrhage; 9 patients (14%), worsening of retinal detachment; 7 patients (11%) required enucleation, 3 due to tumor recurrence, 4 due to painful neovascular glaucoma. Visual acuity significantly declined after RT (P<0.0001); decline in visual acuity was not associated with V70, but was significantly correlated with distance of tumor to foeal avascular zone (P=0.004).	

Lung Cancer

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Chi (2010) Systematic Review **Lung cancer**	35 studies detailing clinical outcome from 2002-2009. Included primarily medically inoperable stage I tumors early stage NSCLC number of pts in each study was listed a table but no total number was provided; number in individual studies varied from 31 to 257. median pt age from 60 to 78 yrs	SBRT F/U: median follow-up varied from 11 to 90 mo Dose: dose varied from 15 Gy in 1 fraction to 70 Gy in 10 fractions. Dose fractionation schedules such as 45 Gy/3 fractions, 60-66 Gy/3 fractions, 40 Gy/4 fractions and 50-60 Gy/5 fractions were commonly used in these studies	Stage I NSCLC, the reported local control was above 80% at 1–5 years, 3- and 5-year OS)and DSS 57.67 ± 15.97% and 45.29 ± 20.10%, and 72.01 ± 11.96% and 56.89 ± 16.27%, respectively	Acute toxicity was mostly mild w/ a sig # of pts w/o any signs of adverse effects during the course of tx. Common toxicities are RP, esophagitis, skin reactions, chest wall pain and general malaise, such as fatigue. However a sig # of pts developed pneumothorax requiring chest tube placement when fiducial markers were placed for CyberKnife SBRT. Reported grade > 3 late toxicity is mainly pulmonary, such as RP, chest (inter-costal) pain, and rib fx; chest pain and rib fx usually associated w/ tumors close to chest wall (Onishi 2007, Lagerwward 2008, Onimaru 2003, Wulf 2004, Van der Voort Van Zyp 2009) The reported grade > 3 late toxicity was 0-28% but 0% to <10% in most studies. Grade 5 toxicity was reported in 6 studies, mainly pulmonary (Fakiris 2009, Uematsu 2008, Le 2006, Song 2009, Inoue 2009). Most grade 5 toxicity was reported in the Indiana phase II trial (Fakiris 2009, Timmerman 2006) where pts were tx w/ 60 Gy or 66 Gy in 3 fractions prescribed to the PTV periphery. 5 (initially 6) tx-related deaths were reported at 4 yrs after SBRT, occurring 0.6-19.5 mo after SBRT tx. All were related to pulmonary toxicity and tumor proximity to the	Poor No quality assessment of studies could be found in the review

				major airways. Initial analysis had hilar/pericentral location as a statistically sig predictor of severe toxicity (p=0.004), and associated w/ an 11-fold increase risk of toxicity compared w/ more peripheral locations. In the final analysis, tumor location was not a statistically sig predictor mainly due to small # of pts evaluated. Deaths due to broncho-pulmonary vein fistula, tracheoesophageal fistula, pneumonitis, pleural effusion, and massive bleeding were reported in other studies (Uematsu 2008, Le 2006, Onimaru 2003, Song 2009, Inoue 2009)	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**<u>Outcomes Assessed</u> Main Findings**	**Harms**	**Quality Comments**
Takeda (2011) Cohort **Lung cancer**	n = 217 Lung Cancer - Primary (localized) and metastatic (oligometastatic lung tumors) Metastatic N=34 Primary N=183 Metastatic group: 15 pts with oligometastatic lung tumors from colorectal	Metastatic group: patients with oligometastatic lung tumors who received SBRT; Tumors defined as well-demarcated, solid tumors in the lung that appeared during follow-up after initial treatment for primary cancer. Primary group:	Comparing outcomes of SBRT treatment in metastatic (colorectal or other) vs. primary lung cancer (diagnosed pathologically or clinically). No concurrent chemotherap	Prescribed dose: 80% of maximal dose in planning target volume Total 50 Gy in 5 fractions to the planning target volume periphery.	Tumor control rates (1 yr): 86% for metastatic group, 97% for primary lung cancer Tumor control rates (2 yr): 82% for metastatic group, 93% for primary lung cancer Multivariate analyses (hazard ratios comparing grps) showed that disease (grps defined by source of metastases or method of	10 pts in metastatic group (29%) received adjuvant chemo at some time after SBRT; no pts with localized primary lung cancer received adjuvant chemo. No acute toxicity observed from SBRT. 2 pts (6%) in metastatic grp grade 2 radiation pneumonitis 1 pts (3%) in metastatic grp grade 3 radiation pneumonitis 24 pts (13%) in primary lung cancer grp grade 2 radiation pneumonitis 6 pts (3%) in primary lung cancer grp grade 3 radiation pneumonitis No Grades 4 or 5 radiation pneumonitis observed.	Fair All subjects in study received SBRT (comparison of interest was type or source of lung cancer). Taking that into account, the results seem

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	cancer, 19 pts with metastases from other sites. Among pts with lung metastases from colorectal cancer: median age 61 (range 52-83), 13 (87%) male, 21 tumors total (in group). Among pts with lung metastases from other sites: median age 69 (range 52-83), 14 (74%) male, 23 tumors total (in group). Primary group: 113 pts diagnosed pathologically, 70 diagnosed clinically. Among pts diagnosed pathologically: median age 78 (range 56-82), 84 (74%) male, 115 tumors total (in group). Among pts diagnosed clinically: median age 70 (range 63-92), 45 (64%) male, 73 tumors total (in group).	Received SBRT at same institutions as metastatic group during same time period (with same total dose, schedule, and methods) as metastatic pts	y and SBRT. SBRT performed with dynamic conformal multiple arc therapy technique F/U: Metastatic group with lung metastases from colorectal cancer: median follow-up: 29 months (7-57). Metastatic group with lung metastases from other sites - median follow-up: 15 months (6-103) Primary group		diagnosis for primary cancer).	No other toxicities of grade 3 or above occurred.	reliable.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			diagnosed pathologically - median follow-up: 24 months (6-98). 70 diagnosed clinically. Primary group diagnosed clinically - median follow-up: 18 months (6-75)				
Verstegen (2011) Cohort **Lung cancer**	n = 591 Lung Cancer (Stage I non-small-cell lung cancer) – primary, metastatic, or recurrent All patients (subgroups reported separately below): Median age: 74 Male sex: 355 (60%) Former smoker: 561 (95%) History of COPD: 467 (79%)	Single stage I lung tumor treated between April 2003 and Dec 2010. Exclusion criteria: pts presenting a synchronous dx of a second malignancy.	All patients received stereotactic ablative radiotherapy (SABR). Two groups were compared in results - those who were diagnosed pathologically (N=209) vs. those diagnosed clinically	60 Gy in 3, 5, or 8 fractions within overall tx time of 2 weeks. Fractionation scheme below. Clinically diagnosed tumor (N=382): 3x20Gy(3x18Gy): 157	Median 3 yr overall survival: 53.7% in clinical dx grp, 55.4% in pathological dx grp (no sig diff). Median 3 yr local control: 91.2% in clinical dx grp, 90.4% in pathological dx grp (no sig diff). Median 3 yr regional control: 88.1% in clinical dx grp, 90.3% in pathological dx grp (no sig diff). Median 3 yr distant control: 73.0% in	18 pts (3%) Grade 3-5 radiation pneumonitis 10 pts (2%) rib fractures on follow-up scans 3 pts (1%) Grade 3-5 chest wall pain (No sig diff in harms by dx group)	Fair All patients received stereotactic ablation radiotherapy (SABR) for Stage I lung cancer. Comparisons made between diagnosis groups (pts diagnosed via clinical or

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Mean FEV1 value: 64% of predicted History of prior malignancy: 201 (34%) (of which 50% had lung cancer) Clinically diagnosed tumor (N=382): Median age: 74 (range 47-91) Male sex: 233 (61%) Mean tumor diameter: 28.4mm (range 10-89) Former smoker: 364 (95%) Mean FEV1: 62% (range 16-130) Inoperable tumor: 265 (69%) Pathologically diagnosed tumor (N=209): Median age: 74 (range 47-90) Male sex: 122 (58%) Mean tumor diameter: 34.2mm (range 11-80) Former smoker: 200 (96%) Mean FEV1: 67% (range 18-129)		(N=382). F/U: Routine follow-up with CT at 3, 6, and 12 mo, and routinely thereafter. Mean/median follow-up not reported.	(41%) 5x12Gy(5x11Gy): 150 (39%) 8x7.5Gy: 75 (20%) Pathologically diagnosed tumor (N=209): 3x20Gy(3x18Gy): 49 (23%) 5x12Gy(5x11Gy): 111 (53%) 8x7.5Gy: 49 (23%) All fractionation schemes were prescribed to the planning target volume encompassing 80% isodose &	clinical dx grp, 79.6% in pathological dx grp (no sig diff).		pathological methods). Multivariable analyses used for outcomes, confounders were taken into account (although it's not completely clear which ones).

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Inoperable tumor: 150 (72%)			had biologically effective dose of >100 Gy.			
Andolino (2011) Case Series **Lung cancer**	n = 331 (347 lesions) lung and liver, metastases to chest wall (CW) base number is 347 lesions, not pts, see comments. Median age 71 (25-100), male: female 200:147	all pts tx w/ SBRT from 2000-2008	no intervention discussed; study examines a subset of CW lesions w/toxicity and w/o toxicity F/U: follow-up 1 mo after tx then every 3 mo for 2 yrs, every 6 mo thereafter; median f/u 19 mo	for total cohort: number of fractions 3(2-5), dose per fraction 18 (6-24), total dose: 54 (18-72),	n/a (no control or comparison group)	Toxicity for all lesions (54/347 - 15.7%)/ CW lesions (49/203 - 24.1%) Grade I - 27 (7.7%) in all lesions; 24 (11.8%) in CW lesions; Grade 2 - 24 (6.9%) in all lesions, 22 (10.8%) in CW lesions; Grade 3 2 in ALL/CW lesions; lesions, Grade 4 - 1 in ALL/CW lesions.	Fair The study used lesions, not patients as the denominator ; and narrowed down from 347 lesions to a subset of 79 CW lesions w/toxicity (n=18) or w/o toxicity (n=61);
Andratschke (2011) Case Series **Lung cancer**	n = 92 non-small cell lung cancer, primary median age 70 (60-100), male: female 64:28; median KPS 70	pts w/ histologically proven Stage I NSCLC pts not suitable for surgery for medical or functional reasons	SBRT F/U: during tx, monitored daily for tx-related toxicity; follow-up at	total of 24-25 Gy in 3-5 fractions within a total tx time of 5-12 days	n/a (no control or comparison group)	(no toxicity tables; percentages reported, but not all pt numbers reported) toxicity: Acute sx included fatigue (30.4%), dermatitis (20.7%), shivering (6.5%), nausea (2.2%), hemoptysis (2.2%), dysphagia (1.1%). No acute grade 3-4 toxicity. 12 (13.0%) pts w/ grade 2 and 2 (2.2%) pts w/ clinically relevant	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(60-100) T stage - 31 TI, 61 T2		4-6 weeks then 4, 7, 12 mo, and every 6 mo thereafter; median 21 mo; 59 (64%) pts died by the time of analysis			pneumonitis. 32 (34.8%) pts had radiographic signs of pneumonitis, 25 (27.2%) had increasing dyspnea over time after SBRT w/ 7 (7.6%) pts having grade 3 and 4 pts grade 4 dyspnea. Minor fatigue reported by 23 (25%; grade 1:n=15; grade 2=7); 1 pt had late grade 3 fatigue. 4 (4.4%) pts developed benign pleural effusion and 2 (2.2%) atelectasis. 5 (5.4%) pts had grade 3 thoracic wall pain and 4 (4.3%) had grade w, with 3 (3.3%) developing rib fx. 2 (2.2%) had subcutaneous fibrosis without requiring intervention.	
Baba (2010) Case Series **Lung cancer**	n = 124 NSCLC, primary Stage 1 median age77 (26-89), male: female 84:40;	histologically confirmed NSCLCdxed as T1N0M0 or T2N0M0, WHO performance status <2. If NSCLC dx could not be confirmed w/ transbronchial or CT-guided biopsy, cases were included if FDG-PET findings were positive and tumor size increased during observation size. Pts w/ prior tx excluded.	SBRT F/U: CT performed at 2 mo intervals until 6 mo, and every 2 to 4 mo thereafter; median follow-up period for living pts 26 mo (range, 7-66 mo)	Dependent on size and stage of tumor - for stage 1A w/ tumors of <1.5 cm , 44 Gy in 4 fractions; for larger T1 tumors 48 Gy in 4 fractions. All stage 1B pts: 52 Gy in 4 fractions.	n/a (no control or comparison group)	Toxicity: Grade 1,2,3 radiation penumonitis in 66 (53.2%), 17 (17.7%), and 2 (1.6%) pts respectively. At 3 yrs, cumulative incidence of grade 2 or 3 pneumonitis was 16%, and it was 11% for stage 1A pts tx w/ 48 Gy in 4 fractions and 30% for stage 1B pts tx w/ 48 Gy in 4 fractions and 30% for stage 1B pts tx w/52 Gy in 4 fractions (p=0.02). Other adverse events include: grade 2 esophagitis in 3 (2.4%) pts, grade 1 and 3 pleural effusion in 23 (18.5%) and 1 (0.8%) pt respectively; grade 1 atelectasis in 6 (4.8%); grade 1 pneumothrax in 3 (2.4%), grade 1 and 2 dermatitis in 7 (5.6%) and 6 (4.8%) pts respectively, grade 1 and 2 rib fx in 7 (5.6%) and 1 (0.8%) respectively, grade 1 soft tissue swelling in 6 (4.8%) pts, grade 2 cardiac muscle damage and effusion in 1	Fair See article for discussion re toxicities and dose schedule

