Washington State Health Care Authority

Health Technology Assessment

# Intensity Modulated Radiation Therapy

## Final Evidence Report

September 6, 2012

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# *Intensity Modulated Radiation Therapy*

**September 6, 2012**

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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

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## List of Abbreviations

**bDFS** – biochemical disease-free survival

**BRT** – brachytherapy

**CBTR –** contralateral breast tumor recurrence

**CRT** – conventional radiation therapy also referred to as EBRT

**2DCRT** – two dimensional conventional radiation therapy

**3DCRT** – three dimensional conventional radiation therapy

**DFS** – disease-free survival

**DSS** – disease-specific survival

**EBRT** – external beam radiation therapy

**GI** – gastrointestinal

**GU** – gastrourinary

**HR** – hazard risk

**IBTR –** ipsilateral breast tumor recurrence

**IGRT** – Image-guided radiation therapy

**IMRT** – intensity-modulated radiation therapy

**MA –** meta-analysis

**NSCLC** – non-small cell lung cancer

**OR** – odds ratio

**OS** – overall survival

**PFS** – progression-free survival

**QoL** – quality of life

**RCT** – randomized controlled trial

**RFS** – recurrence-free survival

**RR** – relative risk

**SCLC** – small-cell lung cancer

**SR** – systematic review

**TA** – technology assessment

**VMAT** – volumetric-modulated arc 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. One of these newer techniques is intensity modulated radiation therapy (IMRT). Intensity modulated radiation therapy, like other forms of EBRT is used as primary treatment or in conjunction with surgery, hormonal therapy and/or chemotherapy; it is used in treatment in primary, recurrent and metastatic cancer.

Intensity modulated radiation therapy has been used for treatment of tumors of the central nervous system, head and neck, breast, prostate, gastrointestinal tract, and gynecologic system. It can be used to treat sites previously treated with radiation and areas in close proximity to organs and vulnerable tissue (American College of Radiology & American Society for Radiation Oncology [ACR-ASTRO] 2011).

### *Technology overview*

Typically, conventional EBRT (also called 2-dimensional conventional radiation therapy (2DCRT) or 3-dimentional conventional radiation therapy (3DCRT))[1] is delivered in 25 to 50 fractions (doses) delivered five days per week for 5 to 10 weeks. Intensity modulated radiation therapy uses hundreds of radiation beam-shaping devices (collimators) to deliver external beam radiation (Tipton 2011b). The collimators allow the intensity of the radiation to vary during a treatment session thus different doses of radiation can be directed at different areas of the tumor and nearby tissues. The goal of IMRT is to increase radiation to the tumor while reducing radiation exposure to normal tissue. Treatment planning for IMRT involves additional steps to contour the radiation dose to the tumor and to reduce radiation to surrounding tissues; these additional steps and the additional time required to administer each treatment fraction during the course of therapy result in considerably more cost for IMRT than EBRT.

### *Cost information*

Intensity modulated radiation therapy typically costs approximately twice as much as EBRT. The following approximate charges for IMRT were identified for this report:

- Non-small cell lung cancer: EBRT$55,000, IMRT $146,000 (Tipton 2011a);
- Breast cancer (whole breast irradiation): EBRT $9,500, IMRT $17,900 (Suh 2005);
- Breast cancer (partial breast irradiation): EBRT $7,200, IMRT $9,200 (Suh 2005); and
- Prostate cancer: EBRT ranging from $10,000 to $27,000, IMRT ranging from $33,000 to $52,000 (Hummel 2010).

[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.

### *Policy context*

Use of new radiation technologies has grown dramatically in the last decade. Among men with prostate cancer receiving external beam radiation, the use of IMRT increased from 29% in 2002 to 82% in 2005 to 96% in 2008 (Jacobs 2012; Sheets 2012). Among women with breast cancer, the likelihood of IMRT use for breast cancer rose from 0.9% in 2001 to 11.2% in 2005 (Smith 2011). Despite this rapid adoption of IMRT, the Federal Food and Drug Administration (FDA) process for approving new radiation therapies does not require a review of safety and efficacy, which has resulted in limited information about efficacy and comparative effectiveness of IMRT.

## Methods

### *Key Questions*

**KQ 1**: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?

**KQ 2**: What are the potential harms of IMRT 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 IMRT has 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 IMRT compared to EBRT?

### *Methods – Evidence*

For this WA HTA report, 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 the MEDLINE® and Cochrane databases.

General inclusion criteria:

- Published, peer reviewed, English-language articles;
- SRs, TAs, RCTs, and observational comparative study designs (prospective, retrospective, and controlled clinical trials);
- 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 malignancy:

*Breast, Head and Neck, Prostate*

- Minimum sample size of 50 participants;

*Less prevalent malignancies (abdomen, brain, female pelvis, lung, sarcoma, skin, thyroid, spinal metastases)*

- SRs, TAs, RCTs, observational comparative study designs (prospective, retrospective, and controlled clinical trials) and *case series*;
- 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, and/or included patients who were concurrently receiving chemotherapy (with the exception of head and neck cancers) were excluded.

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 that are modifications of the 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, poor, based on its adherence to recommended methods and potential for biases. 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 that are modifications of the British Medical Journal (Drummond 1996), the Consensus on Health Economic Criteria list (Evers 2005), and the NICE economic evaluation checklist (NICE 2009). The overall strength of evidence was rated (high, moderate, low, very low) using a modified version of 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 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, then the other review(s) were excluded;
- Additional search of the MEDLINE® and Cochrane databases completed to identify subsequently published studies. Individual studies published after the search dates of the last high quality review were appraised and synthesized with the results of the high quality SR; 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 2002 to April 2012).

For Key Question #4, all relevant economic evaluations were included.

### *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 US Food and Drug Administration (FDA), was searched using the terms intensity modulated, intensity modulated radiation therapy, intensity modulated radiotherapy, and imrt. The search was limited to adverse events reports submitted between 2002 and 2012. Two reports of serious adverse events were identified and are summarized in Appendix L.

### *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 considered in drafting the final report. The full peer reviews and disposition are available in Appendix J. Full comments submitted by the public with disposition are available in Appendix K.

## Findings

This report provides the best available evidence for multiple cancer types. The most completely evaluated cancers are cancers of the **head and neck, breast and prostate**. 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 some are designed to compare IMRT with EBRT but many are non-comparative studies that give outcomes or harms results for IMRT without comparison with EBRT. Because of the absence of randomized trials and comparative studies, the strength of the evidence is very low or low for most of the findings.

## Abdomen (Anus, Esophagus, Liver, Pancreas, Rectum, Stomach, Whole Pelvis Radiation)

In this section, tumors of the anus, liver, pancreas, rectum, and stomach and treatments involving whole pelvis radiation are summarized. One study on cancer of the esophagus is included in this section even though the esophagus is not technically in the abdomen.

### Anal Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low that IMRT is associated with better 3-year OS, 3-year locoregional control, and 3-year PFS when compared to EBRT for treatment of anal cancer.

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

There is very low overall strength of evidence that IMRT had significant reductions in acute greater than Grade 2 nonhematologic toxicity, skin, and mucosal eruptions in the female genital area, and acute Grade 2 diarrhea after treatment compared with EBRT. When treatment is a combination of chemotherapy and IMRT, there is a very low overall strength of evidence that toxicity may be related more to chemotherapy based on one small case series.

**KQ 3: What is the evidence that IMRT has differential efficacy or safety issues in subpopulations?**

Based on one fair quality case series, the overall strength of evidence is very low that there is no difference in 3-year local control and 3-year OS for IMRT compared to EBRT for the treatment of HIV-positive patients with anal cancer.

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

No studies on costs or cost-effectiveness were identified.

### Esophagus

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. One small, poor quality case series reported 1-year OS (79%), 2-year OS (38%), and 2-year actuarial loco-regional control of 64%. Due to the lack of a comparative data, no conclusions can be reached regarding clinical effectiveness.

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

The overall strength evidence is very low.  One poor quality case series reported moderate levels of acute and chronic complications.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

<u>Liver</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. Three poor quality case series reported mean of 5 to 16 months. Due to the lack of a comparative data, no conclusions can be reached regarding clinical effectiveness.

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

The overall strength of evidence is very low. Among patients treated with IMRT in one poor quality case series for hepatocellular cancer, approximately 28% of patients experienced less than or equal to Grade 2 hepatic toxicity. Two poor quality case series reported moderate levels of nausea, vomiting and changes in hepatic function. Due to the lack of comparative data, no conclusions can be reached regarding relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

<u>Pancreas</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. One poor quality case series reported 1- and 2-year OS rates of 79% and 40%, respectively. Due to the lack of comparative data, no conclusions can be reached regarding the clinical effectiveness.

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

The overall strength of evidence is very low. One poor quality case series reported acute and chronic toxicity GI in 9% of patients. Due to the lack of comparative data, no conclusions can be reached regarding relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

The overall strength of evidence is low. One poor quality cost-effectiveness modeling study calculated that IMRT had an ICER of $1,584,100/QALY compared to EBRT.

### Rectum

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. One poor quality case series of 63 patients reported 2-year PFS and OS rates of 90% and 96%, respectively. Due to the lack of comparative data, no conclusions can be reached regarding the clinical effectiveness.

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

The overall strength of evidence is very low. One poor quality case series reported relatively low levels of complications. Due to the lack of comparative data, no conclusions can be reached regarding the relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Stomach

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. Based on two small, poor quality cohort studies, there is inconsistent evidence on whether IMRT improves 2-year OS compared with 3DCRT.

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

The overall strength of evidence is very low. The two poor quality cohort studies report decrease in renal function measured by creatinine levels for 3DCRT compared to IMRT; the difference was significant in one study but not the other study. The effect of chemotherapy on renal toxicity is not investigated in either study.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Whole Pelvis Radiation

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

No studies on effectiveness were identified.

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

Among patients treated with IMRT for whole pelvis radiation[2], there is very low overall strength of evidence that there were no significant differences in toxicity frequency for IMRT compared to EBRT.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

[2] Study included patients with endometrium, cervical, rectum, anal canal, and bladder cancers.

No studies on costs or cost-effectiveness were identified.

## Brain

In this section, evidence on intracranial tumors is summarized. There is limited evidence for all tumor types. No other cancers were identified for this section. The sections are divided up by intracranial malignancy and include the following: astrocytomas, brain metastases, glioblastomas, high-grade gliomas, medulloblastomas, meningiomas, pituitary adenomas, and sacral chodomas. 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.

### Astrocytoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

There is very low overall strength of evidence that patients treated by IMRT had significantly greater 1-year OS and PFS than EBRT. There is very low overall strength of evidence that the IMRT group had greater 2-year OS and PFS compared to EBRT.

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

There is very low overall strength of evidence. One fair quality cohort study reported that patients undergoing treatment with IMRT for astrocytoma had fewer Grade 1 toxicities, but more Grade 2 and 3 toxicities than patients undergoing EBRT. Due to the limitations of small sample size, no conclusions can be reached regarding relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Brain metastases

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. The sole study identified did not compare treatment groups, which precluded any conclusions about the relative effectiveness of volume-modulated arc therapy (VMAT) treatment for patients with brain metastases. Patients treated solely by VMAT had six-month OS of 55.1%, while patients treated by surgery and VMAT had six-month OS of 72.0%. Further, individuals undergoing VMAT treatment had significantly decreased physical functioning and role functioning scores on self-assessments of QOL.

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

The overall strength of evidence is very low. Given the lack of a comparator, no conclusions can be reached regarding the relative harms of VMAT treatment. As reported by one fair quality case series, patients treated by VMAT with brain metastases experienced Grade 1 and 2 alopecia.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Glioblastoma multiforme

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. As reported by three case series, the 2-year OS ranged from 0% to 55.6%, 2-year PFS ranged from 0% to 53.6%, median PFS was 9.0 months (95% CI, 6.0-11.7), and median OS ranged from 14.4 to 20.1 months. Due to the lack of a comparator, no conclusions can be drawn.

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

The overall strength of evidence for all harms is very low. One fair quality case series reports on IMRT alone; two additional case series (one fair quality, one poor quality) report on IMRT plus chemotherapy. Results from the case series are inconsistent. One case series reported Grade 3 or higher toxicity in 38% (8 patients); one case series reported Grade 3 neurotoxicity in 16% (6 patients); and one case series reported no Grade 3 or higher toxicity. Due to the lack of comparative data, no conclusions can be reached regarding relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on cost or cost-effectiveness were identified.

## High-Grade Glioma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. Due to the lack of a comparator in both studies identified, no conclusions can be reached regarding effectiveness. As reported by two fair quality case series, patients undergoing treatment with IMRT for high-grade gliomas had varying ranges of OS, PFS, and actuarial[3] OS. Differences between the studies preclude drawing any conclusions.

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

The overall strength of evidence is very low. Due to the lack of a comparator in the sole study identified, no conclusions can be reached regarding harms. As reported by one fair quality case series, patients undergoing treatment with IMRT for high-grade gliomas had toxicities ranging from grade 1 to 3, including reports of edema or worsening of neurological symptoms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Medulloblastoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. One poor quality case series reported 5-year PFS of 81.4% and 5-year OS of 88.4% for standard risk patients. Rates for 5-year PFS and OS for high risk patients were both 87.5%. Due to the lack of comparative data, no conclusions can be made on clinical effectiveness.

[3] For actuarial OS, OS is calculated for each time interval. This method of OS calculation tends to be more specific than calculating the median or mean OS.

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

The overall strength of evidence is very low that children undergoing treatment with IMRT for medulloblastoma had reduced rates of Grade 3 or 4 ototoxicity compared to those undergoing EBRT, but did not have significant differences in neurocognitive function. Two case series of IMRT and chemotherapy reported ototoxicity levels of 6% to 25%.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Meningioma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. Due to the lack of comparators in all three studies, no conclusions can be reached regarding clinical outcomes based on the limited evidence. As reported by three case series, patients undergoing treatment with IMRT for meningioma had varying reported survival outcomes. Differences in survival outcome measures precluded combination of the findings.

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

The overall strength of evidence is very low. Due to the lack of comparators in the sole study identified, no conclusions can be reached regarding harms based on the limited evidence. As reported by one poor quality case series, patients undergoing treatment with IMRT for meningioma experienced no severe toxicities.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Pituitary Adenoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. Due to the lack of a comparator in the sole study identified, no conclusions can be reached regarding clinical outcomes. As reported by one poor quality case series, patients had a 22% complete response rate and a 78% partial response rate.

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

The overall strength of evidence is very low. Due to the lack of a comparator in the sole identified study, no conclusions can be reached regarding harms based on the limited evidence. Patients experienced toxicities of varying chronicity and type with the most common being fatigue as reported by one poor quality case series. In addition, 29 patients reported long-term (≥ 12 months) harms in cognitive changes, visual decline, and cranial nerve deficits.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Breast

### Whole Breast Irradiation

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

Two SRs reported inconclusive findings for patient survival and one retrospective cohort study (N=240) comparing IMRT to 2DCRT reported no significant differences in OS. The overall strength of evidence is low that there are inconsistent findings for patient survival (OS, DSS).

For cancer recurrence (IBTR, CBTR, and local regional recurrence) and distant metastases, one comparative study reported no significant differences compared to 2DCRT; the other included studies reported a range of 0% to 2.9% with no comparative data. The overall strength of the evidence for these outcomes (i.e., IBTR, CBTR, distant metastases) is low.

There is limited evidence on QoL outcomes from IMRT. There is moderate overall strength of evidence that IMRT compared to EBRT does not result in significant differences in QoL.

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

The overall strength of evidence is low that there is inconsistent evidence for breast cosmesis when IMRT is compared to EBRT.

There is moderate overall strength of evidence that IMRT compared to EBRT does not result in a significant difference in acute toxicities (i.e., Grade 2 or higher acute toxicities, Grade 3 or 4 skin toxicities).

One large prospective RCT (n=815) reported that the EBRT group was 1.68 times more likely to develop any Grade (1, 2, or 3) of telangiectasia compared to IMRT (moderate overall strength of evidence). There are inconsistent findings that IMRT, compared to EBRT, is associated with lower rates of late Grade 2 or greater breast edema or hyperpigmentation (low overall strength of evidence). Limited evidence reported no significant differences in late Grade 2 or greater fat necrosis or induration/fibrosis for IMRT compared to EBRT; the overall strength of evidence is low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

Results of analysis of SEER data demonstrated increased costs for IMRT compared with EBRT. The overall strength of evidence that IMRT costs more than EBRT is low. There are no cost effectiveness studies.

## Partial Breast Irradiation

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

No studies reported on patient survival. Only one patient in all three case series (N=175) had localized ipsilateral tumor recurrence. The overall strength of the evidence for local tumor recurrence is very low.

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

The evidence on breast cosmesis following accelerated partial breast irradiation by IMRT is mixed. There is limited evidence on the harms of accelerated partial breast irradiation with IMRT. The overall strength of evidence for all harms reported is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

One cost-comparison study was identified; no cost effectiveness studies were identified. The overall strength of evidence that IMRT costs more than EBRT is low.

## Female Pelvis

In this section, tumors of the female pelvis are summarized (i.e., cervical cancer and paraaortic lymph node metastases). There is limited evidence for both cancers. No other cancers were identified for this section.

### Cervical Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

For treatment of cervical cancer with IMRT, OS findings are inconsistent. Although two smaller cohort and case series studies found no difference compared to EBRT, one larger cohort study included in an SR found significant benefit for patients treated by IMRT. The overall strength of evidence is low that IMRT was associated with increased DSS and OS for patients with cervical cancer compared to EBRT.

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

Findings from one cohort and two case series studies provide an overall low strength of evidence that IMRT was associated with lower frequency of toxicities than EBRT for cervical cancer.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Endometrial Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. One poor quality cohort study reported a pooled 2-year DFS and 2-year OS of 55% for the IMRT and EBRT groups. Due to the lack of comparative data, no conclusions can be reached regarding clinical effectiveness.

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

The overall strength of evidence is very low. One small poor quality cohort study reported no significant different in toxicity between IMRT and EBRT groups. The effect of chemotherapy on the incidence of toxicities is not considered.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Paraaortic lymph node metastases

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

There is very low strength of evidence that treatment with IMRT for paraaortic lymph node metastases was associated with increased overall 2- and 3-year survival compared to EBRT.

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

There is very low strength of evidence that IMRT was associated with less frequency of GI and GU toxicities compared to EBRT.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Head and Neck Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is low that there was no significant difference between IMRT and EBRT in local tumor control or OS. The findings on xerostomia-related QoL are inconsistent. However, there is a preponderance of the evidence supporting that IMRT compared to 2D- and 3DCRT improves xerostomia-related QoL. Therefore, the overall strength of evidence that IMRT compared to 2D- and 3DCRT improves xerostomia-related QoL is moderate.

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

Six systematic reviews and an additional 49 articles address harms. There is moderate overall strength of evidence that IMRT reduces Grade 2 or greater xerostomia compared to EBRT. There is a very low strength of evidence that there is no significant difference in incidence of osteonecrosis from IMRT compared to EBRT. There is very low strength of evidence that there is no significant difference in hearing loss from IMRT compared to EBRT. The overall strength of evidence for all other harms (i.e., nausea, vomiting, fatigue, dermatitis, mucositis, dysphagia, laryngeal symptoms) is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

One cost study estimated the total cost of IMRT treatment to be €10,916 (SD=€6,454). The overall strength of evidence is low that IMRT costs more compared to EBRT. The overall strength of evidence is low that experienced centers had lower direct costs compared to centers initiating IMRT.

## Lung Cancer

In this section, tumors of the lung are summarized. There is limited evidence for NSCLC, pleural mesothelioma, and SCLC. No other cancers were identified for this section.

### Non-small cell lung cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

One comparative study and five case series were identified. The overall strength of the evidence is low that patients treated with IMRT compared to 3DCRT for non-small cell lung cancer had better OS. The overall strength of evidence is low that there were no significant differences in distant metastasis-free survival or locoregional PFS for IMRT compared to 3DCRT. No conclusions can be drawn from the case series since they did not compare IMRT to EBRT. The overall strength of evidence for all other outcomes is very low.

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

Two comparative studies and six case series were identified. The overall strength of the evidence is low that NSCLC patients treated with IMRT compared to EBRT had significantly lower levels of greater than or equal to Grade 3 pneumonitis.

The remaining outcomes were only reported in noncomparative studies, and therefore no conclusions can be drawn for IMRT compared to other treatments. In general, Grade 1 or 2 toxicities were reported with varying degrees in numbers and the good to fair quality case series reported patients with esophagitis, Grade 2 and 3 late esophageal stricture, Grade 3 or greater treatment-related pneumonitis (including one death), pulmonary fibrosis, and Grade 3 pulmonary toxicities. The overall strength of evidence is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Pleural mesothelioma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of the evidence is very low and is based on two small case series and one small cohort study. The small cohort study reported a statistically significant reduction in local recurrence but did not separate the results for OS. The two case series reported that patients treated with IMRT for pleural mesothelioma had OS rates (1- to 5-year estimates) between 79% and 50% and DFS rates (1- to 5-year estimates) between 88% and 29%.

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

A total of three case-series with small sample sizes were identified. One study reported fatal radiation pneumonitis in 6 of 13 patients and another study reported Grade 3 radiation-induced esophagitis in 7% of cases. A fair quality case series reported common toxicities (varying in Grade and toxicity) among patients treated with IMRT for pleural mesothelioma and two late deaths possibly related to radiation therapy. There are no comparative studies, and therefore no conclusions can be drawn from IMRT compared to other or no treatments. The overall strength of the evidence is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Small-cell lung cancer (SCLC)

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

Based on a single fair quality case series, patients treated with IMRT for SCLC had 2-year OS of approximately 58% and RFS of 43%. There are no comparative studies, and therefore no conclusions can be drawn for IMRT compared to other or no treatments. The overall strength of the evidence is very low.

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

Based on a single fair quality case series (n=60), SCLC patients treated with IMRT experienced acute pneumonitis and esophagitis in 23% and 7% of patients, respectively. No chronic Grade 3 pneumonitis or esophagitis were reported. There are no comparative studies, and therefore no conclusions can be drawn for IMRT compared to other or no treatments. The overall strength of the evidence is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Prostate Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

Three systematic reviews and seven cohort studies were identified. There is low strength evidence that there were no significant differences in overall survival for IMRT compared to EBRT at 30 months. There was low overall strength of evidence for a significant difference in bDFS at 60 months favoring the IMRT group compared to EBRT. There is low strength of evidence that IMRT compared to EBRT had lower rates of cancer recurrence at three years.

Two fair quality cohort studies reported inconsistent findings for QoL in different populations. Therefore no conclusions can be drawn and the overall strength of evidence is low.

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

Comparison of harms is difficult because of the different dosages, treatment regimens, cancer stages, and outcomes studied. However, based on three large cohorts, there is an overall moderate strength of evidence that IMRT improves GI toxicities compared to EBRT. There is an overall low strength of evidence that IMRT improves GU toxicities compared to EBRT.

There is low strength of evidence that the IMRT group was less likely to experience hip fractures compared to CRT. Based on four cohort studies, the evidence on erectile dysfunction is inconsistent. A large, good quality cohort study found that the IMRT group was more likely to receive a diagnosis of erectile dysfunction (RR 1.12; 95% CI 1.03-1.20). However, the effect size was small. There is an overall low strength of evidence for this outcome.

**KQ 3**: **What is the evidence that IMRT has 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 IMRT compared to EBRT?**

One TA encompassing two cost-effectiveness analyses and one cost-minimization analysis addressed the use of IMRT for prostate cancer. The overall strength of evidence for cost-effectiveness of IMRT is very low.

Konski (2004, 2005, 2006) as reported in Hummel (2010) calculated an incremental cost-effectiveness ratio of $16,182/QALY to $40,101/QALY for IMRT as compared to 3DCRT. This meets a commonly-accepted threshold of $50,000/QALY. However, these calculations assumed a 14% difference in survival between groups and essentially a 100% difference in GI and GU utility between groups, which is not supported by evidence. Pearson (2007), as reported in Hummel (2010), assumed no difference in survival and less rectal toxicity with IMRT; this study calculated an ICER of $706,000/QALY, which is well in excess of the usual threshold for cost-effectiveness. Perlroth (2010) was a cost-minimization study that assumed equal effectiveness across treatments and did not consider quality of life measures; this study calculated median overall adjusted 2-year costs of $68,300 for IMRT compared to $21,400 for active surveillance.

## Sarcoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

One case series was identified. No evidence was identified that compared IMRT to EBRT for patients with sarcomas. The case series reported seven patients (26%) had local recurrence. No conclusions can be drawn for local recurrence and the overall strength of evidence is very low.

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

The overall strength of evidence for all reported harms is very low. A single case series reported the following harms: nausea, fatigue, dry mouth, pharyngitis or esophagitis, and pain and one patient developed Grade 4 skin toxicity that required plastic surgery. There are no comparative studies for all other harms and therefore no conclusions can be drawn.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Other Cancers (Skin, Thyroid, Spine)

In this section, tumors of the skin, thyroid, and spine are summarized. There is limited evidence for all three cancers. No other cancers were identified for this section.

### Sacral chordoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. Given the lack of a comparator in the sole study identified, no conclusions can be reached regarding clinical effectiveness. As reported by one poor quality case series, patients undergoing treatment with IMRT for sacral chordoma had actuarial survival estimates (1- to 5-year) between 97% and 70%, DSS estimates (1- to 5-year) between 100% and 80%, and actuarial DSS (1- to 5-year) between 97% and 49%.

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

The overall strength of evidence is very low. Due to the lack of a comparator in the sole study identified, no conclusions can be reached regarding harms. As reported by one poor quality case series, patients experienced less than or equal to Grade 2 toxicities including diarrhea (26%), bladder irritation (6%), erythema (38%), and hyperpigmentation (15%) after treatment with IMRT for sacral chordoma.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Skin Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is very low. There are no comparative studies and therefore no conclusions can be drawn. As reported by a single poor quality case series, 60% of patients treated with IMRT for skin cancer had no disease recurrence at 12 months.

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

The overall strength of evidence is very low. There are no comparative studies and therefore no conclusions can be drawn. As reported by a single poor quality case series, all patients (n=21) experienced grade 1 or 2 erythema over the treatment site.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Thyroid cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

The overall strength of evidence is low that there were no significant differences in all survival measures for IMRT compared to EBRT. There is low overall strength of evidence that IMRT had less late morbidities than the EBRT group. There are few comparative studies addressing other harms and therefore no conclusions can be reached comparing IMRT to other treatments.

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

There is very low overall strength of evidence for harms. In general, acute mucositis, pharyngitis, dysphagia, xerostomia, skin toxicity, laryngeal toxicity, and esophageal stricture were reported.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

### Spinal Metastases

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

For spinal metastases, there is very low overall strength of evidence for all described outcomes (i.e., OS, recurrence, QoL). Differences in outcome measures and time frames used preclude synthesis of these findings. No evidence was identified that compared IMRT to EBRT for patients with spinal metastases.

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

For spinal metastases, there is very low overall strength of evidence for all described harms. Reported toxicities varied across studies, including esophagitis, skin reactions and various acute reactions. No evidence was identified that compared IMRT to EBRT for patients with spinal metastases.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## MAUDE Database

Two reports of serious adverse events were identified. One patient was admitted to the intensive care unit for severe skin reactions and another patient was admitted to the hospital for Grade 3 hematochezia secondary to rectal ulceration and Grade 3 anemia. Full summaries of the events are provided in Appendix L.

### Guidelines

The NCCN guidelines and the ACR Appropriateness Criteria® are consistent in their statements and recommendations for IMRT for anal, prostate, and rectal cancer. There are no ACR Appropriateness Criteria® ratings for breast, central nervous system, colon, esophageal and esophagogastric junction, gastric, general head and neck, mesothelioma, testicular and thymic cancers. Based on poor to fair quality guidelines, IMRT is considered usually appropriate by the ACR and/or recommended by the NCCN for breast cancer, resectable oropharngeal squamous cell carcinoma, nonsurgical treatment of NSCLC, induction and adjuvant therapy for N2 NSCLC, and prostate cancer. Intensity modulated radiation therapy is not recommended by the NCCN or considered appropriate by the ACR for the treatment of colon cancer, rectal cancer, non-spine bone metastases, and testicular cancer. For cervical cancer, the NCCN and the ACR have inconsistent recommendations ranging from usually not appropriate/not recommended to usually appropriate/recommended. For all other cancers discussed, IMRT is considered as a possible appropriate form of treatment by the ACR and NCCN.

### Policy Considerations

Federal and private payer polices vary in the cancer sites included for treatment with IMRT and the criteria needed to meet medical necessity. The three relevant Medicare LCDs cover brain, prostate, lung, pancreas and other upper abdominal sites, spinal cord, head and neck, adrenal and pituitary cancers, as well as some thoracic, breast, pelvic and retroperitoneal tumors meeting medical necessity criteria. Regence BCBS also covers treatment in some cases for anal, head and neck, prostate, breast, lung, and other abdominal or pelvic tumors. Aetna and GroupHealth provide little information about when IMRT is considered medically necessary. Medical necessity criteria for the Medicare LCDs and Regence BCBS are similar including prior radiation to the area and critical structures in the radiation field and shape of the tumor.

### Overall Summary

This report presents evidence about the use of IMRT for malignancies in the following anatomic locations: abdomen (anal/rectal, liver, and pancreas), brain, breast, female pelvis, head and neck, lung, prostate, soft tissue sarcomas, and other cancer sites (skin, thyroid, spinal metastases). Sixteen SRs and 108 individual studies met inclusion criteria. The majority of studies were non-comparative and in adults. Only two studies for medulloblastoma were exclusively in the pediatric population. Overall, there is limited evidence to answer many of the Key Questions and the populations were heterogeneous.

The overall strength of evidence for outcomes (e.g., OS, DSS, DFS, recurrence, QoL, harms, etc.) ranged from moderate to very low with most being low to very low. In general, for patient survival and recurrence outcomes, the results were heterogeneous, and for many locations, there was no comparative data. Therefore, no general conclusions can be drawn for patient survival and recurrence outcomes.

The findings for QoL were inconsistent except in two anatomic locations with moderate overall strength of evidence findings. The first is whole breast irradiation, in which there were no differences in QoL for IMRT compared to standard radiation therapy (EBRT). The second is head and neck cancers, which found an improvement in overall QoL for IMRT compared to 2D- and 3DCRT.

Harms were mostly regional toxicities based on the location of the malignancy and commonly included acute and late toxicities (e.g., GI, GU, xerostomia, skin, pneumonitis, esophagitis, etc.). There was moderate strength of evidence findings for two outcomes for whole breast irradiation and one outcome for head and neck cancer. For whole breast irradiation, there was moderate strength of evidence that the EBRT group was more likely to develop any Grade of telangiectasia compared to patients who received IMRT. In addition, there was moderate strength of evidence that there were no significant differences in acute toxicities (Grade 2 or higher, Grade 3 or 4 skin toxicities) for IMRT compared to EBRT for whole breast irradiation. For head and neck cancer, there was moderate strength of evidence that IMRT reduces Grade 2 or greater xerostomia compared to EBRT. Deaths and serious adverse events (e.g., harms requiring surgery) were not common, but were reported by a few studies across several anatomic cancer locations. For prostate cancer, there was a moderate strength of evidence that IMRT improve gastrointestinal toxicities compared to EBRT.

There was insufficient evidence to address differential safety and efficacy for any subgroup. All of the cost studies consistently reported that IMRT costs more than other treatments for whole breast, partial breast, head and neck, and prostate cancers. For all other malignancy locations, there was insufficient evidence for costs. Prostate cancer was the only malignancy that had cost effectiveness analyses. However, the limitations of the analyses make drawing conclusions difficult.

The NCCN guidelines and the ACR Appropriateness Criteria® are consistent in their statements and recommendations for IMRT for anal, prostate, and rectal cancer. There are no ACR Appropriateness Criteria® ratings for breast, central nervous system, colon, esophageal and esophagogastric junction, gastric, general head and neck, mesothelioma, testicular and thymic cancers. Based on poor to fair quality guidelines, IMRT is considered usually appropriate by the ACR and/or recommended by the NCCN for breast cancer, resectable oropharngeal squamous cell carcinoma, nonsurgical treatment of NSCLC, induction and adjuvant therapy for N2 NSCLC, and prostate cancer. Intensity modulated radiation therapy is not recommended by the NCCN or considered appropriate by the ACR for the treatment of colon cancer, rectal cancer, non-spine bone metastases, and testicular cancer. For cervical cancer, the NCCN and the ACR have inconsistent recommendations ranging from usually not appropriate/not recommended to usually appropriate/recommended. For all other cancers discussed, IMRT is considered as a possible appropriate form of treatment by the ACR and NCCN.

Federal and private payer polices vary by cancer site. The three relevant Medicare LCDs cover brain, prostate, lung, pancreas and other upper abdominal sites, spinal cord, head and neck, adrenal and pituitary cancers, as well as some thoracic, breast, pelvic and retroperitoneal tumors meeting medical necessity criteria. Regence BCBS also covers treatment in some cases for anal, head and neck, prostate, breast, lung, and other abdominal or pelvic tumors. Aetna and GroupHealth provide little information about when IMRT is considered medically necessary. Medical necessity criteria for the Medicare LCDs and Regence BCBS are similar including prior radiation to the area and critical structures in the radiation field and shape of the tumor.

### Limitations of the Evidence

The evidence on IMRT is largely based on cohort and case series studies. These studies have substantial methodological limitations, such as:

- Many of the studies 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 may include
    - Age;
    - Tumor staging prior to treatment;
    - Smoking status; and
    - Other comorbidities;
- Selection bias could be an issue in the study designs included in this report;
- Many of the studies combined different stages of tumor malignancies in their analyses;
- Many of the included studies have relatively small sample sizes making it difficult to infer findings to the broader population; and
- Several studies included patients receiving chemotherapy concurrent with IMRT and current or past treatments received were often not reported.

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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 radiation to the tumor to minimize damage to normal tissue and increase the dose of radiation delivered to the tumor. One of these newer techniques is intensity modulated radiation therapy (IMRT).

### *Clinical and epidemiological overview*

Cancers of the brain, breast, head and neck, lung, and prostate are among the most common in the United States (US) and include those where IMRT is utilized. Background information on these seven most common indications is presented below. Additional incidence and prevalence for other cancers is included in Table 1 (National Cancer Institute [NCI] 2011).

Brain: An estimated 22,340 men and women were diagnosed with cancer of the brain and other 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 for the same time period was 56 years.

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.

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 2008 incidence of small-cell lung cancer (SCLC) 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.

Prostate: An estimated 240,890 men were diagnosed with prostate cancer in 2011 and 33,720 died from the disease. From 2004-2008 the age-adjusted incidence of prostate cancer was 156.0 per 100,000 men annually. The median age of diagnosis for the same time period was 67 years.

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

| Cancer Site | Incidence in US | Prevalence in US |
|---|---|---|
| Prostate | 154.8 per 100,000 men | 2,496,784 |
| Breast | 124.3 per 100,000 women | 2,747,459 |
| Lung | 62.6 per 100,000 men and women | 387,762 |
| Colorectal | 46.3 per 100,000 men and women | 1,140,161 |
| Uterus | 24.4 per 100,000 women | 589,887 |
| Skin | 23.0 per 100,000 men and women | NR |
| Pancreas | 12.1 per 100,000 men and women | 38,308 |
| Thyroid | 11.6 per 100,000 men and women | 496,901 |
| Oral Cavity and Pharynx | 10.8 per 100,00 men and women | 264,442 |
| Cervical | 8.1 per 100,000 women | 247,711 |
| Stomach | 7.6 per 100,000 men and women | 69,986 |
| Liver | 7.5 per 100,000 men and women | 35,557 |
| Brain and other nervous system (invasive) | 6.5 per 100,000 men and women | 135,402 |
| Esophageal | 4.5 per 100,000 men and women | 31,681 |
| Larynx | 3.4 per 100,000 men and women | 89,142 |
| Anal | 1.7 per 100,000 men and women | NR |
| | | NR = not reported |

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. Radiation treatment may cause acute and chronic side effects depending on the area of the body and dose of radiation.

Intensity modulated radiation therapy has been used for treatment of tumors of the central nervous system, head and neck, breast, prostate, gastrointestinal tract, and gynecologic system. It can be used to treat sites previously treated with radiation and areas in close proximity to organs and vulnerable tissue (American College of Radiology & American Society for Radiation Oncology [ACR-ASTRO] 2011).

### *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).

**Figure 1. Modalities Used for the Delivery of Radiation Therapy[4]**

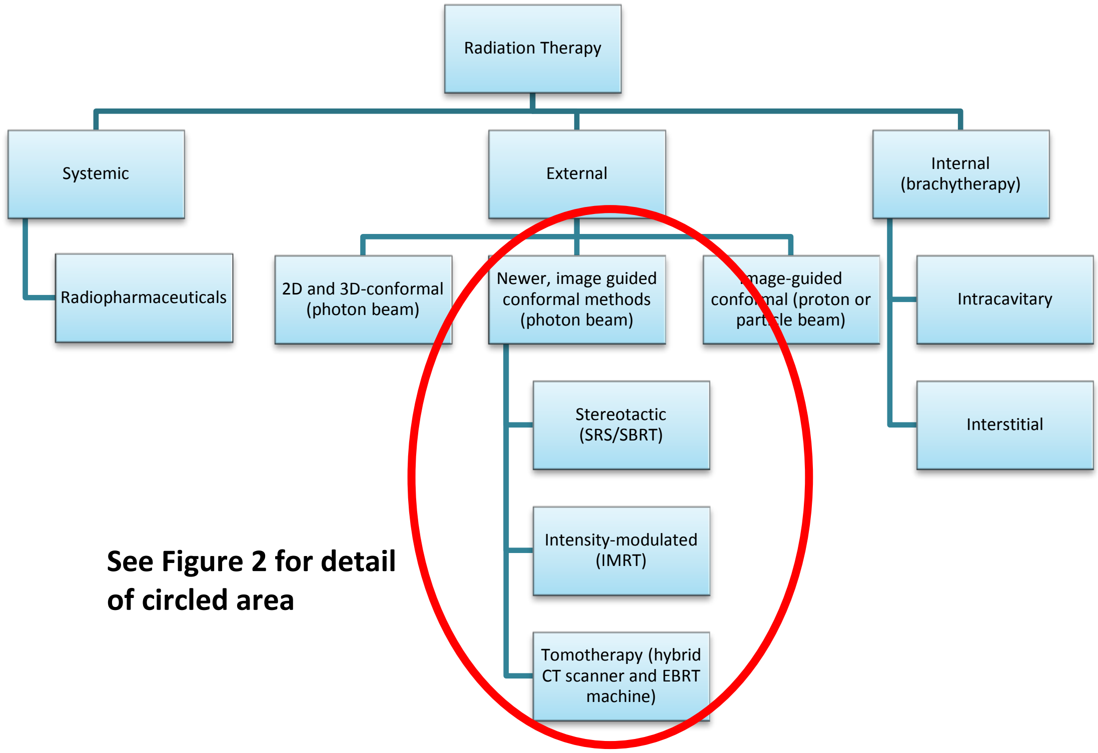
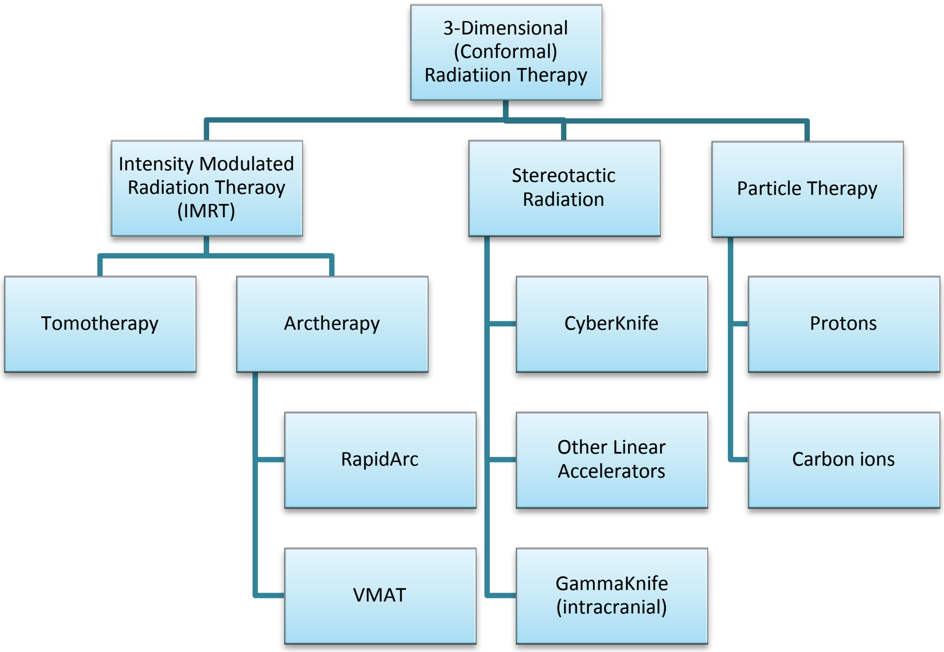



**Figure 2. 3-Dimensional (Conformal) Radiation Therapies** (Adapted from Thariat 2011)

[4] Note: 2D and 3D indicates two and three-dimensional, respectively; SRS stereotactic radiation surgery (single dose)/ therapy (few doses); SBRT stereotactic body radiation therapy; IMRT intensity-modulated radiation therapy; and IGRT image-guided radiation therapy.



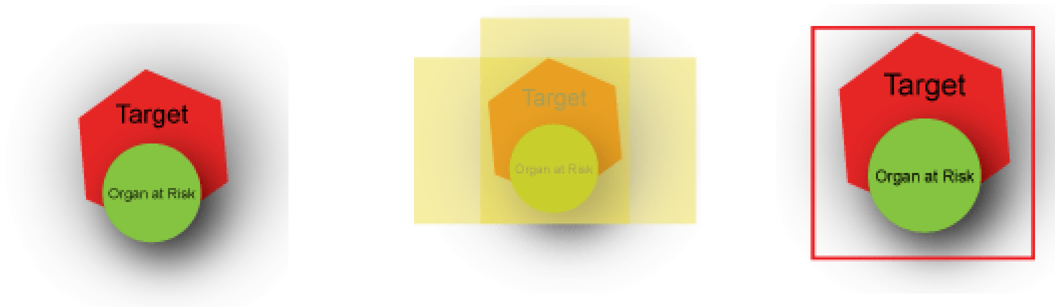

Current conventional EBRT uses three-dimensional (3D) imaging technology for planning purposes and delivers photon beams of uniform intensity to the target tumor using a medical linear accelerator (linac) (Tipton 2011b). Typically, conventional EBRT (also called 2DCRT or 3DCRT)[5] is delivered in 25 to 50 fractions (doses) delivered five days per week for 5 to 10 weeks.

Intensity modulated radiation therapy uses hundreds of radiation beam-shaping devices (collimators) to deliver external beam radiation (Tipton 2011b). The collimators allow the intensity of the radiation to vary during a treatment session thus different doses of radiation can be directed at different areas of the tumor and nearby tissues. The goal of IMRT is to increase radiation to the tumor while reducing radiation exposure to normal tissue. Image-guided radiation therapy (IGRT) uses repeated imaging (CT, PET, MRI) during the course of treatment to identify changes in the tumor and allow adjustments in the position of the patient or the radiation dose during treatment. Tomotherapy is a type of image-guided IMRT that uses a machine that is a hybrid of a CT scanner and a linear accelerator. In tomotherapy, the gantry of the linear accelerator rotates 360 degrees around the patient delivering radiation in a series of slices that cover the tumor from top to bottom also altering the radiation amounts to the tumor and surrounding tissue. Volumetric modulated arc therapy (VMAT) is another form of IMRT. Like tomotherapy, the gantry of the linear accelerator rotates 360 degrees around the patient. However in VMAT the entire dose of radiation for the treatment session is administered in a single gantry rotation. The multi-leaf collimators adjust position and thickness during the single gantry rotation so the intensity of dose delivered is modulated for different anatomic sites.

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

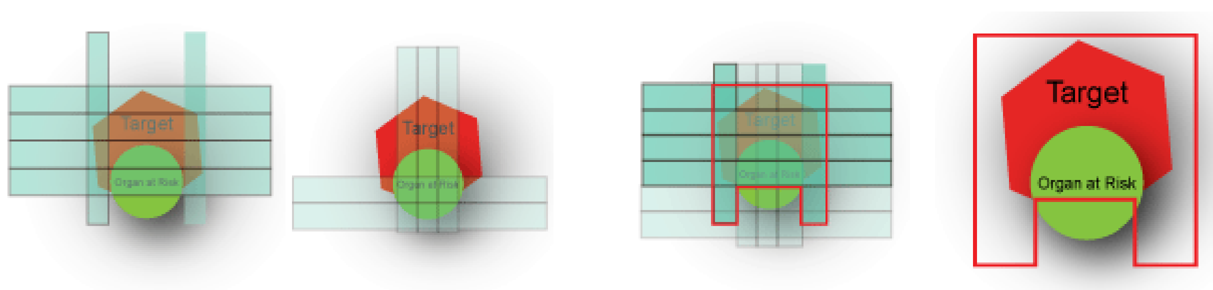
Pre-treatment planning is undertaken before both 3DCRT and IMRT. The tumor is identified on imaging studies and the radiation oncologist selects the target volume. In 3DCRT, collimated beams at 90 degree angles are selected for subsequent administration of radiation.

**Figure 2. 3D-CRT Radiation Field** (Adapted from Holland 2010)




Additional inverse or forward planning is undertaken with IMRT. After the tumor is identified on imaging studies and selected by the radiation oncologist, inverse planning utilizes software algorithms manipulating many hundreds of beamlets iteratively to achieve the oncologist's defined dose targets. Forward planning involves modification of a provisional plan until the tumor dose distribution is optimally improved. Either inverse or forward planning for IMRT is more time consuming than planning for 3DCRT; this contributes to the increase in cost for IMRT.

**Figure 3. IMRT Radiation Field** (Adapted from Holland 2010)




Jacobs (2012) has described a risk of under treatment of target areas, or "geographical miss," related to the dose distribution and longer delivery times; this *under treatment may result in increased risk of local tumor recurrence*.

For optimal use of IMRT for treatment, the ACR and ASTRO (2011) recommend 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;
- Licensed radiation therapist: implementation of treatment plan under supervision of radiation oncologist; and
- Medical dosimetrist: early treatment planning.

### Outcome and Toxicity Measures

Outcome measures for the multiple cancers included in this report include measures of tumor control, measures of patient survival and quality of life (QoL). Tumor control measures include tumor recurrence, development of local and distant metastases and chemical evidence of recurrence (e.g., prostate-specific antigen (PSA) evidence of recurrent prostate cancer). Patient survival measures generally include disease-free survival (DFS), progression-free survival (PFS), recurrence-free survival (RFS), biochemical disease-free survival (bDFS), symptom-free survival, 1-year, 2-year, 5-year and overall survival (OS). Quality of life parameters have been developed for several individual cancers – most notably for head and neck and prostate cancers.

Adverse events are generally reported according to the 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

The technology assessment by Tipton (2011a) included one study (Lanni 2010) describing the *charges* for IMRT and conventional EBRT for 86 patients with inoperable NSCLC. The average charges were:

- $55,705 for 35 fractions (doses) of EBRT (based on 41 patients); and
- $146,570 for 35 fractions of IMRT (based on 2 patients).

For NSCLC, expected reimbursements from Medicare in 2010 were $22,747 for IMRT and $13,639 for EBRT (Tipton 2011a). Medicare's national payment amount for the IMRT plan (CPT 77301) is $1984.73 and $475.85 for the IMRT treatment component (CPT 77418). Payments for CPT 77301 by Medicare local contractors range from $1,424.02 to $2,602.81; payments for CPT 77418 range from $322.48 to 646.86 (CMS 2011a).

Suh (2005) modeled costs for treatment for a hypothetical 60 year old woman with stage I breast cancer. For whole breast radiation, direct medical costs for EBRT ranged from $5,400 to $9,500; IMRT costs were $17,900 for the same hypothetical patient. For accelerated partial breast radation, EBRT cost $7,200 and IMRT cost $9,200. Smith (2011) calculated mean costs for Medicare-aged women with breast cancer. The mean cost of conventional RT was $7,179 and the mean cost of IMRT was $15,230.

Hummel (2010) performed a cost analysis for prostate cancer. Costs for EBRT ranged from $10,000 to $27,000; costs for IMRT ranged from $33,000 to $52,000.

### *Policy context*

Use of new radiation technologies has grown dramatically in the last decade. From analysis of Surveillance, Epidemiology and End Results – Medicare (SEER) among men with prostate cancer receiving external beam radiation, the use of IMRT increased from 29% in 2002 to 82% in 2005 for those covered by Medicare (Jacobs 2012). The increase in likelihood of IMRT was independent of the level of risk of the prostate cancer. Sheets (2012) analyzed SEER data for prostate cancer through 2008 and found the likelihood of IMRT therapy for prostate cancer to be 96% in 2008. Smith (2011) analyzed SEER data that showed an increase in likelihood of IMRT use for breast cancer from 0.9% in 2001 to 11.2% in 2005. A 2004 survey of radiation oncologists by Mell (2005) found more than twice as many radiation oncologists (73% of respondents) used IMRT in 2004 compared to those reported using IMRT in 2002 (32%). The most common reasons given for using IMRT were ability to spare normal tissue (88%), dose escalation (85%), and economic competition (62%).

Despite this rapid adoption, the Food and Drug Administration (FDA) process for approving new radiation therapies does not require a review of safety and efficacy of IMRT, which has resulted in limited information about efficacy and comparative effectiveness of these treatments (Konski 2011). Comparative trials including randomized controlled trials (RCTs) have not been required by the FDA to clear the newer devices for sale. For these moderate risk new devices, the FDA clears the device for sale under their 510(k) process that only requires a manufacturer to demonstrate that the new device 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 IMRT than required by the FDA in granting approval for sale.

## Washington State Data

*Section 1: Agency usage, IMRT*

The purpose of Section 1 is to display basic costs, counts and trends, using the paid amount for each claim, affording a summary of agency expenditures and number of patients served. Coordination of benefits between other payers will cause average payments on this table to be lower than actual treatment costs, which are presented in Section 2.

**Figure 1.1a IMRT Overall Payments by Agency –2008-2011**

| Agency | 2008 | 2009 | 2010 | 2011 | 4 Year Overall Total | Average % Change | |
|---|---|---|---|---|---|---|---|
| PEB | | | | | | | |
| Agency Population | 204,804 | 210,501 | 213,487 | 212,596 | | 1.3% | |
| Patient Ct | 174 | 224 | 219 | 295 | 800 | 19.0% | * |
| Amount Paid | $3,560,542 | $4,524,637 | $3,900,872 | $5,482,926 | $17,468,977 | 16.6% | * |
| Average Paid/ Pt | $20,810 | $22,079 | $17,528 | $19,117 | $23,199 | -2.9% | |
| 95% Range/ Pt | $0 - $66680 | $0 - $64194 | $0 - $55678 | $0 - $55473 | $0 - $65818 | | |
| Maximum per Single Pt | $178,351 | $124,160 | $118,270 | $89,439 | $178,351 | | |
| Procedure Ct (Per Pt Avg) | 4407 (25.3) | 5401 (24.1) | 5218 (23.8) | 7471 (25.3) | 22,497 (28.1) | 19.4% | * |
| Average Paid/ Treatment | $807.93 | $837.74 | $747.58 | $733.89 | $776.50 | 3.0% | |
| Medicaid | | | | | | | |
| Agency Population | 392,808 | 416,871 | 424,230 | 435,187 | | 3.5% | |
| Patient Ct | 232 | 288 | 452 | 537 | 1357 | 29.0% | * |
| Amount Paid | $3,564,431 | $4,048,794 | $4,514,064 | $6,026,766 | $18,154,055 | 15.6% | * |
| Average Paid/ Pt | $15,364 | $14,058 | $9,987 | $11,223 | $13,378 | -8.4% | |
| 95% Range/ Pt | $0 - 36737 | $0 - 37250 | $0 - 29962 | $0 - 33305 | $0 - 36260 | | |
| Maximum per Single Pt | $74,274 | $84,248 | $67,124 | $55,437 | $84,248 | | |
| Procedure Ct (Per Pt Avg) | 5039 (21.7) | 5428 (18.8) | 7472 (16.5) | 10771 (20.1) | 28710 (21.2) | 25.8% | * |
| Average Paid/ Treatment | $707.37 | $745.91 | $604.13 | $559.54 | $632.33 | -7.0% | |

*Adjusted for population growth

L&I data: L&I had four claims that included IMRT procedures during 2008-2011, use of IMRT related services totaled $376,972, averaging around 30,000 per patient per year.

Charges selected for inclusion in IMRT treatment per patient are:

- Specific IMRT codes (77301, 77338, 77418)
- Non-specific planning and navigation codes within the treatment span of the first and last IMRT code (treatment span)
- Charges matching the diagnosis code of the IMRT treatment within 7 days of the treatment span, excluding alternate treatment strategies (chemotherapy, other radiation therapy)
- Closely related non-specific planning codes in the 30 days ahead of the treatment span
- Imaging related by diagnosis code within 30 days of the treatment span

See Related Medical Codes for code lists and more information.

Note that PEB patient count and cost growth is much higher than PEB population growth, though the growth is variable over the 4 years researched. Treatment course cost and single treatment cost growth appear to be low or negative in general, but are also variable by year.

In contrast, Medicaid population and payment growth is steady both by patient and payment. The average growth rate of 29% does not show the whole picture, as population adjusted growth rates were 9.5%, 19.7% and 57.6% for the 2009-2011 years.

**Figure 1.2a PEB - Payments and Patients by Age and Gender**

| | Patient Count | | | | | Amount Paid | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age** | **2008** | **2009** | **2010** | **2011** | **Total*** | **2008** | **2009** | **2010** | **2011** | **4 year Overall** |
| **0-17** | 1 | 2 | 3 | 3 | **8** | $64,711 | $90,328 | $58,776 | $150,730 | **$364,545** |
| **18-34** | 1 | 1 | 0 | 1 | **3** | $715 | $36,640 | | $86,315 | **$123,670** |
| **35 -49** | 5 | 9 | 13 | 13 | **37** | $261,894 | $372,014 | $593,109 | $323,218 | **$1,550,235** |
| **50-64** | 72 | 97 | 82 | 119 | **324** | $2,402,330 | $2,985,849 | $2,496,001 | $3,749,377 | **$11,633,557** |
| **65-79** | 80 | 104 | 111 | 145 | **383** | $762,425 | $995,312 | $707,976 | $1,117,942 | **$3,583,655** |
| **80+** | 15 | 11 | 10 | 14 | **45** | $68,467 | $44,494 | $45,010 | $55,344 | **$213,315** |
| **Total** | **174** | **224** | **219** | **295** | **800** | **$3,560,542** | **$4,524,637** | **$3,900,872** | **$5,482,926** | **$17,468,977** |
| **% Female** | **2008** | **2009** | **2010** | **2011** | **Total*** | **2008** | **2009** | **2010** | **2011** | **4 year Overall** |
| **0-17** | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 75.1% | 89.7% |
| **18-34** | 0.0% | 100% | 0.0% | 100% | 66.7% | 0.0% | 100% | 0.0% | 100% | 99.4% |
| **35 -49** | 60.0% | 55.6% | 61.5% | 53.8% | 56.8% | 31.6% | 50.6% | 44.9% | 55.5% | 46.2% |
| **50-64** | 26.4% | 25.8% | 41.5% | 39.5% | 33.6% | 19.7% | 23.9% | 34.9% | 30.7% | 27.6% |
| **65-79** | 21.3% | 16.3% | 22.5% | 22.8% | 20.9% | 11.3% | 11.4% | 15.7% | 14.8% | 13.3% |
| **80+** | 33.3% | 45.5% | 40.0% | 35.7% | 33.3% | 33.1% | 29.0% | 33.8% | 28.3% | 31.2% |
| **Total** | **20.5%** | **25.5%** | **33.9%** | **31.2%** | **28.1%** | **25.9%** | **24.6%** | **33.8%** | **32.5%** | **29.4%** |

*Patients who receive treatment courses that cross a year end are not counted twice in the 4 Year Total, so the 4 year total may be less than the sum of the individual year patient counts.

**Figure 1.2b Medicaid - Payments and Patients by Age and Gender**

| | Patient Count | | | | | Amount Paid | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age** | **2008** | **2009** | **2010** | **2011** | **Total*** | **2008** | **2009** | **2010** | **2011** | **4 year Overall** |
| **0-17** | 5 | 6 | 12 | 17 | **38** | $56,675 | $49,409 | $159,361 | $292,472 | **$557,917** |
| **18-34** | 18 | 17 | 21 | 28 | **75** | $252,301 | $235,851 | 172979.15 | $337,522 | **$998,653** |
| **35 -49** | 67 | 91 | 105 | 122 | **347** | $995,221 | $1,367,453 | $1,494,350 | $1,915,559 | **$5,772,583** |
| **50-64** | 119 | 155 | 226 | 266 | **674** | $1,906,621 | $2,331,326 | $2,896,945 | $4,433,582 | **$11,568,474** |
| **65-79** | 20 | 18 | 63 | 77 | **165** | $274,587 | $104,031 | $243,333 | $947,314 | **$1,569,265** |
| **80+** | 3 | 2 | 23 | 26 | **53** | $41,779 | $11,959 | $26,516 | $147,144 | **$227,398** |
| **Total** | **232** | **289** | **450** | **536** | **1352** | **$3,527,184** | **$4,100,030** | **$4,993,485** | **$8,073,592** | **$20,694,289** |
| **% Female** | **2008** | **2009** | **2010** | **2011** | **Total*** | **2008** | **2009** | **2010** | **2011** | **4 year Overall** |
| **0-17** | 20% | 33.0% | 42.0% | 35.0% | 34.0% | 31.0% | 1.0% | 37.8% | 30.5% | 29.9% |
| **18-34** | 33.3% | 53.0% | 52.4% | 61.0% | 50.7% | 35.8% | 56.7% | 54.7% | 67.0% | 54.4% |
| **35 -49** | 52.2% | 54.9% | 58.1% | 60.7% | 56.5% | 45.6% | 48.3% | 44.5% | 60.1% | 50.4% |
| **50-64** | 44.5% | 41.3% | 41.6% | 43.6% | 42.4% | 39.0% | 38.4% | 34.6% | 41.4% | 38.6% |
| **65-79** | 20.00% | 27.8% | 47.6% | 36.4% | 37.6% | 22.5% | 8.6% | 53.6% | 33.3% | 28.3% |
| **80+** | 33.3% | 50.0% | 34.8% | 46.2% | 41.5% | 0.0% | 94.5% | 87.8% | 78.2% | 33.3% |
| **Total** | **43.1%** | **45.%** | **46.4%** | **47.2%** | **45.6%** | **38.7%** | **41.8%** | **38.9%** | **47.2%** | **42.3%** |

*Patients who receive treatment courses that cross a year end are not counted twice in the 4 Year Total, so the 4 year total may be less than the sum of the individual year patient counts.

**Note** that there may be several payment strategies represented under one agency's payment total. This table does not address Medicare vs non-Medicare, percentage payments or varying deductibles. The figures are intended for use as an aggregate number for high level comparison and estimation.

*Section II: Per procedure total cost*

Investigation of per person charges use agency "Allowed" amounts so do not reflect any benefit coordination between payers.

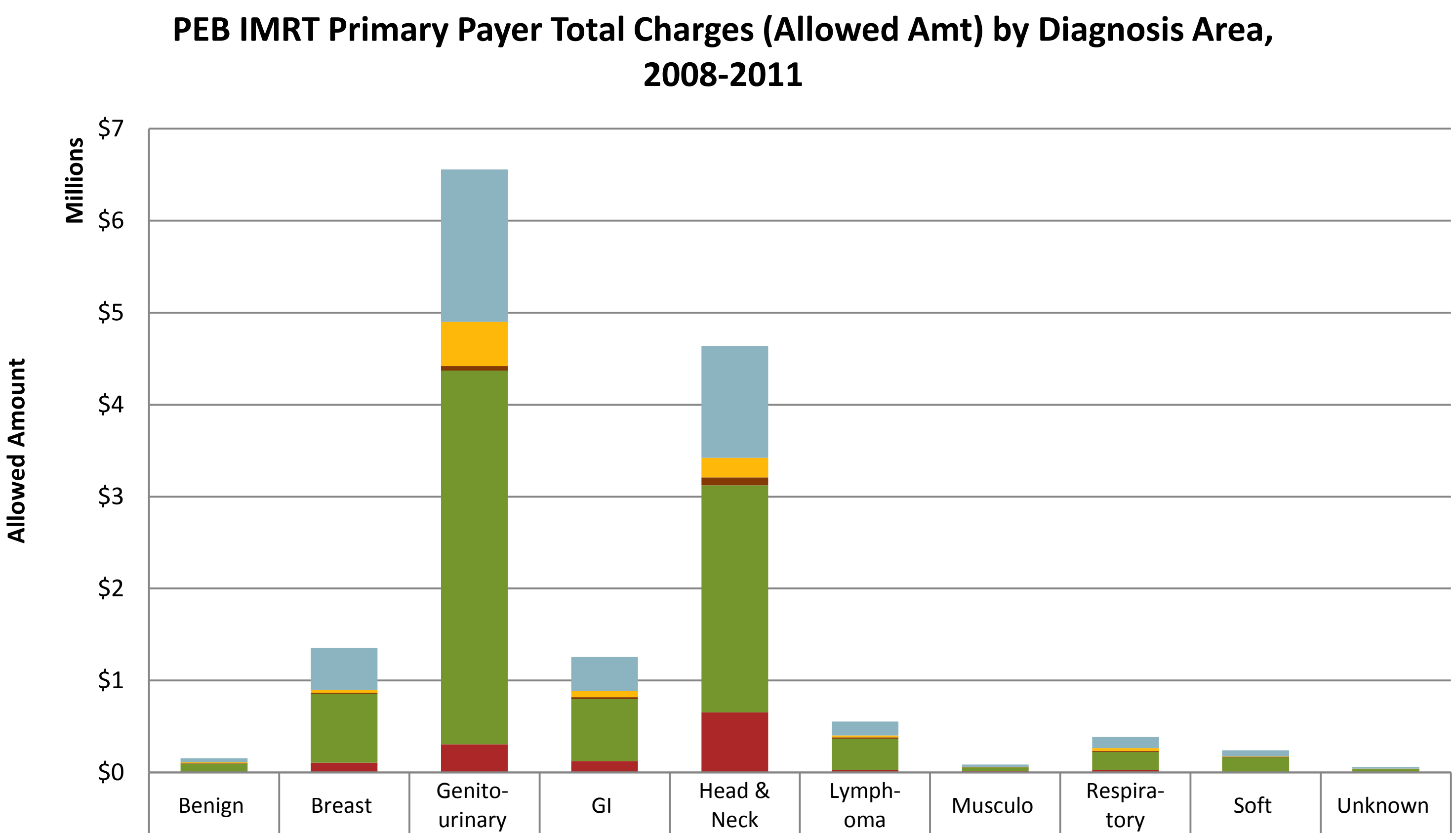
PEB Medicare charges are accumulated separately, since the amount allowed may be consistently different from other payers.

