Washington State Health Care Authority

Health Technology Assessment

Intensity Modulated Radiation Therapy

Final Public Comments and Disposition

Appendix J: Public Comments and Disposition

August 17, 2012

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Intensity Modulated Radiation Therapy

Appendix J. Public Comments and Disposition

August 2012

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Public Comments and Disposition

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RESPONSE TO PUBLIC COMMENTS

The Center for Evidence-based Policy is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the comments process are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

This document responds to comments from the following parties:

Topic Nomination

- Berit L Madsen, MD, FACR (Peninsula Cancer Center)
- Virginia Mason Medical Center

Key Questions

- American College of Radiation Oncology (ARCO)
- American Society of Radiation Oncology (ASTRO)
- Spencer Ashton, MD (Providence St. Mary's Regional Cancer Center)
- Thomas Carlson (Wenatchee Valley Medical Center)
- Joseph R. Hartman (RadiantCare Radiation Oncology)
- Darryl Kaurin, PhD, DABR, CHP (Northwest Medical Physics Center)
- Berit L. Madsen, MD, FACR, R. Alex His, MD, and Heath R. Foxlee, MD (Peninsula Cancer Care)
- Tim Mate, MD
- Mark Phillips, PhD (Department of Radiation Oncology, University of Washington)
- John Rieke, MD (MultiCare Regional Cancer Center)
- Swedish Medical Center
- Tacoma/Valley Radiation Oncology Centers
- Eric W. Taylor (Evergreen Radiation Oncology)
- Tumor Institute Radiation Oncology Group
- University of Washington
- Varian Medical Systems

Draft Report

- American Society of Radiation Oncology (ASTRO)
- James H. Brashears III, MD
- Trevor Fitzgerald, MSc, DABR, CCPM (Wenatchee Valley Medical Center)
- Varian Medical Systems

Specific responses pertaining to each comment are included in Table 1, 2, and 3 below. The full version of each public comment received is available in the Public Comments section, beginning on page 33

Additional resources provided by parties can be found in Appendix A and B starting on page 128.

Table 1. Response to Public Comment on Topic Nomination

Reviewer	Comment	Disposition
Berit L. Madsen, MD, FACR (Peninsula Cancer Center)		
	"Intensity modulated radiation therapy, or IMRT, is a specialized form of three dimensional conformal radiotherapy that allows radiation to be more exactly shaped to fit the tumor. With IMRT, the radiation beam can be broken up into many "beamlets," and the intensity of each beamlet can be adjusted individually. Using IMRT, it may be possible to further limit the amount of radiation received by healthy tissue near the tumor. In some situations, this may also safely allow a higher dose of radiation to be delivered to the tumor, potentially increasing the chance of a cure. IMRT was developed in the 1990's to treat prostate and head and neck cancer but has been broadly adopted since then by most radiation oncologists to treat a wide variety of tumors because it allows higher more effective doses of radiation to be delivered while improving both the acute and late side effects of treatment. There is a large and growing body of clinical evidence to support the use of IMRT for many types of cancer. (see attached partial bibliography and I'd be happy to send the committee any reprints needed). Most radiation oncology experts would agree that IMRT is the standard of care for prostate, head and neck, and many gynecologic and anal malignancies. Other disease sites also benefit from the improved radiotherapy delivery properties of IMRT. Most modern linear accelerators with multi-leaf collimators (Varian, Elekta, Tomotherapy and others) can perform IMRT. IMRT requires considerable additional work for the physician, treatment planners (dosimetrist), and physicist because of the increased complexity of defining treatment volumes and normal tissue constraints as well as increased quality assurance and machine maintenance. While there is extra work involved, IMRT allows for semi-automated treatment which can be delivered faster and can be less error prone that conventional radiotherapy. In summary; IMRT is commonly utilized method of radiotherapy that has enhanced the effectiveness, improved the tolerance and safety of radiation	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Topic Nomination.*

Reviewer	Comment	Disposition
	therapy for many patients with cancer." [*see pages 33 to 36 for full comment and evidence cited*]	
Virginia Mason Medical Center		
	"We are writing to encourage you to remove IMRT from the proposed list of topics for review by the HCA Administrator. We feel that IMRT is of great value and benefit to our patients. There are many areas where IMRT has been proven to be superior to 3D-conformal radiation therapy (3DCRT): in the treatment of prostate cancer, head and neck cancers, brain or skull base tumors, and cases requiring re-irradiation. In prostate cancer, IMRT can spare the rectum, bowel, and bladder better than 3DCRT. Clinical studies demonstrate lower rectal toxicity with IMRT over 3DCRT. In head and neck cancers, IMRT has shown much better parotid gland sparing than 3DCRT. Parotid sparing is very important for reducing the severity of permanent xerostomia which greatly affects the patient's ability to eat and quality of life. In brain or skull base tumors, IMRT can reduce dose to critical structures which are very sensitive to radiation such as retina, optic nerves, and chiasm. In addition, there is data supporting sparing hippocampal regions to reduce permanent neurocognitve dysfunction. IMRT is extremely useful when treatment is needed to an area in close proximity to a region that has previously received radiation in order to keep the dose below dose tolerances for that structure. Furthermore, there are current national NCI sponsored clinical trials using radiation therapy which mandate the use of IMRT for treatment of patients on protocol since it is agreed that it is the best treatment technique in these settings, including RTOG brain studies (0539 and 0933) and head and neck cancer studies (1016 and 0920). It would be a disadvantage to the patients not to be able to offer them these potentially life-saving treatment studies because IMRT was not reimbursed. This technology is of proven benefit to patients, and should not be on the list for review by the HCA. " [*see pages 37 to 39 for full comment and evidence cited*]	*Thank you for your comment.* *No changes to Topic Nomination.*

Table 2. Response to Public Comments on Key Questions

Reviewer	Comment	Disposition
American College of Radiation Oncology (ACRO)		
Sheila Rege, MD, FASTRO, FACRO	"The issues surrounding choices of radiation-emitting modalities (e.g. IMRT) are usually based on physical (physics) data and empirical observation, rather than randomized controlled clinical trials. The US Food and Drug Administration does not require such Level I data for device approval, and once devices are approved and marketed, there is little ability to complete those trials. Proposals to payers to assist in implementing trials, as with *Coverage with Evidence Development*, have been shunned, and patients (and IRBs) will rarely if ever accept randomization to trials where the only presumed differences are related to morbidity. As a delivery system widely available since 1998 (when the CPT© codes and RVUs were established), IMRT has been shown in every and innumerable instances measured, to reduce morbidity to the adjacent organs at risk in proximity to target tumor volumes. In instances where this morbidity-reduction has been used to permit an increase in radiation dose to tumors (e.g. prostate, head/neck, central nervous system, liver, etc.), a concomitant increase in local control has also been demonstrated. Regrettably, in radiation oncology, unlike drug development, since long-term control or cure is often the determinant end-point, years may be required to define the parameters, so physical data and morbidity reduction MUST be used as surrogates. Randomized device trials also require a large installed base of the devices, which is also impractical. Alternatively, drug studies may provide actionable (albeit often non-clinically relevant) information in weeks to months, at minimal cost, since the primary end-points are more often simply measurement of some surrogate tumor marker or internal free from progression. There is clear and increasing evidence that in certain circumstances, SBRT and SRS may be equivalent and/or preferable to conventional fractionated and protracted radiation. SBRT and SRS, unlike IMRT, relate to "biology" and not "technology," in that they merely represent the delivery of high-dose, short-course radiation (5 or fewer treatments, rather than daily, protracted, lower-dose, longer-course therapies). Evidence mounts that numerous sites, including brain, spinal cord,	*Thank you for comments.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	liver, and lung, as well as other emerging indications, are appropriately treated by SRS (for central nervous system) and SBRT (for non-central nervous system). We understand that the American Society for Radiation Oncology (ASTRO) has included its own model coverage policies on SRS, SBRT and IMRT for your review that outline specific technology of each treatment, clinical indications, coding considerations and references. ACRO supports your review of these materials and their conclusions. We also are aware that physicians with the Swedish Medical Center are submitting information regarding studies that have been performed relating to SRS, SBRT and IMRT. We would encourage the committee to review these in detail." [*see pages 40 to 42 for full comment*]	
American Society of Radiation Oncology (ASTRO)		
	"The Key Questions posed for the SRS, SBRT, and IMRT are extensive and ask for a level of detail that we cannot produce within the time frame allotted. The information requested for all three technologies, specifically comparisons to external beam radiation therapy) benefits and harms), and differential efficacy or safety issues in subpopulations including consideration of gender, age, site and type of cancer, stage and grade of cancer and setting, provider characteristics, equipment, quality assurance standards and procedures, constitutes a full research study that would take many months to produce. While ASTRO believes these technologies offer clear benefits to many of the cancer patients our members treat, we would require significantly more time to adequately address the important issues raised in the Key Questions. ASTRO plans on reviewing the draft report that will be produced as a result of the public comment period and we look forward to reviewing this report in early July. We have noted that the Health Technology Clinical Committee that will be reviewing the technology assessment reports and making coverage decisions does not include a radiation oncologist and we strongly recommend that a radiation oncologist be added to this committee. In anticipation of the more detailed comments that we will submit in response to the draft report, we offer a general observation relating to the fundamental basis of some of our positions about IMRT in particular. During the past two decades,	*Thank you for comments.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	an abundant number of clinical studies have characterized the relationship between the dose given to various normal tissues using 3D EBRT and the risk of toxicity to those tissues. There are recognized dose thresholds know to relate to the risk of toxicity for bowel, bladder, spinal cord, and other important organs. Whereas IMRT offers the capacity to avoid exceeding those recognized thresholds for toxicity, it is considered an appropriate standard for numerous indications as a result of this property. The field of radiation oncology has not considered it ethical or resource-efficient to conduct head-to-head tc omparisons of 3D EBRT vs. IMRT in all settings where a clear improvement in a surrogate measure of toxicity risk is easily demonstrated. We have included ASTRO's model coverage policies on SRS, SBRT, and IMRT for your review that outline the specific technology of each treatment, clinical indications, coding considerations, and references." [*see pages 43 to 45 for full comment*]	
Spencer Ashton, MD (Providence St. Mary's Regional Cancer Center)		
	"I am writing to put my support behind the use of Intensity Modulated Radiation Therapy (IMRT) as a vital tool for the treatment of cancer in the State of Washington. The development of IMRT techniques has allowed physicians to deliver more conformal radiation doses to treatment volumes, allowing us to increase dose to target tissues while simultaneously decreasing dose to the surrounding normal tissues. This leads to decreased toxicity/side effects that patients endure as part of their treatment, while in some cases increasing tumor control rates. IMRT is not used in every breast cancer patient, but has made an important impact in the treatment of Head and Neck malignancies, Prostate Cancer, and some abdominal cancers among others. IMRT has decreased both the acute toxicity experienced during treatment as well as the long term toxicity experienced by patients even years down the road. I have read and agree with the position put forth by the Swedish Medical Center in Seattle as linked to above. I ask you to examine the evidence, and would encourage you to continue to support the use of IMRT in the appropriate patients	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	here in the State of Washington." [*see page 46 for full comment*]	
Thomas Carlson, MD (Wenatchee Valley Medical Center)		
	"I am concerned with respect to the path we have been going down regarding the complexity of reimbursement evaluation. We seem to be reimbursing physicians based on the tools they are using to accomplish a task as opposed to the task itself. In the case of IMRT, Stereotactic Radiosurgery (in the brain or body) or brachytherapy, we are reimbursing based on the tool. Do we reimburse a surgeon for using one scalpel blade over another? No. The surgeon chooses what's most appropriate for the situation and is paid for the job. I believe a tremendous amount of waste could be removed from the system if a case rate reimbursement model was initiated." [*see page 47 for full comment*]	*Thank you for your comment.* *No changes to the Key Questions.*
Joseph R. Hartman (RadiantCare Radiation Oncology)		
	Summary – KQ1 [*see pages 48 to 52 for full comment and evidence cited*] • Summarizes clinical outcomes for IMRT treatment for brain, spine, head/neck, lymphoma, breast, pancreas, prostate cancers. Summary – KQ3 [*see page 53 for full comment*] • Discusses the applicability of IMRT in the treatment of different cancers, genders, and ages. Summary – KQ4 [*see page 53 for full comment and evidence cited*] • Discusses submitted cost comparison studies that address IMRT compared to EBRT.	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*
Darryl Kaurin, PhD, DABR, CHP (Northwest Medical Physics Center)		
	KQ1: For head and neck cancers, IMRT allows us to spare important organs that would not be possible with standard EBRT, namely parotid glands (imagine living the rest of your life without saliva), complications with teeth (we can frequently preserve blood flow to the teeth to improve the probably of not needing dentures), decrease spinal cord dose. We can decrease optic system dose (orbits, lens, optic chiasm, and optic nerves) for tumors more superiorly in the	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	nasopharnyx - which also allows us to use higher doses to tumors in this area. For brain, IMRT allows us to limit dose to the tumor areas with lower doses to non-involved brain areas. This is especially important near the optic system (see head and neck). Breast: this is frequently not reimbursed for IMRT, nevertheless there are cases where IMRT is called for, principally for left-sided breast to decrease heart dose (principally to the left ventricle) for young patients who would live long enough to see complications due to heart dose. IMRT can also be used to limit lung dose. Lung: Use of IMRT is not as common due to concerns with respirator motion. Sometimes, use of IMRT may be justified - especially in the case of SBRT where the tumor is given ablative doses that would be extremely harmful to non-involved tissues if not using IMRT. Near spinal cord: Use of IMRT can be used to achieve adequate dose to provide adequate control while minimizing the dose to the cord itself - this is only possible with IMRT. Pancreas: Where I work, we are getting much better outcomes than the national average using IMRT with higher radiation dose per fraction. The complications to organs surrounding the pancreas would be much higher without the use of IMRT with our higher dose per fraction. GI/Prostate/GYN: use of IMRT allows us to limit complications to uninvolved tissues - bladder, rectum, small bowel. Not having IMRT generally limits the dose we can take the target tissues to, which decreases the efficacy of the treatment. Patients may not be able to complete a course of EBRT due to the complications that IMRT can minimize. KQ2: IMRT requires additional time to carry out quality assurance checks on the individual treatments, as well as routine checks for the multileaf collimator. There have been instances where the quality assurance checks have not be done for individual treatments (there was a head and neck case in the North Eastern US written up in the New York Times several years ago) for several days following initiation of the treatment; the patient died from the treatment. This case	

Reviewer	Comment	Disposition
	appears to be an issue with an overworked medical physicist (inadequate staffing) as well as a glitchy treatment planning system, as well as therapists not understanding the importance of monitoring the treatment systems (if they had a window up showing the MLC movement, they would have seen the MLCs were open and not moving at all - the window on their screen was minimized). The incidence of these errors is fortunately low. The individual patient checks still need to occur, sometimes the treatment plans are too modulated for the MLC to deliver accurately, and need to be modified. These checks are especially important when working with more junior treatment planners, for newer treatment planning systems, treatment planning system upgrades, and treatment delivery system upgrades. KQ3: IMRT is extremely helpful for younger populations who will live long enough for radiation complications to become evident; since doses to non-target tissues are lower. IMRT is extremely helpful for older populations in terms of quality-of-life in reducing acute radiation effects to non-target tissues. KQ4: IMRT requires additional work for all the staff - MDs in denoting the target tissues on CT slices, reviewing additional imaging studies (MR, PET) and possibly fusing them with the treatment planning CT. IMRT requires additional training for the Dosimetrist (treatment planners) as well as addition time if they denote normal structures on the treatment planning CT (which are reviewed by the MD). IMRT requires additional time for the physicist to carry out routine as well as individual patient treatment planning checks by measuring the patient plan on a radiation sensitive device, and comparing the expected dose with the treatment planning calculated dose. IMRT requires increased diligence on the part of the therapists who deliver the treatment; if the patient is step up incorrectly with EBRT, the system is generally more forgiving and easier to identify errors using portal films with the treatment area and blocking; if the patient is setup incorrectly for IMRT, the target areas may be missed with avoidance areas receiving the treatment dose. For the IMRT treatment, frequently, additional imaging and motion management techniques are used to ensure correct targeting, which also increases time the patient is on the table as compared to EBRT. [*see pages 54 to 56 for full comment*]	

Reviewer	Comment	Disposition
Berit L. Madsen, MD, FACR, R. Alex His, MD, and Health R. Foxlee, MD (Peninsula Cancer Center)		
	We have received copies of the letters that Dr. Todd Barnett and his associates at the Swedish Cancer Institute have written in support of Intensity Modulated Radiotherapy (IMRT) and Stereotactic Radiotherapy (SRT), currently under review by your board. We have reviewed their letters and supportive documents and applaud their work and endorse their recommendations that IMRT and SRT/SBRT are important treatment techniques that benefit cancer patients while being safe and cost effective. IMRT and stereotactic radiotherapy are techniques that have been in common use in most radiation therapy centers for greater than 10 years; it would be impossible to think of not utilizing these advanced techniques for patients with conditions that warrant such treatment. We are hopeful that your review will support the continued utilization of these beneficial treatment techniques. [*see page 57 for full comment*]	*Thank you for your comment.* *No changes to the Key Questions.*
Tim Mate, MD		
	"The targets for the radiation in gynecological malignancies are typically the lymph node chains that lie along the bony pelvic sidewalls. Frequently there is a substantial amount of small and large bowel that exists in the pelvis, especially after a hysterectomy. Bowel is a very radiation sensitive organ and typically is the main source of serious acute and late toxicity with radiation therapy, and sometimes can be lead to very serious situations requiring bowel surgery to correct. Thus bowel toxicity is a major concern for radiation oncologists. In the decades years prior to the development of IMRT based treatment plans, patients were treated with the traditional "4 field "box" or a "3D" configuration. With these treatment plans, patients would receive a substantial amount of collateral bowel radiation by default. This unfortunately provided a large cohort of patients with injury to whom retrospective clinical data could be compiled upon and analyzed to determine what factors lead to higher rates of bowel complications. Not unexpectedly it the relationship of total dose delivered a volume of bowel that predicts, as it always has. But what's useful about these contemporary publications is that they quantify the doses and volumes that	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	provide radiation oncologists specific treatment planning guidance." "With a the standard "4 field box" treatment, commonly the dose to the bowel exceeds the 195 cc threshold, and only with an IMRT based treatment plan can this be obtained. As a recent example, a 49 year-old female was referred to our facility for adjuvant radiation to the pelvis after radical hysterectomy for cervical cancer. Again the targets for the radiation are the upper vagina and lateral pelvic sidewalls where the potential for residual cancer in the lymph nodes existed. Being post-hysterectomy there was a substantial amount of small and large bowel loops between the areas requiring irradiation. Two radiation treatment plans were then prepared and compared: a standard "4 field box" treatment and an IMRT based plan. The volume of bowel determined to be within the pelvis was 1150 cc. With the "4 field box" plan, 413 cc of bowel would be treated with 45 Gy, exceeding the published guideline quoted above. With the IMRT plan, 125 cc of bowel would receive 45 Gy, well below the recommend threshold of 195 cc. Thus, it was determined through quantitative methods that she would likely be at significantly less risk for bowel toxicity if treated with an IMRT based technique. This data was presented to her insurance carrier and she was approved for the requested IMRT treatment. Commonly radiation oncologists are confronted with an insurance carrier position that no randomized controlled clinical studies have been conducted to compare outcomes with traditional radiation versus IMRT radiation. The dilemma is that such studies will never likely be done, as excellent retrospective analysis, such as the quoted herein, have already provided guidance. All things being equal, one can easily appreciate the ethical challenge of placing a patient in a study which compare "4 field box" irradiation to IMRT when an obvious amount of bowel is being placed at risk. Thus clinical situations exist where the application to have an IMRT service covered should be approved if a rationale and justification can be provided as in the example cited." [*see pages 58 to 59 for full comment and evidence cited*	

Reviewer	Comment	Disposition
Mark Phillips, PhD (Department of Radiation Oncology, University of Washington)		
	"KQ1: The effectiveness of IMRT lies in its ability to localize radiation so that more radiation is delivered to the tumor and less to normal tissues. In some types of cancers (and some stages of cancer), it is unlikely that controlling the primary tumor will cure the cancer since it is likely to have spread. However, radiation is still part of the treatment of these cancers and all patients benefit from having less normal tissue irradiated. In other cases, when cure is more achievable, IMRT allows for a higher tumorcidal dose to be delivered. In this way, IMRT is a great step forward in cancer treatment. It enhances the chance for cure in some cases, and in all cases, its use is likely to decrease the chance for complications and improve the patient's quality of life. KQ2: Potential harms come in two forms. First, the technology is very complex and if delivered without appropriate quality control, there is a greater chance of mis-delivery that could result in patient harm. Therefore, the clinical practice of IMRT always involves significantly more work to do the appropriate quality assurance work. Second, there is a question of inappropriate use and potential harm. While IMRT delivered with appropriate quality assurance measures is no more harmful than EBRT and theoretically provides better normal tissue sparing, there is a question as to whether it is worth the cost. In some cases such as early stage prostate cancer, there may be an overreliance on IMRT and less use of permanent brachytherapy implants. KQ3-KQ4: As stated above, all patients benefit from reduced normal tissue dose. The ability of IMRT to improve cure rates does depend on the stage and type of cancer. Also as stated above, the safe and efficacious use of IMRT requires significantly more resources and training than does EBRT, though EBRT is potentially even more dangerous since larger regions are irradiated. In summary, IMRT has been a great advance in radiation therapy. There are very few disadvantages relative to EBRT. In both cases, the best approach to improving patient care is to insure that the radiation is delivered in a safe manner."[*see*	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	pages 60 to 61 for full comment]	
John Rieke, MD (MultiCare Regional Cancer Center)		
	"Stereotactic radiosurgery is an integral part of the field of neurosurgery with collegial interaction with the field of radiation oncology. At our center, more than 11,300 patients have undergone Gamma Knife stereotactic radiosurgery over the last 25 years since we placed the first Leksell Gamma Knife in North America." "Stereotactic radiosurgery is used for approximately 20% of all brain indications for intervention at our center with an increasing role in the management of metastatic cancer, arteriovenous malformations, chronic pain especially related to trigeminal neuralgia, glial neoplasms, and a wide variety of skull-based tumors including pituitary tumors." "In the last 25 years, more than 500 outcome studies have been published related to Gamma Knife radiosurgery, and it is approved for use by all insurance providers. This type of technique has been a radical transformation in the management of patients with a wide variety of otherwise frequently fatal brain conditions. Because of its superior technology and minimally invasive nature, patients are often done as an outpatient and can return to regular activities on the following day. Therefore, quality assessment, comparative outcomes research, and cost effectiveness research have substantiated the role of this technology in a wide variety of indications." [see *page 62 for full comment*]	*Thank you for your comment.* *No changes to the Key Questions.*
Swedish Medical Center		
	"Approximately 10 years ago, the most advanced technology for the delivery of radiation was 3D-conformal radiation. This is an improvement over previous 2D radiation in that the patient is imaged on a CT scanner and the contour of the skin, tumor, and normal structures can be entered into a planning computer. One can then develop a "3D" plan by selecting beam angles and creating beam shapes that best conformed to the target and the computer can calculate doses to particular structures. 3D conformal radiation is utilized today still in the majority of fairly straightforward cases However over this past decade, Intensity Modulated Radiation Therapy (IMRT) has been developed, refined, clinically	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	tested and utilized in many of the more complex radiation cases. With IMRT non-uniform intensities are assigned to tiny subdivisions of beams, called “beamlets,” enabling custom dosing of optimum dose distributions. For example, if a normal structure overlaps the planning target volume (PTV), one would ideally like to reduce the intensity of those radiation rays that pass through the normal structure. However, using this strategy the target volume would have a "cold spot" of decreased intensity in the shadow of the normal structure. To compensate for this shadow, the intensities of other rays in other beams would need to be increased. While conventional radiation therapy uses wedges and compensators to provide intensity modulation, the unique aspect of IMRT involves the use of a computer-aided optimization process to determine the non-uniform intensity distributions to attain certain specified clinical objectives. Using IMRT, the target volume can be treated with different fraction (i.e. daily dose) sizes simultaneously. This contrasts with conventional radiation therapy, in which the same fraction size is used for all target volumes, but the field sizes are reduced in stages over critical regions in order to protect critical normal structures. One key aspect of IMRT is inverse planning. It would be impossible for a human to create an optimized IMRT radiation plan. There are too many variables at play and the effect of modulating one beam can alter the requirement of other beams in complex manners. The computer iteratively creates hundreds of thousands of radiation plans, constantly optimizing and refining the shape of the beams, until finding the optimal solution. The term ‘inverse planning’ comes from the fact that instead of creating and placing a beam to deliver a particular dose to a tumor, we first define the tumor and other organs or avoidance structures, and then instruct the computer to work backwards and find the best radiation plan. Because of this increased complexity in IMRT planning, very elaborate verification and quality assurance measures are necessary. There are strict guidelines that are published by the American College of Radiology (ACR) and American Society of Therapeutic Radiation Oncology (ASTRO) for the implementation and quality assurance of IMRT. The details of this are beyond the scope of this letter, but the	

Reviewer	Comment	Disposition
	complexity in the safe delivery of IMRT is daunting and is a labor intensive task for the physician, physicist, dosimetrist, and radiation therapists. As technology has developed, linear accelerators have been improved and modified to deliver IMRT. In your statement, TomoTherapy was specifically mentioned. TomoTherapy is a particular linear accelerator made by one vendor that was built from the ground-up to deliver IMRT in a highly conformal manner using entire arcs of treatment instead of fixed beam angles. Other venders have subsequently developed arc-therapy as well, including Varian's RapidArc and Elekta's VMAT (Volumetric Arc-Therapy). However delivered, the goals of IMRT are essentially the same, and this letter would be applicable to all the specific vendors or modalities for delivery of IMRT. IMRT can benefit the patient in three ways. First, by improving conformity with target dose it can reduce the probability of in-field recurrence. Second, by reducing irradiation of normal tissue it can minimize the degree of morbidity associated with treatment. Third, with these techniques the ultimate radiation dose can often be escalated well beyond previous constraints which has in many studies shown increased local control. Whereas there are multiple randomized and nonrandomized trials showing benefits to IMRT, to our knowledge there is no trial that has shown worse outcome with IMRT. Although the initial goal of the key questions was to be limited to comparison of IMRT to 3-D radiation, in the larger context both IMRT and stereotactic radiation therapy represents a much larger advance. Improved outcomes with these highly conformal forms of radiation is allowing for safe alternatives to costly surgery or chemotherapy in many cases. As the general trend in medicine continues towards minimally-invasive outpatient medical treatment, we expect radiation therapy to continue to be an increasing part of that trend allowing safe and effective cancer treatment. " [*see pages 63 to 68 for full comment*]	
	Summary – KQ1 [*see pages 63 to 68 for full comment and evidence cited*] • Summarizes clinical outcomes for IMRT treatment for brain, spine, head/neck, lymphoma, breast, pancreas, prostate, and anal cancers.	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.*

Reviewer	Comment	Disposition
	Summary – KQ2 [*see page 68 for full comment and evidence cited*] • Discusses the difference in clinical outcomes between IMRT and EBRT Summary – KQ3 [*see page 69 for full comment*] • Discusses the applicability of IMRT in the treatment of different cancers, genders, and ages. Summary – KQ4 [*see page 69 for full comment and evidence cited*] • Discusses submitted cost comparison studies that address IMRT compared to EBRT.	*No changes to the Key Questions.*
Sandra Vermeulen	Summary – KQ1 and KQ2 [*see page 70 to 72 for full comment and evidence cited*] • Discusses the effectiveness and potential harms of IMRT for breast cancer Summary – KQ3 [*see page 72 for full comment and evidence cited*] • Discusses ways to stratify patients into risk groups Summary – KQ4 [*see pages 73 for full comment and evidence cited*] • Discusses cost analysis of IMRT	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*
Sandra Vermeulen	Summary – Acoustic Neuroma [*see pages 74 to 76 for full comment and evidence cited*] • Provided a summary of clinical results from Gamma Knife radiosurgery in relation to tumor growth control, hearing preservation, facial nerve and trigeminal nerve preservation, neurofibromatosis 2, and clinical algorithm for decision making. Summary – Trigeminal Neuralgia [*see pages 76 to 77 for full comment and evidence cited*] • Discusses the efficacy of Gamma Knife stereotactic radiosurgery for trigeminal neuralgia, and provides factors to consider in making a recommendation for Gamma Knife stereotactic radiosurgery. Summary – Pituitary Adenoma [*see pages 77 to 80 for full comment and evidence*	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to Key Questions.*

Reviewer	Comment	Disposition
	cited] • Discusses the applicability of stereotactic radiosurgery for pituitary adenoma and tumor growth control after radiosurgery for this condition • Discusses the function effect of radiosurgery (e.g., growth hormone secreting adenomas (acromegaly), ACTH secreting adenomas, prolactin secreating adenomas), radiation tolerance of functioning pituitary tissue, complications of pituitary radiosurgery, clinical algorithms for decision making, and fractionated radiation therapy (EBRT) Summary – Intra-cranial Ateriovenous Malformations [*see page 80 for full comment and evidence cited*] • Discusses the use of stereotactic radiosurgery for patients with unresectable AVMs including the probability of AVM obliteration with radiosurgery, early adverse effects of radiosurgery, late complication after AVM radiosurgery, and factors to be considered in making a recommendation for stereotactic radiosurgery for AVM Summary – Brain Metastases [*see pages 81 to 84 for full comment and evidence cited*] • Discusses the role of radiosurgery for brain metastases including retrospective studies showing support for SRS, local tumor control, survival, the role of SRS for multiple brain metastases, indications for radiosurgery, and a clinical decision making algorithm that includes tumor size and patient preference. Summary – Meningiomas [*see pages 84 to 85 for full comment and evidence cited*] • Discusses long-term outcomes of meningioma after radiosurgery, the use of radiosurgery for malignant meningioma, the use of radiosurgery with cavernous sinus meningiomas, and early complication of radiosurgery for meningiomas. Summary – SRS Thalamotomy for Tremor [*see pages 85 to 86 for full comment and evidence cited*]	

Reviewer	Comment	Disposition
	• Discusses radiofrequency and radiosurgical thalamotomy to treat tremors Summary – Gliomas [*see pages 86 to 87 for full comment and evidence cited*] • Discusses the use of EBRT and Gamma Knife for patients with gliomas	
Tacoma/Valley Radiation Oncology Centers		
	"These technologies are currently available in many places in the State of Washington and are quickly becoming standard of care for many treatment sites throughout the nation. As clearly stated in the summary, these technologies are more expensive than conventional radiation. The trade off, however, is very significant when it comes to not only improvements in outcomes but they are vastly superior in reduction in side effects and toxicity. We are also able to treat specific tumor locations that we never were able to accomplish in the past with minimal morbidity and harm to the patient. There is no question that radiation can be extremely harmful to living tissue. My 20+ year career can certainly attest to that. When I explain these new modalities to patients, one of the very first comments I make is that I wish I'd had these technologies available to me during the early days of my career. The number of patients treated with significant radiation morbidity, both short term and long term, in the form of bowel damage, bladder damage, lung damage, soft and bony structure damage as well as even brain damage, could have been reduced and outright avoided if I'd had these technologies available in the past. These newer modalities allow us to target tissues at risk and greatly reduce surrounding tissues that do not need to be radiated. Not only do these technologies allow us to target the cancer and spare the surrounding normal tissue, but they allow us to give even higher doses of radiation to the cancer, thus improving outcomes. Nowhere has this become more evident than in treatment of cancer of the prostate. The concept of increasing the dose of radiation (known as dose escalation) to prostate cancer has been verified in numerous clinical trials. In the past we were unable to deliver high doses of radiation to the prostate because the organ is "sandwiched" between the bowel and the bladder. " "Stereotactic body (SBRT) and stereotactic radiosurgery (SRS) are again	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	technologies that allow us with pin-point accuracy to deliver very toxic doses of radiation therapy to cancers and eliminate surrounding tissue. One only needs to see a patient who is trying to live with radiation damage of the brain from old conventional treatments to realize the significance of these new technologies. We are now able to treat patients non-surgically for aneurysms, tremors, brain metastases and even gliomas. Patients are alive and function today because of these technologies. They certainly can be treated by more conventional means but the price is higher in side effects and long-term complications. I have seen patients harmed by conventional radiation to a much greater extent. " [*see pages 88 to 98 for full comment*]	
Eric Taylor (Evergreen Radiation Oncology)		
	"The use of IMRT is appropriate for some brain tumors, most head and neck cancers, select lung cancers, many esophageal cancers, pancreatic malignancies, recurrent rectal cancers, some gynecologic cancers, anal canal cancer and many prostate cancers (either alone or with brachytherapy (seeds) for intermediate or high risk prostate cancers). This technology has allowed higher and more appropriate doses to be delivered to where the tumor is and much lower doses to the surrounding tissues. Therefore from a patient safety and toxicity standpoint this is far superior and with higher, better placed doses tumor control has improved. There are data supporting better tumor control coupled with less toxicity for both head and neck cancers and prostate cancer and some recurrent cancers. In the past, for patients with pelvic malignancies, long-term bowel complications were common. With current generation techniques, bowel obstructions that require subsequent surgical repair or other GU problems that require long-term management are much less frequent...a huge plus for the patient and also reducing longer term healthcare costs of managing complications of treatment. IMRT/IGRT for head and neck cancers has both improved tumor control, but with less long-term xerostomia and edema. For brain tumors, we have the dosimetrists and physicists run plans both with 3D conformal beams and IMRT. If they are roughly equivalent, then we use 3D planned fields as the cost is less expensive. We only use IMRT if it is superior.	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	Unfortunately, some places around the country over-utilize IMRT. A relatively more recent improvement for IMRT is volumetric delivery or Rapid Arc (Varian). This greatly speeds up the treatment so that the patient is on the table, immobilized for a shorter period of time. For example, a patient with head and neck cancer is immobilized in a head and shoulder mask typically for about 20 minutes. Rapid Arc treats the same volume in a matter of a few minutes. The outcome is no different, but the patient experience is superior. There is also better through put on the machine allowing greater capacity, thus delaying the need for another linac purchase. In your write-up you put protons in the same sentence with IMRT. I think these are VERY DIFFERENT modalities and COSTS. IMRT is appropriate and is the standard of care for the cancers that I mentioned above generally. Protons have shown NO superiority over current therapies other than some unusual childhood tumors, however the cost of the space and technology and delivery is much more EXPENSIVE. Wearing a public health hat, I am very concerned about the healthcare resources that will be spent on proton therapy for an extremely limited healthcare benefit. The payors have to critically look at this. Two proton facilities are in the process of construction and planning for Seattle ($180 million/ UWNorthwest) and $35-60 million/ Swedish First Hill. I think those resources and future charges to pay for such facilities could be utilized differently to improve broader healthcare outcomes for a greater segment of the population. Using American Cancer Society data, the current likelihood of a man being around in 5 years with a new diagnosis of prostate cancer is 99% with current therapies. For proton facilities to pay for themselves a majority of patients will be those with prostate cancer...with the above noted statistics with current treatments available, how will protons possibly move the bar up and at a much greater cost?" [*see pages 99 to 100 for full comment*]	
Tumor Institute Radiation Oncology Group		
	"As experts in the field of Radiation Oncology, we embrace your concerns regarding safety, efficacy, and cost of contemporary radiation modalities.	*Thank you for your comment.* *All references were forwarded to TAC for*

Reviewer	Comment	Disposition
	Technologies such as IMRT, SRS, and SBRT have broken new ground in their capability to control cancer and minimize side effects. Our goal is to help educate health providers and healthcare payers, as well as government, business, and other professionals as to the patients for whom use of these newer technologies can mean a world of difference in regard to cancer control and a decreased risk of treatment related side effects. The utility of IMRT, SRS, and SBRT in many circumstances is very specifically dependent on a patient's cancer, their anatomy, the proximity of critical structures, and prior radiation dose delivered. The key aspects that all these modalities have in common is better dose distributions: escalated doses to tumors, lower doses (and lower resultant toxicity) to normal tissue. Using IMRT, SRS, and SBRT, it is now potentially feasible to deliver safe curative or safe palliative treatment to many patients where treatment was not even an option with conventional external beam radiation therapy. For example, in cases where tumors recur in a previously irradiated field, re-irradiation with IMRT, SRS, or SBRT may deliver a long term cure that was not previously possible. We realize that a circumstance such as this is not one in which a comparative trial could be conducted, for most of these patients simply would not be a candidate for treatment with a conventional external beam radiation therapy approach. We believe that it is imperative to be able to offer these treatments to patients in an expedient time frame when indicated. We remain readily available and encourage an open dialogue on these topics. We have tried our best given the short comment period to address your questions regard SBRT and SRS. Although there are increased costs associated with newer technologies such as IMRT, SRS, and SBRT, their effectiveness and lower risk for side effects demonstrates long term cost savings. As well, the relevant key comparison is often IMRT, SRS, or SBRT in comparison to other different modalities of treatment, such as surgery, or radiofrequency ablation (rather than to conventional external beam irradiation). For example, there was a publication a few months ago comparing the cost effectiveness, quality of life and safety for medically inoperable lung cancer patients. The study compared conventional radiation, SBRT, and radiofrequency ablation. SBRT was by far the most effective	*consideration in the review process.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	and cost effective treatment, even though it may have the highest upfront direct cost Given the extraordinarily short time period for comment, we have done our best to summarize responses to the four key questions of the Washington State Healthcare Authority with regard to SRS, and SBRT in comparison to conventional (conformal) external beam therapy (EBRT). We must emphasize, though, while there are many well done peer reviewed studies from top academic institutions pertinent to IMRT, SRS and SBRT, and in some cases there are head-to-head comparisons which demonstrate the benefits of this technology, the short response timeframe created by your March 6th deadline, which apparently is not negotiable, does not allow adequate time to research. Therefore, we want to be sure the Washington State Healthcare Authority and its staff are advised that we believe the key questions posed for SRS, SBRT and IMRT are extensive and a more complete level of detail is not possible to produce within the time frame allotted." [*see pages 101 to 112 for full comment and evidence cited*]	
	Summary – KQ 1 [*see pages1025 to 110 for full comment and evidence cited*] • Discusses the use of IMRT and SBRT for the treatment of prostate cancer • Discusses use of SRS/SBRT for the treatment of head and neck cancer • Discusses use of SRS/SBRT for the treatment of central nervous system/spine cancer • Discusses the use of SBRT for the treatment of gastrointestinal/pancreatic cancers • Discusses the use of SBRT for gastrointestinal/liver metastases • Discusses the use of SBRT for gastrointestinal/primary liver cancers • Discusses the use of SBRT for lung cancers • Discusses the effectiveness and safety of SBRT for re-irradiation Summary – KQ2 [*see pages 110 to 111 for full comment and evidence cited*]	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	• Discusses the safety and harms of SRS and SBRT Summary – KQ3 [*see page 111 for full comment and evidence cited*] • Refers to KQ1 and KQ2 Summary – KQ4 [*see page 112 for full comment and evidence cited*] • Discusses the cost and cost-effectiveness of SRS, SBRT, IMRT, and EBRT	
University of Washington Medicine / Seattle Cancer Care Alliance Department of Radiation Oncology and UW Department of Neurological Surgery		
	Summary KQ 1 [*see pages 116 to 119 for full comment and evidence cited*] • Discusses the effectiveness of IMRT for head and neck, thyroid, thoracic, prostate, gastric, rectal, anal, gynecological, breast, sarcomas, and brain cancers. Summary KQ2 [*see page 119 for full comment*] • Discusses the potential harms of IMRT Summary KQ3 [*see pages 119 to 120 for full comment*] • Discusses the efficacy and safety issues of IMRT for subpopulations of gender; age; site and type of cancer; stage and grade of cancer; and setting, provider characteristics, equipment, quality assurance standards and procedures. Summary KQ4 [*see page 120 for full comment and evidence cited*] • Discusses the cost effectiveness of IMRT.	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*
Varian Medical Systems		
Andrew M. Whitman	"Intensity modulated radiation therapy has revolutionized care for cancer patients and has been widely used by clinicians to treat patients since 2001. Medicare has recognized that this is a highly effective treatment for head and neck, prostate, lung and breast cancer. Each year, clinicians around the world use Varian products to deliver more than thirty-five million radiotherapy treatments – accounting for tens of thousands of cancer patients per day. Radiotherapy is a	*Thank you for your comment.* *No changes to the Key Questions.*