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
						(0.8%) pt each. At 3 yrs the cumulative incidence of radiation pneumonitis was 25% in pts w/ central tumors and 13% in pts w/ peripheral tumors (p-0.11)	
Barriger (2012) Case Series **Lung cancer**	n = 251 non-small cell lung cancer, primary, stage 1 median age77 (26-89), male: female 84:40;	histologically confirmed NSCLCdxed as T1N0M0 or T2N0M0, WHO performance status <2. If NSCLC dx could not be confirmed w/ transbronchial or CT-guided biopsy, cases were included if FDG-PET findings were positive and tumor size increased during observation size. Pts w/ prior tx excluded.	SBRT F/U: CT performed at 2 mo intervals until 6 mo, and every 2 to 4 mo thereafter; median follow-up period for living pts 26 mo (range, 7-66 mo)	Dependent on size and stage of tumor - for stage 1A w/ tumors of <1.5 cm , 44 Gy in 4 fractions; for larger T1 tumors 48 Gy in 4 fractions. All stage 1B pts: 52 Gy in 4 fractions.	n/a (no control or comparison group)	Toxicity: Grade 1,2,3 radiation penumonitis in 66 (53.2%), 17 (17.7%), and 2 (1.6%) pts respectively. At 3 yrs, cumulative incidence of grade 2 or 3 pneumonitis was 16%, and it was 11% for stage 1A pts tx w/ 48 Gy in 4 fractions and 30% for stage 1B pts tx w/ 48 Gy in 4 fractions and 30% for stage 1B pts tx w/52 Gy in 4 fractions (p=0.02). Other adverse events include: grade 2 esophagitis in 3 (2.4%) pts, grade 1 and 3 pleural effusion in 23 (18.5%) and 1 (0.8%) pt respectively; grade 1 atelectasis in 6 (4.8%); grade 1 pneumothrax in 3 (2.4%), grade 1 and 2 dermatitis in 7 (5.6%) and 6 (4.8%) pts respectively, grade 1 and 2 rib fx in 7 (5.6%) and 1 (0.8%) respectively, grade 1 soft tissue swelling in 6 (4.8%) pts, grade 2 cardiac muscle damage and effusion in 1 (0.8%) pt each. At 3 yrs the cumulative incidence of radiation pneumonitis was 25% in pts w/ central tumors and 13% in pts w/ peripheral tumors (p-0.11)	Fair See article for discussion re toxicities and dose schedule
Baumann (2008) Case Series **Lung cancer**	n = 57 Stage I NSCLC, primary 54% female, 46% male; mean age: 75 (59-87);	NR	Linac F/U: Median: 23 mo (3-42)	45 Gy in 3 fractions	n/a (no control or comparison group)	No lung-related toxicity: 30%; No side effects: 19%; Grade 1/2: 61% (cough, dyspnoe, pneumonia, pneumonitis, fibrosis, atelectasis, pleural effusion, heart disorder, esophagitis, skin, pain, rib fracture, upper airway infection, fever,	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	median Karnofsky: 80; CVD: 30%; COPD: 70%					nausea, emesis, fatigue); Grade 3: 21% (cough, dyspnoea, penumonia, fibrosis, atelectasis, pleural effusion, heart disorder, pain, rib fracture, fatigue);	
Bradley (2010) Case Series **Lung cancer**	n = 91 Stage I NSCLC Male: 46%, female: 54%; Median age: 71 (31-93); Stage T1: 64%, T2: 24%, T3: 2%; Inoperable for poor performance status 34%, for poor pulmonary function 57%	Inoperable or refusing surgery	Cyberknife F/U: Median: 18 mo (6-42)	Median dose: 54 Gy (30-60) delivered in three fractions of 18 Gy	n/a (no control or comparison group)	3: grade 2 pneumonitis; 1: painful subcutaneous inflammatory reaction adjacent to treated chest wall; 4: rib fracture or chest wall pain; 1: brachial plexopathy	Poor
Brown (2007a) Case Series **Lung cancer**	n = 59 (61 lesions) non-small cell lung cancer, primary median age not calculated (nor is it calculable); youngest 32, oldest are 5 pts in 90-99 age group; male: female 20:41	pts tx for primary NSCLC lesions between Mar 2004 and Mar 2007; excluding those w/ inadequate respiratory reserve, cardiac dysfunction, chronic heart disease, pulmonary hypertension, diabetes w/ severe end-organ damage, vascular disease, general frailty, severe cerebral	Cyberknife image-guided robotic SRS F/U: Pts seen at 1 mo following tx completion, every 3 mo for 2 yrs	total doses ranged from 15 Gy to 67.5 Gy in 1-5 fractions w/ an equivalent dose range of 24-110 Gy normalized tx dose in 2 Gy fractions(α/β = 20 Gy)	n/a (no control or comparison group)	toxicity: (No toxicity tables. Reporting here follows reporting style in the paper) Toxicity occurred in the lung and esophagus, and none were grade 4/5. 3 of 4 cases of RP occurred in the lower lobes and 1 in an upper lobe. In Stage 1A, 3 pts had grade 1/2 RP. One pt had grade 1 esophagitis.	Poor Confounders not addressed, competing interests, reporting style of toxicity

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
		disease, or lesions within 2 cm of proximal bronchial tree or adjacent to the central chest					
Brown (2007b) Case Series **Lung cancer**	n = 95 non-small cell lung cancer or pulmonary metastasis, primary and metastases 57 w/ 58 primary lesions, 31 w/ 46 lung metastases, 7 w/ CKRS boost tx following external beam radiotherapy (EBRT) No pt characteristics table, nor info embedded in article. Only information provided: age range 33-96	pts w/ histologically proven cancer treated between Mar 2004 and Mar 2007, excluding those w/ inadequate pulmonary reserve, severe cardiac dysfunction, chronic heart disease, pulmonary HTN advanced diabetes w/ severe end organ damage, vascular disease, general frailty or severe cerebral disease. Tumors larger than 5 cm excluded. For early stage NSCLC series, lesions w/in 2 cm of proximal bronchial tree adjacent to central chest and pts w/ evidence of mediastinal disease,	Cyberknife (CK)image-guided robotic SRS F/U: Pts seen at 1 mo following tx completion, every 3 mo for 2 yrs	Total doses ranged from 15 Gy to 67.5 Gy delivered in 1-5 fractions w/ an equivalent dose range of 24-110 Gy normalized tx dose in 2 Gy fractions (α/β = 20 Gy)	n/a (no control or comparison group)	Toxicity: (No toxicity tables. Reporting here follows reporting style in the article.) Toxicity occurred in the lung and esophagus, but none of the occurrences were grade 5. 3 of 4 cases of Rpoccurred in the lower lobes and 1 in an upper lobe. 3 pts had grade 1-2 RP and 1 pt who developed grade 3 RP required hospitalization following retreatment of a recurrent tumor. All 4 RP pts had focal pneumonitis corresponding to the area of PTV w/ a time interval of 3-6 mo, resolved w/ tx. Esophagitis developed in 3 pts. Most common side effect was mild fatigue which required no intervention. Other major complications related to the placement of fiducial markers. 5 pts developed pneumothorax, requiring a chest tube and/or hospitalization; 1 of them had cardiac arrest during fiducial placement, successfully resuscitated w/ full recovery and had CK placement. In 2 pts, fiducials moved requiring replacement.	Poor Reporting of patient characteristics, reporting style of toxicities, potential competing interests

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
		pleural or pericardial effusions, or pneumothorax excluded.					
Casamassima (2008) Case Series **Lung cancer**	n = 104 NSCLC or metastases NSCLC (58): men 45, women 13. Metastases (46): men 32 women 14. Primary lung cancer histologic type: SCC (20), Adenocarcinoma (14), others (15), unknown (9)	Pts considered unsuitable for surgery because of comorbid conditions or severely impaired lung function	Elekta Synergy F/U: Median: 13.88 mo (1.37-49.4)	8-26 Gy (median, 15.5 Gy)	n/a (no control or comparison group)	No acute toxicity greater than Grade 1 was observed. 12 pts had signs of acute lung toxicity; 1 pt dysphagia No evidence of late toxicity in any pt.	Poor
Coon (2008) Case Series **Lung cancer**	n = 51 NSCLC, primary (26), recurrent (12) or solitary metastases to the lung from other sites (13) Inoperable due to COPD: 29%, due to previous lung surgery: 10% Median yrs: primary NSCLC (76.5), recurrent (70.5), metastatic (76).	pts with tumor that were surgically inoperable due to existing comorbidities, pts who had previous surgical resection re-presenting with recurrent disease, or pts who refused surgical resection	CyberKnife F/U: Median primary/recurrent: 11 mo (2-24), Median metastases: 12 mo (2-24)	NR	n/a (no control or comparison group)	Grade 2 radiation pneumonitis (1, 2%), exacerbation of preexisting COPD after SBRT (1 pt)	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Tobacco use median (pack years): primary NSCLC (40, range 0-100), recurrent (40, range 30-80), metastatic (50, range 0-100). O2 dependent (n, %): primary NSCLC (8, 31%), recurrent (3, 25%), metastatic (1, 8%)						
Dunlap (2010) Case Series **Lung cancer**	n = 60 primary NSCLC or oligometastatic lesions to the lung Median age 69 yrs (range, 29-88). Median tumor diameter 2.4 cm (range 0.9-9.3), median distance fro	At risk of the development of CW pain and/or rib fracture as defined by lesions within 2.5 cm of the CW receiving a > 20 Gy maximal pt dose to the adjacent CW	Hi-Art Helical TomoTherapy and BrainLAB F/U: performed every 4-6 wks after tx completion, and every 3 months thereafter; median 11.1 mo (range, 3-35)	60 Gy (range, 21-60)	n/a (no control or comparison group)	Grade 1 CW pain (2), Grade 2 CW pain (1), Grade 3 CW pain (17) Rib fractures (5)	Poor F/U times do not match between the table and text. F/U is reported as 11.1 mos in the text, and 9.1 mos in the table
Fritz (2006) Case Series **Lung cancer**	n = 68 lung metastases and stage 1 NSCLC (primary and metastases)	histological confirmation ; < 2 targets, sufficient pulmonary function (FEV 1> 1.0l/s), KPS >60%, no proximity	non-fractionated stereotactic high single-dose RT	standard dose to the epicenter 30 Gy w/ an axial safety	n/a (no control or comparison group)	4 cases of acute grade 1 radiation dermatitis following radiation tx of tumors near the thoracic wall. Otherwise, no symptomatic side effects. At time of 6 mo evaluation, 73% of pts showed characteristics of radiation pneumonitis	Fair Small sample

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Stage 1 NSCLC - 33 pts, lung metastases 25 pts, 31 lesions For NSCLC, median age 72 (59-82), for mets 65 (32-82) Male: female 40:18. For mets pts, tumor origin: 10 NSCLC, 9 rectal, ENT 3, other 3.	to high-risk organs, no signs of mets in other organs. In cases of lung mets, primary tumor under control. Pts w/ mets can be from all primary tumors except those from SCLC or germ cell carcinomas. Radiation exposure to high risk organs <10 Gy, at most planning target volume (PTV) had to be <10Gy, and severe health conditions or technical factors prohibiting surgery or chemo	F/U: All pts reviewed at 6 and 12 wks after tx, further f/u every 3 mo. For NSCLC pts median f/u 18 mo (range 7.7 to 53.4 mo) for mets pts: median f/u 22 mo (range, 6.8 to 63 mo);	margin of 10mm and a longitudinal safety margin of 15mm		on the CT scans, but no pt had to be treated because of pneumonitis. In 8 of 33 pts (24%), w/ NSCLC, CT scans showed pneumonitic alterationsin sites near thorax wall associated with asymptomatic cytologically benign temporary pleural effusions that were of slight volume and disappeared after several mo w/o tx.	
Guckenberger (2010) Case Series **Lung cancer**	n = 59 Primary, recurrent, metastatic median age 67 (43-85.) Primary NSCLC = 21 (35.6%), pulmonary metastases (PM) = 38 (64.4%). primary stage I/II NSCLC, n=15; local	pts tx at clinic between 2005-2008 with SBRT	SBRT F/U: median follow-up 13 months, frequency not noted	3 x 12.5 Gy at 65% (n=40), 1 x 26 Gy at 80% (n=29), 8 x 6 Gy at 65% (n=3), 5 x 6 Gy at 65% (n=2), 3 x 10 Gy at	n/a (no control or comparison group)	radiation-induced pneumonits (RP) grade 2: 11 (16%)	Fair Small sample size at different doses, did not report relationship between outcome and age, sex,

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	recurrence of advanced state NSCLC, n=2; locally advanced primary NSCLC, n=1; cT1-2 cNO cM+ primary NSCLC, n=3; pulmonary metastases, n=54. Mean Karnofsky index for NSCLC pts 70; for PM pts 90.			65% (n=1)			cancer grade
Hiraoka (2007) Case Series **Lung cancer**	n = 147 Primary, metastatic Pts seen between July 1998-Nov. 2005. 79 primary tumors, 53.7%, 54 metastatic, 36.7% Mean age 74 yrs (17-87)	Primary NSCLC: solitary tumor < 4 cm, inoperable or pt refused operation, histologically confirmed malignancy, no necessity for oxygen support, performance status ≤ 2, tumor no close to spinal cord. For metastatic pts: 1-2 tumors < 4 cm each, primary tumor controlled, no other metastasis, no necessity for oxygen support, performance status < 2, tumors not close to spinal cord	SBRT F/U: Follow-up reported for subgroups. For 32 pts with state IA INOMO NSCLC, median follow-up 30 months (6-71). For 13 pts with state IB T2NOMO NSCLC, median follow-up 22 months (6-74). Frequency not reported	in 115 tumors, 48 Gy in 4 fractions in 2 weeks. 27 tumors 60 Gy in 5 fractions. Initial 3 tumors, 40 Gy	n/a (no control or comparison group)	For 32 pts with state IA TINOMO NSCLC, 1 local recurrence (3.1%),4 intrapulmonay recurrence (12.%%), 2 regional lymph node recurrence (6.3%), 1 bone metastasis (3.1%), For 13 pts with stage IB T2NOMO NSCLC, 4 intrapulmonay recurrence (30.8%), 1 liver metastasis (7.7%) and 1 brain metastasis (7.7%). by National Cancer Institute Common Toxicity Criteria, lung toxicity grade II in 4%, grade I in 96% (N for analysis not reported.)	Poor Findings reported only for subgroups, confounding factors not controlled for.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Hoppe (2008) Case Series **Lung cancer**	n = 50 Median age 79 (60-94), males 22, female 28	Pts with early stage NSCLC tx at clinic between May 2006 - Jan. 2008	SBRT F/U: Evaluated at 1 month after tx then every 3 months. Median follow-up 6 months (3-18)	60 Gy in 3 fractions, 36 pts (72%), 44-48 Gy in 4 fractions, 14 pts (28%)	n/a (no control or comparison group)	Skin toxicity: 19 pts Grade 1 (38%), 4 pts Grade 2 (8%), 2 pts Grade 3 (4%), 1 pt Grade 4 (2%). Time to develop Grade 2 or higher toxicity 3-6 wks (median 4 wks).	Fair Did not account for age or describe tumor stage, but did control for variables related to SBRT tx
Matsuo (2011) Case Series **Lung cancer**	n = 101 Primary male 74, female 27, median age 77 (62-87). Type of cancer: adenocarcinoma 49 (48.5%), squamous cell carcinoma 44 (43.6%), large-cell carcinoma 2 (2%), NSCLC not otherwise specified 6 (6%). Median maximal tumor diameter 25 mm (12-43 mm). T-stage: T1a 33 (32.7%), T1b 40 (40%), T2a 28 (27.7%).	Stage 1 lung cancer tx at clinic between Sept. 98 - Dec. 2007., surgery contraindicated or refused, maximal tumor diameter ≤ 40 mm, tumor not adjacent to mediastinal organs (spinal cord, esophagus, heart and main bronchius), pt could remain stable in body frame for 30 minutes with World Health Organization performance status of 0-2, no active interstitial	SBRT F/U: Follow-up at 1,2,4,6,9 and 12 months first year, every 3 months years 2-5 and every 6 months thereafter. Median follow-up 31.4 months (4.2-118.6)	total dose 48 Gy in 4 fractions	n/a (no control or comparison group)	Grade 2 pneumonitis 4 pts (4%), ≥ grade 3 pnemonitis 3 pts (3 %) (one patient grade 5), grade 2 dermatitis 3 pts (3%) and grade 3 dermatitis 2 pts (2%). 4 pts (4%) rib fractures	Fair Analysis accounted for tumor diameter, age, sex, performance status, histology

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
		pneumonia, written consent.					
Milano (2009) Case Series **Lung cancer**	n = 53 Central thoracic lesions age (yrs) 37-88 Stage I (7), stage II (4), stage III (6), recurrent stage III (2), stage IV (oligometastases from NSCLC)(15), stage IV (oligometastases from other primary sites) (19)	Exclusion: pts who had undergone prior radiation to the volume treated with SBRT	Linac F/U: 1-3 mos after radiation, then every 3-6 mos; Median: 10 mo (<1-78)	30 to 63 Gy (mean and median 50 Gy)	n/a (no control or comparison group)	Acute Grade 1 esophageal toxicity (3), Grade 2 (8). No pts experienced Grades 3-5 toxicity. No late esophageal toxicity. Grade 2 radiation pneumonitis (4), acute pneumonia (1), Grades 1-2 hymoptysis (2), Grade 2 pneumonia (2), Grade 3 pneumonia (1), Grade 2 pneumothorax (1) 4 deaths (fatal hemoptysis, progressive disease) Grade 3 pericarditis (1)	Poor
Nambu (2011) Case Series **Lung cancer**	n = 177 stage I-III NSCLC or oligometastatic disease 132 males, 45 females. Mean age 77.3 ± 7.0 yrs (55-92), average tumor diameter 30.0 ± 9.1 mm (8-55 mm)	Pts seen at clinic between Nov. 2001 - April 2009 with primary NSCLC tx with SBRT who consented to study	Computerized tomography after SBRT to check for chest wall injury F/U: Follow-up at 3 and 6 months and then every six months thereafter. Median follow-up 29 months (11-	48 Gy in 4 fractions, 75 pts (42.4%), 60 Gy in 10 fractions, 37 pts (20.9%) or 70 Gy in 10 fractions, 65 pts (36.7%)	n/a (no control or comparison group)	Rib fractures 41 pts (23.2%) at mean follow-up of 21.2 months (4-58). Chest wall edema 45 pts (24.5%) at mean F.U. 12 months (2-57), thinning of cortex 36 pts (20.3%) at 4-36 months, osteosclerosis 26 pts (14.7%) mean F.U. 15 months (4-57), chest wall pain 38 (21.5%)	Poor Did not account for age, sex, tumor stage