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

**Figure 2.1 Average Costs of Treatment, PEB, PEB Medicare, Medicaid, 2008-2011**

| Per Treatment Course Average Charges | PEB Primary (w/o Mdcr) | Medicaid | L&I (na) | PEB Medicare | PEB Primary Sample Provider (Most Pts) | PEB Primary Sample Provider (Highest Total $) | PEB MedicareSample Provider (Most Pts) | PEB MedicareSample Provider (Highest Total $) |
|---|---|---|---|---|---|---|---|---|
| **Breakdown 1** | | | | | | | | |
| **Professional Srvcs** | $23,484 | $5,011 | na | $13,126 | $40,485 | $33,100 | $15,977 | $23,130 |
| **Facility** | $18,275 | $9,880 | na | $50,351 | $2,294 | $16,823 | $39,857 | $214 |
| **Breakdown 2** | | | | | | | | |
| **Planning charges** | $11,275 | $3,248 | na | $21,571 | $9,827 | $11,659 | $13,840 | $5,524 |
| **Navigation/Imaging** | $2,905 | $649 | na | $5,204 | $4,917 | $2,011 | $21,761 | $7,576 |
| **Delivery and Other** | $27,579 | $10,993 | na | $36,703 | $28,003 | $36,253 | $20,233 | $15,338 |
| **Average allowed amount per treatment course** | **$41,759** | **$14,890** | **na** | **$63,478** | **$42,747** | **$49,923** | **$55,834** | **$23,344** |

**Figure 2.2a PEB IMRT Charges by Diagnosis Area, 2008-2011**



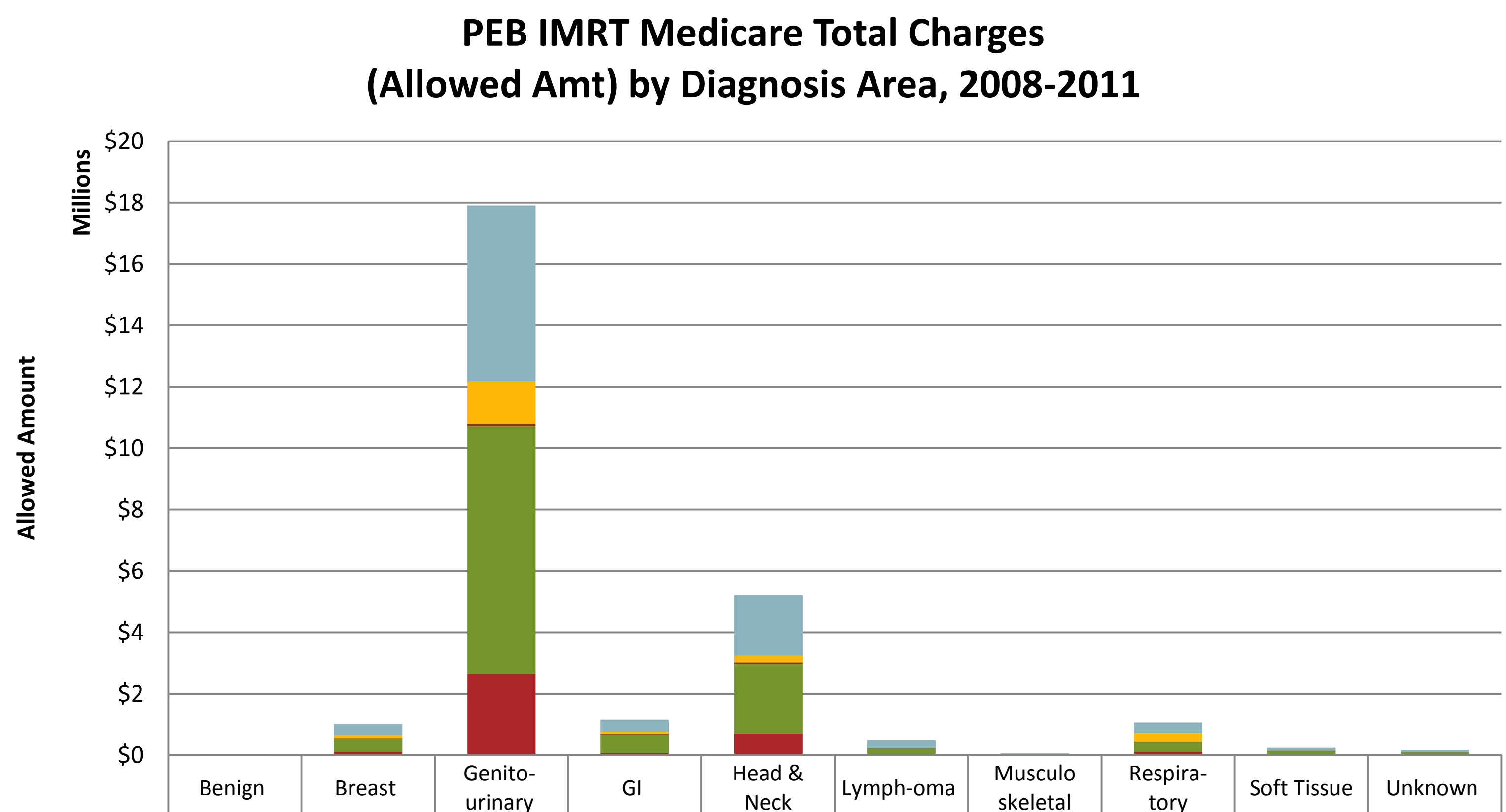

| | Benign | Breast | Genito-urinary | GI | Head & Neck | Lymph-oma | Musculo | Respira-tory | Soft | Unknown |
|---|---|---|---|---|---|---|---|---|---|---|
| Planning | $44,454 | $456,924 | $1,656,963 | $373,782 | $1,215,776 | $150,707 | $24,028 | $119,058 | $66,468 | $18,480 |
| Navigation | $9,202 | $32,423 | $482,888 | $62,913 | $214,279 | $20,114 | $4,757 | $30,052 | $3,707 | $4,652 |
| Imaging | $3,276 | $7,101 | $47,010 | $20,501 | $83,982 | $15,512 | $4,865 | $10,523 | $4,491 | $1,009 |
| Delivery | $96,758 | $752,493 | $4,065,939 | $675,006 | $2,471,489 | $341,718 | $35,093 | $196,271 | $160,031 | $33,759 |
| Other | $1,044 | $105,175 | $304,586 | $123,841 | $652,532 | $25,353 | $18,289 | $28,422 | $6,095 | $146 |

**Figure 2.2b PEB IMRT Average Costs by Diagnosis Type, Primary Payers only, 2008-2011**

| Disease Type by Frequency Descending | Pt Ct | Average Treatment Count (95% Range) | Average Per Treatment Cost | % Delivery Cost | % Planning Cost | Average Total Treatment Course (95% range) |
|---|---|---|---|---|---|---|
| Genito-urinary | 146 | 30.3 (4 - 50) | $1,483.24 | 62.0% | 25.3% | $44,914 ($519 - $89,308) |
| Head & Neck | 98 | 26.7 (3 - 48) | $1,772.96 | 53.3% | 26.2% | $47,327 ($0 - $95,675) |
| Breast | 44 | 19.7 (0 - 33) | $1,561.84 | 55.6% | 33.7% | $30,775 ($0 - $63,456) |
| Gastrointestinal | 33 | 24 (6 - 40) | $1,583.91 | 53.7% | 29.8% | $38,062 ($266 - $75,858) |
| Lymphoma | 18 | 21.2 (4 - 36) | $1,448.70 | 61.7% | 27.2% | $30,745 ($3,801 - $57,689) |
| Respiratory | 12 | 17.3 (0 - 39) | $1,856.65 | 51.1% | 31.0% | $32,027 ($0 - $56,351) |
| Benign | 5 | 23.2 (0 - 33) | $1,333.91 | 62.5% | 28.7% | $30,947 ($6,079 - $42,206) |
| Soft Tissue | 5 | 26.8 (13 - 34) | $1,796.96 | 66.5% | 27.6% | $48,158 ($4863 - $84,553) |
| Musculoskeletal | 3 | 15 (0 - 23) | $1,934.04 | 40.3% | 27.6% | $29,011 ($4,558 - $41,045) |
| Unknown | 2 | 24 (0 - 33) | $1,209.29 | 58.2% | 31.8% | $29,023 ($10,551 - $35,554) |
| **Grand** | **366** | **26.3 (1 - 50)** | **$1,587.28** | **57.8%** | **27.0%** | **$41,759 ($0 - $85,654)** |

Max Treatment Course = 50 treatments (3 patients), Max Treatment Cost was $178,351 in 2008, Genitourinary

**Figure 2.2c PEB Medicare IMRT Charges by Diagnosis Area, 2008-2011**




| | Benign | Breast | Genito-urinary | GI | Head & Neck | Lymph-oma | Musculo skeletal | Respira-tory | Soft Tissue | Unknown |
|---|---|---|---|---|---|---|---|---|---|---|
| Planning | $6,621 | $366,026 | $5,743,563 | $390,094 | $1,973,694 | $279,173 | $19,335 | $355,811 | $94,335 | $68,275 |
| Navigation | $2,732 | $97,173 | $1,375,251 | $69,524 | $225,154 | $8,343 | $414 | $270,711 | $4,848 | $1,269 |
| Imaging | $531 | $1,432 | $87,244 | $28,579 | $47,708 | $5,285 | $1,236 | $12,166 | $1,027 | $2,209 |
| Delivery | $15,107 | $452,187 | $8,075,629 | $606,867 | $2,273,936 | $185,026 | $28,233 | $318,104 | $135,616 | $71,783 |
| Other | $21 | $100,885 | $2,630,573 | $63,245 | $698,495 | $22,933 | $1,876 | $108,626 | $5,993 | $24,058 |

**Figure 2.2d PEB IMRT Average Costs by Diagnosis Type, Medicare only, 2008-2011**

| Disease Type by Frequency Descending | Pt Ct | Average Single Treatment Count (95% Range) | Average Per Treatment Cost | % Delivery Cost | % Planning Cost | Average Total Treatment Course (95% Range) |
|---|---|---|---|---|---|---|
| Genito-urinary | 255 | 34.1 (7 - 61) | $2,0624 | 45.1% | 32.1% | $70,244 ($0 - $230,125) |
| Head & Neck | 73 | 26.5 (3 - 50.2) | $2,693 | 43.6% | 37.8% | $71,493 ($0 - $220,613) |
| Respiratory | 32 | 18.8 (0 - 41) | $1,776 | 29.9% | 33.4% | $33,294 ($0 - $105,089) |
| Gastrointestinal | 26 | 21.2 (0 - 47.3) | $2,102 | 52.4% | 33.7% | $44,550 ($0 - $155,401) |
| Breast | 22 | 21.9 (0 - 48.6) | $2,111 | 44.4% | 36.0% | $46,259 ($0 - $152,211) |
| Lymphoma | 7 | 22 (0 - 39) | $3,252 | 36.9% | 55.7% | $54,575 ($0 - $196,636) |
| Soft Tissue | 6 | 25 (5 - 33) | $1,612 | 56.1% | 39.0% | $40,303 ($0 - $164,163) |
| Musculoskeletal | 4 | 14.3 (6 - 19) | $896 | 55.3% | 37.8% | $12,774 ($3,639 - $17,710) |
| Unknown | 3 | 25.7 (11 - 30) | $2,177 | 42.8% | 40.7% | $55,865 ($0 - $159,044) |
| Benign | 1 | n/a | $1,000 | 60.4% | 26.5% | n/a |
| **Total** | **431** | **29.7 (1 - 58.3)** | **$2,141** | **44.5%** | **34.0%** | **$63,478 ($0 - $211,309)** |

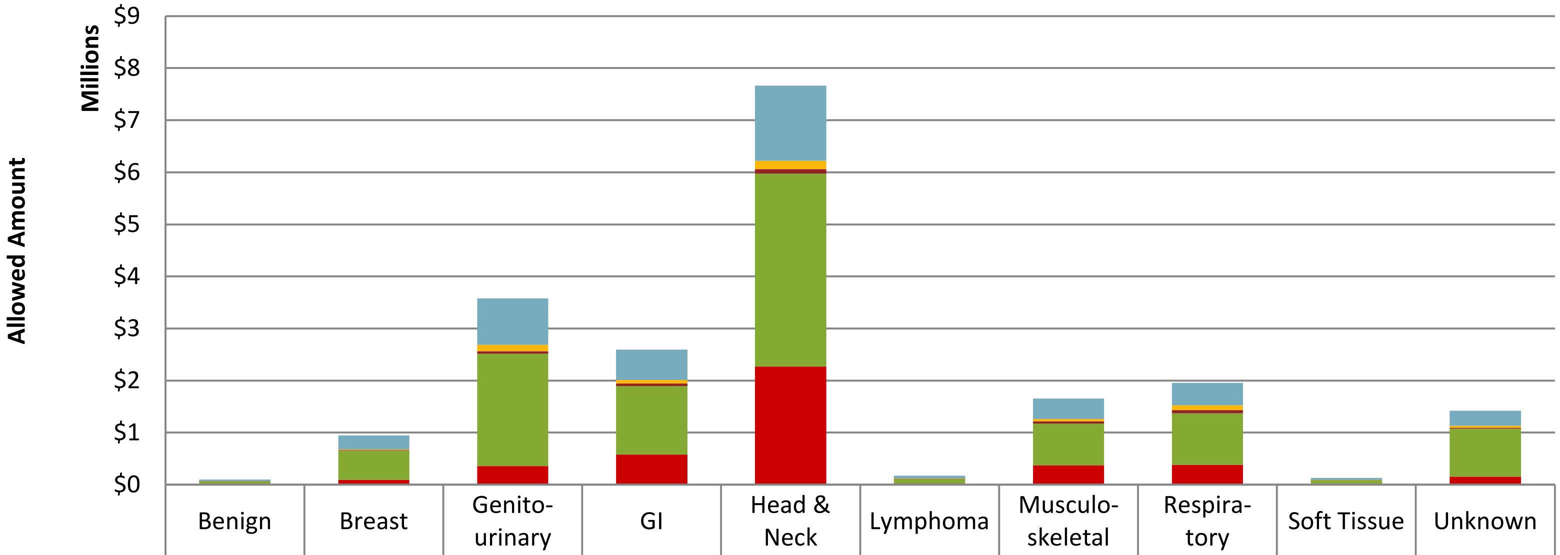
Max Treatment Course = 83 treatments (11 patients had more than 50 treatments), Max Treatment Cost was $467,376 (2011, Genito-urinary category).

**Figure 2.2e PEB Primary vs PEB Medicare Patients by Age**

| Payer, Age Group | Allowed Amounts | | | | | Patient Counts | | | | | Average Per Patient |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2008 | 2009 | 2010 | 2011 | 4 Year Overall | 2008 | 2009 | 2010 | 2011 | 4 Year Overall | |
| **PRIMARY** | | | | | | | | | | | |
| **0-17** | $64,711 | $90,467 | $60,500 | $154,576 | **$370,254** | 1 | 2 | 2 | 3 | **7** | **$52,893** |
| **18-34** | | | | $84,553 | **$84,553** | 0 | 0 | 0 | 1 | **1** | **$84,553** |
| **35-49** | $178,190 | $351,168 | $590,449 | $327,481 | **$1,447,288** | 3 | 7 | 12 | 12 | **32** | **$45,228** |
| **50-64** | $2,138,798 | $2,797,196 | $2,420,781 | $3,506,234 | **$10,863,009** | 57 | 73 | 67 | 101 | **264** | **$41,148** |
| **65-79** | $741,601 | $745,460 | $364,753 | $667,019 | **$2,518,833** | 16 | 23 | 11 | 21 | **62** | **$40,626** |
| **MEDICARE** | | | | | | | | | | | |
| **35-49** | $19,006 | $3,670 | $135,948 | $17,344 | **$175,968** | 1 | 1 | 1 | 1 | **3** | **$58,656** |
| **50-64** | $138,269 | $622,140 | $466,427 | $10,690 | **$1,237,526** | 1 | 6 | 5 | 2 | **12** | **$103,127** |
| **65-79** | $6,028,777 | $8,341,206 | $7,452,231 | $1,089,857 | **$22,912,071** | 77 | 100 | 109 | 133 | **371** | **$61,758** |
| **80+** | $1,059,740 | $564,705 | $831,162 | $577,784 | **$3,033,391** | 15 | 11 | 10 | 14 | **45** | **$67,409** |

**Figure 2.3a Medicaid IMRT Charges by Diagnosis Area, 2008-2011**

## Medicaid IMRT Total Charges (Allowed Amt) by Diagnosis Area, 2008-2011




| | Benign | Breast | Genito-urinary | GI | Head & Neck | Lymphoma | Musculo-skeletal | Respira-tory | Soft Tissue | Unknown |
|---|---|---|---|---|---|---|---|---|---|---|
| Planning | $27,033 | $272,301 | $894,935 | $581,855 | $1,440,267 | $45,453 | $390,971 | $430,570 | $35,987 | $287,534 |
| Navigation | $4,133 | $11,184 | $122,354 | $64,631 | $165,554 | $7,452 | $43,162 | $97,247 | $4,477 | $37,936 |
| Imaging | $1,107 | $12,367 | $44,056 | $54,103 | $83,299 | $5,726 | $43,165 | $58,600 | $3,701 | $16,990 |
| Delivery | $62,930 | $558,412 | $2,158,741 | $1,314,415 | $3,706,552 | $94,436 | $808,288 | $992,593 | $76,088 | $921,173 |
| Other | $1,292 | $92,848 | $358,428 | $576,646 | $2,268,007 | $17,609 | $367,916 | $378,472 | $9,238 | $153,768 |

**Figure 2.3b Medicaid IMRT Average Costs by Diagnosis Type, 2008-2011**

| Disease Type by Frequency Descending | Pt Ct | Average Single Treatment Count (95% Range) | Average Per Treatment Cost | % Delivery Cost | % Planning Cost | Average Total Treatment Course (95% Range) |
|---|---|---|---|---|---|---|
| Head & Neck | 406 | 25.7 (1.3 - 50.1) | $736 | 48.37% | 18.79% | $18923 ($0 - $42487) |
| Genito-urinary | 252 | 23.4 (0 - 53.1) | $608 | 60.33% | 25.01% | $14200 ($0 - $33641) |
| Gastrointestinal | 187 | 20.2 (0 - 42.3) | $688 | 50.72% | 22.45% | $13934 ($0 - $33393) |
| Respiratory | 139 | 21.2 (0 - 50) | $665 | 50.71% | 22.00% | $14083 ($0 - $34957) |
| Musculoskeletal | 136 | 17.4 (0 - 42.6) | $704 | 48.88% | 23.65% | $12158 ($0 - $31318) |
| Unknown | 123 | 17.7 (0 - 46.4) | $660 | 64.99% | 20.29% | $11812 ($0 - $39775) |
| Breast | 74 | 20.3 (0 - 42.4) | $631 | 58.96% | 28.75% | $12799 ($0 - $28335) |
| Lymphoma | 20 | 12.5 (0 - 28.4) | $717 | 55.33% | 26.63% | $8534 ($0 - $18398) |
| Benign | 12 | 14.9 (0 - 40.8) | $539 | 65.22% | 28.01% | $8041 ($0 - $14712) |
| Soft Tissue | 8 | 25.4 (10 - 40.8) | $638 | 58.76% | 27.79% | $16186 ($7720 - $20087) |
| **Total** | **1357** | **21.9 (0 - 48.6)** | **$682** | **52.92%** | **21.81%** | **$14945 ($0 - $37005)** |

Max Treatment Course = 73 treatments (13 patients had more than 50 treatments), Max Treatment Cost was $84,248 (2009, Head & Neck category).

**Table 4. Related Medical Codes**

| Code | Description | Progress | IMRT Non-specific |
|---|---|---|---|
| **77338** | Multi-leaf collimator (MLC) device(s) built for IMRT per IMRT plan | Planning | IMRT |
| **77418** | Intensity modulated treatment delivery, single or multiple fields, via narrow spatially and temporally modulated beams, per treatment session | Delivery | IMRT |
| **77301** | Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications | Planning | IMRT |
| **77014** | Computed tomography guidance for placement of radiation therapy fields | Navigation | Non-specific |
| **77261/2/3** | Radiation Therapy Planning, simple, intermediate, complex | Planning | Non-specific |
| **77280/85 77290/95** | Set radiation therapy field, simple, intermediate, complex (0) or 3 dimensional (5) | Planning | Non-specific |
| **77300** | Radiation Therapy Dose Plan | Planning | Non-specific |
| **77321** | Special Teletx Port Plan | Planning | Non-specific |
| **77332/3/4** | Radiation treatment aids (simple, intermediate, complex) | Planning | Non-specific |
| **77336** | Continuing medical physics consultation | Planning | Non-specific |
| **77370** | Special medical radiation physics consultation | Planning | Non-specific |
| **77417** | Radiology Port Films (not seen w/ SRS/SBRT) | Planning | Non-specific |
| **77421** | Stereoscopic Xray Guidance (not for use with SRS/SBRT) | Navigation | Non-specific |
| **77427/31/99** | Radiation treatment management, 5 treatments (not seen w/ SRS/SBRT) | Planning | Non-specific |
| **77470** | Special Radiation Treatment management (extra planning for SRS) | Planning | Non-specific |
| **70010-70559** | Diagnostic Radiology Head and Neck | Planning | Non-specific |
| **76830/1 76856/7** | US (can be used for other therapy treatment planning) | Alt Tx | Non-specific |
| **71010-71555** | Diagnostic Radiology Head and Neck | Planning | Non-specific |
| **72010-72295** | Diagnostic Radiology Spine and Pelvic | Planning | Non-specific |
| **74000-74190** | Diagnostic Radiology Abdomen | Planning | Non-specific |
| **74210-74363** | Diagnostic Radiology Gastrointestinal Tract | Planning | Non-specific |
| **74400-74485** | Diagnostic Radiology Urinary Tract | Planning | Non-specific |
| **74710-74775** | Diagnostic Radiology Gynecological and Obstetrical | Planning | Non-specific |
| **75557-75564** | Diagnostic Radiology Spine and Pelvic Heart | Planning | Non-specific |
| **96401-96549** | Chemotherapy (can be used as a sensitizer, may indicate failure of SBRT therapy) | Alt Tx | Non-specific |

Note: Highlighted codes are included in our analysis when they are submitted within the 30 days ahead of IMRT treatment.


1. *Smith BD, Pan IW, Shih YC, et al. Adoption of intensity-modulated radiation therapy for breast cancer in the United States. **J Natl Cancer Inst**. 2011; 103(10):798-809. Note – for radiation within the first year of diagnosis, accessed at [http://www.hayesinc.com/hayes/media_center/news-service/the-high-cost-of-intensity-modulated-radiation-therapy/](http://www.hayesinc.com/hayes/media_center/news-service/the-high-cost-of-intensity-modulated-radiation-therapy/), June 6, 2012*
2. *Jacobs BL, Zhang Y, Skolarus TA, Hollenbeck BK ,Growth of High-Cost Intensity-Modulated Radiotherapy for Prostate Cancer Raises Concerns About Overuse, Health Aff April 2012 vol. 31 no. 4 750-759*

## Evidence Review

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

### PICO

**Population**: Adults and children with malignancies where treatment by radiation therapy is appropriate.

**Intervention**: Intensity modulated radiation therapy (IMRT).

**Comparator**: Conventional (conformal) external beam therapy (EBRT or CRT).

**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 intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?

**KQ 2**: What are the potential harms of IMRT 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 IMRT has 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 IMRT compared to EBRT?

### Methods

A systematic review using best evidence methodology for each procedure 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 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, then the other review(s) were excluded;
- An additional search of the MEDLINE® and Cochrane databases was completed to identify subsequently published studies (see Appendix A for search strategies and Appendix B for excluded references). Individual studies published after the search dates of the last high quality review were appraised and synthesized with the results of the high quality SRs (see Appendix C for MEDLINE® search dates); and
- If there were no high quality reviews identified for a procedure, a search, appraisal, and summary of primary individual studies was completed for literature published in the prior 10 years (April 2002 to April 2012).

### *Evidence*

Inclusion Criteria

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. Chemoradiotherapy is considered the standard of care for many malignancies. After consulting with a radiation oncology clinical expert about common current practice, studies evaluating concurrent chemotherapy and IMRT were included for anal, cervical, glioblastoma/CNS, head and neck, lung, pancreas, and rectal cancer. For all other malignancies, studies were excluded if patients received concurrent chemotherapy.

General inclusion criteria:

- Published, peer reviewed, English-language articles;
- SRs, TAs, RCTs, and observational comparative study designs (prospective, retrospective, and controlled clinical trials);
- 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 malignancy:

*Breast, Head and Neck, Prostate*

- Minimum sample size of 50 participants;

*Less prevalent malignancies (abdomen, brain, female pelvis, lung, sarcoma, skin, thyroid, spinal metastases)*

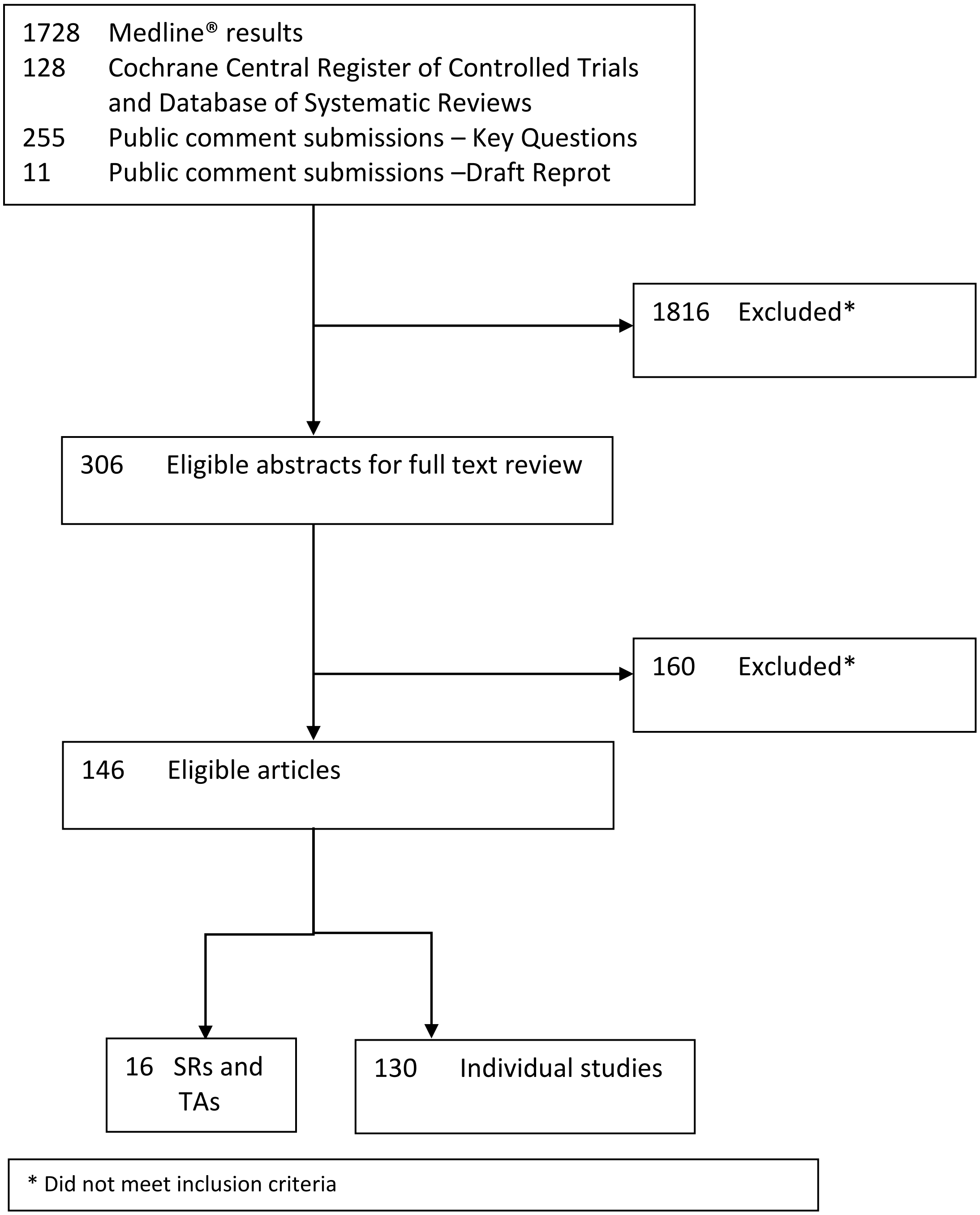
- Case series;
- Minimum sample size of 20 participants;

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
- If a portion of individuals received concurrent chemotherapy, studies that did not stratify results by IMRT alone.

**Figure 4. Search Flow Chart for Inclusion**




[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.

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 that are modifications of the 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.

The overall strength of evidence was rated using a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Guyatt 2008). Each study was assigned a rating of good, fair, poor, based on its adherence to recommended methods and potential for biases. 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 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 very serious limitations or observational studies without special strengths.

**Very low:** Any estimate of effect is *very uncertain.* Typical sets of studies would be observational studies with very 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 that are modifications of the British Medical Journal (Drummond 1996), the Consensus on Health Economic Criteria list (Evers 2005), and the 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 – Guidelines

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, Group Health, 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 intensity modulated, intensity modulated radiation therapy, intensity modulated radiotherapy, and imrt. The search was limited to adverse events reports submitted between 2002 and 2012. Two reports of serious adverse events were identified and are summarized in Appendix L.

### *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.

## Study Results

The MEDLINE search retrieved 1,728 citations, the Cochrane search retrieved 128 citations, and 266 citations were submitted through public comment. A total of 2,122 citations were reviewed and 146 articles met inclusion criteria. Appendix F contains detailed information for all studies cited in the Findings section. The data are presented by malignancy.

All relevant SR findings were integrated into this WA HTA report, regardless of the SR inclusion criteria. 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, and that met inclusion criteria of this report, will not be summarized separately.

Study populations were generally heterogeneous and varied by malignancy and within malignancies. Therefore, it was not possible to generalize population information for every malignancy. The findings from all included studies are reported in Appendix F.

The evidence on IMRT is largely based on cohort and case series studies. These studies have high risk of bias due to substantial methodological limitations. Many of the studies lacked a comparison group, and/or did not adjust for confounding variables in their analyses. Variables that may have a significant impact on outcomes may include age, tumor staging prior to treatment, smoking status, and other comorbidities. Many of the included studies have relatively small sample sizes making it difficult to generalize 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 IMRT.

For the pediatric population, only two small studies specific to children were identified (Huang 2002; Jain 2008). Both of the studies address pediatric medulloblastomas and are summarized in the SR section (De Neve 2012; Staffurth 2010; Veldeman 2008). There are four additional studies that include children within the patient population. However, none of the studies report findings stratified by age and they do not specify how many of the patients were younger than 18 years old (Milker-Zabel 2007 [meningioma]; Franchin 2011; Lai 2011; and Xiao 2011 [all nasopharyngeal cancer]).

### Findings

## Abdomen (Anus, Esophagus, Liver, Pancreas, Rectum, Stomach, Whole Pelvis Radiation)

In this section, tumors of the anus, liver, pancreas, rectum, and stomach and treatments involving whole pelvis radiation are summarized. One study on cancer of the esophagus is included in this section even though the esophagus is not technically in the abdomen, it is directly linked to structures in the abdomen.

### Anal Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

#### *Systematic Reviews*

Veldeman (2008), a fair quality SR, included one case series (Milano 2004). De Neve (2012), a poor quality SR, included one small cohort study (Bazan 2011) that reported effectiveness outcomes.

Veldeman (2008) summarized one case series (Milano 2004) of 17 patients with squamous-cell carcinoma of the anal canal. Two-year OS, DFS, and colostomy-free survival were 91%, 65%, and 82%, respectively.

De Neve (2012) summarized Bazan (2011), a small cohort study (n=46), and reported on IMRT compared to EBRT for 3-year OS (IMRT= 88% vs EBRT=52%, p<0.01), 3-year locoregional control (92% vs 57%, p<0.01), 3-year PFS (84% vs 57%, p<0.01), and 3-year colostomy-free survival (91% for IMRT). The patients in Bazan (2011) received concurrent chemotherapy to IMRT.

#### *Subsequently Published Studies*

One poor quality case series was identified (Call 2011). Call (2011) reported on 34 patients who received chemotherapy and IMRT, of which 28 were stage T1 or T2 and six were stage T2 or T4. Median age was 59 years. Follow-up time was not reported. The 3-year freedom from disease relapse rate was 80%; the estimated 3-year survival was 87%.

#### *Overall Summary*

The overall strength of evidence is very low that IMRT is associated with better 3-year OS, 3-year locoregional control, and 3-year PFS when compared to EBRT for treatment of anal cancer.

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

### *Systematic Reviews*

Veldeman (2008) (fair quality) included one study (Milano 2004). Staffurth (2010), a poor quality SR, included one study (Saarilahti 2008), and De Neve (2012), a poor quality SR, included two studies (Bazan 2011; Saarilahti 2008). Saarilahti (2008) and Bazan (2011) were both cohort studies.

Veldeman (2008) summarized one case series (Milano 2004) of 17 patients with squamous-cell carcinoma of the anal canal. No Grade 3 or higher acute non-haematological, gastrointestinal, or skin toxicities were reported. Staffurth (2010) summarized one cohort study (Saarilahti 2008) of 59 patients with anal cancer and concluded that IMRT resulted in less diarrhea and skin/mucosal toxicity than EBRT.

De Neve (2012) summarized Saarilahti (2008) and Bazan (2011) (n=46), and found significant reductions in greater than acute Grade 2 nonhematologic toxicity, skin and mucosal eruptions in the female genital area, and acute Grade 2 diarrhea after treatment with IMRT. No quantitative data was provided for harms. The patients in both Saarilahti (2008) and Bazan (2011) received concurrent chemotherapy with IMRT.

### *Subsequently Published Studies*

One poor quality case series were identified (Kachnic 2012). Kachnic (2012) retrospectively analyzed 43 patients with primary and metastatic anal cancer treated with chemotherapy and IMRT. Kachnic (2012) reported Grade 3 or greater desquamation in 10%, Grade 3 or greater hematologic toxicity in 61%, Grade 3 or greater GI toxicity in 7%, and Grade 3 or greater GU toxicity in 7%. On multivariate analysis, multiagent chemotherapy was the only variable associated with Grade 3 or greater toxicity; therefore the role of IMRT in patient toxicity is unclear.

### *Overall Summary*

There is very low overall strength of evidence that IMRT had significant reductions in acute greater than Grade 2 nonhematologic toxicity, skin, and mucosal eruptions in the female genital area, and acute Grade 2 diarrhea after treatment compared with EBRT. When treatment is a combination of chemotherapy and IMRT, there is a very low overall strength of evidence that toxicity may be related more to chemotherapy based on one small case series.

**KQ 3: What is the evidence that IMRT has differential efficacy or safety issues in subpopulations?**

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Hauerstock (2010), a fair quality case series, reported on 34 HIV-positive patients with anal cancer. All patients were treated with concurrent chemotherapy and received either 3DCRT or

IMRT. Median follow-up time was 25.5 months. Rates of 3-year RFS (63%) and 3-year OS (69%) were reported. Univariate analyses show no significant differences in local control or OS between the IMRT and 3DCRT groups. Results on harms were pooled for patients in the IMRT and SBRT groups.

*Overall Summary*

Based on one fair quality case series, the overall strength of evidence is very low that there is no difference in 3-year local control and 3-year OS for IMRT compared to EBRT for the treatment of HIV-positive patients with anal cancer.

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

No studies on costs or cost-effectiveness were identified.

## Esophagus

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

No SRs were identified.

*Subsequently Published Studies*

One poor quality, non-comparative case series (La 2010) reported on 30 patients with non-cervical cancer of the esophagus without distant metastases. Patients received chemotherapy and IMRT either as definitive therapy (60%) or after surgery (40%). No comparator was presented. Two-year actuarial loco-regional control was 64%. One-year OS was 79% and 2-year OS was 38%.

*Overall Summary*

The overall strength of evidence is very low. One small, poor quality case series reported 1-year OS (79%), 2-year OS (38%), and 2-year actuarial loco-regional control of 64%. Due to the lack of a comparative data, no conclusions can be reached regarding clinical effectiveness.

**KQ 2: What are the potential harms of IMRT 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, non-comparative case series (La 2010) reported on 30 patients with non-cervical cancer of the esophagus without distant metastases. Patients received chemotherapy and IMRT wither as definitive therapy (60%) or after surgery (40%). Twelve patients (40%) required feeding tube placement, twelve patients (40%) experienced acute Grade 3 or higher complications, and eight patients (27%) experienced late complications.

*Overall Summary*
The overall strength evidence is very low. One poor quality case series reported moderate levels of acute and chronic complications.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

Liver

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*
No SRs were identified.

*Subsequently Published Studies*
Three poor quality case series were identified (Chi 2010; Kang 2011; McIntosh 2009).

Chi (2010), a poor quality case series, reported on 23 patients with primary liver cancer treated with IMRT and antiangiogenic therapy. Median survival was 16 months and 1-year survival was 70%.

Kang (2011), a poor quality case series, reported on 27 patients with advanced hepatocellular cancer without distant metastasis and who were not candidates for local ablative or intraarterial therapy. Median follow-up was five months (range, 2 to 82). Median OS and PFS time after radiotherapy were five and three months, respectively.

McIntosh (2009), a poor quality case series, reported on 20 patients with primary liver cancer treated with IMRT and chemotherapy. No comparator was reported. Actuarial 1-year survival was 73%.

*Overall Summary*
The overall strength of evidence is very low. Three poor quality case series reported mean of 5 to 16 months. Due to the lack of a comparative data, no conclusions can be reached regarding clinical effectiveness.

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

*Systematic Reviews*
No SRs were identified.

### *Subsequently Published Studies*

Three poor quality case series were identified (Chi 2010; Kang 2011; McIntosh 2009).

Chi (2010), a poor quality case series, reported on 23 patients with primary liver cancer treated with IMRT and antiangiogenic therapy. A number of GI and hematologic toxicities including anorexia (78%), nausea and vomiting (65%), hepatitis (65%), pancreatitis (8%) and GI bleeding (13%) were reported.

Kang (2011), a poor quality case series, reported on 27 patients with advanced hepatocellular cancer without distant metastasis and who were not candidates for local ablative or intraarterial therapy. Median follow-up was five months (range, 2 to 82). Grade 0 to 2 hepatic toxicity was reported in 4 out of 14 patients (28%).

McIntosh (2009), a poor quality case series reported on 20 patients with primary liver cancer treated with IMRT and chemotherapy. Authors report acute abdominal pain in 15% of patients, nausea in 35%, esophagitis in 15%, fatigue in 70% and a number of changes in liver function tests.

### *Overall Summary*

The overall strength of evidence is very low. Among patients treated with IMRT in one poor quality case series for hepatocellular cancer, approximately 28% of patients experienced less than or equal to Grade 2 hepatic toxicity. Two poor quality case series reported moderate levels of nausea, vomiting and changes in hepatic function. Due to the lack of comparative data, no conclusions can be reached regarding relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Pancreas

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

Veldeman (2008) summarized four case series studies (Bai 2003; Ben-Josef 2004; Crane 2001; Milano 2004). All of these studies focus on IMRT dose-volume-toxicity relations alone or in combination with concurrent chemotherapy (N=66). Outcomes were not specific to IMRT, and are therefore not described here.

### *Subsequently Published Studies*

Abelson (2012), a poor quality case series of 47 patients of patients receiving chemotherapy and IMRT either as definitive treatment or after surgery reported 1- and 2-year OS of 79% and 40%, respectively. The group was heterogeneous with some patients being treated without surgery and some after surgery. Chemotherapy was given prior or after IMRT.

### *Overall Summary*

The overall strength of evidence is very low. One poor quality case series reported 1- and 2-year OS rates of 79% and 40%, respectively. Due to the lack of comparative data, no conclusions can be reached regarding the clinical effectiveness.

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

### *Systematic Reviews*

Veldeman (2008) summarized four case series studies (Bai 2003; Ben-Josef 2004; Crane 2001; Milano 2004). All of these studies focus on IMRT dose-volume-toxicity relations alone or in combination with concurrent chemotherapy (N=66). Outcomes were not specific to IMRT, and are therefore not described here.

### *Subsequently Published Studies*

Abelson (2012), a poor quality, non-comparative case series of 47 patients of patients receiving chemotherapy and IMRT either as definitive treatment or after surgery reported Grade 1 or 2 anorexia, dehydration, nausea and vomiting in 97 to 100% of patients. Grade 3 or higher acute GI complications were noted in 9% and Grade 3 or higher chronic gastrointestinal complications were noted in 9% of patients.

### *Overall Summary*

The overall strength of evidence is very low. One poor quality case series reported acute and chronic toxicity GI in 9% of patients. Due to the lack of comparative data, no conclusions can be reached regarding relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT 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. The ICER for IMRT plus gemcitabine compared to EBRT plus gemcitabine was $1,584,100. Murphy (2012) concludes that the ICER for SBRT plus gemcitabine is within what society currently considers cost effective; ICER for IMRT and EBRT appear to exceed what society considers cost-effective.

*Overall Summary*

The overall strength of evidence is low. One poor quality cost-effectiveness modeling study calculated that IMRT had an ICER of $1,584,100/QALY compared to EBRT.

## Rectum

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

No SRs were identified.

*Subsequently Published Studies*

One poor quality, non-comparative case series (Li 2012) reported on 63 patients treated for rectal cancer with chemotherapy and IMRT. No comparator was reported. Two-year PFS and OS were 90% and 96%, respectively.

*Overall Summary*

The overall strength of evidence is very low. One poor quality case series of 63 patients reported 2-year PFS and OS rates of 90% and 96%, respectively. Due to the lack of comparative data, no conclusions can be reached regarding the clinical effectiveness.

**KQ 2: What are the potential harms of IMRT 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, non-comparative case series (Li 2012) reported on 63 patients treated for rectal cancer with chemotherapy and IMRT. Li (2012) reported Grade 3 diarrhea in 10%, Grade 3 dermatitis in 3%, and Grade 3 neutrapenia in 2% of patients.

*Overall Summary*

The overall strength of evidence is very low. One poor quality case series reported relatively low levels of complications. Due to the lack of comparative data, no conclusions can be reached regarding the relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on subpopulations were identified.

## Stomach

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Two poor quality cohort studies (Boda-Haggeman 2009; Minn 2010) reported on chemotherapy plus either 3DCRT or IMRT. Boda-Haggemen (2009) reported on 27 patients treated with 3DCRT in the period before adoption of IMRT (historical cohort) and 33 patients treated with IMRT for gastric cancer after surgical resection. Patients also received chemotherapy regimens that changed with time and were thus different for the 3DCRT and IMRT groups. Boda-Haggeman (2009) reported statistically improved actuarial 2-year survival and actuarial DFS with IMRT compared to 3DCRT.

Minn (2010) reported on 26 patients treated with 3DCRT and 31 patients treated with IMRT for non-metastatic gastric cancer; all patients also received chemotherapy. This study used a historical cohort for 3DCRT comparison. Minn (2010) reported no statistical difference for 2-year OS or loco-regional control between 3DCRT and IMRT treated groups.

### *Overall Summary*

The overall strength of evidence is very low. Based on two small, poor quality cohort studies, there is inconsistent evidence on whether IMRT improves 2-year OS compared with 3DCRT.

**KQ 2: What are the potential harms of IMRT 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 cohort studies (Boda-Haggeman 2009; Minn 2010) reported on chemotherapy plus either 3DCRT or IMRT. Boda-Haggemen (2009) reported on 27 patients treated with 3DCRT in the period before adoption of IMRT (historical cohort) and 33 patients treated with IMRT for gastric cancer after surgical resection. Patients also received chemotherapy regimens that changed with time and were thus different for the 3DCRT and IMRT groups. Boda-Haggeman (2009) reported a worsening of creatinine levels in 3DCRT treated patients but no worsening of creatinine in IMRT treated patients; the results were not statistically significant.

Minn (2010) reported on 26 patients treated with 3DCRT and 31 patients treated with IMRT for non-metastatic gastric cancer; all patients also received chemotherapy. Minn reported no difference in Grade 2 or worse GI toxicities between 3DCRT and IMRT treated groups. Minn (2010) reported significant increase in creatinine levels at one year in 3DCRT but not in IMRT treated patients.

### *Overall Summary*

The overall strength of evidence is very low. The two poor quality cohort studies report decrease in renal function measured by creatinine levels for 3DCRT compared to IMRT; the difference was significant in one study but not the other study. The effect of chemotherapy on renal toxicity is not investigated in either study.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## <u>Whole Pelvis Radiation</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

No studies on effectiveness were identified.

**KQ 2: What are the potential harms of IMRT 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 additional poor quality cohort study (Ferrigno 2010) was identified. Ferrigno (2010) reported on 134 patients with pelvic tumors treated with IMRT (n=69) or EBRT (n=65). Malignancies in the EBRT group included endometrium, cervical, rectum, and anal cancer; malignancies in the IMRT group included endometrium, cervical, rectum, anal canal, and bladder cancer. Study finding are not stratified by cancer type. Patients had weekly follow-ups during the course of radiation therapy. Acute GI and GU toxicity rates were not significantly different in the IMRT and EBRT groups. No Grade 3 or higher toxicities were reported in the IMRT group.

*Overall Summary*

Among patients treated with IMRT for whole pelvis radiation[7], there is very low overall strength of evidence that there were no significant differences in toxicity frequency for IMRT compared to EBRT.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Brain

In this section, evidence on intracranial tumors is summarized. There is limited evidence for all tumor types. No other cancers were identified for this section. The sections are divided up by intracranial malignancy and include the following: astrocytomas, brain metastases, glioblastomas, high-grade gliomas, medulloblastomas, meningiomas, pituitary adenomas, and sacral chodomas. Malignancies are discussed as they were reported in the 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.

### Astrocytoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

The SRs by Veldeman (2008) and Staffurth (2010) reported on one study of IMRT for malignant astrocytoma (Iuchi 2006). Iuchi (2006), a fair quality cohort study, reported on 25 patients with anaplastic astrocytoma treated with IMRT compared to 60 historical controls treated with EBRT. IMRT resulted in significant improvement in 1- and 2-year OS (71.4 vs 54.6, 55.6 vs 19.5; p=0.043) and 1- and 2-year PFS (71.4 vs 26.4, 53.6 vs 17; p=0.043).

*Subsequently Published Studies*

No subsequently published were identified.

*Overall Summary*

There is very low overall strength of evidence that patients treated by IMRT had significantly greater 1-year OS and PFS than EBRT. There is very low overall strength of evidence that the IMRT group had greater 2-year OS and PFS compared to EBRT.

[7] Study included patients with endometrium, cervical, rectum, anal canal, and bladder cancers.

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

*Systematic Reviews*

The SRs by Veldeman (2008) and Staffurth (2010) reported on one study of IMRT for malignant astrocytoma (Iuchi 2006). Iuchi (2006), a fair quality cohort study, reported on 25 patients with anaplastic astrocytoma treated with IMRT compared to 60 historical controls treated with EBRT. Acute Grade 1, 2, and 3 toxicities were reported in 20%, 50% and 13% for the IMRT group, and 42%, 42%, and 8% of the EBRT group. Statistical significance of these differences was not provided.

*Subsequently Published Studies*

No subsequently published studies were identified.

*Overall Summary*

There is very low overall strength of evidence. One fair quality cohort study reported that patients undergoing treatment with IMRT for astrocytoma had fewer Grade 1 toxicities, but more Grade 2 and 3 toxicities than patients undergoing EBRT. Due to the limitations of small sample size, no conclusions can be reached regarding relative harms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

<u>Brain metastases</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

No SRs were identified.

*Subsequently Published Studies*

Weber (2011), a fair quality case series, reported on 29 patients with previously untreated brain metastases treated with IMRT (specifically referred to as volumetric-modulated arc therapy [VMAT]). Mean follow-up was 5.4 months (±2.8). Six-month OS was 55.1%. Patients undergoing surgery with VMAT survived significantly longer (72.0%) than patients who only received VMAT (33.5%) (p=0.035). Patients treated with VMAT had decreased QoL, as well as global health, physical, and role functioning. However, only the decreases in physical functioning and role functioning were statistically significant (p=0.05 and p=0.01, respectively).

### *Overall Summary*

The overall strength of evidence is very low. The sole study identified did not compare treatment groups, which precluded any conclusions about the relative effectiveness of volume-modulated arc therapy (VMAT) treatment for patients with brain metastases. Patients treated solely by VMAT had six-month OS of 55.1%, while patients treated by surgery and VMAT had six-month OS of 72.0%. Further, individuals undergoing VMAT treatment had significantly decreased physical functioning and role functioning scores on self-assessments of QOL.

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

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Weber (2011), a fair quality case series, reported on 29 patients with previously untreated brain metastases treated with IMRT (volumetric-modulated arc therapy [VMAT]). Mean follow-up was 5.4 months (±2.8). Grade 1 and 2 alopecia was observed in nine patients (31%).

### *Overall Summary*

The overall strength of evidence is very low. Given the lack of a comparator, no conclusions can be reached regarding the relative harms of VMAT treatment. As reported by one fair quality case series, patients treated by VMAT with brain metastases experienced Grade 1 and 2 alopecia.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## <u>Glioblastoma multiforme</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

There was one fair quality SR (Amelio 2010) on IMRT in newly diagnosed glioblastomas that included 17 studies. Ten studies addressed technical issues and eight studies addressed clinical survival and toxicity. Among the eight studies reporting on clinical issues, there was significant heterogeneity of dosage, treatment regimens and the use of chemotherapy. Stages of glioblastoma multiforme were not given in Amelio (2010). All eight studies were case series that did not provide comparative data. Amelio (2010) noted that the studies were of poor quality.

Study sizes ranged from 19 to 42 patients. Mean patient ages ranged from 55 to 63, with a total age range of 20 to 86 years.

Amelio (2010) summarized the effectiveness findings from the eight studies and reported ranges of 1-year OS (30% to 81.9%), 2-year OS (0% to 55.6%), 1-year PFS (0% to 71.4%), and 2-year PFS (0% to 53.6%). Due to significant heterogeneity among studies, comparison or meta-analysis of these findings was felt by the authors to be inappropriate because of small patient samples and heterogeneity of radiation dosages, treatment plans and the use of chemotherapy.

### *Subsequently Published Studies*

Two fair quality (Monjazeb 2012; Tsein 2012) and one poor quality (Panet-Raymond 2009) case series were identified. Monjazeb (2012), a fair quality case series, followed 21 patients with glioblastoma multiforme until death. Patients had newly diagnosed, non-multifocal glioblastoma multiforme in the supratentorial region measuring smaller than 8 cm in diameter before biopsy. All patients were treated with IMRT; four patients had biopsy only; eight patients had total resection; and nine patients had subtotal resection prior to IMRT. Patients with evidence of recurrence of glioblastoma multiforme were not included in the study. Median OS was 13.6 months (range, 0.9 to 40.2) and median PFS was 6.5 months (range, 0.9 to 40.2).

Tsein (2012), a fair quality case series, reported on 38 patients treated with IMRT and chemotherapy following biopsy only (16%), sub-total resection (45%) or gross total resection (39%). Median PFS of 9.0 months (95% CI, 6.0-11.7) and median OS of 20.1 months (95%CI, 14.0-32.5) were reported.

Panet-Raymond (2009), a poor quality case series, reported on 35 patients treated for glioblastoma with chemotherapy and IMRT either as the definitive treatment (26%) or after surgery (74%). Median survival of 14.4 months (range, 3.2 to 26.5 months) was reported.

### *Overall Summary*

The overall strength of evidence is very low. As reported by three case series, the 2-year OS ranged from 0% to 55.6%, 2-year PFS ranged from 0% to 53.6%, median PFS was 9.0 months (95% CI, 6.0-11.7), and median OS ranged from 14.4 to 20.1 months. Due to the lack of a comparator, no conclusions can be drawn.

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

### *Systematic Reviews*

There was one fair quality SR (Amelio 2010) on IMRT in newly diagnosed glioblastomas that included 17 studies. Ten studies addressed technical issues and eight studies addressed clinical survival and toxicity. Among the eight studies reporting on clinical issues, there was significant heterogeneity of dosage, treatment regimens and the use of chemotherapy. All eight studies were case series that did not provide comparative data. Amelio (2010) noted that the studies were of poor quality.

Amelio (2010) reported that acute toxicities were negligible, while only two included studies reported Grade 3 toxicities: 7% of four patients (Narayana 2006)[8] and 12% of 41 patients (Fuller 2007). Only one study reported Grade 4 toxicity, which occurred in approximately 3% of 42 patients (Narayana 2006). Six studies reported on late toxicities. Only one study reported Grade 4 side effects, which occurred in 20% of 20 patients in that study (Floyd 2004). Two studies reported radiation necrosis rates of 12% of 23 patients (Iuchi 2006) and 20% of 20 patients (Floyd 2004). Three studies reported on the proportion of patients needing to increase or begin corticosteroid treatment patients requiring corticosteroid therapy ranged from 16% to 23% (study sizes 8, 19, and 25 patients, respectively) (Morganti 2010; Nakamatsu 2008; Sultanem 2004).

### *Subsequently Published Studies*

Two fair quality (Monjazeb 2012; Tsein 2012) and one poor quality (Panet-Raymond 2009) case series were identified. Monjazeb (2012), a fair quality case series, followed 21 patients with glioblastoma multiforme, until death. All patients were treated with IMRT; four patients had biopsy only; eight patients had total resection; and nine patients had subtotal resection prior to IMRT. Patients with evidence of recurrence of glioblastoma multiforme were not included in the study. All patients had acute Grade 1 or 2 toxicities; eight patients (38%) had acute Grade 3 toxicity, and one patient had acute Grade 4 toxicity. Specific toxicities were not reported.

Tsein (2012), a fair quality case series, reported on 38 patients treated with IMRT and chemotherapy following biopsy only (16%), sub-total resection (45%) or gross total resection (39%). Acute Grade 3 neurotoxicity was reported in 16%; late radiation necrosis was seen in 8%, and Grade 3 otitis with hearing loss in 3%.

Panet-Raymond (2009), a poor quality case series, reported on 35 patients treated for glioblastoma with chemotherapy and IMRT either as the definitive treatment (26%) or after surgery (74%). Acute toxicity included nausea in 28%, vomiting in 20%, fatigue in 62%, Grade 1 anemia in 38% and Grade 1 to 2 hepatotoxicity in 28%. No Grade 3 or higher toxicities were reported.

### *Overall Summary*

The overall strength of evidence for all harms is very low. One fair quality case series reports on IMRT alone; two additional case series (one fair quality, one poor quality) report on IMRT plus chemotherapy. Results from the case series are inconsistent. One case series reported Grade 3 or higher toxicity in 38% (8 patients); one case series reported Grade 3 neurotoxicity in 16% (6 patients); and one case series reported no Grade 3 or higher toxicity. Due to the lack of comparative data, no conclusions can be reached regarding relative harms.

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[8] The summarized results from Narayana (2006) only included patients with glioblastoma multiforme. Narayana (2006) reported on high-grade glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas. Narayana (2006) is fully summarized under the *High-Grade Glioma* section.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on cost or cost-effectiveness were identified.

## High-Grade Glioma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Two fair quality, single center case series reported on gliomas (Cho 2011; Narayana 2006). Narayana (2006), a fair quality case series, reported on 58 consecutive patients with high-grade gliomas (i.e., glioblastoma, anaplastic astrocytoma, and anaplastic oligodendroglioma) at one study center. The median follow-up was 24 months (range, 12 to 48). Median PFS ranged from 2.5 to 5.6 months and OS ranged from 9 to 36 months, for Grade III and IV tumors. Survival at 1-year was 86.3%, while survival at 2-years was 61.6%.

Cho (2011), a fair quality case series, reported on 40 patients with high-grade gliomas. The median follow-up was 13.4 months (range, 3.7 to 55.9). Median OS was 14.8 months (95% CI, 8.2 to 21.4), median PFS was 11.0 months (95%CI, 7.1-15.0), and 1- and 2-year OS rates were 64% and 42%, respectively. The 1- and 2-year PFS rates were 46% and 31%, respectively.

### *Overall Summary*

The overall strength of evidence is very low. Due to the lack of a comparator in both studies identified, no conclusions can be reached regarding effectiveness. As reported by two fair quality case series, patients undergoing treatment with IMRT for high-grade gliomas had varying ranges of OS, PFS, and actuarial[9] OS. Differences between the studies preclude drawing any conclusions.

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

### *Systematic Reviews*

No SRs were identified.

[9] For actuarial OS, OS is calculated for each time interval. This method of OS calculation tends to be more specific than calculating the median or mean OS.

### *Subsequently Published Studies*

Cho (2011), a fair quality case series, reported on 40 patients with high-grade gliomas. The median follow-up was 13.4 months (range, 3.7 to 55.9). Grade 2 edema was reported in two patients. Grade 3 edema was reported in one patient. Four patients had Grade 1 worsening of neurological symptoms.

### *Overall Summary*

The overall strength of evidence is very low. Due to the lack of a comparator in the sole study identified, no conclusions can be reached regarding harms. As reported by one fair quality case series, patients undergoing treatment with IMRT for high-grade gliomas had toxicities ranging from grade 1 to 3, including reports of edema or worsening of neurological symptoms.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Medulloblastoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Polkinghorn (2011), a poor quality case series, reported on 33 patients treated with IMRT and chemotherapy. Patient ages ranged from 4 to 46 years, with a median age of 9 years. Although the patient population included children and adolescents, results were not stratified by age. Median follow-up was 63 months (range, 5 to 121 months). For standard risk patients, rates of 5-year actuarial PFS (81.4%; 95%CI, 52.1%-93.7%) and 5-year OS (88.4%; 95%CI, 60.8%-97.0%) were reported. For high risk patients, rates of 5-year actuarial PFS and OS were both 87.5% (95%CI, 38.7%-98.1%).

### *Overall Summary*

The overall strength of evidence is very low. One poor quality case series reported 5-year PFS of 81.4% and 5-year OS of 88.4% for standard risk patients. Rates for 5-year PFS and OS for high risk patients were both 87.5%. Due to the lack of comparative data, no conclusions can be made on clinical effectiveness.

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

### *Systematic Reviews*

The SRs by Veldeman (2008) and Staffurth (2010) reported on one study of IMRT for pediatric medulloblastoma (Huang 2002). Huang (2002), a cohort study, reported on 26 children with medulloblastoma. IMRT was associated with reduced Grade 3 and 4 ototoxicity when compared to EBRT (7% vs 55%; 7% vs 9%; $p<0.014$). Grade 1 and 2 toxicities appeared to be higher in the IMRT group than in the EBRT group, but the statistical significance of this difference was not reported.

De Neve (2010) cited one small case series of 25 children with medulloblastoma (Jain 2008). Jain (2008) reported no significant differences in neurocognitive functioning, as measured by 10 different instruments, after treatment with IMRT or EBRT. No quantitative data was provided.

### *Subsequently Published Studies*

Two poor quality case series were identified (Paulino 2010; Polkinghorn 2011). Paulino (2010), a poor quality case series, reported on 44 pediatric patients treated with IMRT plus chemotherapy. Grade 3 or 4 ototoxicity was reported in 25% of patients. Evaluation of individual ears showed Grade 2 ototoxicity in 12%, Grade 3 ototoxicity in 15% and Grade 4 ototoxicity in 3% of patients.

Polkinghorn (2011), a poor quality case series, reported on 33 patients treated with IMRT and chemotherapy. Patient ages ranged from 4 to 46 years, with a median age of 9 years. Although the patient population included children and adolescents, results were not stratified by age. Median follow-up was 63 months (range, 5 to 121 months). In this series, Grade 3 hearing loss was identified in 6% of patients.

### *Overall Summary*

The overall strength of evidence is very low that children undergoing treatment with IMRT for medulloblastoma had reduced rates of Grade 3 or 4 ototoxicity compared to those undergoing EBRT, but did not have significant differences in neurocognitive function. Two case series of IMRT and chemotherapy reported ototoxicity levels of 6% to 25%.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

Meningioma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*
No SRs were identified.

*Subsequently Published Studies*
Three single center case series reported on meningiomas (Estall 2009; Milker-Zabel 2007; Sajja 2005). One was of good quality (Estall 2009) while the other two were of poor quality (Milker-Zebel 2007; Sajja 2005).

Estall (2009), a good quality case series, reported on 128 consecutive patients referred to one center between 1996 and 2000 with meningioma. Median follow-up was 5.3 years (range, 2.1 to 11.9). An 82% survival rate was reported, but the time-frame for this finding was not provided. Among the patients that died (n=24), death due to disease was reported in 37% of these patients.

Milker-Zabel (2007), a poor quality case series, reported on 94 patients. Patient ages ranged from 13.3 to 79.2 years. Although the patient population included adolescents, results were not stratified by age. The median follow-up was 4.4 years (range, 1.6 to 82.7). Recurrence-free survival (RFS) was reported at 3- (96.9%) and 5-years (94.8%).

Sajja (2005), a poor quality case series, reported on 35 patients with intracranial meningiomas from a single center between 1997 and 2003. Median follow-up was 19.2 months (range, 6.4 to 62.4). Overall 3-year actuarial survival was 91% (95% CI, 79%-100%).

*Overall Summary*
The overall strength of evidence is very low. Due to the lack of comparators in all three studies, no conclusions can be reached regarding clinical outcomes based on the limited evidence. As reported by three case series, patients undergoing treatment with IMRT for meningioma had varying reported survival outcomes. Differences in survival outcome measures precluded combination of the findings.

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

*Systematic Reviews*
No SRs were identified.

*Subsequently Published Studies*
Milker-Zabel (2007), a poor quality case series, reported on 94 patients; patient ages ranged from 13.3 to 79.2 years. Although the patient population included adolescents, results were not

stratified by age. The median follow-up time was 4.4 years (range, 1.6 to 82.7). No severe toxicities were reported.

*Overall Summary*

The overall strength of evidence is very low. Due to the lack of comparators in the sole study identified, no conclusions can be reached regarding harms based on the limited evidence. As reported by one poor quality case series, patients undergoing treatment with IMRT for meningioma experienced no severe toxicities.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Pituitary Adenoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

No SRs were identified.

*Subsequently Published Studies*

Mackley (2007), a poor quality case series, reported on 34 patients with pituitary adenoma. Median follow-up was 42.5 months (range, 12 to 80). For hormonally active tumors, overall biochemical response rate was 100% (complete response rate 22%, partial response rate 78%).

*Overall Summary*

The overall strength of evidence is very low. Due to the lack of a comparator in the sole study identified, no conclusions can be reached regarding clinical outcomes. As reported by one poor quality case series, patients had a 22% complete response rate and a 78% partial response rate.

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

*Systematic Reviews*

No SRs were identified.

*Subsequently Published Studies*

Mackley (2007), a poor quality case series, reported on 34 patients with pituitary adenoma. Median follow-up was 42.5 months (range, 12 to 80). Thirty-one patients reported short-term (six months) toxicities of fatigue (65%), headache (61%), nausea or vomiting (29%), visual complaints (29%), alopecia or erytherma (13%), anxiety attack (3%), epistaxis (3%), dry eyes

(3%), and excess tearing (3%). Twenty-nine patients reported long-term (greater than or equal to 12 months) harms of cognitive changes (13%), visual decline (10%), and cranial nerve deficit (10%).

### *Overall Summary*

The overall strength of evidence is very low. Due to the lack of a comparator in the sole identified study, no conclusions can be reached regarding harms based on the limited evidence. Patients experienced toxicities of varying chronicity and type with the most common being fatigue as reported by one poor quality case series. In addition, 29 patients reported long-term (≥ 12 months) harms in cognitive changes, visual decline, and cranial nerve deficits.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Breast

Hayes published two good quality Directory Reports in March 2012 titled *Whole Breast Irradiation for Breast Cancer Using Three-Dimensional Conformal Radiation Therapy or Intensity-Modulated Radiation Therapy* (Hayes 2012b) and Accelerated *Partial Breast Irradiation for Breast Cancer Using Conformal and Intensity-Modulated Radiation Therapy* (Hayes 2012a).

The RCTs included by Hayes (2012a, 2012b) do not address the clinical effectiveness of IMRT. Hayes (2012a, 2012b) rated the quality of the individual studies included in their report as very poor to good[10].

### Whole Breast Irradiation

Hayes (2012b) included 15 studies that evaluated IMRT for whole breast irradiation [three RCTs (Barnett 2009, 2012; Donovan 2007; Pignol 2008), one prospective cohort (Hardee 2012), three retrospective cohort studies (Freedman 2009; Harsolia 2007; MacDonald 2008), one matched cohort study (Freedman 2006), four prospective nonrandomized comparative trials (Formenti 2007; Freedman 2007; Morganti 2009; Vicini 2002), two retrospective chart analyses (Croog 2009; MacDonald 2010), and one initial outcomes analysis of implementation of IMRT in an integrated cancer center system (Bhatanagar 2009)]. The total sample size for all studies

[10] Hayes, Inc. uses a different assessment tool to rate study quality than was used by CEBP in this WA HTA report. These reported study qualities are from the Hayes, Inc. reports. Hayes evaluates the individual quality of each study based on study design and uses individual study ratings to develop a quality assessment rating for each key question and for the overall body of evidence. The overall assessment of the body of evidence is used to establish a Hayes Rating, a proprietary scale reflecting the strength and direction of the evidence.

combined is 4,661. Follow-up ranged from 6 weeks to 6.3 years. In addition, Hayes (2012b) included summaries of four SRs (De Neve 2012; Pignol 2010; Staffurth 2010; Veldeman 2008).

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews and Technology Assessments*

Disease control and survival

Hayes (2012b) included a total of five observational studies (N=1,147) that assessed disease control and survival (Croog 2009; Formenti 2007; McDonald 2008; McDonald 2010; Morganti 2009). Three of the studies were retrospective (Croog 2009; McDonald 2008; McDonald 2010).

MacDonald (2008), a retrospective cohort (n=240) that compared IMRT with 2DCRT, demonstrated no difference in 7-year ipsilateral breast tumor recurrence (IBTR) (95% vs 90%; p=0.36), contralateral breast tumor recurrence (CBTR) (96% vs 98%; p=0.99), distant metastases (95% vs 88%; p=0.18), 7-year OS (91% vs 91%; p=0.86), and DSS (97% vs 95%; p=0.42).

Formenti (2007), a prospective case series (n=91), reported one case of local regional recurrence that was rapidly followed by distant metastases. Croog (2009), a retrospective chart review (n=128), reported that one patient developed an ipsilateral breast tumor recurrence. Morganti (2009), a report on prospective phase I-II studies (n=332), did not report any local or nodal relapse after a median follow-up of 31 months.

McDonald (2010), a retrospective analysis (n=354), reported on 3-year OS (97.6%), local recurrence rate (2.9%), contralateral breast tumor recurrence (0.4%), and distant metastases (2.7%) in patients with invasive breast cancer (n=282), and 3-year OS (98%), local recurrence rate (1.4%), contralateral breast tumor recurrence (0%), and distant metastases (0%) among patients with ductal carcinoma in situ (n=74).

Summarized in Hayes (2012b), Veldeman (2008) reports that comparative evidence related to OS was inconclusive and De Neve (2012) reports uncertainty of comparative anticancer efficacy for survival or DSS. No quantitative data from the summarized SRs was reported.

Quality of Life

Hayes included a total of two comparative studies (N=644) that assessed QoL (Donovan 2007; Pignol 2008). Donovan (2007) was a prospective RCT (n=306), and Pignol (2008) was a multicenter, double blinded RCT (n=358). Neither study reported a significant difference in QoL measures between IMRT and EBRT.

### *Subsequently Published Studies*

No studies were identified.

### *Overall Summary*

Two SRs reported inconclusive findings for patient survival and one retrospective cohort study (N=240) comparing IMRT to 2DCRT reported no significant differences in OS. The overall strength of evidence is low that there are inconsistent findings for patient survival (OS, DSS).

For cancer recurrence (IBTR, CBTR, and local regional recurrence) and distant metastases, one comparative study reported no significant differences compared to 2DCRT; the other included studies reported a range of 0% to 2.9% with no comparative data. The overall strength of the evidence for these outcomes (i.e., IBTR, CBTR, distant metastases) is low.

There is limited evidence on QoL outcomes from IMRT. There is moderate overall strength of evidence that IMRT compared to EBRT does not result in significant differences in QoL.

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

### *Systematic Reviews and Technology Assessments*

Hayes (2012b) included a total of five studies that reported on cosmesis, 14 studies that reported on acute toxicity from IMRT, and five studies that reported on late toxicities from IMRT.

<u>Cosmesis</u>

Hayes (2012b) included a total of five studies (N=1,724) that assessed breast cosmesis (Barnett 2009, 2012; Donovan 2007; Freedman 2007; Harsolia 2007; McDonald 2010). Two of the studies were prospective RCTs (Donovan 2007; Barnett 2009, 2012), one study was a prospective observational study (Freedman 2007), and two studies were retrospective observational studies (Harsolia 2007; McDonald 2010).

Donovan (2007), a prospective RCT that compared IMRT to EBRT for late adverse effects of whole breast irradiation (n=306), reported the control group was 1.7 times more likely to have a change in breast appearance than the IMRT group (95% CI, 1.2-2.5, p=0.008).

Barnett (2009, 2012), a prospective, single center, single-blind RCT (n=814) that compared IMRT to EBRT for late toxicity, reported no significant differences between groups in breast shrinkage or edema, overall cosmesis, pigmentation, and patient reported breast pain or oversensitivity.

Harsolia (2007), a retrospective cohort study (n=172) that compared IMRT relative to EBRT to evaluate acute and late toxicities, reported good and excellent cosmesis in 99% and 97% of patients, respectively. This finding was not statistically significant.

Freedman (2007), a prospective uncontrolled phase II study (n=75) that evaluated acute toxicity of IMRT, reported no significant differences in patient reported cosmesis, breast pain, and function scores between baseline and at six-week follow-up. In McDonald (2010), a retrospective cohort that compared IMRT with 2DCRT (n=354), global breast cosmesis was judged good or excellent (96.5%) or fair (3.5%) by physicians.

Summarized in Hayes (2012b), Pignol (2010) reports that breast IMRT improves long-term cosmetic results and Staffurth (2010) reports that IMRT improves last clinician-assessed cosmesis in relation to EBRT. No quantitative data from the summarized SRs was reported.

Acute toxicity

Of the 14 studies included (N=4,260), there were two RCTs (Barnett 2009, 2012; Pignol 2008), one prospective cohort (Hardee 2012), three retrospective cohorts (Freedman 2009; Harsolia 2007; McDonald 2008), one matched cohort (Freedman 2006), four prospective case series (Formenti 2007; Freedman 2007; Morganti 2009; Vicini 2002), two retrospective chart analyses (Croog 2009; McDonald 2010), and one initial outcomes analysis (Bhatanagar 2009). Due to the volume of studies, only the RCTs will be discussed below. Details of individual studies can be found in the Hayes (2012b) report.

Barnett (2009, 2012), a prospective, single-center, single blind RCT (n=815) that compared IMRT to EBRT, reported no significant differences between groups for Grade 2 or higher acute toxicities (odds ratio (OR) 1.00, 95% CI, 0.76-1.34, p=0.97).

Pignol (2008), a multicenter, phase III, double blind RCT (n=358) that compared IMRT to EBRT, reported no significant differences in Grade 3 and 4 skin toxicities (IMRT = 27.1%; EBRT = 36.7%; p=0.06). Moist desquamation of the whole breast was reduced in the IMRT group compared to EBRT (IMRT = 31%; EBRT = 48%; p=0.002).

Other acute toxicities reported from the remaining 12 studies included breast cellulitis, fatigue, breast pain, breast pruritus, and hematologic toxicity.

Late toxicity

Of the five studies included (N=1,415), one was an RCT (Barnett 2009, 2012), one was a prospective cohort (Hardee 2012), one was a prospective uncontrolled trial (Formenti 2007), and two were retrospective cohorts (Harsolia 2007; McDonald 2008).

Barnett (2009, 2012), a prospective, single-center, single blind RCT (n=815) that compared IMRT to EBRT, reported that patients in the EBRT group were significantly more likely to develop any Grade (1, 2, or 3) telangiectasia than the IMRT group (OR 1.68, 95% CI, 1.13-2.50, p=0.009).