Reviewer	Comment	Disposition
	cost-effective form of cancer treatment. Unlike drugs or surgery, one linear accelerator can perform nearly one hundred thousand treatments during its life cycle." [*see page 122 for full comment*]	
Varian Dossier	Summary – KQ1 [*see pages 124 to 125 for full comment and evidence cited*] • Provided summaries of evidence cited. Summary KQ2 [*see page 125 for full comment*] • Discusses safety mechanisms of IMRT. Summary KQ4 [*see pages 126 to 127 for full comment and evidence cited*] • Provided summaries of evidence cited.	*Thank you for your comment.* *All references were forwarded to TAC for consideration in the review process.* *No changes to the Key Questions.*

Table 3. Response to Public Comment on Draft Report

Reviewer	Comment	Disposition
American Society for Radiation Oncology		
	"One of the primary concerns put forth in this draft report is the lack of randomized data to definitively demonstrate superior clinical outcomes with the use of IMRT as compared to conventional radiation therapy, and the lack of Level One evidence from randomized clinical trials. Much has been written regarding the challenges associated with the use of traditional comparative effectiveness research methodology when applied to new technology. The reasons underlying the lack of randomized, double-blind, placebo controlled trials in radiation oncology are many, primarily related to the challenges in finding funding and willing patients for such research questions given the volume and consistency of literature that supports the use of IMRT for many cancer types. There is certainly precedent for introducing significant technological developments without this level of evidence. Examples include: • CT scanning vs. conventional imaging; • Linear accelerators vs. cobalt; • CT simulation vs. fluoroscopic simulation or worse; • High dose rate remote after loading brachytherapy vs. low dose rate after loading brachytherapy vs. low dose rate non-after loading brachytherapy." [*see pages 128 to 130 for full comment and references cited*]	*Thank you for your comment.* *It is the charge of the evidence vendor to summarize the evidence and not to make a determination of whether to cover IMRT. The strength of the evidence is very low to low for most findings.* *No changes to the report.*
	"The draft report further states that the NCCN guidelines are of poor methodological quality and the ACR guidelines vary from poor to fair methodological quality. Both of these guideline documents are widely accepted and have credibility across the oncology and payer community. The lack of randomized controlled trials does not preclude the necessity to make clinical and coverage decisions every single day, and guidelines such as these represent the best examples in oncology in general and radiation oncology in particular. Absent such guidelines, an environment where "anything goes" would prevail. Specifically, these panels do reflect the consensus of in-field experts, including	*Thank you for your comment.* *The quality assessment of the guidelines assesses the methodological rigor of the guideline development process. We understand that, in the absence of evidence, a consensus of clinical experts is often relied on for the development of clinical practice guidelines. For the NCCN guideline*

Reviewer	Comment	Disposition
	non-radiation oncologists, that IMRT is the standard of care in the management of both prostate and head and neck cancer. ASTRO is concerned that increased toxicity and decreased cure rates might result if this report's findings are adopted over the objections of expert panels due to the authors' belief that the overall strength of evidence in favor of IMRT was relatively weak." [*see pages 128 to 130 for full comment*]	*development process, we made several attempts through email communication to get a clearer understanding of how evidence is identified and selected for inclusion. It is still unclear how the NCCN identifies and selects evidence for inclusion of its guidelines. For this reason, the quality assessment of the NCCN guidelines remains poor quality.* *No changes to the report.*
	"It is ASTRO's opinion that the draft report completely ignores the essential aspect of IMRT's advantage over 3-dimentional conformal radiation therapy (3D-CRT): smaller, more conformal volumes may be irradiated, leading to (a) less toxicity and (b) potential for dose escalation. IMRT allows radiation oncologists to routinely provide 79.2 Gy to prostate cancer patients, based on substantial data indicating that higher doses contribute to better outcomes. IMRT also allows our discipline to provide daily doses exceeding 2.1 Gy with chemotherapy to head and neck cancer patients, again based on data that this approach increases survival over 3D-CRT at lower daily doses. If radiation oncologists stop using IMRT and instead use 3D-CRT, treatment volumes will of necessity become larger, which will increase toxicity." [*see pages 128 to 130 for full comment*]	*Thank you for your comment.* *The"'essential aspect of IMRT's advantage over 3DCRT" of smaller, more conformal volumes to be irradiated is noted in the report. That "essential aspect" should be reflected in improved outcomes or reduced side effects. Advantages where they exist are noted in the report.* *No changes to the report.*
	"ASTRO believes that the results presented by the Sheets et al paper were underutilized by the report writers and may in fact represent some of the highest quality data in favor of IMRT vs. 3D-CRT for the treatment of prostate cancer. Sheets et al reported less GI and hip toxicity when IMRT was used which is not surprising since the hips and GI organs are routinely avoided when performing IMRT. Additionally, patients treated with IMRT had fewer additional episodes of cancer treatment, implying a higher cure rate and fewer downstream costs, although it is a relative weakness of the Sheets paper that they didn't perform a cost-effectiveness analysis. It is noted that Sheets (2012) is a "good quality cohort study." The publication by Sharma, et al, cited below, that we believe was	*Thank you for your comment.* *Sheets (2012) and Sharma (2009) were reviewed for the report. Sheets (2012) was quality assessed as a good quality cohort study. Sharma (2009) was included in the De Neve (2012) systematic review. We have added the De Neve (2012) systematic review to the prostate section.* *No change to the relative weight given to the*

Reviewer	Comment	Disposition
	overlooked in the development of this report, also supports the use of IMRT in the treatment of prostate cancer." [*see pages 128 to 130x for full comment and references cited*]	*results.*
James H. Brashears III		
	"Why is there a dearth of clinical evidence supporting the superiority of IMRT to 3DCRT? Because IMRT is frequently shown to be better than 3DCRT before treatment is ever given to a patient. The concept of applying evidence based medicine (EBM) to the modern provision of radiation therapy for malignancies is indeed very salutary. All radiation oncologists I am familiar with strongly support the use of EBM when appropriate for the improvement of care for our patients and the society of which we are all apart. Applying EBM specifically to compare three dimensional conformal radiation therapy (3DCRT) to intensity modulated radiation therapy (IMRT) or similar technologies like stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) can be inherently problematic and misleading. This is because physicians have the duty to treat patients with what we feel and understand to be most beneficial/least harmful techniques at our disposal to the patient in the short and long term without focusing specifically on the indirect monetary costs. In the vast majority of cases where IMRT/SBRT/SRS is deemed appropriate versus more traditional 3DCRT, the amount of radiation to the target (cancer) is usually higher and the corresponding significant dose of radiation to the normal tissues (frequently organs critical for maintaining health like the lung, kidney, intestines, liver, etc) is almost always less. This becomes evident during the radiation planning process when various radiation delivery plans are evaluated before one is selected to treat the patient. Given the two principles that a higher dose of radiation is more effective in eradicating cancer and keeping radiation dose less in tissues/organs where there is no disease is safer, the fundamental issues of why comparing traditional and more modern techniques like IMRT in randomized controlled trials is clear. To simplify, when my father was diagnosed with prostate cancer and he decided	*Thank you for your comment.* *The report summarizes the available evidence and does not make a recommendation about coverage.* *No changes to the report.*

Reviewer	Comment	Disposition
	that he wanted radiotherapy, there was a choice between treating with 3DCRT and IMRT. When comparing the 2 methods of treatment, the IMRT plan gave less biologically significant dose to the rectum and bladder while maintaining the same dose to the prostate cancer. At this point, there was no need to consult EBM guidelines since the technique of treatment that gave less dose to the normal tissue was known. In fact, it probably would have been unethical and against the Hippocratic Oath for him to be treated with 3DCRT at that point since the IMRT plan was inherently safer. Applying this case more broadly shows why radiation oncologists are reticent to compare IMRT to 3DCRT with a blanket over a population in trials. Please do not take this reticence to knowingly treat patients with prima facie inferior techniques as showing a lack of confidence in the superiority of IMRT/SBRT/SRS over 3DCRT. Indeed the host of research showing the dosimetric superiority of IMRT/SBRT/SRS is well known and fueled the initial adoption of these technologies that radiation oncologists feel are often in the patient's best interest and have contributed meaningfully to disease control and increased tolerability of therapy. It is frightening in the extreme to consider that therapy which could be safer for patients might be disallowed in the future by governmental mandate." [*see pages 131 to 132 for full comment*]	
Trevor Fitzgerald (Wenatchee Valley Medical Center)		
	"I am writing to comment on the draft report on the efficacy of IMRT. The basic flaw in the report is treating all diagnosis groups as homogenous and either benefiting or not from IMRT. Unfortunately every tumor is different and its size, location with respect to critical structures and response to radiation determine whether or not IMRT will be beneficial. Some lung cancers can be treated effectively with CRT, some cannot. To lump them all together and deny patients who need IMRT that option would increase mortality and morbidity, it would increase medical costs in other areas such as managing the increased side effects of CRT and decrease QOL. The need for IMRT should be decided upon by the responsible physician weighing all the appropriate medical data of the patient,	*Thank you for your comment.* *The report summarizes the available evidence and does not make a recommendation about coverage.* *No changes to the report.*

Reviewer	Comment	Disposition
	and not just based on diagnosis type. If wide swaths of diagnosis are deemed inappropriate for IMRT then the hospitals which have invested in the technology to perform such treatments will not be able to remain viable and will close their radiation therapy departments as CRT reimbursement rates alone are not enough to keep these facilities open. This will result in less access to care for the population and more morbidity. I have worked in Radiation therapy for 24 years and have seen the benefits of IMRT over CRT in many cases. Prior to IMRT most Head and Neck, Lung and Prostate Cancer patients did not finish their prescribed course of treatment without lengthy breaks due to the severity of side effects. It would be unethical for a practitioner to treat these patients with CRT based solely on long term survival benefit data, knowing that many more painful and QOL reducing side effects will occur than if IMRT could be used" [*see page 133 for full comment*]	
Varian Medical Systems		
	"Varian has significant concerns that the draft report does not properly highlight the immense benefits of the use of this advanced technology for treating cancer. For example, the overly stringent exclusion criteria led to the inclusion of only 6 percent (or 124) of 2,199 references. The publication of a final report without consideration for other means of assessment than randomized clinical trials will be a significant detriment to patients in Washington State. In addition, other non-clinical factors should be considered when comparing IMRT to 3DCRT and 2DCRT. Patient experience can be greatly improved using IMRT, with decreased time on the treatment table directly related to patient comfort. " [*see pages 134 to 135 for full comment*]	*Thank you for your comment. The exclusion criteria do not seem overly stringent to the evidence vendor. The report considers cohort studies and case series in addition to randomized controlled trials* *Patient experience is not of the Key Questions for this report.* *No changes to the report.*
	"On page 2, 18, 19, 29, 82, 84 etc. the draft report references a study by Hummel (2010) from the United Kingdom. Given the significant differences between the United States and British health systems, it may not be appropriate to compare these costs. When specifically referencing cost, Varian recommends that only U.S. studies should be used in the final report.´[*see page 136 for full comment*]	*Thank you for your comment. Although we agree that cost studies are affected by the structure of the health care system and prices for individual cost inputs, we included the cost information from the UK as the only cost estimates for prostate*

Reviewer	Comment	Disposition
		IMRT. We note in the report that the analysis comes from the UK. From previous experience, the Washington HTA Clinical Committee will be able to consider the Hummel cost information in a sophisticated manner.
	"The references to Tipton, K. et al (2011a and 2011b) are related to Stereotactic Body Radiation Therapy, not IMRT and Varian recommends they should not be included in a final report on IMRT." [*see page 136 for full comment*]	*Thank you for your comment. The Tipton (2011a, 2011b) references are included to provide background information on the cost of IMRT.* *No changes to the report.*
	"It is not appropriate to lump together 2DCRT and 3DCRT. They are significantly different." [*see page 136 for full comment*]	*The evidence report is charged with providing evidence comparing IMRT to EBRT. This inherently lumps 2DCRT and 3DCRT together. The evidence report reports 2DCRT or 3DCRT when the study authors' specify one or the other. Each one is an appropriate comparator to IMRT for the purposes of the evidence report.*
	"Although we understand the need to limit the references to a specified date range in order to ensure review of the most up-to-date information, at least one study from 2001 is worthy of inclusion in the report and is listed below in the section on head and neck cancers. (Chao Washington University study)." [*see page 136 for full comment*]	*Thank you for your comment. In order to remain consistent with the originally chosen methods, we will retain the 2002-2012 inclusion dates.*
	"On page 75 of the report, the Vergeer 2009 study was mentioned and is also included in the References section, but the significant quality of life benefits detailed in that study were not reported in the draft." [*see page 136 for full comment*]	*Thank you for your comment. Vergeer (2009) was included in the Scott-Brown (2010) systematic review. The results of Vergeer (2009) are summarized as part of the findings from the Scott-Brown systematic review on page 86 of the report. Results from Vergeer and Jabbari are both added to the text of the report.*

Reviewer	Comment	Disposition
	"In addition to the above edits, Varian recommends that the studies and clinical guidelines listed below be considered for inclusion and reference in the final report on IMRT." [*see pages 136 to 145 for full comment and references cited*]	*Thank you for the additional references. They have been reviewed according the inclusion criteria outlined in the report. References that met inclusion criteria were added to the report. Excluded references and reasons for exclusion can be found in Appendix B of the report. Four additional references were added to the report.* *The following references were included into the evidence tables and where appropriate into the text of the report:* *Gupta, et al. Radiother Oncol 7/30/12* *Little eta al. Int J Radiat Oncol Biol Phys 83(3):1007-14* *Kuang Clin Transl Oncol 7/24/12* *Spratt, et al. Int J Radiation Oncol Biol Phys 7/12/12 (Electronic publication)* *Du et al. Gynec Oncol 125(1):151-7 was already included in the evidence tables and report*

PUBLIC COMMENTS – TOPIC NOMINATION

From: Berit Madsen
To: HCA ST Health Tech Assessment Prog
Subject: Comments for IMRT and SRT/SBRT review
Date: Tuesday, March 06, 2012 12:34:12 PM
Attachments: Intensity Modulated Radiation Therapy for HCA of WA.docx
HTA letter March 2012.docx

Dear Mr. Morse
Attached please find my original comments regarding IMRT sent earlier this year when the HCA review process was being determined and a letter our group has written in support of the comments submitted by Dr. Todd Barnett and the Swedish Cancer Institute.

Berit L. Madsen, MD, FACR
bmadsen@peninsulacancercenter.com
(360) 697-8000

Intensity Modulated Radiation Therapy (IMRT)

Intensity modulated radiation therapy, or IMRT, is a specialized form of three dimensional conformal radiotherapy that allows radiation to be more exactly shaped to fit the tumor. With IMRT, the radiation beam can be broken up into many "beamlets," and the intensity of each beamlet can be adjusted individually. Using IMRT, it may be possible to further limit the amount of radiation received by healthy tissue near the tumor. In some situations, this may also safely allow a higher dose of radiation to be delivered to the tumor, potentially increasing the chance of a cure.

IMRT was developed in the 1990's to treat prostate and head and neck cancer but has been broadly adopted since then by most radiation oncologists to treat a wide variety of tumors because it allows higher more effective doses of radiation to be delivered while improving both the acute and late side effects of treatment. There is a large and growing body of clinical evidence to support the use of IMRT for many types of cancer. (see attached partial bibliography and I'd be happy to send the committee any reprints needed). Most radiation oncology experts would agree that IMRT is the standard of care for prostate, head and neck, and many gynecologic and anal malignancies. Other disease sites also benefit from the improved radiotherapy delivery properties of IMRT.

Most modern linear accelerators with multi-leaf collimators (Varian, Elekta, Tomotherapy and others) can perform IMRT. IMRT requires considerable additional work for the physician, treatment planners (dosimetrist), and physicist because of the increased complexity of defining treatment volumes and normal tissue constraints as well as increased quality assurance and machine maintenance. While there is extra work involved, IMRT allows for semi-automated treatment which can be delivered faster and can be less error prone that conventional radiotherapy.

In summary; IMRT is commonly utilized method of radiotherapy that has enhanced the effectiveness, improved the tolerance and safety of radiation therapy for many patients with cancer.

Respectfully submitted

Berit L. Madsen, MD, FACR
Washington State Radiologic Society Executive Committee Member
BMadsen@peninsulacancercenter.com
(360)697-8000

References:

Estimating differences in volumetric flat bone growth in pediatric patients by radiation treatment method
Chiaho Hua, Hemant I. Shukla, Thomas E. Merchant, Matthew J. Krasin

International journal of radiation oncology, biology, physics 1 February 2007 (volume 67 issue 2 Pages 552-558 DOI: 10.1016/j.ijrobp.2006.08.069)

Large Cohort Dose-Volume Response Analysis of Parotid Gland Function After Radiotherapy: Intensity-Modulated Versus Conventional Radiotherapy
Tim Dijkema, Chris H.J. Terhaard, Judith M. Roesink, Pètra M. Braam, Carla H. van Gils, Marinus A. Moerland, Cornelis P.J. Raaijmakers

International journal of radiation oncology, biology, physics 15 November 2008 (volume 72 issue 4 Pages 1101-1109 DOI: 10.1016/j.ijrobp.2008.02.059)

Decreasing Temporal Lobe Dose With Five-Field Intensity-Modulated Radiotherapy for Treatment of Pituitary Macroadenomas
Preeti K. Parhar, Tamara Duckworth, Parinda Shah, J. Keith DeWyngaert, Ashwatha Narayana, Silvia C. Formenti, Jinesh N. Shah

International journal of radiation oncology, biology, physics 1 October 2010 (volume 78 issue 2 Pages 379-384 DOI: 10.1016/j.ijrobp.2009.07.1695)

Intensity-Modulated Radiation Therapy Significantly Improves Acute Gastrointestinal Toxicity in Pancreatic and Ampullary Cancers
Susannah Yovino, Matthew Poppe, Salma Jabbour, Vera David, Michael Garofalo, Naimesh Pandya, Richard Alexander, Nader Hanna, William F. Regine

International journal of radiation oncology, biology, physics 1 January 2011 (volume 79 issue 1 Pages 158-162 DOI: 10.1016/j.ijrobp.2009.10.043)

Dosimetric Comparison of Three Different Involved Nodal Irradiation Techniques for Stage II Hodgkin's Lymphoma Patients: Conventional Radiotherapy, Intensity-Modulated Radiotherapy, and Three-Dimensional Proton Radiotherapy
Bhishamjit S. Chera, Christina Rodriguez, Christopher G. Morris, Debbie Louis, Daniel Yeung, Zuofeng Li, Nancy P. Mendenhall

International journal of radiation oncology, biology, physics 15 November 2009 (volume 75 issue 4 Pages 1173-1180 DOI: 10.1016/j.ijrobp.2008.12.048)

Simultaneous Integrated Boost Using Intensity-Modulated Radiotherapy Compared with Conventional Radiotherapy in Patients Treated with Concurrent Carboplatin and 5-Fluorouracil for Locally Advanced Oropharyngeal Carcinoma
Sébastien Clavel, David H.A. Nguyen, Bernard Fortin, Philippe Després, Nader Khaouam, David Donath, Denis Soulières, Louis Guertin, Phuc Felix Nguyen-Tan

International journal of radiation oncology, biology, physics 31 January 2011 (Article in Press DOI: 10.1016/j.ijrobp.2010.10.061)

Influence of Organ Motion on Conformal vs. Intensity-Modulated Pelvic Radiotherapy for Prostate Cancer
Liv Bolstad Hysing, Tone Nybø Skorpen, Markus Alber, Lise Bauge Fjellsbø, Svein Inge Helle, Ludvig Paul Muren

International journal of radiation oncology, biology, physics 1 August 2008 (volume 71 issue 5 Pages 1496-1503 DOI: 10.1016/j.ijrobp.2008.04.011)

Reduced Acute Bowel Toxicity in Patients Treated With Intensity-Modulated Radiotherapy for Rectal Cancer

Jason M. Samuelian, Matthew D. Callister, Jonathan B. Ashman, Tonia M. Young-Fadok, Mitesh J. Borad, Leonard L. Gunderson

International journal of radiation oncology, biology, physics 7 April 2011 (Article in Press DOI: 10.1016/j.ijrobp.2011.01.051)

How Does Intensity-Modulated Radiotherapy Versus Conventional Two-Dimensional Radiotherapy Influence the Treatment Results in Nasopharyngeal Carcinoma Patients?
Shu-Zhen Lai, Wen-Fei Li, Lei Chen, Wei Luo, Yuan-Yuan Chen, Li-Zhi Liu, Ying Sun, Ai-Hua Lin, Meng-Zhong Liu, Jun Ma

International journal of radiation oncology, biology, physics 1 July 2011 (volume 80 issue 3 Pages 661-668 DOI: 10.1016/j.ijrobp.2010.03.024)

Improved Dosimetric and Clinical Outcomes With Intensity-Modulated Radiotherapy for Head-and-Neck Cancer of Unknown Primary Origin
Allen M. Chen, Bao-Qing Li, D. Gregory Farwell, Joseph Marsano, Srinivasan Vijayakumar, James A. Purdy

International journal of radiation oncology, biology, physics 1 March 2011 (volume 79 issue 3 Pages 756-762 DOI: 10.1016/j.ijrobp.2009.11.020)

Radiotherapy for Early Mediastinal Hodgkin Lymphoma According to the German Hodgkin Study Group (GHSG): The Roles of Intensity-Modulated Radiotherapy and Involved-Node Radiotherapy
Julia Koeck, Yasser Abo-Madyan, Frank Lohr, Florian Stieler, Jan Kriz, Rolf-Peter Mueller, Frederik Wenz, Hans Theodor Eich

International journal of radiation oncology, biology, physics 14 November 2011 (Article in Press DOI: 10.1016/j.ijrobp.2011.05.054)

Influence of Technologic Advances on Outcomes in Patients With Unresectable, Locally Advanced Non–Small-Cell Lung Cancer Receiving Concomitant Chemoradiotherapy
Zhongxing X. Liao, Ritsuko R. Komaki, Howard D. Thames, Helen H. Liu, Susan L. Tucker, Radhe Mohan, Mary K. Martel, Xiong Wei, Kunyu Yang, Edward S. Kim, George Blumenschein, Waun Ki Hong, James D. Cox

International journal of radiation oncology, biology, physics 1 March 2010 (volume 76 issue 3 Pages 775-781 DOI: 10.1016/j.ijrobp.2009.02.032)

From: Badiozamani, Kasra[Kasra.Badiozamani@vmmc.org]

To: HCA ST Health Tech Assessment Prog
CC: Mitsuyama, Paul; Badiozamani, Kasra
Subject: Public Comment for: Intensity Modulated Radiation Therapy

To the Washington Health Care Authority:

We are writing to encourage you to remove IMRT from the proposed list of topics for review by the HCA Administrator. We feel that IMRT is of great value and benefit to our patients. There are many areas where IMRT has been proven to be superior to 3D-conformal radiation therapy (3DCRT): in the treatment of prostate cancer, head and neck cancers, brain or skull base tumors, and cases requiring re-irradiation. In prostate cancer, IMRT can spare the rectum, bowel, and bladder better than 3DCRT. Clinical studies demonstrate lower rectal toxicity with IMRT over 3DCRT. In head and neck cancers, IMRT has shown much better parotid gland sparing than 3DCRT. Parotid sparing is very important for reducing the severity of permanent xerostomia which greatly affects the patient's ability to eat and quality of life. In brain or skull base tumors, IMRT can reduce dose to critical structures which are very sensitive to radiation such as retina, optic nerves, and chiasm. In addition, there is data supporting sparing hippocampal regions to reduce permanent neurocognitve dysfunction. IMRT is extremely useful when treatment is needed to an area in close proximity to a region that has previously received radiation in order to keep the dose below dose tolerances for that structure. Furthermore, there are current national NCI sponsored clinical trials using radiation therapy which mandate the use of IMRT for treatment of patients on protocol since it is agreed that it is the best treatment technique in these settings, including RTOG brain studies (0539 and 0933) and head and neck cancer studies (1016 and 0920). It would be a disadvantage to the patients not to be able to offer them these potentially life-saving treatment studies because IMRT was not reimbursed. This technology is of proven benefit to patients, and should not be on the list for review by the HCA.

References supporting the use of IMRT are provided below. Thank you for your consideration.

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2010;18(4):393-402

Respectfully yours,

H. Paul Mitsuyama, MD
Kas Ray Badiozamani, MD
Section of Radiation Oncology
Virginia Mason Medical Center
Mail Stop CB-RO
1100 9th Ave
PO Box 900
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PUBLIC COMMENTS – KEY QUESTIONS

From: Jason Mckitrick
To: HCA ST Health Tech Assessment Prog
Cc: Andrew Woods; Morse, Josiah (HCA)
Subject: ACRO Comment Letter to Mr. Josh Morse (WSHCA HTA) Regarding Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions
Date: Tuesday, March 06, 2012 12:26:38 PM
Attachments: Comment Letter to Mr. Josh Morse (WSHCA Health Technology Assessment) 3-6-2012.pdf
Importance: High

Dear Mr. Morse,

Attached please find the comment letter submitted on behalf of the American College of Radiation Oncology for **Stereotactic Radiation Surgery, Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions**.

Please let me know if you have any questions.

Thank you.
Jason S. McKitrick
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March 6, 2012

Josh Morse, MPH
Program Director
Washington State Health Care Authority
Health Technology Assessment
P.O. Box 42712
Olympia, Washington 98504-2712

Re: Stereotactic Radiation Surgery, Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions

Dear Mr. Morse:

The American College of Radiation Oncology (ACRO) appreciates the opportunity to offer its comments to the Washington State Health Care Authority (WSHCA) draft Technology Assessment Key Questions on the topics of Stereotactic Radiation Surgery (SRS), Stereotactic Body Radiation Therapy (SBRT), and Intensity Modulated Radiation Therapy (IMRT). ACRO represents radiation oncologists in the socioeconomic and political arenas. With a current membership of approximately 1,000, ACRO is dedicated to fostering radiation oncology education and science; improving patient care services; studying the socioeconomic aspects of the practice of radiation oncology; and encouraging education in radiation oncology.

ACRO received notice of the key questions on February 22, 2012 and we understand the deadline for comments is March 6, 2012. Full and appropriate comments to these questions requires months of preparation. Unfortunately, the short time frame within which to answer these questions does not allow for a direct detailed, and fully documented response.

However, ACRO can provide the following more general comments within the allotted time frame:

- The issues surrounding choices of radiation-emitting modalities, (e.g. IMRT) are usually based on physical (physics) data and empirical observations, rather than randomized controlled clinical trials. The US Food and Drug Administration does not require such Level I data for device approval, and once devices are approved and marketed, there is little ability to complete those trials. Proposals to payers to assist in implementing trials, as with *Coverage with Evidence Development*, have been shunned, and patients (and IRBs) will rarely if ever accept randomization to trials where the only presumed differences are related to morbidity.

- As a delivery system widely available since 1998 (when the CPT© codes and RVUs were established), IMRT has been shown in every and innumerable instances measured, to reduce morbidity to the adjacent organs at risk in proximity to target tumor volumes. In instances where this morbidity-reduction has been used to permit an increase in radiation dose to tumors (e.g. prostate, head/neck, central nervous system, liver, etc.), a concomitant increase in local control has also been demonstrated. Regrettably, in radiation oncology, unlike drug development, since long-term control or cure is often the determinant end-point, years may be required to define the parameters, so physical data and morbidity reduction MUST be used as surrogates. Randomized device trials also require a large installed base of the devices, which is also impractical. Alternatively, drug studies may provide actionable (albeit often non-clinically relevant) information in weeks to months, at minimal cost, since the primary end-points are more often simply measurement of some surrogate tumor marker or interval free from progression.

- There is clear and increasing evidence that in certain circumstances, SBRT and SRS may be equivalent and/or preferable to conventional fractionated and protracted radiation. SBRT and SRS, unlike IMRT, relate to "biology" and not "technology," in that they merely represent the delivery of high-dose, short-course radiation (5 or fewer treatments, rather than daily, protracted, lower-dose, longer-course therapies). Evidence mounts that numerous sites, including brain, spinal cord, liver, and lung, as well as other emerging indications, are appropriately treated by SRS (for central nervous system) and SBRT (for non-central nervous system).

We understand that the American Society for Radiation Oncology (ASTRO) has included its own model coverage policies on SRS, SBRT and IMRT for your review that outline specific technology of each treatment, clinical indications, coding considerations and references. ACRO supports your review of these materials and their conclusions. We also are aware that physicians with the Swedish Medical Center are submitting information regarding studies that have been performed relating to SRS, SBRT and IMRT. We would encourage the committee to review these in detail.

We appreciate your consideration of our comments and look forward to reviewing the WSHCA's draft report. Should you have any questions, please contact Jason McKitrick, ACRO Economics Committee consultant, at (202) 442-3754.

Sincerely,

Sheila Rege, MD, FASTRO, FACRO
Chair, Economics Committee
American College of Radiation Oncology
5272 River Road
Suite 630
Bethesda, Maryland 20816

From: Marsha Kaufman
To: HCA ST Health Tech Assessment Prog
Cc: Patton, Gregory A (Gregory.Patton@USOncology.com); Michael Dzeda; Thomas Eichler, M.D. (thomas.eichler@hcahealthcare.com); Joel Cherlow, M.D., Ph.D. (jcherlow@memorialcare.org); Najeeb Mohideen; Brian Kavanagh, M.D. (brian.kavanagh@uchsc.edu); Daneen Grooms; Crystal Carter
Subject: ASTRO comment letter - SRS, SBRT and IMRT Key Questions
Date: Monday, March 05, 2012 9:43:14 AM
Attachments: SRS-SBRT-IMRT KeyQCommentLtr FINAL3-5-12.pdf
SRSModelPolicyFINAL 7-25-11.pdf
SBRT2010 FINAL 11-17-10.pdf
ASTRO IMRT Model FINAL 05.09.07-with disclaimer.pdf

Good afternoon Mr. Morse. Please find attached the American Society for Radiation Oncology's (ASTRO) comment letter on the key questions related to the technologies of Stereotactic Radiation Surgery (SRS), Stereotactic Body Radiation Therapy (SBRT) and Intensity Modulated RadiationTherapy (IMRT). As indicated in our letter, attached are copies of the ASTRO Model Policies on SRS, SBRT and IMRT.

Thank you for your consideration and please do not hesitate to contact me should you have any questions.