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			99)				
Olsen (2011) Case Seroes **Lung cancer**	n = 130 Primary (divided between 3 SBRT tx regimens: Group I: 18 Gy in 3 fractions, 111 pts (85.4%),Group II: 9 Gy in 5 fractions, 8 pts (6.2%) and Group III: 10 Gy in 5 fractions, 11 pts (8.5%)) Characteristics by tx group: Age: Group I: 75 yrs (31-92),Group II: 78 (63-84), Group III: 74 (54-87). Tumor volume: Group I: 8 cm3 (1-124), Group II: 27 cm3 (7-72),Group III: 18 cm3 (1-76). Cancer stage: Group I: T1a: 51 pts (45.9%), T1b: 40 pts (36.0%), T2a: 16 (14.4%), T2b: 3 (2.7%) and T3: 1 (0.9%). Group II: T1a: 1 (12.5%), T1b: 2 (25%), T2a: 4 (50%), T2b: 1 (12.5%). Group III: T1a:	Pts tx at clinic between June 2004 and June 2009 who a) tx for a single lung primary lesion. B) no nodal or metastatic disease. C) no prior malignancy for 2 yrs prior to lung cancer diagnosis. D) received one of 3 tx doses. E) follow-up > 3 months	compared three different doses of SBRT F/U: schedule not provided. Mean follow-up for group I: 13 months, group II: 11 months, group III: 16 months	Group I: 18 Gy in 3 fractions, 111 pts (85.4%),Group II: 9 Gy in 5 fractions, 8 pts (6.2%) and Group III: 10 Gy in 5 fractions, 11 pts (8.5%))	No difference in local control (LC) or overall survival (OS) between tx groups I and III, but both improved LC (p=0.006) and OS (p=0.016) when compared to group II. Tx in group II (9 Gy x 5 fractions) was the only independent prognostic factor for reduced LC on multivariate analysis, and increasing age, increasing tumor size and poor performance status predicted independently for reduced OS.	Chest wall pain 21 pts (16%). Grade 2 radiation pneumonitis 4 pts (3.1%)	Poor Small sample sizes for Group II and II tx regimes; group II pts older and sicker on avg.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	4 (36.4%), T1b: 2 (18.2%), T2a: 4 (36.4%) and T2b: 1 (9.1%).						
Onishi (2011) Case Series **Lung cancer**	n = 87 Primary males 63, females 24. Median age 74 (43-87). Eastern Cooperative Oncology Group performance status 0 = 51 pts (58.6%), 1 = 30 pts (34.5%) and 2 = 6 pts (6.9%). Stage 1A - 64 pts (73.6%) and Stage iB = 23 pts (26.4%). Median tumor diameter 25mm (7-50)	Pts tx between April 1995 and March 2004 at one of 14 Japanese institutions. Pts diagnosed with T1NOMO or T2NOMO primary NSCLC where cancer was operable but pt refused surgery	SBRT F/U: 4 wks after tx and then every 1-3 months. Median follow-up for all pts 55 months, for survivors 63 months.	Varied by tx center. Mean total dose 58.7 Gy (45 - 72.5 Gy) in 3-10 fractions with single doses of 6.25-15 Gy. Median biologically effective dose (BED) 116 Gy (100-141 Gy)	n/a (no control or comparison group)	radiation induced pulmonary complications grade 0: 21 pts (24.1%), grade 1: 61 (70.1%), grade 2: 4 (4.6%) and grade 3: 1 (1.1%). Rib fracture 4 (4.6%). Grade 3 dermatitis: 3 (3.4%) and grade 3 esophagitis: 1 (1.1%)	Poor Accounted for cancer stage and histology but not age or tumor size
Pennathur (2007) Case Series **Lung cancer**	n = 32 Primary (16 pts, 50%), metastatic (5 pts, 15.6%), recurrent (11 pts, 34.4%) Males 19, females 13. Median age 68 (38-82). Primary lung cancer (N=16): stage I: 11 pts (68.8%), stage II: 2	Pts tx at clinic between Dec. 2002-Jan. 2005. Included medically inoperable pts, pts w/failure of other tx including surgery and chemoradiation and pts refusing surgery	SBRT F/U: 3 month intervals	20 Gy in single fraction	n/a (no control or comparison group)	after percutaneous fiducial placement 9 pts (28%) had pneumothorax. One pt admitted for exacerbation of COPD	Poor Heterogeneous group of pts with significant comorbidity not accounted for in analysis, small sample

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(12.5%), stage III: 2 (12.5%), stage IV: 1 (6.2%). Reason for SBRT: poor pulmonary function: 15 (46.9%), increased cardiac risk: 5 (15.6%), failed previous tx: 10 (31.3%), refused surgery: 1 (3.1%) and multiple comorbidities: 15 (46.9%)						size
Peulen (2011) Case Series **Lung cancer**	n = 29 Metastatic, recurrent Males 18, female 11. median age 65 (18-87). Primary tumor: NSCLC 10 (34.5%), colo-rectal carcinoma 7 (24.1%), renal cell carcinoma 6 (20.7%), sarcoma 3 (10.3%), SCLC 1 (3.4%), oesphagus 1 (3.4%) and liver 1 (3.4%)	all pts reirradiated at clinic for lung tumors or lung metastases from 1994-2004	reirradiation with SBRT F/U: median follow-up 12 months (1-97), schedule not reported	several doses, varied by patient. Most common 15 Gy x 2-3 fractions and 8 Gy in 5 fractions	n/a (no control or comparison group)	Atelactasis: grade 1: 3 (10.3%), grade 2: 5 (17.2%); Cough: grade 1: 3 (10.3%), grade 2: 7 (24.1%), grade 3: 3 (10.3%). Dyspnoea: grade 1: 1 (3.4%), grade 2: 6 (20.7%), grade 3: 4 (13.7%). Pnemonitis: grade 2: 3 (10.3%), grade 3: 1 (3.4%). Stenosis of airway: grade 3: 1 (3.4%). Bleeding: grade 5: 3 (10.3%). Pleural effusion: grade 1: 1 (3.4%), grade 2: 5 (17.2%), grade 3: 1 (3.4%). Pulmonary fibrosis: grade 1: 4 (13.8%), grade 2: 7 (24.1%). Fracture: grade 1: 1 (3.4%). Dermatitis: grade 2: 1 (3.4%), grade 3: 1 (3.4%). Hyperpigmentation: grade 1: 1 (3.4%), grade 2: 1 (3.4%). Pain: grade 1: 2 (6.9%), grade 2: 4 (13.8%), grade 3: 1 (3.4%). Mucous production: grade 2: 1 (3.4%). Vena cava superior stenosis grade 4: 1 (3.4%). Fistula grade 4: 1 (3.4%)	Poor Primarily looking at toxicity for reirradiation, controlled for tumor location and radiation dose but not other factors. Small sample size, heterogeneous sample, sicker population
Ricardi (2009) Case Series	n = 60 (63 tumors)	Pts tx at clinic between May 2003	SBRT	15 Gy x 3 fractions	n/a (no control or comparison group)	rated on Radiation Therapy Oncology Group (ROTG) lung toxicity scale. RTOG	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Lung cancer	Primary, metastatic 50 males, 10 females. Median age 71.7 (53-85). 41 primary NSCLC (68.3) and 19 metastases (31.7%)	and June 2006 with stage 1 NSCLC (IA and IB < 5 cm) not operable for medical contraindications or pt refusal or oligo lung metastases ≤ 3, ECOG performance status ≤ 2, and no prior radiation therapy to site of SBRT. Lesions located < 2 cm from major airways or < 1 cm from major blood vessels not eligible for SBRT	F/U: 45 days after tx then every 3 months first year, every six months thereafter. Median follow-up 30.9 months (6.7-56.7)	given to 41 primary tumors and 17 metastatic. 26 Gy in 1 fraction given to 5 metastatic tumors		grade 0-1 pulmonary toxicity in 54/63 lesions (85.7%) and grade 2-3 in 9/63 (14.3%)	Primarily looking at dosage and toxicity. Controlled for mean lung dose (MLD) and tumor location, did not control for other factors
Stephans (2009) Case Series **Lung cancer**	n = 86 (94 lesions) Stage 1 NSCLC Median age: Group 1 (74, range 48-89), Group 2 (72.5, range 49-89). Gender: Group 1 (61% female), Group 2 (48% female). Smoking history (pack-years): Group 1 (53, range 0-140), Group 2 50, range 0-150)	medically inoperable	Novalis F/U: 6-8 wks after SBRT, every 3 mos thereafter Median: 15.3 mo (1.9-47.6)	50 – 60 Gy	n/a (no control or comparison group)	Grade 2 radiation pneumonitis (2); no Grade 3 radiation pneumonitis. grade 1 or 2 chest wall toxicity (9)	Poor
Takeda (2010)	n = 128 (133 tumors)	minimum f/u of 6	NR	50 Gy	n/a (no control or	Grade 1 radiation pneumonitis (69 pts,	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Case Series **Lung cancer**	Lung, primary (111 tumors) and metastatic (22 tumors) Age (yrs) 77 (43-92); Male (93/female(40;	mos or had Grade ≥1 radiation pneumonitis	F/U: monthly f/u for 6 months after study. Median: 12 mo (5-45)		comparison group)	52%), Grade 2 (21 pts, 16%), Grade 3 (7pts, 5%). No Grade 4 RP.	
Taremi (2012) Case Series **Lung cancer**	n = 108 Lung Cancer (Stage I non-small-cell lung cancer) Median age: 72.6 (range 48.3-90) Male sex: 53 pts (49%) Mean tumor size (n=114 tumors in 108 pts) 2.42 cm (+/- 1.14 cm) Tumor size: <3cm=86 of 114 (75%); 3-6 cm=28 of 114 (25%). Previous history of lung cancer: 25 (23%) (mean dx 4.9 yrs before current presentation) Diagnostic pathologic findings available: 80 (75.9%) PET scan before radiotherapy: 88 (81%)	Inclusion criteria: Stage T1-T2N0M0 non-small-cell lung cancer; Eastern Cooperative Oncology Group performance status of 0-3; synchronous early state non-small-cell lung cancer (up to 3 lesions), history of lung or other primary cancer. Cancers identified through biopsy or serial imaging studies.	All patients received SBRT. F/U: Follow-up at 6 wk, then every 3 mo for a yr, then every 6 mo for a yr, then yearly Median FU: 19.1 mo (range 1-55.7)	Most common dose fraction sched: Peripheral lesions=48 Gy in 4 fractions, 54-60 Gy in 3 fractions; Central lesions=50-60 Gy in 8-10 fractions. Fractions delivered a minimum of 48 hours apart.	n/a (no control or comparison group)	Deaths: Of 108 pts, 45 died after tx, 17 (16%) of causes related to treatment. Tx Failure: 38 failures detected in 31 pts (29%) -- 10 local, 11 regional, 17 distant. Toxicity: 77 (71%) experienced any acute toxicity. Most common acute toxicity=fatigue. 75 pts (69%) experienced any late toxicity. 4 pts (4%) had Grade 3 early toxicity (within 3 mo of SBRT) (1 pt with fatigue, 2 pts with dyspena, 1 pt with chest wall pain). 6 pts (6%) had Grade 3 late toxicities (primarily respiratory and fatigue-related). Rib fractures in 16 pts (14.8%) (mostly asymptomatic). No Grade 4 or 5 toxicities reported.	Poor Potential conflict of interest (funding provided by a manufacturer of SBRT equipment)

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	PET scan 3 mo after radiotherapy: 67 (62%)						
Timmerman (2010) Case Series **Lung cancer**	n = 55 Early stage inoperable NSCLC Median age 72 (range, 48-89); race/ethnicity: Asian (2, 4%), black (2, 4%), white (51, 93%); Subrod PS 0 (12, 22%), 1 (35, 64%), 2 (8, 15%)	18 yo or older with Zubrod PS of 0,-2. Cytological or histological proof of NSCLC required. Tumor req'd to be >2cm in all directions Excluded: synchronous malignancy within 2 yrs of entry, history of prior pradiotherpay to the thorax, active systemic, pulmonary or pericardial infection, pregnant or lactating, pts with plans to receive conventional radiotherapy, chemotherapy, biological therapy, vaccine therapy, or surgery, or if pts were operable	Linac Median all evaluable: seen every 3 mos for yrs 1 & 2, every 6 mos until 4 yrs post tx. 34.4 mos (4.8-49.9), Median still living: 38.7 mo (30.2-49.9)	60 Gy (20Gy x 3)	n/a (no control or comparison group)	Grade 3 adverse events (7 pts, 12.7%, 95% CI, 9.6%-15.8%); Grade 4 adverse events (2 pts, 3.6%, 95% CI, 2.7%-2.4%) No Grade 5 tx-related adverse events reported. An additional 6pt reported adverse events (3 pts – complications with skin or ribs).	Fair
Trovo (2010) Case Series	n = 68 (70 tumors)	pts must be treated with SBRT and have	Trilogy	54-60 Gy (59 pts),	n/a (no control or comparison group)	Pleural thickening (30 – first 6 mos after SBRT; add'l 7 pts in 7-12 mos)), pleural	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Lung cancer	Age: 71 (49-93); Male (31), female (27); Race: white (60), black (8), PS: 0 (9), 1 (23), 2 (31), 3 (5); smoker: yes (45), no (23); emphasema: yes (43), no (25)	been followed with chest CT Excluded: pts treated for a relapsing tumor after wedge resection or after conventional radiation therapy	F/U: 6 weeks, 2-6 mo, 7-12 mo, 13-18 mo	45-48 Gy (11 pts)		effusion (4), bronchiectasis (5), radiation fibrosis ; late radiographical injuries including grade 2 lung toxicity (3), Grade 2 pulmonary toxicity (3), grade 2-4 emphysema (23)	
Welsh (2010) Case Series **Lung cancer**	n = 265 (268 tumors) Lung cancer, primary or metastatic Median age: 73 (43-95) Male sex: 142 pts (54%) Median distance between tumor & chest wall: 0.59 cm (range 0-2.47cm) BMI 29 or higher: 66 (22%) Median gross tumor vol: 8.17 mL (0.57-198 mL) Tumor location: posterior thorax N=165 (62%); anterior thorax N=103 (38%)	Inclusion: Pts in institutional database of patients on trial for SBRT at MD Anderson Cancer Center for primary or metastatic lung cancer between 2004 & 2008. Exclusion: pts with centrally located tumors (>2.5 cm from chest wall)	Case series, not a priori hypothesis/comparator. Study sought to identify factors univariately associated with chest wall pain & skin toxicity. F/U: Followed for 1 yr from date of SBRT completion Median follow-up 10.3 mo (range 3-46.6 mo);	95% of planning tx volume (delineated by prescribed isodose line) to 50 Gy delivered in 4 fractions. Median prescribed tumor vol: 69 mL	n/a (no control or comparison group)	Main findings focused on two harms - Skin toxicity and chest wall pain; ascertained from medical records up to 1 yr post tx. Skin toxicity: 104 pts (39%) developed some form of skin toxicity (defined by the NCI-CTCAE V3.0). Unadjusted logistic regression showed association with gross tumor volume and dose). Chest wall pain: 67 pts (25%) developed some form of chest wall pain, including 8 pts with rib fractures. Median time to pain onset=6mo (range 0-11mo). 14 pts (5%) developed acute pain. 45 pts (17%) developed chronic pain, of which 22 were Grade 1 and 23 were Grade 2 or 3. Unadjusted logistic regression showed association between chest wall pain and vol of chest wall receiving 30 Gy (V30) and BMI.	Poor Descriptive study. Unadjusted results do not account for confounding. Case series using previously collected data. Follow-up (mean 11 mo) was short and some outcomes (e.g. rib fx) may occur up to 2-3 yrs post tx.