Hardee (2012), a prospective cohort study (n=97) that evaluated IMRT compared with 3D-CRT, reported late Grade 2 or greater hyperpigmentation in 2% (IMRT) vs 11% (3D-CRT) of patients (p=0.01). Incidence of Grade 2 or greater edema, induration, fibrosis, or retraction was similar between treatment groups and low overall (less than 10%). No case of Grade 2 or greater telangiectasia or skin dimpling was reported.

Formenti (2007), a prospective uncontrolled study (n=91), reported late Grade 1 or 2 toxicities (i.e., pigmentation change (Grade 1 = 70.0%, Grade 2 = 0%), breast fibrosis (Grade 1 = 48.3%, Grade 2 = 3.3%), breast edema (Grade 1 = 13.3%, Grade 2 = 0%), breast pain (Grade 1 = 8.3%, Grade 2 = 1.7%), fatigue (Grade 1 = 8.3%, Grade 2 = 1.7%), retraction (Grade 1 = 5.0%, Grade 2 = 0%), and telangiectasia (Grade 1 = 3.3%, Grade 2 = 1.7%)); no Grade 3 late toxicities were reported.

Harsolia (2007), a retrospective cohort study (n=172) that compared IMRT with EBRT, reported late Grade 2 or greater toxicities for the IMRT vs control group (i.e., breast edema (1% vs 25%, p<0.001), hyperpigmentation (7% vs 17%, p=0.06), fat necrosis (0% vs 1%, NS), and induration/fibrosis (0% vs 6%, NS)).

McDonald (2008), a retrospective cohort study (n=240) that compared IMRT with EBRT for early stage breast cancer, did not differentiate between acute and late toxicities for dermatitis and breast cellulitis.

### *Subsequently Published Studies*

No subsequently published studies were identified.

### *Overall Summary*

The overall strength of evidence is low that there is inconsistent evidence for breast cosmesis when IMRT is compared to EBRT.

There is moderate overall strength of evidence that IMRT compared to EBRT does not result in a significant difference in acute toxicities (i.e., Grade 2 or higher acute toxicities, Grade 3 or 4 skin toxicities).

One large prospective RCT (n=815) reported that the EBRT group was 1.68 times more likely to develop any Grade (1, 2, or 3) of telangiectasia compared to IMRT (moderate overall strength of evidence). There are inconsistent findings that IMRT, compared to EBRT, is associated with lower rates of late Grade 2 or greater breast edema or hyperpigmentation (low overall strength of evidence). Limited evidence reported no significant differences in late Grade 2 or greater fat necrosis or induration/fibrosis for IMRT compared to EBRT; the overall strength of evidence is low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

### *Systematic Reviews*

Hayes (2012b) reports on two studies on costs of IMRT: one review of the Surveillance, Epidemiology and End Results –Medicare (SEER) database (Smith 2011) and one cost-comparison analysis (Suh 2005).

Smith (2011), a review of the SEER data, showed an increase in IMRT use for breast cancer from 0.9% in 2001 to 11.2% in 2005. Increased use of IMRT correlated with areas with a high proportion of radiation oncologists (OR = 2.32, 95% CI = 1.47-3.68, p<0.001), for women treated at freestanding radiation centers (OR = 1.36, 95% CI 1.20-1.53, p<0.001) and in regions where Medicare intermediary allowed IMRT for breast cancer ( OR = 10.87, 95% CI = 9.26-12.76, p<0.001). The mean cost of conventional RT was $7,179 and the mean cost of IMRT was $15,230.

Suh (2005), a cost-comparison analysis, modeled several treatment regimens for radiation treatment after surgery for a prototypical 60 year old female with stage I breast cancer. The treatment regimens included whole, accelerated partial breast radiation and brachytherapy. External beam regimens included conventional RT and IMRT. Direct medical costs and non-medical patient costs were calculated for each treatment regimen. For whole breast radiation, total direct medical costs for conventional RT ranged from $6,100 to $10,900; total IMRT costs were $19,300.

### *Subsequently Published Studies*

No subsequently published studies were identified.

### *Overall Summary*

Results of analysis of SEER data demonstrated increased costs for IMRT compared with EBRT. The overall strength of evidence that IMRT costs more than EBRT is low. There are no cost effectiveness studies.

## Partial Breast Irradiation

For partial breast irradiation, Hayes (2012a) included four studies (three prospective uncontrolled trials, one interim analysis from an RCT). The total sample size for patients receiving IMRT treatment was 434, with sample sizes ranging from 34 to 259; follow-up ranged from 10 to 44.8 months. Studies were rated as very poor to poor quality[11].

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews and Technology Assessments*

Hayes (2012a) included three case series (Jagsi 2010; Leonard 2007; Lewin 2011) for disease control and survival (N=175). Survival rates were not reported in any of the studies. Only one patient in all three studies had a localized ipsilateral tumor recurrence 31 months after radiation treatment.

### *Subsequently Published Studies*

No studies identified.

### *Overall Summary*

No studies reported on patient survival. Only one patient in all three case series (N=175) had localized ipsilateral tumor recurrence. The overall strength of the evidence for local tumor recurrence is very low.

[11] Hayes, Inc. uses a different assessment tool to rate study quality than was used in this WA HTA report. These reported study qualities are from the Hayes, Inc. report.

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

*Systematic Reviews*

Hayes (2012a) included three prospective uncontrolled studies (Jagsi 2010; Leonard 2007; Lewin 2011) and one interim analysis from an RCT (Livi 2010) for the assessment of IMRT related harms (N=434). Three prospective uncontrolled studies (Jagsi 2010; Leonard 2007; Lewin 2011) that evaluated breast cosmesis (N=175). Two of the studies (Leonard 2007; Lewin 2011) reported good to excellent cosmesis in 97% to 100% of patients. The third study (Jagsi 2010) reported 34% of patients (n=7) had unacceptable overall cosmesis.

Reported toxicities included breast edema, breast pain, telangiectasia, erythema, hyperpigmentation, breast-chest wall tenderness, and fibrosis; toxicities were generally Grade 1 or 2. One case of late Grade 3 telangiectasia was reported (Lewin 2011).

*Subsequently Published Studies*

No studies were identified.

*Overall Summary*

The evidence on breast cosmesis following accelerated partial breast irradiation by IMRT is mixed. There is limited evidence on the harms of accelerated partial breast irradiation with IMRT. The overall strength of evidence for all harms reported is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

*Systematic Reviews*

Hayes (2012a) included one economic evalation for accelerated paritial breast irradaiton that provided cost information specific to IMRT (Suh 2005). An additional study (Taghian 2006) was included by Hayes (2012a) for IMRT cost information. Suh (2005), a cost-comparison analysis, modeled eight different treatment regimens for radiation treatment after surgery for a prototypical 60 year old female with stage I breast cancer. The treatment regimens included whole, accelerated partial breast radiation and brachytherapy. External beam regimens included conventional RT and IMRT. Direct medical costs and non-medical patient costs were calculated for each treatment regimen. For accelerated partial breast radation, total direct costs for conventional RT were $7,700, and for IMRT, $9,700. Costs were based on the 2003 Medicare Fee Schedule. Taghian (2006), based on the 2006 Medicare Fee Schedule, did not report costs specific to IMRT.

*Subsequently Published Studies*

No studies were identified.

### *Overall Summary*

One cost-comparison study was identified; no cost effectiveness studies were identified. The overall strength of evidence that IMRT costs more than EBRT is low.

# Female Pelvis

In this section, tumors of the female pelvis are summarized (i.e., cervical cancer, endometrial cancer, and paraaortic lymph node metastases). There is limited evidence for both cancers. No other cancers were identified for this section.

## Cervical Cancer

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

Staffurth (2010), a poor quality SR, included one case series (Chen 2007) and one cohort (Mundt 2003) which compared EBRT with IMRT for cervical and endometrial cancer. Both were small studies (n=68 and n=66, respectively). Patients in the Chen (2007) study were treated with concurrent chemotherapy. The Mundt (2003) study found no significant difference in 1-year locoregional control.

De Neve (2012), a poor quality SR, reported on a single fair quality cohort study (Kidd 2010), which reported on 452 patients treated for cervical cancer with IMRT (n=135) or EBRT (n=317). De Neve (2012) reported that Kidd (2010) found significant improvements in OS and DSS for IMRT compared to EBRT (p<0.0001), but the magnitude of benefit was not provided. A review of the Kidd (2010) study found that although patients were more likely to be alive at last follow-up if they had been treated by IMRT, follow-up time for EBRT was three times as long as IMRT. Nevertheless, graphs of cause-specific survival [DSS] and OS indicated substantially greater survival among the IMRT group at similar time-points. However, the statistical significance of this difference was not tested by the authors.

### *Subsequently Published Studies*

Two additional poor quality cohort study (Du 2012), one poor quality case series (Hasselle 2011), and one poor quality case series (Chen 2011) were identified.

Du (2012), a poor quality cohort study, reported on 122 patients with stage IIB-IIIB cervical cancer treated with IMRT (n=60) or EBRT (n=62) in China. Median follow-up was 47 months (range, 6 to 68). No difference between the IMRT and EBRT groups was noted in complete response (87.7% vs 88.3%, p=0.339), partial response (7.0% vs 6.7%, p=0.280) or OS (no difference).

Hasselle (2010), a poor quality case series, reported on treatment of cervical cancer in 111 consecutive patients between 2000 and 2007; patients had stage I-IVA cervical cancer. Ethnic mixture included 53% Black, 14% Hispanic, and 31% White. Twenty-two patients were post-operative and 89% had an intact cervix. Median follow-up was 26.6 months (range, 5.4 to 99).

Three-year OS (77.7%, 95% CI 68.3-88.4%), 3-year DFS (69.2%, 95% CI 59.4%-80.7%), 3-year pelvic failure (13.6%, 95% CI 5.8%-21.5%), and 3-year distant failure (16.6%, 95% CI 8.3%-24.9%) were reported.

Chen (2011) a poor quality case series, reported on 109 patients with cervical cancer treated with IMRT plus chemotherapy; some patients also received brachytherapy. Median follow-up time was 32 months. Chen (2011) reported 3-year OS as 78.2%, 3-year local failure-free survival as 78.1%, and 3-year DFS as 67.6%.

### *Overall Summary*

For treatment of cervical cancer with IMRT, OS findings are inconsistent. Although two smaller cohort and case series studies found no difference compared to EBRT, one larger cohort study included in an SR found significant benefit for patients treated by IMRT. The overall strength of evidence is low that IMRT was associated with increased DSS and OS for patients with cervical cancer compared to EBRT.

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

### *Systematic Reviews*

Staffurth (2010), a poor quality SR, included two cohort studies (Mundt 2003; Chen 2007) which compared EBRT with IMRT for cervical and endometrial cancer. Both were small studies (n=66 and n=68, respectively). Patients in the Chen (2007) were treated with concurrent chemotherapy. Both studies reported lower rates of late GI toxicity with IMRT than EBRT. One study showed IMRT GI toxicity rates of 11% compared with EBRT of 50% (OR 0.16, 95% CI, 0.04-0.67, Chen 2007) and the other showed IMRT late GI toxicity rates of 6% compared with EBRT of 34% (p= 0.002, Mundt 2003). Late GU toxicity was not significantly different between IMRT and EBRT (9% vs 23%, p=0.231, Mundt 2003).

De Neve (2012), a poor quality SR, reported on a single fair quality cohort study (Kidd 2010), which reported on 452 patients treated for cervical cancer with IMRT (n=135) or EBRT (n=317). Grade 3 to 4 GI and GU symptoms were significantly reduced in the IMRT group (6%) compared to the EBRT group (17%) (p=0.035).

### *Subsequently Published Studies*

One additional poor quality cohort study (Du 2012), one poor quality case series (Hasselle 2011), and one poor quality case series (Chen 2011) were identified.

Du (2012), a poor quality cohort study, reported on 122 patients with stage IIB-IIIB cervical cancer treated with IMRT (n=60) or EBRT (n=62) in China. Median follow-up was 47 months (range, 6 to 68). Significant reduction was seen in the IMRT groups compared with the EBRT group for acute Grade 3 to 4 cyctitis (7.0% vs 18.3%, p=0.033), proctitis (5.3% vs 16.7%, p=0.001), enteritis (5.3% vs 10%, p=0.001) and dermatitis (0% vs 6.7%, p=0.041). Significant reductions were seen in the IMRT groups for chronic greater than Grade 3 enterocolitis (0% vs 18.4%, p=0.017) and cystitis (0% vs 15%, p=0.044).

Hasselle (2010), a poor quality case series, reported on treatment of cervical cancer in 111 consecutive patients between 2000 and 2007; patients had stage I-IVA cervical cancer. Ethnic mixture included 53% Black, 14% Hispanic, and 31% White. Twenty-two patients were post-operative and 89% had an intact cervix. Median follow-up was 26.6 months (range, 5.4 to 99). Hasselle (2010) reported two patients (2%) with acute Grade 3 GI symptoms, four patients (4%) with chronic Grade 3 GI symptoms and five patients (5%) with chronic Grade 3 GU symptoms.

Chen (2011) a poor quality case series, reported on 109 patients with cervical cancer treated with IMRT plus chemotherapy; some patients also received brachytherapy. Chen (2011) reported Grade 3 or greater acute and chronic GI and GU toxicities of 3% to 6% and Grade 3 or greater hematologic toxicity of 24% of patients. The effect of chemotherapy on reported toxicities was not studied.

### *Overall Summary*

Findings from one cohort and two case series studies provide an overall low strength of evidence that IMRT was associated with lower frequency of toxicities than EBRT for cervical cancer.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## <u>Endometrial cancer</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

One poor quality cohort study (Lupe 2007) reported on 33 patients with endometrial cancer stage III-IV. Patients received chemotherapy before and after radiation therapy with EBRT (n= 19) or IMRT (n= 14). Pooled 2-year DFS and 2-year OS were both 55%; separate results were not given for the two cohort groups.

### *Overall Summary*

The overall strength of evidence is very low. One poor quality cohort study reported a pooled 2-year DFS and 2-year OS of 55% for the IMRT and EBRT groups. Due to the lack of comparative data, no conclusions can be reached regarding clinical effectiveness.

**KQ 2: What are the potential harms of IMRT 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 (Lupe 2007) reported on 33 patients with endometrial cancer stage III-IV. Patients received chemotherapy before and after radiation therapy with EBRT (n= 19) or IMRT (n= 14). The EBRT group had one case of acute proctitis and four cases of acute neutropenia; the IMRT group had no acute toxicities. One patient in the EBRT had small bowel obstruction compared to none in the IMRT group. Three patients in the IMRT group had chronic proctitis compared to one in the EBRT group.

*Overall Summary*
The overall strength of evidence is very low. One small poor quality cohort study reported no significant different in toxicity between IMRT and EBRT groups. The effect of chemotherapy on the incidence of toxicities is not considered.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

<u>Paraaortic lymph node metastases</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*
No SRs were identified.

*Subsequently Published Studies*
One poor quality cohort study (Du 2010) and one poor quality case series (Aoki 2002) were identified.

Du (2010), a poor quality cohort study, reported on 60 individuals with paraaortic lymph node metastases of cervical cancer who were alternatively assigned to IMRT or EBRT. Follow-up occurred every three months for a year, then every six months for two years, and annually thereafter. Intensity-modulated radiotherapy resulted in significantly better 2- and 3-year survival than EBRT (58.8% vs 25.0%, p=0.019; 36.4% vs 15.6%, p=0.016).

Aoki (2002), a poor quality case series, reported on treatment of paraaortic lymph node metastasis with IMRT (n=29). Median follow-up was 11 months (range, 2 to 66). Overall 1- and 2-year survival rates were 52% and 29%, respectively.

### *Overall Summary*

There is very low strength of evidence that treatment with IMRT for paraaortic lymph node metastases was associated with increased overall 2- and 3-year survival compared to EBRT.

**KQ 2: What are the potential harms of IMRT 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 (Du 2010) and two poor quality case series (Aoki 2002; Chen 2008) were identified.

Du (2010), a poor quality cohort study of 60 patients, reported on individuals with paraaortic lymph node metastases of cervical cancer. Follow-up occurred every three months for a year, then every six months for two years, and annually thereafter. Significant reductions in acute and chronic GI and GU symptoms (i.e., leukopenia, enteritis, enterocolitis) (p ranges 0.001 to 0.037) were reported.

Aoki (2002), a poor quality case series, reported on treatment of paraaortic lymph node metastasis with IMRT (n=29). Median follow-up was 11 months (range, 2 to 66). Acute Grade 1 GI disorders, acute Grade 2 GI disorders and liver dysfunction in 31%, 17%, and 7% of patients, respectively, were reported. Late Grade 1 and 2 disorders were reported in 21% and 17% of patients, respectively.

Chen (2008), a poor quality case series, reported on 54 patients treated with chemotherapy, IMRT and brachytherapy to the vaginal vault. Chen (2008) reported acute Grade 1 and 2 GI toxicity in 35% and acute Grade 1 and 2 GU toxicity in 33% of patients. Late Grade 1 and 2 GI toxicity were reported in 9% and late Grade 1 and 2 GU toxicity in 11% of patients. The separate contricution of chemotherapy and brachytherapy to toxicity was not analyzed.

### *Overall Summary*

There is very low strength of evidence that IMRT was associated with less frequency of GI and GU toxicities compared to EBRT.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

# Head and Neck Cancer

Head and neck cancer includes cancer of the nasopharynx, oropharynx, hypopharynx, paranasal sinuses, oral cavity, salivary glands and larynx. Many of the studies reviewed combine multiple individual cancer sites in their results. Sub-group analysis of individual head and neck cancer sites did not result in different conclusions except as noted below.

**KQ 1**: **What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

Five SRs compare IMRT to EBRT for survival or tumor control in head and neck cancer (De Neve 2012; Samson 2010; Scott-Brown 2010; Staffurth 2010; Tribius 2011). De Neve (2012) and Staffurth (2010) were general SRs of IMRT in multiple cancer types.

De Neve (2012), a poor quality SR, searched for evidence published between 2007 and 2011 that compared IMRT to "non-IMRT" treatments (treatment types not specified) for head and neck cancer. Two RCTs and 11 cohort studies were identified. However, only one RCT and four cohort studies evaluated clinical effectiveness. The sole RCT of 51 patients randomized to IMRT (n=27) or EBRT (n=24) (Chen, Li 2011) found no significant differences in OS or locoregional PFS for patients with oropharyngeal cancer. Four cohort studies of 249, 104, 51, and 203 patients included in the SR also reported no significant differences in clinical outcomes, although one additional cohort study found greater 3-year OS (92.1% vs. 75.2%, $p<0.001$, Clavel 2011) among those who had received IMRT.

Samson (2010), a good quality comparative effectiveness review of radiation therapy in head and neck cancer from the Agency for Healthcare Research and Quality (AHRQ), identified one RCT and seven comparative observational studies comparing IMRT to 3DCRT, and two RCTS and seven comparative studies comparing IMRT to 2DCRT for various head and neck cancers. Overall, Samson (2010) reported that one of seven studies reported significantly better patient survival among those receiving IMRT compared to 3DCRT or 2DCRT. None of the identified studies reported statistically significant differences in tumor control. Samson (2010) stated that no conclusions could be drawn regarding survival or tumor control due to limitations in the identified evidence. Samson (2010) reported that there was moderate strength of evidence for IMRT's advantages over 3DCRT and 2DCRT in terms of xerostomia related QoL outcomes. Samson reported that six observational studies found large statistically significant or moderate nonsignificant differences favoring IMRT over EBRT (p-values ranged from <0.05 to 0.001). Samson (2010) rated all of the observational studies were of low quality but concluded that the reduction was unlikely the result of bias, as susceptibility to xerostomia is common in the head and neck cancer population and it is unlikely that between-group imbalances account for results. Thus, Samson (2010) concluded that the evidence consistently showed that IMRT reduces the frequency of late xerostomia. Three observational studies reported quality-of-life outcomes and all favored IMRT, especially in domains related to late xerostomia. Samson reported that the observational studies provided insufficient evidence to compare QoL for other measures.

Staffurth (2010), a poor quality SR, identified 30 studies that compared IMRT to 2DCRT or 3DCRT. Of these, three were RCTs and 27 were non-randomized comparative studies. Of the eight studies (three RCTs and five non-randomized studies) that measured tumor control, none found a significant difference between treatment groups.

Scott-Brown (2010), a fair quality SR, compared IMRT to EBRT for the outcome of QoL. Ten comparative studies were heterogeneous and they produced conflicting results about QoL between IMRT and EBRT.

Tribius (2011), a fair quality SR, reviewed 14 studies comparing IMRT to 2DCRT or 3DCRT for treatment of nasopharyngeal and oropharyngeal cancer and found that IMRT improved xerostomia-related QoL by a significant amount in all studies. Some studies showed significant improvement in all QoL measures for IMRT compared to EBRT.

### *Subsequently Published Studies*

One fair quality RCT (Gupta 2012), one fair quality cohort study (Lai 2011) and one poor quality cohort study (Chen 2010) were identified.

Gupta (2012), a fair quality RCT, reported on 28 patients receiving 3DCRT and 32 patients receiving IMRT for head and neck cancer. There were no significant differences between the two groups at baseline. Median follow-up time was 40 months. Three-year actuarial estimates of loco-regional control and OS reported no significant differences between the 3DCRT and IMRT groups.

Lai (2011), a fair quality cohort study (n=1276), compared treatment with IMRT to treatment with 2D-CRT for non-metastatic nasopharyngeal cancer in patients, aged 11 to 78 years, at a single center in China. Although the study population included adolescents, the results were not stratified by age. Lai (2011) reported significantly greater five-year local relapse free survival (RFS) among those who had received IMRT than those who received 2D- EBRT (92.7% vs 86.8%, p=0.007). The study also reported better 5-year nodal relapse free survival, distant metastasis free survival, and DFS among patients receiving IMRT, but these differences were not statistically significant.

Chen (2010), a poor quality cohort study, reported on 130 patients with non-metastatic carcinoma of the head and neck treated with CRT (n=78) or IMRT (52). Median age was 61 years. Median follow-up was 30 months (range, 6 to 75 months). All patients received definitive surgery for gross tumor resection and 65% and 61% of the IMRT and CRT groups respectively received concurrent chemotherapy. No significant differences in 3-year overall survival, 3-year loco-regional control, or 3-year actuarial distant metastasis-free survival were reported.

### *Overall Summary*

The overall strength of evidence is low that there was no significant difference between IMRT and EBRT in local tumor control or OS. The findings on xerostomia-related QoL are inconsistent. However, there is a preponderance of the evidence supporting that IMRT compared to 2D- and 3DCRT improves xerostomia-related QoL. Therefore, the overall strength of evidence that IMRT compared to 2D- and 3DCRT improves xerostomia-related QoL is moderate.

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

### *Systematic Reviews*

Three SRs address harms from IMRT compared to EBRT for radiation treatment of head and neck cancer (Bensadoun 2010; Jensen 2010; Peterson 2010). Radiation therapy was often combined with chemotherapy. The incidence of toxicity was influenced by concurrent chemotherapy, which makes direct comparison of IMRT and EBRT more difficult.

Citing two RCTs, De Neve (2012) reported significantly reduced rates of severe 12-month Grade 2 or greater xerostomia among patients treated with IMRT for oropharyngeal cancer (29% IMRT vs 83% non-IMRT, $p<0.001$, Nutting 2011) or nasopharyngeal cancer (46% IMRT vs 85% non-IMRT, $p=0.002$, Kam 2007).

The good quality AHRQ review by Samson (2010) identified 35% decreased frequency of Grade 2 or greater xerostomia among patients who received IMRT compared to those who received 3DCRT (95% CI, 12.6% to 55.5%). Additionally, Samson (2010) identified six observational studies that reported significant differences in frequency of xerostomia, ranging from 7% to 79% across studies. However, Samson (2010) concluded that there was insufficient strength of evidence to show improvement in other toxicities from IMRT compared to EBRT.

Scott-Brown (2010) identified two studies (Vergeer 2009; Jabbari 2005) and an initial report of the PARSPORT study presented at the 2009 American Society of Clinical Oncology Annual meeting that compared harms associated with IMRT to 3DCRT or 2DCRT. Both studies and the report were described by the authors as indicating a benefit from IMRT in terms of xerostomia. Vergeer (2009) reported on 91 patients treated with IMRT after October 2004 and compared this group with 150 patients treated before 2004 with 3DCRT. All patients received concurrent chemotherapy. Patient rated xerostomia at six months was reduced from 67% with 3DCRT to 46% with IMRT (OR=0.34, $p< 0.001$). Similar significant reductions in Radiation Therapy Oncology Group measures for xerostomia were also reported. Jabbari (2005) reported on 30 patients treated with IMRT who were matched with 10 patients treated with EBRT. All patients filled out standardized head and neck cancer and xerostomia related QoL questionnaires. Both IMRT and EBRT groups showed initial decrease in QoL with treatment; the IMRT group showed improvement of QoL beginning after six months. The findings by Jabbari (2005) were not statistically significant.

Staffurth (2010), a poor quality SR, identified three RCTs (N=1205) and five non-randomized comparative studies (N=347) that compared IMRT to EBRT for various head and neck cancers.

Staffurth (2010) reported an overall significant reduction in Grade 2 to 4 xerostomia with IMRT, but did not fully detail the magnitude of the reduction across studies.

Bensadoun (2010), a fair quality SR, reported on the incidence of trismus in patients receiving radiation therapy; there was no significant difference in incidence between IMRT and EBRT (5% IMRT vs 25.4% EBRT, not statistically significant). Peterson (2010), a fair quality SR, reported on the incidence of osteonecrosis in patients receiving radiation therapy; there was no significant difference in incidence of osteonecrosis between IMRT and EBRT (IMRT 5.2% [95% CI 4.8-10%] vs EBRT 7.4% [95% CI 0.0-12.0]).

Jensen (2010), a poor quality SR on salivary gland hypofunction and xerostomia induced by cancer therapies, included 49 studies (two RCTs, 38 cohort studies, two case-control, and seven cross-sectional studies) evaluating salivary gland hypofunction and xerostomia after IMRT. One of the included studies addressed xerostomia and IMRT in the pediatric population. Jensen (2010) summarized that parotid-sparing IMRT has the potential to decrease the prevalence and severity of salivary gland hypofunction and xerostomia.

### *Subsequently Published Studies*

Forty-nine additional articles on IMRT in head and neck cancer addressed harms (see Appendix F for details on individual studies). Twelve of the 49 were rated as fair in quality; the remaining 37 were rated as poor in quality. Only two subsequently published studies compared IMRT to EBRT (Gupta 2012; Petsuksiri 2011) and are discussed below. The remaining 47 reported only the frequency of harms from IMRT without comparison to EBRT.

A fair quality randomized control trial (Gupta (2012) reported on 28 patients receiving 3DCRT and 32 patients receiving IMRT for squamous cell cancer of the head and neck. There were no significant differences between the two groups at baseline. Median follow-up time was 40 months. Grade 2 or worse xerostomia was significantly higher in patients receiving 3DCRT (89%) than in patients receiving IBRT (59%) ($p = 0.009$).

Petsuksiri (2011), a poor quality cohort study, measured sensorineural hearing loss in 68 patients of median age 48 years undergoing IMRT or EBRT; there was no significant difference in hearing loss between IMRT and EBRT. Hearing loss was related to the mean dose to the internal auditory canal of > 50 Gy ($p=0.04$). Reported toxicities from radiation therapy to the head and neck region include systematic symptoms of nausea, vomiting and fatigue; local symptoms including dermatitis and mucositis; xerostomia; dysphagia; and laryngeal symptoms. There is heterogeneity of cancer location and stage, radiation dose to the tumor and critical adjacent structures and the addition of chemotherapy.

### *Overall Summary*

Six systematic reviews and an additional 49 articles address harms. There is moderate overall strength of evidence that IMRT reduces Grade 2 or greater xerostomia compared to EBRT. There is a very low strength of evidence that there is no significant difference in incidence of osteonecrosis from IMRT compared to EBRT. There is very low strength of evidence that there is no significant difference in hearing loss from IMRT compared to EBRT. The overall strength of evidence for all other harms (i.e., nausea, vomiting, fatigue, dermatitis, mucositis, dysphagia, laryngeal symptoms) is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

Bonastre (2007) is a fair quality prospective cost study conducted in France from July 2003 to April 2005. Consecutive patients (n=99) aged 18 to 83 years with head and neck cancer were enrolled from nine medical centers. Three centers started IMRT treatment with no previous experience at the initiation of the study, and six had previous experience with IMRT (experience not defined). All costs were based on 2005 Euros and were from the perspective of the provider. The cost of IMRT and variation in cost between patients and centers was estimated. The full cost of treatment was estimated to be €10,916 (SD=€6,454): €2,773 (SD=€2,249) for IMRT planning and €247 (SD=€170) per each treatment session. The mean direct cost of IMRT per treatment was €5,962 (SD=€3,735). That cost consisted of €3,174 (SD=€2,877) for manpower (53% of direct costs), €1,693 (SD=529) for equipment, €927 (SD=€692) for IMRT-specific software, and €168 (SD=111) for supplies.

Bonastre (2007) used the unconditional means model to calculate variability of cost between centers and within centers. For a new center initiating IMRT, the direct cost was €14,192. For the same patient starting treatment at an experienced center, the direct cost was €6,332. Patient characteristics explained 46% of the variation of costs within centers and experience explained 42% of the variation of costs between centers (both were statistically significant).

### *Overall Summary*

One cost study estimated the total cost of IMRT treatment to be €10,916 (SD=€6,454). The overall strength of evidence is low that IMRT costs more compared to EBRT. The overall strength of evidence is low that experienced centers had lower direct costs compared to centers initiating IMRT.

## Lung Cancer

In this section, tumors of the lung are summarized. There is limited evidence for non-small cell lung cancer (NSCLC), pleural mesothelioma, and small cell lung cancer (SCLC). No other cancers were identified for this section.

### Non-small cell lung cancer (NSCLC)

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### Systematic Reviews

De Neve (2012), a poor quality SR, included one cohort study (Liao 2010). Liao (2010) reported on 409 patients treated with IMRT (n=91) compared to 3DCRT (n= 318). Overall survival was significantly better in the IMRT group than in the 3DCRT group (hazard ratio (HR) 0.64, 95% CI, 0.41-0.98, p=0.039). However, differences in locoregional progression free survival (PFS) (HR 0.77, 95% CI, 0.43-1.36, p=0.37) and distant metastasis-free survival (HR 1.05, 95% CI, 0.72-1.53, p=0.81) were not statistically significant.

### Subsequently Published Studies

Five subsequently published studies on NSCLC (Bral 2010; Jiang 2011; Song 2010; Sura 2008; Yu 2008) were identified. Of the five case series studies, one was good quality (Jiang 2011), one was fair quality (Yu 2008), and three were poor quality (Bral 2010; Song 2010; Sura 2008).

Jiang (2011), a good quality case series, reported on 165 patients; 136 of the patients with newly diagnosed NSCLC Stage I through Stage IV; 136 of the patients received concurrent chemotherapy. Median follow-up was 16.5 months (range, 0.7 to 47.6). Median OS was 1.8 years. Two- and 3-year survival rates were 46%, 30%, DFS were 38%, 27%, and distant metastasis free survival were 51%, 38%.

Yu (2008), a fair quality case series, reported on 79 patients with stage I to II NSCLC treated with IMRT who either were inoperable or refused surgery. Median age was 76 years. Median follow-up was 38 months for all patients (range, 6 to 83). Median OS (38 months [range, 13.8 to 62.2]), and local PFS (38 months [range, 13.6 to 52.4]) were reported.

Bral (2010), a poor quality case series, reported on 40 patients with inoperable stage III NSCLC treated with moderately fractionated tomotherapy. Patients received follow-up every three months during the first and second years of the study, and every six months thereafter. Median survival was 17 months, with 1- and 2-year OS reported as 65% and 27%, respectively.

Song (2010), a poor quality case series, reported on 37 patients with NSCLC stage I to III; four of 37 patients were recurrent NSCLC at the time of treatment and 17 of 37 had supraclavicular nodal metastases. Median follow-up was 18 months (range, 6 to 27 months). Two-year OS rate in patients who did not receive concurrent chemotherapy was 56%.

Sura (2008), a poor quality case series, reported on 55 consecutive patients with inoperable NSCLC stages I to IIIB, with only 13 of the patients being treated with IMRT alone. Median or mean follow-up time was not reported. For stage I/II tumors, OS was 55%; for stage III (IIIA/IIIB) disease, OS was 58%. Two-year DFS was 41%.

### Overall Summary

One comparative study and five case series were identified. The overall strength of the evidence is low that patients treated with IMRT compared to 3DCRT for non-small cell lung cancer had better OS. The overall strength of evidence is low that there were no significant differences in distant metastasis-free survival or locoregional PFS for IMRT compared to 3DCRT. No conclusions can be drawn from the case series since they did not compare IMRT to EBRT. The overall strength of evidence for all other outcomes is very low.

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

### *Systematic Reviews*

Staffurth (2010) and Veldeman (2008) included one study (Yom 2007) on NSCLC. Yom (2007), a cohort study, compared IMRT and EBRT in 290 patients. Yom (2007) found significantly lower levels of greater than or equal to Grade 3 pneumonitis with IMRT than EBRT (8% vs 32%, p=0.002) at 12 months.

De Neve (2012) included one cohort study (Liao 2010) of 91 patients treated with IMRT compared to 318 patients treated with EBRT. Liao (2010) reported that IMRT resulted in significant reduction in Grade 3-4 radiation pneumonitis (IMRT = 8%; EBRT = 32% p value not given but declared statistically significant).

### *Subsequently Published Studies*

Six subsequently published studies on NSCLC (Adkison 2008; Bral 2010; Jiang 2011; Song 2010; Sura 2008; Yu 2008) were identified. Of the six case series studies, one was good quality (Jiang 2011), one was fair quality (Yu 2008), and four were poor quality (Adkison 2008; Bral 2010; Song 2010; Sura 2008).

Jiang (2011), a good quality case series, reported on 165 patients; 136 of the patients received concurrent chemotherapy. Median follow-up was 16.5 months (range, 0.7 to 47.6). Grade 3 or greater treatment-related pneumonitis was reported in 11% of patients at six months, and 16% at 12 months. One patient had Grade 3 pulmonary fibrosis. Acute Grade 3 or greater esophagitis was reported in 17.6% of patients; three patients and four patients had late Grade 2 and Grade 3 esophageal strictures, respectively.

Yu (2008), a fair quality case series, reported on 79 patients treated with IMRT. Median follow-up was 38 months for all patients (range, 6 to 83). Three patients required steroids and oxygen for Grade 3 radiation pneumonitis. No late esophageal, skin, or pulmonary toxicities or treatment-related deaths were reported.

Adkison (2008), a poor quality case series, reported on 46 patients with NSCLC stage I to IV who were not judged to be surgical candidates. Median age was 67 years. Median follow-up was 8.1 months. No Grade 3 or higher toxicities were reported; Grade 1 and 2 pneumonitis (70%, 13%) and esophagitis (24%, 15%) were reported.

Bral (2010), a poor quality case series, reported on 40 patients with NSCLC treated with moderately fractionated tomotherapy. Patients received follow-up every three months during the first and second years of the study, and every six months thereafter. One patient experienced Grade 3 dysphagia with weight loss in excess of 15%. Grade 3 skin toxicity occurred in one patient. Grade 2 esophageal toxicity (33%), and Grade 2 or greater lung toxicity (43%) were reported. Late toxicities were reported in 31 patients; nine patients died within the first 90 days of radiation therapy, two of which were related to lung toxicity. Grade 2 and 3 late lung toxicities were reported as 23% and 16%, respectively.

Song (2010), a poor quality case series, reported on 37 patients with NSCLC. Median follow-up was 18 months (range, 6 to 27). Grades 0 (8%), 1 (32%), 2 (51%), 3 (8%), and 5 (11%) treatment-related pneumonitis were reported.

Sura (2008), a poor quality case series, reported on 55 patients, with only 13 of the patients being treated with IMRT alone. Median or mean follow-up time was not reported. Acute Grade 3 pulmonary toxicity (11%) and esophagitis (4%) were reported; there were no acute treatment-related deaths. For chronic toxicities, one Grade 3 pulmonary toxicity and one death from radiation pneumonitis were reported.

### *Overall Summary*

Two comparative studies and six case series were identified. The overall strength of the evidence is low that NSCLC patients treated with IMRT compared to EBRT had significantly lower levels of greater than or equal to Grade 3 pneumonitis.

The remaining outcomes were only reported in noncomparative studies, and therefore no conclusions can be drawn for IMRT compared to other treatments. In general, Grade 1 or 2 toxicities were reported with varying degrees in numbers and the good to fair quality case series reported patients with esophagitis, Grade 2 and 3 late esophageal stricture, Grade 3 or greater treatment-related pneumonitis (including one death), pulmonary fibrosis, and Grade 3 pulmonary toxicities. The overall strength of evidence is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Pleural mesothelioma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

Veldeman (2008), a fair quality SR, included one small case series study (Ahamad 2003) that reported 1- and 2-year DFS rates as 88% and 55%, respectively.

### *Subsequently Published Studies*

One fair quality (Tonoli 2011) and one poor quality (Buduhan 2009) case series were identified. Tonoli (2011) reported on 56 patients with stage I to IV mesothelioma treated with extrapleural pneumonectomy followed by IMRT. Median age was 58 years. Mean follow-up was 26.2 months (range, 5 to 74). One-, 2- 3-, 4-, and 5-year DSS (82%, 71%, 62%, 52%, 52%), OS (79%, 64%, 60%, 50%, 50%), and DFS (78%, 70%, 57%, 57%, 29%) rates were reported.

Buduhan (2009), a poor quality case series, reported on trimodality treatment for malignant pleural mesothelioma. Patients received chemotherapy, then extrapleural pneumonectomy, then EBRT (n= 24) or IMRT (n= 14). The EBRT group was treated historically prior to the institution of IMRT. The mean OS was reported as 24 months for both groups pooled; results were not given for the separate cohorts. Incidence of local recurrence was 14% in the IMRT group and 42% in the EBRT group (p = 0.02).

### *Overall Summary*

The overall strength of the evidence is very low and is based on two small case series and one small cohort study. The small cohort study reported a statistically significant reduction in local recurrence but did not separate the results for OS. The two case series reported that patients treated with IMRT for pleural mesothelioma had OS rates (1- to 5-year estimates) between 79% and 50% and DFS rates (1- to 5-year estimates) between 88% and 29%.

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

### *Systematic Reviews*

Veldeman (2008), a fair quality SR, included two small non-comparative studies (Allen 2006; Ahamad 2003). In one study (Allen 2006), fatal radiation pneumonitis was reported in 6 of 13 patients. However, in the other study (Ahamad 2003) (n=28), no Grade 3 or higher toxic effects were reported, with the exception of acute Grade 3 radiation-induced esophagitis in 7% of cases.

### *Subsequently Published Studies*

One additional fair quality case series was identified (Tonoli 2011). Tonoli (2011) reported on 56 patients with mesothelioma. Mean follow-up was 26.2 months (range, 5 to 74). Acute toxicities included nausea, vomiting, and fatigue; no acute respiratory declines were reported. For chronic toxicities, two late deaths (liver, pericarditis) were reported. There were no reports of lung or respiratory function decline.

### *Overall Summary*

A total of three case-series with small sample sizes were identified. One study reported fatal radiation pneumonitis in 6 of 13 patients and another study reported Grade 3 radiation-induced esophagitis in 7% of cases. A fair quality case series reported common toxicities (varying in Grade and toxicity) among patients treated with IMRT for pleural mesothelioma and two late deaths possibly related to radiation therapy. There are no comparative studies, and therefore no conclusions can be drawn from IMRT compared to other or no treatments. The overall strength of the evidence is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Small-cell lung cancer (SCLC)

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Shirvani (2012), a fair quality case series, reported on 60 consecutive patients with SCLC. Median age was 63 years and patients were stage 0 to III. Eighteen underwent induction chemotherapy, and 58 underwent concurrent chemotherapy. Median follow-up was 21 months. Median actuarial OS time was 36 months. Shirvani (2012) reported 2-year OS of 58% and RFS of 43%.

### *Overall Summary*

Based on a single fair quality case series, patients treated with IMRT for SCLC had 2-year OS of approximately 58% and RFS of 43%. There are no comparative studies, and therefore no conclusions can be drawn for IMRT compared to other or no treatments. The overall strength of the evidence is very low.

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

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Shirvani (2012), a fair quality case series, reported on IMRT for SCLC. Of the 60 patients, 18 underwent induction chemotherapy, and 58 underwent concurrent chemotherapy. Median follow-up was 21 months. Acute pneumonitis and esophagitis were reported in 23% and 7%; no chronic Grade 3 pneumonitis or esophagitis were reported.

### *Overall Summary*

Based on a single fair quality case series (n=60), SCLC patients treated with IMRT experienced acute pneumonitis and esophagitis in 23% and 7% of patients, respectively. No chronic Grade 3 pneumonitis or esophagitis were reported. There are no comparative studies, and therefore no conclusions can be drawn for IMRT compared to other or no treatments. The overall strength of the evidence is very low.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

# Prostate Cancer

Multiple RCTs have demonstrated improved tumor related outcomes when radiation dose has been escalated from 65Gy to 74-81Gy. Intensity modulated radiation therapy allows the potential of increasing tumor dose while keeping the dose to surrounding normal tissues (in this case the rectum, bladder and seminal vesicles) within acceptable limits. A number of articles compare IMRT at 74-81Gy with EBRT at 65-70Gy, which makes direct comparison difficult both for clinical outcomes and for harms. Other confounding variables are the addition of hormonal therapy before, during and after radiation therapy and different treatment regimens and treatment volumes (e.g., whole pelvic radiation vs prostate only radiation).

**KQ 1**: **What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews and Technology Assessments*

A comprehensive, good quality, health technology assessment (HTA) from the National Institute for Health Research (NIHR) HTA Program in the United Kingdom (Hummel 2010) and two poor quality SRs (Staffurth 2010; De Neve 2012) were identified. Hummel (2010) identified no evidence on OS. As summarized in Staffurth (2010), two studies (N=698) (Kupelian 2005; Vora 2007) comparing IMRT and EBRT. Kupelian was a retrospective study comparing IMRT (N=166) with 3DCRT (N= 116); Vora was a retrospective study comparing IMRT (N=145) with a historical control of 3DCRT (N=271). These studies demonstrated no significant difference at 30 months (p=0.24) but a significant difference at 60 months (p<0.001) for bDFS[12]. De Neve (2012) and Staffurth (2010) reported that there were no differences between IMRT and EBRT for tumor control. Wilt (2008), a good quality AHRQ comparative effectiveness review, did not identify any evidence regarding the effectiveness of IMRT in comparison with EBRT.

### *Subsequently Published Studies*

Six cohort studies (Goenka 2011; Jacobs 2012; Lev 2009; Pinkawa 2011; Quon 2012; Sheets 2012) were identified. Of the cohort studies two were good quality (Jacobs 2012; Sheets 2012), two were fair quality (Pinkawa 2011; Quon 2012), and two were poor quality (Goenka 2011; Lev 2009). Due to the volume of studies, only the good and fair quality cohort studies are discussed below. Specific details of all individual studies are available in Appendix F.

[12] Defined by the American Society of Therapeutic Radiology and oncology (ASTRO) consensus panel as “the midpoint between the postradiation nadir PSA level and the first three consecutive rises [in PSA]” and more recently defined by ASTRO Pheonix as “a rise in PSA level of ≥2 ng/mL above the nadir (with or without hormone therapy)” (Vora 2007, p. 1054).

Jacobs (2012), a good quality cohort study, evaluated SEER data for 36,490 Medicare patients treated with either IMRT or EBRT (dose not specified) for prostate cancer between 2001 and 2007. After initial treatment, further treatment for cancer recurrence after three years was 6% for IMRT and 9% for EBRT ($p<0.001$).

Sheets (2012), a good quality cohort study, evaluated SEER data for Medicare 12,976 patients who received IMRT (6438 patients), EBRT (6478 patients) or proton therapy (3893 patients) within one year of diagnosis between 2002 and 2006. Propensity modeling was done for the comparison of IMRT with EBRT. Men treated with IMRT, compared with EBRT, were less likely to receive additional cancer therapy (2.5 vs 3.1 per 100 person-years, relative risk (RR) 0.81, 95% CI, 0.73-0.89, $p<0.001$).

Pinkawa (2011), a fair quality cohort study, evaluated treatment-related morbidity in 78 matched pairs with localized T1-3N0M0 prostate cancer comparing 3DCRT to IMRT. Follow-up consisted of a completed validated questionnaire prior to, on the last day, and after the median time of two and 16 months following completion of radiation therapy (range, 12 to 20). No statistically significant QoL changes were reported between 3DCRT and IMRT groups.

Quon (2012), a fair quality cohort study, of 97 men with advanced prostate cancer (stage T3, PSA greater than 20, Gleason score 8 to 10) treated with 3DCRT combined with IMRT (n=67) versus IMRT alone (n=30). Patients also received hormone therapy. No significant differences were noted between the groups at baseline. Median follow-up was 39 months (range, 24 to 54). The 4-year bDFS rate was reported at 90.5% (data reported for the entire group, but not segregated for the comparison groups).

### *Overall Summary*

Three systematic reviews and seven cohort studies were identified. There is low strength evidence that there were no significant differences in overall survival for IMRT compared to EBRT at 30 months. There was low overall strength of evidence for a significant difference in bDFS at 60 months favoring the IMRT group compared to EBRT. There is low strength of evidence that IMRT compared to EBRT had lower rates of cancer recurrence at three years.

Two fair quality cohort studies reported inconsistent findings for QoL in different populations. Therefore no conclusions can be drawn and the overall strength of evidence is low.

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

### *Systematic Reviews and Technology Assessments*

Harms for radiation therapy for prostate cancer are divided into acute GI toxicity, acute GU toxicity, chronic GI toxicity and chronic GU toxicity. Grading scales have been developed for each of these categories. Hummel (2010), a good quality TA, reviewed eight comparative studies evaluating harms, with study sizes ranging from 27 to 830 patients. The radiation dosages often differed between IMRT and EBRT which makes direct comparison difficult. Hummel (2010) also segregated results by the initial extent of prostate cancer. The results are mixed for acute and chronic GI and GU symptoms. For localized prostate cancer, acute GI toxicity ranged from 1% to 30%; IMRT had a lower incidence of acute GI toxicity than 3DCRT. The differences were statistically significant in Kupelian (2002) and Shu (2001), but not significant in Vora (2007) or Zelefsky (2008). Late GI toxicity ranged from 5% to 57% with lower rates for IMRT than EBRT. The results from three of four studies were not significant; the fourth study (Zelefsky 2008) showed significantly lower GI toxicity for IMRT compared to EBRT. Similar results were presented for acute and chronic GU toxicity. Acute GU symptoms ranged from incidence of 15% to 37% with lower incidence for EBRT but no significant differences. For chronic GU symptoms, prevalence ranged from 1% to 66% with incidence levels lower for IMRT; two of four studies showed significant differences in chronic GU toxicity.

Budäus (2012), a good quality SR, compared IMRT and EBRT at different dosages from 68Gy to 78Gy. The two included studies reported significant differences in GI symptoms when EBRT at 68Gy was compared with EBRT at 78Gy; the same study showed no significant difference in GU symptoms. Budäus (2012) cited studies also reported in Hummel (2010).

De Neve (2012), a poor quality SR, included eight cohort studies (Al-Mamgani 2009; Alongi 2009; Dozel 2010; Matzinger 2009; Namiki 2009; Odrazka 2010; Sharma 2011; Zelefsky 2008) reporting on the incidence of late radiation-induced toxicity of IMRT (N=3,662). The quality of the studies was not reported. The results from Zelefsky (2008) were reported in Hummel (2010). De Neve (2012) reported significant reductions in the risk of late Grade 2 or greater rectal toxicities at 10 years compared with non-IMRT, and no change in the rates of late Grade 2 or greater GU toxicity. Consistently fewer acute and late GI toxicities after IMRT were reported.

### *Subsequently Published Studies*

Seven cohort (Bekelman 2009; Goenka 2011; Jacobs 2012; Kim 2011; Pinkawa 2011; Quon 2012; Sheets 2012) and 17 case series (Adkison 2012; Alicikus 2011; Di Muzio 2009; Ghadjar 2010; Ghadjar 2011; Lock 2011; Marchand 2010; Nath 2010; Nath 2011; Ost 2009; Ost 2011; Pervez 2010; Spratt 2011; Wilder 2010; Wong 2009; Zelefsky 2011; Zilli 2011) were identified. Of the cohort studies two were good quality (Jacobs 2012; Sheets 2012), four were fair quality (Bekelman 2009; Kim 2011; Pinkawa 2011; Quon 2012), and one was poor quality (Goenka 2011). Of the case series, one was good quality (Alicikus 2011), five were fair quality (Di Muzio 2009; Ghadjar 2010; Ost 2009; Spratt 2012; Zilli 2011), and eleven were poor quality (Adkison 2012; Ghadjar 2011; Lock 2011; Marchand 2010; Nath 2010; Nath 2011; Ost 2011; Pervez 2010; Wilder 2010; Wong 2009; Zelefsky 2011). Due to the volume of studies, only the good and fair quality cohort studies are discussed below. Specific details of each individual study are available in Appendix F.

Jacobs (2012), a good quality cohort study, reported treatment for bowel complications in 22% of patients treated with IMRT compared to 18% for EBRT; treatment for urinary complications was reported at 8% for IMRT compared to 6% for EBRT.

Sheets (2012), a good quality cohort study, evaluated SEER data for 12,976 patients who received IMRT, EBRT or proton therapy within one year of diagnosis between 2002 and 2006. Propensity modeling was done for the comparison of IMRT with EBRT. Men treated with IMRT were less likely to receive a diagnosis of GI morbidity (13.4 vs 14.7 per 100 persons, RR 0.91, 95% CI, 0.86-0.96, p<0.001), and hip fracture (0.8 vs 1.0, RR 0.78, 95% CI, 0.65-0.93, p=0.006). Men treated with IMRT were more likely to receive a diagnosis of erectile dysfunction than the EBRT group (5.9 vs 5.3, RR 1.12, 95% CI, 1.03-1.20, p=0.006).

Bekelman (2009), a fair quality cohort study, evaluated 12,598 patients diagnosed between 2002 and 2004 with non-metastatic prostate cancer. The authors used registry and administrative claims data from the SEER – Medicare database. The study compared the use of IMRT (n-5,845) with CRT (6,753). Patients in the IMRT group were more likely to have earlier stage and lower grade tumors. The study reported that IMRT was associated with significant reduction in composite bowel complications (hazard ratio [HR] 0.86; 95% CI 0.79-0.93) and proctitis/hemorrhage (HR 0.78; 95% CI 0.64-0.95). Using proportional hazard models, Bekelman (2009) reported that IMRT was associated with a significant increase in impotence diagnosis (HR 1.27, 95% CI, 1.14-1.42).

Kim (2011), a fair quality cohort study, evaluated 28,088 patients diagnosed with T1-T2 clinically localized prostate cancer between 1992 and 2005. The study was based on SEER – Medicare registry data. Patients within the radiation treatment arm either received 3DCRT (n=11,770) or IMRT (n=4645). Compared with 3DCRT, IMRT had lower rates of GI toxicities (HR 0.67; 95% CI, 0.55-0.82)).

Pinkawa (2011), a fair quality cohort study, evaluated treatment-related morbidity in 78 matched pairs with localized T1-3N0M0 prostate cancer. Follow-up consisted of a completed validated questionnaire prior to, on the last day, and two and 16 months after radiation therapy (range, 12 to 20). Two months after treatment, painful bowel movements, and the presence of erections not firm enough for sexual intercourse, were reported more in the 3DCRT versus the IMRT group (10% vs 1%, p = 0.03; 86% vs 71%, p = 0.03). The IMRT group had higher rates of minor rectal bleeding (20% vs 9%, p = 0.06), higher rates of great or moderate rectal bleeding (7% vs 1%, p = 0.09), and higher rates of sexual function scores (IMRT=6 point decrease vs 3DCRT 13 point decrease; p=0.02).

Quon (2012), a fair quality cohort study, of 97 men with advanced prostate cancer (stage T3, PSA greater than 20, Gleason score 8 to 10) treated with 3DCRT combined with IMRT (n=67) versus IMRT alone (n=30). Patients also received hormone therapy. No significant differences were noted between the groups at baseline. Median follow-up was 39 months (range, 24 to 54). No acute Grade 3 to 4 GI toxicities, or acute Grade 4 GU toxicities, were reported. Acute Grade 3 GU toxicities were reported in 4% of patients. No late Grade 3 or 4 rectal toxicities were reported. Late Grade 3 to 4 GU urinary toxicity occurred in 3% and 1% of patients, respectively.

The 17 case series reported a range of harms including acute Grade 0 to 3 GU toxicity, acute Grade 0 to 4 GI toxicity, late Grade 0 to 4 GU toxicity, late Grade 0 to 4 GI toxicity, erectile dysfunction, and impotence. Specific details of each individual study are available in Appendix F.

*Overall Summary*

Comparison of harms is difficult because of the different dosages, treatment regimens, cancer stages, and outcomes studied. However, based on three large cohorts, there is an overall moderate strength of evidence that IMRT improves GI toxicities compared to EBRT. There is an overall low strength of evidence that IMRT improves GU toxicities compared to EBRT.

There is low strength of evidence that the IMRT group was less likely to experience hip fractures compared to CRT. Based on four cohort studies, the evidence on erectile dysfunction is inconsistent. A large, good quality cohort study found that the IMRT group was more likely to receive a diagnosis of erectile dysfunction (RR 1.12; 95% CI 1.03-1.20). However, the effect size was small. There is an overall low strength of evidence for this outcome.

**KQ 3**: **What is the evidence that IMRT has 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 IMRT compared to EBRT?**

*Systematic Reviews and Technology Assessments*

The TA by Hummel (2010) reported on cost effectiveness. Hummel (2010) included three studies by Konski (2004, 2005, 2006) and one study by Pearson (2007). Konski addressed patients with intermediate risk prostate cancers and used 2004 British pounds as the cost basis (converted to US dollars). The 2004 study was an abstract; the 2005 and 2006 studies used the same model but used different time horizons for the calculations of incremental cost effectiveness ratios. Calculated costs for 3DCRT were $21,377 to $21,865. Costs for IMRT were $33,837 to $47,931. Konski (2004, 2005, 2006) calculated survival of 5.52 quality adjusted life years (QALYs)[13] for EBRT and survival of 6.28 QALYs for IMRT. Incremental cost effectiveness ratios[14] (ICER)/QALY were $16,182 from the 2005 data and $40,101 from the 2006 data. The study by Pearson (2007) uses 2005 US dollars and similar costs for inputs to Konski, but different assumptions regarding the effectiveness of IMRT compared to EBRT (see below). Pearson (2007) calculated costs for EBRT of $10,900 and IMRT of $42,450. Pearson (2007) calculated an ICER/QALY of $706,000.

The large difference in ICER in the cost effectiveness calculation of Konski (2004, 2005, 2006) and Pearson (2007) derive from the assumption of Pearson (2007) that there was no difference in survival between IMRT and EBRT. The entire difference in QALYs in Pearson's calculations arose solely from the difference in rectal toxicity between IMRT and EBRT. However, Konski assumed a 14% difference in survival between IMRT and EBRT as well as a relatively large

[13] For cost-effectiveness analysis the value of health effects are measured in terms of QALYs. QALYs are calculated by weighting life-years with utility values, to reflect patients' HR QoL.

[14] ICER is the ratio of the change in costs to incremental benefits of a therapeutic intervention or treatment. The equation for ICER is ICER = (C1 – C2) / (E1 – E2), where C1 and E1 are the cost and effect in the intervention or treatment group and where C2 and E2 are the cost and effect in the control care group. Costs are usually described in monetary units while benefits/effect in health status is measured in terms of QALYs gained or lost.

difference in utility for GI and GU toxicity between IMRT and EBRT. Hummel states, "Thus, the difference in utility post IMRT and post 3DCRT used by Konski et al. is tantamount to assuming that no IMRT patients and all 3DCRT patients suffer from late toxic GI effects until disease progression" (2010, p 33). Hummel (2010) reasons that Konski's assumptions do not agree with the best evidence. In addition, the cost effectiveness of IMRT is inconsistent and highly dependent on the underlying assumptions about costs, effectiveness and toxicity of IMRT.

A fair quality cost minimization study (Perlroth 2010) in the US used claims data from a large commercial database to compute the 2-year national cost savings of migrating patients with localized prostate cancer from the initial treatment strategies reflected in current practice patterns to strategies supported by comparative effectiveness research. The treatment strategies included active surveillance, radical prostatectomy, brachytherapy, EBRT, IMRT, and multiple treatments. Costs were based on actual claims for 2,332 individuals aged 75 years or younger and included all direct healthcare costs. Citing a SR (Wilt 2008) and three RCTs (Bill-Axelson 2005; Iversen 1995; Paulson 1982) and noting the lack of randomized trials comparing one radiation therapy with another, the authors assumed that all treatments were equally effective. Regression analysis was used to predict costs after adjustment for age, a number of prespecified comorbidities, total health expenditures in the one year prior to diagnosis, and the initial treatment strategy. Treatment with radical prostatectomy, brachytherapy, or IMRT was significantly more expensive than treatment with active surveillance. In a 65-year-old without comorbidities, overall adjusted costs for 2 years ranged from $21,400 with active surveillance to $68,300 with IMRT (2004 dollars). The actual frequency of initial treatment strategies in the US was determined by an analysis of 2001 to 2005 data in the SEER database. Claims-based costs and SEER-based practice patterns were combined to estimate potential savings to the national healthcare system. In 2009 dollars, $1.38 billion would be saved over a 2-year period by shifting patients from IMRT to active surveillance as an initial treatment, and $1.27 billion from shifting patients from IMRT to radical prostatectomy and active surveillance, after adjusting for age and preceding healthcare expenditures. This analysis does not reflect any differential QoL impact of side effects and may not be generalizable to individuals older than 75 years. The authors point out that the analysis does not include the cost of active treatment after 2 years for individuals initially managed with active surveillance. On the other hand, the overall impact of switching from IMRT to active surveillance or radical prostatectomy might be greater at this point in time than the study suggests since evidence shows increasing use of IMRT.

### *Subsequently Published Studies*

No subsequently published studies on costs or cost effectiveness were identified.

### *Overall Summary*

One TA encompassing two cost-effectiveness analyses and one cost-minimization analysis addressed the use of IMRT for prostate cancer. The overall strength of evidence for cost-effectiveness of IMRT is very low.

Konski (2004, 2005, 2006) as reported in Hummel (2010) calculated an incremental cost-effectiveness ratio of $16,182/QALY to $40,101/QALY for IMRT as compared to 3DCRT. This meets a commonly-accepted threshold of $50,000/QALY. However, these calculations assumed a 14% difference in survival between groups and essentially a 100% difference in GI and GU utility between groups, which is not supported by evidence. Pearson (2007), as reported in Hummel (2010), assumed no difference in survival and less rectal toxicity with IMRT; this study calculated an ICER of $706,000/QALY, which is well in excess of the usual threshold for cost-effectiveness. Perlroth (2010) was a cost-minimization study that assumed equal effectiveness across treatments and did not consider quality of life measures; this study calculated median overall adjusted 2-year costs of $68,300 for IMRT compared to $21,400 for active surveillance.

## Sarcoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic reviews*
No SRs were identified.

### *Subsequently Published Studies*
One poor quality case series was identified (Terezakis 2007). Terezakis (2007) reported on 27 patients who received IMRT for partially resected or unresected paraspinal tumors between 2001 and 2005. Five patients had previous radiotherapy; four had previous chemotherapy and 22 had previous surgery. The median follow-up was 17.4 months. Seven patients (26%) developed local recurrence.

### *Overall Summary*
One case series was identified. No evidence was identified that compared IMRT to EBRT for patients with sarcomas. The case series reported seven patients (26%) had local recurrence. No conclusions can be drawn for local recurrence and the overall strength of evidence is very low.

**KQ 2: What are the potential harms of IMRT 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 case series was identified (Terezakis 2007). Terezakis (2007) reported on 27 patients who received IMRT. The median follow-up was 17.4 months. One patient developed Grade 4 skin toxicity that required plastic surgery. Other adverse events reported include nausea, fatigue, dry mouth, pharyngitis or esophagitis, and pain.

### *Overall Summary*
The overall strength of evidence for all reported harms is very low. A single case series reported the following harms: nausea, fatigue, dry mouth, pharyngitis or esophagitis, and pain and one

patient developed Grade 4 skin toxicity that required plastic surgery. There are no comparative studies for all other harms and therefore no conclusions can be drawn.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Other Cancers (Skin, Thyroid, Spinal)

In this section, tumors of the skin, thyroid, and spine are summarized. There is limited evidence for all three cancers. No other cancers were identified for this section.

### Sacral chordoma

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

No SRs were identified.

*Subsequently Published Studies*

Zabel-du Bois (2010), a poor quality case series, reported on 34 patients with sacral chordoma. Thirteen patients received IMRT postoperatively; 17 patients had recurrent disease. Median age was 60 years. The median follow-up was 4.5 years (range, 0.3 to 9.1). Actuarial OS at 1-year, 2-years, and 5-years was 97%, 91%, and 70%, respectively. Disease-specific survival at 1-year, 2-years, and 5-years was 100%, 94%, and 80%, respectively. Actuarial DSS[15] at 1-year, 2-years, and 5-years was 97%, 91% and 49%, respectively.

*Overall Summary*

The overall strength of evidence is very low. Given the lack of a comparator in the sole study identified, no conclusions can be reached regarding clinical effectiveness. As reported by one poor quality case series, patients undergoing treatment with IMRT for sacral chordoma had actuarial survival estimates (1- to 5-year) between 97% and 70%, DSS estimates (1- to 5-year) between 100% and 80%, and actuarial DSS (1- to 5-year) between 97% and 49%.

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

*Systematic Reviews*

No SRs were identified.

[15] Similar to actuarial OS, actuarial DSS calculates the DSS for each time interval.

### *Subsequently Published Studies*
Zabel-du Bois (2010), a poor quality case series, reported on 34 patients with sacral chordoma. The median follow-up was 4.5 years (range, 0.3 to 9.1). Reported toxicities included diarrhea (26%), bladder irritation (6%), erythema (38%), and hyperpigmentation (15%). No harms greater than Grade 3 were reported.

### *Overall Summary*
The overall strength of evidence is very low. Due to the lack of a comparator in the sole study identified, no conclusions can be reached regarding harms. As reported by one poor quality case series, patients experienced less than or equal to Grade 2 toxicities including diarrhea (26%), bladder irritation (6%), erythema (38%), and hyperpigmentation (15%) after treatment with IMRT for sacral chordoma.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## <u>Skin Cancer</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*
No SRs were identified.

### *Subsequently Published Studies*
One poor quality case series was identified (Matthiesen 2011). Matthiesen (2011) reported on 21 patients with clinically staged T4 squamous cell (n=11) and basal cell (n=10) skin cancer. Twelve cancers were primary, five were recurrent, and four were postoperative. Median follow-up was 12 months (range, 5 to 48). Of the 10 patients treated with IMRT, 60% had no disease recurrence.

### *Overall Summary*
The overall strength of evidence is very low. There are no comparative studies and therefore no conclusions can be drawn. As reported by a single poor quality case series, 60% of patients treated with IMRT for skin cancer had no disease recurrence at 12 months.

**KQ 2: What are the potential harms of IMRT 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 case series was identified (Matthiesen 2011). Matthiesen (2011) reported on 21 patients with clinically staged T4 skin cancer. Median follow-up was 12 months (range, 5 to 48). All patients experience Grade 1 or 2 erythema over the treatment site.

*Overall Summary*

The overall strength of evidence is very low. There are no comparative studies and therefore no conclusions can be drawn. As reported by a single poor quality case series, all patients (n=21) experienced grade 1 or 2 erythema over the treatment site.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

<u>Thyroid cancer</u>

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

*Systematic Reviews*

No SRs were identified.

*Subsequently Published Studies*

Two studies on thyroid cancer were identified: one good quality cohort study (Schwartz 2009) and one poor quality case series (Rosenbluth 2005).

Schwartz (2009), a good quality cohort study, reported on 131 patients with differentiated thyroid cancer who either received EBRT (n = 74) or IMRT (n=57). Median age was 57 years. Median follow-up time for patients receiving IMRT was 34 months (range, 5 to 84). There was no statistical difference in all survival measures between IMRT compared to EBRT.

Rosenbluth (2005), a poor quality case series, reported on 20 patients with nonanaplastic thyroid cancer. Median age was 57 years. Twelve patients had papillary cancer, three had medullary cancer, and five had other pathologies. A 2-year local progression-free rate of 85% and a 2-year OS rate of 60% were reported.

### *Overall Summary*

The overall strength of evidence is low that there were no significant differences in all survival measures for IMRT compared to EBRT. There is low overall strength of evidence that IMRT had less late morbidities than the EBRT group. There are few comparative studies addressing other harms and therefore no conclusions can be reached comparing IMRT to other treatments.

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

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Three studies on thyroid cancer were identified: one case series (Rosenbluth 2005) and two cohort studies (Bhatia 2010; Schwartz 2009). One of the cohort studies was good quality (Schwartz 2009) and one was poor quality (Bhatia 2010); the case series was poor quality (Rosenbluth 2005).

Schwartz (2009), a good quality cohort study, reported on 131 patients with differentiated thyroid cancer who either received EBRT (n = 74) or IMRT (n=57). Median follow-up time for patients receiving IMRT was 34 months (range, 5 to 84). Nine of 74 (12%) EBRT patients developed late morbid events including esophageal structure, laryngeal stenosis, laryngeal edema requiring tracheostomy and chronic dysphagia. The IMRT group had a reduced rate of late morbidity including esophageal stricture (2%) compared to EBRT (12%) (p value not given).

Bhatia (2010), a poor quality cohort study, reported on 53 patients with anaplastic thyroid cancer who either received 3DCRT (n=40) or IMRT (n=13). Distant metastases were present in 25 patients. Median age was 66 years. Twelve of 53 patients (23%) had radiotherapy-specific acute or chronic morbidity requiring hospitalization and/or interventional procedures.

Rosenbluth (2005), a poor quality case series, reported on 20 patients with nonanaplastic thyroid cancer. Acute mucositis, pharyngitis, dysphagia, xerostomia, skin toxicity, and laryngeal toxicity were the most common harms reported.

### *Overall Summary*

There is very low overall strength of evidence for harms. In general, acute mucositis, pharyngitis, dysphagia, xerostomia, skin toxicity, laryngeal toxicity, and esophageal stricture were reported.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## Spinal Metastases

**KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?**

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Three poor quality case series reported on IMRT in treatment of spinal metastases (Inoue 2011; Wright 2006; Yamada 2008).

Inoue (2010), a poor quality case series, reported on a total of 78 spinal metastases in 50 patients. Forty metastases were in tissues adjacent to areas previously treated with radiation; 20 of these were true in field recurrences. Follow-up intervals are unclear. Recurrence was reported in 4 of the 50 patients.

Wright (2006), a poor quality case series, reported on 49 patients with spinal metastases from varying primary tumor locations. Median follow-up was 8 months (range, 1 to 51). Median survival at 12 months was 76%. Quality of life was evaluated; 25 patients were categorized as "improved after radiation," nine patients as "stable," and four patients as "worse after radiation." Six patients died before follow-up, and an additional six patients were lost to follow-up.