Regards,
Marsha Kaufman
~~~~~~

Marsha Kaufman, MSW
Director of Health Policy
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ASTRO
TARGETING CANCER CARE

March 5, 2012

Josh Morse, MPH
Program Director
Washington State Health Care Authority
Health Technology Assessment
P.O. Box 42712
Olympia, WA 98504-2712

BY ELECTRONIC SUBMISSION to shtap@hca.wa.gov

Re: Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy, and Intensity Modulated Radiation Therapy Technology Assessment Key Questions

Dear Mr. Morse:

The American Society for Radiation Oncology (ASTRO), the largest radiation oncology society in the world representing more than 10,000 members who specialize in treating patients with radiation therapies, appreciates the opportunity to comment on the Washington State Health Care Authority draft Technology Assessment Key Questions on the topics of Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT), and Intensity Modulated Radiation Therapy (IMRT). ASTRO received notice of the Key Questions on February 22, 2012 and we understand the deadline for comments is March 6, 2012. The Key Questions posed for SRS, SBRT and IMRT are extensive and ask for a level of detail that we cannot produce within the time frame allotted. The information requested for all three technologies, specifically comparisons to external beam radiation therapy (benefits and harms), and differential efficacy or safety issues in subpopulations including consideration of gender, age, site and type of cancer, stage and grade of cancer and setting, provider characteristics, equipment, quality assurance standards and procedures, constitutes a full research study that would take many months to produce. While ASTRO believes these technologies offer clear benefits to many of the cancer patients our members treat, we would require significantly more time to adequately address the important issues raised in the Key Questions.

ASTRO plans on reviewing the draft report that will be produced as a result of the public comment period and we look forward to reviewing this report in early July. We have noted that the Health Technology Clinical Committee that will be reviewing the technology assessment reports and making coverage decisions does not include a radiation oncologist and we strongly recommend that a radiation oncologist be added to this committee.

In anticipation of the more detailed comments that we will submit in response to the draft report, we offer a general observation relating to the fundamental basis of some of our positions about IMRT in particular. During the past two decades, an abundant number of clinical studies have characterized the relationship between the dose given to various normal tissues using 3D EBRT

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and the risk of toxicity to those tissues. There are recognized dose thresholds known to relate to the risk of toxicity for bowel, bladder, spinal cord, and other important organs. Whereas IMRT offers the capacity to avoid exceeding those recognized thresholds for toxicity, it is considered an appropriate standard for numerous indications as a result of this property. The field of radiation oncology has not considered it ethical or resource-efficient to conduct head-to-head comparisons of 3D EBRT vs. IMRT in all settings where a clear improvement in a surrogate measure of toxicity risk is easily demonstrated.

We have included ASTRO's model coverage policies on SRS, SBRT and IMRT for your review that outline the specific technology of each treatment, clinical indications, coding considerations and references.

We appreciate your consideration of this material and look forward to the draft report. Should you have any questions please contact Marsha Kaufman, Director of Health Policy, at 703-839-7374 or marshak@astro.org.

Sincerely,

Gregory Patton, MD
Chair, Regulatory Committee

Michael Dzeda, MD
Vice Chair, Regulatory Committee

Enclosure: ASTRO SRS Model Policy
ASTRO SBRT Model Policy
ASTRO IMRT Model Policy

cc: Thomas Eichler, MD
Joel Cherlow, MD, PhD
Najeeb Mohideen, MD
Brian Kavanagh, MD, MPH

From: Ashton, Spencer N
To: HCA ST Health Tech Assessment Prog
Subject: HTA - IMRT
Date: Tuesday, March 06, 2012 4:30:59 PM
Attachments: 120304 IMRT_Douglas_Landis_Mar2_2012.docx

I am writing to put my support behind the use of Intensity Modulated Radiation Therapy (IMRT) as a vital tool for the treatment of cancer in the State of Wahington. The development of IMRT techniques has allowed physicians to deliver more conformal radiation doses to treatment volumes, allowing us to increase dose to target tissues while simultaneously decreasing dose to the surrounding normal tissues. This leads to decreased toxicity/side effects that patients endure as part of their treatment, while in some cases increasing tumor control rates. IMRT is not used in every breast cancer patient, but has made an important impact in the treatment of Head and Neck malignancies, Prostate Cancer, and some abdominal cancers among others. IMRT has decreased both the acute toxicity experienced during treatment as well as the long term toxicity experienced by patients even years down the road.

I have read and agree with the position put forth by the Swedish Medical Center in Seattle as linked to above. I ask you to examine the evidence, and would encourage you to continue to support the use of IMRT in the appropriate patients here in the State of Washington.

Thank-you for your time.

Sincerely,

Spencer Ashton M.D.
Providence St. Mary's Regional Cancer Center
401 W Poplar. Ave.
Walla Walla, WA 99362
509-522-5700

From: Carlson, Thomas MD
To: HCA ST Health Tech Assessment Prog
Subject: Public Comment for: Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy
Date: Monday, March 05, 2012 11:22:53 AM

Members of the Health Technology Committee,

I appreciate the work you do in recognizing the need to evaluate new technologies and the implementation of these technologies in the health care sector.
I am concerned with respect to the path we have been going down regarding the complexity of reimbursement evaluation. We seem to be reimbursing physicians based on the tools they are using to accomplish a task as opposed to the task itself. In the case of IMRT, Stereotactic Radiosurgery (in the brain or body) or brachytherapy, we are reimbursing based on the tool. Do we reimburse a surgeon for using one scalpel blade over another? No. The surgeon chooses what's most appropriate for the situation and is paid for the job. I believe a tremendous amount of waste could be removed from the system if a case rate reimbursement model was initiated.

Thomas Carlson, MD
Department of Radiation Oncology
Wenatchee Valley Medical Center

RadiantCare

March 5, 2012

Mr. Josh Morse, MPH, Program Director and the Health Technology Assessment
Program Board and Staff
Washington State Health Care Authority
P.O. Box 42712
Olympia, Washington, 98504-2712

Dear Mr. Morse and Members of the Board and Staff:

Thank you for allowing us to comment on the Key Questions that where raised pertaining to IMRT. I will be speaking for all members of RadiantCare Radiation Oncology in the following correspondence. Due to the short time frame allowed to comment we have chosen to collaborate with the Tumor Institute Radiation Oncology Group (TIROG) in our response.

We share your concerns pertaining to patient safety, effectiveness, efficiency and the rising cost of contemporary radiation treatment modalities. We have instituted a group designated to address these issues as they relate to the treatment of the patients of RadiantCare.

IMRT is a very precise treatment modality that uses computer generated images to deliver tightly focused beams to cancerous tumors. This computer generated beam optimization allows physicians to reduce dose to healthy tissue while increasing the dose to the cancerous tissue. This precise optimization is not achievable with conventional EBRT.

Key Questions= IMRT
KQ1-
What is the evidence of effectiveness for intensity modulated radiation therapy (IMRT) compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?

There have been many studies that show that IMRT is superior to Conventional ERBT. Please see the following list courtesy of the clinicians at Swedish Medical Center in Seattle, Washington.

Indication	Clinical Outcomes	Source
Brain	• IMRT maintained equivalent target coverage, improved target conformity and enabled dose reductions of normal tissues, including brainstem (D_{mean} by 19.8% and D_{max} by 10.7%), optic chiasm (D_{mean} by 40.6% and D_{max} by 36.7%), $p \leq 0.01$. • Results indicate that IMRT for high-grade gliomas allows for improved target conformity, better critical tissue sparing, and importantly does so without increasing integral dose and the volume of normal tissue exposed to low doses of radiation.	Hermanto U, Frija EK, Lii MJ, et al. Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade gliomas: Does IMRT increase the integral dose to normal brain? Int J Rad Onc Biol Phys 2007;67(4):1135-1144.

Spine	• IMRT TomoTherapy achieved highest mean dose homogeneity index (DHI) of 0.96, 0.91 for conventional IMRT, and 0.84 for 3DCRT. • IMRT TomoTherapy was superior in reducing maximum, mean and integral doses to almost all organs at risk (OARs) • Conclusion: IMRT TomoTherapy for craniospinal irradiation (CSI) is technically easier and potentially dosimetrically favorable compared with conventional IMRT and 3DCRT	Sharma DS, Gupta T, Jalali R, et al. High-precision radiotherapy for craniospinal irradiation: evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical TomoTherapy. Brit J Radiol 2009;82:1000-1009.
Head/neck	• IMRT was associated with statistically significant improvements in certain QoL domains versus 3DCRT, particularly those relating to xerostomia, including dry mouth, sticky saliva and eating-related domains.	Tribius S, Bergelt C. Intensity-modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: is there a worthwhile quality of life gain? Cancer Treat Rev 2011;37(7):511-519.
	• At 12 months, grade 2 or worse xerostomia side-effects were significantly lower in the IMRT group than in the conventional radiotherapy group (74% vs. 38%) • At 24 months, grade 2 or worse xerostomia side-effects were significantly lower in the IMRT group than in the conventional radiotherapy group (83% vs. 29%) • At 12 and 24 months, significant benefits were seen in recovery of saliva secretion in dry-mouth-specific and global quality of life scores…supports role of IMRT in squamous-cell carcinoma of the head and neck	Nutting CM, Morden JP, Harrington JK, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck (PARSPORT): a phase 3 multicentre randomized controlled trial. Lancet Oncol 2011;12(2):127-136.
Head/Neck (cont.)	• IMRT is associated with lower incidence of late xerostomia and improved quality of life for domains related to late xerostomia. For other adverse effects, difference and risks may exist, but there is insufficient evidence from which to permit conclusions about comparative effects. The evidence is insufficient to determine if IMRT confers advantage in overall survival	John M. Eisenberg Center for Clinical Decisions and Communications Science. Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer. 2010 Nov 30. Comparative Effectiveness Review Summary Guides for Clinicians. Rockville MD: Agency for Healthcare Research and Quality (US); 2007 http://www.ncbi.nlm.gov/books/NBK50593
Lymphoma	• Mean lung dose was reduced using IMRT by 14% compared with 3D-CRT. • Conclusion: IMRT provides improved planning target volume coverage and reduces pulmonary toxicity parameters compared to 3DCRT. It is feasible for radiation therapy of large treatment volumes and allows repeat radiation therapy of relapsed disease without exceeding cord tolerance.	Good man KA, Toner S, Hunt M, et al. Intensity-modulated radiotherapy for lymphoma involving the mediastinum. Int J Rad Onc Biol Phys 2005;62(1):198-206.

Indication	Clinical Outcomes	Source
Breast	• IMRT resulted in an improved conformity of dose distribution to the target volume compared to conventional RT • In all IMRT cases with matching adjacent beams, the homogeneity in the target volume was improved • Volume of ipsilateral lung irradiated with a dose higher than 20 Gy was reduced with IMRT from 24.6% to 13.1% compared to conventional RT • For left-sided target volume, the heart volume with a dose higher than 30 Gy was reduced from 6.2% to 0.2% • Conclusion: Presented plan comparison study for irradiation of the breast and the parasternal lymph nodes showed a substantial improvement of the dose distribution by inversely planned IMRT compared to conventional RT	Thilmann C, Sroka-Perez G, Krempien R, et al. Inversely planned intensity modulated radiotherapy of the breast including the internal mammary chain: a plan comparison study. Technol Cancer Res Treat 2004;3(1):69-75.
	• Compared to 3DCRT, IMRT had a 36% and 57% reduction at the 4 and 8-cm contralateral positions • Conclusion: Primary breast irradiation with tangential IMRT technique significantly reduces the dose to the contralateral breast compared to conventional tangential field techniques.	Bhatnagar AK, Brander E, Sonnik D, et al. Intensity modulated radiation therapy (IMRT) reduces the dose to the contralateral breast when compared to conventional tangential fields for primary breast irradiation. Breast Cancer Res Treat 2006;96(1):41-46.
	• A significant reduction in acute Grade 2 or worse dermatitis, edema, and hyperpigmentation was seen with IMRT compared with conventional RT. • Reduced acute Grade 3 or greater dermatitis (6% vs. 1%, p = 0.09) in favor of IMRT. • Chronic Grade 2 or worse breast edema was significantly reduced with IMRT compared with conventional RT. • In patients with larger breasts (> or =1,600 cm(3), n = 64), IMRT resulted in reduced acute (Grade 2 or greater) breast edema (0% vs. 36%, p <0.001) and hyperpigmentation (3% vs. 41%, p = 0.001) and chronic (Grade 2 or greater) long-term edema (3% vs. 30%, p = 0.007) compared to conventional RT.	Harsolia A, Kestin L, Grills I, et al. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. Int J Radiat Oncol Biol Phys 2007;68(5):1375-1380.
	• 245 breasts were treated in 240 patients: 121 with IMRT and 124 with conventional RT. • Treatment with IMRT decreased acute skin toxicity of RTOG Grade 2 or 3 compared with conventional RT (39% vs. 52%; p = 0.047). • For patients with Stages I-III (n = 199), 7-year Kaplan-Meier freedom from ipsilateral breast tumor recurrence (IBTR) rates were 95% for IMRT and 90% for conventional RT (p = 0.36). • For patients with Stage 0 (ductal carcinoma in situ, n = 46), 7-year freedom from IBTR rates were 92% for IMRT and 81% for conventional RT (p = 0.29). • Conclusion: Patients treated with breast IMRT had decreased acute skin toxicity, and long-term follow-up shows excellent local control	McDonald MW, Godette KD, Butker EK, et al. Long-term outcomes of IMRT for breast-cancer: a single-institution cohort analysis. Int J Radiat Oncol Biol Phys 2008;72(4):1031-1040.

Pancreas	• Compared to conventional RT, IMRT reduced the man dose to the liver, kidneys, stomach and small bowel • IMRT was well tolerated, with 80% experiencing Grade 2 or less acute upper GI toxicity • At a median follow-up of 10.2 months, no resected patients had local failure, and only 1 of the 10 assessable patients unresectable cancer had local progression • Median survival and distant metastasis-free survival was 13.4 months and 7.3 months, respectively	Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2004;59(2):445-453.
	• Both helical IMRT and conventional IMRT offer a statistically significant improvement over 3D-CRT in lower dose to the liver, stomach and bowel • Conclusion: Helical IMRT offers improved dose homogeneity over conventional IMRT and several significant benefits to 3D-CRT	Poppe MM, Narra V, Yue NJ, et al. A comparison of helical intensity-modulated radiotherapy, intensity-modulated radiotherapy, and 3D-conformal radiation therapy for pancreatic cancer. Med Dosim 2011;36(4):351-357.
Prostate	• Planning data shows the ability of helical TomoTherapy (HT) in creating highly homogenous dose distributions within the PTVs • Organs at risk (OAR) sparing also showed to be excellent • HT was found to favorably compared to inversely-optimized IMRT in terms of PTVs coverage and dose distribution homogeneity • In the case of pelvic nodes irradiation, a large sparing of bowel was evidenced by HT compared to 3DCRT and conventional IMRT	Fiorino C, Alongi F, et al. Physics aspects of prostate tomotherapy: planning optimization and image-guidance issues. Acta Oncol 2008;47(7)1309-1316.
	• Conformity index (CI) of helical tomotherapy (HT) (0.77, SD = 0.54) plans tended to be better (p = 0.069) compared to conventional sliding window IMRT (SWIMRT) (0.70, SD = 0.01) for prostate PTV. • Helical tomotherapy plans were more homogeneous, with homogeneity index (HI) of 0.04 compared to 0.06 in SWIMRT (p = 0.018) for PTV prostate and HI of 0.06 and 0.15 (p = 0.025) for PTV nodes respectively. • Median dose to bladder (p = 0.025) and rectum (p = 0.012) were less with HT. • Femoral heads were better spared with HT plans (p = 0.012). • Conclusion: HT improves dose homogeneity, target coverage and conformity as compared to SWIMRT, with overall improvement in critical organ sparing.	Murthy V, Mallik S, Master Z, et al. Does helical tomotherapy improve dose conformity and normal tissue sparing compared to conventional IMRT? A dosimetric comparison in high risk prostate cancer. Technol Cancer Res Treat 2011;10(2):179-185.
	• IMRT plan was found to significantly reduce the normal tissue complication probability (NTCP) for the rectum while achieving a small gain in the tumor control probability (TCP) compared to 3D conformal	Pradip D, Fielding AL. Radiobiological model comparison of 3D conformal radiotherapy and IMRT plans for the treatment of prostate. Aust Phys Engin Sci Med 2009;32(2):51-61.
	• Use of IMRT significantly reduced the risk of gastrointestinal (GI) toxicities compared with patients treated with conventional 3D-CRT (13% to 5%; p<0.001). • Risk of proctitis was significantly reduced with IMRT compared to conventional 3D-CRT	Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70(4):1124-1129.

Pancreas	• Compared to conventional RT, IMRT reduced the man dose to the liver, kidneys, stomach and small bowel • IMRT was well tolerated, with 80% experiencing Grade 2 or less acute upper GI toxicity • At a median follow-up of 10.2 months, no resected patients had local failure, and only 1 of the 10 assessable patients unresectable cancer had local progression • Median survival and distant metastasis-free survival was 13.4 months and 7.3 months, respectively	Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2004;59(2):445-453.
	• Both helical IMRT and conventional IMRT offer a statistically significant improvement over 3D-CRT in lower dose to the liver, stomach and bowel • Conclusion: Helical IMRT offers improved dose homogeneity over conventional IMRT and several significant benefits to 3D-CRT	Poppe MM, Narra V, Yue NJ, et al. A comparison of helical intensity-modulated radiotherapy, intensity-modulated radiotherapy, and 3D-conformal radiation therapy for pancreatic cancer. Med Dosim 2011;36(4):351-357.
Prostate	• Planning data shows the ability of helical TomoTherapy (HT) in creating highly homogenous dose distributions within the PTVs • Organs at risk (OAR) sparing also showed to be excellent • HT was found to favorably compared to inversely-optimized IMRT in terms of PTVs coverage and dose distribution homogeneity • In the case of pelvic nodes irradiation, a large sparing of bowel was evidenced by HT compared to 3DCRT and conventional IMRT	Fiorino C, Alongi F, et al. Physics aspects of prostate tomotherapy: planning optimization and image-guidance issues. Acta Oncol 2008;47(7)1309-1316.
	• Conformity index (CI) of helical tomotherapy (HT) (0.77, SD = 0.54) plans tended to be better ($p = 0.069$) compared to conventional sliding window IMRT (SWIMRT) (0.70, SD = 0.01) for prostate PTV. • Helical tomotherapy plans were more homogeneous, with homogeneity index (HI) of 0.04 compared to 0.06 in SWIMRT ($p = 0.018$) for PTV prostate and HI of 0.06 and 0.15 ($p = 0.025$) for PTV nodes respectively. • Median dose to bladder ($p = 0.025$) and rectum ($p = 0.012$) were less with HT. • Femoral heads were better spared with HT plans ($p = 0.012$) • Conclusion: HT improves dose homogeneity, target coverage and conformity as compared to SWIMRT, with overall improvement in critical organ sparing.	Murthy V, Mallik S, Master Z, et al. Does helical tomotherapy improve dose conformity and normal tissue sparing compared to conventional IMRT? A dosimetric comparison in high risk prostate cancer. Technol Cancer Res Treat 2011;10(2):179-185.
	• IMRT plan was found to significantly reduce the normal tissue complication probability (NTCP) for the rectum while achieving a small gain in the tumor control probability (TCP) compared to 3D conformal	Pradip D, Fielding AL. Radiobiological model comparison of 3D conformal radiotherapy and IMRT plans for the treatment of prostate. Aust Phys Engin Sci Med 2009;32(2):51-61.
	• Use of IMRT significantly reduced the risk of gastrointestinal (GI) toxicities compared with patients treated with conventional 3D-CRT (13% to 5%; $p<0.001$). • Risk of proctitis was significantly reduced with IMRT compared to conventional 3D-CRT	Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70(4):1124-1129.

As demonstrated above, IMRT is clearly superior over conventional EBRT at reducing the radiation delivered to surrounding normal tissues while increasing the dose to the tumor region and increasing the clinical outcomes.

KQ3: 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
e. Setting, provider characteristics, equipment, quality assurance standards and procedures

IMRT is capable of treating a large array of cancers in a variety of locations, for both genders and all ages. This precise modality is utilized in freestanding centers and hospitals which allows access to patients everywhere. Due to the required stringent quality measures of IMRT the clinical outcomes remain superior to conventional ERBT regardless of the setting the IMRT is delivered.

KQ4: What is the evidence of cost and cost-effectiveness of IMRT compared to EBRT?

As described in the TIROG IMRT comment letter, there are a few cost comparison studies that specifically address IMRT compared to conventional EBRT. As described, all cost comparison studies have difficulty assigning costs in a changing environment. One specific study by Konski and Pollack et al at the Fox Chase Cancer Center found the mean cost of IMRT was $47,931 with a survival of 6.27 quality adjusted life years (QALY's). This study found IMRT to be cost effective, however at the upper limits of acceptability (Konski A, Watkins-Bruner D, Pollack A, et al. Using decision analysis to determine cost effectiveness of IMRT in the treatment of intermediate risk prostate cancer. Int. J Radiat Oncol biol Phys 2006 Oct;66(2): 408-15).

Cost is always a concern for us. IMRT is chosen as the treatment modality only after it has been clearly evaluated and defined as the superior treatment method. We feel that by utilizing IMRT over conventional EBRT we are able to decrease side effects, improve clinical outcomes and survival and improve the patient's quality of life.

We encourage any questions you may have about this topic. Please feel free to contact any of us.

Regards,

Joseph R. Hartman MD
Senior Partner
RadiantCare Radiation Oncology

From: Kaurin, Darryl G
To: HCA ST Health Tech Assessment Prog
Cc: Holloway, Karen L; Larry Sweeney nmpc
Subject: Public Comment for: Intensity Modulated Radiation Therapy
Date: Friday, March 02, 2012 10:06:30 AM

Hello,
I am a Medical Physicist in Radiation Oncology.

KQ1: For head and neck cancers, IMRT allows us to spare important organs that would not be possible with standard EBRT, namely parotid glands (imagine living the rest of your life without saliva), complications with teeth (we can frequently preserve blood flow to the teeth to improve the probably of not needing dentures), decrease spinal cord dose. We can decrease optic system dose (orbits, lens, optic chiasm, and optic nerves) for tumors more superiorly in the nasopharnyx - which also allows us to use higher doses to tumors in this area.

For brain, IMRT allows us to limit dose to the tumor areas with lower doses to non-involved brain areas. This is especially important near the optic system (see head and neck).

Breast: this is frequently not reimbursed for IMRT, nevertheless there are cases where IMRT is called for, principally for left-sided breast to decrease heart dose (principally to the left ventricle) for young patients who would live long enough to see complications due to heart dose. IMRT can also be used to limit lung dose.

Lung: Use of IMRT is not as common due to concerns with respirator motion. Sometimes, use of IMRT may be justified - especially in the case of SBRT where the tumor is given ablative doses that would be extremely harmful to non-involved tissues if not using IMRT.

Near spinal cord: Use of IMRT can be used to achieve adequate dose to provide adequate control while minimizing the dose to the cord itself - this is only possible with IMRT.

Pancreas: Where I work, we are getting much better outcomes than the national average using IMRT with higher radiation dose per fraction. The complications to organs surrounding the pancreas would be much higher without the use of IMRT with our higher dose per fraction.

GI/Prostate/GYN: use of IMRT allows us to limit complications to uninvolved tissues - bladder, rectum, small bowel. Not having IMRT generally limits the dose we can take the target tissues to, which decreases the efficacy of the treatment. Patients may not be able to complete a course of EBRT due to the complications that IMRT can minimize.

KQ2: IMRT requires additional time to carry out quality assurance checks on the individual treatments, as well as routine checks for the multileaf collimator. There have been instances where the quality assurance checks have not be done for individual treatments (there was a head and neck case in the North Eastern US written up in the New York Times several years ago) for several days following initiation of the treatment; the patient died from the treatment.

This case appears to be an issue with an overworked medical physicist (inadequate staffing) as well as a glitchy treatment planning system, as well as therapists not understanding the importance of monitoring the treatment systems (if they had a window up showing the MLC movement, they would have seen the MLCs were open and not moving at all - the window on their screen was minimized). The incidence of these errors is fortunately low. The individual patient checks still need to occur, sometimes the treatment plans are too modulated for the MLC to deliver accurately, and need to be modified. These checks are especially important when working with more junior treatment planners, for newer treatment planning systems, treatment planning system upgrades, and treatment delivery system upgrades.

KQ3: IMRT is extremely helpful for younger populations who will live long enough for radiation complications to become evident; since doses to non-target tissues are lower. IMRT is extremely helpful for older populations in terms of quality-of-life in reducing acute radiation effects to non-target tissues.

KQ4: IMRT requires additional work for all the staff - MDs in denoting the target tissues on CT slices, reviewing additional imaging studies (MR, PET) and possibly fusing them with the treatment planning CT. IMRT requires additional training for the Dosimetrist (treatment planners) as well as addition time if they denote normal structures on the treatment planning CT (which are reviewed by the MD). IMRT requires additional time for the physicist to carry out routine as well as individual patient treatment planning checks by measuring the patient plan on a radiation sensitive device, and comparing the expected dose with the treatment planning calculated dose. IMRT requires increased diligence on the part of the therapists who deliver the treatment; if the patient is step up incorrectly with EBRT, the system is generally more forgiving and easier to identify errors using portal films with the treatment area and blocking; if the patient is setup incorrectly for IMRT, the target areas may be missed with avoidance areas receiving the treatment dose. For the IMRT treatment, frequently, additional imaging and motion management techniques are used to ensure correct targeting, which also increases time the patient is on the table as compared to EBRT.

Thank you for allowing me the opportunity for comment.

Sincerely,

Darryl Kaurin, PhD, DABR, CHP
Northwest Medical Physics Center
Lynnwood, Washington

Alliance. To view our complete Notice of Privacy Practices, visit our web site at www.seattlecca.org.

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3/5/12

Mr. Josh Morse, MPH, Program Director and the
Health Technology Assessment Program Board & Staff
Washington State Health Care Authority
P.O. Box 42712
Olympia, Washington 98504-2712

Dear Mr. Morse and Members of the Board and Staff:

We have received copies of the letters that Dr. Todd Barnett and his associates at the Swedish Cancer Institute have written in support of Intensity Modulated Radiotherapy (IMRT) and Stereotactic Radiotherapy (SRT), currently under review by your board. We have reviewed their letters and supportive documents and applaud their work and endorse their recommendations that IMRT and SRT/SBRT are important treatment techniques that benefit cancer patients while being safe and cost effective. IMRT and stereotactic radiotherapy are techniques that have been in common use in most radiation therapy centers for greater than 10 years; it would be impossible to think of not utilizing these advanced techniques for patients with conditions that warrant such treatment. We are hopeful that your review will support the continued utilization of these beneficial treatment techniques.

Please do not hesitate to contact us for more information or questions.

Respectfully,

Berit L. Madsen, MD, FACR
Clinic Director
R. Alex Hsi, MD
Heath R. Foxlee, MD

IMRT Use For Those With Gynecological Malignancies

This letter is in response to your request for input regarding re-imbursement for IMRT services.

Patients with gynecological malignancies are frequently referred for pelvic radiation therapy. Typically its patients with endometrial and cervical cancers, but commonly patients with colorectal cancers are also referred for adjuvant or definitive pelvic radiation. So the statements being made here will also apply to any individual being referred for pelvic radiation.

The targets for the radiation in gynecological malignancies are typically the lymph node chains that lie along the bony pelvic sidewalls. Frequently there is a substantial amount of small and large bowel that exists in the pelvis, especially after a hysterectomy. Bowel is a very radiation sensitive organ and typically is the main source of serious acute and late toxicity with radiation therapy, and sometimes can be lead to very serious situations requiring bowel surgery to correct. Thus bowel toxicity is a major concern for radiation oncologists.

In the decades years prior to the development of IMRT based treatment plans, patients were treated with the traditional "4 field "box" or a "3D" configuration. With these treatment plans, patients would receive a substantial amount of collateral bowel radiation by default. This unfortunately provided a large cohort of patients with injury to whom retrospective clinical data could be compiled upon and analyzed to determine what factors lead to higher rates of bowel complications. Not unexpectedly it the relationship of total dose delivered a volume of bowel that predicts, as it always has. But what's useful about these contemporary publications is that they quantify the doses and volumes that provide radiation oncologists specific treatment planning guidance. This is summarized in this abstract:

"The absolute volume of small bowel receiving ≥15 Gy should be held to <120 cc when possible to minimize severe acute toxicity, if delineating the contours of bowel loops themselves. Alternatively, if the entire volume of peritoneal space in which the small bowel can move is delineated, the volume receiving >45 Gy should be <195 cc when possible. Such a limit likely also reduces late toxicity risk, although this correlation is not established. The volume of small bowel receiving higher doses should also be minimized. For SBRT, the small-bowel volume receiving >12.5 Gy in a single fraction should ideally be kept to <30 cc with avoidance of circumferential coverage above that dose; for a three- to five-fraction regimen, the maximum point dose should be <30 Gy."

Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S101-7.

Radiation dose-volume effects in the stomach and small bowel.

Kavanagh BD, et .

With a the standard "4 field box" treatment, commonly the dose to the bowel exceeds the 195 cc threshold, and only with a an IMRT based treatment plan can this be obtained.

As a recent example, a 49 year-old female was referred to our facility for adjuvant radiation to the pelvis after radical hysterectomy for cervical cancer. Again the targets for the radiation are the upper vagina and lateral pelvic sidewalls where the potential for residual cancer in the lymph nodes existed. Being post-hysterectomy there was a substantial amount of small and large bowel loops between the areas requiring irradiation. Two radiation treatment plans were then prepared and compared: a standard "4 field box" treatment and an IMRT based plan. The volume of bowel determined to be within the pelvis was 1150 cc. With the "4 field box" plan, 413 cc of bowel would be treated with 45 Gy, exceeding the

published guideline quoted above. With the IMRT plan, 125 cc of bowel would receive 45 Gy, well below the recommend threshold of 195 cc. Thus, it was determined through quantitative methods that she would likely be at significantly less risk for bowel toxicity if treated with a IMRT based technique. This data was presented to her insurance carrier and she was approved for the requested IMRT treatment.

Commonly radiation oncologists are confronted with an insurance carrier position that no randomized controlled clinical studies have been conducted to compare outcomes with traditional radiation versus IMRT radiation. The dilemma is that such studies will never likely be done, as excellent retrospective analysis, such as the quoted herein, have already provided guidance. All things being equal, one can easily appreciate the ethical challenge of placing a patient in a study which compare “4 field box” irradiation to IMRT when an obvious amount of bowel is being placed at risk.

Thus clinical situations exist where the application to have an IMRT service covered should be approved if a rationale and justification can be provided as in the example cited.

Sincerely,

Tim Mate, M.D.

From: Mark Phillips
To: HCA ST Health Tech Assessment Prog
Subject: Public Comment for: Intensity Modulated Radiation Therapy
Date: Tuesday, February 28, 2012 10:41:03 AM

To Whom it May Concern,

Please accept my responses to the key questions listed in your public comment website.

KQ1: The effectiveness of IMRT lies in its ability to localize radiation so that more radiation is delivered to the tumor and less to normal tissues. In some types of cancers (and some stages of cancer), it is unlikely that controlling the primary tumor will cure the cancer since it is likely to have spread. However, radiation is still part of the treatment of these cancers and all patients benefit from having less normal tissue irradiated. In other cases, when cure is more achievable, IMRT allows for a higher tumorcidal dose to be delivered.

In this way, IMRT is a great step forward in cancer treatment. It enhances the chance for cure in some cases, and in all cases, its use is likely to decrease the chance for complications and improve the patient's quality of life.

KQ2: Potential harms come in two forms. First, the technology is very complex and if delivered without appropriate quality control, there is a greater chance of mis-delivery that could result in patient harm. Therefore, the clinical practice of IMRT always involves significantly more work to do the appropriate quality assurance work.

Second, there is a question of inappropriate use and potential harm. While IMRT delivered with appropriate quality assurance measures is no more harmful than EBRT and theoretically provides better normal tissue sparing, there is a question as to whether it is worth the cost. In some cases such as early stage prostate cancer, there may be an overreliance on IMRT and less use of permanent brachytherapy implants.

KQ3-KQ4: As stated above, all patients benefit from reduced normal tissue dose. The ability of IMRT to improve cure rates does depend on the stage and type of cancer. Also as stated above, the safe and efficacious use of IMRT requires significantly more resources and training than does EBRT, though EBRT is potentially even more dangerous since larger regions are irradiated. In summary, IMRT has been a great advance in radiation therapy. There are very few disadvantages relative to EBRT. In both cases, the best approach to improving patient care is to insure that the radiation is delivered in a safe manner.

Sincerely,
Mark Phillips
--

Mark H. Phillips, Ph.D.
Professor, Department of Radiation Oncology

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SUBJECT: Comments regarding SRS and SBRT
FROM: John.Rieke@multicare.org
TO: shtap@hca.wa.gov
CC: John.Rieke@multicare.org
SENT: Mon 05 Mar 2012 22:30:54 PST
EXPIRES: Fri 04 May 2012 22:30:54 PDT

I am pleased to offer these comments regarding SBRT and SRS per your request. A letter is attached. Please feelfree to call with questions anytime; my office phone is 253-403-4994, and my cell phone is 206-920-3469.

I was asked to review the material you received from Dr. Barnett of TIROG in Seattle regarding IMRT. I support the submittal completely. I think it represents mainstream thinking of radiation oncologists across the state.

I understand there will be a chance to discuss your report due out later this year, at a meeting September 21, 2012. Please add me to relevant mailing list. I have been asked to represent the ASTRO, our national radiation oncology/biology/physics professional society in your proceedings.

Best wishes,

John W. Rieke, MD, FACR
Medical Director
MultiCare Regional Cancer Center
Tacoma, WA

_____

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Mailgate1.multicare.org made the following annotations

Intensity Modulated Radiation Therapy (IMRT)

On behalf of clinicians at Swedish Medical Center in Seattle, Washington, we write to answer the key questions as part of the Washington State Health Care Authority, HTA Program, Intensity Modulated Radiation Therapy (IMRT) Health Technology Assessment. We are users of several forms of radiation therapy including GammaKnife, CyberKnife, TomoTherapy, conventional "3D" radiation therapy, as well as multiple platforms that deliver IMRT.

Approximately 10 years ago, the most advanced technology for the delivery of radiation was 3D-conformal radiation. This is an improvement over previous 2D radiation in that the patient is imaged on a CT scanner and the contour of the skin, tumor, and normal structures can be entered into a planning computer. One can then develop a "3D" plan by selecting beam angles and creating beam shapes that best conformed to the target and the computer can calculate doses to particular structures. 3D conformal radiation is utilized today still in the majority of fairly straightforward cases However over this past decade, Intensity Modulated Radiation Therapy (IMRT) has been developed, refined, clinically tested and utilized in many of the more complex radiation cases.

With IMRT non-uniform intensities are assigned to tiny subdivisions of beams, called "beamlets," enabling custom dosing of optimum dose distributions. For example, if a normal structure overlaps the planning target volume (PTV), one would ideally like to reduce the intensity of those radiation rays that pass through the normal structure. However, using this strategy the target volume would have a "cold spot" of decreased intensity in the shadow of the normal structure. To compensate for this shadow, the intensities of other rays in other beams would need to be increased. While conventional radiation therapy uses wedges and compensators to provide intensity modulation, the unique aspect of IMRT involves the use of a computer-aided optimization process to determine the non-uniform intensity distributions to attain certain specified clinical objectives. Using IMRT, the target volume can be treated with different fraction (i.e. daily dose) sizes simultaneously. This contrasts with conventional radiation therapy, in which the same fraction size is used for all target volumes, but the field sizes are reduced in stages over critical regions in order to protect critical normal structures.

One key aspect of IMRT is inverse planning. It would be impossible for a human to create an optimized IMRT radiation plan. There are too many variables at play and the effect of modulating one beam can alter the requirement of other beams in complex manners. The computer iteratively creates hundreds of thousands of radiation plans, constantly optimizing and refining the shape of the beams, until finding the optimal solution. The term 'inverse planning' comes from the fact that instead of creating and placing a beam to deliver a particular dose to a tumor, we first define the tumor and other organs or avoidance structures, and then instruct the computer to work backwards and find the best radiation plan.

Because of this increased complexity in IMRT planning, very elaborate verification and quality assurance measures are necessary. There are strict guidelines that are published by the American College of Radiology (ACR) and American Society of Therapeutic Radiation Oncology (ASTRO) for the implementation and quality assurance of IMRT. The details of this are beyond the scope of this letter, but the complexity in the safe delivery of IMRT is daunting and is a labor intensive task for the physician, physicist, dosimetrist, and radiation therapists.

As technology has developed, linear accelerators have been improved and modified to deliver IMRT. In your statement, TomoTherapy was specifically mentioned. TomoTherapy is a particular linear accelerator made by one vendor that was built from the ground-up to deliver IMRT in a highly conformal manner using entire arcs of treatment instead of fixed beam angles. Other venders have subsequently

developed arc-therapy as well, including Varian's RapidArc and Eleckta's VMAT (Volumetric Arc-Therapy). However delivered, the goals of IMRT are essentially the same, and this letter would be applicable to all the specific vendors or modalities for delivery of IMRT.

IMRT can benefit the patient in three ways. First, by improving conformity with target dose it can reduce the probability of in-field recurrence. Second, by reducing irradiation of normal tissue it can minimize the degree of morbidity associated with treatment. Third, with these techniques the ultimate radiation dose can often be escalated well beyond previous constraints which has in many studies shown increased local control. Whereas there are multiple randomized and nonrandomized trials showing benefits to IMRT, to our knowledge there is no trial that has shown worse outcome with IMRT.

Although the initial goal of the key questions was to be limited to comparison of IMRT to 3-D radiation, in the larger context both IMRT and stereotactic radiation therapy represents a much larger advance. Improved outcomes with these highly conformal forms of radiation is allowing for safe alternatives to costly surgery or chemotherapy in many cases. As the general trend in medicine continues towards minimally-invasive outpatient medical treatment, we expect radiation therapy to continue to be an increasing part of that trend allowing safe and effective cancer treatment.

Key questions

KQ1: What is the evidence of effectiveness for intensity modulated radiation therapy (IMRT) compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?