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
			Mean follow-up 11 mo.				
Yamashita (2010) Case Series **Lung cancer**	n = 117 primary lung tumors (74), metastatic or recurrent lung tumors (43) Males (98(, females (19); median age 72 yrs (range, 28-84) shadow of interstitial pneumonitis before SBRT (13), high serum KL-6 value (23), high SP-D value (19)	solitary or double lung tumors; tumor diameter < 40 mm; no evidence of regional lymph node metastasis; Karnofsky PS ≥ 80%; tumor not located adjacent to major bronchus, esophagus, spinal cord, or great vessels Exclude: pts with active malignancy lesion other than lung	Synergy F/U:f/u performed at 2,4,6,9,12,15, 18, and 24 mos after SBRT Median: 14.7 mo (0.3-76.2)		n/a (no control or comparison group)	Grade 4 or greater radiation pneumonitis (9, 7.7%). Grade 4 RP with intubation (2), other cases Grade 5 RP.	Fair

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
Grutters (2010) Economic study **Lung Cancer**	n = NR non-small cell lung cancer (NSCLC) Based on health states: whether pts were alive and whether they had grade 3 or	conventional radiotherapy, SBRT, particle therapy (carbon ions, protons) F/U: 5-year	Inoperable Stage 1: (sensitivity analysis using studies from 2005) protons (18.124-28.219K) carbon ions (12.293-25.314K)	Inoperable Stage 1: (sensitivity analysis using studies from 2005) protons 2.79 carbon ions 2.72 SBRT 2.58 CRT 2.05	Inoperable stage 1: carbon-ions and SBRT dominated protons and CRT (€67,257) Operable Stage 1 SBRT dominated carbon-ions -	For a ceiling ratio of €80,000, Inoperable Stage 1: carbon-ion tx had the highest probability of	Fair

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
	higher irreversible dyspnea; intermediate states used to represent acute adverse events in first 6 weeks during and directly after RT	perspective	SBRT (9.308-15.603K) CRT (15.961-23.785K) Operable stage 1 NSCLC SBRT (6.497-11.613K) Carbon-ions (10.231-22.694K)	Operable stage 1 NSCLC SBRT 3.20 Carbon-ions 3.16		being cost effective (52%) followed by SBRT (47%), proton therapy (2%) and CRT (0%), in Operable Stage 1: proton tx had a 46% probability of being cost-effective followed by carbon-ion tx (38%), SBRT (16%), and CRT (0%).	
Lanni (2011) Economic study **Lung Cancer**	n = 86 41 EBRT, 45 SBRT NSCLC All had early stage inoperable early stage NSCLC EBRT/SBRT Median age 76(53-85)/76(63-90); male: female EBRT 18(44%)23(56%) SBRT 18(40%) 27(60%), Clinical stage EBRT IA 27(66%), IB 13(32%),	EBRT (3D-CRT), SBRT F/U: 36 months	Actual cost of tx for a lung CA pt treated w/ 3D-CRT ($50,000-$61,000) was higher than SBRT ($41,000-$57,000) when evaluating 4 fractions in the SBRT group. Average billed cost for tx w/ standard fractionated EBRT using 3D-CRT and assuming a total of	Rates of local failure, regional failure, distant metastasis and survival between SBRT or 3D-CRT were compared. With a median potential follow-up of 36 mo, SBRT was associated w/ superior OS, as compared w/ 3D-CRT, 71% (SBRT) vs 42% (3D-CRT)	n/a	n/a	Poor

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
	IIA (1(2%) SBRT IA 32(71%), 12(27%), 1(2%)		35 tx fractions was $55,705 whereas for SBRT was $52,471 (P>0.01). Expected Medicare reimbursement for tx w/ 3d-CRT (35 fractions) was $13,639, whereas for SBRT was $10,616. Also examined cost of tx for single, 3, or 5 fractions. Different fraction regimens resulted in lower costs, especially when comparing the RTOG standard of 3 SBRT fractions (20 Gyx3) to 3D-CRT; cost savings w/ SBRT would be $69222 per pt (p=0.001)	(p<0.049). Not statistically significant (p=0.10 trend), SBRT was associated w/ lower local failure rates as compared w/ 3D-CRT group. 12% (SBRT) vs 34% (3D-CRT), a 3-fold difference. No significant differences in rates of regional failure or distant metastases between the 2 groups			
Sher (2011) Economic study **Lung Cancer**	Markov Model, probability estimates based on single case series data for outcomes NSCLC	3D CRT, SBRT, radiofrequency ablation (RFA) F/U: NED to local	for both one way and two-way sensitivity analyses 3D-CRT $5,000 - $15,000 BRT $10,000 - $20,000 RFA $3,000 -	See ICER column at right and see also article for more detail on cost-effectiveness for SBRT	One-way sensitivity analyses: in almost all scenarios SBRT was the most cost-effective option w/ ICER values generally less than $25,000/QALY. RFA dominated 3DCRT and SBRT when its associated 3-yr risk of local recurrence was only 10%	probability that SBRT was cost-effective at a societal WTP of $50,000/QALY was 70%, and SBRT was cost-effective in the	Poor

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
		recurrence or metastasis 3 yr, NED to nodal recurrence 2 yr, nodal or local recurrence to death 1 yr, distant metastasis to death 1 yr	$12,000 Palliative care $10,000 - $50,000 Non-CA end of life care $10 - $50,000		while keeping the local recurrence risks of SBRT and 3D-CRT at 12% and 37% respectively; Two-way sensitivity analyses for small (T1, 2cm) and large T2 (4cm) primaries: When only size was varied SBRT was cost-effective for both T1 (ICER of SBRT over RFA of $30,400/QALY) and T2 (ICER of SBRT over 3D-CRT of $3,900/QALY).	majority of the trials once the WTP exceeded only $30,000/QALY	

Prostate Cancer

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Friedland (2009) Case Series **Prostate**	n = 112 mean age 69.6 (55-87); mean PSA 6.0 ng/ml, median PSA 5.2 ng/mL; Gleason score of 3+3 in 81 patients and 3+4 in 23 patients; 21 patients had hormone treatment; 79% patients were Stage T1cN0M0 with the remainder at higher stages	Localized prostate cancer, clinical stage T1bN0M0 to T2cN0M0	SBRT with CyberKnife and 6 MV linear accelerator F/U: Follow-up 10 days after SBRT, 1 mo, every 3 mos for 2 yrs, every 6 mos starting yr 3 if PSA stable; median 24 mos	Total of 35 Gy (5 fractions, 7.0 Gy, 5 consecutive days)	n/a (no control or comparison group)	AUA prostate sx questionnaire: mean BL score was 8.9 (mild-to-moderate sx of urinary obstruction), score increased over first month of tx to 12.8, but returned to BL levels by 4 mos; 7 patients (6.3%), urinary obstruction during first month after SBRT; 1 patient (0.89%), required TURP immediately after SBRT; rectal assessment score (RAS): mean BL score 1.8 (minimal to no rectual urgency or stool frequency), increased to 4.6 at 7-10 days post-tx, then declined to BL by 4 mos post-tx; 1 patient (0.89%), Grade 3 rectal bleeding; Sexual Health Inventory for Mean (SHIM): mean BL score of 14.1 (normal to slightly decreased sexual function), scores decrease during tx, but went back to BL within 1 mos post-tx; erectile function retained by 41/50 (82%) patients at 1 yr, 29/36 (81%) at 2 yrs, and 9/11 (82%) at 3 yrs.	Poor Initial series of patients, longer follow-up likely necessary for late toxicity
Katz (2010) Case Series **Prostate**	n = 304 mean age 69.2 (45-88); mean PSA 6.1 ng/mL, median PSA 5.8 ng/mL (range 0.7-27.7); 92% Stage T1cN0M0, 7.9%	Clinically localized prostate cancer	SBRT with CyberKnife F/U: Follow-up 3 wks after SBRT, 4 mos later, and then every 6 mos;	50 patients received 35 Gy (5 consecutive fractions of 7 Gy), 254 patients received 36.25 Gy (5	n/a (no control or comparison group)	Acute GU toxicity (for 303 patients): 36 low-dose (72%) and 190 high-dose (75.1%) had Grade 1 toxicity; 2 low-dose (4%) and 12 high-dose (4.7%) patients had Grade 2 toxicity; acute GI toxicity: 38 low-dose (76%) and 189 high-dose (74.7%) patients had Grade 1 toxicity; 2 low-dose (4%) and 9 high-dose (3.6%) patients had Grade 2	Poor Potential conflict of interest, not all patients reached late follow-up milestone

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	T2aN0M0; no hormone treatment in 81.3%; 69.4% considered low risk, 26.6% intermediate risk, 3.9% high risk; 73% had Gleason score 6, 23% had Gleason score 7, 4% had Gleason score >8		median 30 mos (26-37) in low dose cohort, median 17 mos (8-27) in high dose cohort	consecutive fractions of 7.25 Gy); mean number of beams 152 (140-170)		toxicity. No patients had Grade 3 or 4 acute toxicities. Late GU toxicity (for 48 low-dose and 206 high-dose patients): 2 low-dose (4%) and 10 high-dose patients (4.8%) had Grade 1 toxicity; 1 low-dose (2%) and 12 high-dose patients (8.8%) had Grade 2 toxicity; Late GI toxicity: 2 low-dose (4.2%) and 11 high-dose patients (5.3%) had Grade 1 toxicity; 6 high-dose patients (2.9%) had Grade 2 toxicity. No Grade 4 late toxicity.	
King (2012) Case Series **Prostate**	n = 67 median age 66 yrs; 92% patients had no urinary issues, 8% had minor issues; 89% had no bowel issues, 11% had minor bowel issues	Inclusion criteria: Clinically localized, newly diagnosed, low-risk prostate cancer; Exclusion criteria: patients with prior treatment	SBRT with CyberKnife F/U: Follow-up every 3 mos during first 2 yrs, then every 6 mos; median 2.7 yrs (IQR 1.8-4.5, maximum 5.9)	36.25 Gy in 5 fractions	n/a (no control or comparison group)	Late GU toxicity (in 57 patients): 13 patients (23%), Grade 1; 3 patients (5%), Grade 2; 2 patients (3.5%), Grade 3; Late GI toxicity (in 57 patients): 8 patients (14%), Grade 1; 1 patient (2%), Grade 2. Every-other day treatment resulted in lower frequency of Grade 1-2 GU toxicity than daily treatment (17% vs 56%, P=0.007), as well as less frequent Grade 1-2 GI toxicity (5% vs 44%, P=0.001).	Poor Study enrolled 67 patients but data only reported for 57 and no explanation provided
Townsend (2011) Case Series **Prostate**	n = 48 mean age 66 yrs (46-80); 69% T1, 29% T2, 2% T3; mean Gleason score 7; BL mean	Inclusion criteria: Dx of biopsy-confirmed prostate adenocarcinoma, stage T1-T3;	SBRT with CyberKnife F/U: mean 12 wks, median 11.5 wks (range 4-24)	SBRT monotherapy (7-7.5 Gy, 5 fractions, total of 35-37.5 Gy); SBRT boost	n/a (no control or comparison group)	Acute GU toxicity: For all 48 patients: 26 patients (54%), Grade 1; 5 patients (10%), Grade 2; 4 patients (8%), Grade 3; For 37 SBRT monotherapy patients: 21 patients (57%), Grade 1; 2 patients (5%), Grade 2; 3 patients (8%), Grade 3; For 11 SBRT boost patients: 5	Poor Retrospective chart review, analysis of initial series

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	PSA 9.16 ng/mL, median 6.05 ng/mL (0.13-59.6); no hormone treatment in 67%	Exclusion criteria: metastatic disease		(2-5 fractions for total of 17.6-25 Gy)		patients (45%), Grade 1; 3 patients (27%), Grade 2; 1 patient (9%), Grade 3; toxicities included frequency/nocturia, retention, and dysuria; Acute GI toxicity: For all 48 patients: 5 patients (10%), Grade 1; no Grade ≥2 toxicities; For 37 monotherapy patients: 5 patients (13.5%), Grade 1; no Grade ≥2 toxicities; for 11 SBRT boost patients: no Grade ≥1 toxicities. Diarrhea was only reported GI toxicity.	of 50 pts

Spine Cancer

Reviews					
Reference Study Design Malignancy	**# of Studies & Subjects**	**Intervention Comparator Follow-up**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Gerszten (2009) SR **Spine**	49 studies of conventional radiotherapy; 29 radiosurgery spinal tumors, metastatic N=NR	conventional RT vs stereotactic RS F/U: NR Dose: For stereotactic RS: dose and fractionation differs by institution; ranging from single fraction RS ranging from 8 to 24 Gy or hypofractionated regimens of 4 Gy x 5 fractions, 6 Gy x 5 fractions, 8 Gy x 3 fractions, 9 Gy x 3 fractions	Median OS 3-4 mos (3 RCT, n=327)	for stereotactic RS: (no table). Complications generally self-limited and mild, including esophagitis, mucositis , paresthesia, transient laryngitis, transient radiculitis (each of these were reported in 1 study each), dysphagia, diarrhea, (both reported in 2 studies). No spinal cord toxicity was reported in 2 studies, one of which was in over 60 mo of f/u. 1 study (Ryu et al 2007) addressed the partial volume tolerance of the spinal cord and complications of single dose RS, and reported a single case of radiation-induced cord injury after 13 mo of RS. A 1075 case multicenter study (Gibbs et al 2009) reported only 6 pts w/ delayed radiation-induced myelopathy at a mean of 6.3 mo (range, 2-9 mo) after spinal RS. Radiation injury to the spinal cord occurred over a spectrum of dose parameters that prevented ID of specific dosimetric factors contributing to this complication Yamada et al (2008) used a maximum dose constraint of 14 Gy to any portion of the spinal cord instead of a dose-volume constraint w/o any cases of spinal cord toxicity. General: the paper's discussion states they cannot comment critically on treatment-related toxicity given difficulties of the study population, including multiple confounding variables and relatively short follow-up, and nonprospective datasets	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Ahmed (2012) Case Series **Spine**	n = 66 spinal tumor, malignant 85 lesions in 66 pts; mean age 56.8 + 13.4 yrs; male: female 48:18; 11 (12.9%) pts w/ hx of prior surgery at site of metastases, 5(5.8%) pts had both previous surgery and RT to site of SBRT tx; most frequent lesions treated were metastatic tumors of renal cell origin (n=19, lung (n=8, sarcomas (n=8, melanoma (n=7)	pts w/ oligometastatic disease (generally <3 sites) radioresistant tumors (primarily sarcomas, melanomas and renal cell ca), or recurrence after prior RT and an Eastern Cooperative Oncology Group performance status of 0-2 and life expectancy of > 3 mo	SBRT F/U: Follow-up exam at 2-3 mo post tx, then every 6 mo for 2 yrs	median dose of 24 Gy (range, 10-40 Gy) in a median of 3 fractions (range 1-5); most common dose was 24 Gy in 3 fractions (n=25) followed by 18 Gy/1 (n=14) and 30 Gy/3 (n=11)	12-month actuarial survival: 52.2% Actuarial survival at 1-yr: 28% (pts with prior RT), 59% (pts w/o prior RT) (p=0.002) Actuarial local control rate: 89.2% (1 yr) Marginal failure rate at 1 yr (86.8%) Overall local control in pts w/ prior RT: 83.3%; w/o prior RT: 91.2% (p=0.050) FACT-G questionnaire used to determine QoL at baseline, 3 mos, 1 yr after SBRT tx. Scores improved from baseline (15.7±6.1) vs 3 mos (18.2±5.2) (p=0.04)	(no toxicity tables) Toxicity: 12 (18.2%) pts had acute grade 1 toxicity, 6 (pts (9%) had grade 2 toxicity, 2 (3%) pts had grade 3: of them, 1 pt had a T12 spinal fx 3 mo post SBRT (and pt had had SBRT prior to this study) , other pt had severe lower back pain radiating down L leg to the knee. Failure: 7 (8.2%) pts experienced both local and marginal failure, 1 pt had marginal but not local failure, and 1 pt had local failure only.	Poor Some baseline characteristics not included in analysis
Gagnon (2009) Case Series **Spine**	n = 200 spinal tumor, benign, malignant,	pts w/ primary and metastatic spinal tumors who were candidates for	Gamma knife SRS F/U: Data collected	dose depended on histology, but ranged from 2100 to 2400	Median survival 14.5 mos (pts with malignancy spinal lesions), and 10.5 mos (pts re-treated with Cyberknife after previous RT)	Acute. Acute complications were self-limited and mild. Most commonly reported acute toxicities were fatigue, nausea, esophagitis, dysphagia and transient diarrhea. Late no evidence of	Poor Potential conflict of interest?