Yamada (2008), a poor quality case series, reported on 93 patients with solid tumor malignancy with spine metastasis and high grade spinal cord compression, mechanical instability or surgery at the region of pathology. Median age was 62 years. Median follow-up was 15 months (range, 2 to 45). Median survival was 10 months (range, 1 to 39). At 45 months, OS was reported to be 35%.

### *Overall Summary*

For spinal metastases, there is very low overall strength of evidence for all described outcomes (i.e., OS, recurrence, QoL). Differences in outcome measures and time frames used preclude synthesis of these findings. No evidence was identified that compared IMRT to EBRT for patients with spinal metastases.

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

### *Systematic Reviews*

No SRs were identified.

### *Subsequently Published Studies*

Five case series reported on IMRT in treatment of spinal metastases (Damast 2011; Inoue 2011; Rose 2008; Wright 2006; Yamada 208). One of the studies was good quality (Rose 2008), one was fair quality (Damast 2011), and three were poor quality (Inoue 2011; Wright 2008; Yamada 2008).

Rose (2009), a good quality case series, reported that 27 of 62 (39%) of patients receiving IMRT for spinal metastases from multiple primary cancer types developed subsequent spinal fractures. Median follow-up was 13 months. No other harms were reported.

Damast (2011), a fair quality case series, reported spinal fractures in 9 of 97 vertebrae (94 patients) treated for metastases. Median follow-up was 12.1 months (range, 0.2 to 63.6). No other harms were reported.

Inoue (2010), a poor quality case series, reported one case of myelitis in 50 patients. Follow-up intervals were unclear.

Wright (2006), a poor quality case series, reported on 49 patients with spinal metastases from varying primary tumor locations. Median follow-up was 8 months (range, 1 to 51). Mild acute symptoms (pharyngitis, fatigue, diarrhea) were reported in 3 of 37 patients. No long-term toxicities were reported.

Yamada (2008), a poor quality case series, reported on 93 patients with solid tumor malignancy with spine metastasis. Median follow-up was 15 months (range, 2 to 45). Three of 93 patients had Grade 1 or 2 skin reactions, two had Grade 2 esophagitis, and none had myelopathy or radiculopathy.

### *Overall Summary*

For spinal metastases, there is very low overall strength of evidence for all described harms. Reported toxicities varied across studies, including esophagitis, skin reactions and various acute reactions. No evidence was identified that compared IMRT to EBRT for patients with spinal metastases.

**KQ 3: What is the evidence that IMRT has 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 IMRT compared to EBRT?**

No studies on costs or cost-effectiveness were identified.

## MAUDE Database

Two reports of serious adverse events were identified. One patient was admitted to the intensive care unit for severe skin reactions and another patient was admitted to the hospital for Grade 3 hematochezia secondary to rectal ulceration and Grade 3 anemia. Full summaries of the events are provided in Appendix L.

## Guidelines

A total of 17 guidelines and 11 ACR Appropriateness Criteria®[16] were identified that address IMRT. Appropriateness Criteria® issued by ACR are considered to be a clinical decision making aid rather than a broadly applied guideline. Two of the guidelines focused on clinical practice (ACR-ASTRO 2011; Holmes [ASTRO] 2009); the remaining were specific to individual malignancies. Guidelines are summarized by malignancy below and in Table 5. We identified guidelines and/or ACR Appropriateness Criteria® for anal, breast, cervical, central nervous system, colon, esophageal and esophagogastric junction, gastric, head and neck, lung, non-spine bone metastases, prostate, rectal, testicular, and thymic cancers (see Appendix G for detail on all guidelines).

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 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.

<u>General IMRT Procedure and Practice</u>: The search identified two poor quality guidelines that provide recommendations about general procedures, personnel, quality control and safety for the performance of IMRT, and documentation (Appendix G). These recommendations are from the ACR-ASTRO (2011) and ASTRO (Holmes 2009) and are similar to those provided by Tipton (AHRQ 2011a). The guidelines are consensus-based with no mention of an evidence review, although some aspects of the guidelines describing good practice (e.g., recommendations on personnel or documentation of treatment) may not warrant an evidence review.

<u>Anal Cancer</u>: The NCCN (2012a) states that IMRT may be used in place of 3D conformal radiation therapy, and that IMRT requires expertise and careful target design. The ACR gives

[16] 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."

IMRT an Appropriateness Criteria® of 6 and "cautiously recommends" the use of IMRT if performed outside of a study protocol setting (Poggi [ACR] 2010).

Breast Cancer: The NCCN (2012b) provides recommendations about IMRT in their local-regional treatment guidelines for stage I, IIA, IIB, or T2N1M0 invasive breast cancer. Tissue wedging, forward planning with segments (step and shoot), or IMRT is recommended.

Central Nervous System Cancers: The NCCN (2012c) states that 3D-planning or IMRT may be appropriate for low-grade astrocytomas and oligodendrogliomas.

Cervical Cancer: The NCCN (2012d) suggests that IMRT may be helpful, but that it is not to be used as a routine alternative to brachytherapy. The guideline stresses that very close attention to detail and reproducibility is needed. The ACR gives IMRT an Appropriateness Criteria® score of 3 to 8 depending on case variability. However, the ACR states that IMRT is "not indicated for routine treatment of cervical cancer" (Gaffney [ACR] 2010, p 2). In addition, the ACR gives an Appropriateness Criteria® score of 7 to IMRT as adjuvant therapy in the management of early stage cervical cancer and notes that great care is required in delineation of clinical target volume (CTV) (Wolfson [ACR] 2011).

Colon Cancer: The NCCN (2012e) suggests that IMRT be reserved for unique clinical situations including re-irradiation of previously treated patients with recurrent disease.

Esophageal and Esophagogastric Junction Cancers: The NCCN (2012f) states that IMRT may be appropriate in selected cases to reduce dose to normal structures.

Gastric Cancer: The NCCN (2012g) states that IMRT may be appropriate in selected cases to reduce dose to normal structures.

Head and Neck Cancers: The NCCN (2012h, 2012j) states that either 3D conformal radiation therapy or IMRT may be appropriate in the treatment of head and neck cancers, and that IMRT may be used at the discretion of the treating physician. Specifically for resectable oropharyngeal squamous cell carcinoma, the ACR gives IMRT an Appropriateness Criteria® score of 8 to 9 depending on case variability.

Lung Cancer: Two guidelines for lung cancer were identified: one on malignant pleural mesothelioma (NCCN 2012i) and one on NSCLC (NCCN 2012k), with an additional three ACR Appropriateness Criteria® documents identified for NSCLC. For mesothelioma, the NCCN (2012i) states that "IMRT […] should only be used in experienced centers or on protocol" (p MPM-C 2) and when IMRT is applied, that the NCI/ASTRO IMRT guidelines should be strictly followed. The NCCN (2012i) guideline further states that "special attention should be paid to minimize radiation to the contralateral lung" and that the "mean lung dose should be kept as low as possible" (p MPM-C 2).

For NSCLC, the NCCN (2012k) states that CT-planned 3DCRT is the minimum standard for treatment and that "use of more advanced technologies [including IMRT] is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints" (p

NSCL-B 1). The ACR has varying Appropriateness Criteria® for the use of IMRT for NSCLC. The ACR Appropriateness Criteria® for IMRT for postoperative adjuvant therapy for NSCLC is a 6 (Decker [ACR] 2011), and is an 8 (with tumor motion strategy required in addition to strict dosimetric criteria) for nonsurgical treatment (Gewanter [ACR] 2010) and induction and adjuvant therapy for N2 for NSCLC (Gopal [ACR] 2010).

For SCLC, the NCCN states that the use of IMRT may be considered (NCCN 2012n).

Non-spine Bone Metastases: The ACR gives IMRT an Appropriateness Criteria® score of two for non-spine bone metastases (Lutz [ACR] 2011).

Prostate Cancer: The NCCN (2012l) states that 3D conformal and IMRT techniques should be employed if radiation treatment is being considered for prostate cancer. For T1 and T2 prostate cancer, the ACR gives IMRT an Appropriateness Criteria® score of 8 (Morgan [ACR] 2011); for postradical prostatectomy irradiation in prostate cancer, the ACR gives IMRT an Appropriateness Criteria® score of 2 to 8, depending on case variability.

Rectal Cancer: The NCCN (2012m) states that IMRT should only be used in clinical trial settings or in unique clinical situations for rectal cancer. The ACR gives IMRT an Appropriateness Criteria® score of 1 for rectal cancer and states that it should be for investigational use only.

Testicular Cancer: The NCCN (2012o) does not recommend IMRT for the treatment of testicular cancer.

Thyomas: The NCCN (2012p) states that IMRT may "further improve the dose distribution and decrease dose to the normal tissue as indicated" and that if IMRT is applied, the NCI/ASTRO guidelines should be strictly followed (p THYM-B 2).

**Table 5. Summary of NCCN and ACR Guidelines by Malignancy**

| Malignancy | Guideline (Year) Quality | Usually Not Appropriate / Not Recommended | May be Appropriate | Usually Appropriate / Recommended |
|---|---|---|---|---|
| **Abdomen** | | | | |
| Anal/Rectal carcinoma | NCCN (2012a) Poor | | IMRT may be used in place of 3D conformal RT. Requires expertise and careful target design. | |
| Anal cancer | Poggi [ACR] (2010) Fair | | ACR 6 "cautiously recommends" the use of IMRT if performed outside of a protocol setting. | |
| Colon cancer | NCCN (2012e) Poor | IMRT reserved only for unique clinical situations including re-irradiation of | | |

| Malignancy | Guideline (Year) Quality | Usually Not Appropriate / Not Recommended | May be Appropriate | Usually Appropriate / Recommended |
|---|---|---|---|---|
| | | previously treated patients with recurrent disease. | | |
| Esophageal and esophagogastric junction cancers | NCCN (2012g) Poor | | In selected cases to reduce dose to normal structures. | |
| Gastric cancers | NCCN (2012g) Poor | | In selected cases to reduce dose to normal structures. | |
| Rectal cancer | NCCN (2012m) Poor | IMRT should only be used in clinical trial setting or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy). | | |
| Resectable rectal cancer | Suh [ACR] (2007) Fair | ACR 1 (investigational use only) | | |
| **Brain** | | | | |
| Central nervous system | NCCN (2012c) Poor | | For low-grade astrocytoma and oligodendroglioma. 3D planning or IMRT. | |
| **Breast** | | | | |
| Breast cancer | NCCN (2012b) Poor | | | Recommended following CT-based treatment planning |
| **Female Pelvis** | | | | |
| Cervical cancer | Gaffney [ACR] (2010) Fair | “not indicated for routine treatment of cervical cancer” ACR (3-8) | | |
| Cervical cancer | NCCN (2012d) Poor | | May be helpful. Not to be used as routine alternative to brachytherapy. Very close | |

| Malignancy | Guideline (Year) Quality | Usually Not Appropriate / Not Recommended | May be Appropriate | Usually Appropriate / Recommended |
|---|---|---|---|---|
| | | | attention to detail and reproducibility needed. | |
| Cervical cancer (role of adjuvant therapy in the management of early stage) | Wolfson [ACR] (2011) Fair | | | ACR 7 (great care required in delineation of CTV) |
| **Head and Neck** | | | | |
| Head and neck cancers | NCCN (2012h) Poor | | Either 3D conformal RT or IMRT. IMRT may be used at the discretion of treating physicians. | |
| Head and neck cancers (mucosal melanoma) | NCCN (2012j) Poor | | IMRT, 3D and 2D conformal techniques may be used as appropriate. IMRT may be used at the discretion of treating physicians. | |
| Resectable oropharyngeal squamous cell carcinoma | Quon [ACR] (2010) Fair | | | Dependent on patient characteristics, ACR 8-9 |
| **Lung** | | | | |
| Malignant pleural mesothelioma | NCCN (2012i) Poor | | IMRT should only be used in experienced centers or on protocol. NCI/ASTRO IMRT guidelines should be strictly followed. | |
| NSCLC (postoperative adjuvant therapy) | Decker [ACR] (2011) Fair | | Dependent on patient characteristics and tumor stage, ACR 6 | |
| NSCLC (nonsurgical treatment) | Gewanter [ACR] (2010) Fair | | | ACR 8 (with tumor motion strategy required in addition to strict dosimetric criteria) |

| Malignancy | Guideline (Year) Quality | Usually Not Appropriate / Not Recommended | May be Appropriate | Usually Appropriate / Recommended |
|---|---|---|---|---|
| NSCLC (induction and adjuvant therapy for N2) | Gopal [ACR] (2010) Fair | | | ACR 8 (with tumor motion strategy required in addition to strict dosimetric criteria) |
| NSCLC | NCCN (2012k) Poor | | Use of IMRT appropriate when need to deliver adequate tumor doses while respecting normal tissue dose constraints. | |
| SCLC | NCCN (2012n) Poor | | In selected pts, IMRT may be considered. | |
| **Prostate** | | | | |
| Prostate cancer (T1 and T2) | Morgan [ACR] (2011) Fair | | | Dependent on patient characteristics, ACR 8 |
| Prostate cancer | NCCN (2012l) Poor | | | 3D conformal or IMRT (no preference given) |
| Postradical prostatectomy irradiation in prostate cancer | Rossi [ACR] (2010) Fair | Dependent on patient characteristics, ACR 2-8 | | Dependent on patient characteristics, ACR 2-8 |
| **Other Cancers** | | | | |
| Non-spine bone metastases | Lutz [ACR] (2011) Fair | Dependent on patient characteristics, ACR 2 | | |
| Testicular cancer | NCCN (2012o) Poor | IMRT not recommended | | |
| Thymomas and thymic carcinomas | NCCN (2012p) Poor | | IMRT may further improve dose distribution and decrease dose to the normal tissues as indicated. Strictly follow | |

| Malignancy | Guideline (Year) Quality | Usually Not Appropriate / Not Recommended | May be Appropriate | Usually Appropriate / Recommended |
|---|---|---|---|---|
| | | | NCI/ASTRO IMRT guidelines. | |

### *Summary of Guidelines*

The NCCN guidelines and the ACR Appropriateness Criteria® are consistent in their statements and recommendations for IMRT for anal, prostate, and rectal cancer. There are no ACR Appropriateness Criteria® ratings for breast, central nervous system, colon, esophageal and esophagogastric junction, gastric, general head and neck, mesothelioma, testicular and thymic cancers. There are no NCCN guidelines for non-spinal bone metastases. Based on poor to fair quality guidelines, IMRT is considered usually appropriate by the ACR and/or recommended by the NCCN for breast cancer, resectable oropharngeal squamous cell carcinoma, nonsurgical treatment of NSCLC, induction and adjuvant therapy for N2 NSCLC, and prostate cancer. Intensity modulated radiation therapy is not recommended by the NCCN or considered appropriate by the ACR for the treatment of colon cancer, rectal cancer, non-spine bone metastases, and testicular cancer.  For cervical cancer, the NCCN and the ACR have inconsistent recommendations ranging from usually not appropriate/not recommended to usually appropriate/recommended.  For all other cancers discussed, IMRT is considered as a possible appropriate form of treatment by the ACR and NCCN.

## Policy Considerations

This section summarizes coverage policies by Medicare, Aetna, Regence Blue Cross Blue Shield (BCBS), and Group Health addressing IMRT. Appendix I provides further detail and direct web links to each policy reviewed.

### *Medicare*

There are no Medicare national coverage decisions (NCDs) for IMRT. Coverage policies are left to regional Medicare contractors. The regional contractor for Washington State has issued two localized coverage determinations (LCDs) for IMRT (L24318 and L31415). Both LCDs cover brain tumors, brain metastasis, prostate cancer, lung cancer, pancreas cancer and other upper abdominal sites, spinal cord tumors, head and neck cancer, adrenal tumors, and pituitary tumors (CMS 2012a; 2012b). An additional LCD (L30316) that covers 40 states (including Washington) states IMRT is indicated as a standard treatment option for central nervous system tumors (including brain and spinal cord), head and neck cancers, prostate cancer, selected cases of thoracic and abdominal malignancies, selected cases of breast cancers (with close proximity to critical structures), and pelvic and retroperitoneal tumors (CMS 2011a). Clinical criteria for medical necessity of IMRT include adjacent critical structures that need to be protected; areas adjacent to a previously irradiated area; concave or convex target volume; and radiation doses in excess of those utilized with conventional treatment. See Appendix I for a more comprehensive summary.

*Aetna*

For approval of IMRT Aetna requires that critical structures located close to tumors cannot be adequately protected using conventional EBRT (Aetna 2011). Specific tumor types are not listed.

*GroupHealth*

GroupHealth does not require a medical necessity review for use of IMRT in head and neck and prostate cancers (GroupHealth 2011).

*Regence BCBS*

Four unique policies are used by Regence BCBS for coverage determinations (Regence BSBC 2011a; 2011b; 2011c; 2011d). Treatment may be considered medically necessary for the treatment of squamous cell cancer of the anal canal and head and neck cancers. In primary prostate cancer IMRT can be used as the main treatment, as a salvage treatment for failed main treatment or recurrence and as adjuvant therapy immediately following prostatectomy. The use of IMRT for the treatment of breast, lung, and other abdominal or pelvic tumors is considered medically necessary when there is prior radiation to the area, or there are critical structures in the radiation field. For other cancers, IMRT is not considered medically necessary.

## Overall Summary

This report presents evidence about the use of IMRT for malignancies in the following anatomic locations: abdomen (anal/rectal, liver, and pancreas), brain, breast, female pelvis, head and neck, lung, prostate, soft tissue sarcomas, and other cancer sites (skin, thyroid, spinal metastases). Sixteen SRs and 108 individual studies met inclusion criteria. The majority of studies were non-comparative and in adults. Only two studies for medulloblastoma were exclusively in the pediatric population. Overall, there is limited evidence to answer many of the Key Questions and the populations were heterogeneous.

The overall strength of evidence for outcomes (e.g., OS, DSS, DFS, recurrence, QoL, harms, etc.) ranged from moderate to very low with most being low to very low. In general, for patient survival and recurrence outcomes, the results were heterogeneous, and for many cancer locations, there were no comparative data. Therefore, no general conclusions can be drawn for patient survival and recurrence outcomes.

The findings for QoL were inconsistent except in two anatomic locations with moderate overall strength of evidence findings. The first is whole breast irradiation, in which there were no differences in QoL for IMRT compared to EBRT. The second is head and neck cancers, which found an improvement in overall QoL for IMRT compared to 2D- and 3DCRT.

Harms were mostly regional toxicities based on the location of the malignancy and commonly included acute and late toxicities (e.g., GI, GU, xerostomia, skin, pneumonitis, esophagitis, etc.). There was moderate strength of evidence findings for two outcomes for whole breast irradiation and one outcome for head and neck cancer. For whole breast irradiation, there was moderate strength of evidence that the EBRT group was more likely to develop any Grade of telangiectasia compared to patients who received IMRT. In addition, there was moderate strength of evidence that there were no significant differences in acute toxicities (Grade 2 or higher, Grade 3 or 4 skin toxicities) for IMRT compared to EBRT for whole breast irradiation. For head and neck cancer, there was moderate strength of evidence that IMRT reduces Grade 2 or greater xerostomia compared to v. Deaths and serious adverse events (e.g., harms requiring surgery) were not common, but were reported by a few studies across several anatomic cancer locations. For prostate cancer, there was a moderate strength of evidence that IMRT improve gastrointestinal toxicities compared to EBRT.

There was insufficient evidence to address differential safety and efficacy for any subgroup. All of the cost studies consistently reported that IMRT costs more than other treatments for whole breast, partial breast, head and neck, and prostate cancers. For all other malignancy locations, there was insufficient evidence for costs. Prostate cancer was the only malignancy for which there were cost effectiveness analyses. However, the limitations of the analyses make drawing conclusions difficult.

The NCCN and ACR Appropriateness Criteria® recommendations for the use of IMRT vary according to malignancy. The NCCN guidelines were all rated as being of poor methodological quality, while the ACR guidelines were rated as fair methodological quality. The NCCN guidelines and the ACR Appropriateness Criteria® are consistent in their statements and recommendations for IMRT for anal, prostate, and rectal cancer. Based on poor to fair quality guidelines, IMRT is considered usually appropriate by the ACR and/or recommended by the NCCN for breast cancer, resectable oropharngeal squamous cell carcinoma, nonsurgical treatment of NSCLC, induction and adjuvant therapy for N2 NSCLC, and prostate cancer. Intensity modulated radiation therapy is not recommended by the NCCN or considered appropriate by the ACR for the treatment of colon cancer, rectal cancer, non-spine bone metastases, and testicular cancer.  For cervical cancer, the NCCN and the ACR have inconsistent recommendations ranging from usually not appropriate/not recommended to usually appropriate/recommended.  For all other cancers discussed, IMRT is considered as a possible appropriate form of treatment by the ACR and NCCN.

Federal and private payer polices vary by cancer site. The three relevant Medicare LCDs cover brain, prostate, lung, pancreas and other upper abdominal sites, spinal cord, head and neck, adrenal and pituitary cancers, as well as some thoracic, breast, pelvic and retroperitoneal tumors meeting medical necessity criteria. Regence BCBS also covers treatment in some cases for anal, head and neck, prostate, breast, lung, and other abdominal or pelvic tumors. Aetna and GroupHealth provide little information about when IMRT is considered medically necessary. Medical necessity criteria for the Medicare LCDs and Regence BCBS are similar including prior radiation to the area and critical structures in the radiation field and shape of the tumor.

## Limitations of the Evidence

The evidence on IMRT is largely based on cohort and case series studies. These studies have substantial methodological limitations, such as:

- The majority of studies 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 may include
  - Age;
  - Tumor staging prior to treatment;
  - Smoking status;
  - Other comorbidities; and
  - Concurrent therapies.
- Selection bias could be an issue in the study designs included in this report;
- Many of the studies combined different stages of tumor malignancies in their analyses;
- Many studies included different radiation dosages making comparison between IMRT and 3DCRT difficult;
- Many of the included studies have relatively small sample sizes making it difficult to infer findings to the broader population; and
- Several studies included patients receiving chemotherapy concurrent with IMRT and current or past treatments received were often not reported.

## Appendix A. Database Search Strategies

**Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** <1946 to May Week 1 2012>
Search Strategy:

--------------------------------------------------------------------------------

1 exp Radiotherapy, Intensity-Modulated/ (2781)

2 (intens$ adj3 modulat$ adj5 (radiother$ or (radiat$ adj3 (therap$ or treat$ or regimen$ or session$)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4899)

3 imrt.mp. (3653)

4 (intens$ adj3 modulat$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (6104)

5 3 or 4 (6580)

6 exp Radiotherapy/ (125089)

7 rt.fs. (145891)

8 6 or 7 (202477)

9 5 and 8 (5609)

10 1 or 2 or 9 (5739)

11 limit 10 to (controlled clinical trial or meta analysis or practice guideline or randomized controlled trial) (114)

12 limit 11 to (english language and yr="2002 -Current") (105)

13 exp Cohort Studies/ (1169990)

14 exp case-control studies/ (549718)

15 10 and 13 (891)

16 limit 15 to (english language and yr="2002 -Current") (833)

17 10 and 14 (470)

18 limit 17 to (english language and yr="2002 -Current") (449)

19 limit 10 to systematic reviews (139)

20 11 or 19 (222)

21 16 or 18 or 20 (1024)

22 limit 21 to (english language and yr="2002 -Current") (1004)

23 limit 22 to english language (1004)

24 Comparative Study/ (1573800)

25 10 and 24 (1073)

26 limit 25 to (english language and yr="2002 -Current") (929)

27 case series.mp. (25119)

28 10 and 27 (8)

29 limit 28 to (english language and yr="2002 -Current") (7)

30 12 or 16 or 18 or 22 or 26 or 29 (1728)

**Database: EBM Reviews - Cochrane Central Register of Controlled Trials** <May 2012>
Search Strategy:

--------------------------------------------------------------------------------

1 imrt.mp. (82)

2 (intens$ adj3 modul$ adj3 (radiother$ or (radiation adj2 (treat$ or therap$)))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (98)

3 1 or 2 (118)

4 limit 3 to yr="2002 -Current" (114)

**Database: EBM Reviews - Cochrane Database of Systematic Reviews** <2005 to May 2012>
Search Strategy:

--------------------------------------------------------------------------------

1 imrt.mp. (8)

2 (intens$ adj3 modul$ adj3 (radiother$ or (radiation adj2 (treat$ or therap$)))).mp. [mp=title, abstract, full text, keywords, caption text] (12)

3 1 or 2 (14)

4 limit 3 to yr="2002 -Current" (14)

## 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** | | April 2002 | April 2002 | April 2002 | April 2002 |
| Anal/Rectal | De Neve (2012); Stafforth (2010); Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| Liver | | April 2002 | April 2002 | April 2002 | April 2002 |
| Pancreas | Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| **Brain** | De Neve (2012); Stafforth (2010); Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| Astrocytoma | Stafforth (2010); Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| Glioma | | April 2002 | April 2002 | April 2002 | April 2002 |
| Glioblastoma | Amelio (2010); Stafforth (2010); Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| Medulloblastoma | De Neve (2012); Stafforth (2010); Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| Meningioma | | April 2002 | April 2002 | April 2002 | April 2002 |
| Spinal Cord | | April 2002 | April 2002 | April 2002 | April 2002 |
| Others | | April 2002 | April 2002 | April 2002 | April 2002 |
| **Breast** | Hayes (2012a, 2012b) | November 2011 | November 2011 | April 2002 | April 2002 |

| Malignancy | Review | MEDLINE Beginning Search Dates | | | |
|---|---|---|---|---|---|
| | | Key Question 1 | Key Question 2 | Key Question 3 | Key Question 4 |
| **Female Pelvis** | De Neve (2012); Stafforth (2010); Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| **Head and Neck** | De Neve (2012); Samson (2010); Stafforth (2010); Scott-Brown (2010); Tribius (2011) | July 2009 | July 2009 Reviews: Bensadoun (2010); Jensen (2010); Peterson (2010) | July 2009 | April 2002 |
| **Lung** | | April 2002 | April 2002 | April 2002 | April 2002 |
| Mesothelioma | Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| Non-small cell lung cancer | De Neve (2012); Stafforth (2010); Veldeman (2008) | April 2002 | April 2002 | April 2002 | April 2002 |
| **Prostate** | Budäus (2012); De Neve (2012); Hummel (2010); Stafforth (2010); Wilt (2008) | March 2009 | March 2009 | July 2007 Review: Wilt 2008 | March 2009 Review: Perlroth (2010) |
| **Sarcoma** | April 2002 | April 2002 | April 2002 | April 2002 | April 2002 |
| **Spine** | April 2002 | April 2002 | April 2002 | April 2002 | April 2002 |
| **Thyroid** | April 2002 | 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*<br>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).<br>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**<br>• Systematic literature search<br>• Study selection criteria clearly described<br>• Quality of individual studies and overall strength of the evidence assessed<br>• Explicit link between evidence & recommendations<br><br>*(If any of the above are missing, rate as poor)* | GOOD FAIR POOR |
| 1.2 | **RIGOR OF DEVELOPMENT: Recommendations**<br>• Methods for developing recommendations clearly described<br>• Strengths and limitations of evidence clearly described<br>• Benefits/side effects/risks considered<br>• External review | GOOD FAIR POOR |
| 1.3 | **EDITORIAL INDEPENDENCE**[17]<br>• Views of funding body have not influenced the content of the guideline<br>• 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**<br>• Objectives described<br>• Health question(s) specifically described<br>• Population (patients, public, etc.) specified | GOOD FAIR POOR |
| **SECTION 2: SECONDARY CRITERIA, CONT.** | | |

17 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**<br>• Relevant professional groups represented<br>• Views and preferences of target population sought<br>• Target users defined | GOOD | FAIR | POOR |
| 2.3 | **CLARITY AND PRESENTATION**<br>• Recommendations specific, unambiguous<br>• Management options clearly presented<br>• Key recommendations identifiable<br>• Application tools available<br>Updating procedure specified | GOOD | FAIR | POOR |
| 2.4 | **APPLICABILITY**<br>• Provides advice and/or tools on how the recommendation(s) can be put into practice<br>• Description of facilitators and barriers to its application<br>• Potential resource implications considered<br>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 Malignancy

### Introduction

This summary of findings provides an overview of the strength of evidence for the use of IMRT compared to EBRT. This summary of findings is intended to *supplement* the Washington Health Technology Assessment Program's *Intensity Modulated Radiation Therapy* report. The findings presented in this document are in aggregate. For specific details and findings per malignancy, please refer to the full report on the WA HTA website.

**Strength of Evidence**

| | |
|---|---|
| ⊕⊕⊕⊕ | High |
| ⊕⊕⊕○ | Moderate |
| ⊕⊕○○ | Low |
| ⊕○○○ | Very Low |

**Outcomes**

| | |
|---|---|
| ↔ | No Significant Difference |
| ↕ | Inconsistent Evidence |
| ↑ | Increased |
| ↓ | Decreased |

### Overview

The summary table provides a detailed summary of the strength and direction of evidence per malignancy, comparator, and outcomes.

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| **Abdomen – Anal Cancer** | 3 SRs (2 cohort, 1 case series), 2 case series | | | |
| KQ # 1 Efficacy | 2 SRs (1 cohort, 1 case series), 1 case series | | | |
| External beam radiation therapy (EBRT) | | | | ↑ 3-yr OS<br>↑ 3-yr locoregional survival<br>↑ 3-yr PFS |
| No comparator[19] | | | | 2-yr OS, 2-yr DFS, 2-yr colostomy-free survival |
| KQ # 2 Harms | 3 SRs (2 cohorts, 1 case series), 1 case series | | | |
| EBRT | | | | ↓ Diarrhea<br>↓ Skin/mucosal toxicity<br>↓ > Grade 2 skin and mucosal eruptions in the female genital area<br>↓ > Grade 2 nonhematologic toxicity |
| No comparator | | | | ≤ Grade 2 non-haematological, gastrointestinal toxicities, ≥ Grade 3 dermatologic toxicities, ≥ Grade 3 hematologic toxicities |
| KQ # 3 Subpopulations – HIV Positive patients | | | | |
| No comparator | 1 case series | | | 3-yr RFS, 3-yr OS |
| KQ # 4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |

[18] No procedure had a high strength of evidence, thus this column is not displayed in this table.
[19] Due to lack of comparative data, no directionality can be given for outcomes

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | **⊕⊕⊕○ Moderate** | **⊕⊕○○ Low** | **⊕○○○ Very Low** |
| **Abdomen – Esophagial Cancer** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | 2-yr actuarial loco-regional control, 1- and 2-yr OS |
| KQ # 2 Harms | 1 case series | | | |
| No comparator | | | | ≥ acute Grade 3 complications, late complications |
| 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** | 3 case series | | | |
| KQ # 1 Efficacy | 3 case series | | | |
| No comparator | | | | 1-yr survival, OS, PFS |
| KQ # 2 Harms | 3 case series | | | |
| No comparator | | | | Grade 0 to 2 hepatic toxicity, hematologic toxicity (anorexia, nausea and vomiting, hepatitis, pancreatitis, GI bleeding), esophagitis |
| KQ # 3 Subpopulations | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ # 4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| **Abdomen – Pancreatic Cancer** | 1 case series, 1 cost-effectiveness study | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | 1- and 2-yr OS |
| KQ # 2 Harms | 1 case series | | | |
| No comparator | | | | ≤ Grade 2 anorexia, dehydration, nausea and vomiting; ≥ Grade 3 acute and late GI complications |
| KQ # 3 Subpopulations | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ # 4 Cost and Cost-Effectiveness | 1 cost-effectiveness study | | | |
| EBRT | | | IMRT is less cost-effective than EBRT | |
| **Abdomen – Rectum** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | 2-yr PFS, 2-yr OS |
| KQ # 2 Harms | | | | |
| No comparator | | | | Grade 3 diarrhea, Grade 3 dermatitis, Grade 3 neutrapenia |
| KQ # 3 Subpopulations | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ # 4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| **Abdomen – Stomach** | 2 cohorts | | | |
| KQ # 1 Efficacy | 2 cohorts | | | |
| EBRT | | | | ↕ 2-yr actuarial DFS<br>↕ 2-yr survival<br>↔ 2-yr loco-regional control |
| KQ # 2 Harms | 2 cohorts | | | |
| EBRT | | | | ↓ renal harms<br>↔ ≥ Grade 2 GI toxicities |
| KQ # 3 Subpopulations | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ # 4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Abdomen – Whole Pelvis Radiation** | 1 cohort | | | |
| KQ # 1 Efficacy | | | | |
| *No studies on efficacy identified.* | | | | |
| KQ # 2 Harms | 1 cohort | | | |
| EBRT | | | | ↔ Acute GI toxicity<br>↔ Acute GU toxicity<br>No ≥ Grade 3 toxicities in IMRT group. |
| KQ # 3 Subpopulations | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ # 4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy**<br>Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○<br>**Moderate** | ⊕⊕○○<br>**Low** | ⊕○○○<br>**Very Low** |
| **Brain - Astrocytoma** | 2 SR (1 cohort) | | | |
| KQ # 1 Efficacy | 1 SR (1 cohort) | | | |
| EBRT | | | | ↑ 1-yr, 2-yr OS<br>↑ 1-yr, 2-yr PFS |
| KQ #2 Harms | 2 SRs (1 cohort) | | | |
| EBRT | | | | ↓ Acute Grade 1 toxicities<br>↑ Acute Grade 2 and 3 toxicities |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Brain – Brain Metastases** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | 6-month OS, quality of life (QoL), global health functioning, physical functioning, role functioning |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | Grade 1 and 2 alopecia |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Brain – Glioblastoma multiforme** | 1 SR (8 case series), 3 case series | | | |
| KQ # 1 Efficacy | 1 SR (8 case series), 3 case series | | | |
| No comparator | | | | 1-yr OS, 2-yr OS, OS, 1-yr PFS, 2-yr PFS, PFS |
| KQ #2 Harms | 1 SR (8 case series), 3 case series | | | |
| No comparator | | | | Acute Grade 3 neurotoxicity, late radiation necrosis, Grade 3 otitis with hearing loss, nausea, vomiting, fatigue, Grade 1 anemia, ≤ Grade 2 hepatotoxicity |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Brain – High-Grade Glioma** | 2 case series | | | |
| KQ # 1 Efficacy | 2 case series | | | |
| No comparator | | | | OS (Grade III and IV tumors), 1-yr OS, 2-yr OS, PFS (Grade III and IV tumors), 1-yr PFS, 2-yr PFS |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | Grade 2 and 3 edema, Grade 1 worsening of neurological |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| | | | | symptoms |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Brain – Medulloblastoma** | 3 SRs (1 cohort, 1 case series), 2 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | 5-yr PFS, 5-yr OS |
| KQ #2 Harms | 3 SRs (1 cohort, 1 case series), 2 case series | | | |
| EBRT | | | | ↓ Grade 3 and 4 ototoxicity (children)<br>↑ Grade 1 and 2 toxicities<br>↔ neurocognitive functioning |
| No comparator | | | | ≥ Grade 3 ototoxicity, hearing loss |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Brain – Meningioma** | 3 case series | | | |
| KQ # 1 Efficacy | 3 case series | | | |
| No comparator | | | | survival, 3-yr actuarial survival, |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| | | | | 3- and 5-yr recurrence free survival (RFS) |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | No severe toxicities reported. |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Brain – Pituitary Adenoma** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | Overall biochemical response |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | Short-term (6 months) toxicities of fatigue, headache, nausea or vomiting, visual complaints, alopecia or ertherma, anxiety attack, epistaxis, dry eyes, excess tearing<br>Long-term (≥ 12 months) toxicities of cognitive changes, visual decline, and cranial nerve deficit |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Breast – Whole Breast Radiation** | 1 SR (4 SRs, 3 RCTs, 9 cohorts, 3 case series, 1 cost, 1 cost-comparison) | | | |
| KQ # 1 Efficacy | 1 SR (2 SRs, 2 RCTs, 3 cohorts, 2 case series) | | | |
| EBRT | | ↔ QoL | ↕ OS<br>↕ DSS<br>↔ Ipsilateral breast tumor recurrence<br>↔ Contralateral breast tumor recurrence<br>↔ Distant metastases | |
| No comparator | | | Local regional recurrence | |
| KQ #2 Harms | 1 SR (4 RCTs, 9 cohorts, 2 case series) | | | |
| EBRT | | ↓ Grade 1 to 3 telangiectasia<br>↔ Acute ≥ Grade 2 toxicities<br>↔ Grade 3 or 4 skin | ↔ Breast cosmesis<br>↔ Late ≥ Grade 2 toxicities | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| | | toxicities ↓ Moist desquamation | | |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | 1 SR (1 cost, 1 cost-comparison) | | | |
| EBRT | | | Costs: IMRT > EBRT | |
| **Breast – Partial Breast Radiation** | 1 SR (1 RCT, 3 case series, 1 cost comparison) | | | |
| KQ # 1 Efficacy | 3 case series | | | |
| No comparator | | | | Tumor recurrence |
| KQ #2 Harms | 1 RCT, 3 case series | | | |
| No comparator | | | | Grade 1 or 2: breast cosmesis, breast edema, breast pain, telangiectasia, erythema, hyperpigmentation, breast-chest wall tenderness, fibrosis<br>Grade 3: telangiectasia |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | 1 cost comparison | | | |
| EBRT | | | Costs: IMRT > EBRT | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| **Female Pelvis – Cervical Cancer** | 2 SR (2 cohort, 1 case series), 1 cohort, 3 case series | | | |
| KQ # 1 Efficacy | 2 SR (2 cohort, 1 case series), 1 cohort, 3 case series | | | |
| EBRT | | | ↑ OS<br>↑ DSS<br>↔ 1-yr locoregional control<br>↔ Complete or partial response (stage IIB – IIIB) | |
| No comparator | | | | 3-yr OS, 3-yr DFS, 3-yr pelvic failure, 3-yr distant failure (stage I-IVA) |
| KQ #2 Harms | 2 SRs (2 cohort, 1 case series), 1 cohort, 3 case series | | | |
| EBRT | | | ↓ Late GI toxicity<br>↔ Late GU toxicity<br>↓ Grade 3 and 4 GI symptoms<br>↓ Grade 3 and 4 GU symptoms | |
| No comparator | | | | Acute Grade 3 symptoms (stage I-IVA), chronic Grade 3 GI symptoms, chronic Grade 3 CU |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| | | | | symptoms<br>Acute ≥ Grade 3 toxicities in leukocytes, lyphopenia, platelets, constitutional fatigue, weight loss, GI, anorexia, diarrhea, renal/GU fistula (female genital tract) |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Female Pelvis – Endometrial Cancer** | 1 cohort | | | |
| KQ # 1 Efficacy | 1 cohort | | | |
| EBRT | | | | 2-yr OS (results were pooled)<br>2-yr DFS (results were pooled) |
| KQ #2 Harms | | | | |
| EBRT | | | | ↓ Acute toxicities<br>↓Small bowel obstruction<br>↑Chronic proctitis |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost-Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| **Female Pelvis – Paraaortic lymph node metastases** | 1 cohort, 2 case series | | | |
| KQ # 1 Efficacy | 1 cohort, 1 case series | | | |
| EBRT | | | | ↑ 2-yr survival<br>↑ 3-yr survival |
| No comparator | | | | 1-yr OS, 2-yr OS |
| KQ #2 Harms | 1 cohort, 2 case series | | | |
| EBRT | | | | ↓ Acute and chronic GI and GU symptoms (i.e., leucopenia, enteritis, enterocolitis) |
| No comparator | | | | Acute Grade 1 GI disorders, acute Grade 2 GI disorder, liver dysfunction, late Grade 1 and 2 disorders |
| 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 Cancer** | 5 SRs[20], 1 RCT, 2 cohort, 45 case series, 1 cost study | | | |
| KQ # 1 Efficacy | 8 SRs, 1 RCT, 1 cohort | | | |
| EBRT | | ↑ QoL (xerostomia- | ↔ OS | |

[20] With multiple overlapping primary studies included

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy**<br>Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○<br>**Moderate** | ⊕⊕○○<br>**Low** | ⊕○○○<br>**Very Low** |
| | | related) | ↔ tumor control<br>↔ local PFS (oropharngeal cancer)<br>↑ 5-yr lcoal RFS (nasopharngeal cancer)<br>↔ 5-yr nodal relapse free survival<br>↔ 5-yr distant metastasis free survival<br>↔ 5-yr DFS<br>↕ QoL (for other outcomes) | |
| KQ #2 Harms | 6 SRs, 1 RCT, 1 cohort, 45 case series | | | |
| EBRT | | ↓ ≥ Grade 2 xerostomia | | ↔ Trimus<br>↔ Sensorineural hearing loss<br>↔ Osteonecrosis |
| No comparator | | | | Nausea, vomiting and fatigue, local symptoms including dermatitis and mucositis, xerostomia, dysphagia, laryngeal symptoms |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| KQ #4 Cost and Cost Effectiveness | 1 cost study | | | |
| EBRT | | | Costs: IMRT > EBRT<br>↓ Direct costs for experienced treatment centers compared to centers initiating IMRT | |
| **Lung Cancer - NSCLC** | 3 SR (2 cohorts), 6 case series | | | |
| KQ # 1 Efficacy | 1 SR (1 cohort), 5 case series | | | |
| EBRT | | | ↑ OS<br>↔ Locoregional PFS<br>↔ Distant metastasis-free survival | |
| No comparator | | | | OS, 2-yr and 3-yr survival, distant metastasis free survival, 2-yr DFS, local PFS |
| KQ #2 Harms | 3 SRs (2 cohort), 6 case series | | | |
| EBRT | | | ↓ ≥ Grade 3 pneumonitis | |
| No comparator | | | | ≥ Acute and late Grade 3 pneumonitis, Grade 3 pulmonary fibrosis, Grade 3 pulmonary fibrosis, ≥ acute |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| | | | | Grade 3 esophagitis, Grade 2 and 3 esophageal strictures, Grade 2 esophageal toxicity, ≥ Grade 2 lung toxicity, Grade 3 dysphagia, Grade 3 skin toxicity, Grade 1-3 radiation pneumonitis, death from radiation pneumonitis |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Lung Cancer – Pleural Mesothelioma** | 1 SR (2 case series), 2 case series | | | |
| KQ # 1 Efficacy | 1 SR (1 case series), 2 case series | | | |
| No comparator | | | | 1yr to 5yr DFS, 1yr to 5yr DSS, local recurrence |
| KQ #2 Harms | 1 SR (2 case series) | | | |
| No comparator | | | | Fatal radiation pneumonitis, acute Grade 3 radiation-induced esophagitis, acute toxicities of nausea, vomiting, and fatigue, late death from liver toxicity and pericarditis |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| KQ #4 Cost and Cost Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Lung Cancer – SCLC** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | Actuarial OS, RFS |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | Acute pneumonitis, esophagitis |
| 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 SRs, 7 cohorts, 19 case series | | | |
| KQ # 1 Efficacy | 3 SRs, 7 cohorts | | | |
| EBRT | | | ↔ bDFS (30 months)<br>↑ bDFS (60 months)<br>↔ Tumor control<br>↓ Recurrence<br>↕ QoL | |
| KQ #2 Harms | 3 SR, 6 cohorts, 19 case series | | | |
| EBRT | | ↓ GI toxicities | ↓ GU toxicities<br>↓ Hip fracture<br>↔Erectile dysfunction | |
| KQ #3 Subgroups | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **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 | 1 SR | | | |
| | | | | ↓ Cost-effectiveness |
| **Sarcoma** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | Local recurrence |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | Nausea, fatigue, dry mouth, pharyngitis or esophagitis, pain, Grade 4 skin toxicity |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Other Cancers – Sacral Chordoma** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | Actuarial 1-, 2-, and 5-yr OS; 1-, 2-, and 5-yr DSS; actuarial 1-, 2-, and 5-yr DSS |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | Diarrhea, bladder irritation, erthema, hyperpigmentation. No harms > Grade 3 reported. |
| KQ #3 Subgroups | | | | |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **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 costs or cost-effectiveness identified.* | | | | |
| **Other Cancers - Skin** | 1 case series | | | |
| KQ # 1 Efficacy | 1 case series | | | |
| No comparator | | | | Disease recurrence |
| KQ #2 Harms | 1 case series | | | |
| No comparator | | | | Grade 1 or 2 erythema |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Other Cancers - Thyroid** | 2 cohort, 1 case series | | | |
| KQ # 1 Efficacy | 1 cohort, 1 case series | | | |
| EBRT | | | ↔ All survival measures | |
| No comparator | | | | 2-yr local PFS, 2-yr OS |
| KQ #2 Harms | 2 cohort, 1 case series | | | |
| EBRT | | | | ↓ Late morbidity (e.g., esophageal structure, laryngeal stenosis, laryngeal edema, chronic dysphagia) |
| No comparator | | | | Acute mucositis, pharyngitis, |

| Procedure | | Strength of Evidence[18] | | |
|---|---|---|---|---|
| **Malignancy** Comparator | **# of SRs (# included studies in SRs), # of subsequently published studies** | ⊕⊕⊕○ **Moderate** | ⊕⊕○○ **Low** | ⊕○○○ **Very Low** |
| | | | | dysphagia, xerostomia, skin toxicity, laryngeal toxicity |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |
| **Other Cancers – Spinal Metastases** | 5 case series | | | |
| KQ # 1 Efficacy | 3 case series | | | |
| No comparator | | | | OS, tumor recurrence, QoL |
| KQ #2 Harms | 5 case series | | | |
| No comparator | | | | Spinal fractures, Grade 1 to 2 skin reactions, Grade 2 esophagitis, myelitis, acute symptoms (pharyngitis, fatigue, diarrhea) |
| KQ #3 Subgroups | | | | |
| *No studies on subpopulations identified.* | | | | |
| KQ #4 Cost and Cost Effectiveness | | | | |
| *No studies on costs or cost-effectiveness identified.* | | | | |

## Appendix F. Evidence Tables by Malignancy

### Abdominal Cancers

*Anal Cancer*

| ***Reviews*** | | | | | |
|---|---|---|---|---|---|
| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Veldeman (2008) Systematic review **Anal Cancer** | 1 non-comparative case series N=17 | Intervention: IMRT Comparator: none Follow-up: NR | 2-year overall survival (91%); disease-free survival (65%); colostomy-free survival (82%) | Grade ≥ 3 acute non-haematological toxicities | Fair<br><br>13 pts. received concurrent chemotherapy, possible confounder |
| Staffurth (2010) Systematic review **Anal Cancer** | 1 comparative study N = 59 | Intervention: IMRT Comparator: 3DCRT Follow-up: NR | NR | Less diarrhea and skin/mucosal toxicity in IMRT cohort | Poor |
| De Neve (2012) Systematic review **Anal Cancer** | 2 studies N = 105 | Intervention: IMRT Comparator: NR Follow-up: NR | NR | Significant reductions in acute Grade > 2 nonhematologic toxicity, skin and mucosal eruptions in the female genital area; acute Grade 2 diarrhea | 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** |
| Call (2011) Case series **Anal Cancer** | n = 34<br><br>Primary<br><br>Median age 59 (46-85). | Pts consecutively treated between June 2005 and Jan. 2009 at Mayo clinic for squamous cell | Pts treated with both chemotherapy (FU or FU+MCC) and Intensity | IMRT dose median 50.40 Gy (48.60-57.60 Gy) in 25-32 | Study looked at results from relatively low fractional IMRT doses (<1.80 Gy.) Three year freedom from disease relapse 80% (27 pts.) 7 pts (20%) had treatment failure: 3 pts local | No harms reported. One patient died of sepsis associated with metastatic anal cancer but death was not tx related | Poor<br><br>No analysis of confounding variables, |

| 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** |
| | Chemo: Fluorouracil (FU) only: 1 pt (2.9%), FU + Mitomycin C (MCC): 33 pts (97%) Cancer stage: T1: 10 (29.4%), T2: 18 (52.9%), T3: 4 (11.8%), T4: 2 (5.9%), N0: 20 (58.8%), N1: 7 (20.6%), N2: 3 (8.8%), N3: 4 (11.8%), M0: 34 (100%) | carcinoma of the anus | Modulated Radiation Therapy (IMRT)<br><br>F/U: scheduled not specified. Median follow-up 22 months | fractions of 1.80 - 2.25 Gy | failure (8.8%), 1 pt (2.9%) regional lymph node failure and 4 pts (11.8%) had cancer recur at distant sites. One patient had both local failure and distant failure. 31 patients (91.2%) alive at manuscript preparation. 3 pts died, 2 were cancer free at death and one pt died of sepsis associated with metastatic anal cancer 10 months after diagnosis. Median survival 23 months. Estimated 3-year survival 87%. | | small sample size, no comparator |
| Hauerstock (2010)<br>Case series<br>**Anal Cancer** | n = 34<br><br>Median age: 47 yrs (range, 30-72). Male (30), female (4); on HAART (27); CD4 ≥350 and VL ≤700 (11), CD4 <350 and VL > 700 (19), CD4/Vl unknown (4); Stage I (5), stage II (12), stage III (17) | HIV positive pts with anal cancer treated w/ concurrent chemo bt 1998 and 2008 at St. Luke's Roosevelt Hospital and Beth Israel Medical Center. Histologically confirmed invasive squamous cell carcinoma | EBRT (either 3DCRT [21 pts] or IMRT [13 pts]) and concurrent chemo<br><br>F/U: response evaluated 8 wks after tx by direct inspection and physical exam | Once-daily fractions of 1.8 Gy<br><br>Median dose 54 Gy, range 45-59.4<br>Median duration 55 days, range 38-94 | 3-yr RFS 63%<br>3-yr OS 69%<br><br>Early stage (I-II) associated with improved 3-yr OS (p=0.02)<br><br>No significant difference between IMRT and 3DCRT for 3-year local control or OS | Grade ≥ 1 dermatologic toxicity reported in all pts: Grade 1 (1), Grade 2 (16), Grade 3 (16), Grade 4 (1)<br><br>Hematologic toxicity: Grade 1 (10), Grade 2 (8), Grade 3 (7), Grade 4 (5)<br><br>3 pts required hospitalization for febrile neutropenia during tx. No tx-related deaths.<br><br>No pts reported ≥ Grade 3 chronic toxicities. | 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** |
| Kachnic (2012) Case series **Anal Cancer** | n = 43<br><br>Primary and metastatic<br><br>Males 14, females 29. T0: 1 (2%), T1: 7 (16%), T2: 21 (49%), T3: 3 (9%), T4: 4 (5%), N0: 23 (53%), N1: 8 (19%), N2: 10 (23%), N3: 2 (5%), Stage I: 7 (16%), II: 16 (27%), III: 18 (42%), IV: 2 (5%), HIV+: 9 (21%), on chronic immunosuppression: 5 (12%) | Pts tx consecutively at clinic between Aug. 2005 and May 2009 for squamous cell carcinoma of the anal canal. Cancer stages T1-4, N0-3 and M0-1 | Dose-painted intensity modulated radiation therapy (DP-IMRT) + concurrent chemotherapy<br><br>F/U: Every four weeks after tx through 12 weeks if signs of residual disease, every three months for two years and then every 6 months. Median follow-up 24 months (0.6-43.5) | T2N0 patients: 42 Gy, 1.5 Gy/fraction (fx) to elective nodal planning target volume (PTV) and 50.4 Gy, 1.8 Gy/fx to anal tumor PTV. T3-4N0-3 patients: 45 Gy, 1.5 Gy/fx to elective nodal PTV and 54 Gy, 1.8 Gy/fx to anal tumor and metastatic nodal PTV > 3 cm in size with 50.4 Gy, 1.68 Gy/fx to nodal PTV ≤ 3 cm | Local control at 2-years 95%. 2-year metastasis free survival 92%. 2-year overall survival 94%. 2-year colostomy free survival 90%. No univariate or multivariate analysis with confounding variables | ≥ Grade 3 desquamation: 4 pts (10%), ≥ Grade 3 GI toxicity: 3 (7%). ≥ Grade 3 GU toxicity: 3 (7%). ≥ Grade 3 hematological toxicity: 26 (61%.) On univariate and multivariate analysis, only the presence of immunosuppresive comorbidity and multiagent chemotherapy were predictive of ≥ Grade 3 toxicity | Poor<br><br>Small sample size, retrospective analysis, no analysis of outcomes by confounding variables |

| 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** |
| | | | | in size. | | | |

*Gastric*

| 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** |
| Boda-Haggeman (2009)<br>Cohort study<br>**Gastric cancer** | 3DCRT (n= 27) or IMRT (n=33) consecutive patients who were post resection for gastric cancer; cohorts were serial (3DCRT until IMRT introduced); chemotherapy regimen also changed | Gastric cancer post resection | Intervention: 3DCRT and IMRT<br>Comparator: same<br>Follow-up: 18-22 months | | Actuarial 2 year survival:<br>3DCRT 37%; IMRT 67% (p=0.049<br>Actuarial Disease free survival:<br>3DCRT 26%; IMRT 52% (p = 0.02) | Renal Toxicity:<br>Worsening of Creatinine levels in first year: 3DCRT; 16% IMRT 7% (p= 0.09)<br>No Grade 2 or higher renal toxicity in either group. | Poor<br><br>Historical cohorts; chemotherapy regimen different for two groups and within the IMRT group. |
| Minn (2010)<br>Cohort study<br>**Gastric cancer** | 3DCRT n= 26<br>IMRT n = 31<br>patients with non-metastatic gastric cancer. Cohorts were separated by time (3DCRT performed earlier than IMRT as | Non-metastatic cancer; 4 patients (2 each 3DCRT and IMRT) excluded because of failure to complete radiation treatment. | Intervention: IMRT<br>Comparator: 3DCRT<br>Follow up: Median 1.3 years for both groups | 45 Gy for both groups | 3DCRT / IMRT / p value<br>2 year overall survival: 51% / 65% / 0.5<br>Loco-Regional control: 81% / 83% / 0.9 | 3DCRT / IMRT / p value<br>Acute Grade ≥2 GI toxicity: 61% / 61%<br>Pre/post treatment creatinine levels: 0.8/0.8 / 0.8/1.0 / 0 .02 | Poor<br><br>Cohorts are historically assigned. Chemotherapy not completed by all participants. Confounders not included |

| *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** |
| | preference for IMRT increased). 53/57 patients received chemotherapy | | | | | | in analysis. |

*Liver*

| *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** |
| Chi (2010)<br>Case series<br>**Liver Cancer** | n = 23<br><br>Primary<br><br>Males 18, females 5. median age 64 (43-78). Performance status 0-1: 22 (96%), 2: 1 (4%). Liver cirrhosis Child A: 15 (65.2%), Child B: 8 (34.8%). Etiology of liver disorder: HBV: 16 (69.6%), HCV: | Pts tx between Feb 2007 and June 2008 for hepatocellular carcinoma who were not candidates for surgery or transarterial chemoembolization (TACE) | image guided intensity modulated radiotherapy (helical tomotherapy) with antiangiogenic therapy (sunitinib)<br><br>F/U: weekly during tx and monthly thereafter. Median follow up 16 months (6-22 months) | Median gross tumor volume (GTV) dose 52 Gy in 15 fractions. Sunitinib 25 mg per day 1 wk prior to RT, during RT and 2 wks post RT. 13 pts continued drug until progression | Median survival 16 months, 1 yr survival rate 70%. On multivariate analysis only significant prognostic factor for survival whether pt on maintenance sunitinib | Anorexia grade 1-2: 18 (78.3%). Nausea and vomiting grade 1-2: 15 (65.2%). Hepatitis grade 1-2: 15 (65.2%), Grade 3: 1 (4.3%). Pancreatisis grade 3: 1 (4.3%). Upper GI bleeding grade 1-2: 1 (4.3%), grade 3: 2 (8.7%). Anemia grade 1-2: 3 (13%). Leukopenia grade 1-2: 3 (13%), grade 3: 1 (4.3%). Thrombocytopenia grade 1-2: 9 (39.1%), grade 3: 5 (21.7%), grade 4: 1 (4.3%). fever grade 1-2: 1 (4.3%). fatigue grade 1-2: 0 (87%). | Poor<br><br>Small sample size, retrospective, multiple tx, didn't control for age or performance status |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 6 (26.1%), No HBV or HCV: 1 (4.3%). Intrahepatic tumor type: Massive (>5cm, margin clear): 8 (34.8%), multinodular 2-4 GTV: 11 (47.8%), infiltrative (>50% liver, margins poorly defined): 4 (17.4%). AFP elevation: yes: 21 (91.3%), no: 2 (8.7%). AJCC tumor stage T1-2: 6 (26.1%), T3-4: 17 (73.9%). Previous tx: none: 9 (39.1%), TACE: 12 (52.2%), TACE + percutaneous ethanol intratumor injection (PEIT): 2 | | | | | | |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (8.7%). Extrahepatic tumor: yes: 5 (21.7%), no: 18 (78.3%) | | | | | | |
| Kang (2011)<br>Case series<br>**Hepatocellular Cancer** | n = 27<br><br>Median age, 47 years (range 30-70); men, 23; women, 4; Child-Pugh class A, 19; class B, 9; T1, 3; T3, 21; T4, 3; N0, 22; N1, 5 | Advanced hepatocellular carcinoma without distant metastasis; not candidate for local ablative therapy, transarterial chemoembolization, or hepatic arterial infusion | Intervention: IMRT<br><br>Comparator: none<br><br>F/U: Median 5 months (range 2-82) | Median dose, 50.4 Gy (range 45-64.8) with 1.8 Gy daily | Median progression-free time after RT: 3 mos<br>Median overall survival time: 5 mos<br>1-yr progression-free survival rate of responders (20.4%) and non-responders (0%) | Hepatic toxicity, 14 patients (51.9%). IMRT only: grade 0, 1 patient (3.7%); grade 1, 2 patients (7.4%); grade 2, 1 patient (3.7%). IMRT + other treatment: grade 0, 1 patient (3.7%); grade 1, 2 patients (7.4%); grade 2, 3 patients (11.1%); grade 3, 2 patients (7.4%); grade 5, 2 patients (7.4%). | Poor<br><br>Many patients treated with other modalities during or immediately after radiotherapy |
| McIntosh (2009)<br>Case series<br>**Liver Cancer** | n = 20<br><br>Primary<br><br>Males 17, females 3. Median age 60.8 (43-79). AJCC tumor T1: 3 (15%), T2: 4 (20%), T3: 13 (65%). AFP IU/mL: >200: 9 (45%), <200: 11 | Pts t between Oct. 2005 and Dec. 2007 with IMRT and capecitabane for primary, unresectable hepatocellular carcinoma. Excluded patients with extrahepatic disease, Child-Pugh class C disease or KPS score < 60. | intensity modulated radiation therapy (helical tomotherapy) and concurrent capecitabane<br><br>F/U: NR | minimum dose for 19 pts 50 Gy in 20 fractions over 4 weeks. 1 pt who had previously received RT of 30 Gy in 12 fractions received IMRT boost | Local control evaluable for 16 pts. Partial response in 1 pt (6.3%), stable disease in 14 pts (87.5%) and disease progression in 1 pt (6.3%). Actuarial one-year survival and median survival for Child-Pugh Class A pts: 73% and 22.5 ± 5.1 months. For Child-Pugh class B: 11% and 8 ± 3.3 months respectively | Acute abdominal pain grade 1: 3 pts (15%), nausea grade 1: 6 (30%), grade 2: 1 (5%). Esophagitis grade 1: 3 (15%), diarrhea grade 1: 4 (20%), fatigue grade 1: 8 (40%), grade 2: 6 (30%). Grade changes from baseline in liver enzyme levels: alkaline phosphatase 1 grade change: 2 pts (10%). Bilirubin: 1 grade change: 4 pts (20%), 2 grades change: 1 (5%). Increase in asparate aminotransferase: 4 (20%), increase in alanine aminotransferase: 2 (10%). 1 grade change from baseline thrombocytopenia: 5 (25%), 2 grade change: 1 (5%). 1 pt (5%) clinical | Poor<br><br>Small sample size, no analysis on outcomes, conflict of interest |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (55%). Baseline bilirubin: within normal limits: 12 (60%), Upper limit normal (ULN) to 2.5 ULN: 2 (10%), >2.5 - 5xULN: 4 (20%), >5-20xULN: 1 (5%). Childs-Pugh Class A: 11 (55%), Class B: 9 (45%). Serum hepatitis diagnosis: Hep B: 2 (10%), Hep C: 10 (50%), no viral markers: 8 (40%). portal vein thrombosis: thrombosed: 8 (40%), compressed but patent: 1 (5%), no thrombosis: 11 (55%). Transarterial | | | of 30 Gy in 12 fractions. Pts given chronomodulated capecitabane 1g in morning and 2g at night | | symptoms of radiation pneumonitis 3 months post tx. 4 hospitalizations: 1 pt (5%) encephalopathy, 1 pt melena secondary to gastric ulcer, 1 pt acute hepatitis, 1 pt sepsis. Hepatitis and sepsis pts later died. | |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | chemoembolization (TACE) performed: 11 (55%). # of TACE procedures, range: 1-3. Tumor size before RT: mean 9 cm (1.3-17.4 cm) | | | | | | |

*Pancreas*

| Reviews | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Veldeman (2008) Systematic review **Pancreatic Cancer** | 4 non-comparative case series<br>N = NR | Intervention: IMRT<br>Comparator: NR<br>Follow-up: NR | NR | NR | Fair<br><br>IMRT in combination with chemotherapy, one study closed due to excessive toxic effects |

| Individual studies (published after review) |
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| Reference Study Design Malignancy | Sample size and Pt Characteristics | Patient Selection Criteria | Intervention Comparator Follow-up | Dose | Outcomes Assessed Main Findings | Harms | Quality Comments |
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| Abelson (2012) Case series **Pancreatic Cancer** | n = 47<br><br>Primary<br><br>Group 1: pts tx with IMRT adjuvant to surgery: 29 (61.7%), Group 2: pts tx with definitive IMRT.: 18 (38.3%) Male/Female: G1: 17/12, G2: 12/6. Grade: well differentiated: G1: 4 (14%). G2: 1 (6%). Moderately differentiated: G1: 14 (48%), G2: 1 (6%). Poorly differentiated: G1: 9 (31%), G2: 2 (11%). NA: G1: 2 (7%), G2: 14 (78%). Stage I: G1: 2 (7%), Stage II: G1: 27 (93%). Stage III: G2: 18 | Pts treated between Jan. 2003-June 2008 with IMRT and chemo for pancreatic cancer. Pts excluded if they had metastatic disease beyond regional lymph nodes. 3 pts excluded for abbreviated RT | Intensity modulated radiation therapy (IMRT) given to 29 pts (61.7%) adjuvant to surgery and to 18 pts (38.3%) as definitive therapy. All pts received concurrent 5-fluorouracil chemo. 18 pts (38.3%) also received chemo prior to RT and 14 pts (29.8%) received chemo post RT<br><br>F/U: weekly during tx, at 6-8 wks following tx, every 4 months first year, every 6 months for next two | median dose for adjuvant patients: 50.4 Gy (44-55.8 Gy). Median dose for definitive patients: 54.0 Gy (39.6-59.4 Gy) | For adjuvant patients, 1 and 2-year overall survival (OS) was 79% and 40%. Median survival 1.7 years. 1 and 2 year recurrence free survival (RFS) was 58% and 17%. 1 and 2-yr local-regional control (LCR) was 92% and 80%. For definitive patients, 1-yr OS, RFS and LCR were 24%, 16% and 64% respectively. At last follow-up, all definitive patients had died. | Grades 0-2 acute anorexia/dehydration, diarrhea and nausea and vomiting experienced by 97%-100% of patients. Grade 3 or higher acute complications in 4 pts (8.5%). 1 pt (2%) grade 3 cholangitis. 1 pt (2%) grade 3 small bowel obstruction requiring surgery. 1 pt (2%) grade 3 biliary stent blockage requiring procedure and 1 pt (2%) grade 5 diarrhea/enteritis followed by ileus. Late complications in 4 pts (8.5%): 1 pt (2%) grade 3 perforation of stented common bile duct. 1 pt (2%) grade 3 small bowel obstruction requiring surgery. 2 pts (4%) grade 3 biliary stricture requiring drain | Poor<br><br>Various txs, no analysis with confounding factors |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (100%). Location: head: G1: 24 (83%), G2: 14 (78%). Body: G1: 4 (14%), G2: 3 (17%). Tail: G1: 1 (3%), G2: 1 (6%). Median pre-RT CA 19-9: G1: 16. G2: 1,444. Surgery in group 1: Whipple: 24 (83%), Distal Pancreatectomy: 5 (17%). Lymph node: positive: G1: 21 (72%), G2: 7 (39%). negative: G1: 8 (28%), G2: 11 (61%). Surgery margins in Group1: positive: 17 (59%). close (<3mm): 5 (17%), negative: 7 (24%). | | years and then annually. Median follow-up for all patients 15.7 months (5.3-66.0) and for living patients 29.3 months (12.6-66.0) | | | | |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| 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**<br>1.Rad costs: $0 / $13412 / $25366 / $7146<br>2.Chemo costs: $13400 / $13400 / $13400 / $13400<br>3.End of life costs: $13040 / $13040 / $13040 / $13040<br>4.Cost of Rad Toxicity event: $15248 / $15248 / $15248 / $15248<br>5.Prob of Rad Toxicity event: 0 / 0.016 / 0.0061 / 0.009<br><br>**Incremental cost effectiveness ratio (ICER)**<br>Chemo & SBRT vs. Chemo alone: ICER = $69,500/QALY<br>EBRT & chemo vs. chemo alone : ICER = $126,800/QALY<br>IBRT & chemo vs. EBRT & chemo: ICER = $1,584,100/QALY | | | Fair<br><br>Values used for clinical effectiveness based on expert opinion |

*Rectal*

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Li (2012) Case series **Rectal Cancer** | n = 63<br><br>Rectal adenocarcinoma, primary<br><br>Males 41 (65.1%), females: 22 (34.9%). Median age: 58 (25-75). ECOG | pts with histologically confirmed rectal adenocarcinoma w/I 10 cm of anal verge tx between May 2007 and Dec. 2009. No evidence of distant metastases. Stage T3 or resectable. T4 | pre-operative concomitant boost intensity modulated radiation therapy (IMRT) combined with capecitabine chemo | 50.6 Gy to Gross Target Volume (GTV) and 41.8 Gy to Clinical Target Volume (CTV). Tx in 22 fractions | complete pathological response in 19 of 58 eligible patients (32.8%). Two-year progression free survival (PFS) and overall survival (OS) were 90.5% (95% CI: 82.5-98.5) and 96.0% ((95% CI: 90.5-100) | Grade 3 diarrhea: 6 (9.5%), grade 3 radiation dermatitis: 2 (3.2%), grade 3 neutropenia: 1 (1.6%) | poor<br><br>Did not report analysis with confounding variables |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | performance score: 0: 13 (20.6%) 1: 50 (79.4%). Tumor stage: T2: 3 (4.8%), T3: 54 (85.7%), T4: 6 (9.5%). Node stage: N0: 11 (17.5%), N1: 18 (28.6%), N2: 34 (53.9%). Tumor differentiation : well differentiated: 15 (23.8%), moderately diff.: 31 (49.2%), poorly diff.: 6 (9.5%). Uncertain: 11 (17.5%). Distance from anal verge in cm: ≤5: 54 (85.7%), 5.1-10: 9 (14.3%). median distance: 4.0 | with any N status or any T with N1 or N2 disease. T2N0 eligible if tumor w/I 5 cm of anal verge. WHO performance status of 0 or 1 with adequate liver, kidney and bone marrow function. Pts excluded for prior chemo or pelvic RT, a hx of other malignancies w/ 5 yrs, acute obstructive symptoms, unresectable tumors, sensitivity to fluoropyrimidines or unable to receive chemo | F/U: weekly during tx, every 3 months first year, every 6 months next 2 years and annually for years 4 and 5 | of 2.3 Gy and 1.9Gy respectively, 5 times a week over 30 days. Capecitabine given 825 mg/m2 orally twice daily, 5 days a week during RT | | | |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | cm. | | | | | | |