The following table shows superior clinical results by indication of IMRT compared to conventional EBRT. Please note that this list is in no way a full representation of the clinical literature or indication types that IMRT can treat.

Indication	Clinical Outcomes	Source
Brain	• IMRT maintained equivalent target coverage, improved target conformity and enabled dose reductions of normal tissues, including brainstem (D_{mean} by 19.8% and D_{max} by 10.7%), optic chiasm (D_{mean} by 40.6% and D_{max} by 36.7%), $p \leq 0.01$. • Results indicate that IMRT for high-grade gliomas allows for improved target conformity, better critical tissue sparing, and importantly does so without increasing integral dose and the volume of normal tissue exposed to low doses of radiation.	Hermanto U, Frija EK, Lii MJ, et al. Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade gliomas: Does IMRT increase the integral dose to normal brain? Int J Rad Onc Biol Phys 2007;67(4):1135-1144.
Spine	• IMRT TomoTherapy achieved highest mean dose homogeneity index (DHI) of 0.96, 0.91 for conventional IMRT, and 0.84 for 3DCRT. • IMRT TomoTherapy was superior in reducing maximum, mean and integral doses to almost all organs at risk (OARs) • Conclusion: IMRT TomoTherapy for craniospinal irradiation (CSI) is technically easier and potentially dosimetrically favorable compared with conventional IMRT and 3DCRT	Sharma DS, Gupta T, Jalali R, et al. High-precision radiotherapy for craniospinal irradiation: evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical TomoTherapy. Brit J Radiol 2009;82:1000-1009.

Indication	Clinical Outcomes	Source
Head/neck	• IMRT was associated with statistically significant improvements in certain QoL domains versus 3DCRT, particularly those relating to xerostomia, including dry mouth, sticky saliva and eating-related domains.	Tribius S, Bergelt C. Intensity-modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: is there a worthwhile quality of life gain? Cancer Treat Rev 2011;37(7):511-519.
	• At 12 months, grade 2 or worse xerostomia side-effects were significantly lower in the IMRT group than in the conventional radiotherapy group (74% vs. 38%) • At 24 months, grade 2 or worse xerostomia side-effects were significantly lower in the IMRT group than in the conventional radiotherapy group (83% vs. 29%) • At 12 and 24 months, significant benefits were seen in recovery of saliva secretion in dry-mouth-specific and global quality of life scores…supports role of IMRT in squamous-cell carcinoma of the head and neck	Nutting CM, Morden JP, Harrington JK, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck (PARSPORT): a phase 3 multicentre randomized controlled trial. Lancet Oncol 2011;12(2):127-136.
Head/Neck (cont)	• IMRT is associated with lower incidence of late xerostomia and improved quality of life for domains related to late xerostomia. For other adverse effects, difference and risks may exist, but there is insufficient evidence from which to permit conclusions about comparative effects. The evidence is insufficient to determine if IMRT confers advantage in overall survival	John M. Eisenberg Center for Clinical Decisions and Communications Science. Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer. 2010 Nov 30. Comparative Effectiveness Review Summary Guides for Clinicians. Rockville MD: Agency for Healthcare Research and Quality (US); 2007 http://www.ncbi.nlm.gov/books/NBK50593.
Lymphoma	• Mean lung dose was reduced using IMRT by 14% compared with 3D-CRT. • Conclusion: IMRT provides improved planning target volume coverage and reduces pulmonary toxicity parameters compared to 3DCRT. It is feasible for radiation therapy of large treatment volumes and allows repeat radiation therapy of relapsed disease without exceeding cord tolerance.	Good man KA, Toner S, Hunt M, et al. Intensity-modulated radiotherapy for lymphoma involving the mediastinum. Int J Rad Onc Biol Phys 2005;62(1):198-206.

Indication	Clinical Outcomes	Source
Breast	• IMRT resulted in an improved conformity of dose distribution to the target volume compared to conventional RT • In all IMRT cases with matching adjacent beams, the homogeneity in the target volume was improved • Volume of ipsilateral lung irradiated with a dose higher than 20 Gy was reduced with IMRT from 24.6% to 13.1% compared to conventional RT • For left-sided target volume, the heart volume with a dose higher than 30 Gy was reduced from 6.2% to 0.2% • Conclusion: Presented plan comparison study for irradiation of the breast and the parasternal lymph nodes showed a substantial improvement of the dose distribution by inversely planned IMRT compared to conventional RT	Thilmann C, Sroka-Perez G, Krempien R, et al. Inversely planned intensity modulated radiotherapy of the breast including the internal mammary chain: a plan comparison study. Technol Cancer Res Treat 2004;3(1):69-75.
	• Compared to 3DCRT, IMRT had a 36% and 57% reduction at the 4 and 8-cm contralateral positions • Conclusion: Primary breast irradiation with tangential IMRT technique significantly reduces the dose to the contralateral breast compared to conventional tangential field techniques.	Bhatnagar AK, Brander E, Sonnik D, et al. Intensity modulated radiation therapy (IMRT) reduces the dose to the contralateral breast when compared to conventional tangential fields for primary breast irradiation. Breast Cancer Res Treat 2006;96(1):41-46.
	• A significant reduction in acute Grade 2 or worse dermatitis, edema, and hyperpigmentation was seen with IMRT compared with conventional RT. • Reduced acute Grade 3 or greater dermatitis (6% vs. 1%, p = 0.09) in favor of IMRT. • Chronic Grade 2 or worse breast edema was significantly reduced with IMRT compared with conventional RT. • In patients with larger breasts (> or =1,600 cm(3), n = 64), IMRT resulted in reduced acute (Grade 2 or greater) breast edema (0% vs. 36%, p <0.001) and hyperpigmentation (3% vs. 41%, p = 0.001) and chronic (Grade 2 or greater) long-term edema (3% vs. 30%, p = 0.007) compared to conventional RT.	Harsolia A, Kestin L, Grills I, et al. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. Int J Radiat Oncol Biol Phys 2007;68(5):1375-1380.
	• 245 breasts were treated in 240 patients: 121 with IMRT and 124 with conventional RT. • Treatment with IMRT decreased acute skin toxicity of RTOG Grade 2 or 3 compared with conventional RT (39% vs. 52%; p = 0.047). • For patients with Stages I-III (n = 199), 7-year Kaplan-Meier freedom from ipsilateral breast tumor recurrence (IBTR) rates were 95% for IMRT and 90% for conventional RT (p = 0.36). • For patients with Stage 0 (ductal carcinoma in situ, n = 46), 7-year freedom from IBTR rates were 92% for IMRT and 81% for conventional RT (p = 0.29). • Conclusion: Patients treated with breast IMRT had decreased acute skin toxicity, and long-term follow-up shows excellent local control	McDonald MW, Godette KD, Butker EK, et al. Long-term outcomes of IMRT for breast-cancer: a single-institution cohort analysis. Int J Radiat Oncol Biol Phys 2008;72(4):1031-1040.

Pancreas	• Compared to conventional RT, IMRT reduced the man dose to the liver, kidneys, stomach and small bowel • IMRT was well tolerated, with 80% experiencing Grade 2 or less acute upper GI toxicity • At a median follow-up of 10.2 months, no resected patients had local failure, and only 1 of the 10 assessable patients unresectable cancer had local progression • Median survival and distant metastasis-free survival was 13.4 months and 7.3 months, respectively	Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2004;59(2);445-453.
	• Both helical IMRT and conventional IMRT offer a statistically significant improvement over 3D-CRT in lower dose to the liver, stomach and bowel • Conclusion: Helical IMRT offers improved dose homogeneity over conventional IMRT and several significant benefits to 3D-CRT	Poppe MM, Narra V, Yue NJ, et al. A comparison of helical intensity-modulated radiotherapy, intensity-modulated radiotherapy, and 3D-conformal radiation therapy for pancreatic cancer. Med Dosim 2011;36(4):351-357.
Prostate	• Planning data shows the ability of helical TomoTherapy (HT) in creating highly homogenous dose distributions within the PTVs • Organs at risk (OAR) sparing also showed to be excellent • HT was found to favorably compared to inversely-optimized IMRT in terms of PTVs coverage and dose distribution homogeneity • In the case of pelvic nodes irradiation, a large sparing of bowel was evidenced by HT compared to 3DCRT and conventional IMRT	Fiorino C, Alongi F, et al. Physics aspects of prostate tomotherapy: planning optimization and image-guidance issues. Acta Oncol 2008;47(7)1309-1316.
	• Conformity index (CI) of helical tomotherapy (HT) (0.77, SD = 0.54) plans tended to be better (p = 0.069) compared to conventional sliding window IMRT (SWIMRT) (0.70, SD = 0.01) for prostate PTV. • Helical tomotherapy plans were more homogeneous, with homogeneity index (HI) of 0.04 compared to 0.06 in SWIMRT (p = 0.018) for PTV prostate and HI of 0.06 and 0.15 (p = 0.025) for PTV nodes respectively. • Median dose to bladder (p = 0.025) and rectum (p = 0.012) were less with HT. • Femoral heads were better spared with HT plans (p = 0.012). • Conclusion: HT improves dose homogeneity, target coverage and conformity as compared to SWIMRT, with overall improvement in critical organ sparing.	Murthy V, Mallik S, Master Z, et al. Does helical tomotherapy improve dose conformity and normal tissue sparing compared to conventional IMRT? A dosimetric comparison in high risk prostate cancer. Technol Cancer Res Treat 2011;10(2):179-185.
	• IMRT plan was found to significantly reduce the normal tissue complication probability (NTCP) for the rectum while achieving a small gain in the tumor control probability (TCP) compared to 3D conformal	Pradip D, Fielding AL. Radiobiological model comparison of 3D conformal radiotherapy and IMRT plans for the treatment of prostate. Aust Phys Engin Sci Med 2009;32(2):51-61.
	• Use of IMRT significantly reduced the risk of gastrointestinal (GI) toxicities compared with patients treated with conventional 3D-CRT (13% to 5%; p<0.001). • Risk of proctitis was significantly reduced with IMRT compared to conventional 3D-CRT	Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70(4):1124-1129.

Prostate (continued)	• 5-year biochemical control rate was 60.4% for 3D-CRT and 74.1% for IMRT ($p < 0.0001$, first ASTRO Consensus definition) • Using the ASTRO Phoenix definition, the 5-year biochemical control rate was 74.4% and 84.6% with 3D-RT and IMRT, respectively ($p = 0.0326$) • Conclusion: IMRT allowed delivery of higher doses of radiation with very low toxicity, resulting in improved biochemical control	Vora SA, Wong WW, Schild SE, et al. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2007;68(4):1053-1058.
	• Decision analysis showed cost-effectiveness of IMRT in treatment of intermediate risk prostate cancer, although at the upper limits of acceptability	Konski A, Watkins-Bruner D, Pollack A, et al. Using decision analysis to determine cost effectiveness of IMRT in the treatment of intermediate risk prostate cancer. Int. J Radiat Oncol Biol Phys 2006 Oct; 66(2): 408-15.
Prostate (continued)	• IMRT is associated with lower incidence of GI side effects vs 3D conformal radiation and improved quality of life.	Lips I, Dehnad H, Kruger AB, et al. Health-related quality of life in pateitns with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs 70 Gy conformal radiotherapy in a prospective longitudinal study. Int J. Radiat Oncol Biol Phys 2007 Nov 1; 69(3): 656-61.
Anal Cancer	• IMRT potentially confers an advantage via improved tumor control through dose escalation. Dose escalation studies with 3D conformal radiation have demonstrated improved local control, but high rates of toxicity necessitated treatment breaks, potentially compromising treatment delivery and efficacy. • IMRT is associated with lower incidence of gastrointestinal, dermatologic, and genitourinary side effects vs 3-D conformal radiation based on phase II single institution studies (ref 1-3). • There is an ongoing RTOG protocol RTOG 0529 "A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0529). The previous study RTOG 98-11 supported higher doses in treatment of anal cancer, however significant toxicity was observed.	Chen YJ, Liu, A, Tsai PT, et al. Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: Dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. Int J Radiat Oncol Biol Phys 2005; 63(1), pg 274-281. Milano, MT, Jani, AB et al. IMRT in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2005; 63(2):354-361 Tsai, HD, Hong, TS, et al. Dosimetric Comparison of Dose-painted IMRT vs Conventional Radiation Therapy for Anal Cancer. Poster presentation at ASCO-GI symposium, San Francisco, CA January 28 2006.

KQ2: 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.

As previously noted, the 2007 CTAF report and the clinical literature results clearly documents that IMRT has improved clinical outcomes compared to conventional EBRT. The CTAF report indicated that when using IMRT, the target volume can be treated with different fraction sizes simultaneously. With conventional RT, the same fraction size is used for all target volumes. The main rationale, supported by the outcomes in the clinical literature, is that IMRT is better able to direct the radiation to the target volume for precisely, thus decreasing the amount of radiation to surrounding normal tissues and increasing the dose to the tumor target, thus reducing recurrence rates.

KQ3: 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
e. Setting, provider characteristics, equipment, quality assurance standards and procedures

IMRT can treat a wide variety of cancer indications that are medically appropriate across both genders, patients of all ages. IMRT is available to patients both in the hospital setting as well as in the freestanding setting; this allows rural patients as well as urban patients to have access to life saving IMRT treatment. Based on our clinical experience, which is supported by the clinical data, IMRT has equivalent and/or superior clinical results across several indications. In any radiation therapy treatment, it is required that the equipment is tested at appropriate time intervals to ensure patient safety and that staff are adequately trained to treat all patient types.

KQ4: What is the evidence of cost and cost-effectiveness of IMRT compared to EBRT?

There are a few true cost-effective analyses of IMRT compared to EBRT. Konski and Pollack et al at the Fox Chase Cancer Center used a Markov model to analyze prostate IMRT. They included treatment, post-treatment, hormone therapy, chemotherapy, and ultimately death in their models. They found the mean cost of IMRT was $47,931 with a survival of 6.27 quality adjusted life years (QALY's). The expected mean cost of 3D conformal radiation was $21,865 with a survival of 5.62 QALY's. The conclusion of this analysis was that IMRT was found to be cost effective, however at the upper limits of acceptability (Konski A, Watkins-Bruner D, Pollack A, et al. Using decision analysis to determine cost effectiveness of IMRT in the treatment of intermediate risk prostate cancer. Int. J Radiat Oncol Biol Phys 2006 Oct; 66(2): 408-15).

Of note, the same group investigated proton radiotherapy in comparison with IMRT and found proton therapy was not cost effective (Konski A, Speier W, Hanlon A, Beck JR, Pollack A. J Clin Oncol 2007 Aug 20;25(24) : 3603-8).

Additional studies are underway, but all are subject to the traditional biases of cost-effective analysis which include difficult in assigning costs in a changing environment, difficult in quantifying the 'transition probabilities' between various states due to the variability of published data, and constantly improving therapies for all disease states.

From our own experience at Swedish Medical Center, we believe that IMRT, delivered in one of several platforms including TomoTherapy, Eleckta, or Varian, provide patients with the best treatment option to improve survival, decrease side effects and improve quality of life compared to conventional EBRT.

Most radiation oncologists in Washington State (this group included) do not own the linear accelerators that deliver theraputic radiation. They are typically owned by the hospitals who charge separately for their use. For linear accelerator based IMRT and 3D treatments, we are paid according to the applicable professional services fee schedule. The actual physician time and work effort involved is vastly greater for IMRT than for 3D yet despite this we are most often paid less for IMRT (in part due to bundling of charges). When we as physicians recommend IMRT over 3D we do so knowing we will

spend three to four times more effort on the case and get paid less. Clearly our incentive for doing so is to provide the very best care and treatment for our patients.
February 29, 2012

To whom it may concern,

My name is Sandra Vermeulen, MD. I am the Executive Director of the Swedish Radiosurgery Center at Swedish Hospital / Cherry Hill in Seattle. I have been a recognized leader in the field of radiosurgery and have served on two international radiosurgical boards. The IRSA (International Radiosurgery Association) has published practice guidelines for the use of SRS in the treatment of benign and malignant tumors of the brain. The ISRS or International Stereotactic Radiosurgical Society, meets every other year to review publications and abstracts on the use of SBRT and SRS on tumor types of CNS and non-CNS.

You may not be aware that IMRT using the Cyberknife, a radiosurgical platform, is now being used by several community and academic centers to reduce the risk of early breast cancer recurrence following a lumpectomy in patients with stage 1 breast cancer. Regarding this issue, I recently completed a book chapter (publication date pending) and an article in the November 2011 issue of **Frontiers in Radiation Oncology.**

The following are two references for the work being performed here in Seattle at Swedish Hospital and at the University of Texas Southwestern and Fox Chase Cancer Center:

http://www.prnewswire.com/news-releases/cyberknife-radiosurgery-for-early-stage-breast-cancer-106401063.html

http://www.frontiersin.org/radiation_oncology/10.3389/fonc.2011.00043/abstract

The following are answers to your questions pulled from the reference articles above:

KQ1 and KQ2:
"Initially clinicians delivered radiation to the whole breast following surgery, but over the last decade a more limited radiation approach has gained interest among clinicians and patients. This approach, called partial breast irradiation, can be as effective as whole breast irradiation and is less likely to damage to the heart, lungs, and skin, leading to improved cosmetic outcomes and reduced toxicities (2).

Partial breast irradiation can be delivered in a number of ways, including invasive options, such as MammoSite, which involves surgical implantation of a catheter in the breast to deliver interstitial brachytherapy, or non-invasive radiation therapy

Each technique has its advantages and drawbacks: For example, invasive brachytherapy can cause infection, hematoma or abscess (3-4). While non-invasive radiation therapy approaches minimize such risks, studies have demonstrated that the larger margins required to compensate for treatment inaccuracies, such as those caused by the movement of the breast with respiration, result in a higher risk for overdosing the skin and nearby critical structures such as the heart and lungs (5-7). One recent study investigating IMRT for partial breast irradiation found 7 out of 32 evaluated patients developed unacceptable cosmesis, leading to premature closure of the study (5).

Because of the non-invasive delivery and high precision that the CyberKnife System offers in treating tumors throughout the body, clinicians see a role for it in breast cancer treatment. The CyberKnife System has the unique ability to not only track tumor movement during respiration, but to also lock onto the tumor as it moves delivering radiation directly to the tumor and avoiding damage to

surrounding critical structures. The CyberKnife System's extreme precision enables clinicians to reduce the treatment margins that are often added with conventional IMRT Systems. For this reason, clinicians believe partial breast irradiation using the CyberKnife System holds the potential to improve toxicity and associated side effects for patients.

"We think that the real-time tracking and high conformality made possible with the CyberKnife System could result in reduced toxicity by reducing the dose to the surrounding breast tissue, skin, chest wall, lung or heart," said Charlie Ma, Ph.D., Professor and Vice-Chairman, Department of Radiation Oncology, Fox Chase Cancer Center.

University of Texas Southwestern recently launched a multi-center early stage breast cancer protocol, which is currently accruing patients. UTSW was one of the first five CyberKnife sites in the world and has remained on the forefront of clinical research.

Physicians at UTSW intend to demonstrate equivalent local control rates or to improve those seen in current treatment for early-stage disease while attempting to increase convenience, limit invasiveness, decrease toxicity and improve cosmesis compared to other methods of radiation treatment. The treatment regimen using the CyberKnife System would be five days compared to 25-30 days typically associated with conventional radiation therapy.

"In particular, we believe a very abbreviated, non-invasive, outpatient treatment would be considered a favorable option to underserved populations of women living in more remote areas for whom longer courses of treatment pose a barrier," said Robert Timmerman, M.D., professor of Radiation Oncology at UTSW and lead author of the ongoing study."

Accelerated partial breast irradiation: using the CyberKnife as the radiation delivery platform in the treatment of early breast cancer

Sandra Vermeulen[1]*, Cristian Cotrutz[1], Astrid Morris[2], Robert Meier[1], Claire Buchanan[2], Patricia Dawson[2] and Bruce Porter[3]

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We evaluate the CyberKnife (Accuray Incorporated, Sunnyvale, CA, USA) for non-invasive delivery of accelerated partial breast irradiation (APBI) in early breast cancer patients. Between 6/2009 and 5/2011, nine patients were treated with CyberKnife APBI. Normal tissue constraints were imposed as outlined in the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413 (NSABP/RTOG) Protocol (Vicini and White, 2007). Patients received a total dose of 30 Gy in five fractions (group 1, n = 2) or 34 Gy in 10 fractions (group 2, n = 7) delivered to the planning treatment volume (PTV) defined as the clinical target volume (CTV) +2 mm. The CTV was defined as either the lumpectomy cavity plus 10 mm (n = 2) or 15 mm (n = 7). The cavity was defined by a T2-weighted non-contrast breast MRI fused to a planning non-contrast thoracic CT. The CyberKnife Synchrony system tracked gold fiducials sutured into the cavity wall during lumpectomy. Treatments started 4–5 weeks after lumpectomy. The mean PTV was 100 cm^3 (range, 92–108 cm^3) and 105 cm^3 (range, 49–241 cm^3) and the mean PTV isodose prescription line was 70% for groups 1 and 2, respectively. The mean percent of whole breast reference volume receiving 100 and 50% of the dose

(V_{100} and V_{50}) for group 1 was 11% (range, 8–13%) and 23% (range, 16–30%) and for group 2 was 11% (range, 7–14%) and 26% (range, 21–35.0%), respectively. At a median 7 months follow-up (range, 4–26 months), no acute toxicities were seen. Acute cosmetic outcomes were excellent or good in all patients; for those patients with more than 12 months follow-up the late cosmesis outcomes were excellent or good. In conclusion, the lack of observable acute side effects and current excellent/good cosmetic outcomes is promising. We believe this suggests the CyberKnife is a suitable non-invasive radiation platform for delivering APBI with achievable normal tissue constraints.

Keywords: breast cancer, CyberKnife, accelerated partial breast irradiation, cosmesis
Citation: Vermeulen S, Cotrutz C, Morris A, Meier R, Buchanan C, Dawson P and Porter B (2011) Accelerated partial breast irradiation: using the CyberKnife as the radiation delivery platform in the treatment of early breast cancer. *Front. Oncol.* **1**:43. doi: 10.3389/fonc.2011.00043
Received: 30 June 2011; **Accepted:** 24 October 2011;
Published online: 21 November 2011.
Edited by: Brian Timothy Collins, Georgetown Hospital, USA
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KQ3

"Various societies have now published recommendations for patient selection criteria for APBI. These include, the American Society of Breast surgeons (ASBS), the American Brachytherapy Society (ABS), American Society for Radiation Oncology (ASTRO) and European Society for Therapeutic Radiology and Oncology (ESTRO) [54,180,181].

The recent GEC-ESTRO recommendations [180] have stratified the patients into three groups: low risk, intermediate and high risk (contraindication for APBI); similarly, ASTRO [181] has stratified them into suitable, cautionary and unsuitable. The low risk (suitable) group describes patients where APBI outside of a clinical trial would be considered acceptable (see Table 2); these criteria are stricter than those recommended by the ASBS or ABS. However, less restrictive criteria could be applied to patients who enrolled in a clinical trial. Generally young patients (<50 years) and those who may harbor disease a significant distance from the edge of the excision cavity or potentially have multi-centric disease should not be treated with APBI off-protocol. It is also worth noting that these recommendations were determined from a systematic review of the APBI literature. The groupings were based primarily on an analysis of the characteristics of patients most frequently included in trials of APBI and not on data that identified subsets of patients with higher rates of ipsilateral breast tumor recurrence (IBTR) when treated with APBI. Recent analysis using ASBS registry trial [182,183] and using data from University of Wisconsin [184] show that the ASTRO consensus groupings may not be optimal in identifying patients for APBI."

http://download.journals.elsevierhealth.com/pdfs/journals/1040-8428/PIIS1040842811000333.pdf

KQ4:

In the present age of rapidly increasing healthcare costs, evaluation of techniques has to include cost effectiveness. Cost might play a key role in the rapid adaptation of a new technology or technique. However, cost analysis is country specific because reimbursement or how healthcare is financed varies from country to country. In the USA for example, re-imbursement changes continually and rates of reimbursement vary substantially between the different APBI and WBI techniques. Hence, this makes the appropriate presentation of a comprehensive cost analysis challenging and its accuracy short-lived. Nevertheless, cost comparisons have been reported by Suh et al. [199,200] and Sher et al. [201]. Sher and colleagues [201] modelled treatment planning and delivery for different WBI fractionation schemes: Mammosite, MIB, APBI–3D-CRT and APBI–IMRT. They found that the least expensive partial breast-based radiation therapy approaches were the external beam techniques (APBI–3DCRT and APBI–IMRT); any reduced cost to patients for the HDR brachytherapy-based APBI regimens were overshadowed by substantial increases in cost to payers, resulting in higher total societal costs. The cost of HDR treatment delivery was primarily responsible for the increased direct medical cost. APBI approaches in general were favored over whole-breast techniques when only considering costs to patients. However, if one were to pursue a partial-breast radiation therapy regimen to minimize patient costs, it would be more advantageous from a societal perspective to pursue external beam-based approaches such as APBI–3D-CRT or APBI–IMRT in lieu of the brachytherapy-based regimens [200]. Similarly, Sher et al. [201] reported that APBI–3DCRT was the most cost-effective strategy for postmenopausal women with early-stage breast cancer. Unless the quality of life after MSB proves to be superior, it is unlikely to be cost-effective [201]. Vaidya and colleagues [66] made a conservative estimates of 66% man hours saving, if intraoperative radiation therapy using intrabeam was used instead of WBI.

They went on to estimate the savings to the UK national health service of about 18 million dollars. So, in general one could expect savings in costs of treatment to be closely related to fraction number.

http://download.journals.elsevierhealth.com/pdfs/journals/1040-8428/PIIS1040842811000333.pdf

At our institution we often substitute APBI-Cyberknife for APBI-IMRT or APBI-3DCRT for two reasons: smaller treatment volumes with APBI-Cyberknife compared with the other two modalities and, because of these smaller treatment volumes, some patients are made eligible for APBI who otherwise would not have been if APBI-3DCRT or APBI-IMRT were their only options.
I hope this information will help in your review. Please let me know if I can be of further assistance.

Sincerely,

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February 29, 2012

To whom it may concern,

As a member of the IRSA (International Radiosurgery Association) Board of Directors, my colleagues and I spent years developing consensus-based radiosurgery practice guidelines for the radiosurgical treatment of conditions as well as for numerous benign and malignant tumor diagnoses in the brain. These areas included the radiosurgical treatment of **Acoustic Neuromas**, **Trigeminal Neuralgia, Pituitary Adenomas**, **AVM (Aterio-Venous Malformations) and Brain Metastases**. Our aim was to improve outcomes for these diagnoses by assisting physicians in applying research evidence to clinical decisions while promoting the responsible use of health care resources. I have attached the link to these documents below. Guidelines from ISRA are pending for the following tumors and conditions **Meningiomas, Essential Tremor and Gliomas.** Nevertheless, the rational to treat them with SRS are included in this letter.

Acoustic Neuroma

http://www.irsa.org/AN%20Guideline.pdf

KQ1 and KQ2:

Gamma Knife Radiosurgery: Clinical Results

Tumor Growth Control

Long-term results of Gamma Knife® radiosurgery for vestibular schwannomas have been documented.[14,22,32,42,45,55] Recent reports suggest a tumor control rate of 93–100% after radiosurgery.[14,16,21-24,31,32,34,36,37,42-45,50-52,54,55,61,67,68] Kondziolka et al studied 5 to 10-year outcomes in 162 vestibular schwannoma patients who had radiosurgery at the University of Pittsburgh.[44] In this study a long-term 98% tumor control rate was reported. Sixty-two percent of tumors became smaller, 33% remained unchanged, and 6% became slightly larger. Some tumors initially enlarged 1–2 mm during the first 6 to 12 months after radiosurgery as they lost their central contrast enhancement. Such tumors generally regressed in volume compared to their pre-radiosurgery size. Only 2% of patients required tumor resection after radiosurgery. Norén, in his 28-year experience with vestibular schwannoma radiosurgery, reported a 95% long-term tumor control rate. Litvack et al reported a 98% tumor control rate at a mean follow-up of 31 months after radiosurgery using a 12 Gy margin dose.[53] Niranjan et al analyzed the outcome of intracanalicular tumor radiosurgery performed at the University of Pittsburgh.[65] All patients (100%) had imaging-documented tumor growth control. Flickinger et al performed an outcome analysis of acoustic neuroma patients treated between August 1992 and August 1997 at the University of Pittsburgh. The actuarial 5-year clinical tumor control rate (no requirement for surgical intervention) was 99.4 + 0.6%.[21,22] The long-term (10–15 year) outcome of benign tumor radiosurgery has been evaluated. In a study which included 157 patients with vestibular schwannomas**,** the median follow-up for the patients still living at the time of the study (n=136) was 10.2 years. Serial imaging studies after radiosurgery (n=157) showed a decrease in tumor size in 114 patients (73%), no change in 40 patients (25.5%), and an increase in three patients who later had resection (1.9%).[45] No patient developed a radiation associated malignant or benign tumor (defined as a histologically confirmed and distinct neoplasm arising in the initial radiation field after at least two years have passed).

Hearing Preservation

Pre-radiosurgery hearing can now be preserved in 60–70% of patients, with higher preservation rates found for smaller tumors. In a long-term (5–10 year follow-up) study conducted at the University of Pittsburgh, 51% of patients had no change in hearing ability.[21,44] All patients (100%) who were treated with a margin dose of 14 Gy or less maintained a serviceable level of hearing after intracanalicular tumor radiosurgery.[65] Among patients treated after 1992, the 5-year actuarial rates of hearing level preservation and speech preservation were 75.2% and 89.2%, respectively, for patients (n=89) treated with a 13 Gy tumor margin dose. The 5-year actuarial rates of hearing level preservation and speech preservation were 68.8% and 86.3%, respectively, for patients (n=103) treated with >14 Gy as the tumor margin dose.[22] Unlike microsurgery, immediate hearing loss is uncommon after radiosurgery. If hearing impairment is noted, it occurs gradually over 6 to 24 months. Early hearing loss after radiosurgery (within three months) is rare and may result from neural edema or demyelination. The exact mechanism of delayed hearing loss after radiosurgery is still unclear. Perhaps gradual obliteration of microvessels or even direct radiation axonal or cochlear injury is implicated. The effect of radiation on normal microvessels supplying the cochlear nerve or cochlea itself is not known. However, with doses as low as 12–13 Gy (which are sufficient to halt the tumor growth) vascular obliteration of normal vessels seems less likely. This dose probably does not adversely affect the vessels as well as the axons. Although with current imaging techniques the cochlear nerve cannot be well visualized, efforts should be made to achieve high conformality at anterior and inferior margin of the tumor. Conformal dose planning using 4 mm collimators for the intracanalicular portion of the tumor may prevent further injury to the cochlear nerve. It is likewise important to avoid radiation of the cochlea.[70]

Facial Nerve and Trigeminal Nerve Preservation

Facial and trigeminal nerve function can now be preserved in the majority of patients (>95%). In the early experience at University of Pittsburgh normal facial function was preserved in 79% of patients after five years and normal trigeminal nerve function was preserved in 73%. These facial and trigeminal nerve preservation rates reflected the higher tumor margin dose of 18–20 Gy used during the CT based planning era before 1991. In a recent study using MR based dose planning, a 13 Gy tumor margin dose was associated with 0% risk of new facial weakness and 3.1% risk of facial numbness (5-year actuarial rates). A margin dose of >14 Gy was associated with a 2.5% risk of new onset facial weakness and a 3.9% risk of facial numbness (5-year actuarial rates).[22] None of the patients who had radiosurgery for intracanalicular tumors developed new facial or trigeminal neuropathies.

Neurofibromatosis 2

Patients with vestibular schwannomas associated with neurofibromatosis 2 represent a special challenge because of the risk of complete deafness. Unlike the solitary sporadic tumors that tend to displace the cochlear nerve, tumors associated with NF2 tend to form nodular clusters that engulf or even infiltrate the cochlear nerve. Complete resection may not always be possible. Radiosurgery has been performed for patients with NF2. Subach et al studied 40 patients (with 45 tumors) who were treated with radiosurgery for NF2. Serviceable hearing was preserved in 6 of 14 patients (43%), and this rate improved to 67% after modifications made to the technique in 1992. The tumor control rate was 98%.[98] Only one patient showed imaging documented growth. Normal facial nerve function and trigeminal nerve function was preserved in 81% and 94% of patients, respectively. In two recent series,[78,80] serviceable hearing was preserved in only 30%[78] and 40%[80] of cases, respectively. The tumor control rate was respectively 71%[78] and 79%.[80] It now appears that preservation of serviceable hearing in patients with NF2 is an attainable goal with modern radiosurgery technique, and some centers propose this early treatment when the hearing level is still excellent."

KQ3:

"Clinical Algorithm

A number of patient related factors are considered in making a recommendation. These factors include:

- Age
- Symptoms
- Hearing status
- Current neurological status
- Medical condition

- Presence or absence of NF2
- Presence or absence of prior procedures
- Concern and risk tolerance for hearing, facial and trigeminal nerve function
- Patient desires
- Patient's decision after informed consent"

KQ4:
EBRT is not the standard of care for Acoustic Neuromas

Trigeminal Neuralgia

http://www.irsa.org/TN%20Guideline-UpdatedJan2009.pdf

KQ1 and KQ2:
"Several reports have documented the efficacy of Gamma Knife® stereotactic radiosurgery for TN.[1,3,16,18,20,26,27,29,32,35,39-42,46,50-53,58,62,68] Because radiosurgery is the least invasive procedure for TN, it is a good treatment option for patients with co-morbidities, high-risk medical illness, or pain refractory to prior surgical procedures. Radiosurgery is a good alternative for most patients with medically refractory trigeminal neuralgia, especially those who do not want to accept the greater risk of an MVD for a greater chance of pain relief.

To date, the largest reported series are still characterized by a wide spectrum of success rates after radiosurgery with Grade I outcome in 21–76.8% of patients and Grade II outcome in 65–88% of patients.[6,7,21,29,38,48,52,58,67] Regis et al reported that 87% of patients were initially free of pain in their series of 57 patients treated with a maximum dose of 75–90 Gy.[52,54] In many patients, they used the higher maximum dose of 90 Gy, and their target was placed at a more anterior site (closer to retrogasserian portion). In a series of 441 patients presented at the 2001 meeting of the International Stereotactic Radiosurgery Society, Young et al noted that 87% of patients were free of pain after radiosurgery, with or without medication (median follow-up period, 4.8 years, including repeat procedures). Brisman et al noted vascular contact with trigeminal nerve on thin section MRI in 59% of patients with TN. These authors reported a complete (100%) pain relief without medicines in 22% of patients, 90% or greater relief with or without small doses of medicines in 30% of patients, 75–89% relief in 11% of patients, 50–74% relief in 7% of patients, and less than 50% relief in 8% of patients. Recurrent pain requiring a second procedure occurred in 24% of patients.[7]

In a study, Petit et al. assessed the safety, efficacy and quality of life associated with radiosurgical treatment for TN in 112 patients treated with Gamma Knife® radiosurgery using a standard questionnaire. Ninety-six patients completed questionnaires for a median follow-up of 30 months. Seventy-four patients (77%) reported pain relief at a median of three weeks after the procedure.[44] A decrease in medication usage was noted in 66% of patients. Seven (7.3%) patients reported new or increased trigeminal dysfunction; however, only 3.1% reported these symptoms as bothersome. Patients with sustained pain relief reported an average of 100% improvement in their quality of life as a direct result of pain relief after radiosurgery, and 100% believed that the procedure was successful. Furthermore, among those patients with temporary pain relief and subsequent recurrence, 65% felt their treatment was a success with an average of 80% improvement in their quality of life.[44] Smith et al. recently published the results of trigeminal neuralgia radiosurgery using a dedicated linear accelerator.[59] These investigators treated 60 patients with central doses of 70–90 Gy delivered to trigeminal nerve root entry zone using a 5-mm collimator. Pain relief was experienced at a mean of 2.7 months. Significant pain relief was obtained in 87.5% of the patients who had essential TN and in 58.3% of the patients who had secondary facial pain. In a recent article, Longhi et al. reported on the results of Gamma Knife® radiosurgery for treatment of medically and, in some instances, surgically refractory TN.[35] These authors found 57% Grade I and 33% Grade II pain control after Gamma Knife® radiosurgery. These favorable results are similar to those reported by Pollock et al.[49] and Kondziolka et al.[28] Recurrence of pain occurred in 18% of patients at a mean interval of 14.2 months after radiosurgery. The side effects of trigeminal paresthesia or hypoesthesia were observed in 9.5% of patients; no cases of anesthesia dolorosa were observed. A higher radiosurgical dose and no previous neurosurgical intervention for TN were positive predictors of a pain-free outcome. The growing body of recent literature suggests that low rates of

complications of Gamma Knife® radiosurgery, coupled with high success rates and patient satisfaction, allow it to be increasingly used as primary intervention for trigeminal neuralgia for appropriate patients.[2,12,13,18,20,22,26,34]

KQ3:

"A number of factors are considered in making a recommendation. These factors include:

1. Patient's age
2. Patient's medical condition
3. Presence or absence of multiple sclerosis
4. Presence or absence of vascular contact and/or compression on thin section MRI
5. Presence or absence of prior procedures
6. The type of prior procedure and its response
7. Severity of pain and how long the patient can reasonably wait for pain relief
8. Patient's concern and risk tolerance for dysesthesias, recurrence or complications from surgery"

Pituitary Adenoma

http://www.irsa.org/Pituitary%20Guideline.pdf

KQ1 and KQ2:

Stereotactic Radiosurgery

The endocrine control aims of radiosurgery are no different from those of surgical resection; namely, normalization of any hypersecretory syndrome without new onset hypopituitarism. Unlike surgical resection, which eliminates the tumor on subsequent neuroimaging, the neoplastic goal of stereotactic radiosurgery is permanent tumor control. This means that a tumor, which has been enlarging, is made incapable of further tumor growth, and this control is confirmed through long-term neuroimaging follow-up. While permanent stabilization of tumor size is the desired goal, the majority of tumors will demonstrate varying degrees of tumor shrinkage over time. Thus the goal of pituitary adenoma radiosurgery is to permanently control tumor growth, maintain pituitary function, normalize hormonal secretion in the case of functional adenomas, and preserve neurological function, especially vision. The small risks of late radiation-induced tumorigenesis and of late cerebrovascular accidents from radiation damage to the internal carotid arteries also exist for patients treated with radiosurgery. Delayed complications are less than that of stereotactic radiotherapy.

Tumor Growth Control After Radiosurgery

Non-functioning pituitary adenomas are usually diagnosed late when patients complain of visual dysfunction. Trans-sphenoidal decompression is recommended as the first line of management for these patients. Radiosurgery is often indicated as an adjuvant management after partial resection or later recurrence of pituitary adenomas. However, radiosurgery can be performed as the primary management of nonfunctioning adenomas in carefully selected patients, including those who are high risk for surgery or consciously choose not to undergo resective surgery. Tumor growth control rates of 90–100% have now been confirmed by multiple centers following pituitary radiosurgery (13, 20, 21, 24, 26, 41). The antiproliferative effect of radiosurgery has been reported in nearly all patients who underwent Gamma Knife® radiosurgery (24, 41). Relatively few patients (who usually had received lower margin doses) eventually required additional treatment (12, 46).

Functional Effect of Radiosurgery

Growth Hormone Secreting Adenomas (Acromegaly)

A biochemical remission is defined as GH level suppressed to below 1 µg/L on OGTT and normal age-related serum IGF-1 levels. OGTT remains the gold standard for defining a cure of acromegaly. IGF-1, however, is far more