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	primary, metastatic median age 56 (3-91), male: female 101:99, primary spine tumor 49, benign 36, malignant 13, metastatic 151, previous surgery or RT 137	spinal RS from Mar 2002 to Sept 2006	before irradiation, at 1,3,6,9 and 12months, and every 6 mo thereafter.	cGy in 3 fractions up to 3750 cGy in 5 fractions		tx-related myelitis or neurological damage in any pt, including pts w/ hx of previous conventional RT. 3 (1.5%) significant complications: 1 (0.5%) pt w/ previous EBRT and 2 spinal ops had breakdown at a surgical site that required debridement and wound reclosure; 2 (1%) pts developed vertebral fx in irradiated spine. 1 pt had previous EBRT, both instrumented with titanium cages and tumor was present in adjacent levels)	
Garg (2011) Case Series **Spine**	n = 59 progressive spinal and paraspinal tumors, metastasis, previously treated w/ irradiation median age 60(28-88); male: female 35:24; KPS 100 - 4, 80 - 16, 80 - 25, 70 - 10, 60 - 4;	pts w/ spinal tumors who had been previously treated w/ conventional RT	computed tomography (CT)-guided SBRT Every 3 mo in yr 1, every 6 mo thereafter; mean follow-up 17.6 (0.9-67.5 mo)	27 Gy in 3 total fractions (n=50) or 30 Gy in 5 total fractions (n=8), or 4 Gy per fraction for 5 total fractions (n=1)	Actuarial 1-yr local progression free (76%) Median survival time 22.5 mos Actuarial survival at 1-yr (76%) Reduced pain levels (≤3 vs ≥4) at 1 mo (p=0.07), 3 mos (p=0.04), and 6 mos (p=0.03)	Neurotoxicity none - 44 pts, grade 1 - 7pts, Grade 2 - 4 pts (Grade 1/2 included transient numbness and tingling - 9 pts, anxiety - 1 pt, headache 1 pt), Grade 3 - 2 pts, (1 pt had persistent neuropathic pain, paresthesia and ipsilateral foot-drop due to lumbar plexopathy, 1 pt had lumbar plexopathy limited to an ipsilateral foot-drop - both pts had retreatment to tumors in the L5 para-spinal region) Grade 4 - 0; hematologic none - 59; Gastrointestinal none - 44 pts, Grade 1 - 6 (10.2%) pts (2 pts w/ anorexia, 1 pt w/ radiation esophagitis, 3 pts w/ transient nausea and vomiting (N&V)) , Grade 2 - 6 (10.2%) pts (4 pts w/ transient N&V, 2 pts w/ diarrhea), Grades 3&4 - none; other toxicity (worst grade) none - 22 (37.3%), Grade	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
						1 - 19 (32.2%) , Grade 2 - 16 (27.1%), Grades 3&4 - none.	
Gerszten (2006) Case Series **Spine**	n = 77 spinal tumors, metastasis from lung tumors Median age 63 (22-85) male: female 42:35. no performance scores. Primary indications - pain - 73 pts, primary tx 7 pts, tumor progression 4 pts, progressive neurologic deficit 3 pts	pts w/ histologically proven lung cancer that was metastatic to the spine, and treated by CyberKnife	CyberKnife image-guided radiosurgery F/U: No statement of follow-up schedule provided in the paper. median follow-up 12 mo (range, 6-40 mo))	mean maximum tumor dose 20 Gy (range, 15-25 Gy), see article for detail on dose according to location of the target	65 of the 73 pts (89%) treated for significant pain from treated lesions reported long-term [undefined] improvement in pain measured on a 10-pt pain scale compared with pain at time of initial evaluation	No complications associated with fiducial placement; no radiation-induced toxicity occurred during the follow-up period.	Poor Confounders identified and described, but not exactly an analysis
Gibbs (2007) Case Series **Spine**	n = 74 (102 lesions) spinal tumors, metastasis mean age 59 (29-82), male: female 38:36; mean KPS 80 (20-90); previous tx 68, radiotherapy +/-	pts w/ established histologic dx of spinal metastases	CyberKnife image-guided radiosurgery F/U: No statement of follow-up schedule provided in the paper. Mean 9 mo (range, 0-33)	16-25 Gy in 1-5 fractions	Median time to death: 11 mos 1-yr actuarial survival: 46.3%	3(4%) pts developed tx-related severe myelopathy; 1 pt was initially asymptomatic. All 3 were female w/ lesions on thoracic spine. 2 had received prior irradiation of doses to 50.4 and 39.6 Gy in 1.8 Gy fractions at 70 and 81 mo, respectively, prior to RS. Mean time to onset of signs and sx 7 mo (range, 6-10 mo) In the 3 pts, classic radiographic signs coincided w/ clinical signs and evolved from spinal cord edema at the onset to contrast enhancement w/in the cord. Edema	Poor Nothing re competing interests, unclear that confounders taken into account in analysis

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	other 50; chemotherapy 11, surgery 3, other 4; histology: renal 20(27%); breast 18(24.3%), lung 12(16.2%), melanoma 12(16.2%), GI 9(12.1%), sarcoma 7(9.5%), head/neck 7(9.5%), prostate 3(4.3%), unknown 3(4.3%), other 11(14.9%)					resolved w/in 3-6 mo, though contrast enhancement persisted. 2 of the pts are alive w/ severely limited mobility; the 3rd died of systemic disease progression at 17 mo post tx and 7 mo after onset of myelopathy. 2 of the 3 also had received an anti-angiogenic or epidermal growth factor inhibitor target tx w/in 2 mo of developing clinical myelopathy.	
Mahadevan (2011) Case Series **Spine**	n = 60 spinal tumors, metastasis median age 56 (36-80), male: female: 36:24; previous radiation dose 8-46 Gy; histology: renal 24(40%), melanoma 16(24.7%), GI 12(20%), other	pts w/ radiological and/or clinical progression of spinal mets w/ spinal canal or cord compromise and w/ previous RT and ineligible for resection	SBRT with fiducial and vertebral anatomy-based targeting F/U: All seen 1 mo after tx; after this follow-up exam performed by the treating medical	if tumor did not touch spinal cord 8 Gy x 3 =24 Gy; if lesion abutted spinal cord, 5 to 6 Gy x 5= 25 to 30 Gy	Median overall survival 11 mos (range, 3-39)	(no toxicity tables) in first mo following reirradiation, in 24 (40%) pts, grade 1 fatigue and in 12 (20%) pts, grade 2 nausea. 4 pts had persistent or worsening neurological sx, 3 of them had persistent radicular pain and 1 pt developed new onset of lower-extremity weakness. All 4 pts had worsening radiological progression directly corresponding to their sx	Poor Follow-up schedule and honoraria vague

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	10(16.7%). Lung (5(8.3%), 3(%)		oncologist or neurosurgeon who evaluated pain and neurological outcomes; this information taken from medical records, no specific schedule was provided in the paper, however, median follow-up 12 mo (range, 4-36 mo)				
Nelson (2009) Case Series **Spine**	n = 32 (33 lesions) spinal tumor, metastasis median age 61 (45-82); male: female 13:19; histology renal 10(31%), breast 6(18.8%), lung	pts w/ spinal lesions	SBRT F/U: patients followed-up every 2-3 m; Median follow-up 7 mo (range, 3-21 mo) for all patients and 8.2 mo (range, 3-23	SBRT dose and fractionation varied; median number of SBRT fractions was 3 (range, 1 to 4 fractions); median dose/fraction and total dose delivered were	Actuarial 1-yr overall survival: 13.5 mos	(no toxicity tables) In 4 (12.5%) pts, there were tx failures at a median of 5.8 mo (range, 4-12 mo) with MRI evidence of progression in the treated vertebral body, paravertebral soft tissues, and/or epidural space.); 7 (21.9%) pts, had Grade 1 nausea.	Fair Cannot determine if a consecutive sample, vague follow-up schedule, potential competing

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	6(18.8%), GI, various 5(15.6%), 1 each of pheochromocytoma, multiple myeloma, eccrine, head and neck, schwannoma		mo) for survivors	7 Gy (range, 5.1-16 Gy and 18 Gy (range, 14-30 Gy) respectively			interests
Nikolajek (2011) Case Series **Spine**	n = 54 (70 lesions) spinal tumor, primary (previously - irradiated) and metastasis median age 56 (17-82), male: female 32:22; median KPS 80 (50-100);13 pts w/ progressive disease at primary spinal/paraspinal tumor site, 41 w/ metastatic disease; see article for histology	patients who had been treated with SRS (Cyberknife) between 2005-2009	SRS (Cyberknife) F/U: Every 3 months	median RS dose 1x18 Gy (range, 10-28 Gy)to the median 70% isodose	Local failure: 12.9% (9pts) Actuarial rate of freedom from local failure at 6/12/18 mos were 93%/88%/85% Median survival after SRS 16.2 mos Median survival after initial RT: 42 mos	(no toxicity tables and no discussion of grades 1-2 toxicity) 1 (1.9%) pt w/ metastatic renal cell CA developed progressive paraparesis 1 yr after the last tx of a widespread spinal mets at lumbar level L3. Due to multiple txs and tumor progression, exact reason for this could be identified. Apart from that no CTC grade 3 or higher toxicity)	Fair
Ryu (2010)	n = 62	pts w/ proven	radiosurgery	median dose	No outcomes of interest	toxicity: transient grade 1 esophageal	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Case Series **Spine**	spinal tumor, metastatic Median age 62 (22-87); male: female 32:30; see article for histology	pathological dx of malignant neoplasm and epidural compression as confirmed by CT and/or MRI between Oct 2003 - Oct 2006; radiosensitive tumors and prior tx to index RS site were excluded	F/U: 1 mo post RS, then every 2 or 3 mo in Yr 1, and every 4 to 6 mo thereafter. Median 11.5 mo.	of 16 Gy (range 12-20 Gy); radiation dose was prescribed to the 90% isodose line to encompass periphery of the target tumor; spinal dose constraint was 10 Gy to the 10% partial volume of the spinal cord	reported	mucositis noted in pts who received RS to thoracic spines, sx subsided w/o tx; no acute grade 2,3,4 toxicity, no clinical or radiographic sign of toxicity to spinal cord during f/u. neurological status remained intact in 33 (94%)of 35 pts who were intact before surgery, among the 27 pts who presented w/ neurological deficit 14 (52%) had complete recovery to nl, 3 (11%) improved and 3 (11%) remained stable. 9 (16%) of 62 pts had neurological progression; 2 were neurologically intact before RS; 7 had initial neuro deficit. Failure sites were: infield, 3 pts, potential causes underdose, radioresistent histology, geographical miss, immediate adjacent site: posterior element 1 pt, due to marginal miss, epidural area, 4 pts due to underestimate of target volume, compression fx 1 pt due to radiation induced bone change, tumor progression.	
Sachdev (2011) Case Series **Spine**	n = 87 (103 lesions) spinal tumor, benign median age 53 (12-86), male: female 43	pts w/ benign intradural extramedullary tumors treated with image-guided RS between 1999 and 2008	SRS Cyberknife post-tx f/u typically conducted at 3 mo, 6 mo, 1 yr, and annually	dose and fractionation based on tumor size, volume, location, degree of potential spinal cord	No outcomes of interest reported	(no toxicity table) late failure: 1 (1.1%) pt had recurrent cervical schwannoma originally tx w/ RS 6 yrs after subtotal resection and had further progression 73 mo after RS. Tumor treated w/ RS, but because of continuing sx and increased volume 73 mo after RS, pt opted for a repeat resection but did not notice improvement in sx.	Poor Potential conflict of interests, potential confounders

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	(49%):44 (51%), meningioma 32(31%), neurofibroma 24 (23%), schwannoma 47 (46%)		thereafter.	exposure, delivered in 1 to 5 sessions (median, 2) w/ mean dose of 19.4 Gy (range 14-30 Gy) to an average tumor volume of 5.24 cm (range, 0.049-54.52 cm)		complications: 1 (1.1%) pt developed transient radiation myelitis 9 mo after tx. The pt had a C7-T2 recurrent (previously debulked) meningioma w/ no previous radiation to the area. (see article for specific dose to tumor, maximum spinal cord dosage 29.9 Gy). pt developed posterior column dysfunction during course of myelitis, but became neurologically stable after intervention w/ corticosteroids.	
Tsai (2009) Case Series **Spine**	n = 69 (127 lesions) spinal tumor, metastases median age 54 (24-76), male: female 34:35; baseline median KPS 80 (60-100); primary tumor: prostate 22%, lung 21%, breast 18%, liver 11%, other 11%, colorectal 9%	pts w/ histological dx of malignant neoplasm and metastasis involving spine segments diagnosed by MRI and treated with CK SRS from Sept 2005 to 1007	Cyberknife image-guided radiosurgery F/U: At 1 week, 1 mo and every 3 mo thereafter	ranged from 10 to 30 Gy (mean 15.5 Gy) prescribed to the 75-85% isodose line that encompassed at least 95% of the tumor volume	Local treatment failure (3 pts) 79% of pts described > 50% pain reduction on VAS at 1 mos fu. Overall VAS improvement after CK found in 110 tx sites (87%) ODI scores ranging from 38-86% (mean 53%) before CK tx. Post tx reduction of 25-50% and > 50% ODI scores for 63% and 15% of site-specific disabilities, respectively (p=0.002)	(no toxicity table and no patient numbers provided for the following) All toxicities Grade 1-2; most common acute toxicities were fatigue (50%), nausea (27%), vomiting (16%), esophagitis (11%), diarrhea (3%), sore throat (5%), anemia (1%), thrombocytopenia (2%), neutropenia (4%) treatment failure local tx failures in 3 (4.3%) pts w/ recurrence rumors over 3 thoracic and 1 lumbar vertebras.	Fair
Wang (2012) Case Series **Spine**	n = 149 Medically stable,	Phase 1-2 trial from Nov 2002-Jan 2011.	Intensity-modulated, near-	27-30 Gy (3 fractions every other day). 10	Median OS 23 mos (95% CI, 18.6-27.2) 1-yr actuarial survival	Grade 1 and 2 transient numbness and tingling, nausea, and vomiting. Grade 3 toxicities were nausea (1), vomiting (1),	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	non-cord compresing spinal metastases Mean age (56.4 ±12.5), median age (58.0 (20.0-88.0); Male 77, female 72; KPS 100 (8), 80-90 (108), 70 (30), <70 (3); previous tx to spinal site: RT along (40), surgery alone (22), RT and surgery (39), none (48); primary histology: breast (15), colon (6), NSCLC (15), melanoma (4), thyroid (14), renal (47), sarcoma (17), other (28),unknown (3); SBRT site: cervical (28), thoracic (66), lumbar (51),	Dx of cancer (excluding multiple myeloma), KPS of ≥ 40, MRI scan documenting spinal or paraspinal metastases within 4 wks of enrollment Acceptable indications: oligometastatic disease arising froma known primary tumor, failure of previous EBRT or surgery, residual tumor after surgery, medical inoperability, or refusal to undergo surgery Max 2 distinct non-contiguous spinal mets allowed Paraspinal tumors	simultaneous, CT-guided SBRT (CT-LINCAC system [ExaCT targeting system, Varian Medical Systems] or Triolgy tx delivery systems w/ On-Board Imager Cone Beam CT [Varian Medical Systems] using a BlueBAG BodyFIX Total Body immobization system [Elekta] F/U: Median fu 15.9 mos (range, 1.0-91.6; IQR 9.5-30.3), mean	Gy radiation volume to spinal chord limited to 0.01 cm^3	68.5% (95% CI, 60.1-75.4) 2-yr actuarial survival 46.4% (95% Ci, 37.8-54.7) Actuarial PFS based on MRI scans at 6 mos (86.1%) (95% CI, 79.4-90.7), 1-yr (80.5%) (95% CI, 72.9-86.1), and 2-yr (72.4%) (95% CI, 63.1-79.7)	diarrhea (1), fatigue (1), non-cardiac chest pain (3), dysphagia (1), neck pain (1), diaphoresis (1), and pain assoc. with severe tongue oedema and trismus (2). No Grade 4 toxicites reported. No radiation-related spinal cord myelopathy during study reported.	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	sacral (4); median metastatic tumor volume in cm^3 38.2 (1.6-357.9)	along cervical, thoracic, or lumbar spine included Pts receiving bisphosphonates or hormonal therapy not excluded Excluded: Pts w/mechanically unstable spine or spidural spinal cord compression, w/ pacemaker, unable to undergo MRI, or had received systemic radiotherapy (strontium 89) or cytotoxic chemo within 30 days of enrollment, or spinal EBRT within 3 mos of enrollment	20.9 mos (SD 17.1)				
Wowra (2008) Case Series **Spine**	n = 102 (134 lesions) spinal tumor,	pts w/ 1 or 2 malignant spinal tumor w/ KPS > 70, histologically	CyberKnife image-guided radiosurgery	to ablate tumors, a median marginal dose	Median survival: 1.4 yrs (CI 1.2-1.6) 5-yr survival after	(no toxicity table). No acute side effects were observed except for 9 (9%) pts w/ nausea that responded to symptomatic medication. local	Fair Potential conflict of