## Brain Cancer

| Reviews | | | | | |
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| Reference<br>Study Design<br>Malignancy | # of Studies & Subjects | Intervention<br>Comparator<br>Follow-up | Outcomes Assessed<br>Main Findings | Harms | Quality<br>Comments |
| Amelio (2010)<br>Systematic review<br>**Glioblastoma** | 8 studies<br>Sample size range 13 to 58<br>N = 204 | Intervention: IMRT.<br>Comparator: none<br>F/U: 8.8 mos to 24 mos | Overall, the eight studies included 204 patients with glioblastoma multiforme stage I and II; chemotherapy was included in six of eight studies. Studies included three retrospective studies, one prospective phase I and four prospective phase II single institution studies.<br><br>1-yr OS range 30% - 81.9%<br>2-yr OS range 0% -55.6%<br>Median OS range 7 – 24 months<br>1-yr PFS range 0% - 71.4%<br>2-yr PFS range 0% - 53.6%<br>Median PFS range 2.5 – 12 months | Almost all patients (96%) were able to complete the treatment regimen. Acute toxicity was reported as negligible. Grade 3 toxicity occurred in 6-13% and grade 4 toxicity in 3%. | Fair<br><br>SR authors rate quality of underlying articles as low. |
| Staffurth (2010)<br>Veldeman (2008)<br>Systematic review<br>**Glioblastoma, anaplastic astrocytoma, medulloblastoma** | 3 comparative case series studies<br>N =153 | Intervention: IMRT<br>Comparator: 3DCRT<br>F/U: NR | Note: The Staffurth SR reported different tumor types for tumor control, patient survival and toxicity.<br>**Tumor control:** In 30 patients with *glioblastoma multiforme*, there was no improvement in tumor control with IMRT compared with EBRT.<br>**Survival:** 25 patients with *anaplastic astrocytoma* treated with IMRT were compared with 60 patients treated with EBRT | In 26 children with *medulloblastoma*, IMRT was reported to reduce the rate of ototoxicity compared to EBRT. | Poor – Staffurth (2010)<br><br>Fair – Veldeman (2008) |

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | (historical control group). There was a significant improvement in 1- and 2-year control, progression free survival and overall survival in the IMRT group. | | |
| De Neve (2012) Systematic review **Medulloblastoma** | 1 case series N = 25 | Intervention: IMRT Comparator: Non-IMRT F/U: NR | No difference in neuropsychological impairment found between the two groups using a battery of neuropsychological measures | NR | Poor |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Cho (2011) Case series **Gliomas** | n = 40<br><br>Median age, 54 years (range 21-75); men, 22; women, 18; World Health Organization grade III, 14; grade IV, 26; astrocytoma, 33; oligodendroglioma, 4; mixed oligoastrocytoma, 3 | High-grade glioma | IMRT<br><br>F/U: Median 13.4 months (range 3.7-55.9) | Planning gross tumor volume: Daily dose of 2.4 Gy in 25 fractions for 5 weeks for total dose of 60 Gy. Planning clinical target volume: Daily doses of 2.0 Gy in | Median OS: 14.8 mos (95% CI 8.2-21.4)<br>Median PFS: 11.0 mos (95% CI, 7.1-15.0)<br>1-yr OS (64%), 2-yr OS (42%)<br>1-yr PFS (46%), 2-yr PFS (31%) | Edema: Grade 2, 2 patients (5%); grade 3, 1 patient (3%); Worsening of neurological symptoms: Grade 1, 4 patients (10%); Late effect (unspecified): Grade 4, 10% | Fair |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | 25 fractions for 5 weeks for total dose of 50 Gy | | | |
| Estall (2009) Case series **Meningioma** | n = 128<br><br>Age 20-82. 65% >50 years. Female: Male 2.2:1. 79% had Grade 1 disease, 16% grade 2, and 8% Grade 3. 31% received radiotherapy alone. 69% received post-op radiotherapy. | All patients with meningioma referred to oncology centre between 11/1/1996 and 10/31/2006 | Intervention : EBRT<br><br>F/U: Median 5.3 y (2.1-11.9 y) | 50-60 Gy in 1.67-2.0 Gy/fraction | 15% (19/128) developed progressive disease. 85% local control rate at median of 5.3 years. 93% local control rate for Grade 1 disease. 82% survival rate. 24/128 died. Death was due to disease in 9/24 (37%) of patients. 78% of disease-related deaths had non-benign pathology. Disease-specific death rate 7%. OR of death or recurrence for Grade 2/3 disease relative to Grade 1 disease= 16.79 (95% CI 4.91-57.39). Radiation dose did not significantly impact local control after adjusting for disease severity. Local control better in radiotherapy alone, although not significant after adjusting for Grade. Age had no effect on recurrence or death. Gender: 30% of men and 8% of women relapsed. 10% of men and 3.4% of women died. This was not significant after adjusting for severity. | NR | Good<br><br>Comparator Study only. Harms not assessed. |
| Mackley | n = 34 | No formal | IMRT | 45 Gy-49.3 | Hormonally active tumors, | Short term toxicity (6 month period | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| (2007)<br>Case series<br>**Pituitary Adenoma** | Median age: 51, range 70-84; Gender: 40% female; median Karnofsky performance status at time of treatment: 90, range 70-900; previously treated with surgery 88%; Secretory tumors treated with hormonal antagonists; non-functional tumors, 73%; Symptoms prior to treatment included: visual effects, 24%; headache, 21%; neurocognitive changes, 12%; other neurological defects, 9%; fatigue, 6%; cerebrospinal fluid, 3% | eligibility criteria. Common reasons for IMRT included progression of symptoms (67%) patients), residual disease after surgery (61%) of patients), medical inoperability (12% patients) | treatment using Peacock system from NOMOS using 6MV beam energy<br><br>F/U:Median 42.5 months (range, 12-80 months) | Gy in 23-29 fractions | overall biochemical response rate: 100% (complete response rate 22%, partial response rate 78%) | n=31)<br>Fatigue: 65%<br>Headache: 61%<br>Nausea or vomiting: 29%<br>Visual complaints: 29%<br>Other neurological complaints: 29%<br>Alopecia or Skin erythema: 13%<br>cerebrospinal fluid: 3%<br>Anxiety attack: 3%<br>Epistaxis: 3%<br>Dry eyes: 3%<br>Excess tearing: 3%<br>Long term toxicity (≥12 months, n=29),<br>Unrelated mortality: 2 patients<br>Cognitive changes (subjective): Overall, 4 patients (13%); short-term memory complaints, 3 patients; dementia, 1 patient<br>Visual decline: overall, 3 patients (10%); Bilateral optic neuropathy, 1 patient; blurry vision, 2 patients<br>Cranial nerve deficit: 3 patients 10%<br>Required new hormone replacement therapy post radiation: 40% | Toxicity data was not systematic-ally gathered or scaled |
| Milker-Zabel (2007)<br>Case series | n = 94<br><br>Median age 57.2 | Meningioma treated with IMRT | Intervention-IMRT.<br>Comparator- | Median 57.6 Gy (50.4-62 | **Radiologic response:** Local control 93.6% at median follow-up of 9 months (3-46 months). | **Harms** (possibly due to disease or treatment): 4.3% had worsening of neurologic symptoms, 2 patients | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| **Meningioma** | (13.3-79.2). 33% sphenoidal, 21.3% petroclival, 9.6% cavernous sinus, 6.4% sella, 5.3% cerebello-pontine angle, 24.4% other. 54.3% benign, 9.5% benign aggressive, 4.2% atypical/ malignant, and 31.9% unknown histology. | | None<br><br>F/U: Median 4.4 years (1.6-82.7 months). 97% followed for more than one year, 75% followed for more than 3 years. | Gy). Delivered in 32 fractions over 6-7 weeks. | 73.4% had stable disease, 20.2% had reduction in tumor volume, 6 patients had local tumor progression at median of 22.3 months (15.8-62 months). **Clinical response:** 39.4% had improvement in neurologic deficits, 4.3% had worsening of neurologic symptoms, 2 patients developed new neurologic symptoms, 1 patient experienced treatment-induced vision loss 9 months after re-radiation of a Grade 3 meningioma. Survival: Recurrence free survival was 96.9% at 3 years and 94.8% at 5 years. | developed new neurologic symptoms. **Harms from treatment**: 1 patient experienced treatment-induced vision loss 9 months after re-radiation of a Grade 3 meningioma. | |
| Monjazeb (2012)<br>Case series<br>**Glioblastoma Multiforme** | n = 21<br><br>Mean age 55 (37-76). 5/21 female. 9 patients were RPA Class III and 12 were RPA Class IV. Eight patients underwent gross total resection, 9 patients underwent subtotal resection, and 4 patients underwent biopsy | Inclusions: ≥18 years, Karnofsky performance score ≥70, histologically confirmed initial presentation of supratentorial GBM. T1 enhancing tumor of ≤ 5 cm diameter after biopsy on MRI or a preoperative T1 enhancing tumor of ≤8 cm before | IMRT to a maximum dose of 80 Gy in which the central tumor volume received a hypofraction ated daily dose of 2.5 Gy<br><br>F/U: Patients were followed until death. | 7 patients were enrolled in each of 3 dose levels: 70 Gy, 75 Gy, and 80 Gy. The prescribed dose was 50.4 Gy to the initial target volume and 70 Gy to the boost | Overall survival: median 13.6 months (0.9-40.2 months). Progression-free survival: median 6.5 months (0.9-40.2 months). 57% of patients alive at one year. 19% were alive at 2 years. No differences in OS or PFS among the different dose groups (also not powered to detect a difference). All patients died at last follow-up. | Toxicity: 21/21 patients had Grade 1 or 2 toxicity acutely. 8 patients had Grade 3 toxicity and 1 patient had Grade 4 toxicity acutely. Most toxicities not attributed to radiation, but rather to disease process itself or steroid therapy. Delayed toxicity- there were zero cases of Grade IV toxicities, 2 Grade III toxicities, and 13 Grade I/II delayed toxicities. No toxicity differences among the group levels. | Fair<br><br>Confounding factors not adequately assessed. Low power to detect any important differences in outcomes or harms. |

| Individual studies (published after review) | | | | | | | |
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| **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. | resection. Exclusions: previous history of brain irradiation or radiotherapy within 6 months of study entry, Recurrent or multifocal glioblastoma. Tumors centered in the pons, medulla, cerebellum, or optic pathway. Patients receiving investigational agents or concurrent chemotherapy. | Patients had follow-up assessment 1 month after radiotherapy, every 3 months for 4 visits followed by every 6 months for two visits, and then yearly thereafter. | target volume. Boost Target Volume dose escalation higher than 70 Gy was achieved with the addition of supplemental fractions of 2.5 Gy/fraction at the end of treatment, extending the total length of treatment beyond 28 days (Table 1) | | | |
| Narayana (2006)<br>Case series<br>**Glioblastoma, ananplastic astrocytoma, anaplastic oligodendrogli** | n = 58<br><br>31/58 male, Median age 54 (24-80),22% temporal, 20% frontal, 11% parietal, 2% | Consecutive patients with high-grade gliomas at study site | Intervention- IMRT.<br>Comparator- 3D CRT (comparative dosimetric analysis performed | Median dose 59.4 (59.4-60 Gy) | **Median progression-free survival**: 5.6 months for Grade III tumors and 2.5 months for Grade IV tumors. **Median overall survival**: 36 months for Grade III tumors and 9 months for Grade IV tumors. **Neurotoxicity**: Rate of freedom from neurotoxicities at | No harms other than dose assessed | Fair<br><br>Retrospectiv e case series, unblinded. |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| **oma** | occipital, 3% posterior fossa. Karnofsky performance status: Median 80 (60-90). 80% received adjuvant CT. | | for a subset of 20 patients treated with IMRT using retrospective planning for 3D CRT).<br><br>F/U: Median follow-up 24 months (12-48 months) | | 24 months= 85%. 21 grade I/II acute neurotoxicities, 4 grade II acute neurotoxicities, 2 grade IV acute neurotoxicities, 6 late grade I/II neurotoxicities, 4 grade III late neurotoxicities, and no grade IV/V late neurotoxicities.<br>**Dose**: No change in planning target volume, mean dose, or D95 coverage in comparing IMRT and 3D CRT. With IMRT, there were significantly lowered dose to the brainstem (-7%), spinal cord (-16%), optic nerve (-7%), and eye (-15%). Volume of normal brain irradiated by ≥18 Gy & ≥24 Gy decreased by 7% and 8% respectively. | | |
| Panet-Raymond (2009)<br>Case series<br>**Glioblastoma** | n = 35<br><br>Primary<br><br>Males 20, females 15. Median age 63 (31-78) RPA class III: 2 (5.7%), IV: 7 (20%), V: 20 (57.1%), VI: 6 (17.1%).<br>Resection: biopsy only: 9 (25.8%), subtotal: 13 (37.1%), gross | Pts tx between March 2004 and June 2006 who were ineligible or decided not to enroll in other protocols. Only exclusion if tumor was w/I 1.5 cm of optic chiasm or brainstem | intensity modulated radiation therapy (IMRT). 29 pts (82.4%) received concomitant chemotherapy with temozolomide (TMZ) and 25 pts (71.4%) received | IMRT: 60 Gy to the gross tumor volume (GTV) and 40 Gy to the planning target volume (PTV) in 20 fractions.<br>Chemo: concomitant | Median survival: 14.4 mos (range, 3.2-26.5) | Acute toxicity: Grade 1-2 nausea: 8 (28%), grade 1-2 vomiting: 6 (20%), grade 1 thrombocytopenia: 1 (3%). Grade 1 leukopenia: 2 (7%). Grade 1 anemia: 11 (38%). Hepatotoxcity 1-2: 8 (28%), Grade 1-2 dermatitis: 11 (38%). Grade 1-2 fatigue: 18 (62%). No Grade 3-4 acute toxicity. .No late toxicity observed | Poor<br><br>Analysis did not account for age, gender, small sample size, retrospective |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | total: 13 (37.1%). MGMT methylation status: methylated: 20 (66.7%), unmethylated: 10 (33.3%). multicentricity: present: 4 (11.4%), absent: 31 (88.6%). concommittant chemo: yes: 29 (82.4%), no: 6 (17.1%). adjuvant chemo: yes: 25 (71.4%), no: 6 (17.1%), unk: 4 (11.4%). | | adjuvant TMZ chemo. 26 pts (74.3%) underwent surgical resection<br><br>F/U: weekly during tx then monthly. Median follow-up 12.6 months | temozolomide (TMZ) 75 mg/m2 daily during RT tx followed by 200 mg/m2 daily for 5 days every 28 days ≤ 1 year. | | | |
| Paulino (2010) Case series **Medulloblastoma** | n = 44 (pediatric patients)<br><br>Primary<br><br>Males 30, females 14. Median age: 9 (33 months - 18 yrs.) Risk category standard: 33 pts (75%), high risk: 11 pts (25%) | Pediatric pts tx at two clinics between 1998-2006 for medulloblastoma | all pts tx with craniospinal irradiation (CSI) + intensity modulated radiotherapy (IMRT) boost to the posterior fossa (PF) and/or tumor bed (TB) + cisplatin- | Standard risk disease pts: 18-23.4 Gy CSI plus either 1) 36 Gy boost to PF and 54-55.8 Gy boost to TB OR 2) 55.8 Gy boost to TB. High risk disease pts: 36-39.6 | Study looked at hearing loss in pts tx with CSI, IMRT boost and cisplatin chemo. See harms column for details | 11 pts (25%) no hearing loss. Grade 3 or 4 ototoxicity found in 11 pts (25%.) Six patients (13.6%) had unilateral and 5 pts (11.4%) bilateral ototoxicity. Of 88 ears, Grade 0,1,2,3, and 4 ototoxicity was found in 29 (33%), 32 (36.4%), 11 (12.5%), 13 (14.8%) and 3 (3.4%) ears respectively. No pt developed hearing loss after RT ad before initatition of chemo. Median time to develop grade 3 or 4 ototoxicity was 8.5 months (3-77 months.) On analysis, only factor associated with the development of | Poor<br><br>Little information given on pts, risk categories not defined, analysis accounted for age, gender, risk group, cisplatin |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | based chemotherapy. 19 pts (43%) also received amifostine.<br><br>F/U: Schedule not specified. Median audiogram follow-up 41 months (11-92.4 months) | Gy CSI + either 1) PF boost of 54-55.8 Gy, 2) PF boost of 45 Gy and TB boost of 55.8 Gy OR 3) TB boost of 55.8 Gy. Median cisplatin dose 300 mg/m2 (75-562.5 mg/m2) | | hearing loss was mean RT dose to the cochlea with higher doses increasing severity of hearing loss (p=0.027.) | dose, RT dose and use of amofostine |
| Polkinghorn (2011)<br>Case series<br>**Medulloblastoma** | n = 33<br><br>Primary<br><br>Males 21 (64%), females 12 (36%), Median age: 9 (4-46) Standard risk: 25 (76%), high risk: 8 (24%). Stage M1: 1 (3%), M2: 3 (9%), M3: 2 (6%). Presence of > 1.5 cm2 residual tumor: 4 (12%) | Pts tx at clinic between Oct. 1999 and Dec. 2007 for newly diagnosed medulloblastoma | All pts tx with surgery + craniospinal irradiation (CSI) + intensity modulated radiotherapy (IMRT) boost to the tumor bed (TB) + chemotherapy. Six standard risk pts also received intrathecal | For six standard risk pts also receiving IIMA, CSI dose was 18 Gy with TB boost of 54 Gy. Other standard risk pts received 23.4 Gy CSI + 55.8 Gy boost to TB except one | Nonprotocol Standard risk patients<br>5-yr actuarial PFS: 81.4% (95% CI, 52.1% - 93.7%)<br><br>5-yr actuarial OS: 88.4% (95% CI, 60.8% - 97.0%)<br><br>High-risk patients<br>5-yr actuarial PFS: 87.5% (95% CI, 38.7% - 98.1%)<br><br>5-yr actuarial OS: 87.5% (95% CI, 38.7% - 98.1%) | Of 31 pts with post tx audiograms, 2 pts (6%) developed Grade 3 hearing loss. No grade 4. No other harms reported. Median time to post tx audiogram 19 months (5-90 months) | Poor<br><br>Wide variety of tx, no analysis with confounding variables, small sample size, some pts not adequately tested for hearing loss (not before tx, short follow-up) |

| *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** |
| | | | iodine-131-labeled monoclonal antibody (IIMA)<br><br>F/U: schedule not specified. Median follow-up 63 months (5-121 months) | adult pt receiving 36 Gy CSI + 55.8 Gy boost to TB. High risk pts received 36-39.6 Gy CSI + 55.8 GY boost to TB | | | |
| Sajja (2005)<br>Case series<br>**Meningioma** | n = 35<br><br># meningiomas: 37; upfront, 17, salvage, 20 median age: 65, range 24-89; Gender: 67% female; median Karnofsky performance status at time of treatment: 90, range 50-100; IMRT as primary treatment: 46% previously treated with surgery: 49%; Previously treated with SRS: 5% Median time from | Patients with intracranial meningiomas treated with IMRT at the Cleveland Clinic Foundation between July 1997 and November 2003; minimum of 6 months follow-up imaging | IMRT treatment using Peacock system from NOMOS using 1X0.5 cm beamlets and 6MV beam energy<br><br>F/U: Median 19.1 months (range 6.4-62.4) | Median does 50.4 Gy (range 27-58 Gy); fraction size ranged from 1.7-2 G | 3-year actuarial cumulative local control: 97% (95% CI, 92-100%) Overall 3-year actuarial survival: 91% (95% CI, 79%-100%) | No severe toxicity reported; no late radiation complications at short-term follow-up; no cases of symptomatic cerebral radiation necrosis | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | previous surgery to IMRT treatment: 18.1, range 1.6-168.9 Location: cavernous sinus/sphenoid region, 51%; other skull base locations, 11%; cerebello-pontine angle, 8%; other intracranial sites, 30%; Treatment planning: CT only, 3; CT and MRI, 20; CT-MRI fusion , 12 | | | | | | |
| Sultanem (2004)<br>Case series<br>**Glioblastoma Multiforme** | n = 25<br><br>Median age 55 (41-77). 18/25 male. All patients underwent surgery initially: 6 had gross total resection, 11 had subtotal resection, and 8 had biopsy only. 15/25 patients had RPA Class V-VI. All had KPS score ≥ 60, 19/25 | Adult patients with histologic dx of GBM, KPS of 60 or higher, Post-op tumor volume of 110 cm3 or less. Patients with tumors within 1.5 cm of a critical structure (such as optic chiasm or brainstem) were not included. | hypofractionated, accelerated IMRT<br><br>F/U: Median 8.8 months (2.8-22.9 months). | 60 Gy in 20 fractions of 3 Gy each | Median survival 9.5 months (2.8-22.9 months). Median progression-free survival 5.2 months (1.9-12.8 months). 1-year OS rate 40%. No survivors at 2 years. Median survival for patients with RPA class III-IV and V-VI is 14 and 7 months, respectively. One-year overall survival rate was 63% and 36% for RPA Class III-IV and V-VI respectively. Age >60 was a poor prognostic factor for disease-free survival. Surgery limited to biopsy was a poor prognostic factor on univariate analysis alone. | 5 patients had symptoms of increased intracranial pressure, which was treated with steroids. One patient did not complete treatment due to refusal to continue. On patient had visual loss at 9 months, and it is unknown it if was related to radiation. | Good |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | had a KPS score ≥ 90. Tumor originated from temporoparietial lobe in 14 patients, from frontal lobe in 7 patients, from occipital love in 2 patients, and thalamic region in one patient. | | | | | | |
| Tsien (2012)<br>Case series<br>**Glioblastoma and Gliosarcoma** | n = 38<br><br>Primary<br><br>Males 19, females 19. median age: 56 (23-75). KPS 90-100: 33 (86.8%), 80: 3 (7.9%), 70: 2 (5.3%). RPA III: 13 (34.2%), IV: 17 (44.7%), V: 8 (21.1%). Resection: gross total: 15 (39.5%), subtotal: 17 (44.7%), biopsy only: 6 (15.8%). Radiation prescription dose: 66 Gy: 1 (2.6%), | 18+ years, KPS ≥ 70, Newly diagnosed Grade IV gliomas including glioblastoma multiforme and gliosarcoma. Adequate bone marrow reserve, liver and renal function. Exclusion criteria: multifocal, recurrent gliomas, infratntorial tumors, evidence of cerebrospinal fluid dissemination, severe concurrent disease, prior | Intensity modulated radiation therapy (IMRT) and concomitant and adjuvant chemotherapy<br><br>F/U: at one month and then every three months. Median follow-up for pts who remain alive 54 months (42-62 months). | IMRT: Gross tumor volume (GTV) expanded by 1.5 cm to make clinical target volume (CTV). Then CTV and GTV both expanded by 0.5 cm respectively to make Planning target volume 1 (PTV1) and PTV2. Dose | Median progression-free survival: 9.0 mos (95% CI, 6.0-11.7)<br><br>Median OS: 20.1 mos (95% CI, 14.0-32.5)<br><br>2 pts developed other cancers: 1 pt primary hepatocellular carcinoma 2 yrs after completing RT, 1 pt stage IB NSCLC 14 mos post tx | Toxicity related to RT: acute grade 3 neurologic toxicity: 6 pts (15.8%) not specified. Late toxicity: 3 pts (7.9%) radiation necrosis, 2 pts at dose of 78 Gy, 1 pt at dose of 81 Gy. 1 pt (2.6%) Grade 3 otitis with conductive hearing loss | Fair |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 72 Gy: 12 (31.6%), 75: 9 (23.7%), 78: 7 (18.4%), 81: 9 (23.7%). | malignancy requiring cytotoxic chemotherapy within one year, prior RT leading to overlap of RT fields, planned final boost exceeding one third of brain or inability to undergo MRI | | to PTV1: 60 Gy in 30 fractions. Dose to PTV2: 66-81 Gy in 30 fractions. Chemo: temozolomide(TMZ) 75 mg/m2 daily concommittant with IMRT then adjuvant TMZ at 200 mg/m2 days 1-5 every 28 days for 6-12 cycles | | | |
| Weber (2011) Case series **Brain Metastases** | n = 29<br><br>55.2% Male, Median age 62.3 (42-78.3) RPA I 20.7%, RPA II 79.3%, Primary tumor: 76% Lung, 10.3% breast, 3.4% melanoma, 10.3% other. | Previously untreated brain mets, histiologically proven Ca, brain MRI consistent with mets, 1-4 BMs, age <80 years, Karnofsky performance status ≥70; RPA | Volume-modulated Arc Therapy VMAT ( type of IMRT delivered in a single arc)<br><br>F/U: Mean follow-up 5.4 months +/- | 40 Gy in 10 fractions | Survival: 6-month OS 55.1%. Patients undergoing surgery survived significantly longer than those who did not: OS 72.0% vs 33.5% (p=0.035).Patients with good performance status lived significantly longer: OS 66.9% for patient with a FPS of 90-100 and OS 37.5% for patients with a KPS 70-80 P=0.025). Estimated 6-month brain PFS was 77.9%23 | No radiation-induced erythema was observed. Grade CTCAE 1 and 2 alopecia observed in 9 patients (31%) | Fair<br><br>Small prospective trial with possibility of selection bias of survey completers. |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 44.8% had one brain met, 30.1% had 2-3, and 24.1% had 4. 51.7% underwent surgery and 34.5% had concomitant CT. | <III; total volume of BM ≤40 ml and no previous cranial RT | 2.8 months. Toxicity and QOL assessment made during VMAT (weeks 1 and 2) and every 3 months thereafter. | | (77.4%) were controlled locally and distantly in the brain. 74% presented with progressive extra-cranial systemic disease. Treatment: 6 treatment failures were observed overall. 3 (13%) had distant failure and a different 3 (13%) had local failure. QoL and Neurocognitive function: KPS decreased, but not significantly during VMAT, and it decreased significantly after 3 months. MMSE improved significantly (27.1 +/-2.7 vs 28.1 +/- 2.5, p=0.04) among VMAT and remained stable at 3 months. QoL decreased with VMAT, global health functioning was worse. Physical functioning and role functioning significantly decreased during and after VMAT. Emotional functioning was stable. Bladder control and Headache scores improved; however motor dysfunction, visual disorders, and communication deficits remained stable. Hair loss and leg weakness worsened. | | |

## Breast Cancer

| *Reviews* | | | | | |
|---|---|---|---|---|---|
| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Hayes (2012) Technology assessment **Partial Breast Irradiation** | 4 studies compared IMRT to 2DCRT. Sample sizes ranged from 20 to 259 patients; Total N = 715 | Interventions: IMRT and 3DCRT. Comparator: 2D CRT. F/U: ranged from 10 months to 5 years.<br><br>Note that this report does not compare IMRT to 3DCRT. | **Survival**: No studies<br><br>**Cost:** Hayes reports data from an analysis of costs by Suh (2005). Conventional partial breast irradiation cost $7,700. Partial breast IMRT cost $9,700. | **Toxicity**: Three studies reported mild to moderate toxicities of breast edema, breast pain, telangiectasia, erythema, hyperpigmentation and chest wall pain with IMRT. No comparative data. Cosmesis was reported to be acceptable in 97-100% of patients. | Good<br><br>TA authors rate 15 articles as very poor to poor in quality. |
| Hayes (2012b) Technology assessment **Whole Breast Irradiation** | 19 studies. 3 RCTs, 5 comparative studies Sample sizes ranged from 306 to 815 patients; total N = 5904 | Interventions: IMRT and 3D CRT Comparator: 2D CRT. F/U: ranged from m 6 weeks to 6 years.<br><br>Note that this report does not compare IMRT to 3DCRT. | The Hayes report separates IMRT into three dose regimens: standard fractionation schedule; hypofractionation with accelerated IMRT and hypofractionated with simultaneous-integrated boost IMRT.<br><br>**Improved disease control, increased survival and acceptable cosmesis**: one non-randomized study comparing IMRT with 2DCRT demonstrated no difference in any survival or disease control measure. For all dose regimens, cosmesis was judged satisfactory for IMRT. Two comparative studies showed no change in cosmesis for IMRT compared to 2DCRT; a third comparative study reported a 1.7 times increased likelihood of altered breast appearance with | **Toxicity**: Acute toxicity levels with IMRT are reported to be mild to moderate. The most common acute toxicities are radiation dermatitis, breast edema, breast pain, breast pruritus and fatigue. One study comparing IMRT to 3DCRT reported reduction of dermatitis from 13% with 3DCRT to 2% for IMRT and reduction of pruritus from 28% to 11%.<br><br>Study (Study Type) : N IMRT ; N EBRT; Results<br>**Freedman** (NR comp): 73; 60; 1. moist desquamation lower with IMRT<br><br>**Donovan** (RCT): 150; 156; 1. EBRT group 1.7 times more likely to have change in breast appearance (p=0.008); 2. IMRT group lower induration than EBRT group (p=0.02-0.001) | Good<br><br>TA authors rate 19 articles as very poor to good in quality. |

| *Reviews* | | | | | |
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| **Reference<br>Study Design<br>Malignancy** | **# of Studies & Subjects** | **Intervention<br>Comparator<br>Follow-up** | **Outcomes Assessed<br>Main Findings** | **Harms** | **Quality<br>Comments** |
| | | | 2DCRT than IMRT.<br><br>**Costs:** Hayes reports data from an article (Smith, 2011) on costs of IBRT and non-IMRT whole breast irradiation. Their review of the SEER Medicare database showed mean costs of conventional whole breast RT of $7,179 compared to IBRT of $15,230. | **Harsolia** (NR comp): 93; 79; 1. Acute edema, dermatitis, hyperpigmentation lower with IMRT (p=0.001 for all); 2. Chronic edema, hyperpigmentation lower with IMRT (p=0.06)<br><br>**McDonald** (NR comp): 121; 124; 1. Acute and late toxicities lower with IMRT (p=0.04); 2. Overall survival, disease-specific survival no difference between IMRT and EBRT.<br><br>**Pignol** (RCT): 170; 161; 1. Grade 3 skin toxicity lower with IMRT (p=0.06); 2.Moist desquamation whole breast lower with IMRT (p=0.002) 3.moist desquamation inframammary fold lower with IMRT (p = 0.001)<br>4. No differences in QoL<br><br>**Barnett** (NR comp): 411; 404; 1. No difference in breast shrinkage;<br>2. Telangiectasia lower with IMRT (p=0.009) | |

## Female Pelvic Cancer

| *Reviews* | | | | | |
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| **Reference<br>Study Design<br>Malignancy** | **# of Studies & Subjects** | **Intervention<br>Comparator<br>Follow-up** | **Outcomes Assessed<br>Main Findings** | **Harms** | **Quality<br>Comments** |
| Veldeman (2008)<br>Systematic review<br>**Endometrial and Cervical Cancer** | 5 comparative case series<br><br>N = 373 | Intervention: IMRT<br>Comparator: non-IMRT<br>F/U: | 1-yr locoregional control comparable bt groups | One study reported significantly lower rates of acute and chronic gastrointestinal toxicity in IMRT group. Another study reported that sparing pelvic bone marrow with IMRT may decrease haematological toxicity (not consistent between studies).<br>One study reported significantly lower rates of acute and chronic GI and acute GU toxicity for IMRT group. Acute haematological toxicity or chronic genitourinary toxicity not significantly different between groups | Fair |
| Staffurth (2010)<br>Systematic Review<br>**Endometrial and Cervical Cancer** | Four studies from two research groups; sample sizes ranged from 35 to 68. | Intervention: IMRT<br>Comparator: 3DCRT.<br>F/U: 20 to 30 months | **Tumor control:** One study compared IMRT (n=33) with a historical group of 3DCRT (n = 35). There was no difference in loco regional control rates. | **Toxicity**: Two studies from one group contained heterogeneous populations of IMRT and comparator groups. Two studies compared IMRT to 3DCRT. In one, women with IMRT had a lower rate of chronic GI toxicity; IMRT = 11%; 3DCRT = 50% (odds ratio = 0.16; 95% confidence interval = 0.04-0.67).<br>In the second study, IMRT patients had a lower rate of acute GI toxicity (IMRT =6%; 3DCRT = 34% p= 0.002); acute GU toxicity differences were not significant (IMRT = 9%; 3DCRT = 23% p = 0.23). | Poor |
| De Neve (2012)<br>Systematic review<br>**Cervical cancer** | 1 study<br><br>N = 452 | Intervention: IMRT<br>Comparator: NR<br>F/U: NR | | Less late Grade ≥ 3 GI and GU toxicity (6%) than non IMRT (17%) | Poor |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Aoki (2002)<br>Case series<br>**Paraaortic Lymph Node Metastasis** | n = 29<br><br>performance status < 2; no other characteristics given | pts with isolated paraaortic lymph node recurrences from various primary tumors between June 1994 and Feb 1999 | IMRT (dynamic arc conformal radiotherapy)<br><br>F/U: median 11 mo (2-66 mo) | 50-65 Gy, reduced if GI toxicity | In-field survival rates 58%; overall 1 year and 2 year survival rates 52% and 29% respectively, median survival period 15 months | Acute toxicity: Grade 1 and Grade 2 GI disorders in 9/29 (31%) and 5/29 (17%); Grade 2 liver dysfunction in 2/29 (7%). All recovered. Late toxicity Grade 1 in 6 (21%) and Grade 2 in 5 (17%). | Poor<br><br>Small sample, information lacking on pt characteristics, follow-up, drop-out, confounders |
| Chen (2008)<br>Case series<br>**Cervical Cancer** | n = 54<br><br>Primary<br><br>Median age 54.5 (35.2-82.6). Tumor stage IB1: 31 (57%), IB2: 13 (24%), IIA: 10 (19%). Histology: squamous cell: 37 (68.5%), adenocarcinoma: 10 (18.5%), other: 7 (13%). Pretreatment tumor marker SCC and/or CEA: elevated: | Pts tx between June 2004 and Feb. 2007 with early stage cervical cancer. Stage IB-IIA with high risk factors (full thickness invasion, deep lymphatic penetration, pelvic lymph node metastases involved surgical margin and only simple hysterectomy performed.) | All patients received Chemo, intensity modulated radiation therapy (IMRT) and vaginal brachytherapy<br><br>F/U: Every three months first two years and then every 4-6 months thereafter. Median follow-up 20 months (6.6- | IMRT: 50.4 Gy in 28 fractions. Chemo: cisplatin 50mg/m2 weekly for 4-6 weeks. Brachytherapy: 6 Gy vaginal cuff in three insertions | 3-yr loco-regional control rate 93% (95% CI: 86.5-99.5%). 3-year disease free survival 78% (95% CI: 64.7-91.3%). 3-yr overall survival: 98% (95% CI: 94-100%.) On univariate analysis, only nonsquamous cell histology (p=0.0489) and pelvic lymph node metastases (p=0.0477) were associated with poorer disease free survival. No variables were significant in multivariate analysis. | Acute toxicity: Grade 1 GI: 7 (13%), Grade 2 GI: 12 (22%), Grade I GU: 11 (20%), Grade 2 GU: 7 (13%), No acute Grade 3 GI or GU toxicity. Hematologic toxicity during adjuvant chemo: Grade 1: 13 (24%), Grade 2: 15 (28%) and Grade 3: 3 (5.6%). Late toxicity: GI toxicity: Grade 1: 4 (7.4%), Grade 2: 1 (1.8%). GU toxicity: Grade 1: 4 (7.4%), Grade 2: 2 (3.7%), Grade 3: 1 (1.8%) | Poor<br><br>Small sample size, retrospective analysis, analysis accounted for age, pre-tx markers, cancer stage, histology and lymph node mets |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 17 (31.4%), w/I normal limits: 37 (68.6%.) pelvic lymph node mets: yes: 22 (41%), no: 32 (59%). Surgery: abdominal total hysterectomy: 8 (15%), radical abdominal hysterectomy: 46 (85%) | | 40.5 months) | | | | |
| Chen (2011)<br>Case series<br>Cervical Cancer | 109 patients with Stage Ib-IVA cervical cancer; treated with IMRT plus brachytherapy and chemotherapy. | The inclusion criteria were (a) pathologically proven denocarcinoma or squamous cell carcinoma of the cervix, (b) no evidence of distant metastasis, and (c) patients receiving IMRT with concurrent cisplatin-based chemotherapy. | Intervention: IMRT<br>Comparator: none<br><br>F/U: median 32 months | Gross tumor volume (cervix tumor and uterus): 50.4 – 54 Gy, 1.8 Gy per fraction, 5 fractions/ wk<br>GTV-N (pelvic lymph nodes): | 3-yr OS: 78.2%<br>3-yr local failure-free survival: 78.1%<br>3-yr DFS: 67.6% | Incidence of toxicity:<br>Acute Grade ≥3 GI toxicity 3%<br>Acute Grade ≥ 3 hematological toxicity = 24%<br>Chronic Grade ≥3 GI toxicity = 5%<br>Chronic Grade ≥ 3 GU toxicity = 6% | Poor<br><br>Large number of patients excluded from series. Cannot exclude confounding effects of chemotherapy on reported toxicities. |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | The exclusion criteria were (a) pathologically proven small cell carcinoma, (b) patients who received an incomplete treatment course and (c) patients who received previous surgery, chemotherapy or radiotherapy.. A total of 46 patients were excluded in this study. There were 109 eligible patients out of 146 patients entered.. | | 54-60 Gy Clinical target volume: 45-58 Gy in 28-30 fractions<br><br>Cisplatin 30-40 $mg/m^2/wk$ | | | |
| Du (2010)<br>Cohort<br>**Paraaortic Lymph Node Metastasis of Cervical Cancer** | n = 60<br><br>No significant difference in age, pathologic type, grade, or prior treatment between groups | New dx PALN mets, prev rec'd conventional RT or surgery; KPS score ≥ 70. Serially assigned IMRT or PAFRT | IMRT (28) vs Para-Aortic Field RT or PAFRT (32)<br><br>F/U: Followed every 3 months x 1 year, then q 6 months x 2 years, then | IMRT median dose 63.5 Gy (58-68 Gy)<br>PAFRT median dose 47.5 Gy (45-50 Gy) both at 1.8-2.0 Gy/fractio | IMRT vs PAFRT Complete Response 1-3 mos after tx: 57.1% vs 28.1%, p=0.023 Partial Response: 32.1% vs 12.5%, p=0.039; 1-yr OS 67.7% vs 51.3%, p=0.201; 2-yr OS: 58.8% vs 25.0%, p=0.019; 3-yr OS 36.4% vs 15.6%, p=0.016 | Grade 1 or 2, not reported. Grade 3/4 leukopenia, 1 (3.6%) IMRT vs 6 (19%) PAFRT; Grade 3 dermatitis, 2 (6.3%) PAFRT; Grade 3/4 acute enteritis, 1 (3.6%) IMRT vs 6 (19%) PAFRT; Grade 3/4 late enterocolitis 6 (19%) PAFRT | Poor<br><br>Small N, no confounders inconsistent assessment of response, high dropout rate without intent-to-treat analysis |

| Reference Study Design Malignancy | Sample size and Pt Characteristics | Patient Selection Criteria | Intervention Comparator Follow-up | Dose | Outcomes Assessed Main Findings | Harms | Quality Comments |
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| ***Individual studies (published after review)*** | | | | | | | |
| | | | annually. | n | | | |
| Du (2012) Cohort **Cervical Cancer** | n = 122<br><br>Mean age: RF-IMRT 52, EBRT 55; no difference in stage, pathology, grade, chemo | Stage IIB-IIIB cervical CA; 60 pts w/RF-IMRT and 62 w/conv. RT (c-RT) | Reduced-field IMRT (RF-IMRT) vs conventional radiotherapy (c-RT) at Shandong Cancer Hospital F/U: F/u q 3 mos x 1 year, then q 6 mos x 2 year, then annually. Median f/u: 47 mos (range 6-68 mos) | RF-IMRT 61.5 Gy; c-RT 50.8 Gy; p=0.046 | Complete Response: RF-IMRT 87.7%, c-RT 88.3%, p=0.339; Partial Response: RF-IMRT 7.0%, c-RT 6.7%, p=0.280; 1-yr & 3-yr OS: no difference; 5-yr OS: RF-IMRT 71.2%, c-RT 60.3%; p=0.064 (approaching SS); No difference in 1-yr and 3-yr pelvic failure and distal failure | RF-IMRT vs c-RT: Acute: Grade 3/4 cystitis: 7.0% vs 18.3%, p=0.033; Grade 3-4 proctitis: 5.3% vs 16.7%, p=0.001; Grade 3-4 enteritis: 5.3% vs 10%, p=0.001; Grade 3-4 leukopenia: 0% vs 1.7%, p=0.026; Grade 3-4 Dermatitis: 0% vs 6.7%, p=0.041 Chronic: Grade >3 enterocolitis: 0% vs 18.4%, p=0.017; Grade >3 cystitis 0% vs 15%, p=0.044 | Poor<br><br>Downgraded for small N, failure to report confounders potential selection bias in CRT arm |
| Ferrigno (2010) Cohort **Pelvic Tumors, all types** | n = 134<br><br>Median age 62 IMRT, 64 CRT; sig. differences in primary tumor and treatment goal between groups (table 1) | All pelvic tumors undergoing whole pelvic CRT (69) or whole pelvic IMRT (65) | whole pelvic IMRT vs whole pelvic CRT<br><br>F/U: Weekly f/u | dose ranged 45 to 50.4 Gy, in 25-28 fractions | NR | Acute GI: Grade 0 43.1% vs 8.7%, p<0.001; Grade 1 18.5% vs 18.8%, p=0.955; Grade 2 38.5% vs 65.2%, p=0.002; Grade 3 0% vs 7.2%, p=0.058 Acute GU Grade 0 61.5% vs 66.6%, p=0.54; Grade 1 20% vs 8.7%, p=0.06; Grade 2 18.5% vs 23.5%, p=0.50; Grade 3 0% vs 1.5%, p>0.99 | Poor<br><br>Retrospective cohort, significant difference in tumor type and goal of treatment, unblinded assessment of outcomes |
| Hasselle (2011) Case series | n = 111 | All FIGO stage I-IVA cervical CA | IMRT, no comparator | Median dose 45 | 3-yr OS 77.7% (95% CI 68.3-88.4%) 3-yr DFS 69.2% (95% CI | Acute Grade 3: 2 GI, 0 GU Late Grade 3: 4 GI (rectovag fistula, SBO), 5 GU | 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** |
| **Carcinoma of the Cervix** | Median age 48 (range 25-92); 53% Black, 14% Hispanic, 31% White. 22 postop, 89 intact cervix | tx'd with IMRT from 2000-2007 | F/U: Median f/u 26.6 months (range 5.4-99 months). Intervals not reported | Gy; 35 patients rec'd parametri al boost, median dose 7.2 Gy | 59.4-80.7%). No significant differences according to RT dose. 3-yr Pelvic Failure (PF) 13.6% (95% CI 5.8-21.5%) 3-yr Distant Failure (DF) 16.6% (95% CI 8.3-24.9%) | (vesicovag fistula, hematuria, vag necrosis) | Unblinded, no confounder assessment, multiple disease stages at entry |
| Lupe (2007)<br>Cohort study<br>**Endometrial cancer** | 33 patients with Stage III-IV endometrial cancer. EBRT n = 19; IBRT n = 14.<br>30/33 patients received chemo before radiation and 25/33 received chemotherapy after radiation therapy. | Exclusion criteria (*1*) received previous systemic chemotherapy or pelvic radiation, (*2*) a Karnofsky Performance Scale score of _60, (*3*) history of previous malignancy within the last 5 years with the exception of basal cell carcinoma or squamous cell carcinoma of the skin, (*4*) leiomyosarcoma, or (*5*) hepatic or pulmonary metastases. | Intervention: IMRT<br>Comparator: EBRT<br>Follow up: median 21 months | | Two year disease free and overall survival rates were both 55%. Results are not separated between EBRT and IMRT cohorts. | Grade ≥ 3 Acute Toxicities<br>EBRT(n=19) IMRT (n=14)<br>Diarrhea 0 0<br>Urinary 0 0<br>N/V 0 0<br>Proctitis 1 0<br>Neutropenia 4 0<br><br>Chronic Grade ≥3 toxicities<br>EBRT(n=19) IMRT (n=14)<br>Cystitis 0 2<br>Proctitis 1 3<br>Sm Bowel obstruction 1 0 | Poor<br><br>Pre radiation treatment chemothera py incomplete in 30/33 and post radiation treatment in 25/33. Some patients received additional extended field radiation. Results not segregated by these confounders . |

## Head and Neck Cancer

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Bensadoun (2010). Systematic Review **Mixed sites of head and neck cancers** | 22 studies (no RCTs, 3 nonrandomized clinical trials, 2 before and after studies, 17 cohort studies)<br><br>N = NR | Intervention: IMRT (2 studies)<br>Comparator: conventional RT (10 studies), RT with chemotherapy (8 studies)<br>F/U: NR | NR | ***Weighted mean prevalence of trismus (12 studies total): for IMRT (2 studies),*** 5% (95% CI 0.0-16.6); **for conventional RT** (10 studies), 25.4% (95% CI 6.5-44.2); **for RT with chemotherapy (8 studies),** 30.7% (95% CI 8.3-53.0); ***maximum vertical opening***: 1 study w/ 16 IMRT pts and 24 conventional RT pts reported no significant difference (38.8±9.0 vs 33.7±10.1 mm, P=0.11); 1 study assessed QOL in HNC pts w/ or w/o trismus, but results not reported in review; no studies evaluating economic impact of trismus; no recommendations could be made for prevention or management of trismus. | Fair |
| De Neve (2012) Systematic Review **Mixed sites of head and neck cancers** | Two RCTs and 11 comparative studies. | Intervention: IMRT<br>Comparator: 3DCRT.<br>F/U: NR | **Tumor control**: Loco regional control at two years did not differ between IMRT and 3DCRT. | Toxicity: : Two RCTS consolidate clinical evidence defending the use of IMRT as a treatment for head and neck cancer as a treatment that preserves parotid gland function and significantly reduces rates of severe xerostomia (study data not given in this SR). | Poor |
| Jensen (2010). Systematic Review. **Mixed sites of head and neck cancers** | 49 studies.<br>Sample size and total N not given. | Intervention: IMRT (2 RCTs, 41 cohort studies, 2 case-control studies, 4 cross-sectional studies); 22 studies were uncontrolled<br>Comparator: no stated comparator<br>F/U: NR | NR | ***IMRT and salivary gland hypofunction (18 studies) or xerostomia (44 studies)***: the RCTs, cohort, case-control, and cross-sectional studies generally showed that parotid-sparing IMRT has potential to decrease prevalence and severity of salivary gland hypofunction and xerostomia. Salivary secretion from spared glands | Poor |

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | may increase over time after therapy, unlike following conventional RT. Therefore, the benefits of IMRT on salivary gland function, xerostomia, and xerostomia-related QOL are most pronounced late (≥6 mos) after RT and produces improvement in xerostomia-related QOL over time (up to 2 yrs after RT). Mean doses of ≤26-30 Gy, <38 Gy, or < 40 Gy to parotid glands have been suggested, as well as submandibular/sublingual-sparing IMRT can be appropriate in selected pts. A mean dose of ≤39 Gy to submandibular/subligual glands may result in potential for recovery of gland function over time. ***IMRT and salivary gland hypofunction/xerostomia-related QOL (11 studies)***: Association between xerostomia and QOL after parotid-sparing IMRT, with decline in QOL in 6 mos after IMRT, following by improvement of xerostomia-related QOL up to 24 mos after RT. Several studies showed that whole saliva, parotid, and submandibular flow rates were not associated with QOL scores up to 2 yrs after IMRT, but one study contradicted this finding. Based on these findings, parotid-sparing IMRT is recommended for prevention of salivary gland hypofunction and xerostomia in HNC pts (Level II evidence, grade A recommendation). | |

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Peterson (2010) Systematic Review **Mixed sites of head and neck cancers** | 43 studies (42 of interest) (4 IMRT, 38 conventional radiotherapy, 1 brachytherapy). 2 RCTs, 10 pre-post studies, 29 cohorts, 2 case-controls<br><br>N = 4287 | Interventions: IMRT<br>Comparator: Unspecified conventional radiotherapy<br>F/U: NR | Prevalence of osteoradionecrosis among patients having undergone IMRT versus conventional radiotherapy using indirect analysis. Overall findings: Further study is needed to determine if IMRT can be considered a prevention strategy for osteoradionecrosis in comparison to conventional radiotherapy | **Osteoradionecrosis Prevalence, Mean raw %:** Conventional radiotherapy, 7.3%; IMRT, 3.1;<br>**Osteoradionecrosis Prevalence, Mean weighted % (95% CI):** Conventional radiotherapy: 7.4% (4.8-10); IMRT: 5.2 (0.0-12.0). | Fair |
| Samson (AHRQ) (2010). Comparative Effectiveness Review **Mixed sites of head and neck cancers** | 14 studies compare IMRT to 3DCRT; total N = 1752.<br>22 studies compare IMRT to 2DCRT; total N = 2441. | Intervention: IMRT<br>Comparators: 3DCRT and 2DCRT<br>F/U: NR | **Survival or tumor control:** No conclusions about relative tumor control or survival for IMRT compared to 3DCRT or 2DCRT. | **Toxicity**: Moderately strong evidence for reduction of late xerostomia with IMRT compared to 3DCRT or 2DCRT. Insufficient strength of evidence for reduction of other side effects (acute xerostomia, mucositis, acute dysphagia, skin toxicity, osteonecrosis) with IMRT compared to 3DCRT or 2DCRT.<br><br>**From Samson:**<br>**Outcome: # studies; # significant (diff of IMRT < EBRT); # NS; # no p; # unquantifiable**<br>Acute xerostomia: 4; 2; 1; NR; 1<br>Late xerostomia: 7; 4; 2; NR; 1<br>Acute mucositis: 6; 1; 5; NR; NR<br>Late mucositis: 2; 1; 1; NR; NR<br>Acute dysphagia: 2; 0; 1; 1; NR<br>Late dysphagia: 2; 1 (IMRT> EBRT); 1; | Good<br><br>CE authors rate studies as poor quality (n = 35) or fair quality ( n = 1) |

| Reviews | | | | | |
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| **Reference<br>Study Design<br>Malignancy** | **# of Studies & Subjects** | **Intervention<br>Comparator<br>Follow-up** | **<u>Outcomes Assessed</u><br>Main Findings** | **Harms** | **Quality<br>Comments** |
| | | | | NR; NR<br>Acute skin toxicity: 5; 2; 1; 2; NR<br>Late skin toxicity: 3; 0; 3; NR; NR<br>Late osteonecrosis: 2; 0; 1; 1; NR<br>Tumor control: 8; 0; 8; NR; NR<br>Patient survival: 8; 1; 7; NR; NR | |
| Scott-Brown (2010). Systematic Review<br>**Mixed sites of head and neck cancers** | 6 comparing IMRT with conventional radiotherapy, 1 RCT, 2 case-controls, 1 prospective cohort, 2 retrospective cohorts<br><br>N = 900 | Intervention: IMRT (5 studies) IMRT with SIB (1 study)<br>Comparator: 2D conventional radiotherapy, 3D conventional radiotherapy, 3D conformal radiotherapy, Unspecified conventional radiotherapy<br>F/U: Range, 6 months to 3 years | **Functional**: 4 found benefit, 1 no benefit, 1 not reported. **Quality of life:** 2 statistically significant benefit, 1 clinically significant benefit, 3 no benefit | **Xerostomia**: 1 statistically significant benefit, 1 clinically significant benefit, 4 not reported. | Fair<br><br>Quantitative results were provided for each individual study but not synthesized across studies. Four additional IMRT studies were discussed in this review but they were not comparative. Of the 3 studies that did not show a quality of life benefit, all had doses >26GY tolerance dose |
| Staffurth (2010) Systematic Review<br>**Mixed sites of** | 30 studies (3 RCTs, (N=1205) | Intervention: IMRT<br>Comparator: 2DRCT or 3DCRT.<br>F/U: NR | **<u>Tumor control</u>** Three RCTs (n=1205) and five non-randomized comparative studies | **<u>Toxicity</u>**: Three RCTs (n=1205) and five non-randomized comparative studies (n=347) compare CRT to IMRT. Significant reduction in Grade 2-4 | Poor |

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **<u>Outcomes Assessed</u> Main Findings** | **Harms** | **Quality Comments** |
| **head and neck cancers** | | | (n=347) comparing EBRT vs. IMRT. No difference in tumor control. | xerostomia with IMRT, improved QoL with IMRT. | |
| Tribius (2011)<br>Systematic Review<br>**Nasopharyngeal and Orophayngeal Cancer** | 14 studies.<br>Sample sizes ranged from 51 to 356.<br>Total N = 1424. | Intervention: IMRT<br>Comparator: 2DRCT or 3DCRT.<br>F/U: NR | **<u>Quality of Life</u>**: 14 studies, including 5 prospective and 9 retrospective studies (including one prospective RCT) measured QoL parameters.<br>**Study: # of pts; Comparator; p value for improved QoL**<br>Pow (RTC): 51; 2DCRT; p < 0.05<br>Fang: 203; 3DCRT; p< 0.05<br>Vergeer: 241; 3DCRT; p = 0.001 to p = 0.04<br>Fang: 237; 2DCRT; p= 0.001 to p = 0.04<br>Fang: 356; 2DCRT; p = 0.001 to p = 0.04<br>Graff: 134; 2DCRT; p = 0.0001 to p = 0.01<br>Huang: 307; 2/3DCRT; p < 0.01 | NR | Fair |

| *Individual studies (published after review)* | | | | | | | |
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| **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** |
| Gupta (2012)<br>RCT<br>**Head and Neck Cancer** | 60 patients; EBRT (n=28), IMRT (n=32)<br>Previously untreated | Patients at Tata Memorial Hospital, India | Intervention: 3DCRT or IMRT<br>Comparator: same; | Ave mean dose to contralateral parotid gland: 3D-CRT- 49.8 | Locoregional control and survival: No significant differences between IMRT and 3DCRT.<br>1.Three year Kaplan-Meier estimates of locoregional control: | Physician rated salivary gland toxicity using RTOG grading<br>1.Grade 2 or worse acute salivary gland toxicity:<br>IMRT 59% (95% CI 42-75%) | Fair |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | head and neck cancer (T1-3, NO-2b) | | F/U: 4-6 weeks after completion of RT and then every 3-4 months for 2 years and every 6 months thereafter. Median follow-up = 40 months | Gy (95% CI, 46.5-53.1); IMRT 28.8 GY (95% CI, 27-30.7); p<0.0001<br><br>Ave mean dose to ipsilateral parotid gland: 3D-CRT- 39.8 Gy (95% CI, 36.3-43.2); IMRT 56.2 GY (95% CI, 52.5-60.1); p<0.0001 | IMRT = 80% (95% CI 66-95%) 3DCRT 88% (95% CI 75-100%)<br><br>2.Three year Kaplan-Meier estimates of overall survival: IMRT: 68% (95%CI 51-84% 3DCRT: 71% (95%CI 53-88%) | 3DCRT 89% (95% CI 72-97%), p=0.009; 2.No significant differences in acute dermatitis, mucositis, dysphagia, weight loss between IMRT and 3DCRT. | |
| Bhide (2010) Cohort **Laryngeal or Hypopharyngeal Cancer** | n = 90<br><br>Dose escalation trial: Dose #1: 22 men, 4 women; median age 57 yrs (24-84); staging: 1 pt Stage I, 1 pt Stage II, 10 pts Stage III, 14 pts Stage IV; Dose #2: 23 men, 6 | Dose escalation trial: laryngeal or hypopharyngeal SCC; Midline trial: oropharyngeal SCC | IMRT with induction and concurrent chemotherapy (identical chemotherapy regimens for both trials)<br><br>F/U: NR | Dose escalation study: Dose #1 (n=26): 2.25 Gy/fraction (63 Gy in 28 fractions); Dose #2 (n=29): 2.4 Gy/fraction (67.2 Gy in 28 fractions); Midline study: Dose #3 (n=30): 2.17 Gy (65 Gy in | Survival and recurrence outcomes not reported in this study. | Incidence of Grade 3 toxicities (overall # pts not reported, so only % reported here): Oral mucositis (Dose #1, Dose #2, Dose #3): 34%, 43%, 43%; Dose #1: peak prevalence of 30% at 1 wk after tx; Dose #2: peak prevalence of 30% at wk 6 during tx; Dose #3: peak prevalence of 36% at wk 6 during tx; all patients recovered from mucositis by 8 wks after tx; dysphagia (Dose #1, Dose #2, Dose #3): 61%, 87%, 56% (Dose #1 vs Dose #2, P=0.05; Dose #2 vs Dose #3, P=0.02); Dose #1: peak prevalence of 50% at 2 wks after tx; Dose #2: peak prevalence of 79% at wk 6 during tx; Dose #3: peak prevalence of 50% at 1 | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | women; median age 62 yrs (44-78); staging: 16 pts Stage III, 14 pts Stage IV; Midline trial: Dose #3: 23 men, 7 women; median age 59 yrs (32-82); 1 pt Stage II, 5 pts Stage III, 23 pts Stage IV | | | 30 fractions) | | wk after tx; grade 3 dysphagia had not recovered by 8 wks after tx in all 3 groups; 1 pt needed pharyngo-laryngectomy at 1 yr for post-cricoid stricture; 1 pt developed post-cricoid stricture at 9 mos post-tx and underwent dilatation; of 16 pts with Grade 3 dysphagia for >12 wks, 12 patients (75%) had late dysphagia (at 6 mos). Peak prevalence of grade 3 dysphagia was higher and recovery was slower in patients with lower overall treatment time (median 38 days vs 42 days). There was a significant correlation between length of pharyngeal mucosa receiving 50 Gy (L50) and 60 Gy (L60) and grade 3 dysphagia; L50 or L60 >8 cm resulted in more than 60% and 70% incidence of grade 3 dysphagia, respectively. | |
| Chen, Farwell (2010) Cohort **Head and Neck Cancer** | n = 130<br><br>Median age, 61 years (range 27-92); men, 77; women, 53; T1, 19%; T2, 23%; T3, 29%; T4, 29%; N0, 14%; N1, 19%; N2, 57%; N3, 10% | Non-metastatic carcinoma of oral cavity, oropharynx, larynx, or hypopharynx; total surgical resection; postoperative radiation therapy | Radiation: Conventional, 60%; IMRT, 40% Chemotherapy: Concurrent chemotherapy, 63%; chemotherapy with conventional radiation, | 60-66 Gy to planned target volume 1; 59.4-54 Gy to planned target volume 2; 50-54 Gy to planned target volume 3; all patients treated at 1.8 - 2 Gy daily fractions to | 3-yr OS CRT (69%) vs IMRT (72%) (p=0.49)<br><br>3-yr locoregional control: CRT (70%) vs IMRT (73%) (p=0.33)<br><br>3-yr actuarial distant metastasis-free survival: CRT (66%) vs IMRT (70%) (p=0.44) | NR | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | 61%; chemotherapy with IMRT, 65%<br><br>F/U: Median 30 months (range, 6-75 months) | planned target volumes 1 and 2 | | | |
| Lai (2011)<br>Cohort<br>**Nasopharyngeal Cancer** | n = 1276<br><br>Median age 45 (range, 11-78), male/female ratio 3:1 (949/317); 98%/6% WHO Type II or III/type I; 0.6% of pts had adenocarcinoma | Newly diagnosed biopsy-proven nonmetastatic NPC between January 2003 and Dec 2006 | 764 (59.9%) treated with 2D-CRT, 512(40.1%) treated with IMRT<br><br>F/U: median 52.8 mo (3-78) | 2D-CRT 68-76 Gy (median 70 Gy); 2 Gy/fraction to primary, 60-64 Gy to involved areas of neck, 50 Gy to uninvolved areas; IMRT 2.27 Gy/fraction to planning target volume (PTV) of gross tumor volume (GTV) of primary, 60-64 to PTV of nodal GTV, 60 Gy to high risk regions, 54 Gy to PTV of low-risk regions, and neck | LFRS-NRFS-DMFS-DFS 2D-CRT 86.8%,95.5%,82.6%,71.4% IMRT 92.7%,97.0%,84.0%,75.9%Only significant difference in paper is that LFRS is significantly higher in IMRT group than in 2D-CRT group for stage T1 (p=0.016). Overall 313 (24.5%) pts failed at 1 or more sites; distant metastasis most common (13.4%), followed by local failure alone (6.2%) | Harms not examined in this paper. | Fair |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | nodal regions | | | |
| Murphy (2009) Cohort **Head and Neck Cancer** | n = 75 (34 IMRT, 41 conventional radiation therapy (EBRT))<br><br>Mean age: 59 yrs (range 40-86); Sex: 61 men, 14 women; Primary tumor site: 17 oral cavity, 28 oropharynx, 6 hypopharynx, 3 nasopharynx, 17 larynx, 4 unknown; Stage at diagnosis: 2 Stage I, 8 Stage II, 12 Stage III, 35 Stage IVa, 6 Stage IVb,2 Stage IVc, 10 Unknown; Karnofsky Performance | Inclusion criteria: Histologically confirmed carcinoma of the neck, larynx, hypopharynx, nasopharynx, oropharynx, or oral cavity of unknown origin; radiotherapy as primary or postoperative therapy; age ≥18 yrs; Exclusion criteria: Prior radiotherapy of the head or neck, using an investigation al treatment for mucositis | IMRT in 34 patients, EBRT in 41 patients; Chemothera py in 50 patients (number of patients with chemothera py combined with IMRT versus EBRT not reported)<br><br>F/U: NR | Radiation dosage and fractionation schedule not reported | Differences between the IMRT and EBRT treatment groups in mouth and throat pain soreness were not statistically significant; Mean Mucositis Quality of Life Scores at weeks 5-6 (IMRT group, EBRT group): Swallowing (1.4, 2.7); Drinking (2.4, 2.5); Eating (2.5, 2.9); Talking (1.8, 2.3); Sleeping (1.4, 1.7); Differences between the IMRT and EBRT groups in Mucositis Quality of Life Scores were not statistically significant. Harms other than mucositis not reported separately for the different treatment groups (see Outcomes column for mucositis results) | See outcomes | Poor<br><br>Study funded and conducted in part by Amgen Inc.; Poor quality due to small size and lack of randomization to treatment groups and failure to consider that chemotherapy in some but not other patients could cause or greatly aggravate harms of radiation therapy; Demographics of treatment groups not reported separately |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | Status: Six <80, Eleven 80-89, Thirty 90-99, Twenty-eight 100 | | | | | | |
| O'Neill (2011) Cohort **Head and Neck Cancer** | n = 143<br><br>Mean age, 62±12.8 years; men, 105; women, 38; pretreatment quality of life survey, 48%; hypopharynx, 7%; larynx, 26.6%; oral cavity, 14.7%; oropharynx, 35%; salivary gland, 7%; sinus, 4.2%; thyroid, 5.6%; stage I, 5.6%; stage II, 17.5%; stage III, 26.6%; stage IVa, 33.6%; stage IVb, 6.3%; stage IVc, 0.7%; | Primary or salvage intent treatment for head and neck cancer | IMRT<br><br>F/U: 2 yrs | Mean dose to primary site: 65 Gy (range, 35-76); mean dose to parotid, 27 Gy (left side) or 28 Gy (right side); 80 patients (55.9%) received <26 Gy and 59 patients (41.2%) received ≥26 Gy | None reported | Symptom-related QOL: Scores decreased after initiation of treatment. Size of decrease was significantly larger at most measurement times for swallowing, chewing, taste, and saliva QOL in group receiving higher dose of radiation; significant difference in QOL-pain only at 200 days. Nonsignificant and/or negligible differences at 2 years, all symptoms. Saliva change score was significantly and independently correlated with mean dose to best spared parotid gland, and swallowing change score with parotid volume <15 Gy, both at 6 mo and last follow-up. | Poor<br><br>Discrepancy between number of patients in study and sum total of patients in the two exposure subgroups; data presented graphically |

| *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** |
| | unknown, 4.1%; recurrence, 3.5% | | | | | | |
| Petsuksiri (2011) Cohort **Head and Neck Cancer** | n = 68, 134 ears<br><br>Median age 47.5 yrs, 65% pts ≤50 yrs, 35% pts >50 yrs; 22.1% Stage 1-2, 77.9% Stage 3-4; 25.4% pre-RT otitis media and 23.1% had post-RT otitis media | Inclusion: Pts w/ T1-T4, N0-N3, M0 disease who underwent IMRT or conventional RT; baseline pre-RT audiograms; Exclusion: no medical records; no post RT audiograms; did not complete RT; tumor invasion into inner ear; recurrent disease; severe hearing impairment on pre-RT audiograms | IMRT (n=27); conventional RT (n=41); concurrent platinum-based chemotherapy in pts w/ locally advanced disease<br><br>F/U: median for all pts 27.5 mos (8-65); median for audiological assessment for all pts of 14 mos (6-43), for convention RT 15 mos (6-43), and for IMRT 13 mos (6-29) | IMRT: 66-70 Gy to high risk region, 59.4-63 Gy to intermediate risk region, 50.4-57 Gy to low-risk region, 33-35 fractions; conventional RT: total dose of 66-70 Gy, 2 Gy/ fraction, 5 fractions/wk | Survival and control outcomes not reported by cohorts. Overall, 2-yr PFS was 76.4% with 2-yr locoregional control rate of 88.5%. | By individual ear evaluation, incidence of sensorineural hearing loss (SNHL) was 44% (59/134 ears) at 4 kHz (high frequency) and 6% (8/134 ears) at pure tone average (PTA). For conventional RT group, frequency of SNHL was 48.75% (39/80) at 4 kHz and 5% (4/80 ears) at PTA. With IMRT, the frequencies were 37% (20/54 ears) at 4 kHz and 7.4% (4/54) at PTA. Univariate analysis found that internal auditory canal (IAC) mean dose >50 Gy appeared to increase risk of SNHL at high frequency (4 kHz) (RR 2.02, 95% CI 1.01-4.03, P=0.047). | Poor<br><br>Retrospective |
| Studer (2011) | n = 198 | Inclusion | 11 patients | 70 Gy in 33-35 | Outcomes other than dermatitis | Dermatitis occurred in 34% Cetuximab | Poor |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Cohort **Head and Neck Cancer** | Mean age: 62 yrs (range 25-83); Sex: 154 men, 44 women; Tumor site: 90 oropharyngeal, 40 oral cavity, 24 hypopharynx, 14 glottic, 8 unknown primary, 12 supraglottic, 7 sinonasal, 3 other; T-stage: 7 unknown primary, 14 T1, 61 T2, 37 T3, 61 T4, 11 recurrent T, 7 T0 recurrent N; N-stage: 41 N0, 19 N1, 47 N2a/b, 54 N2c, 12 N3, 13 recurrent N | criteria: Squamous cell carcinoma; Exclusion criteria: Nasopharyngeal carcinoma | underwent IMRT with simultaneous integrated boost, 99 patients underwent treatment with cisplatin (Control group); 99 patients underwent treatment with cetuximab (Cetuximab group)<br><br>F/U: NR | fractions in patients treated definitively; 66 Gy in 33 fractions in patients treated post-operatively (Fraction of patients treated definitively versus post-operatively not reported) | not reported | group patients versus 3% Control group patients (P<0.01); (No other harms reported) | Investigators stated that they had no conflict of interest; Poor quality due to failure to randomized patients to treatment groups and switching of 30 patients in Cetuximab group from cisplatin to cetuximab treatment after adverse reactions; Not reported whether differences between groups at baseline were statistically significant |
| Chakraborty (2009) Case series **Head and Neck Cancer** | n = 28<br><br>Median age 54.5 (34-70); majority 23/28 | Pathologically confirmed squamous cell carcinomas | 2 treatment schedules SIB72 and SIB66 | SIB72: 72-66-57 for 33 fractions over 45 days; SIB66 66-60-54 for | n/a (no control or comparison group) | Mucositis > incidence of maximum grade, 28 total pts Grade 1 - 1(3.6%), Grade 2 -14 (50%) Grade 3 -12 (42.9%), Grade 4 - 1 (3.6%); number of pts experiencing mucositis: Grade 1 - 28 | Poor<br><br>Analysis of toxicities seems quite |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (82.1%) Stage IVA, Performance status 90 8/28 (28.6%), 80 14/28 (50%), 70 6/28 (21.4%) | (SCC) of oral cavity, oropharynx, supraglottic larynx and hypopharynx; Age > 20, clinical stages I-IVA, performance > 70 | F/U: median 13 months (range 2-25 months at time of analysis); first follow-up 4 weeks after completion of radiation, subsequent visits planned at 2 month intervals | 33 fractions over 42 days (for pts with GTV in laryngopharngeal region) | | (100%); Grade 2 - 27 (96.4%), Grade 3 - 13 (46.4%), Grade 4 - 1 (3.6%) median duration of maximum grade of mucositis in days: Grade 2 - 54; Grade 3 - 31.5, Grade 4 - 70, all - 42.5 ; median duration of any mucositis in days (range; 95% CI) 64.5 (39-149) Functional impairment secondary to mucositis, incidence of maximum grade (no grade 4 for any of the following) Pain incidence of maximum grade Grade 1 - 1 (3.6%), Grade 2 - 7 (25%), Grade 3 - 20 (71.4%); number of pts experiencing Grade 1 - 28 (100%), Grade 2 - 26 (92.6%), Grade 3 - 20 (71.4%); maximum toxicity experienced in (median) week median duration of maximum grade of toxicity 95% CI (days) 58.5 (47.8 - 73.1) Actuarial estimate of persistence of toxicity >0 (days) (median; 95%CI) 262 (103.3-420.7); Dysphagia Incidence of maximum grade Grade 1 - 9 (32.5%), Grade 2 - 16 (57.1%), Grade 3 -3 (10.7%); number of pts experiencing dysphagia Grade 1 - 28 (100%), Grade 2 - 22 (78.6%), Grade 3 - 3 (10.7%); maximum toxicity experienced in (median) week 3 (2.5-3.9); median duration of maximum grade of toxicity 95% CI (days) 64 (51.9- 97.1) Actuarial estimate of persistence of toxicity >0 (days) (median; 95%CI) 211 (62.9- | carefully done, but there are other (possibly unavoidable) issues in the study, such as patient compliance, failure (of journal) to publish competing interests, small number of patients (28) |