practical. Decrease of random GH to less than 2.5 µg/L is achieved more frequently than the normalization of IGF-1 but it is necessary to obtain the fulfillment of both criteria. Microsurgery results in biochemical remission in 31–80% of patients (1, 5, 19, 53, 59). The suppression of hormonal hyperactivity is more effective when higher doses of radiation are used. Hormonal normalization after radiosurgery was achieved in 29–82% of cases in the published series (3, 4, 11–14, 17, 19, 20, 22, 24, 25, 30, 32, 33, 35, 36, 41, 42, 45, 47–49, 57, 62, 68). Because hormone suppressive medication during radiosurgery may act as a radioprotective agent, this medication should be discontinued at least six to eight weeks prior to radiosurgery (25, 49) and may be resumed after a week. In a study at the University of Pittsburgh, 38% of patients were cured (GH <1 µg/L) and overall, 66% had growth hormone levels <5 µg/L, 3–5 years after radiosurgery (44). An important goal of resective surgery is to achieve an immediate postoperative effect, while the results of radiosurgery have a latency of about 20–28 months (18, 28) that must be sometimes temporized through the temporary use of hormone suppressive medications.

ACTH Secreting Adenomas

Cushing's disease: The results to date achieved by radiosurgery (usually used after failed resective surgery) are slightly inferior to those reported after primary surgical resection in regard to secretory normalization. In addition there is a latency of approximately 14–18 months for maximal therapeutic response (18, 28). Patients with Cushing's disease respond to radiosurgery but more than one procedure may be needed. In various published series 63–98% hormone normalization after radiosurgery has been observed (10, 16, 29, 33, 36, 38, 40, 43, 46, 50, 51, 54, 55, 58, 63). *Nelson's syndrome:* Maintenance of elevated ACTH levels indicates continued biochemical activity of a pituitary adenoma after prior adrenalectomy for Cushing's disease. Strict hormonal normalization is not as important for the treatment of pituitary adenomas associated with Nelson's syndrome as it is for other secretory pituitary adenomas. The most important task of radiosurgery in the case of Nelson's syndrome is to control the growth of the tumor, which has been achieved in the majority of cases (66).

Prolactin Secreting Adenomas

Most prolactinomas can be controlled successfully by medical treatment. Surgery is indicated for cases of intolerance to medical treatment, in cases where women desire to have children, or when patients are dopamine agonist resistant (5–10% of patients). Some patients prefer microsurgery or radiosurgery to the need for life long medical treatment. In published studies of patients treated with radiosurgery, 25–29% showed normalization (26, 49). The possible radioprotective effect of dopaminergic drugs should be taken into account. In one of the studies patients treated with dopamine agonist had lower remission rates. It is therefore recommended that radiosurgery for prolactinoma be performed during a period of drug withdrawal (26).

Radiation Tolerance of Functioning Pituitary Tissue

The most important factor influencing post-irradiation hypopituitarism seems to be the mean dose to the hypophysis (pituitary stalk). Vladyka et al. observed some worsening of gonadotropic, corticotropic or thyrotropic functions 12–87 months after radiosurgery and usually 4–5 years after radiosurgery (61). There was no post radiation worsening of gonadotropic and thyrotropic functions when the mean dose to the hypophysis did not exceed 15 Gy. The limiting mean dose to the hypophysis for adrenocorticotropic function was 18 Gy (61). In another study, deterioration in pituitary functions was observed when the pituitary stalk received higher doses (10). The risk for hypopituitarism after stereotactic radiosurgery thus becomes a primary function of the anatomy of the tumor and the dose prescribed. For recurrent tumors primarily involving the cavernous sinus, where the pituitary stalk (and even at times the residual pituitary gland) is separate from the tumor, easily visualized, and can be excluded from the treatment volume, the risk of hypopituitarism is extremely small, even when high doses are utilized for secretory adenomas. For adenomas that cannot be visually separated from the normal gland, particularly if they extend upward to involve or compress the pituitary stalk, the risk is predominantly related to the dose necessary to effectively achieve all treatment goals for the functional status of the tumor (higher for secretory than non-secretory adenomas).

Complications of Pituitary Radiosurgery

Complications of pituitary radiosurgery fall into three categories: hypopituitarism, visual deterioration and hypothalamic damage. The following rates of hypopituitarism have been reported: Levy et al. (32), 33%; Thoren et al. (57), 24%; Rocher et al. (52), 33%; and Lunsford et al. (34), 0%. As discussed in the section above,

hypopituitarism risks vary with tumor anatomy relative to the pituitary stalk and gland, and vary with whether the adenoma is secretory or non-secretory (higher dose needed in the former). Stereotactic radiosurgery for residual or recurrent non-secretory adenomas solely involving the cavernous sinus carries the lowest risk of subsequent hypopituitarism, while secretory tumors close to the median eminence or requiring targeting of the whole pituitary gland carry the highest risk. Future studies must stratify for these variables in order to better predict hypopituitarism risk after stereotactic radiosurgery in an individual patient. Levy et al. (32) reported <1% increase in visual deficit in their large series. Lunsford et al. (34) reported one patient with visual compromise. Using LINAC radiosurgery, Rocher et al. reported a 39% incidence of some visual compromise (6% of patients were blinded) (52). The key to avoiding this complication lies in proper patient selection (adequate space between the optic apparatus and the superior edge of the tumor for the radiosurgery technique you are employing), insisting on strictly conformal planning at the critical structure interface, and accurate dose delivery. Lunsford et al. reported one death due to hypothalamic injury in a patient who had multiple operations, prior pituitary apoplexy and prior fractionated radiation therapy (34). Voges et al. reported one patient who developed a severe hypothalamic syndrome (62). Mitsumori et al., using LINAC radiosurgery for tumor invading the cavernous sinus, reported three cases of temporal lobe necrosis (39). As discussed above, there is a theoretical risk of late radiation induced tumorigenesis for patients receiving radiosurgical treatment. A small risk also exists of late cerebrovascular accidents from the effect of the ionizing radiation on the cerebral circulation passing adjacent to the pituitary gland. Fortunately, while the risk of major morbidity or mortality is not zero with radiosurgery, these occurrences appear to be extremely rare.

KQ3:

Clinical Algorithms
"The final recommendation is usually influenced by the cumulative experience of the medical management team. Combinations of different treatments may be necessary and/or desired under certain circumstances. Common examples include patients with cavernous sinus involvement present at diagnosis who undergo first stage microsurgery for the extra-cavernous portion of their tumor followed by second stage radiosurgery for the cavernous sinus component, and patients with secretory adenomas who undergo radiosurgery but are then maintained on their anti-secretory medications during the latency period for hormonal normalization after radiosurgery. The common need for staged or tandem treatments with multiple modalities underscores the importance of the presence of a comprehensive and coordinated multidisciplinary team in the optimal management of pituitary adenoma patients."

KQ4:

"Fractionated Radiation Therapy (EBRT)
Fractionated radiation therapy has been used for the treatment of unresectable pituitary adenomas. Rates of tumor control have been reported to vary from 76% to 97%. Fractionated radiation therapy, however, has been less successful (38–70%) in reducing hypersecretion of hormones by hormonally active tumors. It may take years before the full therapeutic effect is exhibited. The delayed complications of fractionated radiation therapy (2–10 years) include a relatively high risk of hypopituitarism (12–100%) and a low but definite risk of optic neuropathy (1–2%) and secondary tumor formation. Some investigators have reported a higher likelihood of cerebrovascular disease in patients treated with radiation therapy for pituitary tumors. In patients with a benign 3 neoplasm and an otherwise normal expected life span, external beam fractionated radiotherapy (EBRT) leads to exposure of normal surrounding brain to potential long term cognitive effects of radiotherapy. Newer fractioned radiotherapy techniques such as intensity modulated radiotherapy (IMRT) can minimize the amount of normal brain exposed to radiation compared with conventional or standard 3-D conformal techniques. However, the medial temporal lobes on either side, which are intimately involved in memory processing and learning, often remain exposed as the radiation distribution is shifted away from the optic nerves and chiasm. Minimal long-term outcome data exist for IMRT."

Intra-cranial Ateriovenous Malformations:

http://www.irsa.org/AVM%20Guideline.pdf

KQ1, KQ2 and KQ3:

"Stereotactic radiosurgery is considered for patients with unresectable AVMs. Such patients may warrant treatment based on age, location, volume or medical history.[77] Radiation technologies for stereotactic radiosurgery include Gamma Knife® radiosurgery, proton beam radiosurgery, and linear accelerators (LINACs) modified at Centers of Excellence with extensive AVM experience. Multi-modal management teams are essential for proper patient selection and patient care. Because of the delayed obliteration rate of AVMs after radiosurgery, comprehensive long-term management and observational strategies are necessary.

Probability of AVM Obliteration with Radiosurgery

Current studies indicate a success rate between 50–95% at the end of three years of observation after a single radiosurgery procedure.[1,4,5,7–10,17,21,22,33–35,38–43,47,48,51,52,56,57,61–63,66,71,74,76–79,82,84] The long-term (5–14 years) results of Gamma Knife® radiosurgery suggest that the majority of AVM patients (73%) are protected from the risk of future hemorrhage and continue their normal daily activities after radiosurgery.[63]

In a study of rate of AVM obliteration after Gamma Knife® radiosurgery at the University of Pittsburgh, obliteration was documented by angiography in 73% and by MR alone in 86% of patients who refused further angiography.[17] Assuming a 96% accuracy for MR-detected obliteration, the corrected obliteration rate for all patients was 75%.[65] Persistent out-of-field nidus (marginal failure) was identified in 18% of previously embolized versus 5% of non-embolized patients ($p = 0.006$). This was the only significant factor associated with marginal failure. Multivariate analysis correlated in-field obliteration with marginal dose ($p < 0.0001$) and sex (slightly lower in women [$p \leq 0.026$], but overall obliteration was not significantly lower [$p = 0.19$]).

Early Adverse Effects of Radiosurgery

Adverse effects of radiosurgery include short-term problems such as headache from the frame, nausea from pain medication, and perhaps a small increased risk of seizure in patients with cortical lobar AVMs, particularly if a prior history of episodic seizures is present.[14,16,18,65] For this reason we use perioperative anticonvulsants in lobar AVMs.

Late Complications After AVM Radiosurgery

Delayed complications of radiosurgery on AVMs include hemorrhage despite angiographically documented complete obliteration of the AVM, temporary or permanent radiation injury to the brain such as persistent edema, radiation necrosis, radiation-induced tumors and cyst formation. Cyst formation after AVM radiosurgery was first reported by Japanese investigators who reviewed the outcomes of patients initially treated in Sweden.[24] Jokura et al. 6

KQ3:

A number of factors are considered in making a recommendation. These factors include:

1. Patient's age
2. Patient's medical condition
3. Previous bleed
4. Prior procedures
5. Volume of AVM
6. Location of AVM
7. Presenting symptoms

KQ4:

The standard of care does not include EBRT in the treatment of AVM's.

Brain Metastases

http://www.irsa.org/Metastatic%20Guideline.pdf

KQ1 and KQ2:

"Radiosurgery as the sole initial management or as a boost before or after WBRT has emerged as a widely practiced treatment modality for brain metastases. The goal of radiosurgery without WBRT is to achieve brain control without the possible long term neurotoxic or cognitive side effects of WBRT.[17] The rationale for radiosurgery, when used as a boost after WBRT, is to achieve improved local brain tumor control. Radiosurgery boost improves survival in selected patients in whom the predominant problem is brain disease rather than extracranial disease. Radiosurgery is also used as salvage treatment for progressive intracranial disease after surgery or WBRT. Traditionally radioinsensitive histologies tend to be more responsive to SRS than to conventional fractionated radiation treatment. In addition, SRS causes indirect vascular injury and subsequent sclerosis of blood vessels, and eventual compromise of the blood supply and circulation within the tumor.[121] The overall side effects of SRS are limited but can occasionally be serious. There are very few acute side effects of SRS related to the radiation. Stereotactic radiosurgery may cause mild fatigue and sometimes a temporary patch of hair loss if the tumor is close to the skull and scalp. There is a risk of late side effects that can develop, the most common and serious of which is tumor radionecrosis.[134] Radiation necrosis is damage to the tumor and or adjacent brain in the high-dose area. This can result in edema and additional side effects produced by the mass including seizures and neurological deficits. Radionecrosis can often be managed with corticosteroids. Occasionally surgical intervention is required to reduce the mass effect. The risk of symptomatic radionecrosis is usually less than 5%.[2,5,56] A multicenter phase I RTOG trial involving SRS documented safe SRS in patients previously treated with standard external beam radiation therapy.[111] Early publications showed good control rates and led to further investigation.[24,64,76,120] Retrospective series have consistently revealed local control of the target lesions in the range of 80–85% or even higher with a very acceptable side effect profile.[5,10,20,30,37,51,70] Prospective randomized trials have demonstrated that the one-year local control rate of target lesions with radiosurgery is 73%, which increases to 82–89% with the addition of WBRT.[2,4]

Retrospective Studies for SRS

Patients treated with conventional open surgical resection without WBRT had a 46% risk of failure at the site of the resection in a randomized trial evaluating the role of WBRT after surgical resection.[89] In subsequent studies patients were treated with SRS alone (without WBRT). These studies 8 found excellent local control (70–80% at one year).[21,83] Other published series of patients treated with SRS have demonstrated a risk of distant brain failure at one year, ranging from 43% to 57%.[22,49,66,117] In general, the risk of new metastasis in patients with solitary tumors is approximately 37% (crude), but the actuarial risk is 50% at one year.[62,89] The histologic features or tumor type may play a role, with melanoma being more likely to be associated with multiple metastases than some other tumor types.[95] Despite a relatively high risk of new metastases outside the radiosurgery volume in patients who have SRS alone, retrospective studies have not confirmed a survival benefit to adjuvant WBRT.[94,117,118] Freedom from local progression in the brain at one year was significantly superior in patients who received both SRS and WBRT compared with SRS alone (28% vs. 69%), although the overall survival rate was not significantly different.[49] A retrospective, multi-institutional study in which patients were treated with SRS alone (n = 268) or SRS + WBRT (n = 301) also reported no significant difference in the overall survival rate.[161] Despite the higher rate of new lesions developing in patients treated with SRS alone, the overall survival appears to be equivalent to SRS + WBRT since salvage therapies are fairly effective and patients' extracranial disease is frequently the cause of death.[117] Only 24% of patients managed initially with radiosurgery alone required salvage WBRT. Pirzkall et al. reported that there was no survival benefit for an overall group of 236 patients with adjuvant WBRT but these authors noted a trend toward improved survival in a subset of patients with no extracranial tumor (15.4 vs. 8.3 months, p = 0.08).[94] Chidel et al. reported on 78 patients managed initially with SRS alone and 57 patients treated with SRS and adjuvant WBRT.[157] Whole-brain radiation therapy did not improve the overall survival rate but was useful in preventing both the local progression and the development of new brain metastases (74% vs. 48%, p = 0.06). These retrospective studies suggest that WBRT will improve local and distant control in the brain, but do not clearly demonstrate a survival advantage.[117]

A multicenter retrospective analysis was performed with 502 patients treated at 10 institutions in which all of the patients were treated with WBRT and SRS. The patients were stratified by the recursive partitioning analysis and compared with similar patients from the RTOG database who had been treated with WBRT alone.[104] The study revealed that patients with higher KPS, controlled primary tumor, absence of extracranial metastases and lower RPA class had statistically superior survival. The addition of an SRS boost resulted in a median survival of 16.1, 10.3 and 8.7 months, respectively, for RPA classes I, II and III. This is in comparison to 7.1, 4.2 and 2.3 months for similar RPA class patients from the RTOG database. This improvement in overall survival, stratified by RPA class with an SRS boost, was statistically significant.[104] In a recent study SRS alone was found to be as effective as resection plus WBRT in the treatment of one or two brain metastases for patients in RPA classes I and II.[98]

Local Tumor Control

In a randomized trial reported in abstract form by Chougule et al.,[23] patients were randomized to Gamma Knife® radiosurgery alone vs. WBRT and Gamma Knife® radiosurgery vs. WBRT alone. The local brain control rate was higher in the two radiosurgery arms: 87% for Gamma Knife® radiosurgery alone and 91% for Gamma Knife® radiosurgery and WBRT, compared with 62% in the WBRT only arm. Another randomized trial compared the use of radiosurgery with WBRT plus radiosurgery as initial therapy in selected patients with brain metastases.[4] Aoyama et al. reported the results of a prospective, multi-institutional, randomized controlled trial comparing WBRT plus SRS vs. SRS alone for patients with limited (defined as < 4) brain metastases with a maximum diameter of 3 cm on contrast-enhanced MRI scan.[4] Patients with metastases from small cell carcinoma, lymphoma, germinoma and multiple myeloma were excluded. Eligible patients had a KPS score of 70 or higher. The WBRT dosage schedule was 30 Gy in 10 fractions over 2–2.5 weeks. Metastases with a maximum diameter of up to 2 cm were treated with SRS doses of 22–25 Gy and those larger than 2 cm were treated with doses of 18–20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT. Local tumor progression was defined as a radiographic increase of 25% or more in the size of a metastatic lesion. The primary end point of the study was overall survival. Secondary end points were cause of death, functional preservation, brain tumor recurrence, salvage treatment and toxic effects of radiation. One hundred thirty-two patients were randomized (65 to WBRT + SRS and 67 to SRS alone). The interim analysis was performed with 122 patients (approximately 60 in each group). The Japanese Radiation Oncology Study Group 99-1 trial[4] reported an actuarial one-year local tumor control rate of 88.7% in the WBRT + SRS group and 72.5% in the SRS-alone group (p = 0.002). The one-year actuarial rate of developing new brain metastases was 41.5% in the WBRT + SRS group and 63.7% in the SRS-alone group (p = 0.003). A prospective, single arm, multi-institutional Eastern Cooperative Oncology Group (ECOG) Phase II study of radiosurgery alone for "radioresistant" histologies (melanoma, sarcoma, renal cell carcinoma) in patients with one to three brain metastases has also been reported.[69] Inclusion criteria were one to three newly diagnosed brain metastases with a maximum diameter of 4 cm. In patients with multiple lesions and any lesion > 3 cm, all remaining lesions were required to be < 3 cm. Of 36 patients accrued, 31 were eligible and evaluable; 14 had melanoma, 14 had renal cell carcinoma and three had sarcoma. Three of thirty-one patients (10%) had partial response, 10 of 31 (32%) had stable disease, 14 of 31 (42%) had progressive disease, and 4 of 31 (14%) were not evaluable. At six months, 39.2% failed within the radiosurgery volume and 39.4% failed outside the radiosurgery volume. Several retrospective studies[21,94,113,117,128] compared local brain control rates of those patients receiving initial radiosurgery alone with those receiving whole-brain radiation therapy. Chidel et al.[21] found a statistically significant improvement in two-year brain control with the use of WBRT in addition to radiosurgery boost: 80% vs. 52% in patients treated with radiosurgery alone (p = 0.034). Pirzkall et al.[94] found one-year local control rates to be inferior with the radiosurgery alone group: 89% vs. 92% in the WBRT and radiosurgery boost group. Shehata et al.[113] reported that patients who had whole-brain radiation therapy had superior local tumor control rates (97%) compared with patients treated with radiosurgery alone (87%; p = 0.0001). Sneed et al.[117] reported a statistically significant improvement in one-year brain freedom from progression rate in those patients treated with WBRT + SRS boost (69%) compared with those patients treated with initial radiosurgery only (28%). It was commented that the one-year brain control rate allowing for salvage (using WBRT or serial SRS) at first failure was not statistically different between those treated with initial WBRT + SRS boost (73%) vs. those treated initially with SRS alone (62%). Wang et al.[128] found that the local brain control rate of patients treated with SRS alone was 93.3%, compared with 95.6% in patients treated with WBRT + SRS boost.

Survival

The Japanese trial[4] found no significant survival difference between the groups receiving WBRT + SRS and SRS alone. The median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone. In addition, no significant difference in the frequency of death due to neurologic causes was observed. Death was attributed to neurologic causes in 22.8% in the WBRT + SRS group and in 19.3% in the SRS alone group. In Chougule et al.'s abstract,[23] median survivals were seven, five and nine months for Gamma Knife® radiosurgery alone vs. WBRT and Gamma Knife® radiosurgery vs. WBRT, respectively. Survival was reported as not different among the three arms. The ECOG 12 Phase II trial[69] of radiosurgery alone for radioresistant histologies found median survival to be 8.2 months (95% CI, 7.4–12.2 months) in its cohort of patients. Lutterbach performed a prospective study[66] using radiosurgery alone for the initial management of brain metastases. However, no survival comparisons were made with patients treated with WBRT. Several retrospective studies have reported on the use of radiosurgery alone as initial management of selected patients with brain metastases.[15,21,39,49,53,105,109,113,115,117,118,124,128] Survival outcomes ranged from 8–15 months. Chidel et al.[21] reported the median survival of patients treated with radiosurgery alone as 10.5 months compared with 6.4 months in patients treated with radiosurgery boost and whole-brain radiation therapy (p value not stated). Sneed et al.[117] reported that the median survival of patients treated initially with radiosurgery alone was 11.3 months, which was not statistically different from the survival of patients treated with WBRT + SRS boost (11.1 months). Wang et al.[128] reported a median survival of 15 months in patients treated with SRS alone vs. 20 months in patients treated with WBRT + SRS boost vs. 8.5 months for patients treated with WBRT alone. Pirzkall et al.[94] found no difference in overall survival for patients treated with radiosurgery alone or radiosurgery and WBRT; however, in the subset of patients without extracranial disease, omitting whole-brain radiation therapy resulted in a survival decrement from 15.4 to 8.3 months. Sneed et al.[118] collected data from 10 institutions to compare the survival probabilities of patients with newly diagnosed brain metastases managed initially with SRS alone vs. SRS and WBRT. Of the 569 evaluable patients, 268 had radiosurgery alone initially (24% of these ultimately needed salvage WBRT) and 301 had radiosurgery and up-front WBRT. The median survival times for patients treated with SRS initially vs. SRS + WBRT were 14.0 vs. 15.2 months for RPA Class 1, 8.2 vs. 7.0 months for Class II, and 5.3 vs. 5.5 months for Class III. With adjustment by RPA class, there was no survival difference comparing radiosurgery alone initially with radiosurgery and up-front whole-brain radiation therapy. There is Level I evidence from the recently published Japanese trial[4] and Level II-3 evidence from literature that addition of up-front WBRT does not improve survival in patients treated with up-front radiosurgery. Thus patients with newly diagnosed brain metastases can be treated with up-front SRS alone, reserving WBRT for salvage."

Role of SRS for Multiple Brain Metastases

Stereotactic radiosurgery is an effective treatment for patients with multiple brain metastases. A substantial amount of published literature now supports use of radiosurgery in the treatment of multiple brain metastases. Stereotactic radiosurgery offers a very high control rate with a low risk of serious side effects. The RTOG 95-08 study authors concluded that addition of stereotactic radiosurgery to WBRT improved functional autonomy for all patients; therefore WBRT and stereotactic radiosurgery should be considered for patients with two or three brain metastases. For patients with good performance status up to three brain metastases, SRS with or without the addition to WBRT is reasonable."

Indications for Radiosurgery

- Newly diagnosed single or multiple brain metastases without significant mass effect documented on imaging
- Boost after WBRT for single or multiple brain metastases
- Recurrent brain metastases after WBRT
- Radiosurgery for residual tumor after resection

KQ3:

"Clinical Algorithm

Several factors are considered in making a recommendation. These factors include:

1. Patient's age
2. Patient's symptoms
3. Status of systemic disease
4. Patient's current neurological status
5. Patient's medical condition
6. Presence or absence of other organ metastases
7. History of prior WBRT
8. History of prior brain procedures
9. Patient's concern and risk tolerance for neuro-cognitive functions
10. Patient's wishes

Tumor Size
Radiosurgery can be performed for tumors up to 4 cm in maximum diameter. However, tumor volume, dose and location are more important variables.

Patient Preference
Patients' preferences are also considered in selecting a management approach. A broad outline of brain metastases diagnostic work-up and management algorithms for single tumor, limited brain disease (2–4 tumors) and multiple metastases are shown. However, the final recommendation is usually influenced by the recommending surgeon's, radiation oncologist's and neuro-oncologist's experiences along with patient preference.

Conclusion
There is Level I to Level II-3 evidence that addition of WBRT in patients treated with radiosurgery for 1–3 newly diagnosed brain metastases does not improve survival, compared with radiosurgery alone with WBRT reserved for salvage therapy. There is Level I evidence that omission of WBRT results in decreased tumor control, both at the site of radiosurgery and also in the remaining untreated brain. Level II-1 and Level II-3 evidence further support this observation"

Meningiomas: This information is from an on-line journal (Brain Talk, Volume 6, Number 2).
References are stated below each paragraph

KQ1 and KQ2:

MENINGIOMALONG-TERM OUTCOMES AFTER RADIOSURGERY...
In an effort to determine long-term outcomes of radiosurgery for meningioma, researchers at the University of Pittsburgh followed 99 patients for 5-10 years after radiosurgery Ninety-three percent of the tumors were controlled by radiosurgery. Sixty-three percent of the tumors became smaller, the size of 32% did not change and 5% were enlarged. Three to thirty-one months after radiosurgery, neurological deficits developed in 5% of patients. Fourteen percent of patients reported at least one complication which resolved in nearly half (44%) of these cases. Ninety-six percent of patients completing an outcomes questionnaire 5-10 years after radiosurgery believed it was successful. The authors concluded that long-term tumor control, preservation of neurological function and patient satisfaction were afforded by radiosurgery.
– from the Journal of Neurosurgery 1999;91(1):44-50.

RADIOSURGERYFOR MALIGNANT MENINGIOMA...
Twenty-two patients with malignant meningioma were treated with Gamma Knife® radiosurgery. The five-year survival estimate was 40% and the five-year progression-free survival estimate was 26%. Patient age and tumor volume were significant predictors of time to progression and survival. Twenty-three percent of patients developed radiation necrosis. Complications, treatment variables and patient characteristics were unrelated. Greater tumor control after Gamma Knife® radiosurgery was observed in younger patients and in those with

smaller tumors. The authors concluded that malignant meningiomas may be treated with Gamma Knife® radiosurgery with acceptable toxicity, and recommended that the relative efficacies of recurrent malignant meningioma therapies be further evaluated.
– *from the Journal of Neurosurgery 2000;93(Suppl.3):62-67.*

CAVERNOUS SINUS MENINGIOMAS AND RADIOSURGERY...
The functional tolerance and tumor control rate of benign cavernous sinus meningiomas treated with Gamma Knife® radiosurgery was evaluated in 80 patients. After radiosurgery, the tumor stabilized in 51 patients, shrank in 25 patients and enlarged in four patients. The five-year progression-free survival was 92.8%. New oculomotor deficits were not observed. Fifty-four patients had existing oculomotor nerve deficits; of these, 15 improved, eight recovered, and one worsened. Thirteen patients had trigeminal neuralgia; of these, four improved, five were unchanged, three recovered and one worsened (coincident with tumor growth). The authors concluded that Gamma Knife® radiosurgery was an effective tool for the low-morbidity treatment of cavernous sinus meningioma. Oculomotor function was restored in a significant number of patients. The authors suggested that Gamma Knife® radiosurgery was an alternative to surgical removal of confined enclosed cavernous sinus meningiomas.
– *from the Journal of Neurosurgery 2000;93(Suppl.3):68-73.*

MENINGIOMAS, RADIOSURGERYAND EARLY COMPLICATIONS...
Complications arising within one year of Gamma Knife® radiosurgery for intracranial meningiomas were assessed in 77 patients. Gamma Knife® radiosurgery followed surgery in 49 patients and was the primary therapy in 28 patients. Fifty patients had basal meningiomas and 27 had non-basal meningiomas. The most common sites were the cerebellopontine angle (14 patients) and parasagittal (23 patients). Five patients experienced seizures and four had increased headaches. Two patients with parasagittal tumors experienced a temporary worsening of hemiparesis. Perilesional edema was observed in nine patients and was symptomatic in six. Six (22%) of the 27 patients with non-basal tumors had edema (all parasagittal); four patients were symptomatic. Three (6%) of the 50 patients with basal meningiomas had edema, and only one patient was symptomatic. Occurrence of edema was not related to radiation received by adjacent brain or tumor volume, margin or maximum dose. Tumor size was reduced in seven patients. The authors concluded that although Gamma Knife® radiosurgery provides good results for selected patients with meningiomas, patients with parasagittal tumors should be treated with caution because of the high incidence of perilesional edema.
– *from the Journal of Neurosurgery 2000;93(Suppl.3):57-61.*

KQ3 and KQ4
Radiosurgery is considered a standard of care in the treatment of Meningiomas. SRS treats far less normal brain tissue than EBRT which is significant in reducing the long-term side effects in all age groups. These are generally benign tumors and the life expectancy of patients treated is usually not related to this condition. As a result, chronic toxicity from EBRT can present as a life long struggle.

SRS thalamotomy for tremor (Essential and Parkinsons). This information is from an on-line journal (Another Perspective, Volume 4, Number 4) **which was submitted by one of our Neurosurgeons, Dr Ronald Young**

KQ1 and KQ2;
Both radiofrequency and radiosurgical thalamotomy can be expected to relieve tremor in about 85% of patients. In some patients, the tremor is markedly suppressed but not totally relieved and in other patients, the tremor is completely relieved. Examples of a patient's handwriting before and after a thalamotomy was performed with the Gamma Knife® are shown in figures one and two. Virtually all of the treatment of movement disorders using radiosurgery has been with the Gamma Knife®. There is little or no experience in using the other forms of radiosurgery, that is, the linear accelerator or heavy particle beam radiosurgery, to make such lesions for treatment of movement disorders. Therefore, results achieved with Gamma Knife® may not be indicative of results

achieved with other types of radiosurgical equipment. The Gamma Knife® is designed to perform this type of treatment. We have performed more than 200 thalamotomies for the relief of tremor over a period of more than eight years. Only two relatively mild side effects have been seen in these 200 patients. Both involve mild weakness or coordination difficulty in the side of the body opposite to the thalamotomy. No other complications of any kind have been seen in any of the other patients. For radiofrequency thalamotomy, the complication rate has been variously estimated from as low as five percent to as high as 20% or 25%. These complications can include paralysis, loss of feeling, difficulties with speech and, in a rare case, severe hemorrhage requiring a major operation (craniotomy) to remove a large blood clot within the brain or on the surface of the brain. It is our belief that radiosurgical thalamotomy with the Gamma Knife® offers the safest method for treatment of tremor. Figure 3 shows a lesion created in the thalamus by radiosurgical thalamotomy.

KQ3 and KQ4

By the end of 1998, it had been reported that 814 patients had received Gamma Knife® treatment for Parkinson's disease at all Gamma Knife® centers throughout the world, and a significant number of additional patients had received treatment for essential tremor and other forms of tremor. The interest in using radiosurgery to treat movement disorders is increasing. It is attractive to patients and their families because of its effectiveness and safety. Many radiosurgical centers perform the procedures on an outpatient basis and, at maximum, an overnight stay is required. Patients are able to return to normal activities immediately without the recovery period generally required after an open skull procedure, such as a radiofrequency thalamotomy or deep brain stimulator implantation.

This procedure is not performed with EBRT.

Dr. Deane B. Jacques is a practicing neurosurgeon at Good Samaritan Hospital in Los Angeles, California. He can be reached at +213-977-2920. Dr. Ronald F. Young is a practicing neurosurgeon at both Good Samaritan Hospital in Los Angeles, California, and Swedish Hospital in Seattle, Washington. He can be reached in Los Angeles at +213-977-2920 and in Seattle at +206-320-7130.

Gliomas

KQ1, KQ2, KQ3 and KQ4

Stereotactic Radiosurgery Prolongs Survival

GLIOBLASTOMA MULTIFORME...

Researchers at the University of Maryland examined the results of treating 64 glioblastoma multiforme patients with either external beam radiotherapy (EBRT) alone or EBRT followed by Gamma Knife® radiosurgery. Forty-five and 19 patients had previously undergone craniotomies and stereotactic localization needle biopsies, respectively. Subsequently, 33 patients were treated with EBRT alone, while 31 patients were treated with EBRT and Gamma Knife® within four weeks of EBRT. External beam radiotherapy was delivered in a three-dimensional conformal manner. Median survival for the group with EBRT alone was 13 months from the time of diagnosis, while median survival for the group that received EBRT and a Gamma Knife® boost was 25 months from the time of diagnosis.

- *from Neurosurgery 2002;50(1):41-47.*

ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA MULTIFORME...

During an 8 year period, University of Pittsburgh researchers studied the effect of stereotactic radiosurgery with the Gamma Knife on the survival of patients with anaplastic astrocytoma or glioblastoma multiforme. Tumor diagnosis was obtained either through craniotomy or stereotactic biopsy. Sixty-four glioblastoma multiforme patients and 43 anaplastic astrocytoma patients were included in the study. Two year survival time for glioblastoma multiforme patients was 51%, and for anaplastic astrocytoma patients was 67%. The authors concluded that compared to historical controls, radiosurgery provided an improved survival benefit for glioblastoma multiforme and anaplastic astrocytoma patients. Radiosurgery was and is well tolerated with no

acute neurological complications after treatment. Further studies with radiosurgery as an adjunct treatment are warranted.

- *from Neurosurgery 1997;41(4):776-785.*

I hope this information will help in your review. Please let me know if I can be of further assistance.

Sandra Vermeulen, MD
Executive Director, Swedish Radiosurgery Center
Swedish Hospital/Cherry Hill
Seattle, Washington

Phone: 206-320-7130

From: Zemanek, Julie
To: HCA ST Health Tech Assessment Prog
Cc: Willis, Brett; "James.Dingels@swedish.org"
Subject: HTA Program Response
Date: Monday, March 05, 2012 2:56:14 PM
Attachments: 2012 0305 DGM RDS Letter to State.docx
120304 Vermeulen Letter to the State CNS Tumors 2-29-12.doc
2012 03 MPH Supporting Doc IMRT.docx

Thank you for allowing Tacoma/Valley Radiation Oncology Centers the opportunity to provide responses to Key Questions, which are attached.

Should you have any questions, please feel free to contact me.

Julie J. Zemanek | Practice Manager
253.627.6172 (main) | 253.779.6328 (direct) | 253.627.5967 (fax)
Jackson Hall Medical Center

March 5, 2012

Mr. Josh Morse, MPH, Program Director
Health Technology Assessment Program Board & Staff
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712

Dear Mr. Morse, Members of the Board and Staff:

I am writing this letter as part of a public response to the state regarding the healthcare technology program (HTA) policies that are currently being drafted.

I am a radiation oncologist who is in a large multicenter practice that covers most of the south sound. We are free standing and independent cancer centers. We are very familiar with the technologies of Intensity Modulated Radiation Therapy (IMRT), stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) that the healthcare technology program is now looking at. I can speak from a position of complete familiarity with these treatment modalities.

These technologies are currently available in many places in the State of Washington and are quickly becoming standard of care for many treatment sites throughout the nation. As clearly stated in the summary, these technologies are more expensive than conventional radiation. The trade off, however, is very significant when it comes to not only improvements in outcomes but they are vastly superior in reduction in side effects and toxicity. We are also able to treat specific tumor locations that we never were able to accomplish in the past with minimal morbidity and harm to the patient. There is no question that radiation can be extremely harmful to living tissue. My 20+ year career can certainly attest to that. When I explain these new modalities to patients, one of the very first comments I make is that I wish I'd had these technologies available to me during the early days of my career. The number of patients treated with significant radiation morbidity, both short term and long term, in the form of bowel damage, bladder damage, lung damage, soft and bony structure damage as well as even brain damage, could have been reduced and outright avoided if I'd had these technologies available in the past. These newer modalities allow us to target tissues at risk and greatly reduce surrounding tissues that do not need to be radiated. Not only do these technologies allow us to target the cancer and spare the surrounding normal tissue, but they allow us to give

even higher doses of radiation to the cancer, thus improving outcomes. Nowhere has this become more evident than in treatment of cancer of the prostate. The concept of increasing the dose of radiation (known as dose escalation) to prostate cancer has been verified in numerous clinical trials. In the past we were unable to deliver high doses of radiation to the prostate because the organ is "sandwiched" between the bowel and the bladder.

The use of IMRT actually allows us to bend the radiation around these crucial structures, therefore allowing us not only to spare these normal tissues but allowing us to give more radiation to the prostate, thus improving the outcomes in the long term and ultimately curing the patient of his cancer. IMRT has become standard of care for most tumor sites.

I sit down on a day to day basis and explain the treatment course to a patient which is often combined with very extensive chemotherapy. I am now able, with confidence, to say to patients that they will make it through treatment with greatly minimized side effects that we have seen in the past. Above all, as stated in the Hippocratic Oath, is to "do no harm." All cancer therapy walks a fine line between trying to eradicate the patient's malignancy without destroying normal tissue. IMRT and other related technologies have allowed us to increase the "therapeutic window" to accomplish that goal, increasing radiation and decreasing side effects. Until the so-called "Magic Bullet" is invented for cancer therapy, this is one of the most significant breakthroughs in radiation therapy in the 20th century. To simply say that we can treat cancers using standard therapy brings us back to the 1980s, a time when we only dreamed about having the ability to eradicate tumors without eradicating the patient in the process.

Stereotactic body (SBRT) and stereotactic radiosurgery (SRS) are again technologies that allow us with pin-point accuracy to deliver very toxic doses of radiation therapy to cancers and eliminate surrounding tissue. One only needs to see a patient who is trying to live with radiation damage of the brain from old conventional treatments to realize the significance of these new technologies. We are now able to treat patients non-surgically for aneurysms, tremors, brain metastases and even gliomas. Patients are alive and function today because of these technologies. They certainly can be treated by more conventional means but the price is higher in side effects and long-term complications. I have seen patients harmed by conventional radiation to a much greater extent.