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	metastases median age 58.6 (18.4-82.6) male: female 66:36; primary tumor: breast 23(22.6%), renal 20(19.6%), various 19(18.6%), GI 12(11.8%), prostate 12(11.8%), lung 9(8.9%), sarcoma 7(6.9%)	confirmed dx, estimated life expectancy of > 3 mo	F/U: at 1 week, 3,6,12, and 18 mo post treatment.	of 19.4 Gy (range, 15-24 Gy) was delivered to the 70% (range, 50%-85%) isodose	diagnosis of primary breast cancer 95% (CI, 70-99), renal cancer 61% (CI, 30-81), various other malignancies 81% (CI, 54-94), GI cancer 33% (CI, 3-70), prostate cancer 83% (CI, 27-97), lung cancer 48% (CI, 13-76), and sarcoma 83% (CI, 27-97)	treatment failure: 2 (2%) local tx failures: 1 pt had a malignant peripheral nerve sheath tumor in the thoracic spine (recurrence 19 mo after RS), another pt had a cervical melanoma metastasis, evident 4 mo post RS. late complications after RS in 2 (2%) pts. 1 had segmental neuopathy due to a circumscribed hemorrhage into a metastasis that had been tx by CKRS, another developed vertebral instability due to pathological fx	interest

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
Haley (2011) Economic study **Spinal Tumors**	n = 44 spine metastases EBRT/SBRT Median age 57/56; male: female EBRT 3(14%)19(86%) SBRT 8(36%) 14(64%), primary tumor site for both EBRT and SBRT lung 8(36%), breast 11 (50%), renal 2(9%), unknown	Compare stereotactic body radiation therapy (SBRT) (cyber Knife) to external beam radiotherapy (EBRT) in the	cost modeling analysis done. 23% of EBRT pts later had further SBRT to the same vertebral area but only 9% of the SBRT pts had a 2nd SBRT course. If	At 1 mo f/u, no statistically significant difference in pain relief between the two interventions. Median survival was 10 mo in EBRT group and 10.5 mo in SBRT group. 38 (86%) pts	n/a	n/a	Poor Pts not matched on some key variables

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
	1 (5%)	primary RT tx of spinal metastatic disease F/U: 1 month	applied to 100 pts, total cost of RS w/ 9% of pts requiring repeat SBRT is $842,420. Total cost of 30 Gy in 10 fractions, assuming 23% need later RS tx is $676,309. For 20 Gy in 5 fractions, total cost is $499,911. This amounts to 80% for the 30 Gy EBRT course and 59% for the 20 Gy EBRT course when SBRT is used as the benchmark total cost.	completed longer term f/u (>90 days). More EBRT group pts developed acute toxicities (p=0.01), 3 of whom developed Grade 1 or 2 esophagitis. 1 pt developed fatigue, 1 had Grade 1 nausea and 1 developed Grade 1 thrombocytopenia. In the SBRT group, 1 pt had Grade 2 N&V. No late complications for pts that were followed >90 days, nor late complications for either tx modality.			
Papateofanis (2009) Economic study **Spinal Tumors**	Age > 18y, median age of selected pt samples was 57y; MRI/histologically confirmed or presumed mets spinal tumor from histologically confirmed primary malignancy; KPS > 50; ambulatory before tx, no overt evidence of spinal	Cyberknife SRS (CSRS); comparator external beam radiation therapy (EBRT)	EBRT: $13.7K; CSRS $11.8K	EBRT: 0.20 QALY; CSRS: 0.28 QALY	EBRT: $67,956 CSRS: $41,500 CSRS dominated	CSRS dominates across all willingness to pay thresholds	Good

Economic studies (published after review)							
Reference Study Design	**Pt Characteristics**	**Intervention Comparator Follow-up**	**Cost Range**	**Effectiveness (Range)**	**ICER (95% CI)**	**CEA Curve**	**Quality Comments**
	instability, no previous irradiation at the tolerance dose of spinal cord; minimal spinal cord compromise, primary indication for tx - pain relief	F/U: 12 mos					

Other Cancers/Multiple Sites

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
Levine (2009) Case Series **Multiple Sites**	n = 24 (30 tumors) Sarcoma, Primary (14 patients with 14 tumors) and metastatic (10 patients with 16 tumors) Primary sarcoma: 14 patients; mean age, 61 years (range, 29-88 years); males, 7 (50%); females, 7 (50%); fibromyxosarcoma, 28.6%; chondrosarcoma, 21.4%; leiomyosarcoma, 14.3%; dedifferentiated liposarcoma, 7.1%; angiosarcoma, 7.1%; synovial sarcoma, 7.1%; undifferentiated sarcoma, 14.3% Metastatic sarcoma: 10	Patients with primary biopsy-proven spinal or paraspinal sarcoma who refused surgical treatment, could not tolerate surgery due to medical conditions, were not eligible for surgery due to tumor location near critical structures, or failed other treatments; patients with prior en bloc spondylectomy for spinal sarcoma with positive margin or resection of all gross diseases without evaluable margins; and patients with symptomatic sarcoma	Robotic robotic SRS using CyberKnife (Accuray). Group 1 (7 patients with primary sarcoma): alone as definitive treatment; Group 2 (7 patients with primary sarcoma): with surgery as adjuvant treatment; Group 3 (10 patients with sarcoma metastases): alone as palliative treatment. F/U: Minimum, 12 months or, if sooner, death. Group 1: mean, 33 months (range, 20-49	Median, 30 Gy (range, 20-36 Gy) in 3 (range, 1-5) fractions to 80% (range, 70%-85%) isodose line	No outcomes of interest reported.	Adverse effects not requiring treatment: 5 patients (21%): Group 1, nausea , malaise, or skin irritation (3 patients); Group 2, delayed but transient radiculopathy with dysesthesias and partial motor loss (2 patients); Group 3, no major adverse effects. Adverse effects requiring treatment: 1 patient (4.2%) in Group 1 (rectal tumor cavity fistula, requiring diverting colostomy and drainage)	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	patients; mean age, 59 years (range, 44-84 years); males, 2 (20%); females, 8 (80%); leiomyosarcoma, 50%; chondrosarcoma, 20%, angiosarcoma, 20%, pleomorphic sarcoma, 10%	metastasis to the spine and unremitting spinal pain with or without radiculopathy	months); Group 2: 43.5 months (range not reported); Group 3: 11.1 months (range, 1.0-21 months).				
McCammon (2009) Case Series **Multiple Sites**	n = 141 (246 tumors) Adenocarcinoma, squamous cell carcinoma, sarcoma, melanoma, renal cell carcinoma, neuroendocrine, other unspecified cancers Primary or recurrent (65 tumors, or 26%) and metastatic (181 tumors, or 74%)	Consecutive patients treated at participating center with 3-fraction SBRT delivered to thoracic sites or liver	SBRT with stereotactic frame and conventional linear accelerator with multileaf collimation (model and manufacturer not reported) up to mid-2002 SBRT using Novalis dedicated linear (BrainLAB) accelerator with image-guidance	Mean, median, or range not reported; all doses delivered in 3 fractions; 60 Gy, 30.5%; 54 Gy, 12.2%; 45-53.9 Gy, 18.7%; 30-44.9 Gy, 22%; <30 Gy, 16.7%	54-60 Gy: 1- and 3- yr local control: 100%, 89.3% 36.1-53.9-60 Gy: 1- and 3-yr local control: 89.0%, 59.0% < 36.1 Gy: 1- and 3- yr local control: 40.5%, 8.1%	Grade 2-4 SBRT-related toxicity: 28 patients (19.9%), including Grade 2-4 pneumonitis (6.4%), Grade 2 or 3 dermatitis (4.3%), Grade 2 or 3 soft-tissue/muscle inflammation or fibrosis (4.3%), unspecified Grade 2 or 3 effects (3.5%), and vertebral fracture within radiation field (1.4%)	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Median age, 62 years (range, 26-88 years); males, 76 (54%); females, 65 (46%); median gross tumor volume, 8.9 cc (range, 0.1-185.0 cc); median planning target volume, 38.6 cc (range, 2.8-370.2 cc); adenocarcinoma, 39%; squamous cell carcinoma, 13%; sarcoma, melanoma, or renal cell		system and ExacTrac positioning system (BrainLAB) F/U: Median in all patients, 8.2 months (range, 1.4-44.4 months); median in survivors (40 patients, or 28%), 18.3 months (range not reported; median in deceased (101 patients, or 72%), 5.9 months (range not reported)				
Milano (2008) Case Series **Multiple Sites**	n = 121 Sarcoma or breast, colorectal, lung, head and neck, esophageal, pancreatic/biliary, hepatic, or nonspecified other cancer , metastatic	Limited oligometastic disease (≤5 metastases) located in ≥1 organs and treated with SBRT or cranial SRS	SBRT using Novalis ExacTrac patient positioning platform (BrainLAB) for immobilization and dose markers,	SBRT: Allowable+I6 dose/ fraction calculated to yield 85% tumor control according to a linear	2- and 4-year local control rate: 77%, 73%	Grade 3: 1 patient (nonmalignant pleural and pericardial effusion). Grade ≥4: None. Grade 1-2: Patients treated for adrenal, pelvic lymph node, or abdominal lymph node metastases: no discernible toxicity excluding grade 1-2 fatigue and/or skin toxicity (2), vaginal bleeding (1), diarrhea (1), nausea (1), flank pain (1); Patients treated for bone metastases: no discernible	Fair

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	Demographic data not reported Primary cancer (% of 293 metastases): Breast, 29%; colorectal, 29.7%; lung, 12.6%; head and neck, 2.7%; esophagus, 1.7%; pancreas/biliary, 2.7%, hepatic, 2.4%; sarcoma, 7.5%; other (types not reported), 11.6% Metastases: Mean gross tumor volume, 21.5 mL (range, 0.03-422.4 mL; median, 6.7 mL); lung, 35.2%; thoracic lymph nodes, 11.3%; liver, 41%; abdominal or pelvic lymph nodes, 2.0%; adrenal, 0.7%; bone, 7.5%; central nervous system, 2.4%		BrainSCAN (BrainLAB) for treatment planning, and Novalis linear accelerator (BrainLAB) for radiation delivery; Cranial SRS using stereotactic head frame (BrainLAB) for immobilization and dose markers, BrainSCAN (BrainLAB) for treatment planning, and Novalis linear accelerator (BrainLAB) for radiation delivery F/U: 1.5- 6.0 years (mean or median not reported)	quadratic model. Acceptable schemes included: 51-57 Gy in 17-19 fractions of 3 Gy, 48-56 Gy in 12-14 fractions of 4 Gy, 45-55 Gy in 9-11 fractions of 5 Gy, 42-48 Gy in 7-8 fractions of 6 Gy, or 40-48 Gy in 5-6 fractions of 8 Gy with 80% isodose line covering planned target volume. SRS: 10-20 Gy at isocenter with 80% isodose line covering planned target volume. Dose		toxicity excluding grade 1-2 fatigue and/or skin toxicity (11), nausea (1), cough (1), dysphagia (1), allopecia (1)	

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
				fractionation scheme selected according to dose-volume histogram of organs at risk. Mean or median values not reported			
Milano (2010) Case Series **Multiple Sites**	n = 77 oligometastases (OM), metastases Median age 60 (36-88), Male: female 27:50, primary CA breast 30(39%), Colorectal 20(26%), Lung, head and neck or esophagus 7(9%), Pancreas, biliary or hepatic 7(9%), sarcoma 4(5%), other 9(11%)	pts between Feb 2001 and Dec 2006 w/ OM confined to 1 organ. Pts excluded who represent only 1 or 2 pts w/ OM confined to 1 organ, and 1 who died 2 mo after SBRT from local progression of a tx liver metastases	SBRT F/U: 1 mo after SBRT completion, every 3 mo for 2 yrs, and every 3-6 mo thereafter	for liver and lung preferred schedule was 10 fractions of 5 Gy, for bulky lesions or lesions abutting critical structures, smaller fractional doses were used	Pts w/ initial liver-confined oligometastases (42 pts): 30 deceased at 6-67 mos (median 20 mos), 12 alive at last follow-up 35-61 mos (median 48 mos). 4 pts had not developed new metastases at 39-53 mos (median 43 mos) Pts w/ initial lung-confined oligometastases (21 pts): 14 deceased at 5-55 mos (median 17 mos), 7 alive at last follow-up 14-85 mos (median 40 mos). 4 pts had not developed new metastases at 14-64 mos (median 34 mos) Pts w/ initial thoracic lymph node--confined	NR	Poor Competing interests; large generalized study, all potential confounders recognized but not addressed nor analyzed

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
					oligometastases (5 pts): 3 alive at last follow-up 72-82 mos.2 pts developed local recurrences. Pts w/ initial thorax-confined oligometastases (13 pts): 11 deceased at 8-42 mos (median 16 mos), 2 alive at last follow-up (42 and 66 mos), both of which developed new oligometastatic lesions		
Scorsetti (2011) Case Series **Multiple Sites**	n = 37 Colorectal, esophageal, pancreas, biliary, breast, kidney/renal pelvis, lung, ovary, prostate, or hepato-cellular cancer Primary (11 patients, or 30%) and metastatic (26 patients, or 70%) Median age, 66 years (range, 330-83 years); males, 24 (65%); females,	Consecutive patients with primary or metastatic tumor(s) in abdominal region treated with hypo-fractionated SBRT at participating center	SBRT using external stereotactic frame and RapidArc (Varian Medical Systems) F/U: Median, 12 months (range, 6-22 months)	Median, not reported (range, 45-75 Gy in 3-6 fractions); 45 Gy in 6 fractions of 7.5 Gy for nodal and pancreatic tumors; 50-75 Gy in 3 fractions of 16.7-25 Gy for liver tumors	Local control at 6 mos (freedom from local progression) 19 pts	Early toxicity resolving spontaneously within 3 months: Grade 1: acute enteritis developing early and resolving within 3 months (3 patients, 8.1%), transient liver damage (2 patients, 5.4%). Late toxicity: Grade 1: diarrhea and abdominal pain due to chronic enteritis (treated for normal metastases) (1 patient, 2.7%); Grade 3: gastric bleeding developing at 3 months in patient with pancreatic cancer and resolving after repeated endoscopic treatments (1 patient, 2.7%).	Poor

Individual studies (published after review)							
Reference Study Design	**Sample size and Pt Characteristics**	**Patient Selection Criteria**	**Intervention Comparator Follow-up**	**Dose**	**Outcomes Assessed Main Findings**	**Harms**	**Quality Comments**
	13 (35%); median maximal axial tumor diameter, 35 mm (range, 16-83 mm); colorectal, 40.5%; esophageal, 2.7%, biliary tract, 2.7%; pancreas, 27%; breast, 2.7%; kidney/renal pelvis, 8.1%; lung, 5.4%; ovary, 2.7%; prostate, 2.7%; hepato-cellular, 5.4%						