| Individual studies (published after review) | | | | | | | |
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| Reference Study Design Malignancy | Sample size and Pt Characteristics | Patient Selection Criteria | Intervention Comparator Follow-up | Dose | Outcomes Assessed Main Findings | Harms | Quality Comments |
| | | | | | | 359.1; Hoarseness Incidence of maximum grade Grade 1 -21 (75%), Grade 2 - 17(25%), Grade 3 - (0%); number of pts experiencing pain Grade 1 - 28 (100%), Grade 2 - 7 (25%), Grade 3 - 30(0%); maximum toxicity experienced in (median) week (95% CI) 4 (3.4-7.0); median duration of maximum grade of toxicity (days(95% CI) 63 (57.4- 93.2); Actuarial estimate of persistence of toxicity >0 (days) (median; 95%CI) 205 (0-506.8) Xerostomia Incidence of maximum grade Grade 1 -1 (3.6%), Grade 2 - 24(85.7%), Grade 3 - (0%); Grade 4 0 number of pts experiencing at least Grade 1 - 28 (100%), Grade 2 - 27 (96.4%), Grade 3 - 3 (10.7%); week maximum toxicity experienced (median 95% CI) 3 (1.8-4.6); Actuarial estimate of persistence of toxicity >0 (days) (median; 95%CI) 63 (57.4- 93.2); Dysguesia Incidence of maximum grade Grade 1 -3 (10.7%), Grade 2 - 25 (89.3%), Grade 3 - NA; Grade 4 - NA number of pts experiencing at least Grade 1 - 28 (100%), Grade 2 - 25 (89.3%), Grade 3 - NA; week maximum toxicity experienced (median 95% CI) 2 (1.7-2.4); Actuarial estimate of persistence of toxicity >0 (days) (median; 95%CI) 267.5 (216.5-354.3) Fatigue Incidence of maximum grade Grade 1 -7 (25%), Grade 2 - 11(39.3%), | |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | | | Grade 3 - 9(32.1%) Grade 4 - 0 number of pts experiencing at least Grade 1 - 27 (96.4%), Grade 2 - 18 (64.2%), Grade 3 - 9(32.1%); maximum toxicity experienced in (median) week 2 (1.7-2.6); Actuarial estimate of persistence of toxicity >0 (days) (median; 95%CI) 222 (158.4- 285.6); | |
| Chan, Sanghera (2011) Case series **Head and Neck Cancer** | n = 150<br><br>Median age, 58 yrs, range 31-78; men 84.7%; Stage distribution, Stage II 10%, stage III 28%, stage IV 62%; Site of primary tumor, oropharynx 58%, larynx 30.7%, hypopharynx 8.7%, oral cavity 2.6% | Consecutive pts with biopsy-proven carcinoma who underwent hyopfractioned accelerated radiotherapy with concurrent carboplatin between November 2002 and August 2008 | IMRT; concurrent outpatient carboplatin chemotherapy in wks 1 and 4 (dose ranged from area under the curve 3.5 to 6)<br><br>F/U: Median follow up 25 months, range 4-70 months | 55 Gy in 20 fractions to the isocentre; treating 5 days per wk over 4 wks. 50 Gy in 20 fractions was given to neck after pre-radiotherapy neck dissection. 41.25 Gy in 15 fractions was given as prophylactic dose to clinically and radiologically negative but at risk nodal areas; no comparison group | n/a (no control or comparison group) | Incidence of acute toxicity grade 0 to 2 (number of patients listed, percentages not reported): anemia 142; neutropenia 141; thrombocytopenia 147; mucositis 28, prolonged mucositis NA, dysphagia 64, skin reaction 91; Incidence of acute toxicity grade 3: anemia 4%; neutropenia 3%; thrombocytopenia 1%; mucositis 78%, prolonged mucositis 9%, dysphagi 55%, skin reaction 39%; Incidence of acute toxicity grade 4: anemia 1%; neutropenia 2%; thrombocytopenia 1%; mucositis 3%, prolonged mucositis 0.7%, dysphagi 1%, skin reaction 0%; hospital admission 33% (median duration of admission 5 days, range 1-7); feeding tube (before or during treatment) 89%; dependence on feeding tube at 1 yr (13%); death: 2pts, pt died after 2 fractions of radiotherapy due to airway obstruction, 1 pt died due to progressive disease and pneumonia | Poor<br><br>Potential conflict of interest for two authors |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | | | after 15 fractions. | |
| Chen, Jennell (2009)<br>Case series<br>**Head and Neck Cancer** | n = 77<br><br>46 men, 31 women; median age 58 yrs (27-92); primary sites of oropharynx (51%), oral cavity (17%), larynx (8%), hypopharynx (7%), nasopharynx (7%), paranasal sinus/nasal cavity (7%), unknown site (5%); HT alone in 55%, surgery + postop HT in 45%; concurrent chemotherapy in 48 pts (62%) | Inclusion: Localized squamous cell HNC; Exclusion: non-squamous cell histology, tx'd w/ boost HT after conventional RT, recurrent disease, failure to complete planned course of HT | HT (helical tomography) alone or surgery + postoperative HT<br><br>F/U: Every 2-8 wks for first 6 mos, then every 3 mos; median 21 mos (3-29) for all pts and median 24 mos (3-29) for surviving pts | Median dose of 66 Gy (60-72) | n/a (no control or comparison group) | Acute toxicities: Skin erythema, odynophagia, taste alterations, and xerostomia occurred in essentially all pts. Late toxicities: 57 pts (74%), some subjective degree of xerostomia; 10 pts (13%), Grade 3 esophageal toxicity (inability to swallow solids) and 7 of these pts had esophageal stricture; 2 cases (2.6%) of osteoradionecrosis (12 and 15 mos after definitive RT when significant areas of mandible received >70 Gy); 2 cases (2.6%) of orocutaneous fistula (tx'd postoperatively and needed later surgical intervention; no cases of neurological or CNS toxicity. | Poor |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Collan (2011)<br>Case series<br>**Oropharyngeal Cancer** | n = 102<br><br>Mean age: 57 yrs (range 30-79); Sex: 68 men, 34 women; Tumor site: 40 oral, 62 oropharyngeal; Tumor Stage: 4 stage I, 17 stage II, 17 stage III, 64 stage IV | NR | Surgical resection and IMRT in all patients and chemotherapy in 39% patients<br><br>F/U: Mean 55 months (range 26-106) | Mean 60 Gy in 2 Gy fractions | n/a (no control or comparison group) | Acute dermatological toxicity: Grade 1 in 90% patients, Grade 2 in 10% patients; Mucositis: Grade 1 in 6% patients, Grade 2 in 69% patients, Grade 3 in 25% patients; Mucosal pain treatment: Strong opioids in 25% patients, non-opioids in 15% patients; Hospitalization: 6 patients needed hospitalization for a mean of 5 days (range 3-7); Permanent percutaneous endoscopic gastrostomy needed in 5% patients; Xerostomia after radiotherapy: Grade 0-1 in 70% patients, Grade 2 in 30% patients | Poor<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator group; Inclusion and exclusion criteria not reported; Criteria for tumor staging not reported |
| Daly (2010)<br>Case series<br>**Oropharyngeal Cancer** | n = 128<br><br>No median age provided; range 37.9 - 77.3), < 60 70 (66%), >60 37(34%) M/F ratio 97:10 (91:9%); Stage II 3 (4%), III 12 (11%); IV 92 (85%); 84 (79%) | pts treated for SCC of the oropharynx with no prior head-and-neck radiotherapy (RT), mixed non-IMRT and IMRT treatment or metastatic disease at presentation | IMRT provided as definite treatment or post-op<br><br>F/U: Evaluation by treating physician at least 1x/week; post-treatment | 66 Gy at 2.2 Gy/fraction for definitive treatment; 60 Gy at 2 Gy/fraction for post-op | n/a (no control or comparison group) | Acute toxicity: Mucosal toxicity (n=103 pts evaluable): Grade 0 1 (1%); Grade 1 6( 6%); Grade 2 39 (39%); Grade 3 56 (54%); Grade 4 0 (0); Grade 5 (1 (1%); Grade 5 - was 59 yo man receiving definitive chemoradiation for T4N2cSCC of base of tongue required hospitalization during tx for severe mucositis and died 9 days after completion of RT, 1 day after revision of gastrostomy tube at local hp. No postmortem. Skin toxicity (n=101 pts evaluable) Grade 0 5 (5%); Grade 1 55 (54%); Grade 2 36 (36%); Grade 3 36 | Fair<br>Retrospective record review |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | underwent definitive RT, 22 (21%) treated for high risk features, 6 underwent pre-RT neck dissection w/o surgery on primary site | | imaging study at 2-6 mo following treatment completion and as indicated. PET-CT at 3 mo following RT completion, repeated for cause or every 12 to 18 mo for years 1-3 if no recurrence; Following tx, complete evaluation done every 1-2 mo in Yr1, every 2-3 mo in yr 2, every 3-6 mo in yrs 3-5, annually thereafter | | | (36%). No Grade 4 or 5. Other median weight loss during tx 6.4 Kg (range, 0.5-16.3kg); 16% of pts lost > 10 kg.; 2 pts had NG feeding tubes, 1 had total parenteral nutrition while on tx due to gastrostomy tube complications; 82 (77%) required narcotic pain meds during tx. Late complications6 (6%) developed > Grade 4 post-tx late complications; 3 pts dependent on gastrostomy tube > 1yr post treatment, including 52 yo M treated with definitive chemoradiotherapy for a T2N2c CA at base of tongue that recurred within the GTV at 9 mo post tx, the developed orocutaneous fistula with exposed bone. as complication of salvage surgery, req gastrostomy tube until death from locally progressive disease. Other complications were nonhealing area of exposed mandibular bone (n=1 pt), pharyngocutaneouse fistula (n=1 pt), severe post-tx tracheal stenosis requiring multiple dilatations (n=1 pt) | |
| Daly (2011) Case series **Laryngeal and Hypopharynge** | n = 107<br><br>Median age: 44 yrs (range | Inclusion criteria: Age >17 yrs and <70 yrs, | All patients underwent IMRT or 3D- | 60-70 Gy in 30 to 35 fractions (details not reported) | n/a (no control or comparison group) | Mucositis: Grade 1 in 12% patients, Grade 2 in 44% patients, Grade 3 in 37% patients, Grade 4 in 7% patients; Skin reaction: Grade 1 in 44% patients, | Poor<br><br>Conflict of interest not |

| *Individual studies (published after review)* | | | | | | | |
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| **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 Cancer** | 21-69); Sex: 46 men, 13 women; AJCC stage: 30 Stage III, 29 Stage IV | pathology proven World Health Organization type II or III nasopharyngeal carcinoma, AJCC Stage III or IV, no distant metastasis, projected lifespan >6 months, Karnofsky Performance Status >70, bilirubin <1.5 mg/dL, creatinine <1.5 mg/dL; Exclusion criteria: Prior radiotherapy of head or neck, prior surgery at tumor site, history of malignant tumors, simultaneous | EBRT and chemotherapy; Unidentified number of patients underwent conformal radiation therapy, a variant of IMRT<br><br>F/U: Median 14 months (range 3-25) | | | Grade 2 in 49% patients, Grade 3 in 7% patients; Xerostomia: Grade 1 in 22% patients, Grade 2 in 49% patients, Grade 3 in 27% patients; Leukopenia: Grade 1 in 22% patients, Grade 2 in 54% patients, Grade 3 in 9% patients; Neutropenia: Grade 1 in 37% patients, Grade 2 in 25% patients, Grade 3 in 2% patients; Thrombocytopenia: Grade 1 in 12% patients, Grade 2 in 5% patients, Grade 3 in 7% patients; Anemia: Grade 1 in 42% patients, Grade 2 in 36% patients, Grade 3 in 2% patients; Nausea/Vomiting: Grade 1 in 29% patients, Grade 2 in 42% patients, Grade 3 in 22% patients, Grade 4 in 2% patients; Liver dysfunction: Grade 1 in 3% patients; Kidney dysfunction: Grade 1 in 9% patients | addressed; Poor quality due to no control or comparator group; patient characteristics not reported in detail; No outcomes or demographics were reported for 57 (49%) of the patients enrolled |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | multiple tumors, pregnancy, uncontrolled active infections | | | | | |
| Diaz (2010)<br>Case series<br>**Head and Neck Cancer** | n = 128<br><br>Mean age, 56.9±9.2 yrs; men, 112; women, 16; larynx, 28%; nasopharynx, 9%; hypopharynx, 5%; oropharynx, 76%; oral cavity, 5%; sinus, 2%; unknown site, 3%; TII, 3%; TIII, 31%; TIVa, 79%; TIVb, 15% | Locally-advanced head and neck cancer; no thyroid disease; Karnofsky performance status ≥60%; normal organ function; squamous cell cancer | IMRT concurrently with weekly chemotherapy; additional patients treated with conventional radiotherapy (n=10) or IMRT with thyroid constraints (n=16)<br><br>F/U:Median 28.3 months (range, 4.1-65.3) | Daily fractions of 2.1 Gy to gross disease and 1.7 Gy to prophylactic nodal sites | n/a (no control or comparison group) | Hypothyroidism in 61 patients (48%) at median 1.08 yrs (range, 2.4 months to 3.9 years) after completion of chemoradiotherapy. IMRT resulted in higher dose and percentage thyroid volume receiving 10, 20, and 60 Gy compared with conventional radiotherapy. IMRT with thyroid dose constraints resulted in lower median dose and percentage thyroid volume receiving 30, 40, and 50 Gy. | Fair |
| Duprez (2010)<br>Case series<br>**Head and Neck Cancer** | n = 285 (in final analysis)<br><br>Characteristics were listed for 305 patients instead of the | Patients with squamous cell carcinoma larynx (except Stage T102N0M0 | IMRT<br><br>F/U: Median follow up 27.4 months, range 0.3 to | Median dose 70 Gy in 33-35 fractions prescribed to the high dose PTV in 20 patients (7%) | n/a (no control or comparison group) | Tube placement during IMRT (because of Grade 3 or greater dysphagia): 21% (44 patients that went into the procedure without a tube in place); Incidence of acute toxicity grade 0 to 2: mucositis 74% , dermatitis 74%, dysphagia 74%; Incidence of acute | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | final sample of 285, Median age, 58.6 years, range 36.7-85.7. 254 male patients. Differentiation : 19 well differentiated, 157 moderately differentiated, 52 poorly differentiated, 57 unknown; Tumor site: 18 oral cavity, 101 oropharynx, 59 hypopharynx, 79 larynx, 28 metastases with unknown primary tumor; T stage: 28 Tx, 26 T1, 69 T2, 70 T3, 92 T4; N stage: 64 N0, 47 N1, 150 N2, 20 N#, 4 Nx; Stage group: 8 | glottic tumors), oropharynx, oral cavity, and hypopharynx or metastases of squamous cell carcinoma in the cervical lymph nodes from cancer of an unknown primary | 99.0 | and 69.12 Gy in 32 fractions in 163 patients (57%). After complete surgery median prescribed dose 66 GY in 33 fractions (doses were escalated for some patients and some patients received an interstitial boost) | | toxicity grade 3: mucositis 25% , dermatitis 25%, dysphagia 26%; Incidence of acute toxicity grade 4: mucositis 0.4% , dermatitis 1%, dysphagia 0%; Incidence of late toxicity grade 0 to 2: xerostomia 98% , fibrosis 98%, dysphagia 89.3%, mucosal integrity 97%; Incidence of late toxicity grade 3: xerostomia 2% , fibrosis 2%, dysphagia 8%, mucosal integrity 1%; Incidence of late toxicity grade 4: xerostomia 0% , fibrosis 1%, dysphagia 1%, mucosal integrity 1% | |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | I, 12 II, 47 III, 177 IVA, 36 IVB, 5 NN; 18F-FDG-PET CT: 178 yes, 107 no; Surgery: 76 yes, 209 no; Lymph node dissection: 145 yes, 110 unilateral, 35 bilateral, 140 no; Chemotherapy : 92 yes, 193 no | | | | | | |
| Eisbruch (2011)<br>Case series<br>**Orophyngeal Cancer** | n = 73<br><br>Median age: 55 yrs (range 50-78); Sex: 65 men, 8 women; Tumor location: 38 tongue base, 35 tonsil; Median gross tumor volume: 110 mL (range 19-378); T-stage: 9 T1, 29 T2, 17 T3, 18 | NR | IMRT combined with chemotherapy<br><br>F/U: Up to 24 months (average not reported) | Mean dosages were 34 Gy to the esophagus, 48 Gy to the glottal and supraglottal larynx, and 58 Gy to the pharyngeal constrictors | n/a (no control or comparison group) | Worsened videofluoroscopy scores in 16 patients; Increased videofluoroscopic aspirations in 21 patients; Worsened Head & Neck Quality of Life eating domain scores in 8 patients; Worsened University of Washington Quality of Life swallowing scores in 5 patients | Poor<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator group and no reporting of inclusion and exclusion criteria; Average follow-up not |

| Individual studies (published after review) | | | | | | | |
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| Reference Study Design Malignancy | Sample size and Pt Characteristics | Patient Selection Criteria | Intervention Comparator Follow-up | Dose | Outcomes Assessed Main Findings | Harms | Quality Comments |
| | T4; N-stage: 6 N0, 6 N1, 55 N2, 6 N3; AJCC Stage: 9 stage III, 58 stage IVa, 6 stage IVb; Smoking status: 26 never, 31 previous, 16 current | | | | | | reported; Severity of complications not reported |
| Feng (2010) Case series **Oropharyngeal Cancer** | n = 73<br><br>Median age: 55 yrs (range 50-78); Sex: 65 men, 8 women; Tumor location: 38 tongue base, 35 tonsil; Median gross tumor volume: 110 mL (range 19-378); T-stage: 9 T1, 29 T2, 17 T3, 18 T4; N-stage: 6 N0, 6 N1, 55 N2, 6 N3; AJCC Stage: 9 stage III, 58 stage | Inclusion criteria: Stage III to IV squamous cell carcinoma of the oropharynx, tumor medial to the carotid arteries; Exclusion criteria: Radiologic evidence of involvement of the retropharyngeal nodes | IMRT combined with chemotherapy<br><br>F/U: Median: 36 months (range 2-73) | Mean dosages were 34 Gy to the esophagus, 48 Gy to the glottal and supraglottal larynx, and 58 Gy to the pharyngeal constrictors | n/a (no control or comparison group) | Neutropenia: Grade 2 in 10% patients, Grade 4 in 1% patients; Thrombocytopenia: Grade 2 in 1% patients; Acute mucositis: Grade 2 in 44% patients, Grade 3 in 55% patients; Acute dermatitis: Grade 2 in 62% patients, Grade 3 in 18% patients; Skin fibrosis/ induration: Grade 2 in 9% patients, Grade 3 in 1% patients; Xerostomia: Grade 0-1 in 84% patients, Grade 2 in 16% patients; Dysphagia: Grade 3 (enteral feeding needed) in 6% to 7% of patients at 3 to 6 months, Grade 0-1 in 94% patients and Grade 2 in 4% patients and Grade 3 in 1% patients at 12 months; Feeding tubes were needed in 29% patients due to acute dysphagia | Poor<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator group; Limited reporting of Grade 1 complications; This study seems to involve the same patients as the study above by Eisbruch et al. (2011) |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | IVa, 6 stage IVb; Smoking status: 26 never, 31 previous, 16 current | | | | | | |
| Franchin (2011) Case series **Nasopharyngeal Cancer** | n = 52<br><br>37 men, 15 women; median age 48 yrs (13-70); median time from sx to dx 3.5 mos (1-23); UICC/AJCC staging: 26.9% Stage IIb, 30.8% Stage III, 32.7% Stage IVa, 9.6% Stage IVb; all pts received cisplatin-based neoadjuvant chemotherapy | Inclusion: Previously untreated pts w/ stage IIB to IVB undifferentiated NPC; histological confirmation of UCNT; Exclusion: metastatic disease; contraindications to cisplatin-based CT; partial neck dissection | IMRT w/ SIB delivered by linear accelerator (n=37) or Tomotherapy (n=15) using 6 MV beams<br><br>F/U:Follow-up every 3 mos; median 38.5 mos (12.3-64.1) | 66 Gy in 30 fractions for mean dose of 65.5 Gy (n=15), 70.95 Gy in 33 fractions for mean dose of 71 Gy (n=37) | n/a (no control or comparison group) | 3 pts hospitalized during IMRT for parenteral nutritional support due to severe dysphagia; Acute RT toxicity: Nausea/vomiting: Grade 0, 41 pts (78.9%); Grade 1, 8 pts (15.4%); Grade 2, 3 pts (5.7%); Grades 3-4, 0 pts; mucositis: Grade 0, 0 pts; Grade 1, 8 pts (15.4%); Grade 2, 23 pts (44.2%); Grade 3, 17 pts (32.7%); Grade 4, 4 pts (7.7%); dysgeusia: Grade 0, 17 pts (32.3%); Grade 1, 17 pts (32.3%); Grade 2, 12 pts (22.6%); Grade 3, 7 pts (12.8%); Grade 4, 0 pts; xerostomia: Grade 0, 0 pts; Grade 1, 32 pts (61.5%); Grade 2, 16 pts (30.8%); Grade 3, 4 pts (7.7%); Grade 4, 0 pts; otitis: Grade 0, 42 pts (80.8%); Grade 1, 10 pts (19.2%); Grades 2-4, 0 pts; dermatitis: Grade 0, 0 pts; Grade 1, 32 pts (61.5%); Grade 2, 16 pts (30.8%); Grade 3, 4 pts (7.7%); Grade 4, 0 pts; weight loss >10%: 10 pts (19.3%); total of 30 pts (57.6%) had Grade 3-4 acute toxicities. Late toxicities: xerostomia: Grade 0, 6 pts (11.5%); Grade 1, 40 pts (77.0%); Grade 3, 6 pts (11.5%); severity of grade 2 xerostomia decreased over time w/ only 4 pts not improving | Poor |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | | | salivation and w/ range of improvement of 6-19 mos; hearing loss: Grade 0, 23 pts (44.2%); Grade 1, 24 pts (46.2%); Grade 2, 5 pts (9.6%); trismus: Grade 0, 49 pts (94.2%); Grade 1, 2 pts (3.9%); Grade 2, 1 pt (1.9%); chronic dysgeusia: Grade 0, 28 pts (54.8%); Grade 1, 20 pts (38.1%); Grade 2, 4 pts (7.1%); hypothyroidism: 2 pts (3.8%) at 14 and 18 mos after IMRT; 1 pt (1.9%) had collated muscle tx'd w/ steroid therapy. | |
| Frank (2010) Case series **Head and Neck Cancer** | n= 52<br><br>Median age: 56 yrs; Sex: 46 men, 6 women; 39 patients with history of smoking; Pathological type: 46 squamous cell carcinoma, 3 basaloid squamous cell carcinoma, 1 cystic squamous cell carcinoma, 2 undifferentiated carcinoma; | Inclusion criteria: Pathologically confirmed diagnosis of metastatic squamous cell carcinoma including papillary, basaloid, sarcomatoid, and undifferentiated subtypes; Exclusion criteria: Adenocarcinoma, melanoma, | Surgery and IMRT, Chemotherapy in 14 patients<br><br>F/U: Median 3.7 yrs (range 1.0-7.6) | Median dose to the Clinical Target Volume was 66 Gy (range 60-72) IMRT delivered in 30 fractions | n/a (no control or comparison group) | Grade 3 dysphagia requiring long-term gastrostomy in 1 patient; Grade 3 esophageal stricture requiring dilatation in 1 patient; Grade 2 xerostomia in 3 patients; Grade 2 hypothyroidism requiring medication in 1 patient; Grade 1 xerostomia in 6 patients; (No Grade 4 complications occurred) | Poor<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator group and retrospective analysis |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | N-stage: 3 Nx, 5 N1, 10 N2a, 18 N2b, 6 N2c, 4 N3 | sebaceous gland carcinoma, leukemic infiltration, soft tissue carcinoma, prior surgery without radiation therapy, or prior radiation therapy | | | | | |
| Gomez (2011) Case series **Head and Neck Cancer** | n = 168<br><br>Site distribution, nasopharynx (15%), oral cavity (21%), larynx/hypopharynx (18%), paranasal sinus (21%), oropharynx (25%); T-stage, T1 (11%), T2 (34%), T3 (23%), T4 (29%), TX (2%); N-stage, N0 (38%), N1 (19%), N2 | Patients at Memorial Sloan-Kettering Cancer Center between December 2000 to July 2007 | IMRT<br><br>F/U: Follow up for Osteoradionecrossis: Median follow up 37.4 month, range 0.8 - 89.6 months. Follow up for dental outcomes: Median follow-up of 7.6 mos, range < 1 - 82 months. | Median dose 6,996 cGy (range, 3,960-7,200cGy) delivered in 1.8 Gy to 2.12 Gy fractions. | n/a (no control or comparison group) | Presence of osteoradionecrosis: 1.2% of patients (2 total) both with oral cavity primaries. Dental events: dental caries 9%, dental extractions 12%, median time to dental event 21.3 months | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (41%), N3 (2%); Dental Status, Dentulous (96%), Edentulous (4%); Mandibular invasion, No (96%), Yes (4%); Preradiation dental extractions, No (82%), Yes (18%); Surgery, No (58%), Yes (42%); Chemotherapy, No (35%), Yes (65%) | | | | | | |
| Han (2010) Case series **Nasopharyngeal Cancer** | n = 305<br><br>230 men, 75 women; median age of 45 (11-86); Karnofsky performance scores of 90 in 85.6%, 80 in 13.4%, 70 for | Inclusion: histologically confirmed, newly dx'd w/ NPC; Exclusion: doses <66 Gy, distant metastases | IMRT delivered by Elekta Precise linear accelerator w/ 40-leaf MLC<br><br>F/U: every 3 mos for first | 66.0-69.8 Gy in 30-33 fractions to GTV | n/a (no control or comparison group) | Acute toxicities: skin reactions: Grade 1 in 184 pts (60.3%), Grade 2 in 107 pts (35.1%), Grade 3 in 14 pts (4.6%); oral mucositis: Grade 1 in 59 pts (19.4%), Grade 2 in 156 pts (51.1%), Grade 3 in 90 pts (29.5%); leukopenia due to bone marrow suppression: Grade 1 in 101 pts (33.1%), Grade 2 in 136 pts (44.6%), Grade 3 in 19 pts (6.2%), Grade 4 in 9 pts (0.3%); 1 pt with Grade 4 myelosuppression and other | Poor |

| Individual studies (published after review) | | | | | | | |
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| **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%; Fuzhou staging: 0.3% stage I, 14.4% Stage II, 55.1% Stage III, 30.2% Stage IVa; 260 pts w/ Stage III-Iva NPC had induction chemotherapy; 40 pts had concurrent chemotherapy; 55 pts w/ Stage III-IVa NPC had adjuvant chemotherapy; 85 pts had RT boost | | 2 yrs, then every 6 mos thereafter; median 35 mos (5-61) | | | pts w/ Grade 3 acute toxicities were not affected from tx after symptomatic therapy. NOTE: # pts not reported for late toxicities so only frequency data presented here. Late toxicities: xerostomia at 3 mos after IRMT: Grade 1 in 5%, Grade 2 in 95%; xerostomia at 24 mos: Grade 0 in 7.6%, Grade 1 in 85.4%, Grade 2 in 7%; xerostomia at 36 mos: Grade 1 in 18.1%, Grade 1 in 78.4%, and Grade 2 in 3.4%; neck fibrosis: Grade I in 30.5%; Grades 2-3 in 1%; hearing loss: Grade 1 in 15.4%, Grades 2-3 in 0.7%; trismus: Grade 1 in 4.3%, Grades 2-3 in 1%; Other harms: 8 pts had cranial nerve injury, 3 pts had radiation encephalopathy; no Grade 4 late toxicities. | |
| Iseli (2009) Case series **Head and Neck Cancer** | n = 87<br><br>Mean age, 61.2 years (range, 39.5-88.1); men, 73; women, 14; recurrence, 58%; second primary, 26%; neck-only | Head and neck squamous cell carcinoma; reirradiation for carcinoma in an area previously irradiated to >45 Gy; no distant | non-IMRT (43 patients) or IMRT (44 patients); 72.4% had concurrent chemotherapy<br><br>F/U: Median 5 years | NR | n/a (no control or comparison group) | 11 patients (13%) stopped reirradiation treatment early because of toxicity Grade 3-5 early toxic effects: non-IMRT, 16 patients (37%); IMRT, 17 patients (41%); ≤120 Gy cumulative dose, 22 patients (55%); >120 Gy cumulative dose, 11 patients (23%); reirradiation >58 Gy, 14 patients (30%); reirradiation ≤58 Gy, 19 patients (48%); second primary carcinoma, 8 patients (35 %); recurrent carcinoma, 25 patients (39%) Grade 3-5 late toxic | Fair<br><br>Procedural information not well reported; radiotherapy methods and dosing unknown |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | recurrence, 14%; resection before reirradiation, 44% | metastasis; no primary cancers | | | | effects: non-IMRT, 12 patients (30%); IMRT, 17 patients (40%); ≤120 Gy cumulative dose, 11 patients (31%); >120 Gy cumulative dose, 18 patients (39%); reirradiation >58 Gy, 20 patients (43%); reirradiation ≤58 Gy, 9 patients (25%); second primary carcinoma, 8 patients (36%); recurrent carcinoma, 21 patients (35%) Early grade 5 toxic effects: Overall, 5 patients (6%); septic neutropenia, 2 patients (2.3%); stroke, 2 patients (2.3%); death from aspiration pneumonia, 1 patient (1.1%); carotid rupture, 5 patients (6%) | |
| Kao (2011) Case series **Head and Neck Cancer** | n = 33<br><br>Median age 59 (range, 18-77) 32 (97%) had Stage IV disease, 2 had stage III. 18 pts (58%) had T3 or T4 primary tumors and 24 pts (73%) had N2 or N3 lymph node disease. Performance score 0 in 12 (36%), 1 in 18 | HNSCC or poorly differentiated carcinoma, stage IVA and IVB or high-risk or high - risk stage III according to AJCC cancer staging manual. Performance status < and adequate bone marrow, kidney, and liver function | cetuximab and radiation alone; concurrent cetuximab, 5-FU, and hydroxyurea plus hyperfractio nated RT<br><br>F/U: median 24 mo (range, 17-32 mo) | median 72 Gy (range, 60-72 Gy) administered in 1.5 Gy fractions 2x/day during weeks 1,3,5,7,9 | n/a (no control or comparison group) | **Note: Article gives harms in percentages only**, Mucositis Grade 1 - 16%, Grade 2 -52% Grade 3 -33%, Grade 4 - 0; Dermatitis Grade 1 - 21%, Grade 2 - 64%' Grade 3 - 15%, Grade 4 0; Pain Grade 1 - 6%, Grade 2 - 52%, Grade 3 -42%, Grade 4 - 0; Xerostomia Grade 1 - 52%, Grade 2 - 48%,, Grade 3 -0, Grade 4 - NA; Late toxicities; Grade >3 include 1 case each of grade 3 frontal bone necrosis and grade 3 esophageal stricture. 1 pt with tumor that extended to the middle ear developed cartilage necrosis and unilateral hearing loss. Rates of long term (>6 mo) percutaneous endoscopic gastrostomy (PEG) tube dependence - 3%, 2 pts reported solid food dysphagia; 1 pt had a PEG tube in place | Fair |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (58%), 2 in 2 (6%) | | | | | for 1 yr that was removed after successful esophageal dilatation. 1 pt developed grade 2 skin hypopigmentation and grade 2 telangiectasia at site of Grade 3 acute dermatitis. Grade 2 xerostomia noted in 33% of pts. | |
| Kuang (2012) Case series; **Nasopharyngeal cancer** | IMRT = 182; EBRT = 198 patients with poorly differentiated nasopharyngeal cancer; 274 males 99 females most had chemotherapy. | All patients with nasopharyngeal cancer; so selection criteria noted | Intervention: EBRT and IMRT Comparator: same<br><br>F/U: initial analysis 3 months after treatment ended; then followed until 4/2011 or death; | IMRT: parotid gland: 26 Gy; brain stem ≤ 54 Gy; spinal cord ≤ 40 Gy; lens ≤ 8 Gy; optic nerve and optic chiasm ≤ 54 Gy, temporomandibular joint B60 Gy, and temporal lobe B60 Gy. A total dose of 71.94 to 73.92 Gy in 33 fractions at 2.18 to 2.24 Gy/fraction to the PGTVnx, 69.96 to 71.94 Gy in 33 fractions at 2.12 to 2.18 Gy/fraction to | IMRT EBRT<br><br>4-year loco-regional control:<br>93% 65% NS<br>Distant metastasis free survival<br>85% 83% NS<br>Disease free survival<br>79% 72% NS | IMRT EBRT<br><br>Grade 3-4 xerostomia<br>0% 0%<br>Grade 2 xerostomia<br>37% 64% p=0.000 | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | the PGTVnd, 60.06 Gy in 33 fractions at 1.82 Gy/fraction to the PTV1 and 50.96 Gy in 33 fractions at 1.82 Gy/fraction to the PTV2 were prescribed. All patients were treated with one fraction daily, 5 days per week.<br><br>CRT: total irradiation dose of 34 Gy/17 times, the rear boundary of the radiation field was moved forward to avoid radiation of the spinal cord. | | | |
| Kong (2010) | n = 59 | Inclusion | All patients | 60-70 Gy in 30 | n/a (no control or comparison | Mucositis: Grade 1 in 12% patients, | Poor |

| Individual studies (published after review) | | | | | | | |
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| **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 **Nasophaynge al Cancer** | Median age: 44 yrs (range 21-69); Sex: 46 men, 13 women; AJCC stage: 30 Stage III, 29 Stage IV | criteria: Age >17 yrs and <70 yrs, pathology proven World Health Organization type II or III nasopharyng eal carcinoma, AJCC Stage III or IV, no distant metastasis, projected lifespan >6 months, Karnofsky Performance Status >70, bilirubin <1.5 mg/dL, creatinine <1.5 mg/dL; Exclusion criteria: Prior radiotherapy of head or neck, prior surgery at tumor site, history of malignant | underwent IMRT or 3D-EBRT and chemothera py; Unidentified number of patients underwent conformal radiation therapy, a variant of IMRT<br><br>F/U: Median 14 months (range 3-25) | to 35 fractions (details not reported) | group) | Grade 2 in 44% patients, Grade 3 in 37% patients, Grade 4 in 7% patients; Skin reaction: Grade 1 in 44% patients, Grade 2 in 49% patients, Grade 3 in 7% patients; Xerostomia: Grade 1 in 22% patients, Grade 2 in 49% patients, Grade 3 in 27% patients; Leukopenia: Grade 1 in 22% patients, Grade 2 in 54% patients, Grade 3 in 9% patients; Neutropenia: Grade 1 in 37% patients, Grade 2 in 25% patients, Grade 3 in 2% patients; Thrombocytopenia: Grade 1 in 12% patients, Grade 2 in 5% patients, Grade 3 in 7% patients; Anemia: Grade 1 in 42% patients, Grade 2 in 36% patients, Grade 3 in 2% patients; Nausea/Vomiting: Grade 1 in 29% patients, Grade 2 in 42% patients, Grade 3 in 22% patients, Grade 4 in 2% patients; Liver dysfunction: Grade 1 in 3% patients; Kidney dysfunction: Grade 1 in 9% patients | Conflict of interest not addressed; Poor quality due to no control or comparator group; patient characteristics not reported in detail; No outcomes or demographics were reported for 57 (49%) of the patients enrolled |

| Reference Study Design Malignancy | Sample size and Pt Characteristics | Patient Selection Criteria | Intervention Comparator Follow-up | Dose | Outcomes Assessed Main Findings | Harms | Quality Comments |
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| ***Individual studies (published after review)*** | | | | | | | |
| | | tumors, simultaneous multiple tumors, pregnancy, uncontrolled active infections | | | | | |
| Lee (2009) Case series **Nasophaynge al Cancer** | n = 68<br><br>51 men, 17 women; median age 48.5 yrs (18-73); AJCC staging: Stage I 13.2%, Stage IIA 2.9%, Stage IIB 25.0%, Stage III 30.9%, Stage IVA 16.2%, Stage IVB 11.8%; 57 pts (83.8%) w/ Stage IIB-IVB disease needed chemotherapy | Inclusion: previously untx'd stages I to IVB NPC; ECOG performance status 0-1; WBC ≥4000/ul; platelets 100,000/ul; serum creatinine ≤1.6 mg/dL; Exclusion: pts <18 yrs; prior (w/in 5 yrs) or synchronous malignancy | IMRT w/ SIB; pts at Stage T2b or greater and/or N+ disease also received concurrent cisplatin, adjuvant cisplatin, and fluorouracil<br><br>F/U: Follow-up every 3 mos during first 2 yrs, every 6 mos during yrs 3-5, then annually; median for surviving pts 2.6 yrs (0.5- | 70 Gy to PTV or primary tumor plus any N+ disease, 59.4 Gy to subclinical disease, delivered over 33 tx days | n/a (no control or comparison group) | Adverse events affected a wide variety of tissues/systems and effects of IMRT were not distinguished from those of chemotherapy. Acute toxicities (68 pts): allergy/immunology: Grade 1 in 4.4%; auditory/hearing: Grade 1 in 10.3%, Grade 2 in 29.4%, Grade 3 in 14.7%; blood/bone marrow: Grade 1 in 7.3%, Grade 2 in 20.6%, Grade 3 in 45.6%, Grade 4 in 5.9%; cardiovascular: Grade 1 in 13.2%, Grade 2 in 7.4%, Grade 3 in 7.4%; constitutional sx: Grade 1 in 25%, Grade 2 in 35.3%, Grade 3 in 23.5%; Grade 4 in 1.5%; dermatologic/skin: Grade 1 in 23.5%, Grade 2 in 44.1%, Grade 3 in 13.2%; endocrine: Grade 1 in 1.5%, Grade 2 in 8.8%, Grade 3 in 1.5%; GI: Grade 1 in 4.4%, Grade 2 in 27.9%; Grade 3 in 60.3%; Grade 4 in 5.9%; Grade 5 in 1.5%; hemorrhage: Grade 1 in 19.1%; hepatic: Grade 1 in 30.8%, Grade 2 in 13.2%, Grades 3 and 4 in 1 pt each (1.5%); infection febrile neutropenia: Grade 1 in 5.9%, Grades 2 and 3 in 5 | Poor |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | 4.6) | | | pts each (7.4%), Grades 4 and 5 in 1 pt each (1.5%); lymphatic: Grade 1 in 2.9%, Grade 2 in 1.5%; metabolic: Grade 1 in 23.5%, Grade 2 in 13.2%, Grade 3 in 16.1%, Grade 4 in 4.4%; musculoskeletal: Grade 1 in 1.5%, Grades 2 and 3 in 2 pts each (2.9%); neurology: Grade 1 in 30.8%, Grade 2 in 8.8%, Grade 3 in 4.4%, Grade 4 in 1.5%; ocular/visual: Grade 1 in 2.9%, Grade 2 and 3 in 1 pt each (1.5%); pain: Grade 1 in 10.3%, Grade 2 in 30.9%, Grade 3 in 14.7%, Grade 4 in 1.5%; pulmonary: Grade 1 in 14.7%, Grade 2 in 10.3%, Grades 4 and 5 in 1 pt each (1.5%); renal/genitourinary: Grade 1 in 17.6%, Grade 2 in 10.3%, Grade 3 in 2.9%; sexual/reproductive function: Grade 1 and 2 in 1 pt each (1.5%), Grade 3 in 4.4%; worst overall acute toxicity: 3 pts (4.4%) died (Grade 5 acute toxicity) due to complications of IMRT (dysphagia/esophagitis at 83 days, febrile neutropenia at 80 days, pneumonitis at 74 days after start of IMRT); 8 pts (11.8%), Grade 4; 42 pts (61.8%), Grade 3; 12 pts (17.6%), Grade 2; 3 pts (4.4%), Grade 1; most common acute Grade 4 toxicities: 4 cases leukopenia; 3 cases anorexia; 3 cases radiation mucositis; 2 cases hyponatremia; 2 cases neutropenia; mucositis/stomatitis toxicities were 20 pts (29.4%) Grade 2, 25 pts (36.8%) | |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | | | Grade 3, and 3 pts (4.4%) Grade 4. Late toxicities (64 pts): skin (w/in radiation field): Grade 1 in 25%, Grade 2 in 4.7%; mucous membrane: Grade 1 in 40.6%, Grade 2 in 20.3%, Grade 3 in 3.1%; subcutaneous tissue (w/in radiation field): Grade 1 in 23.4%, Grade 2 in 4.7%, Grade 3 in 1.6%; salivary gland: Grade 1 in 42.6%, Grade 2 in 29.7%, Grade 3 in 3.1%; esophagus: Grade 1 in 21.9%, Grade 2 in 14.1%, Grade 3 in 4.7%; larynx: Grade 1 in 15.6%, Grade 2 in 3.1%; spinal cord: Grade 1 in 4.7%; brain: Grade 1 in 3.1%; bone (including osteonecrosis): Grades 1 and 2 in 1.6% each; joint: Grade 1 in 15.6%, Grade 2 in 1.6%; auditory/hearing: Grade 1 in 21.9%, Grade 2 in 6.3%, Grade 3 in 7.8%; worst late toxicity: 13 pts (20.3%), Grade 3 late toxicity, most commonly hearing impairment and dysphagia; 28 pts (43.8%, Grade 2 late toxicity); 18 pts (28.1%, Grade 1 late toxicity); worst late xerostomia scores: 19 pts (29.7%), grade 2; 2 pts (3.1%), grade 3; 1-yr estimated rates of grade 1 and 2 xerostomia were 51.9% (95% CI, 37.6-66.0) and 13.5% (95% CI, 5.6-25.8); total of 7 pts had grade 2 xerostomia at 1 yr. | |
| Lin (2009)<br>Case series<br>**Nasophaynge** | n = 323<br><br>248 men, 75 | Inclusion: histological dx'd, | IMRT delivered with Elekta | Before July 2006: Total dose of 66 Gy, | n/a (no control or comparison group) | Acute toxicities (n=323 pts): Grade 3 mucositis in 89 pts (27.5%); Grade 3 skin desquamation in 15 pts (4.6%); | Poor |

| Individual studies (published after review) | | | | | | | |
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| 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 Cancer** | women; 83% pts were <60 yrs, 17% were ≥60 yrs; 19.5% Stage II, 51.4% Stage III, 29.1% Stage IVA/B; Karnofsky performance status >90 in 86.4%, 80-90 in 12.7%, and 70-80 in 0.9%; 64 pts received boost tx; all 260 pts w/ Stage II-IVB disease and 25 Stage II pts received cisplatin-based neoadjuvant chemotherapy ; concurrent cisplatin-based chemotherapy in 47 pts w/ locregionally advanced disease | nonmetastati c NPC; Exclusion: failure to complete planned irradiation to definitive dose | Precise linear accelerator and 40-leaf MLC<br><br>F/U:Follow-up every 3 mos in first 2 yrs, every 6 mos for yrs 2-5, then annually; median 30 mos (4-53) | 30 fractions, 2.2 Gy/fraction; After July 2006: total dose of 69.75 Gy, 31 fractions, 2.25 Gy/fraction | | Grade 3 leukocytopenia in 19 pts (5.9%) and Grade 4 leukocytopenia in 1 pt (0.3%). Late toxicities: Grade 1-2 xerostomia was most frequent late effect. There were no cases of Grade 3 or 4 xerostomia. Xerostomia at 3 mos (n=315): Grade 1, 16 pts (5.1%); Grade 2, 299 pts (94.9%); at 6 mos (n=303): Grade 0, 2 pts (0.7%); Grade 1, 32 pts (10.9%); Grade 2, 269 pts (88.5%); at 12 mos (n=235): Grade 0, 9 pts (3.8%); Grade 1, 76 pts (32.3%); Grade 2, 150 pts (63.8%); at 24 mos (n=131): Grade 0, 7 pts (5.4%); Grade 1, 114 pts (86.8%); Grade 2, 10 pts (7.8%). Other harms: 2 pts developed infection or bleeding followed by necrosis in postnasal space at 6 and 12 mos after IMRT; both pts declined medical attention and deceased, which was considered Grade V toxicity. | |
| Little (2012) Case series **Oropharyngea** | Prospective case series 78 patients with | Stage III-IV cancer; no previous | Intervention : IMRT Comparator: | mean dose of <39 Gy Concurrent | See harms | Salivary flow rates, patient reported xerostomia, observer-graded xerostomia: | Fair |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| **l and nasopharyngeal cancer** | Stage III-IV cancer; all receiving chemotherapy | therapy; Karnofsky performance status > 60. | none<br><br>F/U:24 months | carboplatin (area under the curve, 1) and paclitaxel 30 mg/m2 once weekly were delivered to the oropharyngeal cancer patients and cisplatin 100 mg/m2 every 3 weeks to the nasopharyngeal cancer patients | | Xerostomia is related to the dose given to the oral cavity, minor salivary glands and contralateral parotid glands. | |
| Mendenhall (2009)<br>Case series<br>**Oropharyngeal Cancer** | n = 130<br><br>Primary tumor site: 67 tongue base, 46 tonsillar fossa, 11 soft palate, 4 anterior tonsillar pillar, 2 posterior tonsillar pillar; T-stage: 30 T1, 53 T2, 26 T3, 21 T4; N-stage: 27 N0, | Inclusion criteria: Advanced squamous cell carcinoma of the oropharynx that had no prior treatment; Exclusion criteria not reported | IMRT in all patients and chemotherapy in 61% patients<br><br>F/U: Median 3.5 yrs (range 0.2-7.7) | 70 Gy in 35 fractions (9% patients) or 72 Gy in 42 fractions (2% patients) or 74.4 Gy in 62 fractions (89%) patients | n/a (no control or comparison group) | Acute toxicity: Temporary gastrostomy tube needed in 39% patients and 15% patients hospitalized primarily for dehydration and/or neutropenic fever during or shortly after IMRT; Death from dehydration 1 month after IMRT in 1% patients who did not have gastrostomy; Late complications: Osteoradionecrosis in 3% patients, permanent gastrostomy in 2% patients, permanent gastrostomy and tracheostomy in 1% patients, soft tissue necrosis and hemorrhage in 1% patients, fusion of soft palate and oropharyngeal wall in 1% patients, | Poor<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator group and retrospective analysis; Exclusion criteria not |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 17 N1, 7 N2a, 61 N2b, 10 N2c, 8 N3; AJCC stage: 3 stage I, 10 stage II, 24 stage III, 65 stage IVa, 28 stage IVb; Histological differentiation: 73 well or moderate or not otherwise specified, 57 poorly differentiated | | | | | soft-tissue and cerebellar necrosis in 1% patients | reported; Patient age and sex not reported; Grade of complications not reported |
| Miah (2012) Case Series **Laryngeal and Hypopharyngeal Cancer** | n = 60<br><br>#1 (n=29): Mean age 58 yrs, range 35-80; men, 79%; performance status 0, 83%; 1, 17%; Larynx, 59%; Hypopharynx, 41%; T1-2, 31%, T3, 48%, T4a, 21%; N0, 35%, N1, 24%; N2, 35%; N3, 6%; TNM stage | Adults with histologically proven malignancy suitable for primary chemotherapy-IMRT | IMRT; induction chemotherapy plus chemotherapy on Days 1 and 29 of IMRT<br><br>F/U: #1: Median 49 mos. #2: Median 36 | #1: 63 Gy/28 fractions/38 days to primary site and involved nodal levels; 51.8 Gy to elective nodal levels. #2: 51.8 Gy/28 fractions (9% increase in biologically equivalent dose) and 56 Gy/28 fractions | #1: Outcomes at 2 years from initial diagnosis (Kaplan-Meier analysis for survival): #1. Follow-up*, median 51.2 mo (12.1-77.3 mo); local control, 70.8% (49.7-84.3%); locoregional control, 67.6% (46.7-81.7%); locoregional progression-free survival, 64.2% (43.5-78.9%); disease-free survival, 61.5% (58.8-89.9%); larynx preservation, 88.7% (68.5-96.3%); overall survival, 72.4% (52.3-85.1%). #1. Follow-up*, median 36.2 mo (4.2-63.3 mo); local control, 85.9% (66.7-94.5%); locoregional control, 81.8% (61.6-92.1%); locoregional progression- | #1: Dermatitis: 22 patients (76%), grade 1 or 2; 7 patients (24%), grade 3. Dysphagia-pharyngeal: 11 patients (38%), grade 0-2; 17 patients (59%), grade 3; 1 patient (38%), grade 3. Dysphagia-esophageal: 11 patients (59%), grade 1 or 2; 17 patients (59%), grade 3; 1 patient (4%), grade 4. Dysphagia-esophageal at 8 weeks: 22 patients (84%), grade 0-2; 3 patients (12%), grade 3; 1 patient (4%), grade 4. Fatigue: 25 patients (68%), grade 1 or 2; 4 patients (14%), grade 3. Mucosis: 16 patients (55%), grade 0-2; 13 patients (45%), grade 3. Pain: 23 patients (80%), grade 1 or 2; 6 patients (21%), grade 3. Xerostomia: 26 | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | III-IVB, 94%; neoadjuvant chemotherapy according to protocol, 100%; concomitant chemotherapy completed full schedule, 100%. #2 (n=31): Mean age 31 yrs, range 18-63; performance status 0, 97%; 1, 3%; Larynx, 52%; Hypopharynx, 48%; T1-2, 23%, T3, 54%, T4a, 23%; N0, 42%, N1, 23%; N2, 35%; N3, 0; TNM stage III-IVB, 94%; neoadjuvant chemotherapy according to protocol, 100%; concomitant chemotherapy | | | | free survival, 78.4% (58.1-89.7%); disease-free survival, 78.4% (58.1-89.7%); larynx preservation, 96.4% (77.2-99.5%); overall survival, 74.2%% (55.0-86.0%). Functional outcomes: 1 patient (Dose level #2) died of aspiration despite gastrotomy feeding; no cases, silent aspiration; 4 cases (14%) Dose Level 1 and 6 cases (19%) with Dose Level 2, aspiration risk; 2 cases (6%) laryngeal penetration, resolved with therapy. (Videofluoroscopy performed in 6 Dose Level 1 and 9 Dose Level 2 patients within 90 days after RT.) Response rate: Complete (#1, #2): 79%; 84%; partial (#1, #2): 21%, 13%; progressive disease, 1 patient. *Unclear why these follow-up rates differ from those reported for study overall. Neither survival curve reached median survival. | patients (89%), grade 0-2; 3 patients (10%), grade 3. #2: Dermatitis: 24 patients (77%), grade 1 or 2; 7 patients (23%), grade 3. Dysphagia-pharyngeal: 2 patients (6%), grade 2; 27 patients (87%), grade 3. Dysphagia-esophageal: 4 patients (13%), grade 2; 27 patients (87%), grade 3. Dysphagia-esophageal at 8 weeks: 23 patients (77%), grade 0-2; 7 patients (23%), grade 3. Fatigue: 26 patients (84%), grade 1 or 2; 5 patients (16%), grade 3. Mucosis: 17 patients (55%), grade 1 or 2; 14 patients (45%), grade 3. Pain: 21 patients (68%), grade 1 or 2; 10 patients (32%), grade 3. Xerostomia: 23 patients (75%), grade 1 or 2; 8 patients (26%), grade 3. LATE EFFECTS-SUBJECTIVE, OBJECTIVE, MANAGEMENT, AND ANALYTIC SCALE: #1: Skin: 21 patients (95%), grade 1 or 2. Mucosa: 21 patients (100%), grade 0-2. Subcutaneous tissue: 21 patients (100%), grade 1 or 2. Larynx: 21 patients (100%), grade 0-2. Esophagus: 20 patients (96%), grade 1 or 2; 1 patient (5%), grade 3. Salivary gland: 21 patients (100%), grade 0-2. Spinal cord: 21 patient (100%), grade 0. #2: Skin: 24 patients (100%), grade 1 or 2. Mucosa: 24 patients (100%), grade 0-2. Subcutaneous tissue: 24 patients (100%), grade 0-2. Larynx: 24 patients | |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | completed full schedule, 97%. | | | | | (100%), grade 0-2. Esophagus: 22 patients (89%), grade 1 or 2; 1 patient (4%), grade 3; 1 patient (4%), grade 4. Salivary gland: 24 patients (100%), grade 0-2. Spinal cord: 24 patients (100%), grade 0. FAILURE: #1: 9 patients (31%), locoregional; 8 patients (28%), persistent/relapsed disease at primary site; 1 patient, relapsed in neck. 4 patients (14%) proceeded to laryngectomy, 5 patients (17%) inoperable or unfit to proceed to radical surgery. 11 patients (38%), distant metastases. #2: 5 patients (16%), locoregional; 4 patients (13%), persistent/relapsed disease at primary site; 1 patient, relapsed in neck. 2 patients (6%) proceeded to laryngectomy, 5 patients (17%) inoperable or unfit to proceed to radical surgery. 11 patients (38%), distant metastases. MORTALITY: #1: 11 PATIENTS (38%); #2: 8 PATIENTS (28%) | |
| Moon (2011) Case series **Head and Neck Cancer** | n = 51 <br><br> Median age: 57 yrs (range 24-77); Sex: 34 men, 17 women; Primary tumor site: 19 tongue, 3 tongue base, 1 | Inclusion criteria: Newly diagnosed head and neck squamous cell carcinoma treated with curative | All patients underwent surgery followed by IMRT but IMRT was administered as tomotherapy in 35% patients; | Planning Clinical Target Volume of 63 Gy in 30 fractions | n/a (no control or comparison group) | Grade 3 acute skin toxicity in 6 patients; Grade 3 acute mucous membrane toxicity in 6 patients; Grade 3 acute esophageal toxicity in 1 patient; Late Grade 3 skin toxicity in 1 patient; Late Grade 3 xerostomia in 5 patients | Poor |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | mouth floor, 1 hard palate, 1 gingiva, 1 retromolar trigone, 15 tonsil, 2 vallecula, 5 larynx, 3 hypopharynx; AJCC stage: 2 Stage I, 6 Stage II, 8 Stage III, 35 Stage IV | intent; Exclusion criteria: Not reported | chemotherapy in 4% patients<br><br>F/U: Median 32 months (range 5-78) | | | | |
| Ng (2011)<br>Case series<br>**Nasophayrngeal Cancer** | n = 193<br><br>69% men, 31% women; median age 50 yrs (21-88); 98% had performance status of 0-1; 7% Stage I-II, 93% Stage III-IV; 41.5% induction and concurrent chemotherapy, 42.5% concurrent and adjuvant chemotherapy | Inclusion: dx of NPC; Exclusion: evidence of distant metastasis | IMRT delivered by Varian Millennium MLC (120 leaves) using 6 MV X-ray beams<br><br>F/U: Follow-up every 2-3 mos during first 2 yrs, then every 3-4 mos during yrs 3-5; median 30 mos (4-46) | Before September 2005: 59.4 or 70 Gy in 33 fractions, depending on the target area; from October 2005: 61.25 or 70 Gy in 35 fractions or 52.5 in 30 fractions, depending on the target area; 5-6 fractions/wk; median IMRT tx length 41 | n/a (no control or comparison group) | Frequency of worst acute toxicity related to IMRT (n=193): skin toxicity: Grade 3, 26 pts (13.5%); mucosa: Grade 3, 125 pts (64.8%); dysphagia: Grade 3, 28 pts (14.5%); no Grade 4 acute toxicities. Acute Grade 5 toxicities related to pneumonia or fulminant sepsis occurred in 3 pts (1.5%); 2 events occurred 2 wks after concurrent chemoradiotherapy, the other one occurred in frail elderly women after tx w/ 56 Gy RT. | Fair |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | ; accelerated fractionation in 62% | | | days (39-68) | | | |
| Palazzi (2009) Case series **Nasophaynge al Cancer** | n = 87<br><br>61 men, 21 women; median age 48 yrs (21-75); conventional 2D RT in 45%, conventional 3D in 29%, IMRT in 26%; Stage III in 36% and Stage IV in 39%; 93% received concomitant chemotherapy , 69% received both induction and concomitant chemotherapy | Pathologically confirmed NPC tx'd by RT | RT (IMRT, conventiona l 2D RT, or conventiona l 3D RT)<br><br>F/U: Follow-up at 2-3 mos after RT completion, then every 3-6 mos for first 3 yrs, then annually; median 3.8 yrs (1.04-8.02) | For IMRT: mean PD for low-dose PTV 50.6 Gy (50-54) and for high-dose PTV 69.1 Gy (66-70); for 3D RT: mean PD for low-dose PTV 52.3 Gy (50-54) and for high-dose PTV 68.9 Gy (66-70) | n/a (no control or comparison group) | No deaths related to tx. Severity of nearly all acute local toxicity increased in pts tx'd with induction chemotherapy. Severe dysphagia Grade >2 showed increase from 7% to 35%, weight loss Grade >1 showed increase from 14% to 36%, and risk of severe mucositis Grade >3 increased from 11% to 18%. Preliminary analysis of late toxicity suggests that xerostomia at 1 yr is milder in pts tx'd with IMRT (Grade 0 in 21%, Grade 1 in 47%, Grade 2 in 21%, and Grade 3 in 11%) than in pts tx'd w/ conventional RT (Grade 0 in 0%, Grade 1 in 12%, Grade 2 in 80%, and Grade 3 in 8%) | Fair |
| Pederson (2011) Case series **Oral Cavity** | n = 21<br><br>median age 52 (34-81); 81% men, 100% ECOG performance status 0-1; most had well- | Stage III-IVB or high-risk stage II squamous cell OCC, performance 0-2, no prior radiation, surgery or | concurrent chemothera py and IMRT, no comparator<br><br>F/U: median 53 mos for all pts, 60 | 1.5 Gy 2x/day (15 Gy per week) or with 2 Gy 1x/day (10 Gy per week fractionation to a total dose of 72-75 Gy | n/a | (**Note - below is taken from article toxicity text, no tables were in article**) feeding tubes: 14/21 pts required feeding tube at some point during tx; 12 had them placed during therapy, 2 before starting tx 3 pts had a feeding tube at death or last follow-up. Tracheostomy 2 pts with extensive T4a floor of mouth CA needed one placed | Fair |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (33%) or moderately- (57%) differentiated tumors; 61% had stage IV disease | chemo. No prior surgery. | mos for surviving pts. | | | before tx, 1 pt died with it in place, in other pt, it was removed after tx completion. Hematologic toxicity 4 pts with grade 4 including 4 cases of neutropenic fever. Skin toxicity Acute grade 2 (n=6), grade 3 (n-6) Grade 4 - 0 mucositis. Acute grade 2 (n=9), grade 3 (n=6), Grade 4 - 0. Late toxicity: included esophageal stricture in 2 pts in 1 pt, osteoradionecrosis in 3 pts. Mild or moderate xerostomia in 17 pts. Osteoradionecrosis occurred in 2 pts with buccal mucosa CA and in 1 pt with floor of mouth CA at 2-3 yrs post therapy. The tumors invaded the mandible in each case. Dental extraction preceded osteoradionecrosis in at least 1 instance. | |
| Peponi (2011) Case series **Head and Neck Cancer** | n = 82<br><br>68 men, 14 women; mean age 61 yrs (34-80); primary site of central oropharynx in 32%, lateral oropharynx in 35%, hypopharynx in 22%, and larynx in 11%; | Inclusion: Stage III/IV squamous cell carcinoma of larynx, oropharynx, or hypopharynx, tx'd by IMRT-SIB; Exclusion: locoregional recurrence at | Extended-field IMRT delivered by 6 MV dynamic MLC system from Varian<br><br>F/U: Subjective assessment at mean 20 mos (4-40), objective | For definitive IMRT: total dose 63-75 Gy (2.00-2.35 Gy/day) (n=63); for postoperative IMRT: total dose of 60-66 Gy (1.80-2.00 Gy/day) (n=19); mean total tx time 45.3 days (32- | n/a (no control or comparison group) | No acute toxicities reported. Late toxicities: overall subjective toxicity at first assessment (mean 20 mos, n=80): 14 pts (18%), Grade 3-4 (1 pt with swallowing pain, 2 pts with dysphagia, 9 pts with taste alteration, 3 pts with xerostomia); 66 pts (82%), Grade 0-2 toxicity; overall objective toxicity at second assessment (mean 32 mos, n=78): 8 pts (10%), Grade 3-4 toxicity (2 pts with dysphagia, 6 pts with xerostomia); study did not indicate whether other toxicities were noted at this follow-up assessment; prevalence | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | definitive IMRT in 77%, postoperative IMRT in 23%; concomitant chemotherapy in 85% | assessment of swallowing dysfunction; follow-up <4 mos at first assessment; tracheostomy tubes and/or laryngectomy; locoregional tumor stage ≤T1/2 N0 | assessment at mean of 32 mos (16-60), last follow-up assessment mean 50 mos (16-85) | 55) | | of long-term dysphagia: at first assessment (mean 20 mos, n=79): 77 pts (97%), Grade 0-2 dysphagia; 5 pts (6%), Grade 2 dysphagia; 1 pt (1.3%), Grade 3-4 dysphagia; no cases of aspiration pneumonia; at second assessment (mean 32 mos, n=77): 1 pt (1.3%), Grade 2-3 dysphagia (subjective and objective); weight loss/percutaneous endoscopic gastrotomy tubes (PEGs): before or during IMRT (n=82): 21 pts (26%), PEG tube placement, mean time to PEG tube removal 8 mos (5-25); at first assessment (mean 20 mos): 6 pts (7%), still using PEG tube for some or all nutrition; 2 pts remained PEG-dependent, the other 4 pts gained independence from PEG tube at 14, 16, 33, and 36 mos after end of IMRT; weight loss: median 5.1 kg (0-20), at 1 yr post-IMRT no pt had lost >10% body weight | |
| Saba (2009) Case series **Laryngeal and Oropharyngeal Cancer** | n = 80<br><br>62 men, 18 women; median age 57 yrs (34-79); primary tumor site of larynx in 19%, oropharynx in 81%; staging: | Pathologically proven squamous cell carcinoma (SCC) of larynx or oropharynx, tx'd definitively with IMRT | IMRT with concurrent chemotherapy; IMRT delivered by 6 MV photons use Varian linear accelerator with dynamic | Median dose 70.29 Gy (69.3-70.29) with median of 2.13 Gy/fraction (1.9-2.13) to primary gross target volume (GTV) and neck node GTV | n/a (no control or comparison group) | NOTE: Authors did not distinguish between IMRT and chemotherapy toxicities. Toxicities noted in red font are likely attributable to chemotherapy. Acute toxicities (Grade ≥2 in 80 patients): gastrointestinal: 11 patients (14%); hematologic: 11 patients (14%); renal: 2 patients (2.5%); cytopenias: 12 patients (15%); mucositis: 50 patients (62%); Chronic toxicities (Grade ≥2 in 80 patients): | Poor<br><br>Potential conflict of interest |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | Stage III 10%, Stage IVa 83%, Stage IVb 7% | and concurrent chemotherapy; Exclusion: Unknown primary malignancies; prior RT to head and neck; alternate fractionation schemes, oncologic resection of primary tumor as part of tx program | MLC<br><br>F/U: Median 31.2 mos | | | permanent feeding tube: 3 patients (4%); neck fibrosis: 1 patient (1%); ulcer: 1 patient (1%); xerostomia: 19 patients (24%); esophageal stricture: 8 patients (10%) (all had oropharyngeal malignancies, 2 needed permanent PEG tubes); all pts PEG tubes placed prophylactically, median duration 4.95 mos. | |
| Sanguineti (2011)<br>Case series<br>**Oropharyngeal Cancer** | n = 59<br><br>Mean age: 55 yrs (range 34-83); Sex: 48 men, 11 women; Primary tumor site: 37 tonsil, 10 tongue base, 9 soft palate, 3 pharyngeal wall; T-stage: 10 T1, 28 T2, | Inclusion criteria: Oropharyngeal cancer treated with IMRT; Exclusion criteria: Treatment with induction or concomitant chemotherapy | IMRT<br><br>F/U: Median 3 months (range 1 - >28 months) | 25 patients: 78 Gy in sixty 1.3 Gy fractions; 34 patients: 66 Gy in thirty 2.2 Gy fractions or 70 Gy in thirty-five 2 Gy fractions | n/a (no control or comparison group) | Confluent mucositis in 48 patients; Mean weight loss of 8% (range 1%-20%); Hospital admission for 9 patients for a median of 10 days (range 7-20); Percutaneous endoscopic gastrostomy tube needed by 22 patients for a median duration of 3 months (range 1.3->28); Enteral nutritional support required by 6 patients for >9 months and by 2 patients for >12 months | Poor<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator group and retrospective analysis; Incomplete reporting of |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 20 T3, 1 T4; N-stage: 17 N0, 8 N1, 7 N2a, 20 N2b, 2 N2c, 5 N3; AJCC stage: 2 stage I, 6 stage II, 16 stage III, 35 stage IV | | | | | | inclusion and exclusion criteria; Average follow-up <6 months; This study seems to involve the same patients as the study below by Feng et al. (2010) |
| Setton (2012)<br>Case series<br>**Oropharyngeal Cancer** | n = 442<br><br>Median age: 57 yrs (range 27-91); Sex: 379 men, 63 women; Tumor site: 221 tonsil, 202 tongue base, 12 pharyngeal wall, 7 soft palate; T-stage: 118 T1, 185 T2, 78 T3, 61 T4; N-stage: 41 N0, 94 N1, 296 N2, 11 N3; AJCC stage: 7 Stage I, 17 Stage II, 94 Stage III, | Inclusion criteria: Histologically confirmed oropharyngeal squamous cell carcinoma; Exclusion criteria: IMRT without chemotherapy, metastatic disease at baseline, prior head or neck radiotherapy | IMRT combined with chemotherapy<br><br>F/U: Median follow-up 37 months (range 3-135) | 70 Gy in 2.12 Gy fractions for 412 definitive cases; 66 Gy for 30 postop cases | n/a (no control or comparison group) | Acute gastrointestinal toxicities: Grade 1 in 588 patients, Grade 2 in 662 patients, Grade 3 in 202 patients, Grade 4 in 3 patients; Acute hearing toxicities: Grade 1 in 436 patients, Grade 2 in 204 patients, Grade 3 in 38 patients, Grade 4 in 1 patient; Peak of late xerostomia: Grade 1 in 272 patients, Grade 2 in 111 patients, Grade 3 in 6 patients; Other late toxicities: Dysphagia Grade 2-4 in 11% patients, Pharyngeal or esophageal stricture requiring dilatation in 8% patients (perforation during dilatation in 1 patient), Long-term gastrostomy in 7% patients (median gastrosomy duration 4 months, range 0-68) | Fair<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator group and retrospective analysis; Fractionation schedule for 66 Gy dosage not reported |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 324 Stage IV | | | | | | |
| Sher (2010) Case series **Head and Neck Cancer** | n = 35<br><br>Median age at first dx 51 (46-57), median age at 2nd tx (51-63), 71% male; ECOG performance status at retreatment was 0 in 18 pts, 1 in 16 pts, 2 in 1 pt | pts with hx of head and neck RT for SCC who had nonmetastatic SCC initially and subsequently | IMRT, + concurrent chemotherapy, no comparator<br><br>F/U: every 4-6 weeks in Year 1; every 2-3 mo in Year 2. | initial radiation dose 67.5 Gy (interquartile range 63-70 Gy) | n/a (no control or comparison group) | Acute toxicity: (within 90 days of tx completion) Mucositis No grades 0 or 1; Grade 2 9 (26%); Grade 3 15 (43%), Grade 4 0; Dermatitis No grades 0 or 1; ; Grade 2 16 (46%); Grade 3 8(23%); Grade 4 3(9%); Respiratory No grades 0 to 3; Grade 4 1(3%); Esophagitis - No grades 0 or 1; Grade 2 7(20%); Grade 3 - 27(77%); Grade 4 - 0; Other Grade 4 sepsis; Late toxicity >90 days after completion of radiotherapy, No Grades 0-2 in series Soft tissue necrosis Grade 3 1 (3%); Grade 4 0; Grade 5 1 (3%); Osteonecrosis Grade 3 1 (3%); Grade 4 1 (3%); Grade 5 0 Fibrosia Grade 3 2(6%); Grades 4 and 5 0; Trismus Grade 3 4(11%) Grades 4 and 5 0; Respiratory Grade 3 0; Grade 4 3(9%); Grade 5 2(6%); Esophageal Grade 3 17(49%); Grades 4 and 5 0; Dermatitis Grade 3 1(3%); Grade 4 3(9%) Grade 4 - 0; Other Grade 3 6(17%); Grade 4 0; Grade 5 1(3%). 4 pts died with late treatment-related events without evidence of disease These 4 grade 5 toxicities were 2 aspiration events (at 8 mo and 2.6 yrs, respectively, after tx); 1 fatal oropharyngeal hemorrhage (10 mo post tx) and 1 persistent infection leading to debilitation and hospice care (6 mo post tx). | Poor |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Sher (2011)<br>Case series<br>**Oral Cavity** | n = 42<br><br>Mean age at dx 56.5 yrs (+ 13.3)<br>28M/14F; ECOG performance status 0 37(88%); 1 5(12%). 55% had oral tongue cancer | All pts treated for OCSCC with adjuvant or definitive IMRT between Aug 2004 and Dec 2009 | Adjuvant RT or primary RT<br><br>F/U: Every 4 to 6 weeks in Year one and every 2 to 3 mo in Year 2; median follow-up for all pts 2.1 years(1.1-1.3 yrs) and median follow-up for all surviving pts was 2.4 yrs (1.3-3.2 yrs) | Varying schemes: differential dosing to target volumes was based on risk of harboring microscopic disease | n/a (no control or comparison group) | *Note: info given on adjuvant RT (ART) (n=30); primary RT (PRT) (n=12) and Total (n=42); percentages indicate percentages of the 42 pt total* Acute Toxicities Mucositis No grades 0 or 1; Grade 2 ART 2(7%)-PRT 1(8%)-Total3(7%); Grade 3 ART -28(93%)-PRT 11(92%)-TOTAL39(93%); No grades 4 Dermatitis Grade 2 ART 6(20%)-PRT 2(17%)-Total`34(10%); No grade 4; Esophagitis ART 3(10%)-PRT 2(17%)-Total 5(12%); Grade 3 ART 25(83%)-PRT 10(83%)-total 35(83%) No Grade 4 Soft tissue grade No grade 2; grade 3 ART 2(7%)-PRT 0-Total 2(5%); No grade 4; Late toxicity Dysphagia ART 9(30%)-PRT 1(8%)-Total 10(24%); Grade 3 ART 3(10%)-PRT 5(42%)-Total 8(19%); no grade 4; Xerostomia Grade 1 ART 12(40%)-PRT 5(42%)-Total17(40%); Grade 2 ART10(33%)-PRT 7(58%)-Total 17(40%); No grades 3 or 4; Bone and soft tissue grade Grade 1: 1 ART(3%)-Total 1(2%); Grade 2 ART 2(7%)-Total 2(5%); Grade 3 PRT 1(8%)-Total 1(2%) ***Please see article for more detail on individual cases from table above and for extensive discussion of 38 pts treated with prophylactic PEG tubes.*** | Poor |
| Strigari (2010)<br>Case series<br>**Head and Neck Cancer** | n = 63<br><br>43 men, 20 women; tumor site of | Inclusion: biopsy-proven epithelial carcinoma of | IMRT delivered using Varian 2100CD linear | PD to PTV of GTV was 70 Gy, to PTV of CTV1 was 60 Gy, and PTV of | n/a (no control or comparison group) | Univariate analysis showed that primary tumor site and mean dose/volume of major salivary glands were prognostic factors of xerostomia. Multivariate analysis showed that | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | nasopharynx in 70%, mouth/oral cavity in 3%, oropharynx in 17%, hypopharynx in 7%, unknown in 3%; 78% received chemotherapy ; 27% had Stage I-II, 73% had Stage III-IV cancer | head-and-neck; Exclusion: distant metastasis | accelerator w/ 120-leaf MLC<br><br>F/U: NR | CTV2 was 54 Gy in 33 fractions with the SIB; mean dose to parotid gland of 31.8 Gy (7.7-46.7) and 55 Gy (13-65.4) to submandibular glands; mean dose to TG (whole organ or both glands) 35.9 Gy (8.8-50.3) | | mean dose to TG (P=0.00066) and pre-tx stimulated salivary flow (SSF) (P=0.00420) were significant independent predictors of xerostomia in the whole group. However, in the NPC cohort the multivariate analysis found that TG mean dose was not a significant predictor of xerostomia, but SSF at pre-tx had a trend toward significance (P=0.033). The duration of xerostomia seem to depend on mean dose of TG and showed a borderline correlation (r=0.265, P=0.042). <u>Frequency of harms not reported</u> | |
| Studer (2010)<br>Case series<br>**Laryngeal and Hypopharyngeal Cancer** | n = 123<br><br>Age range, 34-87 years; men, 105; women, 18; hypopharynx, 52.8%; glottis, 21.9%; supraglottis, 25.2%; T1, 7.3%; T2, 39%; T3, 26.8%; T4, 21.9%; recurrence, 4.8%; N0, | Hypopharyngeal or laryngeal carcinoma; IMRT with curative intent; no postoperative IMRT; no early glottic tumors | IMRT with SIB<br><br>F/U:Mean 26 months (range, 3-83 months) | First 7 patients: 2.2 Gy/fraction in 30 fractions to 66 Gy (5 fractions/week ); 72 patients received 2.11 Gy/fraction in 33 fractions to 69.6 GY to the boost planning target volume (5 fractions/week ); 44 patients | n/a (no control or comparison group) | Tracheostoma: 2 patients (1.6%) during IMRT because of edema and 3 patients 2.4%) after IMRT because of dyspnea, stenosis, or dysfunction. Laryngectomy: 13 patients 10.6%) after IMRT because of necrosis or salvage. Feeding tube: 36 patients (29%) before or during IMRT. At last follow-up, 75% of patients were without laryngectomy, tracheostoma, or feeding tube. | Fair<br><br>Harms comparison to results of other studies was within discussion of article |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 29.2%; N1, 10.6%; N2a/b, 31.7%; N2c, 21.9%; N3, 4.9%; recurrence, 1.6% Concomitant systemic therapy: Cisplatin, 80.4%; cetuximab, 4.9%; none, 14.6% | | | received 2.0 Gy/fraction to 70 Gy (5-6 fractions/week ) | | | |
| Su (2012) Case series **Nasopharyngeal Cancer** | n = 198<br><br>146 men, 52 women; median age 45 yrs (31-77); Stage I 25.8%, Stage IIa 3.0%, Stage IIb 71.2%; no pts received chemotherapy | Inclusion: histologically proven, newly dx'd Stage I-IIB NPC Exclusion: distant metastases | IMRT using SMART boost RT<br><br>F/U: Follow-up monthly for 3 mos, every 3 mos through 3 yrs, every 6 mos for next 2 yrs, then annually; median 50.9 mos (range 12-104) | 68 Gy at 2.27 Gy/fraction, 30 fractions | n/a (no control or comparison group) | Acute toxicities (in 198 pts): mucositis: Grade 1, 54 pts (27.3%); Grade 2, 117 pts (59.1%); Grade 3, 27 pts (13.6%); pharyngitis: Grade 0, 2 pts (1.0%); Grade 1, 141 pts (71.2%); Grade 2, 53 pts (26.8%); Grade 3, 2 pts (1.0%); xerostomia: Grade 0, 14 pts (7.0%); Grade 1, 113 pts (57.1%); Grade 2, 71 pts (35.9%); no Grade 3 acute xerostomia; no Grade 4 acute toxicities for any category. Late toxicities (in 64 pts): xerostomia at 12 mos (n=78): Grade 0, 20 pts (25.6%); Grade 1, 46 pts (59.0%); Grade 2, 12 pts (15.4%); xerostomia at 24 mos (n=78): Grade 0, 30 pts (38.4%); Grade 1, 41 (52.6%); Grade 2, 7 pts (9.0%); no Grade 3 or Grade 4 xerostomia; 62 pts (96.9%) did not have trismus; 2 pts (3.1%) had | Poor<br><br>Late toxicity data only from 64 pts (32%) of study sample |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | | | Grade 1 trismus; no pts had late radiation encephalopathy or cranial nerve injury. | |
| Tham (2009) Case series **Nasopharyngeal Cancer** | n = 195<br><br>median age 52 yrs (24-86); male:female ratio of 2:1; 11% Stage I, 2% Stage IIA, 24% Stage IIB, 33% Stage III, 23% Stage IVA, 7% Stage IVB; 10% received intracavitary brachytherapy, 19% neoadjuvant chemotherapy, 57% concurrent chemotherapy, 35% adjuvant chemotherapy | Newly dx'd, histologically proven, nonmetastatic NPC; fit enough to tolerate RT or chemotherapy-enhanced RT | IMRT delivered using Varian 21EX linear accelerator w/ dynamic 120-leaf MLC; IMRT median tx duration 47 days (39-56)<br><br>F/U: monthly for yr 1, every 2 mos for yr 2, every 3-6 mos for yrs 3-5, then annually; median 36.5 mos | 70 Gy, 2.0-2.12 Gy/fraction over 33-35 fractions over 6.6 wks, 1x/day, 5x/wk | n/a (no control or comparison group) | Acute toxicities: dermatitis: Grades 0-2 in 102 pts (98%) (chemo +) and in 77 pts (100%) (chemo -); Grade 3 in 2 pts (2%) (chemo +) and 0 (chemo -); no Grade 4 dermatitis toxicities; mucositis: Grades 0-2 in 75 pts (71%) (chemo +) and in 63 pts (80%) (chemo -); Grade 3 in 30 pts (29%) (chemo +) and 15 pts (20%) (chemo -); dysphagia: Grades 0-2 in 83 pts (79%) (chemo +) and in 73 pts (92%) (chemo -); Grade 3 in 22 pts (21%) (chemo +) and 6 pts (8%) (chemo -); xerostomia: Grades 0-2 in 101 pts (97%) (chemo +) and in 77 pts (100%) (chemo -); Grade 3 in 3 pts (3%) (chemo +) and 0 (chemo -); no Grade 4 acute toxicities for any pts. Median weight loss 4 kg (-1.2 to 15.1). | Poor |
| Tham (2010) Case series **Nasophaynge al Cancer** | n = 107<br><br>67 men, 40 women; median age 48 yrs (21-86); 9 pts Stage T1, 4 | Biopsy proven, stage IIB NPC | IMRT delivered using Varian 21 EX linear accelerator w/ 120-leaf MLC or | 66-70 Gy delivered in 30-35 fractions | n/a (no control or comparison group) | Acute toxicities: dermatitis: Grade 1, 76 pts (71%); Grade 2, 27 pts (25%); Grades 3, 0 pts; 4 pts were missing data; mucositis: Grade 1, 36 pts (34%); Grade 2, 43 pts (40%); Grade 3, 24 pts (22%); 4 pts missing data; neutropenia: Grade 1, 27 pts (25%); Grade 2, 20 pts | Fair<br><br>Longer follow-up may be needed for late toxicity, findings may |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | pts Stage T2a, 94 pts Stage T2b; 18% received boost tx; 43% received any chemotherapy, 36% received abbreviated neoadjuvant chemotherapy, 7% concurrent chemotherapy, 15% adjuvant chemotherapy | | Elekta Precise linear accelerator w/ 40-leaf MLC; IMRT delivered 1x/day, 5 days/wk; median IMRT tx duration 45 days (40-54)<br><br>F/U: Follow-up every 1-3 mos for 2 yrs, every 6 mos for yrs 3-5, then annually; median 39 mos (7-77) | | | (19%); Grade 3, 1 pt (0.9%); 3 pts missing data. No Grade 4 acute toxicities. Late toxicities: generally mild, mainly mild-to-moderate xerostomia (no data reported). | not be generalizable to pts who have later stages of NPC |
| Traynor (2010)<br>Case series<br>**Head and Neck Cancer** | n = 57<br><br>Median age: 55 yrs (range 36-77); Sex: 50 men, 7 women; Karnofsky Performance Status: 52 ≥90, 5 between 70 | Inclusion criteria: Stage III or IV sqamous cell carcinoma or the head and neck, curative intent, unilateral neck metastasis, | All patients treated with IMRT and concurrent chemotherapy with cisplatin<br><br>F/U: Median 27 months | Median dose to the high-risk Planning Target Volume was 70 Gy IMRT delivered in 2.0 to 2.2 Gy fractions | n/a (no control or comparison group) | Acute leukopenia, neutropenia or anemia: Grade 2 in 50% patients, Grade 3 in 14% patients, Grade 4 in 4% patients; Acute mucositis: Grade 2 in 42% patients, Grade 3 in 51% patients; Acute anorexia: Grade 2 in 30% patients, Grade 3 in 23% patients; Acute nausea and vomiting: Grade 2 in 48% patients, Grade 3 in 23% patients; Acute dehydration: Grade 2 in 39% patients, Grade 3 in 14% patients; | Poor<br><br>Conflict of interest not addressed; Poor quality due to no control or comparator group and retrospective |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | and 90; Tumor site: Nasopharynx 6, tongue base 21, tonsil 18, larynx 3, hypophayrnx 2, maxillary sinus 2, parotid 1, unknown 4; T-stage: 4 T0 or Tx, 11 T1, 20 T2, 11 T3, 11 T4; N-stage: 9 N0, 4 N1, 3 N2a, 30 N2b, 4 N2c, 4 N3; Stage III in 6 patients, Stage IV in 51 patients | bilateral disease below the parotid glands, superior pharyngeal disease and desire to spare the optic structures and central nervous system, patients medically eligible for cisplatin chemotherapy; Exclusion criteria: Not reported | | | | Acute fatigue: Grade 2 in 40% patients, Grade 3 in 5% patients; Chronic xerostomia: Grade 1 in 48% patients, Grade 2 in 46% patients; Chronic laryngeal edema: Grade 1 in 14% patients, Grade 2 in 12% patients; Chronic neck fibrosis: Grade 1 in 10% patients, Grade 2 in 30% patients; Chronic esophageal strictures: Grade 2 in 4% patients; Grade 3 hyperkalemia in 4% patients; Hospitalization required in 21% patients; Gastrostomy tube placed before treatment in 60% patients and retained in 20% patients at 6 months and 3% patients at 12 months | analysis; Acute Grade 1 complications not reported |
| Van Gestel (2011)<br>Case series<br>**Head and Neck Cancer** | n = 78<br><br>54 men, 24 women; median age 60 yrs (34-82); performance status 0 in 34 pts, 1 in 43 pts, unknown | Newly dx'd early and locoregionally advanced HNC, tx'd w/ IMRT | IMRT as definitive tx (n=48) or postoperatively (n=30); inverse-planned step-and-shoot IMRT delivered w/ | PD varied from 66-70 Gy when IMRT was definitive tx or 60-70 Gy when IMRT was used postoperatively | n/a (no control or comparison group) | ACUTE TOXICITIES: all pts (n=78): skin: 7 pts (9.0%), Grade 0; 44 pts (56.4%), Grade 1; 22 pts (28.2%), Grade 2; 5 pts (6.4%), Grade 3; mucosa: 0 pts, Grade 0-1; 13 pts (16.7%), Grade 2; 64 pts (82.1%), Grade 3; 1 pt (1.3%), Grade 4; IMRT only (n=18): Skin: 3 pts (16.7%), Grade 0; 8 pts (44.4%), Grade 1; 6 pts (33.3%), Grade 2; 1 pt (5.6%), Grade 3; mucosa: 0 pts, Grade 0-1; 1 pt (5.6%), | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | in 1 pt; primary tumor stage Stage I in 9.0%, Stage II in 25.6%, Stage III in 20.5%, Stage IV in 43.6%, unknown in 1.3% | | Elekta SLi accelerator using 6 MV photons; pts tx'd on 5 consecutive days/wk<br><br>F/U: Follow-up every month for first yr, every 2 mos in second yr, then every 3-6 mos; median (18.7 mos (4 days to 51.7 mos) | | | Grade 2; 17 pts (94.4%), Grade 3; IMRT + concurrent chemo (n=10): skin: 1 pt (10%), Grade 0; 6 pts (60%), Grade 1; 3 pts (30%), Grade 2; mucosa: 0 pts, Grade 0-1; 3 pts (30%), Grade 2; 7 pts (70%), Grade 3; postoperative IMRT (n=23): skin: 1 pt (1.3%), Grade 0; 13 pts (56.5%), Grade 1; 5 pts (21.7%), Grade 2; 4 pts (17.4%), Grade 3; mucosa: 0 pts, Grades 0-1; 4 pts (17.4%), Grade 2; 19 pts (82.6%), Grade 3; postoperative IMRT + concurrent chemo (n=7): skin: 0 pts, Grade 0; 5 pts (71.4%), Grade 1; 2 pts (28.6%), Grade 2; mucosa: 0 pts, Grades 0-1; 2 pts (28.6%), Grade 2; 5 pts (71.4%), Grade 3; induction chemo + IMRT (n=2): skin: 2 pts (100%), Grade 1; mucosa: 2 pts (100%), Grade 3; induction and concurrent chemo + IMRT (n=18): skin: 2 pts (11.1%), Grade 0; 10 pts (55.6%), Grade 1; 6 pts (33.3%), Grade 2; mucosa: 0 pts, Grades 0-1; 3 pts (16.7%), Grade 2; 14 pts (77.8%), Grade 3; 1 pt (5.6%), Grade 4. LATE TOXICITES: All pts (n=78): xerostomia, 34 pts (43.6%); neck fibrosis, 7 pts (9.0%); loss of taste, 11 pts (14.1%); bone problems, 3 pts (3.8%); dysphagia, 2 pts (2.6%); teeth problems, 3 pts (3.8%), ; IMRT only (n=18): xerostomia,7 pts (38.9%); neck fibrosis, 3 pts (16.7%); loss of taste, 3 pts (16.7%); bone problems, 1 pt | |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | | | (5.6%); dysphagia, 1 pt (5.6%); IMRT + concurrent chemo (n=10): xerostomia, 6 pts (60%); neck fibrosis, 1 pt (10%); loss of taste, 3 pts (30%); teeth problems, 1 pt (10%); postoperative IMRT (n=23): xerostomia, 10 pts (43.5%); neck fibrosis, 2 pts (8.7%); loss of taste, 1 pt (4.3%); bone problems, 2 pts (8.7%); postoperative IMRT + concurrent chemo (n=7): xerostomia, 2 pts (28.6%); teeth problems, 1 pt (14.3%); induction chemo + IMRT (n=2): no late toxicities; induction and concurrent chemo + IMRT (n=18): xerostomia, 9 pts (50%); neck fibrosis, 1 pt (5.6%); loss of taste, 4 pts (22.2%); dysphagia, 1 pt (5.6%); teeth problems, 1 pt (5.6%); tx'd by definitive IMRT still had feeding tube 2 yrs after end of IMRT, 1 pt (1.3%) . | |
| Wang (2011) Case series **Head and Neck Cancer** | n = 52<br><br>Mean age: 52 yrs (range 22-78); Sex: 28 men, 24 women; Tumor site: 17 tongue, 5 floor of mouth, 4 buccal mucosa, 11 gingiva, 3 hard | Inclusion criteria: Age >17 yrs, Eastern Cooperative Oncology Group performance status range 0-2, Intact contralateral submandibular salivary | IMRT which was postoperative for 47 patients and definitive for 5 patients<br><br>F/U: Median 25 months (range 19-30) | 30 to 33 fractions of 1.8 to 2.12 Gy (mean planning target volume 1 dose 69 Gy, range 62-72) | n/a (no control or comparison group) | Xerostomia 2 months after IMRT: Grade 1 in 23 patients, Grade 2 in 13 patients, Grade 3 in 2 patients; Xerostomia 6 months after IMRT: Grade 1 in 22 patients, Grade 2 in 11 patients, Grade 3 in 3 patients; For 26 patients who were able to undergo salivary gland sparing IMRT protocols, xerostomia was less severe at 2 months and 6 months (P<0.05) | Poor<br><br>Investigators reported they had no conflict of interest; Poor quality due to no control or comparator therapy; complications other than |