I have another patient whom I am currently treating as I write this letter. She is not a surgical candidate. She has a large metastasis to her liver. She is unable to go through a big procedure. There is no other means of treating this metastasis. Her options are either to fight her disease or simply let nature take its course. If faced with that situation, I would do the same thing and fight for my survival. IMRT and stereotactic body radiosurgery offer the chance of fighting cancer. I cannot pass judgment on whether or not these treatments are useful unless faced with that same situation.

It is very difficult from this letter or from reading the literature to pass judgment on any of this unless you come in and experience it for yourself.

I welcome anyone involved in reviewing this information to please visit our center. I would be more than happy to sit down for as long as needed to explain the differences between conventional radiation therapy and modern technologies of Intensity Modulated Radiation Therapy and the others listed above. I can show you examples and even have you talk to patients. We can search the literature together and find you examples of their utility. I would be more than happy to sit on any review committee and assist anyone in the field currently, gathering data and researching the information. I am available any time you should require.

Our free-standing cancer center's goal is to give the best possible treatment to our patients. Our mission statement is precisely that. Utilizing these technologies allows us to accomplish that mission statement. There is no question that these modern technologies are expensive. As a free-standing center, we can keep our costs to a minimum.

Sincerely,

Dean G. Mastras, MD

Randy D. Sorum, MD

President

Intensity Modulated Radiation Therapy (IMRT)

On behalf of clinicians at Tacoma/Valley Radiation Oncology Centers we write to answer the key questions as part of the Washington State Health Care Authority, HTA Program, Intensity Modulated Radiation Therapy (IMRT) Health Technology Assessment. We are users of several forms of radiation therapy including GammaKnife, conventional "3D" radiation therapy, as well as multiple platforms that deliver IMRT.

Approximately 10 years ago, the most advanced technology for the delivery of radiation was 3D-conformal radiation. This is an improvement over previous 2D radiation in that the patient is imaged on a CT scanner and the contour of the skin, tumor, and normal structures can be entered into a planning computer. One can then develop a "3D" plan by selecting beam angles and creating beam shapes that best conformed to the target and the computer can calculate doses to particular structures. 3D conformal radiation is utilized today still in the majority of fairly straightforward cases However over this past decade, Intensity Modulated Radiation Therapy (IMRT) has been developed, refined, clinically tested and utilized in many of the more complex radiation cases.

With IMRT non-uniform intensities are assigned to tiny subdivisions of beams, called "beamlets," enabling custom dosing of optimum dose distributions. For example, if a normal structure overlaps the planning target volume (PTV), one would ideally like to reduce the intensity of those radiation rays that pass through the normal structure. However, using this strategy the target volume would have a "cold spot" of decreased intensity in the shadow of the normal structure. To compensate for this shadow, the intensities of other rays in other beams would need to be increased. While conventional radiation therapy uses wedges and compensators to provide intensity modulation, the unique aspect of IMRT involves the use of a computer-aided optimization process to determine the non-uniform intensity distributions to attain certain specified clinical objectives. Using IMRT, the target volume can be treated with different fraction (i.e. daily dose) sizes simultaneously. This contrasts with conventional radiation therapy, in which the same fraction size is used for all target volumes, but the field sizes are reduced in stages over critical regions in order to protect critical normal structures.

One key aspect of IMRT is inverse planning. It would be impossible for a human to create an optimized IMRT radiation plan. There are too many variables at play and the effect of modulating one beam can alter the requirement of other beams in complex manners. The computer iteratively creates hundreds of thousands of radiation plans, constantly optimizing and refining the shape of the beams, until finding the optimal solution. The term 'inverse planning' comes from the fact that instead of creating and placing a beam to deliver a particular dose to a tumor, we first define the tumor and other organs or avoidance structures, and then instruct the computer to work backwards and find the best radiation plan.

Because of this increased complexity in IMRT planning, very elaborate verification and quality assurance measures are necessary. There are strict guidelines that are published by the American College of Radiology (ACR) and American Society of Therapeutic Radiation Oncology (ASTRO) for the implementation and quality assurance of IMRT. The details of this are beyond the scope of this letter, but the complexity in the safe delivery of IMRT is daunting and is a labor intensive task for the physician, physicist, dosimetrist, and radiation therapists.

As technology has developed, linear accelerators have been improved and modified to deliver IMRT. In your statement, TomoTherapy was specifically mentioned. TomoTherapy is a particular linear accelerator made by one vendor that was built from the ground-up to deliver IMRT in a highly conformal manner using entire arcs of treatment instead of fixed beam angles. Other venders have subsequently developed arc-therapy as well, including Varian's RapidArc and Eleckta's VMAT (Volumetric Arc-

Therapy). However delivered, the goals of IMRT are essentially the same, and this letter would be applicable to all the specific vendors or modalities for delivery of IMRT.

IMRT can benefit the patient in three ways. First, by improving conformity with target dose it can reduce the probability of in-field recurrence. Second, by reducing irradiation of normal tissue it can minimize the degree of morbidity associated with treatment. Third, with these techniques the ultimate radiation dose can often be escalated well beyond previous constraints which has in many studies shown increased local control. Whereas there are multiple randomized and nonrandomized trials showing benefits to IMRT, to our knowledge there is no trial that has shown worse outcome with IMRT.

Although the initial goal of the key questions was to be limited to comparison of IMRT to 3-D radiation, in the larger context both IMRT and stereotactic radiation therapy represents a much larger advance. Improved outcomes with these highly conformal forms of radiation is allowing for safe alternatives to costly surgery or chemotherapy in many cases. As the general trend in medicine continues towards minimally-invasive outpatient medical treatment, we expect radiation therapy to continue to be an increasing part of that trend allowing safe and effective cancer treatment.

Key questions

KQ1: What is the evidence of effectiveness for intensity modulated radiation therapy (IMRT) compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?

The following table shows superior clinical results by indication of IMRT compared to conventional EBRT. Please note that this list is in no way a full representation of the clinical literature or indication types that IMRT can treat.

Indication	Clinical Outcomes	Source
Brain	• IMRT maintained equivalent target coverage, improved target conformity and enabled dose reductions of normal tissues, including brainstem (D_{mean} by 19.8% and D_{max} by 10.7%), optic chiasm (D_{mean} by 40.6% and D_{max} by 36.7%), $p \leq 0.01$. • Results indicate that IMRT for high-grade gliomas allows for improved target conformity, better critical tissue sparing, and importantly does so without increasing integral dose and the volume of normal tissue exposed to low doses of radiation.	Hermanto U, Frija EK, Lii MJ, et al. Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade gliomas: Does IMRT increase the integral dose to normal brain? Int J Rad Onc Biol Phys 2007;67(4):1135-1144.
Spine	• IMRT TomoTherapy achieved highest mean dose homogeneity index (DHI) of 0.96, 0.91 for conventional IMRT, and 0.84 for 3DCRT. • IMRT TomoTherapy was superior in reducing maximum, mean and integral doses to almost all organs at risk (OARs) • Conclusion: IMRT TomoTherapy for craniospinal irradiation (CSI) is technically easier and potentially dosimetrically favorable compared with conventional IMRT and 3DCRT	Sharma DS, Gupta T, Jalali R, et al. High-precision radiotherapy for craniospinal irradiation: evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical TomoTherapy. Brit J Radiol 2009;82:1000-1009.
Head/neck	• IMRT was associated with statistically significant improvements in certain QoL domains versus 3DCRT, particularly those relating to xerostomia, including dry mouth, sticky saliva and eating-related domains.	Tribius S, Bergelt C. Intensity-modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: is there a worthwhile quality of life gain? Cancer Treat Rev 2011;37(7):511-519.

Indication	Clinical Outcomes	Source
Head/Neck (cont)	• At 12 months, grade 2 or worse xerostomia side-effects were significantly lower in the IMRT group than in the conventional radiotherapy group (74% vs. 38%) • At 24 months, grade 2 or worse xerostomia side-effects were significantly lower in the IMRT group than in the conventional radiotherapy group (83% vs. 29%) • At 12 and 24 months, significant benefits were seen in recovery of saliva secretion in dry-mouth-specific and global quality of life scores…supports role of IMRT in squamous-cell carcinoma of the head and neck	Nutting CM, Morden JP, Harrington JK, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck (PARSPORT): a phase 3 multicentre randomized controlled trial. Lancet Oncol 2011;12(2):127-136.
	• IMRT is associated with lower incidence of late xerostomia and improved quality of life for domains related to late xerostomia. For other adverse effects, difference and risks may exist, but there is insufficient evidence from which to permit conclusions about comparative effects. The evidence is insufficient to determine if IMRT confers advantage in overall survival	John M. Eisenberg Center for Clinical Decisions and Communications Science. Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer. 2010 Nov 30. Comparative Effectiveness Review Summary Guides for Clinicians. Rockville MD: Agency for Healthcare Research and Quality (US); 2007 http://www.ncbi.nlm.gov/books/NBK50593.
Lymphoma	• Mean lung dose was reduced using IMRT by 14% compared with 3D-CRT. • Conclusion: IMRT provides improved planning target volume coverage and reduces pulmonary toxicity parameters compared to 3DCRT. It is feasible for radiation therapy of large treatment volumes and allows repeat radiation therapy of relapsed disease without exceeding cord tolerance.	Good man KA, Toner S, Hunt M, et al. Intensity-modulated radiotherapy for lymphoma involving the mediastinum. Int J Rad Onc Biol Phys 2005;62(1):198-206.

Indication	Clinical Outcomes	Source
Breast	• IMRT resulted in an improved conformity of dose distribution to the target volume compared to conventional RT • In all IMRT cases with matching adjacent beams, the homogeneity in the target volume was improved • Volume of ipsilateral lung irradiated with a dose higher than 20 Gy was reduced with IMRT from 24.6% to 13.1% compared to conventional RT • For left-sided target volume, the heart volume with a dose higher than 30 Gy was reduced from 6.2% to 0.2% • Conclusion: Presented plan comparison study for irradiation of the breast and the parasternal lymph nodes showed a substantial improvement of the dose distribution by inversely planned IMRT compared to conventional RT	Thilmann C, Sroka-Perez G, Krempien R, et al. Inversely planned intensity modulated radiotherapy of the breast including the internal mammary chain: a plan comparison study. Technol Cancer Res Treat 2004;3(1):69-75.
	• Compared to 3DCRT, IMRT had a 36% and 57% reduction at the 4 and 8-cm contralateral positions • Conclusion: Primary breast irradiation with tangential IMRT technique significantly reduces the dose to the contralateral breast compared to conventional tangential field techniques.	Bhatnagar AK, Brander E, Sonnik D, et al. Intensity modulated radiation therapy (IMRT) reduces the dose to the contralateral breast when compared to conventional tangential fields for primary breast irradiation. Breast Cancer Res Treat 2006;96(1):41-46.
	• A significant reduction in acute Grade 2 or worse dermatitis, edema, and hyperpigmentation was seen with IMRT compared with conventional RT. • Reduced acute Grade 3 or greater dermatitis (6% vs. 1%, p = 0.09) in favor of IMRT. • Chronic Grade 2 or worse breast edema was significantly reduced with IMRT compared with conventional RT. • In patients with larger breasts (> or =1,600 cm(3), n = 64), IMRT resulted in reduced acute (Grade 2 or greater) breast edema (0% vs. 36%, p <0.001) and hyperpigmentation (3% vs. 41%, p = 0.001) and chronic (Grade 2 or greater) long-term edema (3% vs. 30%, p = 0.007) compared to conventional RT.	Harsolia A, Kestin L, Grills I, et al. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. Int J Radiat Oncol Biol Phys 2007;68(5):1375-1380.
	• 245 breasts were treated in 240 patients: 121 with IMRT and 124 with conventional RT. • Treatment with IMRT decreased acute skin toxicity of RTOG Grade 2 or 3 compared with conventional RT (39% vs. 52%; p = 0.047). • For patients with Stages I-III (n = 199), 7-year Kaplan-Meier freedom from ipsilateral breast tumor recurrence (IBTR) rates were 95% for IMRT and 90% for conventional RT (p = 0.36). • For patients with Stage 0 (ductal carcinoma in situ, n = 46), 7-year freedom from IBTR rates were 92% for IMRT and 81% for conventional RT (p = 0.29). • Conclusion: Patients treated with breast IMRT had decreased acute skin toxicity, and long-term follow-up shows excellent local control	McDonald MW, Godette KD, Butker EK, et al. Long-term outcomes of IMRT for breast-cancer: a single-institution cohort analysis. Int J Radiat Oncol Biol Phys 2008;72(4):1031-1040.

Pancreas	• Compared to conventional RT, IMRT reduced the man dose to the liver, kidneys, stomach and small bowel • IMRT was well tolerated, with 80% experiencing Grade 2 or less acute upper GI toxicity • At a median follow-up of 10.2 months, no resected patients had local failure, and only 1 of the 10 assessable patients unresectable cancer had local progression • Median survival and distant metastasis-free survival was 13.4 months and 7.3 months, respectively	Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2004;59(2);445-453.
	• Both helical IMRT and conventional IMRT offer a statistically significant improvement over 3D-CRT in lower dose to the liver, stomach and bowel • Conclusion: Helical IMRT offers improved dose homogeneity over conventional IMRT and several significant benefits to 3D-CRT	Poppe MM, Narra V, Yue NJ, et al. A comparison of helical intensity-modulated radiotherapy, intensity-modulated radiotherapy, and 3D-conformal radiation therapy for pancreatic cancer. Med Dosim 2011;36(4):351-357.
Prostate	• Planning data shows the ability of helical TomoTherapy (HT) in creating highly homogenous dose distributions within the PTVs • Organs at risk (OAR) sparing also showed to be excellent • HT was found to favorably compared to inversely-optimized IMRT in terms of PTVs coverage and dose distribution homogeneity • In the case of pelvic nodes irradiation, a large sparing of bowel was evidenced by HT compared to 3DCRT and conventional IMRT	Fiorino C, Alongi F, et al. Physics aspects of prostate tomotherapy: planning optimization and image-guidance issues. Acta Oncol 2008;47(7)1309-1316.
	• Conformity index (CI) of helical tomotherapy (HT) (0.77, SD = 0.54) plans tended to be better (p = 0.069) compared to conventional sliding window IMRT (SWIMRT) (0.70, SD = 0.01) for prostate PTV. • Helical tomotherapy plans were more homogeneous, with homogeneity index (HI) of 0.04 compared to 0.06 in SWIMRT (p = 0.018) for PTV prostate and HI of 0.06 and 0.15 (p = 0.025) for PTV nodes respectively. • Median dose to bladder (p = 0.025) and rectum (p = 0.012) were less with HT. • Femoral heads were better spared with HT plans (p = 0.012). • Conclusion: HT improves dose homogeneity, target coverage and conformity as compared to SWIMRT, with overall improvement in critical organ sparing.	Murthy V, Mallik S, Master Z, et al. Does helical tomotherapy improve dose conformity and normal tissue sparing compared to conventional IMRT? A dosimetric comparison in high risk prostate cancer. Technol Cancer Res Treat 2011;10(2):179-185.
	• IMRT plan was found to significantly reduce the normal tissue complication probability (NTCP) for the rectum while achieving a small gain in the tumor control probability (TCP) compared to 3D conformal	Pradip D, Fielding AL. Radiobiological model comparison of 3D conformal radiotherapy and IMRT plans for the treatment of prostate. Aust Phys Engin Sci Med 2009;32(2):51-61.
	• Use of IMRT significantly reduced the risk of gastrointestinal (GI) toxicities compared with patients treated with conventional 3D-CRT (13% to 5%; p<0.001). • Risk of proctitis was significantly reduced with IMRT compared to conventional 3D-CRT	Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70(4):1124-1129.

Prostate (continued)	• 5-year biochemical control rate was 60.4% for 3D-CRT and 74.1% for IMRT (p < 0.0001, first ASTRO Consensus definition) • Using the ASTRO Phoenix definition, the 5-year biochemical control rate was 74.4% and 84.6% with 3D-RT and IMRT, respectively (p = 0.0326) • Conclusion: IMRT allowed delivery of higher doses of radiation with very low toxicity, resulting in improved biochemical control	Vora SA, Wong WW, Schild SE, et al. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2007;68(4):1053-1058.
	• Decision analysis showed cost-effectiveness of IMRT in treatment of intermediate risk prostate cancer, although at the upper limits of acceptability	Konski A, Watkins-Bruner D, Pollack A, et al. Using decision analysis to determine cost effectiveness of IMRT in the treatment of intermediate risk prostate cancer. Int. J Radiat Oncol Biol Phys 2006 Oct; 66(2): 408-15.
Prostate (continued)	• IMRT is associated with lower incidence of GI side effects vs 3D conformal radiation and improved quality of life.	Lips I, Dehnad H, Kruger AB, et al. Health-related quality of life in pateitns with locally advanced prostate cancer after 76 Gy intensity-modulated radiotherapy vs 70 Gy conformal radiotherapy in a prospective longitudinal study. Int J. Radiat Oncol Biol Phys 2007 Nov 1; 69(3): 656-61.
Anal Cancer	• IMRT potentially confers an advantage via improved tumor control through dose escalation. Dose escalation studies with 3D conformal radiation have demonstrated improved local control, but high rates of toxicity necessitated treatment breaks, potentially compromising treatment delivery and efficacy. • IMRT is associated with lower incidence of gastrointestinal, dermatologic, and genitourinary side effects vs 3-D conformal radiation based on phase II single institution studies (ref 1-3). • There is an ongoing RTOG protocol RTOG 0529 "A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0529). The previous study RTOG 98-11 supported higher doses in treatment of anal cancer, however significant toxicity was observed.	Chen YJ, Liu, A, Tsai PT, et al. Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: Dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. Int J Radiat Oncol Biol Phys 2005; 63(1), pg 274-281. Milano, MT, Jani, AB et al. IMRT in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2005; 63(2):354-361 Tsai, HD, Hong, TS, et al. Dosimetric Comparison of Dose-painted IMRT vs Conventional Radiation Therapy for Anal Cancer. Poster presentation at ASCO-GI symposium, San Francisco, CA January 28 2006.

KQ2: 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.

As previously noted, the 2007 CTAF report and the clinical literature results clearly documents that IMRT has improved clinical outcomes compared to conventional EBRT. The CTAF report indicated that when using IMRT, the target volume can be treated with different fraction sizes simultaneously. With conventional RT, the same fraction size is used for all target volumes. The main rationale, supported by the outcomes in the clinical literature, is that IMRT is better able to direct the radiation to the target volume for precisely, thus decreasing the amount of radiation to surrounding normal tissues and increasing the dose to the tumor target, thus reducing recurrence rates.

KQ3: 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
e. Setting, provider characteristics, equipment, quality assurance standards and procedures

IMRT can treat a wide variety of cancer indications that are medically appropriate across both genders, patients of all ages. IMRT is available to patients both in the hospital setting as well as in the freestanding setting; this allows rural patients as well as urban patients to have access to life saving IMRT treatment. Based on our clinical experience, which is supported by the clinical data, IMRT has equivalent and/or superior clinical results across several indications. In any radiation therapy treatment, it is required that the equipment is tested at appropriate time intervals to ensure patient safety and that staff are adequately trained to treat all patient types.

KQ4: What is the evidence of cost and cost-effectiveness of IMRT compared to EBRT?

There are a few true cost-effective analyses of IMRT compared to EBRT. Konski and Pollack et al at the Fox Chase Cancer Center used a Markov model to analyze prostate IMRT. They included treatment, post-treatment, hormone therapy, chemotherapy, and ultimately death in their models. They found the mean cost of IMRT was $47,931 with a survival of 6.27 quality adjusted life years (QALY's). The expected mean cost of 3D conformal radiation was $21,865 with a survival of 5.62 QALY's. The conclusion of this analysis was that IMRT was found to be cost effective, however at the upper limits of acceptability (Konski A, Watkins-Bruner D, Pollack A, et al. Using decision analysis to determine cost effectiveness of IMRT in the treatment of intermediate risk prostate cancer. Int. J Radiat Oncol Biol Phys 2006 Oct; 66(2): 408-15).

Of note, the same group investigated proton radiotherapy in comparison with IMRT and found proton therapy was not cost effective (Konski A, Speier W, Hanlon A, Beck JR, Pollack A. J Clin Oncol 2007 Aug 20;25(24) : 3603-8).

Additional studies are underway, but all are subject to the traditional biases of cost-effective analysis which include difficult in assigning costs in a changing environment, difficult in quantifying the 'transition probabilities' between various states due to the variability of published data, and constantly improving therapies for all disease states.

From our own experience at Tacoma/Valley Radiation Oncology Centers, we believe that IMRT, delivered in one of several platforms including TomoTherapy, Eleckta, or Varian, provide patients with the best treatment option to improve survival, decrease side effects and improve quality of life compared to conventional EBRT.

Our free-standing cancer center's goal is to give the best possible treatment to our patients. Our mission statement is precisely that. Utilizing these technologies allows us to accomplish that mission statement. There is no question that these modern technologies are expensive. As a free-standing center, we can keep our costs to a minimum.

From: Eric W. Taylor, MD
To: HCA ST Health Tech Assessment Prog
Cc: Eric W. Taylor, MD
Subject: Public Comment for: Intensity Modulated Radiation Therapy
Date: Sunday, February 26, 2012 3:07:42 PM

Thank you for the opportunity to comment on Intensity Modulated Radiation Therapy. This modality oftreatment delivery was approved by the FDA in 2001 and has been a game changer (improvement) bycomparison to prior techniques of radiation delivery. 3D conformal therapy which became common atthe end of the 90's was a significant improvement, but IMRT more so. Toward the latter part of the lastdecade, IGRT (image guided radiation therapy) with either kv/kv imaging or cone beam CT on thetreatment machine just prior to turning on the beams has improved accuracy remarkably. Therefore, either 3D conformal therapy with daily IGRT or IMRT/IGRT have become commonly used therapies forexcellent reasons.

The use of IMRT is appropriate for some brain tumors, most head and neck cancers, select lung cancers, many esophageal cancers, pancreatic malignancies, recurrent rectal cancers, some gynecologic cancers, anal canal cancer and many prostate cancers (either alone or with brachytherapy (seeds) for intermediate or high risk prostate cancers). This technology has allowed higher and more appropriate doses to be delivered to where the tumor is and much lower doses to the surrounding tissues. Therefore from a patient safety and toxicity standpoint this is far superior and with higher, better placed doses tumor control has improved. There are data supporting better tumor control coupled with less toxicity for both head and neck cancers and prostate cancer and some recurrent cancers. In the past, for patients with pelvic malignancies, longterm bowel complications were common. With current generation techniques, bowel obstructions that require subsequent surgical repair or other GU problems that require longterm management are much less frequent...a huge plus for the patient and also reducing longer term healthcare costs of managing complications of treatment. IMRT/IGRT for head and neck cancers has both improved tumor control, but with less longterm xerostomia and edema.

For brain tumors, we have the dosimetrists and physicists run plans both with 3D conformal beams and IMRT. If they are roughly equivalent, then we use 3D planned fields as the cost is less expensive. We only use IMRT if it is superior. Unfortunately, some places around the country over-utilize IMRT.

A relatively more recent improvement for IMRT is volumetric delivery or Rapid Arc (Varian). This greatly speeds up the treatment so that the patient is on the table, immobilized for a shorter period of time. For example, a patient with head and neck cancer is immobilized in a head and shoulder mask typically for about 20 minutes. Rapid Arc treats the same volume in a matter of a few minutes. The outcome is no different, but the patient experience is superior. There is also better through put on the machine allowing greater capacity, thus delaying the need for another linac purchase.

In your write-up you put protons in the same sentence with IMRT. I think these are VERY DIFFERENT modalities and COSTS. IMRT is appropriate and is the standard of care for the cancers that I mentioned above generally. Protons have shown NO superiority over current therapies other than some unusual childhood tumors, however the cost of the space and technology and delivery is much more EXPENSIVE. Wearing a public health hat, I am very concerned about the healthcare resources that will be spent on proton therapy for an extremely limited healthcare benefit. The payors have to critically look at this.
Two proton facilities are in the process of construction and planning for Seattle ($180 million/ UWNorthwest) and $35-60 million/ Swedish First Hill. I think those resources and future charges to pay for such facilities could be utilized differently to improve broader healthcare outcomes for a greater segment of the population. Using American Cancer Society data, the current likelihood of a man being around in 5 years with a new diagnosis of prostate cancer is 99% with current therapies. For proton facilities to pay for themselves a majority of patients will be those with prostate cancer...with the above noted statistics with current treatments available, how will protons possibly move the bar up and at a much greater cost?

Thank you for the opportunity to comment.

Respectfully submitted,

Eric Taylor, MD, FACR, FACRO
Evergreen Radiation Oncology
Evergreen Healthcare
Kirkland, Wa

Sent from my iPad

From Tumor Institute Radiation Oncology Group:

Stereotactic Radiosurgery (SRS), Stereotactic Body Radiation Therapy (SBRT) and Key Question 4 IMRT Reimbursement Information

Thank you for the opportunity to comment on questions regarding Intensity Modulated Radiation Therapy (IMRT), Stereotactic Radiosurgery (SRS), and Stereotactic Body Radiation Therapy (SBRT). We recognize that approximately half of all cancer patients receive some form of radiation therapy, and that radiation dose delivery techniques and practices have rapidly evolved over the last decade.

As experts in the field of Radiation Oncology, we embrace your concerns regarding safety, efficacy, and cost of contemporary radiation modalities. Technologies such as IMRT, SRS, and SBRT have broken new ground in their capability to control cancer and minimize side effects. Our goal is to help educate health providers and healthcare payers, as well as government, business, and other professionals as to the patients for whom use of these newer technologies can mean a world of difference in regard to cancer control and a decreased risk of treatment related side effects.

The utility of IMRT, SRS, and SBRT in many circumstances is very specifically dependent on a patient's cancer, their anatomy, the proximity of critical structures, and prior radiation dose delivered. The key aspects that all these modalities have in common is better dose distributions: escalated doses to tumors, lower doses (and lower resultant toxicity) to normal tissue. Using IMRT, SRS, and SBRT, it is now potentially feasible to deliver safe curative or safe palliative treatment to many patients where treatment was not even an option with conventional external beam radiation therapy. For example, in cases where tumors recur in a previously irradiated field, re-irradiation with IMRT, SRS, or SBRT may deliver a long term cure that was not previously possible. We realize that a circumstance such as this is not one in which a comparative trial could be conducted, for most of these patients simply would not be a candidate for treatment with a conventional external beam radiation therapy approach.

We believe that it is imperative to be able to offer these treatments to patients in an expedient time frame when indicated. We remain readily available and encourage an open dialogue on these topics. We have tried our best given the short comment period to address your questions regard SBRT and SRS.

Although there are increased costs associated with newer technologies such as IMRT, SRS, and SBRT, their effectiveness and lower risk for side effects demonstrates long term cost

savings. As well, the relevant key comparison is often IMRT, SRS, or SBRT in comparison to other different modalities of treatment, such as surgery, or radiofrequency ablation (rather than to conventional external beam irradiation). For example, there was a publication a few months ago comparing the cost effectiveness, quality of life and safety for medically inoperable lung cancer patients. The study compared conventional radiation, SBRT, and radiofrequency ablation. SBRT was by far the most effective and cost effective treatment, even though it may have the highest upfront direct cost (reference: [1] Sher, Wee and Punglia, **Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, e767-74, 2011).

Given the extraordinarily short time period for comment, we have done our best to summarize responses to the four key questions of the Washington State Healthcare Authority with regard to SRS, and SBRT in comparison to conventional (conformal) external beam therapy (EBRT). We must emphasize, though, while there are many well done peer reviewed studies from top academic institutions pertinent to IMRT, SRS and SBRT, and in some cases there are head-to-head comparisons which demonstrate the benefits of this technology, the short response timeframe created by your March 6th deadline, which apparently is not negotiable, does not allow adequate time to research. Therefore, we want to be sure the Washington State Healthcare Authority and its staff are advised that we believe the key questions posed for SRS, SBRT and IMRT are extensive and a more complete level of detail is not possible to produce within the time frame allotted.

KQ1: What is the effectiveness for SRS and SBRT compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer.

RESPONSE:

Prostate – SBRT

A conventional radiotherapeutic treatment for prostate cancer consists of 8-9 weeks of daily external beam radiotherapy (EBRT) – such treatment is typically implemented with IMRT and daily image guidance, which helps align the patient prior to delivering each fraction of treatment. An alternative approach is prostate brachytherapy – using either a high dose rate (HDR) delivery system, or the implantation of approximately 100 permanent radioactive seeds. These procedures require anesthesia, and for HDR brachytherapy, hospitalization. Often brachytherapy is combined with a five week course of IMRT.

A newer method of delivering radiotherapy is called “stereotactic body radiotherapy” (SBRT); this differs from conventional radiotherapy in several important ways. First, SBRT uses new technology to deliver radiotherapy with extreme precision. Second, the target is treated

from numerous different beam angles, which concentrates dose to the target and minimizes dose to surrounding organs. By contrast, EBRT/IMRT commonly uses 4-7 beam angles, treating from a single rotational plane. Finally, the extreme accuracy and rapid dose fall-off of SBRT allows very high doses of radiation to be safely delivered to the cancer in 1-5 fractions. The CyberKnife is an SBRT platform that uses robotic technology to adjust in real-time for patient and organ motion, thus treating with an accuracy of less than 1mm.

In order to account for prostate motion during EBRT/IMRT treatment delivery, the prostate plus a 5-10mm margin around it is treated. This gives unnecessary radiation to surrounding organs. The CyberKnife is capable of tracking motion of the prostate during treatment delivery, while still treating with sub-mm accuracy (Xie et al., 2008). This exceptional accuracy minimizes radiation exposure to surrounding normal tissues (e.g., rectum and bladder). The Cyberknife can duplicate the radiation delivered with HDR brachytherapy (Fuller et al., 2007) while avoiding anesthesia, hospitalization, and trauma from numerous need punctures. Like HDR, the CyberKnife delivers dose in only a few (five) fractions.

The feasibility of CyberKnife for treating early-stage prostate cancer was first described in 2003 (King et al.), and the first clinical outcomes from Stanford University were published in 2009 (King et al.). Later that year, Friedland reported on a series of 112 prostate cancer patients treated with SBRT. In 2010, Katz published a report of 304 CyberKnife SBRT prostate patients. These publications showed exceptionally good PSA response rates, low relapse rates, acceptable toxicity, and excellent quality of life outcomes. Early results from a large multi-institutional study (Meier et. 2010) employing Cyberknife for prostate cancer recently reported acceptable toxicity and favorable PSA responses. The first 5-year SBRT outcomes have now been reported by Freeman and King (2011): toxicity was low and the rate of cancer remission was similar to other radiation modalities. Finally, the long-term outcomes of prostate SBRT at Stanford Univerisy conclude “The current evidence supports consideration of stereotactic body radiotherapy among the therapeutic options for localized prostate cancer” (King and Brooks, 2011). Thus multiple peer-review studies, including mature 5-year outcomes, have confirmed that CyberKnife SBRT is safe and effective in treating early-stage prostate cancer.

Selected reference(s):

- Xie Y, Djajaputra D. Intrafractional Motion of the Prostate During Hypofractionated Radiotherapy*. International Journal of Radiation Oncology, Biology, Physics.* 72(1), 236-246, 2008

- Fuller DB, Naitoh J et al. Virtual HDR CyberKnife Treatment for Localized Prostatic Carcinoma: Dosimetry Comparison With HDR Brachytherapy and Preliminary Clinical

Observation. *International Journal of Radiation Oncology Biology Physics* 70(5),1588-97, 2007

- King CR, Lehmann J, Adler JR, Hai J. CyberKnife radiotherapy for localized prostate cancer: Rationale and technical feasibility. *Tech Can Res Treat*: 2003; 2: 25-29.

- King C, Brooks, et al. Stereotactic Body Radiotherapy for Localized Prostate Cancer: Interim Results of a Prospective Phase II Clinical Trial. *International Journal of Radiation Oncology Biology Physics*, 73(4):1043-1048 (2009).

- Friedland J, Freeman D, et al. Stereotactic Body Radiotherapy: An Emerging Treatment Approach for Localized Prostate Cancer. *Technology in Cancer Research and Treatment,* 8(5): 387-392 (2009)

- Katz A, Santor M et al. Stereotactic body radiotherapy for organ confined prostate cancer. BMC Urology, 10(1):2010

- Meier R, Beckman A et al. Stereotactic Radiotherapy for Organ-confined Prostate Cancer: Early Toxicity and Quality of Life Outcomes from a Multi-institutional Trial. *International Journal of Radiation Oncology Biology Physics*. 78(3):S57 (2010)

- Freeman D, King C. Radiation Oncology. 6(3):2011

- King CR, Brooks JD et al. Long-term outcomes for a prospective trail of stereotactic body radiotherapy for low-risk prostate cancer. *International Journal of Radiation Oncology Biology Physics*, in press (2011).

Head and Neck Cancer – SRS/SBRT

SRS and SBRT in Head and Neck cancer play a critical role in patients with locally advanced disease in the region of the skull base in multiple settings. These patients represent a small subgroup of patients for whom SRS/SBRT offer a potentially curative treatment with potentially very low risk in a situation in which historically conventional EBRT simply was not a treatment option.

Head and Neck patients for whom making access to this treatment is critical are

- Patients with recurrent cancer in a previously irradiated field.

Selected reference(s):

[2] Unger, Lominska, Deeken, Davidson, Newkirk, Gagnon, Hwang, Slack, Noone and Harter, **Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer**. Journal/Int J Radiat Oncol Biol Phys, 77, 1411-9, 2010

- Patients with skull base invasion at the time of presentation. For these patients, a combined approach of IMRT and a radiosurgical boost with SRS or SBRT can be curative with minimal morbidity.

Selected Reference(s):

[3] Uno, Isobe, Ueno, Fukuda, Sudo, Shirotori, Kitahara, Fukushima and Ito, **Fractionated stereotactic radiotherapy as a boost treatment for tumors in the head and neck region**. Journal/J Radiat Res (Tokyo), 51, 449-54, 2010

[4] Chen, Tsai, Wang, Wu, Hsueh, Yang, Yeh and Lin, **Experience in fractionated stereotactic body radiation therapy boost for newly diagnosed nasopharyngeal carcinoma**. Journal/Int J Radiat Oncol Biol Phys, 66, 1408-14, 2006

[5] Ahn, Lee, Kim, Huh, Yeo, Lim, Kim, Shin, Park and Chang, **Fractionated stereotactic radiation therapy for extracranial head and neck tumors**. Journal/Int J Radiat Oncol Biol Phys, 48, 501-5, 2000

Central Nervous System – SRS/SBRT/IMRT

Please refer to the separate letter and commentary of Dr. Sandra Vermeulen.

CNS/Spine – SRS/SBRT

SBRT plays and increasing role in the management of patients with spinal tumors in three key settings:

- Re-irradiation of the spine.
  For patients that have undergone prior radiation therapy for spine metastases that have progression of spine disease, SBRT offers dramatic control of tumor, protection of neurologic function, and pain control

Selected reference(s):

[6] Garg, Wang, Shiu, Allen, Yang, McAleer, Azeem, Rhines and Chang, **Prospective evaluation of spinal reirradiation by using stereotactic body radiation therapy: The University of Texas MD Anderson Cancer Center experience**. Journal/Cancer, 117, 3509-16, 2011

- Treatment of radioresistant histologies.
  For patients with radioresistant cancers such as renal cell carcinoma and melanoma, conventional external beam radiation therapy offered poor durability of cancer control. With SBRT, cancer control rates are dramatically improved. With SBRT, long term pain

improvement and cancer control is 75 to 100% for classically radioresistant cancers. Traditional radiation therapy offered control on average for only 1 to 3 months for radioresistant histologies.

Selected reference(s):

[7] Gerszten, Burton, Ozhasoglu and Welch, **Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution**. Journal/Spine (Phila Pa 1976), 32, 193-9, 2007

- Treatment of radioresistant tumors after decompressive surgery.
  Increasingly, patients with advanced spine disease are undergoing less invasive surgery. As demonstrated in the article cited below from Memorial Sloan Kettering, patients treated with minimal surgery followed by stereotactic radiosurgery for radioresistant tumors

[8] Moulding, Elder, Lis, Lovelock, Zhang, Yamada and Bilsky, **Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases**. Journal/J Neurosurg Spine, 13, 87-93, 2010

Gastrointestinal/Pancreas – SBRT

For patients with unresectable pancreatic cancer, the strategy of chemotherapy and stereotactic radiosurgery has been shown to yield excellent local cancer control with low morbidity. Across these studies, tumor control ranges 85 to 95%, and late grade 3 or greater late toxicities occurred in 5 to 10% of patients. Utilizing chemotherapy and stereotactic radiosurgery, long term overall survival is approximately 20%.

Selected reference(s):

[9] Mahadevan, Miksad, Goldstein, Sullivan, Bullock, Buchbinder, Pleskow, Sawhney, Kent, Vollmer and Callery, **Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, e615-22, 2011

[10] Schellenberg, Kim, Christman-Skieller, Chun, Columbo, Ford, Fisher, Kunz, Van Dam, Quon, Desser, Norton, Hsu, Maxim, Xing, Goodman, Chang and Koong, **Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, 181-8, 2011

[11] Chang, Schellenberg, Shen, Kim, Goodman, Fisher, Ford, Desser, Quon and Koong, **Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas**. Journal/Cancer, 115, 665-72, 2009

Gastrointestinal/Liver Metastases

Based on prior experience at this institution and other major medical centers in the United States, Europe and Asia, stereotactic body radiotherapy (SBRT) for liver metastases is effective and safe. Initial reports of phase I/II data for stereotactic body radiation to the liver metastases have been published (Schefter and Colleagues, IJROBP 2005; Kavanagh and colleagues, Acta Oncol 2006). Investigators at the University of Colorado/Denver have demonstrated 92% control of liver lesions at 2 years when treating up to 3 liver lesions. For liver tumors < 3cm, 2 year control was 100%. For this mixed population of cancer patients, median survival was 20.5 months (Rusthoven et al, JCO 2009).

More recently, data from Stanford University (Chang et al, Cancer 2011), detailed a pooled analysis on liver metastases from colorectal primary tumors similarly showing that this treatment is effective and well tolerated. On multivariate analysis, it was found that sustained local control through use of SBRT is closely correlated with overall survival. This was true even for patients heavily pretreated with chemotherapy.

SBRT for liver metastases has been best studied in "oligometastatic situations" (≤4 liver metastases). Extensive published literature exists showing that surgical resection of limited metastatic liver disease is associated with favorable outcome (Gayowski et al, Surgery 1994; Rosen et al, Ann Surg 1992; Nordlinger et al, Ann Surg 1987; Fong et al, JCO, 1997; Singletary et al, Oncologist 2003). Even in a noncurative situation, patients who do not fit this criterion can also safely derive palliative benefit from SBRT by undergoing treatment to symptomatic metastases as detailed above.

Selected reference(s):

[12] Schefter, Kavanagh, Timmerman, Cardenes, Baron and Gaspar, **A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases**. Journal/Int J Radiat Oncol Biol Phys, 62, 1371-8, 2005

[13] Kavanagh, Schefter, Cardenes, Stieber, Raben, Timmerman, McCarter, Burri, Nedzi, Sawyer and Gaspar, **Interim analysis of a prospective phase I/II trial of SBRT for liver metastases**. Journal/Acta Oncol, 45, 848-55, 2006

[14] Rusthoven, Kavanagh, Cardenes, Stieber, Burri, Feigenberg, Chidel, Pugh, Franklin, Kane, Gaspar and Schefter, **Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases**. Journal/J Clin Oncol, 27, 1572-8, 2009