Appendix G. Guideline Summary Table

Recommending Body, Year Published	Recommendation(s)	Evidence Base Quality
Abdomen		
ACR [Konski] 2011	In four case variants of recurrent rectal cancer presented, SBRT therapy was considered "usually not appropriate" in all cases.	**Fair**
NCCN 2012c	**Principles of Locoregional Therapy** *Stereotactic body radiotherapy (SBRT) and external-beam radiotherapy* There is growing evidence for the usefulness of radiotherapy in the management of HCC. All tumors irrespective of location may be amenable to SBRT or external-beam conformal radiation. SBRT is often used for 1-3 tumors with a cumulative diameter under 6 cm. SBRT could be considered for larger lesions, if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected. There should be no extra-heptic disease or it should be minimal and addressed in a comprehensive management plan. Most patients treated today were in the Child-Pugh A category. Radiotherapy can be considered as an alternative to the ablation/embolization techniques mentioned above or when these therapies have failed. All recommendations are Category 2A unless otherwise noted: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	**Poor**
NCCN 2012h	**Principles of Radiation Therapy** In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal radiotherapy, IMRT or stereotactic body radiosurgery (SBRT) (category 3). Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.	**Poor**

NCCN 2012b	**Principles of Radiation Therapy** In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal radiotherapy, IMRT or stereotactic body radiosurgery (SBRT) (category 3). Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.	**Poor**
NCCN 2012g	**Principles of Radiation Therapy** *General Principles* Radiation is typically given concurrently with chemotherapy, except in the palliative setting, with intraoperative radiation therapy (IORT), or with stereotactic body radiation therapy (SBRT). *Unresectable/Locally advanced (non-metastatic)* No standard dose or dose per fraction has been established for SBRT; therefore, it should preferably be utilized as part of a clinical trial. *Radiation Therapy Treatment Planning Principles* Elective nodal irradiation is commonly used for adjuvant cases but is controversial for unresectable/neoadjuvant/borderline resectable cases. Standard margin expansions for unresectable cases include the gross tumor and any pathologic lymph nodes (GTV) plus a 0.5-1.5 cm margin to target microscopic extension (CTV) and an additional 0.5-2 cm volume to account for tumor/breathing motion and patient set-up errors (PTV). With these expansions, peri-pancreatic nodes are generally included. With SBRT, smaller margins are used (0.2-0.5 cm) and the PTV does not cover locoregional elective nodal regions. All recommendations are Category 2A unless otherwise noted: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	**Poor**
Brain and CNS		
ACN 2008	**Chapter 15 – Treatment of disseminated melanoma** Recommendation 3. To improve survival, patients with limited or no extracranial disease and with favorable prognosis brain metastases can be considered for surgical resection and if unresectable, for stereotactic radiosurgery. Grade C recommendation (Body of evidence provides some support for recommendation but care should be taken in its application)	**Good**

ACR [Patel] 2011	**Radiosurgery** Radiosurgery for recurrent brain metastases is a viable option if size and number permit. Radiographic responses following salvage radiosurgery have been well documented, although evidence for a survival benefit is not strong. This modality is increasingly available at many centers. The data suggests that SRS is one valid approach in managing those patients having brain relapses even after prior WBRT and especially if no more than three metastatic foci are present. When recurrence of brain metastasis is confirmed, surgery and particularly radiosurgery may be useful in improving disease control.	**Fair**
ACR [Videtec] 2009	**Surgery and Stereotactic Radiosurgery** Results suggest the value of WBRT in patients with multiple brain metastases and the influence of patient selection on the effectiveness of SRS. Given the finding that SRS does not increase survival of patients with two or more brain metastases, clinicians need to practice careful selection of patients for this intervention. The RTOG® RPA brain metastasis classification may prove useful in making this selection.	**Fair**
ACR [Suh] 2010	**Surgery versus Stereotactic Radiosurgery** Whether stereotactic radiosurgery (SRS) is as effective as surgical resection has not been evaluated within a phase III randomized trial for patients with single brain metastasis. For tumors greater that 4 cm in greatest diameter or causing significant mass effect, surgery rather than SRS is the preferred treatment. **Summary** If patients have no evidence of progressive extracranial disease, surgical resection or radiosurgery is appropriate therapy. Since much controversy exists regarding optimal treatment for a patient with a single brain metastasis, patient participation in clinical trials is important to evaluate best treatment. For those patients who do not participate in clinical trials, the roles of surgery and SRS in improving outcomes for patients with a single lesion are evident.	**Fair**
American Thyroid Association 2009	**Recommendation 96** Patients with isolated or limited brain metastases should be considered for surgical resection. EBRT (including stereotactic radiosurgery) may be indicated for brain metastases not amenable to surgery. Grade C recommendation (based on expert opinion).	**Poor**

Ammirati 2010	**Discussion and Conclusions** It is recommended that treatment of recurrent/progressive brain metastases be individualized based on functional status, extent of disease, volume/number of metastases, recurrence or progression at original versus non-original site, previous treatment and type of primary cancer. In this context, re-irradiation (either WBRT and/or SRS), surgical excision or, to a lesser extent, chemotherapy, can be recommended depending on a patient's specific condition and based on the judgment of the patient's treating physician.	**Poor**

ASTRO [Tsao] 2012

Table 1 Single brain meatases – initial management (adapted from Tsao 2012)

Prognostic Category (*)	Other Features	Treatment Options (evidence grade) References
Good prognosis Expected survival 3 months or more	Complete resection possible	If brain metastasis ≤ 3-4 cm: • Surgery and SBRT (level 1) • Radiosurgery and WBRT (level 1) • Radiosurgery along (level 1) • Surgery with radiosurgery/ radiation boost to the rection cavity with or without WBRT (level 3) If brain metastasis > 3-4 cm: • Surgery and SBRT (level 1) • Surgery with radiosurgery/ radiation boost to the rection cavity with or without WBRT (level 3)
Good prognosis Expected survival 3 months or more	Not resectable	If brain metastasis ≤ 3-4 cm: • Radiosurgery and WBRT (level 1) • Radiosurgery along (level 1) If brain metastasis > 3-4 cm: • WBRT (level 3), with consideration of biopsy, if primary unknown
Poor prognosis Expected survival less than 3 months		If brain metastasis > 3-4 cm: • WBRT (level 3) • Palliative care without WBRT (level 3)

Fair

Table 2. Multiple brain metastases-initial management (adapted from Tsao 2012)

Prognostic Category (*)	Other Features	Treatment Options (evidence grade) References
Good prognosis Expected survival 3 months or more	All brain metastases ≤ 3-4 cm	• Radiosurgery and WBRT (level 1) • Radiosurvery alone (level 1) • WBRT (level 1)
Good prognosis Expected survival 3 months or more	Brain metastasis/metastases causing significant mass effect	• Safe surgical resection for the brain metastasis/metastases causing significant mas effect and postoperative WBRT (level 3) • WBRT (level 3)
Poor prognosis Expected survival 3 months or more		• WBRT (level 3) • Palliative care without WBRT (level 3)

Level I: Evidence obtained from at least 1 properly designed randomized controlled trial.
Level II-1: Evidence obtained from well-designed controlled trials without randomization.
Level II-2: Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than 1 center or research group.
Level II-3: Evidence obtained from multiple time series with or without the intervention.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

IRSA 2008	***Radiosurgery*** *Radiosurgery Versus Resection for Single Brain Metastases* The available data indicate that SRS and open surgical resection (where feasible) are both excellent treatment options for patients with solitary brain metastases. *Role of SRS for Multiple Brain Metastases* Stereotactic radiosurgery is an effective treatment for patients with multiple brain metastases. A substantial amount of published literature now supports use of radiosurgery in the treatment of multiple brain metastases. WBRT and stereotactic radiosurgery should be considered for patients with two or three brain metastases. For patients with good performance status up to three brain metastases, SRS in addition to WBRT is reasonable. *Role of Radiosurgery and Resection for Multiple Brain Metastases* The role of surgery and SRS may be complementary for patients with multiple metastases, particularly in cases where the largest lesion causes symptoms of mass effect and small lesions are unresectable because of their small size or deep location. In this context, the ideal treatment may be surgical resection of the larger or more symptomatic lesions combined with SRS for the surgically inaccessible lesions. This combination approach allows for local treatment of all the brain lesions, which may be the critical factor for a successful outcome.11 Since the University of Kentucky study clearly demonstrated the need for adjuvant therapy after resection of a brain metastasis, WBRT is required for these patients. Alternatively, some authors advocate the use of radiosurgery in the resection cavity when WBRT is withheld,54 though this is controversial. *Radiosurgery in Addition to WBRT: Level I Evidence* There is Level I evidence (three randomized trials) that radiosurgery boost with WBRT, compared with WBRT alone, significantly improves local brain control rate for patients with up to four metastases. There is Level I evidence to indicate that radiosurgery boost with WBRT improves survival in selected patients with a single brain metastasis, and there is Level I evidence that the ability to taper down steroid dose and improvement of KPS was statistically better in the radiosurgery arm at six months. *Radiosurgery Alone as Initial Therapy: Level I Evidence* Conclusion There is Level I to Level II-3 evidence that addition of WBRT in patients treated with radiosurgery for 1–3 newly diagnosed brain metastases does not improve survival, compared with radiosurgery alone with WBRT reserved for salvage therapy. There is Level I evidence that omission of WBRT results in decreased tumor control, both at the site of radiosurgery and also in the remaining untreated brain. Level II-1 and Level II-3 evidence further support this observation. *Repeat Radiosurgery*	**Poor**
	Since tumor control rate after radiosurgery is 80–90%, other management options after radiosurgery may be needed for patients with documented tumor growth. Whole-brain radiation therapy, microsurgery, and in selected cases repeat radiosurgery, can be considered for patients with tumor growth despite radiosurgery. Very little data are available on repeat radiosurgery for brain metastases	

NCCN 2012a	**LTD-2, LTD-3** **Principles of Brain Tumor Radiation Therapy** *Low Grade Gliomas (Grades I/II)* SRS has not been established to have a role in the management of low grade gliomas. Phase I trials using SRS do not support its role as initial treatment. *Meningiomas* WHO grade 1 meningiomas may also be treated with stereotactic radiosurgery doses of 12-14 Gy in a single fraction when appropriate. *Brain Metastases* Stereotactic radiosurgery: recommended maximum marginal doses of 24, 18, or 15 Gy according to tumor volume is recommended. *Metastatic Spine* Doses to vertebral body metastases will depend on patient's performance status and primary histology. Generally doses of 20-37.5 Gy are delivered in 5-15 fractions over 1-3 weeks. In selected cases, or recurrences after previous radiation, stereotactic radiotherapy is appropriate. All recommendations are Category 2A unless otherwise noted: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	**Poor**
NCCN 2012c	**External-Beam Radiation and Surgical Excision of Metastases** For solitary brain lesions, either neurosurgical resection or stereotactic radiosurgery is preferred. **Recurrent and Metastatic Disease** For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred (see Central Nervous System Guidelines). ** algorithm should be reviewed to determine if it includes additional information All recommendations are Category 2A unless otherwise noted: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	**Poor**

Head and Neck		
ACR [McDonald] 2010	In five case variants presented, SBRT therapy "may be appropriate" in one case. SBRT was not considered in the treatment for the remaining four cases.	**Fair**
Lung		
ACCP [Scott] 2007	**Recommendation 2.** For patients with clinical stage I and II NSCLC, it is recommended that they be evaluated by a thoracic surgical oncologist with a prominent part of his/her practice focused on lung cancer, even if patients are being considered for nonsurgical therapies such as percutaneous ablation or stereotactic body radiation therapy (SBRT). Grade of recommendation, 1B [Note: 1B means strong recommendation based on moderate quality evidence and the benefits outweigh the risks and burden of treatment] Other local therapies such as **stereotactic radiation** or radiofrequency ablation may be appropriate for **patients who are medically inoperable**. The use of these techniques in patients who are surgical candidates should not occur outside of the context of a clinical research study.	**Fair**
ACR [Gewanter] 2010	**Stereotactic Body Radiation Therapy** (pg 9) Recently, early-stage tumors have been treated with a hypofractionated approach using advanced treatment delivery techniques such as extracranial stereotactic body radiotherapy (SBRT). A multi-institutional retrospective study in Japan reported the clinical outcomes in 245 patients treated for stage I NSCLC [49]. They observed an extremely favorable local recurrence rate of 14.5% and toxicity in only 2.4% of patients. A phase II trial in the U.S. reported 2-year local control of 95% [50]. However, tumors in the central portion of the lung had excessive toxicity, which led them to recommend not treating lesions in the proximal bronchial tree with doses of 20 Gy per fraction. Emerging institutional data suggest that central early-stage lung lesions can be treated safely with lower doses per fraction (e.g., 10-12 Gy per fraction), and this is the subject of RTOG® dose escalation study.	**Fair**
ACR [Rosenszweig] 2008	(Pg 10) Currently **extracranial stereotactic body radiotherapy (SBRT)** is being examined as an alternative to conventionally fractionated radiotherapy in patients with inoperable stage I disease.	**Fair**

NCCN 2012g	**Principles of Radiation Therapy** *General Principles* Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4DCT simulation, IMRT/VMAT, stereotactic ablative radiotherapy (SABR, also known as SBRT), IGRT, motion management strategies, and proton therapy. Daily IGRT is recommended to ensure accurate delivery when using highly conformal therapy or complex motion management techniques, and should be required for dose-intensified or hypofractionated therapy such as SABR. *Early Stage Lung Cancer (Stage I)* • SABR (traditionally known as SBRT) is recommended for patients who are medically inoperable and is also an appropriate option for many older patients (e.g., > age 75). • For potentially operable patients who refuse surgical therapy despite the complete thoracic surgery consultation, SABR is recommended based on comparable outcomes in non-randomized retrospective comparisons, especially in older patients. *Early stage/SABR* • Treatment of centrally located tumors (defined as within 2 cm of the proximal bronchial tree) using the most intensive SABR regimens (i.e., 54-60 Gy in 3 fractions) is unsafe, but modified/risk-adapted SABR regimens appear to be effective and safe. Normal organ dose limits for centrally located tumors are being studied prospectively. • SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected. All recommendations are Category 2A unless otherwise noted: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	**Poor**
Prostate		
ACR [Morgan] 2011	The use of hypofractionation in general and a stereotactic approach looks very promising, but more robust studies with longer follow-up clearly are needed.	**Fair**
Other cancers/Multiple sites		
ACR [Janjan] 2008	In eight case variants of bone metastases presented, SBRT therapy was considered to be “usually not appropriate” in seven cases. SBRT was not considered in the treatment for the remaining case.	**Fair**

ACR [Lutz] 2011	In five case variants of non-spine bone metastases presented, SBRT therapy was considered to be "usually not appropriate" in four cases. SBRT was not considered in the treatment for the remaining case.	**Fair**
NCCN 2012i	**Limited Metastases** Patients can also receive stereotactic radiosurgery or chemotherapy as an alternate method for control of metastatic lesions. **Disseminated Metastases** The guidelines have included ablation procedures (e.g., radiofrequency ablation or cryotherapy), embolization procedures or stereotactic radiosurgery/RT as options for symptomatic patients with disseminated metastases. The guidelines are intentionally nonspecific about this group of options, because many different issues are factored into this decision (e.g., patient performance status, patient preferences, specific clinical problems from the metastases, treatment availability), and specific details are best left to clinical judgment. All recommendations are Category 2A unless otherwise noted: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	**Fair**

Appendix H. Quality Assessment of Guidelines

Criteria	Guideline Developer, Year													
	American Thyroid Association [Kloos] 2009	Ammirati 2010	Australian Cancer Network 2008	IRSA 2008	NCCN 2012a	NCCN 2012c	NCCN 2012d	NCCN 2012e	NCCN 2012f	NCCN 2012g	NCCN 2012h	NCCN 2012i	Scott [ACCP] 2007	Tsao [ASTRO] 2012
Section 1: Primary Criteria														
Rigor of Development: Evidence	Poor	Good	Good	Poor	Poor	Poor	Poor	Poor	Poor	Poor	Poor	Poor	Fair	Fair
Rigor of Development: Recommendations	Poor	Fair	Fair	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Fair
Editorial Independence	Poor	Poor	Good	Poor	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Good
Section 2: Secondary Criteria														
Scope and Purpose	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Stakeholder Involvement	Good	Fair	Good	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair
Clarity and Presentation	Good	Poor	Good	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Applicability	Fair	Fair	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Fair
Section 3: Overall Assessment of the Guideline														
How well done is this guideline?	**Poor**	**Poor**	**Good**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**	**Fair**	**Fair**