| *Individual studies (published after review)* | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | palate, 2 soft palate, 5 nasopharynx; Pathology: 43 squamous cell carcinoma, 9 other; T-stage: 10 T1, 26 T2, 8 T3, 8 T4; N-stage: 22 N0, 19 N1, 10 N2, 1 N3; UICC stage: 1 Stage I, 16 Stage II, 16 Stage III, 19 Stage IV | glands and more than 1 intact parotid salivary gland; Exclusion criteria: Prior head and neck radiation therapy, distant metastasis, concomitant malignancy, severe concurrent disease, Sjorgren's syndrome or any medical cause for xerostomia, chemotherapy, use of any medication that is known to affect salivary gland function | | | | | xerostomia not reported |
| Wong (2010) Case series **Nasopharyngeal Cancer** | n = 175<br><br>135 men, 40 women; | Biopsy proven, newly dx'd, non- | IMRT using whole-field SIB | 70 Gy delivered in 33 fractions w/in 6.5 wks; total | n/a (no control or comparison group) | Acute toxicities: skin reaction: Grade 1, 142 pts (81.1%); Grade 2, 26 pts (14.9%); no Grade 3 skin reactions; salivary function: Grade 1, 106 pts | Poor<br><br>Median follow-up |

| Individual studies (published after review) | | | | | | | |
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| **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 48 yrs (20-89); Stage IA in 10.9%, Stage IIA in 2.3%, Stage IIB in 21.7%, Stage II in 41.1%, Stage IVA in 14.9%, Stage IVB in 9.1%; 26% w/ early T-stage disease received brachytherapy boost, 127 w/ advanced local or regional disease received chemotherapy | metastatic NPC, tx'd by IMRT | F/U: median 34 mos (9-50) | median dose 70 Gy (66-76); median overall tx time of 44 days (38-58) | | (60.6%); Grade 2, 68 pts (38.9%); Grade 3, 1 pt (0.6%); mucositis (including pharyngitis): Grade 1, 57 pts (32.6%); Grade 2, 77 pts (44%); Grade 3, 41 pts (23.4%); no Grade 4 acute toxicities. Median weight loss just after IMRT completion was 8.5% (0.2-21.5%). Cox regression analysis showed that pts w/ Stage T4 disease had significantly greater risk of Grade 3-4 acute mucositis/pharyngitis (P=0.021) than pts w/ less severe T-stage disease. Late toxicities: neck fibrosis: Grade 1, 20 pts (11.4%); Grade 2, 3 pts (1.7%); trismus: Grade 1, 33 pts (18.9%); no Grade 2 trismus; deafness: Grade 1, 33 pts (18.9%); Grade 2, 1 pt (0.6%); xerostomia: Grade 1, 48 pts (27.4%); Grade 2, 4 pts (2.3%); no pt developed Grade 3 or 4 late toxicities. | likely too short for definitive conclusions regarding late toxicity |
| Xiao (2011) Case series **Nasopharyngeal Cancer** | n = 81<br><br>66 men, 15 women; median age 42 yrs (15-73); AJCC/UICC Stage: Stage III 60.5%, Stage IVa 39.5%; median | Inclusion: histologically confirmed NPC by biopsy; Stage T3-4N0-1M0 by AJCC/UICC criteria; adequate liver, renal, and bone | IMRT delivered by Varian linear accelerator (6 MV) using SMART boost technique; all pts received concurrent | 68 Gy to nasopharynx GTV delivered in 30 fractions | n/a (no control or comparison group) | No acute toxicities reported. Late toxicities (in 68 pts w/ ≥4 yrs follow-up): skin dystrophy: Grade 0, 44 pts (64.7%); Grade 1, 21 pts (30.9%); Grade 2, 3 pts (4.4%); Grades 3-4, 0 pts; subcutaneous fibrosis: Grade 0, 4 pts (5.9%); Grade 1, 41 pts (60.3%); Grade 2, 22 pts (32.4%); Grade 3, 1 pt (1.5%); Grade 4, 0 pts; hearing loss: Grade 0, 6 pts (8.8%); Grade 1, 38 pts (55.9%); Grade 2, 24 pts (35.3%); | Poor |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | volume of nasopharynx GTV 44.0 cm3 (7.88-205.49) | marrow function; Karnofsky performance status ≥80; Exclusion: evidence of distant metastasis; previous tx for NPC; previous malignancy or other concomitant disease | cisplatin chemotherapy during IMRT<br><br>F/U: Follow-up at 1 mo, 3 mos, then every 3 mos through 3 yrs, then annually; median 54 mos | | | xerostomia: Grade 0, 26 pts (38.2%), Grade 1, 39 pts (57.4%); Grade 2, 3 pts (4.4%); Grades 3-4, 0 pts; trismus: Grade 0, 63 pts (92.6%); Grade 1, 5 pts (7.4%); Grades 2-4, 0 pts; cataract: Grade 0, 67 pts (98.5%), Grade 1, 1 pt (1.5%); Grades 2-4, 0 pts; chronic dysphagia: Grade 0, 68 pts (100%); neuropathy: Grade 0, 65 pts (95.6%); Grade 1, 3 pts (4.4%), 2 pts had nerve injury prior to RT; Grades 2-4, 0 pts; temporal lobe necrosis: Grade 0, 57 pts (83.8%); Grade 1, 9 pts (13.2%); Grade 2, 2 pts (2.9%); brainstem injury: Grade 0, 67 pts (98.5%); Grade 1, 1 pt (1.5%); Grades 2-4, 0 pts; all pts w/ temporal lobe or brainstem injury after RT had primary bulky tumors w/ extensive skull base and intracranial tissue invasion; mandible necrosis: Grade 0, 68 pts (100%). Xerostomia appeared to decrease with time after tx; # of pts w/ Grade 2-3 xerostomia decreased gradually whereas # w/ Grade 0-1 xerostomia increased during follow-up period. No Grade 4 toxicities noted. | |
| Bonastre 2007<br>Prospective cost study (France)<br>**Head and Neck Cancer** | 99 (26 women, 73 men)<br><br>Head and neck cancer, average age 53 (range 18-83 years) | Patients undergoing IMRT at 9 French medical centers. Three centers began using | Patients were followed to end of treatment | Mean 68 Gy<br><br>Delivered in 33 fractions | *Cost of IMRT*<br>Mean direct cost per treatment was €5,962 (SD=€3,735)<br>Mean direct cost per treatment consisted of €3,174 (SD=€2,877) for manpower (53% of direct costs),<br>€1,693 (SD=529) for equipment, | N/A | Fair<br><br>All costs were based on 2005 Euros<br><br>Direct costs were assessed |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | IMRT at initiation of the study and 6 had previous experience using IMRT.<br>Studied variation of the direct cost of IMRT between patients and centers using a two level model with a random intercept<br>The learning process was modeled using a fixed rate of learning and random initiation levels | | | €927 (SD=€692) for IMRT-specific software, and €168 (SD=111) for supplies.<br><br>The full cost of treatment (including logistics and overhead) was estimated at €10,916 (SD=€6,454): €2,773 (SD=€2,249) for IMRT planning and €247 (SD=€170) per each treatment session<br><br>*Modeling learning effects*<br>Patient characteristics explained 46% of the variation of costs within centers and experience explained 42% of the variation of costs between centers (both were statistically significant).<br><br>For a new center initiating IMRT, the direct cost was €14,192. For the same patient starting treatment at an experienced, the direct cost was €6,332 | | from the perspective of the healthcare provider |

## Lung Cancer

| *Reviews* | | | | | |
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| **Reference<br>Study Design<br>Malignancy** | **# of Studies & Subjects** | **Intervention<br>Comparator<br>Follow-up** | **<u>Outcomes Assessed</u><br>Main Findings** | **Harms** | **Quality<br>Comments** |
| Staffurth (2010)<br>Veldeman (2008)<br>Systematic Review<br>**Non-small Cell Lung Cancer** | 1 study<br><br>N = 290 | Intervention: IMRT<br>Comparator: 3DCRT.<br>F/U: NR | NR | <u>Toxicity:</u> One non-randomized comparative study of IMRT (n=68) vs. 3DCRT (n= 222) both with the same dose of 63 Gy. Incidence of Grade 3 pneumonitis IMRT = 8%, 3DCRT = 32% p = 0.002. | Poor |
| De Neve (2012)<br>Systematic review<br>**Non-small Cell Lung Cancer** | 1 study<br><br>N = 409 | Intervention: 4DCT-base dIMRT<br>Comparator: non-IMRT (not specified)<br>F/U: NR | **Outcome: IMRT; non-IMRT, p-value**<br>**Overall survival**: HR 0.64 (95% CI, 0.41-0.98), p=0.039<br>**Locoregional progression –free survival**: HR 0.77 (95% CI, 0.43-1.36), p=0.37<br>**Distant metastasis-free survival**: HR 1.05 (95% CI, 0.72-1.53), p=0.81 | IMRT allowed significant reduction in the rates of Grade 3 or greater of radiation pneumonitis (although there were smokers and pretreatment PET investigations in the IMRT group) | Poor |
| Veldeman (2008)<br>Systematic review<br>**Non-small Cell Lung Cancer** | 1 study<br><br>N = 68 | Intervention: IMRT and concurrent chemotherapy<br>Comparator: Historical control<br>F/U: NR | NR | Lower incidence of Grade 3 or higher radiation pneumonitis in IMRT group (8%) than non-IMRT group (intervention not specified) (32%) (p=0.002) at 12 months.<br><br>Non-pulmonary toxic effects were not reported | Fair |
| Veldeman (2008)<br>Systematic review<br>**Pleural Mesothelioma** | 2 studies<br><br>N = NR | Intervention: IMRT<br>Comparator: n/a<br>F/U: NR | NR | One study (n=13) reported fatal (Grade ≥4) radiation pneumonitis in 6 pts who received a combination of extrapleural pneumonectomy, chemotherapy and postoperative IMRT.<br><br>The second study did not report any occurrences of Grade 3 or higher acute | Fair |

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **<u>Outcomes Assessed</u> Main Findings** | **Harms** | **Quality Comments** |
| | | | | toxic effects (except for 7% of cases of acute Grade 3 radiation-induced oesophagitis) | |

| *Individual studies (published after review)* | | | | | | | |
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| **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** |
| Adkison (2008)<br>Case series<br>**Non-small Cell Lung Cancer** | n = 46<br><br>Median age 67, (43-85) 19 F 27 M; 15% Stage I or II, 30% Stage IIIA, 50% Stage IIIB, 5% Stage IV | Stage I-V NSCLC pts with newly diagnosed or recurrent histologically confirmed Stage I-IV NSCLC with no prior thoracic RT or malignant pleural effusion who were not judged to be surgical candidates | to determine rate of radiation pneumonitis<br><br>F/U: primary endpoint of study was to determine maximum tolerated dose - median follow-up 8.1 mos | pts placed in 1 of 5 dose bins according to disease stage, , all treated for 25 fractions, with dose/fraction ranging from 2.28 to 3.22 Gy | toxicities | At median follow-up of 8.1 months, no pts developed < Grade 3 pneumonitis or esophagitis, incidence of Grade 2 pneumonitis was 13%, asymptomatic Grade 1 pneumonitis in 70%. Grade 2 esophatitis recorded in 15%, Grade 1 esophagitis in 24%. Average weight loss was 2.3% for Grade 1 and 2 esophagitis while under treatment. For entire cohort, average weight loss was 1.6% while under treatment. Adjuvant chemotherapy after completion of radiation therapy conferred a statistically significant (p=0.018) higher incidence of pneumonitis compared to induction chemotherapy prior to RT or RT alone. | Poor<br><br>Small sample |
| Bral (2010)<br>Case series<br>**Non-small Cell Lung Cancer** | n = 40<br><br>Mean age 65 (40-85), 25/40 65%) male, 14/40 (35%) female; mixed | pts with cytological or histological dx of Stage III inoperable locally advanced non-small cell lung | moderately hypofractionated tomotherapy<br><br>F/U: Seen every 3 | 70 Gy in 6 weeks (30 fractions of 2.35 Gy) resulting in | Survival: With a median follow-up of 16 months in 14 surviving pts, median survival was 17 mo with a 1 yr and 2 yr overall survival (OS) of 65% and 27% respectively. Median survival higher for pts with Stage IIIA cancer compared | Acute toxicity 2 pts died within 90 days following start of RT with treatment-related lung toxicity. For all 40 pts: Grade 2 esophageal toxicity in 33%; Grade 2 or more lung toxicity in 43%; Grade 3 dysphagia with weight loss in excess of 15% in 1 pt. Grade 3 skin | Poor<br><br>Small sample |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | carcinoma types, | cancer (LANSCLC); | months during Years 1-2 of follow-up and every 6 months thereafter | biologically effective dose (BED) of 80 Gy | with Stage IIIb (p= 0.03); 30% of pts alive at 1 year without any cancer related event. 1 and 2 yr local progression-free survival (LPFS) 66% and 50% respectively. (see article for more detail on survival) Mean volumetric analysis on megavoltage computed tomography (+ SD) (MVCT) images that could be performed on 30 pts showed 50% (+ 15%) with range of 20% to 73%; mean individual entire group was 0.018 (SD+0.008), highly significant for correlation, slope and intercept) | toxicity in 1 pt with primary tumor invading the anterior thoracic wall; Mean decreases in FEV1 and DLCO 5% and 10% respectively. Decline in Grades 2 and 3 toxicity observed in 29% and 7% of pts. Sig correlations between PFT and median lung dose, correlations stronger for DLCO than for FEV1. Late toxicity for 31 pts. 9 pts died during first 90 days after start of radiotherapy. Incidences of Grades 2 and 3 RTOG late lung toxicity 23% and 16%, respectively. | |
| Jiang (2011) Case series **Non-small Cell Lung Cancer** | n = 165<br><br>Median age 63 (range 42-83); 41% Female; Stage I: 4% Stage II: 7% Stage IIIA: 35% Stage IIIB: 41% Stage IV: 13% COPD 26% | New dx & path-conf'd NSCLC, definitive IMRT, prescribed & received dose ≥60 Gy | IMRT; no comparator<br><br>F/U Median f/u 16.5 mo (0.7 to 47.6 mo) for all pts; 31.3 mo (16.5 to 47.6 mo) for survivors; 10.4 mo (0.7 to 40.4 mo) for those who died | Median dose 66 Gy in 33 fractions (range 60-76 Gy, 1.8-2.3/fraction) | OS: Median 21.6 mos 2-year 46% 3-year 30% Local recurrence-free survival 2 year 57% 3 year 41% Distant metastasis-free survival 2 year 51% 3 year 38% Disease-free survival 2 year 38% 3 year 27% | Treatment-related pneumonitis grade ≥3: 6 months 11% 12 months 14% Only one patient with Grade 3 pulmonary fibrosis. Esophageal Toxicity Acute esophagitis grade ≥3 17.6% Late esophageal stricture 3pts grade 2, 4 pts grade 3 | Good<br><br>Based on this retrospective case series, IMRT is now standard of care for NSCLC at MD Anderson |
| Shirvani (2012) Case series | n = 60<br><br>Median age 63 | Consecutive histo-proven LS-SCLC, no prior RT, | IMRT guided by PET/CT staging. 68% | 68% rec'd 45 Gy in 30 twice- | Recurrence during f/u: 50% Metastatic recurrence: 38% Locoregional failure 12% Elective | Acute grade 3 radiation esophagitis: 23% Acute grade 3 radiation pneumonitis: 7% Neutropenic fever: | Fair<br><br>Single- |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| **Small Cell Lung Cancer** | yr (range 39-86); Nodal disease present in 94%; 58% female; Node Stage 0: 7%; Stage I: 17%; Stage 2: 40%; Stage 3: 37% | staged using PET/CT, definitive IMRT | rec'd 45 Gy in 30 twice-daily fractions; other doses ranged from 40.5 Gy in 27 fractions to 63.8 Gy<br><br>F/U:Median f/u 21 mo (all pts), 26 mo (survivors) | daily fractions; other doses ranged from 40.5 Gy in 27 fractions to 63.8 Gy | nodal failure: 13% Median actuarial overall survival: 36 mo (95% CI 22-51); 2-year OS 58%; 2-yr recurrence-free survival 43% | 17% No chronic grade 3 pulmonary or esophageal toxicities One late grade 4 pulmonary fibrosis in a chronic smoker | center retrospective study. Suggests that using IMRT targeted by PET/CT allows higher radiation doses with less toxicity & better outcomes |
| Song (2010) Case series **Non-small Cell Lung Cancer** | n = 37<br><br>Median age 64 yr (37-80 range), 31 (84%) male, 5 (13%) stage I or II, 28 (76%) stage III, 4 (11%) recurrent; 10 (27%) ipsilateral supraclavicular nodal metastases, 7 (19%) contralateral | Consecutive pts treated with curative intent by HT, doses greater than 50 Gy | IMRT, no comparator (Case Series)<br><br>F/U:Median 18 months (6-27 month range); 74% of pts surviving at one year were followed for more than one year | Median prescribed dose 64.8 Gy (60-70.4 range) for PTV2 and 54 Gy (50-64 range) PTV1; median daily dose per fraction 2.4 Gy (2.0-2.4) PTV2 and 2.0 Gy | 2-year LC rate 63%; 2-year OS rate 56%; 2-year LC rate among stage III pts 62%, 2-year OS rate 59%. Pts treated w/chemo 42% 2-year OS rate, w/o chemo 75%; 2-year LC rate 78% (w/o chemo) and 39% (w/chemo) | Treatment-related mortality: 4 pts (11%); median time from HT completion to symptom onset: 11 days (0-24 days); OR=20 (1.7-245.4) for pts with CL V5 > 80%<br>5 (14%) grade 3 AET, no grade 4 or 5 AETs. No sig predictors identified of age, gender, pre-RT performance status, greater than 5% weight loss at diagnosis, intro or concurrent chemo<br><br>Sig univariate predictors of AET: mean esophageal dose (p=0.046), relative volume of esoph receiving 50+ Gy (p-0.029), and total 55+ Gy received (p=0.049)<br><br>Treatment-related pneumonitis (TRP) | Poor<br><br>Single center series. Korean population, 87% male, mostly stage III malignancy. 11% fatal pneumonitis. |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | supraclavicular nodal metastases, 11 (30%) contralateral mediastinal nodal metastases. 18 (49%) N3 disease. 5 (13%) prior surgical intervention. 29 (78%) chemo as part of tx, 24 (65%) concurrent chemo (9 had chemo before RT), 5 (14%) sequential chemo and RT | | | (1.8-2.2) PTV1 | | Grade 0: 3 pts (8%), grade 1: 12 (32%), grade 2: 19 (51%), grade 3: 3 (8%), grade 5: 4 (11%)<br><br>Multivariate prediction of TRP: only sig predictor was CL V5 (% vol of organ receiving 5 Gy or more) | |
| Sura (2008)<br>Case series<br>**Non-small Cell Lung Cancer** | n = 55<br><br>Median age 67 yr, 23M & 32 F, Stage I/II 15 (27%), Stage IIIA 6 (11%), Stage IIIB 23 (42%), recurrent 6 (11%); AdenoCA 20 | Consecutive pt with inoperable histo-proven NSCLC stages I-IIIB, 2001-2005 at MSKCC, dose ≥ 60 Gy | IMRT, no comparator (Case Series)<br><br>Length not reported. First f/u 1 month, then q 3-4 month x 2 years, then biannually x 3 years, then | Included all pts receiving ≥60 Gy. Mean rx'd dose was 69.5 Gy (range 60-90 Gy) | 2-year Overall Survival 57%, Median Survival 25 months Median f/u all pts 21 mos Median f/u survivors only 26 mos Stage I/II: 2-year local control (LC) 50% 2-year OS 55% Stage IIIA/IIIB: 2-yr LC 58% 2-yr OS 58% All pts 2-year DFS 41% Median DFS 12 months 2-year Cancer-specific survival (CSS) 63% | Acute: Grade 3 pulm toxicity 11%; Grade 3 esophagitis 4%; no acute treatment-related deaths Chronic: one late grade 3 pulm toxicity; one death from radiation pneumonitis. No late esophageal toxicity | Poor<br><br>Retrospective case series, does not account for confounders, funding not reported, combines CA at multiple |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | (36%), SCC 20 (36%), NSCLC NOS 15 (27%); Median GTV 136 cc, range 4-1060 cc | | annually | | | | stages. |
| Buduhan (2009) Historical cohort **Mesothelioma** | EBRT n= 24; IBRT n = 14 Patients with malignant pleural mesothelioma treated with induction chemotherapy followed by extra pleural pneumonectomy then radiation therapy | Inclusion criteria istologic confirmation of MPM confined to the ipsilateral hemithorax, Eastern Cooperative Oncology Group performance status 0 to 1, predicted postoperative forced expiratory volume 1 second of 40% or more, normal serum creatinine level, and no major systemic comorbidities . | Intervention: EBRT and IMRT Comparator: same<br><br>F/U: Mean 20.6 months 9range 1-75 months | EBRT median total dose 30 Gy (range, 18 to 70 Gy) in a daily fractionated dose of 1.8 to 2 Gy<br><br>IMRT median dose 50.4 Gy (range, 49 to 56 Gy) for 6 weeks | Median overall survival for combined groups was 24 months. (differences between groups not reported) Incidence of local recurrence: IMRT 14% EBRT 42% (p = 0.03) | 1 pt died after complications from massive stroke<br>1 pt died of repiratory failure from pulmonary embolus and pneumonia<br><br>In IMRT group: sig. dehydration(4 pts), mild esophagitis (2 pts), radiation pneumonitis (2 pts), late empyema (1 pt)- required surgical drainage and serial packing | Poor<br><br>Historical cohort; many patients at different stages of treatment when entered into the study; results not segregated for all endpoints |
| Tonoli (2012) Case series **Mesothelioma** | n = 56 (50 IMRT)<br><br>Mean age 57.8 | MPM, treated with extrapleural pneumonectomy followed by IMRT | Four 3DCRT, 50 IMRT, two helical tomotherapy. | 3DCRT: 45 Gy in 25 fractions IMRT: 32 | 3-year locoregional control (LRC): 90 ± 5 (13%) distant metastasis-free (DMF): 66 ± 9 (11%), disease-free (DF): 57 ± 9 (10%), disease- | Acute: Nausea, vomiting and fatigue put most pts in hospital during treatment. No acute respiratory decline. Chronic: Two late deaths | Fair<br><br>Funding not reported. No |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | yr, 46M & 10F, preop staging with CT PET Stage I-4 (7.1%), Stage II-8 (14.3%), Stage III: 34 (60.7%), Stage IV: 10 (17.9%) | or 3DCRT | No comparator (Case Series) but published stats on no adjuvant RT are given (3-yr survival 17%)<br><br>F/U: Median f/u 20 mo, mean 26.2, range 5-74. In survivors, mean 31.7 mo, median 27.6 mo, range 5.7-56.3 | cases got 50 Gy in 25 fractions; 18 cases got boost up to 60 Gy | specific survival (DSS): 62 ± 8 (14%), overall survival (OS): 60 ± 7 (14%). No difference between different doses. Median time to recurrence: 10.7 mo Mean time from relapse to death: 5.2 mo | possibly related to tx: one liver, one pericarditis. No pulmonary complications or decline in resp function. | confounders considered. Outcomes not broken down by 3DCRT vs IMRT vs HT |
| Yu (2011) Case series **Non-small Cell Lung Cancer** | n = 79<br><br>median age 76y; 47 inoperable & 32 refused surg; T1-20, T2-37, T3-22; N0-48, N1-31; 39 in GTV>100.8cm 3 group and 40 in GTV≤100.8cm | Stage I/II NSCLC, Karnofsky performance status ≥70, age ≥70 yr, no prior chemo/rad, measurable lesion, no organ failure, medically inoperable, weight loss <10% in prior 3 mos | IMRT 66.6 Gy to involved-field including primary tumor and clinically enlarged lymph nodes; no comparator<br><br>F/U: Median f/u 72mo for | Total 66.6 Gy in 37 fractions of 1.8 Gy (five fractions per week) | Median overall survival: 38 mo (range 13.8-62.2 mo) Median local-progression-free survival: 33 mos (range 13.6-52.4 mos). OS rates significantly associated with T stages and GTV (p=0.005 for each). Complete response: 38 (48.1%); partial response: 32 (40.5%); Stable disease: 5 (6.3%); Tumor progression: 4 (5.1%). Median TTP: 25.0 mo for CR, 19.0 mo for PR; (p=0.041). Elective Nodal Failure (ENF): 29 (36.7%) with median TTF 55 mos (49-61 | No treatment-related deaths. 3 patients required steroids/O2 for grade 3 radiation pneumonitis. No late toxicity in esophagus, skin, or lungs | Fair<br><br>Multicenter prospective case series |

| Individual studies (published after review) | | | | | | | |
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| **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 group | | surviving pts; 38mo for all (range 6-83 mos) | | mos) | | |

## Prostate Cancer

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Budäus (2012) Systematic review. **Prostate Cancer** | 15 studies address GI and GU toxicity. Sample sizes range from 96 to 843.<br><br>N = 6050<br><br>11 studies address erectile dysfunction. Sample sizes range from 34 to 667.<br><br>N = 2518 | Intervention: IMRT, 2DCRT, 3DCRT, brachytherapy<br>Comparator: same<br>F/U: Median follow-up 6 to 100 months | NR | The authors note heterogeneity of the reported studies relating to definition of functional end points, patient selection bias, inherent differences in RT modalities and presence or absence of hormonal treatment. This limited the ability to perform meta-analyses.<br>**GI Symptoms:**<br>Two studies (n=301 and n = 669) showed Grade 2 GI symptoms were twice as frequent after EBRT at 78Gy than EBRT at 68-70Gy (p = 0.013 and p = 0.007).<br>Two studies (also reported in Samson above) show conflicting comparative results between IMRT and 3DCRT.<br>**GU Symptoms:**<br>One study (n = 669) noted no significant difference in late GU toxicity comparing EBRT at 68Gy and 78Gy.<br>One study (also reported in Samson above) (n= 830) showed that IMRT at 81Gy resulted in a higher dose of late GU symptoms than EBRT at 66Gy. | Good |
| De Neve (2012) Systematic Review **Prostate Cancer** | 8 comparative studies.<br>N = 3,662 | Intervention: IMRT<br>Comparator: 3DCRT<br>F/U: NR | **Tumor control**: No difference in disease control or survival at 7 years between IMRT and non-IMRT. | **Toxicity**: IMRT significantly reduced the risk of late grade ≥2 rectal toxicities.<br>IMRT did not reduce the rate of | Poor |

| Reviews | | | | | |
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| **Reference<br>Study Design<br>Malignancy** | **# of Studies & Subjects** | **Intervention<br>Comparator<br>Follow-up** | **Outcomes Assessed<br>Main Findings** | **Harms** | **Quality<br>Comments** |
| | | | | grade ≥2 genitourinary (GU) symptoms ***if*** radiation dose to the prostate was increased to 81Gy but IMRT did reduce GU symptoms at lower prostate doses. | |
| Hummel (2010). Technology Assessment<br>**Prostate Cancer** | 8 comparative studies. Sample sizes range from 27 to 1571<br><br>N = 2867 | Intervention: IMRT.<br>Comparator: 3DCRT.<br>F/U: Mean follow up 6 to 60 months. | **Overall survival**: no evidence<br><br>**Biochemical relapse-free survival**:<br><br>**Study (F/U time): # pts (IMRT); # pts (3DCRT); % survival (IMRT); % survival (3DCRT); p value**<br><br>Kupelian (30 mos): 166; 116; 87%; 80%; p= 0.24<br>Vora (36 mos): 145; 271: 94%; 89%; NR<br>Vora (60 mos): 145; 271; 85%; 75%; p <0.0326<br><br>**Differential efficacy and safety in sub-groups**. No studies are identified.<br><br>**Cost effectiveness**:<br><br>**Study (Pt group) (Time horizon): Year (cost); Cost (IMRT); Cost (3DCRT); QALYs (IMRT); QALYs (3DCRT); ICER[21]** | **Acute GI toxicity in localized prostate cancer**<br><br>**Study (F/U time): # pts (IMRT); # pts (3DCRT); % toxicity (IMRT); % toxicity (3DCRT); p value**<br><br>Kupelian (acute): 166; 116; 30%; 12%; p=0.002<br>Shu (< 6 months): 18; 26; NR; NR; p= 0.003 (IMRT > 3DCRT)<br>Vora (acute): 145; 271; 16%; 27%; p=0.83<br>Zelefsky (< 3 month): 472; 358; 3%; 1%; p=0.04<br><br>**Acute GI toxicity in locally advanced prostate cancer**:<br><br>**Study (F/U time): # pts (IMRT); # pts (3DCRT); % toxicity (IMRT); % toxicity (3DCRT); p value**<br><br>Ashman (< 3 months): 13; 14; 7%; 40%; NA | Good<br><br>TA authors rate strength of evidence as low. |

[21] ICER = incremental cost effectiveness ratio.

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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | Konski (intermediate risk) (2004): 70 yrs; 15 yrs; NR; $52,170; $27,357; 7.62; 6.65; $25,580<br>Konski (intermediate risk) (2005): 70 yrs; 10 yrs; 2004; $33,837; $21,377; 6.29; 5.52; $16,182<br>Konski ( intermediate risk) (2006): 70 yrs; NR; 2004; $47,931; $21,865; 6.27; 5.52; $40,101<br>Pearson (low to intermediate risk) (2007): 69 yrs; Lifetime; 2005; $42,450; $10,900; NR; NR; $706,000 | **Acute GU toxicity in localized prostate cancer**<br><br>**Study (F/U time): # pts (IMRT); # pts (3DCRT); % toxicity (IMRT); % toxicity (3DCRT); p value**<br><br>Kupelian (acute): 166; 116; 15%; 19%; p= 0.64<br>Shu (< 6 months): 18; 26; NR; NR; p=0.535<br>Vora ( acute): 145; 271; 28%; 38%; p=0.094<br>Zelefsky (< 3 month): 472; 358; 37%; 22%; p= 0.001<br><br>**Late GI toxicity in localized prostate cancer:**<br><br>**Study (F/U time): # pts (IMRT); # pts (3DCRT); % toxicity (IMRT); % toxicity (3DCRT); p value**<br><br>Kupelian (acute): 166; 116; 5%; 12%; p= 0.24<br>Shu (< 6 months): 18; 26; NR; NR; p=0.163<br>Vora (acute): 145; 271; 56%; 57%; p=0.24<br>Zelefsky (< 3 month): 472; 358; 5%; 13%; p=0.001<br><br>**Late GI toxicity in locally advanced prostate cancer:** | |

| Reviews | | | | | |
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| **Reference<br>Study Design<br>Malignancy** | **# of Studies & Subjects** | **Intervention<br>Comparator<br>Follow-up** | **Outcomes Assessed<br>Main Findings** | **Harms** | **Quality<br>Comments** |
| | | | | **Study (F/U time): # pts (IMRT); # pts (3DCRT); % toxicity (IMRT); % toxicity (3DCRT); p value**<br><br>Ashman (< 3 months): 12; 13; 0%; 15%; NA<br><br>**Late GU toxicity localized prostate cancer:**<br>**Study (F/U time): # pts (IMRT); # pts (3DCRT); % toxicity (IMRT); % toxicity (3DCRT); p value**<br><br>Kupelian (acute): 166; 116; 1%; 2%; NA<br>Shu (< 6 months): 18; 26; NR; NR; p=0.025<br>Vora (acute): 145; 271; 45%; 66%; p=0.33<br>Zelefsky (< 3 month): 472; 358; 20%; 12%; p= 0.01 | |
| Perlroth (2010) | 2332 (claims database)<br><br>Inclusion criteria: Localized prostate cancer. Exclusion criteria: Age older than 75 years, disseminated disease, bone cancer, pelvic or other lower extremity lymph node cancer during 1 year prior to | (1) Active surveillance, (2) radical prostatectomy, (3) brachytherapy, (4) EBRT, (5) IMRT, (6) multiple treatments. FU: 2 years following diagnosis for all patients | **Cost**<br>2004 DOLLARS. Median unadjusted total 2-year costs: Active surveillance ($29,900), radical prostatectomy ($34,000), brachytherapy ($57,700), EBRT ($54,000), IMRT ($84,200), multiple treatments ($101,200). Adjusted incremental total 2-year costs, range across subgroups: Active surveillance ($14,900- | n/a | Fair<br><br>Assumption of equivalent effectivenes s across therapies, based on systematic literature |

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **<u>Outcomes Assessed</u> Main Findings** | **Harms** | **Quality Comments** |
| | diagnosis | | $53,900), radical prostatectomy ($22,200-$59,700), EBRT ($21,500-$59,000), brachytherapy ($33,900-$72,700), IMRT ($61,800-$100,800). Higher costs for treatment with radical prostatectomy, brachytherapy, or IMRT compared with active surveillance was statistically significant. Range across treatments for 65-year-old without comorbidities: $21,400 (active surveillance) to $68,300 (IMRT). Unadjusted total prostate cancer-related 2-year costs: Active surveillance ($1350), EBRT ($17,150), radical prostatectomy ($21,180), brachytherapy ($23,230), IMRT ($50,700), $59,200 (multiple treatments). INFLATED TO 2009 DOLLARS. Total national 2-year savings adjusted for age 65 and preceding health expenditures: Shifting patients receiving IMRT to active surveillance: $1.38 billion; shifting patients receiving IMRT to radical prostatectomy and active surveillance: $1.27 billion. | | search for randomized comparator trials and systematic reviews.<br><br>Analysis does not take into account quality-adjusted benefits, i.e., differential side effects; results may not be generalizabl e to patients over age 75. |
| Staffurth (2010) Systematic Review | 26 studies; no RCTs. N = 6039 | Intervention: IMRT Comparator: 3DCRT F/U: NR | **<u>Tumor control</u>**: Five non-randomized studies have reported no difference in | **<u>Toxicity</u>**: 14 studies (IMRT n = 2357; EBRT n = 3682). Seven studies | |

| *Reviews* | | | | | |
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| **Reference Study Design Malignancy** | **# of Studies & Subjects** | **Intervention Comparator Follow-up** | **<u>Outcomes Assessed</u> Main Findings** | **Harms** | **Quality Comments** |
| **Prostate Cancer** | | | biochemical control between EBRT and IMRT except one where the dose from 3DCRT was 68Gy for EBRT compared to 76Gy for IMT; in this study IMRT patients had better biochemical control.<br>**<u>QoL</u>**: Three studies (n = 183) reported on QoL at several time intervals up to 24 months following RT. Only one study showed improvement in bowel toxicity at 6 and 12 months with IMRT compared to 3DCRT. | reported statistical reduction in late GI symptoms; seven studies reported NO statistical difference. Only one of fourteen studies reported a statistically significant reduction in late GU symptoms for IMRT. | |
| Wilt (2008)<br>Comparative Effectiveness Review<br>**Localized Prostate Cancer** | This review does not identify any studies that addressed IMRT in comparison with EBRT. | | | | n/a |

| *Individual studies (published after review)* | | | | | | | |
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| **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** |
| Bekelman (2009)<br>Cohort<br>**Prostate** | n = 12,601<br>(5,845 IMRT 6,753 EBRT)<br><br>diagnosis of non-metastatic CA > | ICD-9 codes consistent with possible radiotherapy (RT) injury and corresponding | complications following IMRT vs three-dimensional conformal radiotherapy | dose is not reported in Medicare data | n/a (no control or comparison group) | IMRT was associated with 24 month cumulative incidence of complications requiring an invasive procedure: bowel complications: 18.8% (95% CI, 17.8-19.9) ; urinary complications 10.4% (95% CI, 9.6- | Fair<br><br>SEER-Medicare database limitations, |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | 65 and receiving IMRT or EBRT between 2002-2004; in IMRT group no median patient age; 55% 65-74 yrs; 45% 75 or older | HCPCS/CPT-4 procedure code | (EBRT)<br><br>F/U: Diagnosis between 1/1/2002 and 1/31/2004 with follow-up through 12/31/2006 | | | 11.1) , erectile complications 1.0% (95% CI, 0.8 - 1.3), an increase in new diagnoses of impotence (HR 1.27, 95% CI, 1.14-1.42) | could only obtain data equivalent to > Grade 3 |
| Goenka (2011)<br>Cohort<br>**Prostate** | n = 285<br><br>median time from prostatectomy to recurrence 31 mos (3 mos - 16.7 yrs); median age 62.5 yrs (42-80); 30.5% androgen deprivation therapy | Biochemical recurrence following radical prostatectomy | IMRT (94% received > 70 Gy) vs. 3D-CRT (37% received > 70 Gy)<br><br>F/U: 75 mos (52 IMRT vs. 97 EBRT) | 94% received > 70 Gy | Toxicities | Acute > grade 2 GI toxicity, 7.6% IMRT vs. 13.2% EBRT, p =0.14; Late (5 yr) > grade 2 GI toxicity, 1.9% IMRT vs. 10.2% EBRT, p =0.02, HR = 0.29, p =0.04; Acute > grade 2 GU toxicity, 13.4% IMRT vs. 20.8% EBRT, p =0.12, HR 0.61, p =0.15; Late (5 yr) > grade 2 GU toxicity, 16.8% IMRT vs. 15.8% EBRT, p =0.86, HR = 1.1, p =0.76; | Poor<br><br>Unclear which confounders were controlled in analysis, some pts had hormonal and surgical tx too. |
| Jacobs (2012)<br>Cohort<br>**Prostate** | n = 36,490 | > 65 yo; newly diagnosed; no other treatments; | IMRT (dose not specified) vs. 3D-EBRT (dose NS)<br><br>F/U: 3 years for outcome of recurrence | NR | Recurrence (pts with > 3 yrs follow-up): 6% IMRT vs 9% EBRT | Treatments for bowel complications: 22% IMRT vs. 18% EBRT; Treatments for urinary complications: 8% IMRT vs. 6% EBRT | Good<br><br>Emphasis is on growth of use of IMRT, not outcomes. Controlled for medical conditions plus others. |

| ***Individual studies (published after review)*** | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Kim (2011)<br>Cohort<br>**Prostate** | n = 28,088 (4645 IMRT)<br><br>patients 66-85 yr diagnosed with T1-T2 clinically localized prostate CA between 1992-2005, those with radiation were provided it within 1 year of diagnosis | late (> 6 mo post diagnosis) men who survived > 5 yrs with grade 3/4 toxicities that required intervention, (determined by ICD-9 or CPT-4 codes) | comparison of GI toxicities in men treated with primary radiation or conservative management for T1-T2 prostate cancer<br><br>F/U: No, but review was conducted on 4 years of data for IMRT | dose is not reported in Medicare data | n/a (no control or comparison group) | Rate of Grade 3/4 toxicity for IMRT 8.9 per 1000 person-years, all EBRT modalities had more GI toxicity than did conservative management Cumulative incidence of GI toxicity at 4 years (3.3%); | Fair<br><br>According to article: limitations of Medicare-SEER database includes the need to depend on the accuracy of disease and procedural codes; higher age cohort of study participants may not be applicable to younger men, subtle differences between SEER-Medicare and general population, and little details on specific |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | | | | treatments |
| Lev (2009) Cohort **Prostate** | n = 159<br><br>IMRT+HDR (n=49), IMRT + seed (n=61), RP (n=49); Median age 63.8 yrs (42-82), median Gleason 6 (5-10), median PSA 7 (1.2-116); Demographic data w/significant differences among tx groups | Organ-confined early-stage prostate CA, scheduled to begin tx, able to hear, understand, and speak English | Examine differences among men treated w/RT (IMRT and IMRT + seed implantation) v. radical prostatectomy at 6 and 12 mo after beginning of treatment; examine QOL outcomes<br><br>F/U: Baseline at treatment initiation, then at 6 and 12 months after beginning of treatment | n/a | Physiological and psychological symptoms are predictors of QOL. 7 instruments used and validated. Men received HDR higher bowel sx scores than men with RP at baseline, 6, 12 mo. Men received seeds significantly higher bowel sx scores than those with RP at 6 and 12mo. HDR w/sig higher urinary sx at baseline, 6, 12 mos than RP. Men w/seeds significantly higher urinary sx score at 12 mos than men w/RP. | n/a | Poor<br><br>Significant demographic differences among treatment groups. Psychological factors predictive of QOL need further study, no control for medical comorbidities |
| Pinkawa (2011) Cohort **Prostate** | n = 78 matched pairs<br><br>Median age 3DCRT 71 (55-83); IMRT 72 (57-83); baseline characteristics well-balanced in matched pairs | Localized T1-3N0M0 with 3CFRT in years 2003-2007 and IMRT 2006-2008 | Evaluate treatment-related morbidity after tx w/IMRT and image-guided radiotherapy (IGRT) v. 3DCRT; IGRT w/IMRT reduces PTV | IMRT 76 Gy, 3DCRT 70-72 Gy | No statistically significant QOL changes after dose-escalated IMRT. | Painful bowel movements reported more after 3DCRT (10%) v. IMRT (1%) (p=0.03) 2 mo after tx, however higher rectal bleeding rates after IMRT (≥ rarely in 20%) v. 3DCRT (9%) > 1yr after RT (p=0.06). Great or moderate problem with bloody stools IMRT (7%) vs 3DCRT (1%) (p=0.09); in pts w/o prior rectal bleeding, rare rectal bleeding report after IMRT (17%) vs 3DCRT (8%) | Fair |

| Individual studies (published after review) | | | | | | | |
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| | | | F/U: complete validated questionnaire prior to, on the last day, after median time 2 and 16 mo after RT (12-20 mo) | | | (p=0.08). Presence of erections not firm enough for sexual intercourse sig higher after 3DCRT (86%) v. IMRT (71%) (p=0.03) at 12 to 20 months follow-up. | |
| Quon (2012) Cohort **Prostate** | n = 97<br><br>3D+IMRT median age 71.5 (66.2-77.3); IMRT median age 71.7 (65.4-75.8); Clinical T stage (3D+IMRT, IMRT) T1 (18,9), T2 (33,8), T3 (16,13); Gleason score (3D+IMRT, IMRT) 6 (4,1), 7 (28, 8), 8-10 (35, 21); Median PSA level (ng/mL) (3D+IMRT, IMRT) (18.7, 13.81) | Clinical Stage T3, PSA 100, Gleason score 8-10, 2004-2007, no stat sig diff in baseline characteristics | 3D CRT + IMRT (67) vs IMRT (30)<br><br>F/U: Median 39 mo (24-54 mo), 88% w/ minimum of 24 mo f/u | 45 Gy delivered to pelvic LN with concomitant 22.5 Gy prostate IMRT boost for total 67.5 Gy in 25 fractions | Four-year biochemical disease-free survival rate = 90.5%. | Acute GI toxicity: grade 0 = 4%, 1 = 59%, 2 = 37%, no grade 3 or 4 acute GI toxicity. Acute GU toxicity: grade 0 = 8%, 1 = 50%, 2 = 39%, 3 = 4%. Late GI rectal toxicity: grade 0 = 54%, 1 = 40%, 2 = 7% with no grade 3 or 4higher noted. Late GU urinary toxicity: grade 0 = 82%, 1 = 9%, 2 = 5%, 3 = 3%, 4 = 1%. All severe (grade 3 or 4) toxicities had resolved at last f/u visit. | Fair<br><br>More study needed to determine long-term biochemical control and histologic findings |
| Sheets (2012) Cohort **Prostate** | n = 12,976<br><br>Men who received radiation as primary tx | From SEER-Medicare database: dx of prostate cancer between 2002-2006, no | Propensity modeling was done for:2 comparisons: IMRT/ EBRT | not specified | IMRT/CRT men treated with IMRT were less likely to receive additional CA therapy than men treated with EBRT (2.5 for IMRT vs 3.1; RR, 0.81, 95% CI, 0.73- | IMRT/ EBRT men treated with IMRT were less likely to receive dx of GI morbidity than men with EBRT: (13.4 for IMRT vs 14.7 cor EBRT per 100 person-years; RR 0.91, 95% CI, | Good |

| Individual studies (published after review) | | | | | | | |
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| | (IMRT, conformal radiation therapy (EBRT), proton therapy) within 1 yr of dx between 2002 2006 Numbers after propensity weighting: IMRT/ EBRT IMRT n=6438 EBRT n=6478; IMRT/Proton IMRT n=3843, proton n=3893 | additional cancers, metastatic disease or disease dx at autopsy. Restricted to men with > 1 yr claims data before dx; not enrolled in HMO within 1 yr of dx, enrolled in both Medicare A&B and who received radiation as primary tx within 1 yr of dx | and IMRT/proton therapy<br><br>F/U: IMRT/ EBRT: IMRT 44 mo (0.1-91.5 mo); EBRT 64 mo (0-91.7 mo); IMRT/proton IMRT 46 mo (0.4-88.3 mo); proton therapy 50 mo (0.3-90.2 mo) | | 0.89; P<.001) | 0.86-0.96; P<.001); and hip fracture (0.8 for IMRT vs 1.0, RR, 0.78; 95% CI, 0.65-0.93; p=.006) but more likely to receive a dx of erectile dysfunction (5.9 for IMRT vs 5.3; RR, 1.12; 95% CI, 1.03-1.20; p=.006) IMRT/Proton Men treated with IMRT were less likely to receive a dx of GI morbidity than men treated with proton (12.2 for IMRT vs 17.8 proton; RR 0.66(0.56-0.79) or GI procedures (17.7 for IMRT vs 21.4 proton RR 0.82(0.70-0.97) ; No significant differences for IMRT-EBRT or IMRT-proton for urinary noncontinence or incontinence events, erectile dysfunction procedures. There were no significant differences between IMRT/proton for hip fracture or additional CA therapy. | |
| Adkison (2012) Case series **Prostate** | n = 53<br><br>median IPSS score 11 (0-27) median age 70 (49-80) | high-risk prostate adenocarcenoma with > 10% pelvic node involvement | 56 Gy to 70 Gy<br><br>F/U: median follow-up time 24 months; Followed 1 month on completion, then every 3 months for year 1, every 4 months in years 2 and 3, | 56 Gy in 2 Gy fractions with concomitant treatment to 70 Gy in 2.5 Gy fractions | n/a (no control or comparison group) | Acute GU toxicity: Grade 0 in 6 (11%); Grade 1 in 27 (51%), and Grade2 in 20 (38%). Acute GI toxicity: Grade 0 in 9 (17%). Grade 1 in 27 (51%), Grade 2 in 17 (32%). Late GU Toxicity: Grade 0 in 23 (43%), Grade 1 in 16 (30%), Grade 3 in 1 (2%) who developed urinary retention 7 months after radiotherapy requiring foley catheter for 26 days with acute renal failure. Late GI toxicity: Grade 0 in 33 | Poor<br><br>Small sample, dose escalation study |

| ***Individual studies (published after review)*** | | | | | | | |
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| | | | every 6 months in years 4 and 5, then annually | | | (62%), Grade 1 in 16 (30%), Grade 2 in 4 (8%). All late Grade 2 GI toxicities were rectal bleeding. | |
| Alicikus (2011)<br>Case series<br>**Prostate** | n = 170<br><br>Median age 69 (51-82); AJCC tumor classification T1c (71), T2a (37), T2b (33), T2c(21), T3a (2), T3c (2), T4 (1); Gleason score ≤6 (97), 7 (60), ≥8 (13); PSA (ng/mL) ≤10 (110), >10 (60); NCCN risk stratification: low (49), intermediate (89), high-risk (32); 54% also received N-ADT before radiotherapy | Clinically localized, Histologically proven prostate CA treated with IMRT at Memorial Sloan-Kettering b/w 1996-1998 | Cohort followed for recurrence outcomes and development of harms following IMRT<br><br>F/U: Weekly during treatment, every 3-6 mo for 5 years, then yearly thereafter. Median f/u 99 mo calculated from completion of radiation therapy. | 81 Gy using 5-field technique, 1.8 Gy daily in 45 fractions | n/a (no control or comparison group) | 10-year likelihood to develop GU/GI toxicity: grade 2 (11%), grade 3 (6%), Late GI toxicity: grade 2- 4 pts (2%), grade 3 - 2 pts (1%). No late grade 4 GU or rectal toxicities observed. Erectile dysfunction at 10 years postradiation: 44% | Good |
| Di Muzio (2009)<br>Case series<br>**Prostate** | n = 60<br><br>Median age 75 (60-79), median Gleason 6 (2+2to 5+5), median | histologically confirmed adencarcinoma, stage T1b-c, T2a-c,; NO, Mo, age <80, ECOG | 3 treatment groups: 31 low risk: (Stage T1-T2, Gleason <6, PSA < 10; 20 intermediate | See table of prescribed doses by risk group provided in article | n/a (no control or comparison group) | Acute GU toxicity: Grade 0 in 25/60 (42%); Grade 1 in 21/60 (35%); Grade2 in 12/60 (20%) Grade 3 in 2/60 (3%). Median time to occurrence of GU toxicity 28 days (range 6-42); Acute GI toxicity: rectal | Fair<br><br>Combined treatment - IMRT and tomotherap |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | initial PSA 7 ng/ml (1.2 to 24.0 ng/ml). | performance status 0-1, neg bone scan | risk: (Stage T1-T2, Gleason .6, PSA >10 or Stage T3, Gleason ,6, PSA ,10 , 9 high risk (Stage T1-T3, Gleason >7, PSA >10;<br><br>F/U: Median follow-up 13 months (6-28 months) Every week during treatment, at 4 and 12 weeks after completion of treatment, every 4 months in year 1, then every 6 months. | | | toxicities Grade 0 in 42/60 (70%) Grade 1 18/60 (30%), mainly proctitis; median time to grade 1 proctitis 27 days , range 18-72) 12/60 (20%) upper GI, median time to event 28 days (6-41) | y |
| Ghadjar (2010) Case series **Prostate** | n = 102<br><br>Median age 69 years (50-81 yrs); Tumor classification cT1 (37), cT2 (21), cT3a (24), cT3b (18), cT4 (2); Gleason score 2-6 (47), 7 (43), 8-10 (12) | 2004-2008; histologically proven prostate CA and cN0 cM0 status; low, intermediate, high-risk | Comparison of acute and late toxicity in patients treated w/high-dose IMRT w/daily image guidance<br><br>F/U: Median 39 mo (16-61 mo); weekly during radiotherapy, 2- | 80 Gy IMRT w/daily image guidance; 66 pts received concomitant and either neoadjuvant or adjuvant hormonal therapy, median | n/a (no control or comparison group) | Acute/late grade 3 GI toxicity absent, acute and late grade 2 GI toxicity in 2%/5%; late grade 1 GI toxicity in 30%. Acute grade 2/3 GU toxicity 43%/5%; late grade 2/3 toxicity 21%/1%. Pretreatment GU morbidity (PGUM) independent predictor of decreased acute and late grade 2 or higher GU toxicity-free survival, p<0.001. End of f/u, incidence late grade 2 and 3 GU toxicity decreased to 7%/1%. | Fair<br><br>Retrospectiv e/somewhat limited f/u |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | 4 weeks after completion, then Q3-6 mo for first 2yrs, then annually (including DRE and PSA) - visits alternated with Rad Onc and Urology. No loss to F/U. | duration 6 mos (1-34 mos) | | | |
| Ghadjar (2011) Case series **Prostate** | n = 64<br><br>median 66.1 (45-77); patient characteristics described in a previous study | histologically confirmed PCA classified as being cNO cMO; seminal vescicle involvement on MRI excluded | n/a<br><br>F/U: seen weekly by radiation oncologist during treatment; follow-up visits arranged 2-4 weeks after completion of IMRT, every 3-6 months during years 1-2, then annually. Median follow-up 5.1 years.(3-6.4 years) | See article | n/a (no control or comparison group) | Late GU toxicity: Median 5.1 yr follow-up Grade 2 in 15 (23.4%), Grade 3 in 7 (10.9%), Grade 4 in 2 (3.1%) - The patients with >3 toxicity: 1 severe dysuria, 1 urinary frequency of > every hour, 1 obstructive urinary symptoms, 6 with bulbar urethral structure after median time of 62 months. Late GI Toxicity: After median 5.1 yr follow-up: Grade 1 in 7 (10.9%), Grade 3 in 3 (4.7%) 5 year actuarial Grade 1 or higher late GI toxicity free survival significantly lower in patients who had experienced acute GI toxicity. Sexual function- sexual preservation rate 40% - 6 of 15 sexually functional patients who had not received hormonal therapy retained sexual function. | Poor<br><br>combined treatment - brachytherapy and IMRT |
| Lock (2011) Case series | n = 66 | biopsy-proven localized | simplified intensity | Treatment to the | n/a (no control or comparison group) | Acute GU toxicity: Grade 0 in 3/66 (4.4%), ; Grade 1 in 34/66 (51.5%); | Poor |