[15] Chang, Swaminath, Kozak, Weintraub, Koong, Kim, Dinniwell, Brierley, Kavanagh, Dawson and Schefter, **Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis**. Journal/Cancer, 117, 4060-9, 2011

Gastrointestinal/Primary Liver Cancers

For primary liver lesions such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), SBRT can also play an important role as a local ablative therapy. A multicenter report published this year (Ibarra et al, Acta Oncol, 2012) showed median time to local progression of 6.3 mo for HCC and 4.2 mo for ICC, better than historical averages for these respective diseases. 1 year survival rates were 87% and 45% for HCC and ICC, respectively. Similar data are reported in a publication by Indiana University (Andolino, IJROBP, 2011). In a separate publication by this same institution, nearly 75% of patients responded to SBRT treatment with the majority of these patients showing complete nonenhancement on followup imaging (Price et al, Cancer 2011).

For primary tumors such as HCC, the data suggests safe, effective treatment for smaller lesions such as those < 6 cm in size (Andolino, IJROBP 2011; Takeda et al, Radiother Oncol, 2012).

Selected reference(s):

[16] Ibarra, Rojas, Snyder, Yao, Fabien, Milano, Katz, Goodman, Stephans, El-Gazzaz, Aucejo, Miller, Fung, Lo, Machtay and Sanabria, **Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors**. Journal/Acta Oncol, 2012

[17] Andolino, Johnson, Maluccio, Kwo, Tector, Zook, Johnstone and Cardenes, **Stereotactic body radiotherapy for primary hepatocellular carcinoma**. Journal/Int J Radiat Oncol Biol Phys, 81, e447-53, 2011

[18] Price, Perkins, Sandrasegaran, Henderson, Maluccio, Zook, Tector, Vianna, Johnstone and Cardenes, **Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma**. Journal/Cancer, 2011

Lung – SBRT

Stereotactic body radiation therapy for lung cancer in medically inoperable patients has dramatically improved local control and survival for patients with early stage lung cancers. Historic local control of early stage, medically inoperable lung cancer was approximately 50%. In the SBRT era, cancer control rates range 85 to 98%.

In a multi institution trial, RTOG 0236 demonstrated 3 year local control of 90% in patients with medically inoperable T1-T2 lung cancer (Timmerman, JAMA, 2010). Similarly excellent results have been reiterated in multiple single institution studies in the US, as well as internationally.

As well, in the case of lung SBRT, direct comparisons to conventional radiation therapy have demonstrated superior cost effectiveness of SBRT (Sher, 2011)

Selected references:

[19] Timmerman, Paulus, Galvin, Michalski, Straube, Bradley, Fakiris, Bezjak, Videtic, Johnstone, Fowler, Gore and Choy, **Stereotactic body radiation therapy for inoperable early stage lung cancer**. Journal/JAMA, 303, 1070-6, 2010

[20] Fakiris, McGarry, Yiannoutsos, Papiez, Williams, Henderson and Timmerman, **Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study**. Journal/Int J Radiat Oncol Biol Phys, 75, 677-82, 2009

[21] Zimmermann, Wulf, Lax, Nagata, Timmerman, Stojkovski and Jeremic, **Stereotactic body radiation therapy for early non-small cell lung cancer**. Journal/Front Radiat Ther Oncol, 42, 94-114, 2010

[1] Sher, Wee and Punglia, **Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer**. Journal/Int J Radiat Oncol Biol Phys, 81, e767-74, 2011

CNS - SRS/SBRT/IMRT

Please refer to the separate letter and commentary of Dr. Sandra Vermeulen.

Re-irradiation – SRS/SBRT

Multiple lines of evidence exist showing the effectiveness and safety of using stereotactic body radiotherapy (SBRT) for re-irradiation (either for salvage or palliation).

1) Cengiz et al, IJROBP, 2010. Salvage reirradiation with stereotactic body radiotherapy for locally recurrent hand and neck tumors

2) Comet et al, IJROBP, 2012. Salvage stereotactic reirradiation with or without cetuximab for locally recurrent head and neck cancer.

3) Dworzecki et al, Noeplasma 2012. Stereotactic radiotherapy as sole or salvage therapy in non small cell lung cancer patients.

4) Heron et al, IJROBP, 2009. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck.

5) Kunos et al, Technol Cancer Res Treat, 2008. Cyberknife radiosurgery for squamous cell carcinoma of vulva after prior pelvic radiation therapy.

6) Thariat et al, Br J Radiol, 2010. Innovative image guided Cyberknife stereotactic radiotherapy for bladder cancer. (Includes previously irradiated bladder cancer patient data).

KQ2: What are the potential harms of SRS/SBRT compared to conventional external beam radiation therapy (EBRT)? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

SRS/SBRT have been shown in multiple studies to be safe as primary treatment and in cases of re-irradiation. Specific toxicities and risks for harm vary across cancer sites and depend on the specific cancer scenarios, prior radiation dose, and anatomy as well as proximity of normal organs.

After an initial course of radiation, normal adjacent tissue has decreased tolerance to additional radiation delivered over the same region. In many cases, surgery and chemotherapy are not viable treatment options. In these situations, a highly conformal technique with the most rapid dose falloff within adjacent normal tissue is necessary to minimize side effects. SRS, and SBRT techniques can safely provide good salvage or palliative results.

For example, for gastrointestinal/liver tumors, side effects related to radiation therapy can include adjacent soft tissue and bony necrosis (including abdominal wall, surrounding liver, and kidney), skin reaction, fatigue, nausea/vomiting, bowel adhesions, and secondary malignancies. However, when the appropriate constraints are used in terms of total adjacent tissue dose, the incidence of high grade toxicity in SBRT is relatively low due to the much higher degree of conformality and steeper dose falloff in tissue outside the target. Multi-institutional trial data show that only 2% of patients treated for liver metastases had greater than grade 2 toxicity and none had grade 4 or higher toxicity (Rusthoven, JCO 2009).

Given the short time period allowed for comment, it is not possible to organize a comprehensive site related characterization of potential toxicities related to SRS/SBRT. However, we remain available at any time to answer and site or technology specific questions.

Additional References:

1) Cengiz et al, IJROBP, 2010. Salvage reirradiation with stereotactic body radiotherapy for locally recurrent hand and neck tumors

2) Comet et al, IJROBP, 2012. Salvage stereotactic reirradiation with or without cetuximab for locally recurrent head and neck cancer.

3) Dworzecki et al, Noeplasma 2012. Stereotactic radiotherapy as sole or salvage therapy in non small cell lung cancer patients.

4) Heron et al, IJROBP, 2009. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck.

5) Kunos et al, Technol Cancer Res Treat, 2008. Cyberknife radiosurgery for squamous cell carcinoma of vulva after prior pelvic radiation therapy.

6) Thariat et al, Br J Radiol, 2010. Innovative image guided Cyberknife stereotactic radiotherapy for bladder cancer. (Includes previously irradiated bladder cancer patient data).

7) Barney et al, Am J Clin Oncol, 2011. Clinical outcomes and dosimetric considerations using SBRT for abdominopelvic tumors.

8) Peulen et al, Radiother Oncol 2011. Toxicity after reirradiation of pulmonary tumors with SBRT.

9) Scorsetti et al, Strahlenther Onkol, 2011. SBRT for adrenal metastases: a feasibility study of advanced techniques with modulated photons and protons.

10) Rwigema et al, 2011 The impact of tumor volume and radiotherapy dose on outcome in previously irradiated recurrent squamous cell carcinoma of the head and neck treated with SBRT.

KQ3: What is the evidence that SRS/SBRT 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**
e. **Setting, provider characteristics, equipment, quality assurance standards, and procedures.**

The above discussion applies to nearly all patient subpopulations as evidenced by the wide range of anatomical subsites, patient demographics, and tumor characteristics described in the studies listed above.

KQ4: What is the evidence of cost and cost-effectivenss of SRS/SBRT/IMRT compared to EBRT?

Our ability to uncover cost and cost-effectiveness comparisons between these modalities has been significantly affected by the time frame allotted for responding. Except for studies of medically inoperable, early-stage non-small cell lung cancer which were readily available, our response is limited to generalizing our own clinical experience. Further, when determining the true, total "cost" and "cost-effectiveness" of each of these treatment alternatives, one needs to quantify the less obvious, indirect costs and benefits of these alternative therapeutic options. For example, how does one quantify the quality of life improvement for patients cured of head and neck cancers with IMRT? What dollar value do we assign to the improved long-term dental health of the patient who is able to receive IMRT instead of EBRT? Or as a second example, what is the financial cost/benefit dollar value assigned to the longer life expectancy of the SRS/SBRT patient receiving a potentially curative treatment with potentially very low risk rather than not having a treatment option since EBRT is not able to be used as a treatment option? Our analysis does NOT address these less obvious, indirect cost/benefit factors so if anything, the benefits of the appropriate use of SRS, SBRT and IMRT are understated in our own clinical experience generalizations.

Sher, Wee and Punglia in "Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage non-small cell lung cancer". (Journal/Int J Radiat Oncol Biol Phys, 81, e767-74, 2011) in a comparison of 3-D EBRT, RFA and SBRT concluded that "SBRT was the most cost-effective treatment for medically inoperable NSCLS over a wide range of treatment and disease assumptions. On the basis of efficacy and cost, SBRT should be the primary treatment approach for this disease".

This is consistent with an earlier study by Lanni, Grills, Kestin and Robertson in "Stereotactic Radiotherapy Reduces Treatment Cost While Improving Overall Survival and Local Control Over Standard Fractionated Radiation Therapy for Medically Inoperable Non-Small-Cell Lung Cancer". (American Journal of Clinical Oncology, 34(5):494-498, October 2011) which concluded that "SBRT was found to be less expensive than standard fractionated EBRT, with the cost savings highly dependent on the number of SBRT fractions and EBRT technique (3-D conformal RT vs. IMRT). SBRT was also associated with superior local control and overall survival."

Most radiation oncologists in Washington State (this group included) do not own the linear accelerators that deliver theraputic radiation. They are typically owned by the hospitals who charge separately for their use. For linear accelerator based IMRT and 3D treatments, we are paid according to the applicable professional services fee schedule. The actual physician time and work effort involved is vastly greater for IMRT than for 3D yet despite this we are most often paid less for IMRT (in part due to bundling of charges). When we as physicians recommend IMRT over 3D we do so knowing we will spend three to four times more effort on the case and get paid less. Clearly our incentive for doing so is to provide the very best care and treatment for our patients.

From: JASON K. ROCKHILL [jkrock@u.washington.edu]
Sent: Tuesday, March 06, 2012 4:20 PM
To: HCA ST Health Tech Assessment Prog
Cc: mail=jkrock@uw.edu
Subject: Comments on IMRT from UW Medicine
Attachments: UW Medicine Response IMRT.docx

Please see the attached comments on the use of IMRT

March 6, 2012

To: Washington State Health Care Authority, HTA Program

Please see attached comments below from the UW Medicine/ Seattle Cancer Care Alliance Department of Radiation Oncology regarding the Health Technology Assessment for Intensity Modulated Radiation Therapy.

Michael Brown MD
Assistant Professor of Radiation Oncology

Ralph Ermoian MD
Assistant Professor of Radiation Oncology

Christine Fang MD
Assistant Professor of Radiation Oncology

Eric Ford PhD
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Gabrielle Kane MB EdD FRCPC
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Edward Kim MD
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Janice Kim MD
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Wui-Jin Koh MD
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George Laramore MD PhD
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Jay Liao MD
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Jason Rockhill MD PhD
Associated Professor of Radiation Oncology

Ken Russell MD
Professor of Radiation Oncology

George Sandison PhD FCCPM
Professor, Clinical Director of Medical Physics

KQ1: What is the evidence of effectiveness for intensity modulated radiation therapy (IMRT) compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?

Intensity modulated radiotherapy is a technique that allows delivery of radiation in a highly conformal fashion. When compared to 3D conformal radiotherapy (CRT), this (in some instances) may allow better sparing of normal tissues and organs adjacent to tumor targets. IMRT also allows differential prescription of radiation doses simultaneously. In contrast, 3D CRT requires all targets being treated in the same radiotherapy plan to receive the same dose of radiation. With an IMRT plan, however, it is possible to deliver a high dose of radiotherapy to a tumor target, an intermediate dose of radiotherapy to adjacent tissue that is at risk of harboring subclinical disease, and a low dose of radiotherapy to other non-target tissues all in the same treatment.

It is the geometry of a patient's tumor and the proximity to adjacent normal structures that determines the potential benefit or advantage of IMRT over 3D conformal radiotherapy, rather than a specific histologic diagnosis. Certain disease sites, such as head and neck cancers, typically involve tumors located in close proximity to multiple critical structures. In these cases, IMRT frequently offers an advantage over 3D CRT. In other disease sites, such as intrathoracic tumors, the benefit or equivalence of IMRT to 3D CRT will depend largely on the tumor geometry and patient's anatomy.

Sometimes, the benefit of IMRT over 3D CRT may not lie in superior tumor control but equivalent tumor control with reduced toxicity.

Head and neck cancer

IMRT has become standard of care for most patients with head and neck cancers. Given the close proximity of tumors of the head and neck to critical structures, IMRT allows more conformal and often improved coverage of tumor volumes, while also decreasing doses to adjacent critical structures to decrease the risk of toxicity and normal tissue complications. Survival outcomes appear to be similar compared to conventional radiotherapy techniques. However, IMRT has been shown to decrease toxicity by reducing the doses to salivary glands, temporal lobes, auditory structures, and optic structures. Xerostomia is one of the major late toxicities of H&N radiotherapy and an important quality of life factor. Numerous phase II studies have demonstrated decreased xerostomia without compromise in tumor control. Three randomized trials have now also been reported supporting the benefit of IMRT in head and neck cancer with regard to xerostomia (Pow et al IJROBP 2006;66:981-991, Kam et al 2007 JCO;25:4873-4879, Nutting et al, Lancet Oncology 2011). The recent PARSPORT phase III randomized study compared IMRT with conventional RT in patients with oropharyngeal and hypopharyngeal cancer (Nutting et al JCO 2009;27(Suppl 18). This study found a dramatic improvement in Grade 2 or higher xerostomia rates at 1 year after treatment with IMRT (74% vs 38%), importantly without any decrement in locoregional control or survival. Vergeer et al reported a comparison of IMRT and 3D-CRT with other health-related QOL outcomes including xerostomia in a series of patients with cancers of the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx or H&N unknown primary. IMRT had a positive impact on a number of H&N cancer-specific QOL dimensions in addition to xerostomia (IJROBP 2009;74(1):1-8). Per the NCCN Guidelines (v 2.2011), IMRT is the preferred technique for cancers of the oropharynx, nasopharynx, maxillary sinus and paranasal/ethmoid sinuses to minimize dose to normal structures. The application of IMRT to other sites (oral cavity, larynx, hypopharynx, salivary glands) may be used at the discretion of the treating physicians.

Thyroid cancer
External beam RT is infrequently used in the definitive management of thyroid cancers, typically in patients with anaplastic thyroid cancer or high risk resected or recurrent well-differentiated cancers. The data examining IMRT is therefore limited to small series, as it is impractical to conduct comparative studies of radiotherapy technique. In sum, these studies demonstrate that IMRT is safe, associated with an acceptable toxicity profile, and may facilitate improved target volume coverage and dose escalation while reducing doses to normal structures, in particular spinal cord and salivary gland in patients requiring coverage of the cervical nodes (Foote et al Thyroid; Vol 21, Number 1, 2011; Radiotherapy and Oncology 85 (2007) 58–63; IJROBP, Vol. 63, No. 5, pp. 1419–1426, 2005; Nutting et al Radiotherapy and Oncology 60 (2001) 173-180; IJROBP, Vol. 48, No. 2, pp. 475–483, 2000). Recent reviews by Princess Margaret Hospital and Memorial Sloan Kettering support the use of IMRT as the preferred approach in these patients (Brierley et al J Clin Endocrinol Metab 96: 2289–2295, 2011; Lee et al Head Neck 29: 387-400, 2007).

Thoracic tumors
IMRT has been shown to reduce normal lung dose (typically described as V20, or the volume of lung receiving a dose of 20 Gy) in select scenarios. Lung V20 is a validated predictor of radiation pneumonitis risk. In many instances, 3D conformal techniques may offer the best means of reducing lung V20 and therefore reducing the risk of developing post-treatment radiation pneumonitis. In certain instances, however, IMRT may reduce normal lung doses beyond what can be achieved with 3D conformal radiotherapy. MD Anderson Cancer Center published a comparison of 68 patients treated with IMRT versus 222 patients treated with 3D CRT for non-small cell lung cancer. Despite the IMRT group's larger gross tumor volumes, the rate of grade 3 or high treatment-related pneumonitis at 12 months was 8% (95% confidence interval 4%-19%) with IMRT, compared with 32% (95% confidence interval 26%-40%) for 3D-CRT ($p = 0.002$). (Yom, et al. Int J Radiat Oncol Biol Phys 2007, 68, 94-102). A later update including 165 patients treated with IMRT showed low rates of lung and esophageal toxicity. (Jiang et al. In J Radiat Oncol Biol Phys 2011, [epub ahead of print] PMID 22079735)

Prostate
Multiple studies have demonstrated the importance of delivering high doses to the prostate to maximize cure. The results of randomized trials suggest that dose escalation is associated with improved biochemical outcomes (Peeters et al JCO 2006;24:1990-1996, Pollack et al IJROBP 2002;53:1097-1105, Zietman et al JAMA 2005;294:1233-1239, Kuban et al IJROBP 2008;70-67-74). From a recent review from the group at Memorial Sloan Kettering, they note that “The dosimetric superiority of IMRT over conventional techniques to produce conformal dose distributions that allow for organ sparing has been shown…IMRT is the safest way to deliver high doses of external-beam irradiation to the prostate and the regional lymph nodes” (Cahlon et al Semin Radiat Oncol 18:48-57). IMRT is associated with excellent tumor control outcomes and has permitted safer dose escalation while limiting the doses to rectum and bladder with very low rates of complications. Per the NCCN guidelines for Prostate Cancer (v 1.2011), “The second generation of 3D technique, intensity-modulated radiation therapy (IMRT), is now state-of-the-art and required.”

Gastric Cancer
Stanford published a comparison of 57 patients treated with either 3D CRT or IMRT after surgery for gastric cancer. Mean kidney and liver doses were lower for patients treated with IMRT than 3D CRT. Patients treated with 3D conformal radiotherapy required more treatment breaks and had a statistically

significant increase in median serum creatinine (indicating an adverse effect on renal function) when compared to patients treated with IMRT (p=0.02). (*Minn et al. Cancer 2010, 15, 3943-52*)

Rectal

MDACC published a treatment planning comparison study of 3D vs IMRT for 10 rectal cancer patients. IMRT plans were found to have superior target coverage, homogeneity, and conformality, while lowering dose to adjacent organs-at-risk – particularly small bowel. (Mok H, et al. Radiat Oncol 2011, 8,6, 63) The dose to small bowel has been shown to directly correlate with treatment toxicity. (Kavanagh BD, et al: Int J Radiat Oncol Biol Phys 76: S101-S107, 2010)

Mayo Clinic published a retrospective comparison of patients treated at their institution with either 3D radiotherapy or IMRT. Patients treated with IMRT had a lower risk of grade 2 GI toxicities (32% vs 61%, p = 0.006). Among 3D CRT patients, ≥Grade 2 diarrhea and enteritis was experienced among 48% and 30% of patients, respectively, compared with 23% (p= 0.02) and 10% (p= 0.015) among IMRT patients. (Samuelian J, Int J Radiat Oncol Biol Phys 2011 [epub ahead of print] PMID 21477938)

Anal cancer

Radiation and chemotherapy are the primary curative therapy for anal cancer. Lymphatic drainage pathways for anal cancers include the inguinal nodes. In order to cover these lymph nodes with 3D conformal techniques, the bladder, femoral heads, and genitals receive significant doses of radiotherapy. IMRT allows significant reductions in dose to these normal tissues.

A multi-institutional phase II trial of IMRT for anal cancer showed excellent tumor control with 2 yr local control rates of 95% and significantly reduced grade 3 or higher hematologic (51%), dermatologic (10%), and gastrointestinal (7%) toxicity when compared to toxicity from prior trials. (*Kachnic et al. Int J Radiat Oncol Biol Phys 2012, 82, 153-8*) By comparison, the RTOG 9811 trial, which utilized 3D conformal radiotherapy, reported much higher grade 3 or higher toxicities: hematologic (61%), dermatologic (48%), gastrointestinal (35%). (*Ajani et al. JAMA 2008, 16, 1914-21)* Stanford also published a retrospective series comparing results with IMRT and conventional radiotherapy reporting less toxicity and reduced need for treatment breaks with IMRT (*Bazan et al. Cancer 2011, 117, 3342-51*)

Vaginal and vulvar cancers drain to the inguinal lymphatics. Locally advanced (T4) rectal cancers or rectal cancers with involvement of the anal canal may also involve the inguinal lymphatics. In these scenarios, IMRT would be expected to offer similar benefits to those seen in anal cancer as the treatment targets and involved anatomy are very similar.

Gynecologic Cancers:

Du and colleagues compared 62 patients treated with IMRT to 60 patients treated with conventional radiotherapy for cervical cancer between 2005 – 2010, reporting better dose conformity to the target and better sparing of the rectal, bladder and small intestine with IMRT plans. Patients treated with IMRT experienced significantly lower acute and chronic toxicities (*Du et al, Gynecol Oncol. 2011 Dec 22. [Epub ahead of print] PMID: 22198339*). The University of Pittsburgh published a series of patients treated with IMRT after hysterectomy for endometrial cancer with a 3.3% grade 3 toxicity rate. (*Beriwal et al. Gynecol Oncol 2006, 102, 195-9*)

Breast Cancers

Radiation has only been recently recognized as a risk factor for long term development of heart disease among breast cancer patients. For patients with left breast cancers that receive radiotherapy, multiple dosimetric studies have shown that IMRT can reduce dose to the heart and reduce skin toxicity.

(Mcdonald et al. Int J Radiat Oncol Biol Phys 2008, 72, 1031-40; Pignol et al. J Clin Oncol 2008, 26, 2085-92)

Sarcomas

Memorial Sloan Kettering has published a retrospective analysis of patients treated with IMRT vs brachytherapy for sarcomas with improved local control (92% vs 81%, p = 0.04) with IMRT. (*Alektiar, et al. Cancer 2011, 117, 3229-34*). In the post-operative treatment of retroperitoneal sarcoma, IMRT has been shown to reduce both acute and late gastrointestinal toxicity in comparison to conventional post-operative radiation, even though the tumor specifics were too heterogeneous to draw conclusions about survival outcomes. (*Pezner, et al. Am J Clin Oncol 2011, 34(5), 511-6).* Preoperatively, the use of IMRT has resulted in reduced GI toxicities, and improved sparing of the kidneys. (*Bossi, et al. Int J Radiat Oncol Biol Phys 2012, 67(1), 164-170.)* Most of the published research on sarcoma at the moment are comparative dosimetric studies; these all demonstrate reduced dose to organs at risk (e.g., the femur, the skin and subcutaneous "flap" that must be preserved to reduce the risk of extremity edema) using IMRT in comparison to conventional conformal techniques, but clinical outcomes research on this rare tumor type is underway, although not yet completed.

Brain tumors

In certain cases, when brain tumors are adjacent to vital organs at risk such as optic nerves, chiasm, and brainstem, IMRT is associated with a decrease in the mean doses to organs at risk and a decrease of healthy brain dose. Multiple planning studies have shown that IMRT decreases the risk of toxicity of treatment while maintaining adequate dose to brain tumors (*Amelio et al. Radiother Oncol 2010, 97(3):361-9.*

KQ2: 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.

IMRT is typically employed to reduce treatment related toxicity. In order to concentrate dose on targets, a larger amount of non-target tissue typically receives a low dose of radiotherapy. In young patients, this could theoretically increase the risk of developing a secondary malignancy later in life. This risk would have to be balanced against the reduction of treatment related toxicities facilitated by IMRT.

KQ3: What is the evidence that IMRT has differential efficacy or safety issues in subpopulations? Including consideration of:

a. Gender

IMRT does not have differential efficacy or safety issues in different genders.

b. Age

Generally, the efficacy and safety of IMRT is not impacted by age as treatment related toxicity affects patients of all ages. However, in cases where IMRT decreases dose to normal tissues, young patients with good prognosis may especially benefit from IMRT as the risk of late effects are minimized.

c. Site and type of cancer

As detailed in KQ1, the efficacy and safety of IMRT depend on the site of cancer as well as the doses required for the specific type of cancer.

d. Stage and grade of cancer

As detailed in KQ1, the efficacy and safety of IMRT depend on the site of cancer as well as the doses required for the specific type of cancer.

e. Setting, provider characteristics, equipment, quality assurance standards and procedures

The American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) have published practice guidelines for IMRT, revised in 2011. Attempts to treat with IMRT in settings that fail to meet consensus guidelines for expertise, equipment, and quality assurance procedures may adversely affect safety and efficacy.
(http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/IMRT.pdf)

KQ4: What is the evidence of cost and cost-effectiveness of IMRT compared to EBRT?

Measures of cost effectiveness depend not only on endpoints of survival and local disease control, but also toxicity and quality of life.

Fox Chase Cancer Center performed an analysis of IMRT for treatment of prostate cancer, reporting cost-effectiveness for IMRT on the basis of improved biochemical disease free survival, less need for salvage therapy, and improved quality of life after treatment (Konski et al. Int J Radiat Oncol Biol Phys. 2006, 66(2):408-15)

From: Sarah Svoboda
To: HCA ST Health Tech Assessment Prog
Cc: Andy Whitman
Subject: 2012 Washington HTA Review of IMRT: Varian Comments and Clinical Evidence
Date: Tuesday, March 06, 2012 3:06:03 PM
Attachments: IMRT Review by Washington HTA- Varian Comments 6 March 2012.pdf
Enclosure 1- Varian Comments- Washington HTA 12 28 11.pdf
Enclosure 2- IMRT White Paper.pdf
Enclosure 3- pg82.pdf
Enclosure 4- 20101116 Final V4.0_RapidArc Bibliography External.pdf
Importance: High

Dear Mr. Morse,

Please find attached Varian Medical Systems' submittal of clinical evidence answering the Key Questions in regards to the Washington Health Tech Assessment's 2012 review of Intensity Modulated Radiation Therapy with related enclosures. Thank you and please let me know if you have any questions regarding these materials.

Sincerely,

Sarah Svoboda

Sarah Svoboda
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December 28, 2011

Ms. Denise Santoyo
Program Coordinator
Washington State Health Care Authority
Health Technology Assessment
Denise.Santoyo@hca.wa.gov

Dear Ms. Santoyo:

Enclosed please find documentation of clinical studies that demonstrate overwhelming support for the use of intensity modulated radiation therapy as a cancer treatment technique. In addition, we have also included two white papers from Varian Medical Systems, Inc. referencing published clinical evidence in this area as well. These documents, focusing on various cancer types, are evidence that intensity modulated radiation therapy (IMRT) has already been thoroughly studied and should be approved in its 2012 review by the Washington Health Technology Assessment (WHTA) panel.

Intensity modulated radiation therapy has revolutionized care for cancer patients and has been widely used by clinicians to treat patients since 2001. Medicare has recognized that this is a highly effective treatment for head and neck, prostate, lung and breast cancer. Each year, clinicians around the world use Varian products to deliver more than thirty-five million radiotherapy treatments ---accounting for tens of thousands of cancer patients per day. Radiotherapy is a cost-effective form of cancer treatment. Unlike drugs or surgery, one linear accelerator can perform nearly one hundred thousand treatments during its life cycle.

We hope you will consider the enclosed information when reviewing intensity modulated radiation therapy in its 2012 evidence based review.

If you have any questions about the enclosed material, please do not hesitate to contact me.

Sincerely yours,

Andrew M. Whitman
Vice President, Government Affairs

Enclosures (3)

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March 6, 2012

Mr. Josiah Morse, MPH
Program Director
Health Technology Assessment Program
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712
shtap@hca.wa.gov

Dear Mr. Morse:

Thank you for the opportunity to submit clinical evidence to answer the Key Questions for your upcoming review of Intensity Modulated Radiation Therapy (IMRT). In addition to this information, please also find included our initial comment letter and the significant data that was submitted at the time. I hope this information is helpful. Should you have additional questions, please do not hesitate to contact me by phone at (202) 629 3441.

Sincerely yours,

Andrew M. Whitman
Vice President, Government Affairs

Enclosures (4)

KQ1: What is the evidence of effectiveness for intensity modulated radiation therapy (IMRT) compared to conventional external beam radiation therapy (EBRT) for patients with cancer by site and type of cancer?

Please see below a list of studies citing evidence on the benefits of IMRT. Among the reasons to use IMRT cited below, researchers have found that the use of IMRT can improve tumor control and reduce damage to surrounding healthy tissue

. Evidence/Quote	Reference
However, at most institutions, radiotherapy is still considered the mainstay of treatment... IMRT results in better target coverage than conventional planning... Based on this, it is reasonable to postulate that this reduction in dose will decrease the future rate of radiation related carotid artery disease... and dysphagia. Perhaps the most important conclusion that can be drawn from this study is that regardless of what is determined to be the appropriate margin in delineating the CTV (and thus the PTV) for early laryngeal cancer, IMRT maximizes the freedom of the clinician to choose a margin that is most appropriate for them.	Gomez, D., Cahlon, O., Mechalakos, J., Lee, N. (2010). An investigation of intensity-modulated radiation therapy versus conventional two-dimensional and 3D-conformal radiation therapy for early stage larynx cancer. Radiation Oncology, 5(74), 1-9. doi:10.1186/1748-717X-5-74
IMRT results in better target coverage than conventional planning... IMRT seems to have increased tumor control in both prostate and head and neck tumors by allowing for dose escalation and better target coverage... IMRT demonstrated a significant improvement in terms of the dose to the carotid arteries... IMRT can decrease the dose to the pharyngeal constrictor muscles, potentially decreasing rates of long-term dysphagia... IMRT can spare normal tissues in early stage laryngeal disease without a decrease in tumor dose, both compared to conventional techniques and 3D conformal therapy... IMRT maximizes the freedom of the clinician to choose a margin that is most appropriate for	Gomez, D., Cahlon, O., Mechalakos, J., & Lee, N. (2010). An investigation of intensity-modulated radiation therapy versus conventional two-dimensional and 3D-conformal radiation therapy for early stage larynx cancer. Radiation Oncology, 5(74), 1-9. doi: 10.1186/1748-717X-5-74

them.

Tangential beam IMRT significantly reduced the dose-volume of the ipsilateral lung and heart in unselected postmastectomy breast cancer patients.	Rudat, V., Alaradi, A.A., Mohamed, A., Al-Yahya, K., & Altuwaijri, S. (2011). Tangential beam IMRT versus tangential beam 3D-CRT of the chest wall in postmastectomy breast cancer patients: A dosimetric comparison. Radiation Oncology, 6(26). doi:10.1186/1748-717X-6-26
Tangential beam IMRT for the radiotherapy of the chest wall of postmastectomy breast cancer patients offers the potential to significantly reduce the dose-volume of the ipsilateral lung, and in patients with left-sided cancer the dose-volume of the heart compared to tangential beam 3D-CRT.	Rudat, V., Alaradi, A.A., Mohamed, A., Al-Yahya, K., & Altuwaijri, S. (2011). Tangential beam IMRT versus tangential beam 3D-CRT of the chest wall in postmastectomy breast cancer patients: A dosimetric comparison. Radiation Oncology, 6(26). doi:10.1186/1748-717X-6-26

KQ2: 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.

Modern linear accelerators used for radiotherapy (and specifically for IMRT) include a wide variety of features designed to protect the safety of patients and operators. A significant portion of these safety systems are mandated by internationally recognized safety standards, including those published by the International Electrotechnical Commission (IEC).

In general, known conditions that can be expected to cause a hazard have additional or redundant system checks wherever practical. This general design philosophy is implemented to avoid a single fault condition and is verified through risk and hazard analysis.

Many safety mechanisms are in the form of interlocks that detect errant conditions and prevent irradiation unless those conditions are resolved. Interlocks require direct operator action and where appropriate require a Physics password to proceed after the error condition is resolved. Other significant safety mechanisms include: independent dose monitoring systems; radiation protection shielding; and protection against electrical and mechanical hazards as described below. In addition, state of the art systems include diagnostic quality imaging in the treatment room to verify patient positioning.

KQ4: What is the evidence of cost and cost-effectiveness of IMRT compared to EBRT?

Both clinical and cost effectiveness are reviewed in the studies below, which compare IMRT to 3D Conformal Radiotherapy.

Evidence/Quote	Reference
IMRT benefits more than 3DCRT from IGPR (Image-Guided Patient Repositioning) with the Weekly Shrinking Action Level approach yielding the lowest cost-outcome ratio... ...it is generally acknowledged that RT is an efficient, effective and highly cost-effective treatment for cancer... Image guidance used solely for translational patient repositioning for prostate cancer adds costs with relatively little improvement in dosimetric quality. Full exploitation of the potential of IGRT, particularly through margin reduction (decreased surrounding tissue damage), can be expected to result in a reduction in the cost-outcome ratios reported here.	Ploquin, N., & Dunscombe, P. (2009). A cost-outcome analysis of Image-Guided Patient Repositioning in the radiation treatment of cancer of the prostate. Radiotherapy and Oncology, 93, 25–31. doi:10.1016/j.radonc.2009.03.023
The comparative data of IMRT versus 3DCRT seem to support the theory that higher doses, up to 81 Gy, can improve biochemical survival for patients with localised PC, concurring with dataon CRT. The data also suggest that toxicity can be reduced by increasing conformality of treatment, particularly with regard to GI toxicity, which can be more easily achieved with IMRT than 3DCRT. Whether differences in GI toxicity between IMRT and 3DCRT are sufficient for IMRT to be cost-effective is uncertain, depending on the difference in incidence of GI toxicity, its duration and the cost difference between IMRT and 3DCRT. A systematic literature search was undertaken for previous economic studies of IMRT for PC. An example search strategy for MEDLINE is shown in Appendix 8. A total of 587 studies were identified.	Hummel, S., Simpson, E.L., Hemingway, P., Stevenson, M.D., & Rees, A. (2010). Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. Health Technology Assessment, 14(47), 1-108. doi: 10.3310/hta14470

PUBLIC COMMENTS – DRAFT REPORT

ASTRO

August 2, 2012

Christine Valkyrie Masters
Program Specialist
Health Technology Assessment
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

BY ELECTRONIC SUBMISSION to shtap@hca.wa.gov

Dear Ms. Masters:

The American Society for Radiation Oncology (ASTRO), the largest radiation oncology society in the world representing more than 10,000 members who specialize in treating patients with radiation therapies, appreciates the opportunity to comment on the Washington State Health Care Authority Health Technology Assessment Program Draft Evidence Report on Intensity Modulated Radiation Therapy, published on July 5, 2012.

The 274 page draft report provides evidence comparing Intensity Modulated Radiation Therapy (IMRT) with conventional radiation therapy for multiple cancer types, and also includes non-comparative studies identifying outcomes or harms results for IMRT alone. The report also notes that due to the absence of randomized trials and comparative studies, the strength of the evidence is very low, or low for most of the findings. Given the short timeframe allowed for comments regarding this lengthy report, ASTRO will limit its response to this finding.

One of the primary concerns put forth in this draft report is the lack of randomized data to definitively demonstrate superior clinical outcomes with the use of IMRT as compared to conventional radiation therapy, and the lack of Level One evidence from randomized clinical trials. Much has been written regarding the challenges associated with the use of traditional comparative effectiveness research methodology when applied to new technology[1]. The reasons underlying the lack of randomized, double-blind, placebo controlled trials in radiation oncology are many, primarily related to the challenges in finding funding and willing patients for such research questions given the volume and consistency of literature that supports the use of IMRT for many cancer sites. There is certainly precedent for introducing significant technological developments without this level of evidence. Examples include:

- CT scanning vs. conventional imaging;
- Linear accelerators vs. cobalt;
- CT simulation vs. fluoroscopic simulation or worse;
- Minimally invasive surgery vs. conventional surgery;
- High dose rate remote afterloading brachytherapy vs. low dose rate afterloading brachytherapy vs. low dose rate non-afterloading brachytherapy.

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

The draft report further states that the NCCN guidelines are of poor methodological quality and the ACR guidelines vary from poor to fair methodological quality. Both of these guideline documents are widely accepted and have credibility across the oncology and payer community. The lack of randomized controlled trials does not preclude the necessity to make clinical and coverage decisions every single day, and guidelines such as these represent the best examples in oncology in general and radiation oncology in particular. Absent such guidelines, an environment where "anything goes" would prevail. Specifically, these panels do reflect the consensus of in-field experts, including non-radiation oncologists, that IMRT is the standard of care in the management of both prostate and head and neck cancer. ASTRO is concerned that increased toxicity and decreased cure rates might result if this report's findings were adopted over the objections of expert panels due to the authors' belief that the overall strength of evidence in favor of IMRT was relatively weak.

It is ASTRO's opinion that the draft report completely ignores the essential aspect of IMRT's advantage over 3-dimensional conformal radiation therapy (3D-CRT): smaller, more conformal volumes may be irradiated, leading to (a) less toxicity and (b) potential for dose escalation. IMRT allows radiation oncologists to routinely provide 79.2 Gy to prostate cancer patients, based on substantial data indicating that higher doses contribute to better outcomes. IMRT also allows our discipline to provide daily doses exceeding 2.1 Gy with chemotherapy to head and neck cancer patients, again based on data that this approach increases survival over 3D-CRT at lower daily doses. If radiation oncologists stop using IMRT and instead use 3D-CRT, treatment volumes will of necessity become larger, which will increase toxicity.

ASTRO believes that the results presented by the Sheets et al [2] paper were underutilized by the report writers and may in fact represent some of the highest quality data in favor of IMRT vs. 3D-CRT for the treatment of prostate cancer. Sheets et al reported less GI and hip toxicity when IMRT was used which is not surprising since the hips and GI organs are routinely avoided when performing IMRT. Additionally, patients treated with IMRT had fewer additional episodes of cancer treatment, implying a higher cure rate and fewer downstream costs, although it is a relative weakness of the Sheets paper that they didn't perform a cost-effectiveness analysis. It is noted that Sheets (2012) is a "good quality cohort study." The publication by Sharma[3], et al, cited below, that we believe was overlooked in the development of this report, also supports the use of IMRT in the treatment of prostate cancer.

We appreciate your consideration of our comments and look forward to the September 21, 2012 public meeting on this topic.

Sincerely,

Gregory Patton, MD
Chair, Regulatory Committee

Michael Dzeda, MD
Vice-Chair, Regulatory Committee

Enc: ASTRO Comment Letter AHRQ re: CE for Head and Neck Cancer, August 2009

cc: Thomas Eichler, MD
Joel Cherlow, MD
Najeeb Mohideen, MD
Brian Kavanagh, MD

CITATIONS

1. Concato, J. Is It Time for Medicine-Based Evidence? *JAMA*. 2012;307(15):1641-1643. doi:10.1001/jama.2012.482
2. Sheets, N.C., Goldin, G.H., Meyer, A.M., Wu, Y., Sturmer, T., Holmes, J.A., et al. (2012). Intensity modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *Journal of the American Medical Association, 307*(15), 1611-1620.
3. Sharma NK, Li T, Chen DY, Pollack A, Horwitz EM, Buyyounouski MK. Intensity-modulated radiotherapy reduces gastrointestinal toxicity in patients treated with androgen deprivation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2011 Jun 1;80(2):437-44. Epub 2010 Nov 2.

From: James Brashears [mailto:jbrashears@sightlinehealth.com]
Sent: Monday, August 06, 2012 10:00 AM
To: HCA ST Health Tech Assessment Prog