Quality Assessment of ACR Appropriateness Criteria

Criteria	Guideline Developer, Year								
	Gewanter 2010	Janjan 2008	Konski 2011	Lutz 2011	McDonald 2010	Morgan 2011	Patel 2011	Rosenzweig 2008	Suh 2010
Rigor of Development: Evidence	Fair	Fair	Fair	Good	Fair	Good	Fair	Fair	Fair
Rigor of Development: Recommendations	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair
Editorial Independence	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair
Section 2: Secondary Criteria									
Scope and Purpose	Fair	Fair	Fair	Good	Fair	Good	Fair	Fair	Fair
Stakeholder Involvement	Poor	Poor	Poor	Poor	Poor	Poor	Poor	Poor	Poor
Clarity and Presentation	Fair	Poor	Poor	Fair	Poor	Fair	Fair	Fair	Fair
Applicability	Poor	Fair	Poor	Poor	Poor	Poor	Poor	Poor	Poor
Section 3: Overall Assessment of the Guideline									

Criteria	Guideline Developer, Year								
How well done is this guideline?	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair

Appendix I. Summary of Federal and Private Payer Policies

Payer	Coverage Criteria
Medicare	
L28366 07/01/2011 Alaska, Alabama, Arkansas, Arizona, Connecticut, Florida, Georgia, Iowa, Idaho, Illinois, Indiana, Kansas, Kentucky, Louisiana, Massachusetts, Maine, Michigan, Minnesota, Missouri - Entire State, Mississippi, Montana, North Carolina, North Dakota, Nebraska, New Hampshire, New Jersey, Ohio, Oregon,	**Indications for SBRT** SBRT is covered for primary and metastatic tumors of the lung, liver, kidney, or pancreas when and only when each of the following criteria are met, and each specifically documented in the medical record: 1. The patient's general medical condition (notably, the performance status) justifies aggressive treatment to a primary cancer or, for the case of metastatic disease, justifies aggressive local therapy to one or more discreet deposits of cancer within the context of efforts to achieve total clearance or clinically beneficial reduction in the patient's overall burden of systemic disease. Typically, such a patient would have also been a potential candidate for alternate forms of intense local therapy applied for the same purpose (e.g. surgical resection, radiofrequency ablation, cryotherapy, etc). 2. Other forms of radiotherapy, including but not limited to external beam and IMRT, cannot be as safely or effectively utilized, and 3. The tumor burden can be completely targeted with acceptable risk to critical normal structures 4. If the tumor histology is germ cell or lymphoma, effective chemotherapy regimens have been exhausted or are otherwise not feasible. 5. Other forms of focal therapy, including but not limited to radiofrequency ablation and cryotherapy, cannot be as safely or effectively utilized. **Other Indications for SBRT:** Except as above, any lesion with a documented necessity to treat using a high dose per fraction of radiation.

Payer	Coverage Criteria
Rhode Island, South Carolina, South Dakota, Tennessee, Utah, Virginia, Virgin Islands, Vermont, Washington, Wisconsin, West Virginia, Wyoming	When using high radiation doses per fraction, high precision is required to avoid surrounding normal tissue exposure. Lesions which have received previous radiotherapy or are immediately adjacent to previously irradiated fields, where the additional precision of stereotactic radiotherapy is required to avoid unacceptable tissue radiation will be covered when other conditions of coverage are met (see Limitations below) and this necessity is documented in the medical record. **Limitations & Exclusions** Coverage will be denied for each of the following: • Treatment unlikely to result in clinical cancer control and/or functional improvement. • Patients with wide-spread cerebral or extra-cranial metastases • Patients with poor performance status (Karnofsky Performance Status less than 40), or ECOG Performance Status greater than 3) SBRT for Prostate Neoplasms SBRT of the prostate is covered as monotherapy for patients with low risk and low/intermediate risk prostate cancer when: 1. The patient's general medical condition (notably, the performance status) justifies aggressive treatment to a primary cancer. Typically, such a patient would have also been a potential candidate for alternate forms of intense local therapy applied for the same purpose. 2. Other forms of radiotherapy, including but not limited to external beam and IMRT or seed implantation, cannot be as safely or effectively utilized, and 3. The tumor burden can be completely targeted with acceptable risk to critical normal structures Other Neoplasms: Lesions of bone, breast, uterus, ovary and other internal organs not listed above are not covered for primary definitive SBRT as literature does not support an outcome advantage over other conventional radiation modalities, but may be appropriate for SBRT in the setting of recurrence after conventional radiation

Payer	Coverage Criteria
	modalities.
L30318 9/01/2011 Alaska, Alabama, Arkansas, Arizona, Connecticut, Florida, Georgia, Iowa, Idaho, Illinois, Indiana, Kansas, Kentucky, Louisiana, Massachusetts, Maine, Michigan, Minnesota, Missouri, Mississippi, Montana, North Carolina, North Dakota, Nebraska, New Hampshire, New Jersey, Ohio, Oregon, Rhode Island, South Carolina, South Dakota, Tennessee, Utah, Virginia, Virgin Islands, Vermont, Washington, Wisconsin, West	**Indications for SRS** Intracranial lesions are covered under the following conditions: 1. The lesion(s) has an image-distinct margin. 2. The Karnofsky Performance Scale is greater than 50% (range is 0 - 100% with 100% = maximum functional level) or the ECOG performance status should be 2 or less. 3. Specific indications will include: a. Neuromas of the cranial nerves including acoustic, trigeminal, etc. b. Intracranial unresectable meningioma and/or residual meningioma where the neurosurgeon determines the patient's medical condition precludes surgery; and where, because of the location of the tumor, surgery would result in devastating neurodeficits. c. Coverage for treatment of metastatic brain lesions under the following conditions: – Patients should have essentially otherwise stable disease. – The lesion(s) margins should be radiographically distinct. – The number of lesions treated should not exceed five. d. As a boost treatment for larger cranial lesions that have been treated initially with external beam radiation therapy or surgery: i.e., grade III and IV gliomas: pilocytic astrocytoma, oligodendrogliomas, sarcomas, chordomas. e. Trigeminal neuralgia refractory to medical treatment 4. AV Malformations 5. Acoustic neuromas 6. Pituitary adenomas 7. Craniopharyngiomas 8. Glomus Jugulare tumors **Indications for SRT**

Payer	Coverage Criteria
Virginia, Wyoming	Fractionated cranial stereotactic radiotherapy is considered medically necessary for treatment of intracranial tumors in hard-to-reach locations, tumors with very unusual shapes, or for tumors located in such close proximity to a vital structure (e.g., optic nerve or hypothalamus) that even a very accurate high-dose single fraction of stereotactic radiosurgery could not be tolerated. Current indications for SRT include: 1. Benign Lesions a. Arteriovenous Malformations b. Pituitary Adenoma c. Vestibular schwannoma d. Meningioma 2. Also for benign neoplasms that were previously treated with conventional radiotherapy. a. Craniopharyngiomas b. Pineocytomas c. Low grade astrocytic and ganglioneuronal tumors d. Hemangioblastomas e. Nonacoustic schwannomas. 3. Malignant Lesions a. Lesions within 5 mm of the optic nerves or chiasms b. Recurrent malignant gliomas c. Brain metastasis d. Base of skull e. Certain types of recurring malignancies - head and neck cancers, such as cancer of the tonsil, larynx, tongue, sinus, and mouth
Private Payers	
Aetna	Clinical Policy Bulletin: Stereotactic Radiosurgery

Payer	Coverage Criteria
01/11/2011	Aetna considers stereotactic radiosurgery medically necessary according to the following selection criteria. 1. Cranial SRS is considered medically necessary when used for *any* of the following indications: 1. For treatment of members with symptomatic, small (less than 3 cm) arterio-venous (AV) malformations, aneurysms, and benign tumors (acoustic neuromas (vestibular schwannomas), meningiomas, hemangiomas, pituitary adenomas, craniopharyngiomas, and neoplasms of the pineal gland) if the lesion is unresectable due to its deep intracranial location or if the member is unable to tolerate conventional operative intervention; *or* 2. For members with trigeminal neuralgia that has not responded to other more conservative treatments; *or* 3. For treatment of brain malignancies (primary tumors and/or metastatic lesions). 2. SBRT is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required (e.g., lung or liver metastases not amenable to surgery, medically inoperable early stage lung cancer, primary liver cancer not amenable to surgery, spinal and para-spinous tumors, not an all inclusive list). 3. Fractionated stereotactic radiotherapy is considered medically necessary when criteria for SRS are met. Fractionated stereotactic radiotherapy is useful for treatment of tumors in hard-to-reach locations, tumors with very unusual shapes, or for tumors located in such close proximity to a vital structure (e.g., optic nerve or hypothalamus) that even a very accurate high-dose single fraction of stereotactic radiosurgery could not be tolerated.
Regence BCBS 01/01/2012	**SRS and SBRT** 1. SRS and SBRT using Gamma Knife®, LINAC, Cyberknife®, BrainLAB Novalis®, or TomoTherapy® units may be considered medically necessary for the following indications: a. Intracranial arteriovenous malformations b. Acoustic neuromas (also known as Vestibular Schwannomas) c. Pituitary adenomas d. Non-resectable, residual, or recurrent meningiomas e. Solitary or multiple brain metastases in patients who meet both of the following:

Payer	Coverage Criteria
	i. Karnofsky performance score ≥70 (or an ECOG score £2); AND ii. Life expectancy >6 months. f. Primary malignancies of the CNS, including but not limited to high-grade gliomas (initial treatment or treatment of recurrence) g. Spinal or vertebral body tumors (metastatic or primary) in patients who have received prior radiation therapy h. Trigeminal neuralgia (also known as tic douloureux) refractory to medical management i. Stage 1 non-small cell lung cancer (NSCLC) when the patient is an unsuitable candidate for surgical resection. i. Stage 1 NSCLC is defined by the following clinical stage groupings: 1. T1, N0, M0 2. T2, N0, M0 j. Lung metastases when all of the following criteria are met: i. Life expectancy >6 months ii. Karnofsky performance score ≥70 iii. Adequate lung function iv. Locally controlled primary tumor v. £3 metastatic lung lesions (oligometastases) vi. Targeted tumor diameter £5cm vii. Clinical records from a cardiothoracic surgeon document at least one of the following: – The tumor is not resectable; or – The patient is not a good surgical candidate.

Payer	Coverage Criteria
	ii. No other metastatic disease 2. SRS and SBRT are considered investigational for all other indications including but not limited to: a. Treatment of extracranial sites (e.g. prostate, ovaries), except for the cases of spinal tumors and stage 1 non-small cell lung cancer as noted above
GroupHealth 4/05/2011	**Stereotactic Radiation, Fractionated Stereotactic Radiotherapy, CyberKnife Robotic Radiosurgery System** **Indications for SRS** 1. For treatment of members with symptomatic, small (less than 3 cm) arterio-venous (AV) malformations, aneurysms, and benign tumors (acoustic neuromas (vestibular schwannomas), meningiomas, hemangiomas, pituitary adenomas, craniopharyngiomas, and neoplasms of the pineal gland) if the lesion is unresectable due to its deep intracranial location or if the member is unable to tolerate conventional operative intervention; or 2. For members with trigeminal neuralgia that has not responded to other more conservative treatments or 3. For treatment of brain malignancies. **Indications for SBRT** Primary or metastatic tumors of the lung, liver, kidney, adrenal gland, or pancreas and each of the following criteria must be met, and each specifically documented in the medical record: 1. The patient's general medical condition (notably, the performance status) justifies aggressive treatment to a primary cancer or, for the case of metastatic disease, justifies aggressive local therapy to one or more discreet deposits of cancer within the context of efforts to achieve total clearance or clinically beneficial reduction in the patient's overall burden of systemic disease. Typically, such a patient would have also been a potential candidate for alternate forms of intense local therapy applied for the same purpose (e.g. surgical resection, radiofrequency ablation, cryotherapy, etc). 2. Other forms of radiotherapy, including but not limited to external beam and IMRT, cannot be as

Payer	Coverage Criteria
	safely or effectively utilized, and 3. The tumor burden can be completely targeted with acceptable risk to critical normal structures 4. If the tumor histology is germ cell or lymphoma, effective chemotherapy regimens have been exhausted or are otherwise not feasible. 5. Other forms of focal therapy, including but not limited to radiofrequency ablation and cryotherapy, cannot be as safely or effectively utilized. Clinical documentation submitted with the request must include all of the following: 1. Support of the necessity and frequency of treatment 2. Standard history and physical 3. The patient's current functional status and a description of the current performance status (Karnofsky Performance Status)

Appendix M. MAUDE Database

Search terms: stereotactic radiation therapy, stereotactic radiosurgery, sbrt, srs, cyberknife, cyber knife, gamma knife and gammaknife

Dates: 2002-2012

Outcomes of interest: serious injury (surgery, hospitalization, death)

Manufacturer	Brand Name	Report Date	Summary of Reported Harms
Unknown	Unknown	3/14/2005	Pt had craniotomy for metastatic adenocarcinoma with a lung primary in the left lower lobe. Pt rec'd stereotactic radiosurgery to the left lung 18 days later. They started whole brain radiation 11 days later. They rec'd 2500 cgy in 10 fractions. Two weeks later they presented with increased sob, poor appetite and weakness. A cxr showed a large density in the right lower lobe. The next day they became unresponsive and were admitted to hospice. Their condition continued to decline and pt expired 3 days later. Probable cause of death is either pneumonia, progressive tumor or pe unlikely related to treatment.
Varian	CLINAC 21 EX Linear Accellerator	9/15/2006	Varian medical systems received a report involving a patient death. The customer stated, a female patient, with a case of stomach cancer that had metastasized to the brain was exposed to an over-dose of radiation during stereotactic radiosurgery (srs) treatment. This was due to the radiologist failing to attach the accessory cone mount to the clinac. The over-dose was estimated to be 20-30gy. The hospital has taken the position that there is no cause and effect due to the radiation over-dose. The cause of death was stated as, "cessation of breathing due to complications from lung cancer."
Angiodynamics	Nanoknife	9/15/2011	A male pt of unk age presented for a nanoknife ablation procedure of a large (4-5cm) unresectable pancreatic lesion incasing the superior mesenteric artery

Manufacturer	Brand Name	Report Date	Summary of Reported Harms
			(sma) and superior mesenteric vein (smv) on (b)(6) 2011. The physician originally planned to treat with four (4) probes and place them caudo-cranially along the sma and smv. Due to the vasculature and anatomy of the lesion, the physician placed two (2) probes via an anterior approach perpendicular to the sam and smv, between the sma and smv to de-bulk the lesion. The sma and smv were in the treatment area during the procedure. There was no report of a device malfunction during the course of the procedure. On (b)(6) 2011, it was reported by the physician who performed the procedure, that approx two weeks post-procedure, the pt developed a portal vein thrombosis and has an occluded hepatic artery resulting in significant cirrhosis over most of the liver. It was noted that the pt did not present any liver problems pre-ablation. It was reported that the pt has had several treatments of neoadjuvant chemotherapy and cyberknife prior to the nanoknife ablation.

Appendix N. Report Errata

Report Location	Action
pg 2, para 2	Typo (replaced “IMRT” with “SRS and SBRT”)
pg 23, para 3	Typo (replaced “one [study] focuses” with “two focus”
pg 60 - 66	Typo (replace all instances of “Linskey 2009” with “Linskey 2010”)
pg 61	Typo (corrected quality assessment rating for Chang 2009b and Kocher 2011)
pg 66, para 4	Inserted “Chang 2011b” as a citation under KQ 4
pg 72, para 6	Typo (replaced “two fair quality” with “one fair quality and one poor quality”)
pg 83, para 3	Deleted “and range from $10,200/QALY to $40,300/QALY”
pg 121, para 1	Typo (replaced “IMRT” with “SBRT”)
pg 124, para 3	Replaced search results numbers to match report body and executive summary
Appendix G	Inserted guideline quality ratings into table
Appendix G	Replaced images with adapted tables for ASTRO [Tsao] (2012) guideline

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