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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| **Prostate** | median age 73; initial PSA average 7.2 (0.32-19.6); CT simulation prostate size 42.6 (16.6-81.2) | adenocarcinoma, negative bone scan required for PSA >10, Gleason score >7, or staging >T2B, nodal involvement <15%, Any nodes > 1.5 cm required negative pathology; prostate volume < 75cc. | modulated arc therapy (SIMAT)<br><br>F/U: At 3 months, every 6 months for 3 years, yearly afterward. | prostate and proximal seminal vesicles (Dmin to PTV1 of 41Gy in 20 fractions) concurrent with a simultaneous boost to the prostate (PTV2) to a Dmin of 60 Gy and a D95 of 63.2 Gy in 20 fractions. | | Grade2 in 23/66 (33.8%)1 patient had G2 frequency for 11 months after treatment; Grade 3 in 6/66 (8.8%); 1 had grade 2 frequency at months 10-24 after treatment and 1 patient with a baseline G1 frequency developed G2 urinary incontinence for 11 months .Acute GI toxicity: Grade 0 in 13/66 (19.7%), Grade 1 in 28/66 (42.4%), Grade 2 in 17/66 (25.0%), Grade 3 in 7/66 (10.3%), Grade 4 in 1/66 (1.5%). Late GU Toxicity: Grade 0 in 17/64 (26.6%), Grade 1 in 35/64 (54.7%), Grade 2 in 9/64 (14.1%), Grade 3 in 3/64 (4.7%) (urinary stricture, gross hematuria, urinary sx requiring a suprapublic catheter Late GI toxicity: Grade 0 in 20/64 (31.2%), Grade 1 in 25/64 (39.1%),, Grade 2 in 16/64 (25%), Grade 3 in 2/64: 1 fecal incontinence, 1 diarrhea associated with fecal urgency and incontinence (3.1%), Grade 4 in 1/64 (1.6%) - failed argon plasma coagulation for radiation proctitis failed, requiring abdominoperineal resection at 10 months, then small bowel obstruction at 17 months secondary to ischemic gut syndrome which led to death | Small sample, but baseline measurements included in analysis |
| Marchand (2010)<br>Case series | n = 55<br><br>Median age 73 | all patients with localized adenocarcinoma | Quality of life (QoL) at baseline, 2,4, 6 | 76 Gy | n/a (no control or comparison group) | Physician-assessed acute general toxicity: 54.5% (mainly anemia, grade 1 - sig reduced at 6 and 18 | Poor<br><br>Small |

| Individual studies (published after review) | | | | | | | |
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| **Prostate** | (54-80); 28 (51%) pts with lymphadenectomy; 25 (45.5%) pts received hormonal therapy (3 mo (n=4), 6 mo (n=11), 2-3 yr (n=10) | and candidates for RT | and 18 months<br><br>F/U: Toxicity assessments done immediately after IMRT, at 6 months, 18 months; patients did QoL questionnaire before IMRT, at 2, 6, and 18 months | | | months) Acute GU toxicity: Grade 1 in 56.4% (mainly dysuria and pollkisuria); Grade 2 in 38.2%; Grade 3 - 1 patient; 56.4% ; sig reduced at 6 months and at 18 months, but not sig different from that at 6 months) Acute GI toxicity: immediately after IMRT Grade 1 (in (36.4%), Grade 2 in (12.7%), at 6 mo Grade 1 in (30.9%), Grade 2 in (3.6%) at 18 mo Grade 1 in (20.0%), Grade 2 in (10.9%) main sx of acute and 6 mo toxicity Grade 1 diarrhea, (20.0% and 16.4%, respectively; Grade 1 flatulence (14.5%, 14.5%) , Grade 2 flatulence (10.9%, 1.8%) , Grade 1 rectitis. (14.5%, 10.9%, at 18 mo. 4 pts with Grade 1 rectitis with rectal bleeding, 1 pt with Grade 2 rectal bleeding (anal fissure) and 5 pts with recurrence of hemorrhoids, with slight bleeding in 2 pts. Sexual impotence increased over time but not significantly, QoL- at 2 mo. sig impairment in emotional, social, cognitive and physical functioning compared with baseline, but not at 6 or 18 mo; fatigue and dyspnea sig increased at 2 mo; by 18 mo. pts recovered earlier QoL other than increase in nausea/vomiting and dyspnea; urinary sx sig increased a 6 mo, and sig above baseline at 18 mo. | sample size, failure to assess sexual impotence in all pts at all time points makes this aspect of the analysis difficult to interpret. Direct impact of hormonal therapy on dyspnea, insomnia, treatment-related symptoms and sexual function has also been observed. |

| Individual studies (published after review) | | | | | | | |
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| **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 (2010) Case series **Prostate** | n = 50<br><br>Median age 63 (52-77); median Gleason 7 (6-9); median time from RP to adjuvant therapy 3.0 mo (1.8-8.4 mo); salvage therapy for rising PSA after RP; medium time from RP to salvage RT 31.8 mo; (3.4-167.6 mo); 28% rec'ed androgen deprivation for median of 24 mo (3-73 mo) | post radical retropubic or robot-assisted prostatectomy for localized prostate adenocarcenoma | acute and late GI and GU toxicity after image-guided adjuvant or salvage radiotherapy<br><br>Routine follow-up every 3 to 6 months with radiation oncologist or urologist; patients not seen within last 3 months contacted by phone and interviewed for GU/GI sx. Median follow-up 24 mo (13-38 mo) | 68 Gy | n/a (no control or comparison group) | General 46/50 (92%) experienced acute side effects; 36/50 (70%) GU; 34/50 (68%); GI; Grade 1 in 35/50 (70%); Grade 2 in 11/50 (22%); no Grade 3. Acute GU toxicity: Grade 1 in 28/50 (56%) most common frequency; Grade2 in 7/50 (14%) (obstruction, dysuria, stenosis) Acute GI toxicity: Grade 1 in 30/50 (60%), most common diarrhea Grade 2 in 4/50 (8%), Late toxicity general 18/50 (36%) had late radiation effects; 13/50 (26%) chronic GU; 5/50 (10%) had GI sx; 8/50 (16%) Grade 1 and 10/50 (20%) GI. Late GU Toxicity: Grade 1 in 4/50 (10%), Grade 2 in 8/50 (16 %) (diarrhea); Grade 3 1/50 - macroscopic hematuria, Late GI toxicity: Grade 1 in 4/50 (8%), Grade 2 in 1/50 (2%), Most common was mild bleeding; | Poor<br><br>Small sample size |
| Nath (2011) Case series **Prostate** | n = 100<br><br>median age 69 (46-85); no other pt info highlighted outside of table | pts treated consecutively between Dec 2005 and March 2008 with definitive external beam IMRT for T1c-T4 disease | acute and late GU and GI toxicity in 100 image guided (IG) IMRT<br><br>F/U: weekly evaluation during treatment, one month after RT | median 76 Gy (74-78 Gy in 2 Gy fractions; 22 selected high risk pts received pelvic nodal IMRT to doses of 46-50 Gy, | n/a (no control or comparison group) | Acute GU toxicity: Grade 1 in 40/100 (40%), Grade2 in 39/100 (39%), most common frequency and dysuria Acute GI toxicity: Grade 1 in 42/100 (42%), Grade 2 in 11/100 (11%), most common diarrhea. Late GU Toxicity: Grade 1 in 17/94 (18%), Grade 2 in 15 /94(2%) Late GI toxicity: Grade 1 in 7/94 (7%), Grade 2 in 2/94 (2%). | Poor |

| *Individual studies (published after review)* | | | | | | | |
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| | | | completion, and every 3-6 months thereafter. median 22 months (7-36 months) | followed by boost to bring prostate and proximal seminal vesicles to full dose | | | |
| Ost (2009)<br>Case series<br>**Prostate** | n = 104<br><br>Median age 64 (51-77); Tumor stage pT2 (19), pT3a (51), pT3b (27), pT4 (7); Gleason score 2-7 (70), 7-9 (34); median PSA (ng/mL) 12.0 (3.0-47.9) | 1999-2008; Indications for adjuvant IMRT after RP = capsule perforation, seminal vesicle invasion, +/- positive surgical margins | Report on biochemical outcome of adjuvant IMRT with doses >70Gy following RP<br><br>F/U:Median 36 mo (6-108), weekly during treatment, at 1 and 3 mo after RT, Q3 mo during 1st year, Q6 mo thereafter | Median dose 74 Gy (72-80 Gy) | n/a (no control or comparison group) | Acute toxicity = no grade 3 GI toxicity, grade 3 GU 8%, grade 2 GI toxicity (22%), grade 2 GU toxicity 26%. Late toxicity no grade 3 GI toxicity, 4% grade 3 GU toxicity, grade 2 GI toxicity (7%), grade 2 GU toxicity (2%). | Fair<br><br>Retrospective |
| Ost (2011)<br>Case series<br>**Prostate** | n = 136<br><br>median age 64 (43-81) no other pt info highlighted outside of table | pts with persisting or rising PSA following radical prostatectomy (RP) | high dose salvage IMRT (HD-SIMRT) with and without androgen deprivation (AD)<br><br>F/U: weekly | 76 Gy salvage IMRT | n/a (no control or comparison group) | late GU toxicity - at 3 months 5 yr actuarial grade 2-3 GU toxicity 22%; absolute incidence of grade 3 GU toxicity 3% (n=4) from which 2 pts recovered. Late GI toxicity 5 yr actual grade 2 GI toxicity 8%; Grade 3 - 1 pt, anal pain and recovered after 2 yr; recuperation from grade 2 GI | Poor<br><br>Mixed cohort - Significant differences in tumor stage, |

| Individual studies (published after review) | | | | | | | |
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| | | | during treatment and at 1 and 3 mo after RT; every 3 months in year 1, every 6 months thereafter. | | | toxicity in 82% of cases after median time of 6 months | seminal vesicle and perineural invasion between HD-IMRT and HD-IMRT + AD groups |
| Pervez (2010) Case series **Prostate** | n = 60<br><br>Mean age 68.2 (55-88) mean Gleason score 7.6 (6-10), mean initial PSA 21.61 (4.3-80.0) ng/ml | newly diagnosed high-risk prostatic adenocarcinoma (cT3/4 N0 M0 and/or a Gleason score of 8,9, or 10 and/or pretreatment PSA of > ng/ml or combination of Gleason score of 7 and PSA of > 15); | IMRT with tomotherapy combined with androgenic suppression therapy (ADT) for all pts; no comparator<br><br>F/U: Acute toxicity scores recorded weekly during RT and at 3 months post RT | 68 Gy in 25 fractions over 5 weeks to prostate and proximal seminal vesicles; 45 Gy in 25 fractions to pelvic lymph nodes and distal seminal vesicles | n/a (no control or comparison group) | Acute GU toxicity: Grade 1 in 28/60 (46.67%) Grade 2 in 20/60 (33.33%) Grade 3 in 4/60 (6.67%) Acute GI toxicity: Grade 1 in 31/60 (51.7%), most common diarrhea Grade 2 in 21/60 (35/60%)<br><br>At 3 months follow-up, GU toxicity Grade 1 in 11/60 (18.97%), Grade 2 in 5/60 (18.62%); GI toxicity Grade 1 8/60 (13.6%) | Poor |
| Spratt (2012) Retrospective Case series **Prostate cancer** | 1002 patients with localized prostate cancer varying in risk group from very low to high. Adjuvant or concurrent androgen deprivation | No evidence of distant metastasis at time of diagnosis. | Intervention: IMRT<br>Comparator: none:<br>Follow up: median 5.5 years (range 1-14 years) | 86 GY | n/a (no control or comparison group) | Actuarial 7 year Grade 2 or higher late GI and GU toxicities were 4% (GI) and 21% (GU). Late grade 3 GI toxicity in 7/1002 (0.7%) and GU toxicity in 22/1002 (2%).<br>Full potency retained in 74% of men with full potency at onset of treatment. | Fair |

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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | therapy in 59% | | | | | | |
| Wilder (2010) Case series **Prostate** | n = 284<br><br>Median age HDR brachytherapy/IMRT: 71, IMRT alone: 72. IMRT alone group had participants with higher Gleason scores, PSAs, and NCCN recurrence risk scores (p=0.01) | NR | High dose rate brachytherapy + IMRT (n=240) and IMRT alone (n=44)<br><br>F/U: Median 2.2 years | | n/a (no control or comparison group) | No patients experienced Grade 4 or 5 toxicity. No significant difference in acute or late toxicity by treatment group. | Poor<br><br>Methods not adequately described--> uncertain risk of bias |
| Wong (2009) Case series **Prostate** | n = 853 (314 high dose IMRT)<br><br>No median age, or performance scores provided, see article for table of T classification, PSA, Gleason Score, perineural invasion, ADT, risk group per intervention, also stratified into risk: low, intermediate, and high risk according to PSA | pts treated for localized prostate cancer (T1c-T3N0M0) between May 1993 and July 2004 | Interventions: 3D-CRT, IMRT, permanent transperineal brachytherapy (BRT), and external beam radiotherapy + BRT (EBRT + BRT) | Every 3 to 6 months during years 1 and 2, then every 6 to 12 months thereafter; median follow-up for IMRT 56 months | n/a (no control or comparison group) | Acute defined as within 3 months of treatment, late > 3 months; only percentages provided. Acute GU toxicity: Grade 1 in 22%%, Grade2 in 49%, Grade 3 in 6%, Acute GI toxicity: Grade 1 in 26%, Grade 2 in 45%, Grade 3 in 1%, 12 pts had grade 3 late GU toxicity: 6 requiring urethral dilatation, DVIU (1), TURP (3), prolonged SIC (1), hematuria requiring treatment with formalin (1). Late GU Toxicity: Grade 1 in 22%, Grade 2 in 27%, Grade 3 in 5% Late GI toxicity: Grade 1 in 23%, Grade 2 in 14%, Grade 3 in 1% - 1 pt developed fecal incontinence. | Poor<br><br>Dose escalation study, intervention comparisons |

| Individual studies (published after review) | | | | | | | |
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| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | control | | | | | | |
| Zelefsky (2011)<br>Case series<br>**Prostate** | n = 729 (281 received IMRT)<br><br>no median age provided; 86 <65; 195 > 65; pretreatment PSA <4 43; > 4; T stage T1c 197; T2a 84; ADT 192 no, 89 yes | pts with low-risk prostate cancer treated with high-dose conformal EBRT | brachytherapy and IMRT<br><br>F/U: Every 3-6 months for 5 years, yearly thereafter, median follow-up time 77 months (range 1-11 years) | 81 Gy IMRT | n/a (no control or comparison group) | Late GU Toxicity: Grade 2 in 12/281 (4.3%) Grade 3 in 4/281 (1.4%) Late GI toxicity: Grade 2 in 4/281 (1.4%), post-treatment impotence 44% of 185 previously potent IMRT pts developed post-treatment impotence (average age 66); 51% of patients who had undergone ADT were impotent post-operatively | Poor<br><br>Intervention comparison study |
| Zilli (2011)<br>Case series<br>**Prostate** | n = 82<br><br>median age 67 (51-86); risk: 28% low, 44% intermediate, 28% high risk | localized prostate cancer, selected according to clinical stage of cT1 to cT3 cN0 M0 and Roach risk for nodal involvement <20% | IMRT (see dose) no comparator<br><br>F/U: median follow-up 48 months (9-67). All seen on routine follow-up once a week during treatment and at 6 weeks after treatment completion; every 3 months for year 1, every 6 months afterwards. All had follow-up of >25 months; 1 patient died at 9 months (of lung | total dose of 56 Gy in 4-GY fractions twice weekly for an overall treatment time of 6.5 weeks | n/a (no control or comparison group) | Acute GU toxicity: During IMRT Grade 1 in 27/82 (32%), Grade 2 in 29/82(35%); at 6 weeks Grade 1 in 18/82 (22%), Grade 2 in 3/82 (4%) Acute GI toxicity: during treatment 17/82 (21%), Grade 2 in 10/82 (12%), at 6 weeks Grade 1 in 7/82 (8%), Grade 2 in 3/82 (4%). Late GU Toxicity: Grade 1 in 10/82 (12%), Grade 2 in 5/82 (6%), Grade 4 in 1/82 (1%) temporary urinary retention 32 months after treatment Late GI toxicity: Grade 1 in 16/82 (19%), Grade 2 in 43/82 (4%), Grade 3 in 1/82 (1%)persistent rectal bleeding 30 mo after IMRT. | Fair<br><br>Dose escalation study |

| *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** |
| | | | cancer) | | | | |

## Sarcoma

| *Individual studies* | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| Terezakis (2007)<br>Case series<br>**Sarcoma** | n = 27<br><br>Age 51 (range 22-74), male:female 16:11, histologic type: 18 sarcoma, 7 chordoma, 2 ependymoma, 23 primary lesion type, 4 metastatic lesion type, 12 high/int tumor grade, 4 low tumor grade, 11 unspecified tumor grade; 22 previous surgery tx, 4 previous chemo, 5 previous radiotherapy; 25 pretreatment pain, 12 sensory deficit, 10 motor deficit | Inclusions: pts treated for partially resected or unresectable parapsinal tumors to radiation doses >5,3000 cGy between 2001 and 2005 with at least 2 months of follow-up | Intervention: image-guided IMRT > 5,300 cGy in standard fractionation, fraction size of 180 or 200 cGy<br><br>F/U: Median follow-up 17.4 months (range 2.1-47.3) | Median prescribed dose 6,600 cGy (range 5396-7080); 22 of 27 pts rec'd >6000 cGy, median PTV volume 164 cubic cm (range 29-1116); median maximal dose within PTV 7746 cGy (range 5378-8781)<br><br>Median mean dose for cauda equina 4597 cGy (range 2130-5510), median maximal | Local recurrence in 7 pts (26%) at median 9.4 months (range 2.4-18.7); 3 of 4 pts w/metastatic lesions developed recurrence; 2-year survival estimate 79%; 5 pts died at median 16 months (range 6.5-40.7); 84% reported pain palliation; 80% motor deficit palliation; 83% sensory deficit palliation | Grade 1 acute toxicity (n) skin erythema (12), pharyngitis or esophagitis (6), fatigue (6), nausea (3), pain (1), dry mouth (1)<br><br>Grade 2 acute toxicity: skin toxicity (3), nausea (1), pain (1)<br><br>Grade 3 toxicity: 1 skin toxicity<br><br>Grade 4 toxicity: skin toxicity, referred to plastic surgery service | Poor<br><br>Potential for selection bias of unknown direction. >40% had unknown tumor grade. Study combined multiple tumor types, but still had relatively small sample (n=27). Wide range in follow-up but no discussion of pt characteristics of those who were lost to follow-up early on. |

| *Individual studies* | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Reference Study Design Malignancy** | **Sample size and Pt Characteristics** | **Patient Selection Criteria** | **Intervention Comparator Follow-up** | **Dose** | **Outcomes Assessed Main Findings** | **Harms** | **Quality Comments** |
| | | | | cauda equina dose 5759 (5386-5916) | | | |

## Other cancers (Skin, Spine, Thyroid)

| *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** |
| Zabel-du Bois (2010)<br>Case series<br>**Sacral chordoma** | n = 34<br><br>17 pts with primary disease: 13 men, 4 women; median age 58.2 yrs (28.2-77.6); total dose >60 Gy in 14 pts, total dose ≤60 Gy in 3 pts; 13 pts received postoperative IMRT, 4 pts had definitive IMRT; 17 pts with recurrent disease: 11 men, 6 women; median age 59.7 yrs (73.4-75.8); total dose >60 Gy in 13 pts, total dose ≤60 Gy in 4 pts; 11 pts had postoperative IMRT, 6 had definitive IMRT | Histologically proven sacral chordoma | IMRT delivered with 6/15 MV linear accelerator from Siemens<br><br>F/U: Follow-up at 6 wks, 3 mos, 6 mos, then annually; median 4.5 yrs 0.3-9.1) for all pts | Median dose to target volume 54 Gy (40-66) in 1.8 Gy/fraction; median total dose to boost volume using integrated boost was 66 Gy (60-72) as 2 Gy/fraction | Local control: 35% (12/34)<br>OS: 74% (25/34)<br>**Actuarial overall survival**: 1-yr (97%), 2-yrs (91%), 5-yrs (70%)<br>**Disease-specific survival**: 1-yr (100%), 2-yrs (94%), 5-yrs (80%)<br>**Actuarial disease-specific survival**: 1-yr (97%), 2-yrs (91%), 5-yrs (49%)<br>**Actuarial local control**: 1-yr (79%), 2-yrs (55%), 5-yrs (27%) | No severe side effects Grade >3. Toxicities (primary disease group, recurrent disease group): diarrhea requiring oral medication: 3 patients (17.6%), 6 patients (35.3%); irritation of bladder: 0 patients, 2 patients (11.8%); self-limiting erythema within radiation field: Grade 1 in 6 patients (17.6%), Grade 2 in 4 patients (11.8%), Grade 3 in 3 patients (8.8%) (1 primary disease group, 2 recurrent disease group); hyperpigmentation at last follow-up: 5 patients (14.7%), 4 in primary disease group, 1 in recurrent disease group. | Poor |
| Mattiesen (2011)<br>Case series<br>**Skin Cancer** | n = 21<br><br>Median age 63 (48-90) male/female 19(90.5%)/ 2(9.5%); 11(52.4%) | clinically staged T4 NMSC who gave consent for RT, completed RT, and gave consent for before-and- | not a comparison - 3 pts treated with 3D conformal RT, 8 with | dose and fractionation schedules were based on size and gross tumor | For the 10 pts treated with IMRT 6(60%) had no disease recurrence. Of these 6, 2 received initial definitive tx, 3 were treated postop, 1 for tumor recurrence. | All pts experienced grade 1 or 2 erythema over treatment site. Other harms and complications are described, but are not linked to treatment modality. | Poor<br><br>Dropout or withdrawal not described, |

| 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** |
| | squamous cell carcinoma; 10(47.6%) basal cell carcinoma; 12(57.1%) primary lesion, 5(23.8%) recurrent, 4(19.1%) post-op tx 4(19.1%) | after photos | electrons and 10 with IMRT<br><br>F/U: median 12 mos (5-48 mos). Follow-up was weekly during treatment, monthly thereafter | volume, location near critical structures and lesion histology | | | cannot tell if harms and complication s pertained to IMRT of other treatment types |
| Damast (2011)<br>Case series<br>**Spinal Metastases** | n = 94 (97 tumors)<br><br>Median age initial RT 58 (range 17-86)<br>Median age re-RT 60 (range 20-87)<br>Male:Female 58:39 (60%:40%)<br>Race/ethnicity 84 (87%) white, 7 (7%) African-American, 5 (5%) Asian-American, 1 Other (1%)<br>Median performance status at re-RT: 80 (range 50-100)<br>Ambulatory at re-RT: 88 (91%) | Pts age 18+, who had rec'd salvage, hypo-fractionated IG-IMRT for recurrent PSMs at single site, Jan 2003 through Aug 2008. PSMs = tumors involving vertebral body and/or adjacent soft tissue.<br><br>Exclusions: new spinal metastases occurring within different previously radiated portal, or previous close radiation to the | Image-guided IMRT, 6-MV and/or 15-MV photons, no comparator<br><br>F/U: Median 12.1 months (range 0.2-63.6)<br>Median follow-up among survivors: 17.5 months (range 0.2-63.6) | 20-Gy group: 42 tumors in 52 pts; 95% pts received 5 x 4 Gy, 1 pt rec'd 6 x 4 Gy, 1 pt rec'd 4 x 4 Gy<br>30-Gy group: 55 tumors in 53 pts; all rec'd 5x6 Gy<br>Maximal IG-IMRT point dose to SC: 14 Gy<br>Maximal IG-IMRT point | no comparative outcomes assessed (dosing study) | 9 vertebral fractures, 1 benign esophageal stricture 2 months post-IMRT (T7-T8, out of field with second radiation field) | Fair<br><br>Some potential for selection bias of unknown direction due to convenience sampling. Limited follow-up may have caused bias towards the null in terms of toxicity outcomes. No indication of |

| 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** |
| | Level of spinal involvement: 14 (14%) cervical, 51 (53%) thoracic, 27 (28%) lumbar, 5 (5%) sacrum | spinal segment (but nonoverlapping spinal fields) | | dose to cauda equina: 16 Gy | | | pt characteristics of those lost to follow-up. |
| Inoue (2011) Case series **Spinal Metastases** | n = 50 (78 lesions)<br><br>Median age 61 (range, 36-93); gender: 31 males, 19 females | vertebral metastases 40/78 lesions in tissues adjacent to previous radiation; 20/78 were true in field recurrences | IMRT or IM radiosurgery - no comparator<br><br>F/U: Follow-up intervals not clear (24 of 50 followed more than 1 yr) | median dose 40 Gy (range, 16-67.5) | Recurrence: 4 pts (5%) | 1 pt, transverse myelitis | Poor<br><br>Potential conflict of interest |
| Rose (2008) Case series **Spinal Metastases** | n = 62<br><br>Median age 62; | solid tumor malignancy with spine metastases | IMRT - no comparator<br><br>F/U: Median 13 mos; followed at 8 wks and then every 3-4 mos until hospice admission or death | Median IMRT dose 24 Gy | Recurrence: 7 pts (11%) ; post-IMRT fracture or fracture progression- 27 vertebral bodies (39%); median time to fracture: 25 mo (lytic lesions 19 mos; sclerotic and mixed lesions 32 mos (P<0.002) | NR | Good |
| Wright (2006) Case series **Spinal Metastases** | n = 49<br><br>Median age 59 (range 24-87); | Inclusion: reirradiation at single site between March | Image-guided IMRT<br><br>F/U: Median | Median initial dose 3000 cGy (range 1600- | Recurrence occurred in 11/49 patients, progression requiring surgical intervention occurred in 4/49 pts. Survival probability at | 6 pts died before follow-up, not included in analysis. Add'l 6 lost to follow-up, not included in analysis. Of those included: mild acute toxicity in 3 | Poor<br><br>Substantial potential 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** |
| | male:female 24:13; Primary cancer: 11 renal, 2 breast, 1 chordoma, 6 sarcoma, 2 NSCLC, 3 thyroid, 2 peripheral nerve sheath, 1 plasmacytoma, 7 prostate, 1 colon, 1 cholangiocarcinoma | 2000 and Nov 2005, local tumor recurrence in previously irradiated field<br><br>Exclusion: pts lost to follow-up: death, return to home country, or failure to present for post-tx imaging; tumor recurrences in different locations within a radiation portal | 8 months (range 1-51 months). | 6600); 1 pt w/peripheral nerve sheath tumor tx w/ single fraction 1600 cGy. Most common was 3000 cGy in 10 fractions. 7 pts rec'd doses >4500 cGy. | median F/U (12 mos) was 72%.<br><br>QoL: 67% of pts report "improved after radiation," 9 pts categorized as "stable," 4 pts categorized as "worse after radiation." | pts (12%), 1 pharyngitis, 1 fatigue, 1 diarrhea; no long-term toxicity reported, including cord edema | selection bias of unknown direction. 24% of those treated not included in report because of loss to follow-up. Study combined multiple tumors at single site. Limited pt characteristics provided. |
| Yamada (2008)<br>Case series<br>**Spinal Metastases** | n = 93<br><br>no high grade epidural SC compression, mechanical instability, history of RT, or surgical resection of lesion of interest; median age 62 (range, 38-91) | solid tumor malignancy with spine metastases | IMRT - no comparator<br><br>F/U: Median 15 mos (range 2-45 mos); followed at 8 wks and then every 3-4 mos | median dose 24 Gy (18-24), maximum spinal cord dose 14 Gy | Local treatment failure: 7 patients (local control rate of 90%); median survival from IMRT: 10 mo (1-39); overall survival at 45 mos: 37 (36%), | 3 patients, grade 1-2 skin reactions; 2 patients, grade 2 acute esophagitis ; 1 patient experienced severe pain 3 hrs after RT; no radiculopathy or myelopathy | Poor |
| Bhatia (2010)<br>Cohort | n = 53 (40 3DCRT, 13 IMRT) | anaplastic thyroid CA | IMRT; 3D-CRT | IMRT median | Overall survival at 1 yr: 19%; disease-specific survival: 19%; | 12 pts (23%) RT specific acute or chronic morbidity requiring | 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** |
| **Thyroid Cancer (Anaplastic)** | Mean age 66.1 (range 27-88); Gender 29 females, 24 males; Distant metastasis at presentation: 28 none, 25 distant; Gross disease: 37 yes, 16 no; | | F/U: Follow-up intervals not clear (median follow-up 4 mos(range 1-56) for entire cohort; 28 months (range 12-49 months) for surviving pts) | dose 50 Gy (39.9 - 69.0); 3DRT median dose 46.5 (range 4.0 - 70.0) | median OS & DSS: 3 mos; IMRT vs 3DRT for disease specific survival: HR 0.63 (0.30-1.30 95% CI, p=0.2078); IMRT vs 3DRT for overall survival: HR 0.60 (0.29-1.25 95%CI, p=0.1705) | hospitalization or interventional procedure | Potential conflict of interest |
| Schwartz (2009) Cohort **Thyroid Cancer (Differentiated)** | n = 131 (74 EBRT, 57 IMRT)<br><br>Median age 57 (range 18-83); Gender 56 females, 75 males; | differentiated thyroid CA | IMRT; EBRT<br><br>F/U: Follow-up intervals not clear (median follow-up from completion of RT 38 mos(0-134)); pts receiving IMRT 34 mos (range, 5-85 mos) | Median dose IMRT: 60 Gy (56-66); median dose 3DRT: 60 Gy (range 38-72) | 4 yr locoregional relapse-free survival: 79%; 4-yr disease-specific survival: 76%; 4 yr overall survival: 73%; 3DRT vs IMRT for locoregional control: HR 0.68 (0.31-1.50 95% CI, p=0.3386); 3DRT vs IMRT for disease-specific survival: HR 1.67 (0.76-3.67 95% CI, p=0.1983); 3DRT vs IMRT for overall survival: HR 1.72 (0.82-3.60 95% CI, p=0.1497) | IMRT associated with less frequent severe late radiation morbidity; IMRT: 1 pt, esophageal stricture tx'ed with dilatation | Good |
| Rosenbluth (2005) Case series **Thyroid Cancer (Nonanaplastic)** | n = 20<br><br>Median age: 57 yrs (range 15-73); Sex: 12 men, 8 women; Histology: 12 papillary, 3 | Inclusion criteria: Histologically confirmed thyroid cancer; Exclusion criteria: Anaplastic cancer | All patients underwent IMRT, treatment with radioactive iodine in 70% | Median dosage was 58 Gy (range 54-68) in 1.6 to 2.25 Gy fractions | No outcomes reported other than development of secondary primary cancers | Differences between the IMRT and surgery treatment groups in development of secondary primary cancers were not statistically significant (No other harms reported) | Poor<br><br>Investigators stated that they had no conflict of interest; |

| 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** |
| | medullary, 2 insular, 1 mucoepidermoid, 1 insular/follicular, 1 poorly differentiated; T-stage: 2 T2, 18 T4; N-stage: 2 N0, 16 N1, 2 Nx; M-stage: 13 M0, 7 M1 | | patients, chemotherapy in 40% patients<br><br>F/U: Median 13 months (range 1-28) | | | | Poor quality due to failure to randomize patients to treatment groups, retrospective analysis, and no reporting of dosage or patient characteristics other than age |

## Appendix G. Guideline Summary Table

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| ACR – ASTRO (2011)<br>*ACR-ASTRO Practice Guideline for Intensity Modulated Radiation Therapy (IMRT)* | This guideline focuses on multileaf collimator (MLC)-based IMRT techniques for photon treatment, such as multiple static segment (step-and-shoot) treatment, dynamic segment (sliding-window) treatment, volumetric modulated arc therapy (VMAT), and binary-collimator tomotherapy. Compensator-based beam modulation is also used as a means of achieving IMRT.<br>Personnel – appropriate certification, credentialing, continuing medical education<br>• Coordinated team effort between the radiation oncologist, the medical physicist, the medical dosimetrist, and the radiation therapist.<br>Quality assurance (QA) program includes:<br>• Systematic testing of the hardware and software used in the IMRT treatment-planning and delivery process<br>• Review of each patient's treatment plan, and<br>• Review of the physical implementation of the treatment plan.<br>IMRT treatment plan implementation requirements:<br>• Correct Patient Positioning<br>• Correct Beam Delivery Parameters<br>IMRT delivery system QA elements:<br>• MLC Leaf Position Accuracy<br>• Segmental MLC and Dynamic MLC IMRT Delivery<br>• Volumetric Modulated Arc Therapy<br>• Compensator-Based System<br>• Benchmark End-To-End Testing<br>Patient-specific QA elements:<br>• Treatment Unit Verification Data<br>• Image-Based Verification Data<br>• Dose Delivery Verification by Physical Measurement<br>• Backup Monitor Unit Calculations<br>Successful IMRT programs involve integration of many processes: patient selection, patient positioning/immobilization, target definition, treatment plan development, and accurate treatment delivery. Appropriate QA procedures, including patient specific QA measures, are essential for maintaining the quality of | Consensus panel<br><br>Poor |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| | an IMRT program and assuring patient safety. | |
| Decker [ACR] (2011)<br>*ACR Appropriateness Criteria® Postoperative Adjuvant Therapy in Non-Small Cell Lung Cancer* | • T2N2 with careful mediastinal staging, highest node negative. Negative surgical margins postresection – ACR Appropriateness Criteria® for IMRT: 6<br>• Clinically staged T2N0, pathologically staged T2N1, no sampling of mediastinal nodes. Negative surgical margins postresection. Clinically staged T2N0 by PET/CT. – ACR Appropriateness Criteria® for IMRT: 6<br>• T3N2 with mediastinal node staging. Positive margins at the primary site. ACR Appropriateness Criteria® for IMRT: 6 | RCTs<br><br>Fair |
| Gaffney [ACR] (2010)<br>*ACR Appropriateness Criteria® Advanced Cervical Cancer* | "IMRT is not felt by the panel to be indicated for the routine treatment of cervix cancer at this time due to significant organ motion issues" (p. 2)<br><br>- note: varying appropriateness levels depending on cases (3 vs 8) | Literature review<br><br>Fair |
| Gewanter [ACR] (2010)<br>*Nonsurgical Treatment for Non-Small-Cell Lung Cancer: Good Performance Status/Definitive Intent* | - note: ACR Appropriateness Criteria®: 8 (with tumor motion strategy required in addition to strict dosimetric criteria)<br>- varies slightly according to cases | Literature review<br><br>Fair |
| Gopal [ACR] (2010)<br>*Induction and Adjuvant Therapy for N2 Non-Small-Cell Lung Cancer* | - note: ACR Appropriateness Criteria®: 8 (with tumor motion strategy required in addition to strict dosimetric criteria)<br>- for all cases presented | Literature review<br><br>Fair |
| Holmes [ASTRO] (2009)<br>*American Society of Radiation Oncology Recommendations for Documenting Intensity-Modulated Radiation Therapy Treatments* | This guideline provides recommendations for documenting IMRT treatments, as well as image-guidance procedures, with example forms provided.<br>IMRT DOCUMENTATION RECOMMENDATIONS<br>I. Recommendations for Current Practice<br>A. Recommendations for Dose and Volume Specification<br>1. Clinicians should specify the gross target volume (GTV), clinical target volume (CTV), planning target volume (PTV), integrated target volume (ITV), organ at risk (OAR), and planning organ at risk (PRV) following the recommendations of ICRU Reports 50 and 62 (4, 5).<br>2. The PTV must (at least attempt to) ensure proper coverage of the CTV in the presence of inter- and intrafraction variation of treatment setup and organ motion. The conventional approach of assigning a uniform margin around the CTV is generally no longer adequate when IMRT plans are considered. | Consensus panel<br><br>Poor |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| | 3. Information should be reported for the purpose of correlating the dose with the clinical outcome<br>a. Prescribed (intended) dose, as well as the point or volume to which it is prescribed; a fractionation prescription should also be included<br>b. D95: The dose that covers 95% of the PTV and CTV volume<br>c. D100: The dose that covers 100% of the PTV and CTV volume (i.e., the minimal dose)<br>d. V100: The percentage volume of the PTV and CTV that receives the 100% of the prescribed dose<br>e. Mean and maximal doses within the PTV and CTV<br>f. For each organ at risk, the maximal, minimal, and mean doses, the volume of the organ receiving that dose, and other relevant dose–volume data.<br>B. Recommendations for IMRT Documentation (Paper Copy or Digital form)<br>1. IMRT Treatment Planning Directive (include prescription, target definition, organs at risk, plan parameters, treatment planning goals, physician signature and date, and treatment planner signature and date)<br>2. IMRT Treatment Goal Summary<br>3. Image-Guidance Summary<br>4. Motion Management Summary (include body site, treatment method, respiratory management method and device, expected positioning uncertainty using the motion management system, method used to define the ITV and PTV)<br>5. Physician's treatment summary note<br>6. A copy of the daily treatment record<br>7. Treatment plan printout<br>8. Record retention<br><br>The guideline also describes ongoing development of electronic documentation and provides recommendations for future development of electronic documentation. | |
| Lutz [ACR] ) (2011)<br>*ACR Appropriateness Criteria® Non-Spine Bone Metastases* | "There is no data to suggest that highly conformal therapy with intensity modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), or proton therapy would improve the outcome for this patient [variant 2, 3, 4, 5 discussion]" (p 2-3)<br>- note ACR Appropriateness Criteria®: 2 | Literature Review<br><br>Fair |
| Morgan [ACR] (2011)<br>*ACR Appropriateness Criteria® Definitive External Beam Irradiation in State* | - note: ACR Appropriateness Criteria®: 8 (for multiple cases presented) | Literature Review |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| *T1 and T2 Prostate Cancer* | | Fair |
| NCCN (2012)<br>*Anal Carcinoma* | "The consensus of the panel is that IMRT may be used in place of 3-D conformal RT in the treatment of anal carcinoma. IMRT requires expertise and careful target design to avoid reduction in local control by so-called "marginal-miss"." (MS-8) | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Breast Cancer* | **Stage I, IIA, IIB, or T2N1M0 Invasive Breast Cancer: Local-regional treatment**<br>"A number of randomized trials document that mastectomy with axillary lymph node dissection is equivalent to breast-conserving therapy with lumpectomy, axillary dissection, and whole breast irradiation, as primary breast treatment for the majority of women with stage I and stage II breast cancers (category 1).<br>The Panel recommends whole breast irradiation to include the majority of the breast tissue; breast irradiation should be performed following CT-based treatment planning so as to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the primary tumor and surgical site. Tissue wedging, forward planning with segments (step and shoot), or intensity-modulated radiation therapy (IMRT) is recommended." p.74 (MS-10) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Cervical Cancer* | "Intensity-modulated radiation therapy (IMRT) and similar highly conformal methods of dose delivery may be helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting and in treating the paraaortic nodes when this is necessary. These techniques can also be useful when high doses are required to treat gross disease in regional lymph nodes. However, conformal external beam therapies (such as IMRT) should not be used as routine alternatives to brachytherapy for treatment of central disease in patients with an intact cervix. Very careful attention to detail and reproducibility (including consideration of target and normal tissue definitions, patient and internal organ motion, soft tissue deformation, and rigorous dosimetric and physics quality assurance) is required for proper delivery of IMRT and related highly conformal technologies." (p CERV-A 1) – *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Central Nervous System Cancers* | Low-Grade Infiltrative Astrocytoma and Oligodendrogliomas: "Every attempt should be made to decrease the radiation dose outside the target volume. This can be achieved with 3-dimensional planning or IMRT (Intensity Modulated Radiation Therapy)." (pg MS-4) | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012) | "Conformal external beam should be routinely used for T4 non-metastatic disease and intensity modulated | Consensus |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| *Colon Cancer* | radiotherapy (IMRT) reserved only for unique clinical situations including re-irradiation of previously treated patients with recurrent diseases" (pg COL-F) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).*<br><br>"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 radiation therapy (SBRT). *Category 3 recommendation (based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate)* | panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Esophageal and Esophagogastric Junction Cancers* | "Intensity modulated radiation therapy (IMRT) may be appropriate in selected cases to reduce dose to normal structures such as heart and lungs. In designing IMRT plans, for structures such as the lungs, attention should be given to the lung volume receiving low to moderate doses, as well as the volume receiving high doses." (pg ESOPH-F 1) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Gastric Cancer* | "Intensity modulated radiation therapy (IMRT) may be appropriate in selected cases to reduce dose to normal structures such as heart, lungs, kidneys and liver. As discussed above, target volumes need to be carefully defined and encompassed while designing IMRT plans. Uncertainties from variations in stomach filling and respiratory motion need to be taken into account. For structures such as the lungs, attention should be given to the volume receiving low to moderate doses, as well as the volume receiving high doses." (GAST-F 1) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Head and Neck Cancers* | "Either intensity-modulated RT (IMRT) or 3-D conformal RT is recommended for cancers of the oropharynx in order to minimize dose to critical structures, especially the parotid glands." (pg ORPH-A) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).*<br><br>"Either IMRT or 3-D conformal RT is recommended in cancer of the nasopharynx to minimize dose to critical structures" (pg NASO-A) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).*<br><br>"Either IMRT or 3-D conformal RT is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures." (pg ETHM-A) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| | "Either IMRT or 3-D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures, especially the parotid glands" (pg OCC-A) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).*<br><br>"Target delineation and optimal dose distribution require experience in head and neck imaging, and a thorough understanding of patterns of disease spread. Stands for target definition, fractionation (with and without concurrent chemotherapy), and normal tissue constraints are still evolving. IMRT, 3D and 2D conformal techniques may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support. Close interplay exists between radiation technology, techniques, fractionation, and chemotherapy options resulting in a large number of combinations that may impact toxicity or tumor control. Close cooperation and interdisciplinary management are critical to treatment planning and radiation targeting, especially in the postoperative setting or after induction chemotherapy.<br><br>Intensity-Modulated Radiotherapy (IMRT)<br>IMRT has been shown to be useful in reducing long term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea), and optic structures. The application of IMRT to other sites (e.g., oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians." (pg RAD-A) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | |
| NCCN (2012)<br>*Malignant Pleural Mesothelioma* | "CT stimulation simulation guided planning with conventional photon/electron RT is recommended. IMRT is a promising treatment technique that allows a more conformal high-dose RT and improved coverage to the hemithorax. IMRT or other modern technology (such as tomotherapy or protons) should only be used in experienced centers or on protocol. When IMRT is applied, the NCI/ASTRO IMRT guidelines (http://www.astro.com/Research/ResearchHighlights/documents/Imrt.pdf) should be followed strictly. Special attention should be paid to minimize radiation to the contralateral lung, as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied. The mean lung dose should be kept as low as possible, preferably < 8.5 Gy. The low dose volume should be minimized" (pg MPM-C 2) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Mucosal Melanoma of the* | "Target delineation and optimal dose distribution require experience in head and neck imaging, and a thorough understanding of patterns of disease spread. Stands for target definition, fractionation (with and without | Consensus panel w/lit |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| *Head and Neck* | concurrent chemotherapy), and normal tissue constraints are still evolving. IMRT, 3D and 2D conformal techniques may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support. Close interplay exists between radiation technology, techniques, fractionation, and chemotherapy options resulting in a large number of combinations that may impact toxicity or tumor control. Close cooperation and interdisciplinary management are critical to treatment planning and radiation targeting, especially in the postoperative setting or after induction chemotherapy.<br><br>Intensity-Modulated Radiotherapy (IMRT)<br>IMRT has been shown to be useful in reducing long term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea), and optic structures. The application of IMRT to other sites (e.g., oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians." (pg RAD-A) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | review<br><br>Poor |
| NCCN (2012)<br>*Non-Small Cell Lung Cancer* | "To maximize tumor control and to minimize treatment toxicity, critical components of modern radiation therapy include appropriate simulation, accurate target definition, conformal RT planning, and ensuring accurate delivery of the planned treatment. A minimum standard is CT-planned 3DCRT.<br><br>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), 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. In non-randomized retrospective comparisons in patients with locally advanced NSCLC treated with concurrent chemotherapy, 4DCT planned IMRT significantly reduced rates of high grade pneumonitis and higher overall survival compared to 3DCRT, and proton therapy reduced esophagitis and pneumonitis despite higher doses compared to 3DCRT or IMRT, while a prospective clinical trial demonstrated favorable outcomes compared to historical results.<br><br>Of note, the higher complexity of advanced technologies increases the risk of errors, and the relatively higher cost of some raises concern about their cost-effectiveness. Thus, centers using these technologies should implement and document modality-specific quality assurance measures. Useful references include the ACR-ASTRO Practice Guidelines for Radiation Oncology. Minimum requirements for thoracic IMRT are specified in NCI Advanced Technology Consortium IMRT Guidelines, and safety considerations for contemporary RT are | Consensus panel w/lit review<br><br>Poor |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| | detailed in a series of ASTRO commissioned white papers. The ideal is external credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials employing advanced technologies." (pg NSCL-B 1) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | |
| NCCN (2012)<br>*Prostate Cancer* | "3D conformal and IMRT (intensity modulated radiation therapy) techniques should be employed. Image-guided radiation therapy (IGRT) is required if dose ≥ 78 Gy." (pg PROS-C) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).*<br><br>"The second generation 3D technique, intensity-modulated radiation therapy (IMRT), significantly reduced the risk of gastrointestinal toxicities compared to 3D-CRT." (pg MS-7) | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Rectal Cancer* | "Intensity modulated radiotherapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy." (pg REC-D) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).*<br><br>"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 radiosurgery (SBRT). " (pg REC-D) *Category 3 recommendation (based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate)* | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Testicular Cancer* | The mean dose (D mean) and dose delivered to 50% of the volume (D50%) of the kidneys, liver, and bowel are lower with computed tomography (CT)-based anteroposterior-posteroanterior (AP-PA) three-dimensional conformal radiation therapy (3D-CRT) than intensity-modulated radiation therapy (IMRT). As a result, the risk of second cancers arising in the kidneys, liver, or bowel may be lower with 3D-CRT than IMRT, and IMRT is not recommended" (TEST-A 1) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |
| NCCN (2012)<br>*Thymomas and Thymic Carcinomas* | "RT should be given by 3D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, and spinal cord). Intensity-modulated RT (IMRT) may further improve the dose distribution and decrease dose to the normal tissue as indicated. If IMRT is applied, the NCT/ASTRO IMRT guidelines (http://www.astro.org/Research/ResearchHighlights/documents/Imrt.pdf) should be followed strictly." (pg THYM-B 2) *Category 2A recommendation (based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate).* | Consensus panel w/lit review<br><br>Poor |
| Poggi [ACR] (2010) | "Until the publication of Radiation Therapy Oncology Group® (RTOG®) 0529 a phase II study examining the role | Literature |

| Recommending Body, Year Published | Recommendation(s) | Evidence Base Quality |
|---|---|---|
| *ACR Appropriateness Criteria® Anal Cancer* | of IMRT in anal cancer in order to reduce morbidity, the ACR Appropriateness Committee cautiously recommends the use of IMRT as "may be appropriate" if performed outside of a protocol setting. Even for patients enrolled on RTOG® 0529, quality control and technical issues with IMRT were thought to be challenging." (pg 2)<br><br>ACR Appropriateness Criteria®: 6 (based on several variant cases) | Review<br><br>Fair |
| Quon [ACR] (2010)<br>*ACR Appropriateness Criteria® Local-Regional therapy for Resectable Oropharyngeal Squamous Cell Carcinoma* | ACR Appropriateness Criteria®: 8-9 (based on several variant cases) | Literature Review<br><br>Fair |
| Rossi [ACR] (2010)<br>*ACR Appropriateness Criteria® Postradical Prostatectomy Irradiation in Prostate Cancer* | ACR Appropriateness Criteria®: 2-8 (based on several variant cases) | Literature Review<br>Fair |
| Suh [ACR] (2007)<br>*ACR Appropriateness Criteria® Resectable Rectal Cancer* | ACR Appropriateness Criteria®: 1 (investigational use only) (based on several variant cases) | Literature Review<br><br>Fair |
| Wolfson [ACR] (2011)<br>*ACR Appropriateness Criteria® Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer* | ACR Appropriateness Criteria®: 7 (Great care is required in delineation of CTV.) (based on several variant cases) | Literature Review<br><br>Fair |

## Appendix H. Quality Assessment of Selected Guidelines

| Criteria | Guideline Developer, Year | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NCCN (2012a) | NCCN (2012b) | NCCN (2012c) | NCCN (2012d) | NCCN (2012e) | NCCN (2012f) | NCCN (2012g) | NCCN (2012h) | NCCN (2012i) | NCCN (2012j) | NCCN (2012k) | NCCN (2012l) | NCCN (2012m) | NCCN (2012n) | NCCN (2012o) | NCCN (2012p) |
| Section 1: Primary Criteria | | | | | | | | | | | | | | | | |
| Rigor of Development: Evidence | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor |
| Rigor of Development: Recommendations | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good |
| Editorial Independence | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good |
| Section 2: Secondary Criteria | | | | | | | | | | | | | | | | |
| Scope and Purpose | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good |
| Stakeholder Involvement | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair |
| Clarity and Presentation | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good |
| Applicability | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good |
| Section 3: Overall Assessment of the Guideline | | | | | | | | | | | | | | | | |
| **How well done is this guideline?** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** | **Poor** |

| Criteria | Guideline Developer, Year | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Decker [ACR] 2011 | Gaffney [ACR] 2010 | Gewanter [ACR] 2010 | Gopal [ACR] 2010 | Lutz [ACR] 2011 | Morgan [ACR] 2011 | Poggi [ACR] 2010 | Quon [ACR] 2010 | Rossi [ACR] 2010 | Suh [ACR] 2007 | Wolfson [ACR] 2011 | ACR-ASTRO 2011 | Holmes [ASTRO] 2009 |
| Section 1: Primary Criteria | | | | | | | | | | | | | |
| Rigor of Development: Evidence | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Poor | Poor |
| Rigor of Development: Recommendations | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Poor | Poor |
| Editorial Independence | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Poor | Fair |
| Section 2: Secondary Criteria | | | | | | | | | | | | | |
| Scope and Purpose | Poor | Fair | Fair | Poor | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Fair | Good |
| Stakeholder Involvement | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Fair | Poor | Fair | Fair |
| Clarity and Presentation | Fair | Fair | Fair | Poor | Fair | Fair | Fair | Poor | Poor | Poor | Fair | Fair | Good |
| Applicability | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Poor | Fair | Fair |
| Section 3: Overall Assessment of the Guideline | | | | | | | | | | | | | |
| **How well done is this guideline?** | **Fair** | **Fair** | **Fair** | **Fair** | **Fair** | **Fair** | **Fair** | **Fair** | **Fair** | **Fair** | **Fair** | **Poor** | **Poor** |

## Appendix I. Summary of Federal and Private Payer Policies

| Payer | Coverage Criteria |
|---|---|
| **Medicare** | |
| **L24318**<br>02/27/2012<br>Washington<br><br>**L31415**<br>2/27/2012<br>Washington | The decision process for using IMRT requires an understanding of accepted practices that take into account the risks and benefits of such therapy compared to conventional treatment techniques. While IMRT technology may empirically offer advances over conventional or three dimensional (3-D) conformal radiation, a comprehensive understanding of all consequences is required before applying this technology.<br><br>IMRT is not a replacement therapy for conventional and 3-D conformal radiation therapy methods. IMRT is considered reasonable and necessary in instances where sparing the surrounding normal tissue is essential and the patient has <u>*at least one*</u> of the following conditions met:<br><br>1. Important dose limiting structures adjacent to, but outside the PTV, are sufficiently close and require IMRT to assure safety and morbidity reduction.<br>2. An immediately adjacent volume has been irradiated and abutting portals must be established with high precision.<br>3. Gross Tumor Volume (GTV) margins are concave or convex and in close proximity to critical structures that must be protected to avoid unacceptable morbidity.<br>4. Only IMRT techniques would decrease the probability of grade 2 or grade 3 radiation toxicity as compared to conventional radiation in greater than 15% of radiated similar cases.<br><br>Currently, IMRT is indicated for primary brain tumors, brain metastasis, prostate cancer, lung cancer (with special provision for organ motion), pancreas cancer and other upper abdominal sites (with special provision for organ motion), spinal cord tumors, head and neck cancer, adrenal tumors, pituitary tumors and situations in which extremely high precision is required. Indications will include some left breast tumors due to risk to immediately adjacent cardiac and pericardial structures, though it would only rarely if ever be medically necessary for tumors of the right breast.<br><br>IMRT may be necessary in some gynecologic tumors or in *some* genitourinary tumors where its high precision is especially necessary to avoid immediately adjacent structures such as bowel or where there is a special need to avoid marrow. It may also be necessary in <u>*some*</u> lymphomas, malignant lymph nodes or sarcomas where anatomic location gives rise to a need for special care to avoid adjacent structures. Since these are likely to be only a relatively small fraction of gynecologic tumors, genitourinary |

| Payer | Coverage Criteria |
|---|---|
| | tumors, lymphomas, malignant nodes or sarcomas, in each case particular care is required to document the necessity for IMRT. |
| **L30316**<br>12/01/2011: 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 Virginia, Wyoming | IMRT is not a replacement therapy for conventional and 3D conformal radiation therapy methods.<br>IMRT is considered reasonable and necessary where sparing the surrounding normal tissue is of added benefit and at least one of the following conditions is met:<br>1. The target volume is in close proximity to critical structures that must be protected.<br>2. The volume of interest must be covered with narrow margins to adequately protect immediately adjacent structures.<br>3. An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision.<br>4. The target volume is concave or convex, and critical normal tissues are within or around that that convexity or concavity.<br>5. Dose escalation is planned to deliver RADIATION doses in excess of those commonly utilized for similar tumors with conventional treatment.<br>IMRT is indicated as a standard treatment option for:<br>1. Primary, metastatic or benign tumors of the central nervous system, including the brain, brain stem and spinal cord;<br>2. Primary, metastatic tumors of the spine where spinal cord tolerance may be exceeded by conventional treatment;<br>3. Primary, metastatic, or benign lesions to the head and neck area including orbits, sinuses, skull base, aerodigestive tract and salivary glands;<br>4. Carcinoma of the prostate;<br>5. Selected cases of thoracic and abdominal malignancies;<br>6. Selected cases (i.e., not routine) of breast cancers with close proximity to critical structures;<br>7. Other pelvic and retroperitoneal tumors that meet the requirements for medical necessity; and<br>8. Reirradiation that meets the requirements for medical necessity.<br>Although IMRT is not indicated as the routine management for other cancers, IMRT is often reasonable and necessary for other sites. There is no definitive list of “approved sites” nor is it possible to preclude some cancers solely on the basis of primary site origin. The radiation oncologist must consider the five criteria detailed above (proximity to critical structures, narrow margins, previous radiation, target shape, and dose escalation requirement) and then determine if IMRT is indicated. For example, IMRT may be indicated in the treatment of lung cancers and intra-abdominal and pelvic malignancies where the effect of organ |

| Payer | Coverage Criteria |
|---|---|
| | motion must be considered. In the case of breast cancer, while not routine, IMRT may be indicated when the tumor is in proximity to the heart. For all instances, the physician should document the indications for IMRT. It may be used as the primary/sole modality or as a boost to conventional therapy. |
| **Private Payers** | |
| **Aetna**<br>2/12/2012 | Clinical Policy Bulletin: Intensity Modulated Radiation Therapy<br>Aetna considers intensity modulated radiation therapy (IMRT) medically necessary for radiosensitive tumors where critical structures cannot be adequately protected with standard 3D conformal radiotherapy.<br>Interfraction image guidance (i.e., image guidance between fractions) is considered medically necessary for delivering IMRT and other conformal radiotherapy. |
| **GroupHealth** | Intensity Modulated Radiation Therapy (IMRT)<br>IMRT for Head and Neck Cancer<br>IMRT for Prostate Cancer<br>Medical necessity review is no longer required for this service. For Medicare members, refers to LCD L24318 for Part B service, and L31415 for facility-based services billing using UB. |
| **Regence BCBS** | IMRT of the Abdomen and Pelvis 08/01/2011<br>1. Intensity modulated radiation therapy (IMRT) may be considered medically necessary as a treatment for squamous cell cancer of the anal canal.<br>2. IMRT for other tumors of the abdomen or pelvis may be considered medically necessary when one or more of the following criteria are met:<br>a. There is documented prior radiation treatment to the planned target area(s)<br>b. A critical anatomical structure (spinal cord, heart, pancreas, kidney or small bowel) is located in the radiation field<br>c. The organ targeted for treatment has documented significantly impaired function or limited capacity<br>3. IMRT for the treatment of all other abdominal or pelvic tumors is considered investigational.<br><br>IMRT for Head and Neck Cancers and Thyroid Cancer 08/01/2011<br>Intensity-modulated radiation therapy may be considered medically necessary for the treatment of head and neck cancers. |

| Payer | Coverage Criteria |
|---|---|
| | Intensity-modulated radiation therapy is considered investigational for the treatment of thyroid cancer.<br>**IMRT of the Prostate** 01/11/2012<br>Intensity-modulated radiation therapy (IMRT) as a treatment of prostate cancer without prostatectomy and without metastases may be medically necessary as the primary treatment or as a salvage treatment for failed primary treatment.<br>IMRT for post-prostatectomy treatment of prostate cancer without metastases may be medically necessary<br>• as adjuvant therapy immediately following prostatectomy<br>• as salvage therapy for failed prostatectomy, or<br>• as salvage therapy for suspected recurrence of localized prostate cancer as evidenced by detectable PSA that increases on two subsequent measures<br>IMRT is considered investigational for treatment of metastatic prostate cancer.<br><br>**IMRT of the Breast and Lung** 08/01/2011<br>1. Breast Cancer<br>a. Intensity modulated radiation therapy (IMRT) may be considered medically necessary to deliver whole breast irradiation following breast-conserving surgery, when at least one of the following criteria are met:<br>i. There is prior documented radiation to the chest wall or<br>ii. The radiation treatment field includes the heart.<br>b. Except as defined in I.A.1 and I.A.2 above, IMRT as a technique of whole breast irradiation is considered not medically necessary. The clinical outcomes with this treatment have not been shown to be superior to other approaches such as 3D-conformal radiation therapy, yet IMRT is generally more costly than these alternatives.<br>c. IMRT as a technique of partial breast irradiation following breast-conserving surgery is considered investigational.<br>2. Lung<br>a. IMRT may be considered medically necessary as a treatment for lung cancer when at least one of the following criteria are met:<br>i. There is documented prior radiation treatment to the planned target area(s)<br>ii. A critical anatomical structure (such as the spinal cord or heart) is located in the radiation field |

| Payer | Coverage Criteria |
|---|---|
| | iii. There is documented significantly impaired pulmonary function or limited pulmonary capacity<br>b. Except as defined in II.A, IMRT is considered not medically necessary for the treatment of lung cancer. The clinical outcomes with this treatment have not been shown to be superior to other approaches such as 3D-conformal radiation therapy, yet IMRT is generally more costly than these alternatives. |

## Appendix L. MAUDE Database Search Results

Search terms: intensity modulated radiation therapy, intensity modulated radiotherapy, IMRT, intensity modulated, tomotherapy, volume modulated arc therapy, VMAT

Dates: 2002-2012

Outcomes of interest: serious injury (surgery, hospitalization, death)

| Manufacturer | Brand Name | Report Date | Summary of Reported Harms |
|---|---|---|---|
| Tomotherapy Inc | Hiart System | 6/6/2009 | One patient with severe skin reactions from radiotherapy admitted to intensive care unit. Targets were near skin level (2-4mm). Dose at skin level was approximately 4,000-7,000 cGy. |
| Unknown | Unknown | 11/22/2007 | Pt. admitted to hospital for Grade 3 hematochezia secondary to rectal ulceration and Grade 3 anemia. Pt's protocol treatment was radiation (ebrt/imrt) + brachytherapy + taxotere + prednisone. Pt also had a history of diabetes mellitus, aspirin therapy, and persistent use of tobacco and alcohol. |

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