Subject: Public Comment for: Intensity Modulated Radiation Therapy

To the Health Technology Assessment Group:

Why is there a dearth of clinical evidence supporting the superiority of IMRT to 3DCRT? Because IMRT is frequently shown to be better than 3DCRT before treatment is ever given to a patient.

The concept of applying evidence based medicine (EBM) to the modern provision of radiation therapy for malignancies is indeed very salutary. All radiation oncologists I am familiar with strongly support the use of EBM when appropriate for the improvement of care for our patients and the society of which we are all apart. Applying EBM specifically to compare three dimensional conformal radiation therapy (3DCRT) to intensity modulated radiation therapy (IMRT) or similar technologies like stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) can be inherently problematic and misleading. This is because physicians have the duty to treat patients with what we feel and understand to be most beneficial/least harmful techniques at our disposal to the patient in the short and long term without focusing specifically on the indirect monetary costs.

In the vast majority of cases where IMRT/SBRT/SRS is deemed appropriate versus more traditional 3DCRT, the amount of radiation to the target (cancer) is usually higher and the corresponding significant dose of radiation to the normal tissues (frequently organs critical for maintaining health like the lung, kidney, intestines, liver, etc) is almost always less. This becomes evident during the radiation planning process when various radiation delivery plans are evaluated before one is selected to treat the patient. Given the two principles that a higher dose of radiation is more effective in eradicating cancer and keeping radiation dose less in tissues/organs where there is no disease is safer, the fundamental issues of why comparing traditional and more modern techniques like IMRT in randomized controlled trials is clear.

To simplify, when my father was diagnosed with prostate cancer and he decided that he wanted radiotherapy, there was a choice between treating with 3DCRT and IMRT. When comparing the 2 methods of treatment, the IMRT plan gave less biologically significant dose to the rectum and bladder while maintaining the same dose to the prostate cancer. At this point, there was no need to consult EBM guidelines since the technique of treatment that gave less dose to the normal tissue was known. In fact, it probably would have been unethical and against the Hippocratic Oath for him to be treated with 3DCRT at that point since the IMRT plan was inherently safer. Applying this case more broadly shows why radiation oncologists are reticent to compare IMRT to 3DCRT with a blanket over a population in trials.

Please do not take this reticence to knowingly treat patients with prima facie inferior techniques as showing a lack of confidence in the superiority of IMRT/SBRT/SRS over 3DCRT. Indeed the host of research showing the dosimetric superiority of IMRT/SBRT/SRS is well known and fueled the initial adoption of these technologies that radiation oncologists feel are often in the patient's best interest and have contributed meaningfully to disease control and increased tolerability of therapy. It is frightening in the extreme to consider that therapy which could be safer for patients might be disallowed in the future by governmental mandate.

If you have any questions please feel free to contact me.

Yours sincerely,

James H Brashears III, MD
Radiation Oncologist
206-922-6400

From: Fitzgerald, Trevor [mailto:tfitzgerald@wvmedical.com]
Sent: Monday, August 06, 2012 11:40 AM
To: HCA ST Health Tech Assessment Prog
Cc: Sexton, Larry; 'Greg Courlas'
Subject: Public Comment for: Intensity Modulated Radiation Therapy

Hello,

I am writing to comment on the draft report on the efficacy of IMRT. The basic flaw in the report is treating all diagnosis groups as homogenous and either benefiting or not from IMRT. Unfortunately every tumor is different and its size, location with respect to critical structures and response to radiation determine whether or not IMRT will be beneficial. Some lung cancers can be treated effectively with CRT, some cannot. To lump them all together and deny patients who need IMRT that option would increase mortality and morbidity, it would increase medical costs in other areas such as managing the increased side effects of CRT and decrease QOL. The need for IMRT should be decided upon by the responsible physician weighing all the appropriate medical data of the patient, and not just based on diagnosis type.

If wide swaths of diagnosis are deemed inappropriate for IMRT then the hospitals which have invested in the technology to perform such treatments will not be able to remain viable and will close their radiation therapy departments as CRT reimbursement rates alone are not enough to keep these facilities open. This will result in less access to care for the population and more morbidity.

I have worked in Radiation therapy for 24 years and have seen the benefits of IMRT over CRT in many cases. Prior to IMRT most Head and Neck, Lung and Prostate Cancer patients did not finish their prescribed course of treatment without lengthy breaks due to the severity of side effects. It would be unethical for a practitioner to treat these patients with CRT based solely on long term survival benefit data, knowing that many more painful and QOL reducing side effects will occur than if IMRT could be used.

Sincerely,

Trevor Fitzgerald, MSc, DABR, CCPM
Medical Physicist
Rad.Onc. Dept
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August 6, 2012

Christine V. Masters
Program Specialist
Health Technology Assessment
Washington State Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

By Electronic Submission

Dear Ms. Masters,

Thank you for the opportunity to comment on the Washington State Healthcare Authority Health Technology Assessment Program Draft Evidence Report on Intensity Modulated Radiation Therapy (IMRT). Varian is pleased to provide additional data to you that we hope will be considered before final publication of this report. Varian is expertly poised to submit this information, as well as additional technical support if necessary, due to our position as the world's leading producer of radiotherapy technology for treating cancer. Varian products include linear accelerators, simulators, and a broad range of accessories and interconnected software tools for planning, verifying, and delivering the most advanced radiotherapy and radiosurgery treatments.

Varian has significant concerns that the draft report does not properly highlight the immense benefits of the use of this advanced technology for treating cancer. For example, the overly stringent exclusion criteria led to the inclusion of only 6 percent (or 124) of 2,199 references.

The publication of a final report without consideration for other means of assessment than randomized clinical trials will be a significant detriment to patients in Washington State. In addition, other non-clinical factors should be considered when comparing IMRT to 3DCRT and 2DCRT. Patient experience can be greatly improved using IMRT, with decreased time on the treatment table directly related to patient comfort.

Attached, please find several edits to the report as well as additional pieces of evidence that should be considered before the report is finalized. Many critical trials of IMRT vs. other forms of radiotherapy are currently ongoing. Varian would like to provide additional clinical references by August 13th, 2012.

Thank you for your consideration of this information. Should you have any questions, please do not hesitate to contact me.

Sincerely,

Andrew M. Whitman
Vice President, Government Affairs

Edits for Draft Evidence Report:

1) On page 2, 18, 19, 29, 82, 84 etc. the draft report references a study by Hummel (2010) from the United Kingdom. Given the significant differences between the United States and British health systems, it may not be appropriate to compare these costs. When specifically referencing cost, Varian recommends that only U.S. studies should be used in the final report.

2) The references to Tipton, K. et al (2011a and 2011b) are related to Stereotactic Body Radiation Therapy, not IMRT and Varian recommends they should not be included in a final report on IMRT.

3) It is not appropriate to lump together 2DCRT and 3DCRT. They are significantly different.

4) Although we understand the need to limit the references to a specified date range in order to ensure review of the most up-to-date information, at least one study from 2001 is worthy of inclusion in the report and is listed below in the section on head and neck cancers. (Chao Washington University study)

5) On page 75 of the report, the Vergeer 2009 study was mentioned and is also included in the References section, but the significant quality of life benefits detailed in that study were not reported in the draft.

In addition to the above edits, Varian recommends that the studies and clinical guidelines listed below be considered for inclusion and reference in the final report on IMRT.

Head and Neck:

1) Radiother Oncol. 2012 Jul 30. [Epub ahead of print]

Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial. Gupta T, Agarwal J, Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, Murthy V, Budrukkar A, Dinshaw K, Prabhash K, Chaturvedi P, D'Cruz A.

http://www.ncbi.nlm.nih.gov/pubmed/22853852

Source: Advanced Centre for Treatment, Research & Education in Cancer (ACTREC), Tata Memorial Centre, Navi Mumbai, India.

PURPOSE: To compare three-dimensional conformal radiotherapy (3D-CRT) with intensity modulated radiation therapy (IMRT) in curative-intent irradiation of head-neck squamous cell carcinoma (HNSCC).

METHODS: Previously untreated patients with biopsy-proven squamous carcinoma of oropharynx, larynx, or hypopharynx (T1-3, N0-2b) were randomly assigned using computer-generated permuted-block design to either 3D-CRT or IMRT, with incidence of physician-rated Radiation Therapy Oncology Group (RTOG) grade 2 or worse acute salivary gland toxicity as primary end-point.

RESULTS: Between 2005 and 2008, 60 patients randomly allocated to either 3D-CRT (n=28 patients) or IMRT (n=32) were included and analyzed on an intention-to-treat basis. The proportion [95% confidence intervals (CI)] of patients with RTOG grade 2 or worse acute salivary gland toxicity was significantly lesser in the IMRT arm [19 of 32 patients (59%, 95%CI: 42-75%)] as compared to 3D-CRT [25 of 28 patients (89%, 95%CI: 72-97%; p=0.009)]. Late xerostomia and subcutaneous fibrosis were also significantly lesser with IMRT. There was significant recovery of salivary function over time in patients treated with IMRT (p-value for trend=0.0036). At 3-years, there were no significant differences in loco-regional control or survival between the two arms.

CONCLUSION: IMRT significantly reduces the incidence and severity of xerostomia compared to 3D-CRT in curative-intent irradiation of HNSCC.

2) Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. K.S. Clifford Chao, Navneet Majhail, Chih-jen Huang, Joseph R. Simpson, Carlos A. Perez, Bruce Haughey, Gershon Spector.

http://www.ncbi.nlm.nih.gov/pubmed/11730997

aDepartment of Radiation Oncology, Washington University Medical Center, St. Louis, MO, USA
bDepartment of Otolaryngology, Washington University Medical Center, St. Louis, MO, USA
Received 6 February 2001; received in revised form 21 August 2001; accepted 14 September 2001

Note: Although this study is from 2001, is it extremely important and should be considered for inclusion.

Conclusions: When IMRT was compared with conventional techniques, the dosimetric advantage of IMRT did translate into a significant reduction of late salivary toxicity in patients with oropharyngeal carcinoma. No adverse impact on tumor control and disease-free survival was observed in patients treated with IMRT.

3) INTENSITY-MODULATED RADIOTHERAPY REDUCES RADIATION-INDUCED MORBIDITYAND IMPROVES HEALTH-RELATED QUALITY OF LIFE: RESULTS OF A NONRANDOMIZED PROSPECTIVE STUDY USING A STANDARDIZED FOLLOW-UP PROGRAM. MARIJE R. VERGEER, M.D.,PATRICIA A. H. DOORNAERT, M.D.,DEREK H. F. RIETVELD, M.D.,C. RENE' LEEMANS, M.D., PH.D., BEN J. SLOTMAN, M.D., PH.D., AND JOHANNES A. LANGENDIJK, M.D., PH.D.

http://www.ncbi.nlm.nih.gov/pubmed/19111400

Department of Radiation Oncology, VU University Medical Center, Amsterdam, the Netherlands; Department of
Otolaryngology/Head and Neck Surgery, VU University Medical Center, Amsterdam, the Netherlands; and Department of Radiation
Oncology, University Medical Center Groningen, Groningen, the Netherlands
Conclusions: IMRT results in a significant reduction of patient- and observer-rated xerostomia, as well as other head and neck symptoms, compared with standard 3D-CRT. These differences translate into a significant improvement of the more general dimensions of HRQoL.

4) Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):1007-14. Epub 2011 Nov 4.
Reducing xerostomia after chemo-IMRT for head-and-neck cancer: beyond sparing the parotid glands. Little M, Schipper M, Feng FY, Vineberg K, Cornwall C, Murdoch-Kinch CA, Eisbruch A.

http://www.ncbi.nlm.nih.gov/pubmed/22056067

Source: Department of Radiation Oncology, University of Michigan, Ann Arbor, MI 48109, USA. eisbruch@umich.edu

PURPOSE: To assess whether, in addition to sparing the parotid glands (PGs), xerostomia after chemotherapy plus intensity-modulated radiotherapy (chemo-IMRT) for head-and-neck cancer is affected by reducing the dose to the other salivary glands.

PATIENTS AND METHODS: In a prospective study, 78 patients with Stage III-IV oropharynx/nasopharynx cancer underwent chemo-IMRT, with the aim of sparing the parts of the bilateral PGs, oral cavity (OC) containing the minor salivary glands, and contralateral submandibular gland (SMG) outside the target (when contralateral level I was not a target). Before therapy and periodically for 24 months, validated patient-reported xerostomia questionnaire (XQ) scores and observer-graded xerostomia scores were recorded. Also, the stimulated and unstimulated saliva was measured selectively from each of the PGs and SMGs. The mean OC doses served as surrogates of minor salivary gland dysfunction. Regression models assessed the XQ and observer-graded xerostomia predictors.

RESULTS: Statistically significant predictors of the XQ score on univariate analysis included the OC, PG, and SMG mean doses and the baseline XQ score, time since RT, and both stimulated and unstimulated PG saliva flow rates. Similar factors were statistically significant predictors of observer-graded xerostomia. The OC, PG, and SMG mean doses were moderately intercorrelated ($r = 0.47$-0.55). On multivariate analyses, after adjusting for the PG and SMG doses, the OC mean dose ($p < .0001$), interval from RT ($p < .0001$), and stimulated PG saliva ($p < .0025$) were significant predictors of the XQ scores and the OC mean dose and time for observer-graded xerostomia. Although scatter plots showed no thresholds, an OC mean dose of

<40 Gy and contralateral SMG mean dose of <50 Gy were each associated with low patient-reported and observer-rated xerostomia at almost all post-therapy points.

CONCLUSION: The PG, SMG, and OC mean doses were significant predictors of both patient-reported and observer-rated xerostomia after chemo-IMRT, with OC doses remaining significant after adjusting for the PG and SMG doses. These results support efforts to spare all the salivary glands by IMRT, beyond the PGs alone.

5) Clin Transl Oncol. 2012 Jul 24. [Epub ahead of print]
Outcomes and prognostic factors of conformal radiotherapy versus intensity-modulated radiotherapy for nasopharyngeal carcinoma.
Kuang WL, Zhou Q, Shen LF.

http://www.ncbi.nlm.nih.gov/pubmed/22855156

Source: Department of Oncology, Xiangya Hospital, Central South University, No. 87, Xiangya Road, Changsha, 410008, Hunan province, People's Republic of China.

INTRODUCTION: This study retrospectively compared outcomes and prognostic factors of nasopharyngeal carcinoma (NPC) treated with conformal radiotherapy (CRT) and intensity-modulated radiotherapy (IMRT).

MATERIALS AND METHODS: The treatment records of 182 patients treated with IMRT and 198 patients treated with CRT from April 2005 to December 2007 in our hospital were reviewed. The clinical characteristics, treatment outcomes (including survival analysis and acute and late toxicity), and prognostic factors of the two groups were compared.

RESULTS: The 4-year local-regional control (LRC), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) of the IMRT and CRT groups were 93.6 and 85.3 %, 79.1 and 73.6 %, 74.7 and 65.0 %, and 83.5 and 72.1 %, respectively. The acute radiation dermatitis and xerostomia of the two groups were significantly different ($P < 0.05$). In the IMRT group, OS between different T stages could not be well separated. Multivariate analysis revealed that, in the CRT group, the clinical stage and T and N stages were significant prognostic factors for OS, DMFS, and DFS and that T stage was a significant prognostic factor for LRC. In the IMRT group, T and N stages had no predictive value for outcomes.

CONCLUSIONS: Compared with CRT, IMRT has a better prognosis and less adverse effects. For IMRT, T stage was not a significant prognostic factor for LRC, DMFS, DFS, or OS. An effective treatment strategy is needed for distant control. With the increasing use of IMRT and continued modulation of treatment strategies for NPC, the current staging system faces great challenges.

6) Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer
http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=448&pageaction=displayproduct

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850

Prepared by:
Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center
Chicago, IL
Investigators
David J. Samson, M.S.
Thomas A. Ratko, Ph.D.
Barbara Mauger Rothenberg, Ph.D.
Heather M. Brown, M.D.
Claudia Bonnell, B.S.N., M.L.S.
Kathleen M. Ziegler, Pharm.D.
Naomi Aronson, Ph.D.

Key Quote: "...The strength of the body of evidence for IMRT reducing late xerostomia and improving quality of life compared with 3DCRT was graded as low, because of the overall poor quality of the available studies. However, the consistent results reported in favor of IMRT suggest a true effect. The observed reduction is unlikely the result of bias as susceptibility to xerostomia is common in the head and neck cancer population and it is unlikely between-group imbalances account for results. Thus, the evidence is consistent enough to suggest a true effect in favor of IMRT, but not precise enough to quantify the magnitude of effect..."

7) Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
http://www.ncbi.nlm.nih.gov/pubmed/20555078
Note: Not only US professional organizations but also groups around the world recommend the use of IMRT.

Prostate:

1) Preliminary Analysis of 3DCRT vs IMRT on the High Dose Arm of the RTOG 0126 Prostate Cancer Trial: Toxicity Report

http://www.oncolink.org/conferences/article.cfm?id=2166

Reporter: J Taylor Whaley
Affiliation: The Abramson Cancer Center of the University of Pennsylvania
Last Modified: October 3, 2011

Presenter: Jeff Michalski , MD
Presenter's Affiliation: Washington University Medical Center, St. Louis, MO
Trial was funded by the NCI and run by RTOG.

Background

- Numerous dosimetric and several single institution retrospective studies have evaluated the role of IMRT in the treatment of prostate cancer as a mechanism of dose escalation while limiting GU and GI toxicity. IMRT utilizes multiple beams and computerized planning to modulate the radiation beam, increasing target coverage while decrease the radiation dose to organs at risk.
- Dosimetric studies have consistently demonstrated decreased doses to bowel, bladder, and erectile structures with IMRT vs. 3D conformal radiation.
- Single institution data demonstrate decreased GI and GU toxicities with IMRT.
- The authors present preliminary analysis of clinical & treatment characteristics associated with acute & late toxicity in men receiving high dose RT on a phase III RTOG dose escalation trial.
- The trial was designed to evaluate dose-escalation for 79.2 vs 70.2 Gy; however, after 1.5 years of enrollment, the trial was amended to allow IMRT planning. This was an unplanned analysis of toxicity of IMRT vs 3D conformal in the high dose arm.

Materials and Methods

- 1548 patients were included in the trial. 748 patients were treated on the high dose arm. Patients were enrolled with Gleason Score 6 and PSA 10-20 or Gleason Score 7 and PSA <15.
- Patients treated with 3DCRT received 55.8 Gy to a PTV that included the prostate & proximal seminal vesicles (P+pSV) followed by a 23.4Gy to prostate only. IMRT patients were treated to the P+pSV to 79.2Gy.
- All radiation treatment plans were centrally reviewed.
- Physician reported toxicity was recorded.

Results

- 748 of 763 patients were randomized to the 79.2 Gy arm of RTOG 0126 were eligible & evaluable. 491 & 257 patients were treated with 3DCRT & IMRT, respectively.
- Median follow-up was 4.6 years & 3.5 years for 3DCRT & IMRT patients.
- Dosimetry outcomes were statistically improved with IMRT:

- The percent of the bladder receiving 65 Gy, 70 Gy and 75 Gy were 25.3%, 22.2%, and 17.7% for 3DCRT
- The percent of the bladder receiving 65 Gy, 70 Gy and 75 Gy were 19.7%, 16.6% and 13.1% for IMRT.
- The median rectum V65, V70 & V75 were 27.4%, 21.7%, & 15.8% for 3DCRT and 23.0%, 18.2% & 13.0% for IMRT.

- Acute GI/ GU toxicity:

	Grade 2	Grade 3	Grade 4/5
3D-CRT	16.90%	2.50%	0.00%
IMRT	13.90%	2.40%	0.00%

- Late GI/GU toxicity:

	Grade 2	Grade 3	Grade 4/5
3D-CRT	23.60%	8.90%	0.60%
IMRT	19.90%	4.70%	0.40%

- For Grade 2+ acute GI/GU toxicity, both univariate and multivariate analyses, show a statistically significant decrease in Grade 2+ acute collective GI/GU toxicity for IMRT. This translates into a 39% reduction in acute Grade 2+ toxicity with IMRT.
- There are no significant differences with 3DCRT or IMRT for acute or late Grade 2+ or 3+ GU toxicities.
- Despite a small number of events, univariate analysis shows a statistically significant decrease in late Grade 2+ GI toxicity for IMRT (p=0.039). On multivariate analysis, IMRT shows a trend for a 28% reduction in Grade 2+ late GI toxicity (p=0.099).
- Acute Grade 3+ toxicity was significantly associated with late Grade 3+ toxicity.
- In the multivariate analysis, RT modality is not significant whereas white race & a rectal V70 (volume receiving greater than 70 Gy)>15% are significantly associated with Grade 2+ rectal toxicity.

Author's Conclusions

- IMRT is associated with a statistically significant reduction in high dose volume of bladder and rectum doses.
- IMRT is associated with a statistically significant reduction in acute and late Grade 2+ GI toxicity.
- Rectum V70 <15% and V75< 10% are associated with increased risks of late GI toxicity. The occurrence of acute GI toxicity and large (>15%) volumes of rectum exceeding 70Gy are associated with late rectal toxicity.
- Race differences with increased toxicity documented in white patients was noted in the study.

Clinical Implications

- Dose-escalation has been demonstrated in randomized trials to improved biochemical failure free survival with external beam radiation therapy for prostate cancer; however, it must be done with appropriate constraints in place to minimize toxicities.
- Single institution data suggest IMRT allows dose escalation while decreasing acute and late toxicity.
- This trial is the first multi-institutional trial that demonstrates IMRT can be used for dose-escalation with decreased rates of toxicity. This study was not randomizing IMRT vs conventional radiation, and results should be evaluated with this in mind. Additionally, these data were recorded prior to the use of daily imaging guidance radiation therapy.
- Research should continue to attempt to develop mechanisms to allow dose escalation while minimizing dose to organs at risk.

2) Int J Radiat Oncol Biol Phys. 2012 Jul 12. [Epub ahead of print]
Long-term Survival and Toxicity in Patients Treated With High-Dose Intensity Modulated Radiation Therapy for Localized Prostate Cancer. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ.
http://www.ncbi.nlm.nih.gov/pubmed/22795805

Source: Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York

PURPOSE: To report long-term survival and toxicity outcomes with the use of high-dose intensity modulated radiation therapy (IMRT) to 86.4 Gy for patients with localized prostate cancer.

METHODS AND MATERIALS: Between August 1997 and December 2008, 1002 patients were treated to a dose of 86.4 Gy using a 5-7 field IMRT technique. Patients were stratified by prognostic risk group based on National Comprehensive Cancer Network risk classification criteria. A total of 587 patients (59%) were treated with neoadjuvant and concurrent androgen deprivation therapy. The median follow-up for the entire cohort was 5.5 years (range, 1-14 years).

RESULTS: For low-, intermediate-, and high-risk groups, 7-year biochemical relapse-free survival outcomes were 98.8%, 85.6%, and 67.9%, respectively (P<.001), and distant metastasis-free survival rates were 99.4%, 94.1%, and 82.0% (P<.001), respectively. On multivariate analysis, T stage (P<.001), Gleason score (P<.001), and >50% of initial biopsy positive core (P=.001) were predictive for distant mestastases. No prostate cancer-related deaths were observed in the low-risk group. The 7-year prostate cancer-specific mortality (PCSM) rates, using competing risk analysis for intermediate- and high-risk groups, were 3.3% and 8.1%, respectively (P=.008). On multivariate analysis, Gleason score (P=.004), percentage of biopsy core positivity (P=.003), and T-stage (P=.033) were predictive for PCSM. Actuarial 7-year grade 2 or higher late

gastrointestinal and genitourinary toxicities were 4.4% and 21.1%, respectively. Late grade 3 gastrointestinal and genitourinary toxicity was experienced by 7 patients (0.7%) and 22 patients (2.2%), respectively. Of the 427 men with full potency at baseline, 317 men (74%) retained sexual function at time of last follow-up.

CONCLUSIONS: This study represents the largest cohort of patients treated with high-dose radiation to 86.4 Gy, using IMRT for localized prostate cancer, with the longest follow-up to date. Our findings indicate that this treatment results in excellent clinical outcomes with acceptable toxicity.

3) Int J Radiat Oncol Biol Phys. 2012 Jun 1;83(2):630-5. Epub 2011 Nov 16.
Intensity-modulated radiotherapy causes fewer side effects than three-dimensional conformal radiotherapy when used in combination with brachytherapy for the treatment of prostate cancer. Forsythe K, Blacksburg S, Stone N, Stock RG.

http://www.ncbi.nlm.nih.gov/pubmed/22099032

Source: Department of Radiation Oncology, Mount Sinai School of Medicine, New York, NY 10029, USA.

PURPOSE: To measure the benefits of intensity-modulated radiotherapy (IMRT) compared with three-dimensional conformal radiotherapy (3D-CRT) when used in combination with brachytherapy for the treatment of prostate cancer.

METHODS AND MATERIALS: We conducted a retrospective review of all patients with localized prostate cancer who received external-beam radiotherapy (EBRT) in combination with brachytherapy with at least 1 year follow-up (n = 812). Combination therapy consisted of (103)Pd or (125)I implant, followed by a course of EBRT. From 1993 to March 2003 521 patients were treated with 3D-CRT, and from April 2003 to March 2009 291 patients were treated with IMRT. Urinary symptoms were prospectively measured with the International Prostate Symptom Score questionnaire with a single quality of life (QOL) question; rectal bleeding was assessed per the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema. The Pearson $\chi(2)$ test was used to compare toxicities experienced by patients who were treated with either IMRT or 3D-CRT. Logistic regression analyses were also performed to rule out possible confounding factors.

RESULTS: Within the first 3 months after treatment, patients treated with 3D-CRT scored their urinary symptoms as follows: 19% mild, 44% moderate, and 37% severe; patients treated with IMRT scored their urinary symptoms as follows: 36% mild, 47% moderate, and 17% severe ($p < 0.001$). The 3D-CRT patients rated their QOL as follows: 35% positive, 20% neutral, and 45% negative; IMRT patients rated their QOL as follows: 51% positive, 18% neutral, and 31% negative ($p < 0.001$). After 1 year of follow-up there was no longer any difference in urinary morbidity between the two groups. Logistic regression confirmed the differences in International Prostate Symptom Score and QOL in the acute setting ($p < 0.001$ for both). Grade

≥ 2 rectal bleeding was reported by 11% of 3D-CRT patients and 7% of IMRT patients (p = 0.046); logistic regression analysis also confirmed this observation (p = 0.040).

CONCLUSIONS: When used in combination with brachytherapy, IMRT offers less Grade ≥ 2 rectal bleeding, less acute urinary toxicities, and is associated with a higher QOL compared with 3D-CRT.

Cervical:

1) Gynecol Oncol. 2012 Apr;125(1):151-7. Epub 2011 Dec 22
Intensity-modulated radiation therapy for advanced cervical cancer: a comparison of dosimetric and clinical outcomes with conventional radiotherapy. Du XL, Tao J, Sheng XG, Lu CH, Yu H, Wang C, Song QQ, Li QS, Pan CX.

http://www.ncbi.nlm.nih.gov/pubmed/22198339

Source: Department of Gynecologic Oncology, Shandong Cancer Hospital, Jinan, People's Republic of China

OBJECTIVE: The aim of this study is to evaluate the dosimetry, efficacy and toxicity of reduced field intensity-modulated radiation therapy (RF-IMRT) for patients with advanced cervical cancer.

METHODS: From August 2005 to August 2010, 60 patients with stage IIB-IIIB cervical cancer underwent reduced field IMRT (RF-IMRT group) and 62 patients treated with conventional radiotherapy (c-RT group) were enrolled. The RF-IMRT plans were as follows: whole pelvic IMRT plan was performed to deliver a dose of 30Gy firstly, then the irradiated volume was reduced to lymphatic drainage region as well as paracervix and parametrium for an additional 30Gy boost. Intracavitary brachytherapy and concurrent chemotherapy were performed during external irradiation. The tumor coverage and normal tissue avoidance were evaluated. Treatment response, toxicities and survival were assessed.

RESULTS: The mean dose delivered to the planning target volume was significantly higher in RF-IMRT group than in c-RT group (61.5 vs. 50.8Gy, P=0.046). IMRT plans yielded better dose conformity to the target and better sparing of the rectal, bladder and small intestine. The RF-IMRT patients experienced significantly lower acute and chronic toxicities with comparable short-term effects than did those treated with conventional RT (CR: 87.7% vs. 88.3%, P=0.496; PR: 7.0% vs. 6.7%, P=0.440). No significant differences were found between treatment groups for 1year, 3year, and 5year overall survival (OS) levels, although the latter approached statistical significance in favor of IMRT, while a significantly higher progression-free survival (PFS; P=0.031) was seen for IMRT.

CONCLUSIONS: RF-IMRT yields improved dose distributions, with lower toxicities, while providing comparable clinical outcomes. The increased PFS may be an advantage.

APPENDIX A. SAMPLE IMRT POLICY SUBMITTED BY ASTRO

American Society for Therapeutic Radiation and Oncology (ASTRO) Model Policy on Intensity Modulated Radiation Therapy (IMRT)

Intensity Modulated Radiation Therapy (IMRT)

DESCRIPTION:
Intensity Modulated Radiation Therapy (IMRT) is a technology for delivering highly conformal external beam radiation to solid tumors. The radiation beams are customized for each patient; the treatment volume is well-defined and the beam intensity is modulated. The delivery of treatment with radiation beams whose intensity varies across the beam surface makes IMRT particularly useful for obtaining the highly conformal dose distributions needed to irradiate complex targets positioned near, or immediately adjacent to, sensitive normal tissues.

IMRT Treatment Planning:
IMRT treatment plans are geometrically more accurate and tailored to the target volumes than are conventional or three-dimensional radiation plans. The IMRT planning computer algorithm describes the necessary field sizes, gantry angles, and other beam characteristics needed to achieve the desired dose distribution. The essential feature of an IMRT plan is that it describes the means to deliver treatment utilizing non-uniform beam intensities.

Three-dimensional image acquisition by simulation (e.g., CT, MRI, PET or similar image fusion technology) is a prerequisite to IMRT treatment planning. The physician then outlines (contours) the visible abnormality seen on each slice of the image set. The three-dimensional summation of these contours defines the Gross Tumor Volume (GTV). The physician draws a margin around the GTV to generate a Clinical Target Volume (CTV) which encompasses the volume of tissue at risk for microscopic disease (not visible on imaging studies). To account for potential patient set-up variation or organ and patient motion, a final margin is then added to create what is termed the Planning Target Volume (PTV). The physician also contours nearby normal structures that potentially could be damaged by radiation ("organs at risk").

The physician must assign specific dose requirements for the PTV (minimum dose and dose homogeneity) and dose constraints for the organs at risk (maximum allowable doses). A treatment plan that satisfies these requirements and constraints should maximize the potential for disease control and minimize the risk of radiation injury to normal tissue.

Finally, the radiation physicist or a supervised dosimetrist calculates a complex multi-beam treatment plan that will deliver the prescription dose to the PTV and satisfy the normal tissue dose constraints. The radiation beam is, in effect, a collection of "beamlets," each with a different level of radiation intensity. The summation of these "beamlets" delivers the characteristic, highly conformal IMRT dose distribution. The PTV, therefore, receives a high dose of radiation while nearby organs receive significantly lower doses.

Prior to treatment delivery the physicist performs basic dose calculations on each of the modulated beams. These patient specific monitor unit computations verify through a second (independent of treatment planning) dose calculation method that the computer has correctly performed the

treatment planning calculations. The calculated beams are then delivered either to a phantom or a dosimetry measuring device to confirm that the point dose and dose distribution are physically verifiable and that the intensity modulated beams are technically feasible.

Documentation of all aspects of the planning process is essential.

IMRT Treatment Delivery:
IMRT treatment delivery can be accomplished through a variety of technologies. The most common approach utilizes a multi-leaf collimator (MLC) to modulate the intensity of the beam. Various forms of MLC technology include fixed gantry types such as *static* MLC (step and shoot) where the **leaves** do not move when the beam is on and *dynamic* MLC (sliding window) where they move during treatment. There are also moving **gantry** technologies including fan-beam therapy that uses a binary collimator to deliver slice-by-slice treatment and intensity modulated arc therapy, in which the gantry rotates while moving MLCs create non-uniform dose to the planning target volume during individual arc segments. A different technical solution for IMRT is to use a solid compensator with varying thickness filters to modulate the beam. The basic requirement for all forms of IMRT treatment delivery is that the technology must accurately produce the calculated dose distribution described by the IMRT plan.

The highly conformal dose distribution produced by IMRT results in much sharper spatial dose gradients than conventional or three-dimensional conformal radiation therapy. Consequently, small changes in patient or target position within the body can cause large changes in the dose delivered to the PTV and to the organs at risk. Thus patient immobilization is required for precision IMRT. A number of imaging techniques (e.g., ultrasound, kilovoltage or megavoltage cone beam CT scan, stereoscopic X-ray) may also be utilized to account for the daily motion of the PTV and more accurately deliver the treatment (Image Guided Radiation Therapy or IGRT). Changes in the location of the target within the body during a single fraction can arise from respiratory motion or other physiologic variances. To accommodate such changes the PTV may be drawn based upon published studies of organ motion or on dynamic imaging studies, or treatment delivery may be actively modulated by direct measures of motion during treatment.

INDICATIONS AND LIMITATIONS OF COVERAGE AND/OR MEDICAL NECESSITY:

INDICATIONS OF COVERAGE:

IMRT may offer advantages over conventional or three-dimensional conformal radiation. Before applying this technology, however, a comprehensive understanding of the benefits and consequences is required.

IMRT is not a replacement therapy for conventional or three-dimensional conformal radiation therapy methods. IMRT is considered reasonable and necessary in instances where sparing the surrounding normal tissue is of added benefit and *at least one* of the following conditions is met:

- The target volume is in close proximity to critical structures that must be protected.
- The volume of interest must be covered with narrow margins to adequately protect

immediately adjacent structures.
- An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision.
- The target volume is concave or convex, and critical normal tissues are within or around that convexity or concavity.
- Dose escalation is planned to deliver radiation doses in excess of those commonly utilized for similar tumors with conventional treatment.

IMRT is indicated as a standard treatment option for:

- Primary, metastatic or benign tumors of the central nervous system including the brain, brain stem and spinal cord;
- Primary, metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment
- Primary, metastatic, or benign lesions to the head and neck area including:
  - Orbits
  - Sinuses
  - Skull base
  - Aero-digestive tract
  - Salivary glands;
- Carcinoma of the prostate;
- Selected cases of thoracic and abdominal malignancies;
- Selected cases (i.e. not routine) of breast cancers with close proximity to critical structures;
- Other pelvic and retroperitoneal tumors that meet the requirements for medical necessity; and
- Reirradiation that meets the requirements for medical necessity.

Although IMRT is not indicated as the routine management for other cancers, IMRT is often reasonable and necessary treatment 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 of 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 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.

LIMITATIONS OF COVERAGE:
IMRT is not considered reasonable and necessary unless at least one of the criteria listed in the "Indications of Coverage" section of this policy is present.

PHYSICIANS' CURRENT PROCEDURAL TERMINOLOGY (CPT™)/HCPCS SECTION & BENEFIT CATEGORY (Note – CPT is a trademark of the American Medical Association (AMA) :
Therapeutic Radiology

CPT™/HCPCS CODES:

CPT Category I Code IMRT Treatment Planning

- **77301** *Intensity Modulated Radiation Therapy (IMRT) plan, including dose-volume histograms for target and critical structure partial tolerance specifications.*

  (Dose plan is optimized using inverse or forward planning technique for modulated beam delivery (e.g., binary dynamic MLC) to create highly conformal dose distribution. Computer plan distribution must be verified for positional accuracy based on dosimetry verification of the intensity map with verification of treatment set-up and interpretation of verification methodology)

  This code is typically reported only once per course of IMRT.

CPT Category I Code for Collimator-based IMRT Treatment Delivery

- **77418** *Intensity Modulated Radiation Therapy (IMRT) delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session*

CPT Category III Code Compensator-based IMRT Treatment Delivery

- **0073T** *Compensator-based beam modulation treatment delivery of inverse planned treatment using three or more high resolution (milled or cast) compensator convergent beam modulated fields, per treatment session*

Medical Radiation Physics, Dosimetry and Treatment Devices

Basic Radiation Dosimetry

Basic radiation dosimetry is a separate and distinct service from IMRT planning and should be reported accordingly. The radiation dose delivered by each IMRT beam must be individually calculated and verified before the course of radiation treatment begins. Thus, multiple basic dosimetry calculations (up to 10) are typically performed and reported on in a single day. Supporting documentation should accompany a claim for more than ten (10) calculations in a single day.

CPT Category I Codes for IMRT Dosimetry

77300 *radiation therapy dose plan*

Treatment Devices

There are several categories of treatment devices used in conjunction with the delivery of IMRT radiotherapy. Immobilization treatment devices are commonly employed to ensure that the beam is accurately on target. In addition, the radiation oncologist is responsible for the design of the series of treatment devices that define the beam geometry. The beam aperture, the dose constraints per beam, the couch and gantry angles for each portal, and the coverage requirements all must be evaluated in order to guide the generation of the multi-leaf collimator segments. It is appropriate to report a treatment device CPT code for each complex IMRT field (i.e., gantry/table angle for step and shoot and sliding windows). It should not be billed for each segment within the field. CPT code 77334 is typically billed multiple times (often on the same day of service), once for each of the separate IMRT fields as required by the

plan during the course of IMRT treatment. The typical case will require up to ten (10) devices. A claim for the use of more than ten (10) should be submitted with supporting documentation.

CPT Category I Codes for IMRT Treatment Devices

77332 *treatment devices, design and construction; simple*

77333 *treatment devices, design and construction; intermediate*

77334 *treatment devices, design and construction; complex*

Image Guided Radiation Therapy

Image Guided Radiation Therapy (IGRT) utilizes imaging technology to modify treatment delivery to account for changes in the position of the intended target. IGRT is used in conjunction with IMRT in patients whose tumors are located near or within critical structures and/or in tissue with inherent setup variation. Thus, although IGRT is a distinct service, it may be used and documented along with IMRT treatment delivery (77418) when necessary.

CPT Category I Codes for IGRT

76950 *Ultrasonic guidance for placement of radiation therapy fields*

77014 *Computed tomography guidance for placement of radiation fields* (*this code replaces 76370)

77421 *Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy.*

ICD-9-CM CODES THAT SUPPORT MEDICAL NECESSITY:

ICD-9 Code	Description
140.0 – 140.9	MALIGNANT NEOPLASM OF UPPER LIP VERMILLION BORDER – MALIGNANT NEOPLASM OF LIP UNSPECIFIED VERMILLION BORDER
141.0 – 141.9	MALIGNANT NEOPLASM OF BASE OF TONGUE – MALIGNANT NEOPLASM OF TONGUE UNSPECIFIED
142.0	MALINANT NEOPLASM OF PAROTID GLAND
142.1	MALIGNANT NEOPLASM OF SUBMANDIBULAR GLAND
142.2	MALIGNANT NEOPLASM OF SUBLINGUAL GLAND
142.8	MALIGNANT NEOPLASM OF OTHER MAJOR SALIVARY GLANDS
142.9	MALIGNANT NEOPLASM OF SALIVARY GLAND, UNSPECIFIED
144.0	MALIGNANT NEOPLASM OF ANTERIOR PORTION OF FLOOR OF MOUTH
144.1	MALIGNANT NEOPLASM OF LATERAL PORTION OF FLOOR OF MOUTH
144.8	MALIGNANT NEOPLASM OF OTHER SITES OF FLOOR OF MOUTH
144.9	MALIGNANT NEOPLASM OF FLOOR OF MOUTH, PART UNSPECIFIED
145.0	MALIGNANT NEOPLASM OF CHEEK MUCOSA
145.1	MALIGNANT NEOPLASM OF VESTIBULE OF MOUTH
145.2	MALIGNANT NEOPLASM OF HARD PALATE
145.3	MALIGNANT NEOPLASM OF SOFT PALATE
145.4	MALIGNANT NEOPLASM OF UVULA
145.5	MALIGNANT NEOPLASM OF PALATE, UNSPECIFIED
145.6	MALIGNANT NEOPLASM OF RETROMOLAR AREA
145.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED PARTS OF MOUTH
145.9	MALIGNANT NEOPLASM OF MOUTH, UNSPECIFIED
146.0	MALIGNANT NEOPLASM OF TONSIL
146.1	MALIGNANT NEOPLASM OF TONSILLAR FOSSA
146.2	MALIGNANT NEOPLASM OF TONSILLAR PILLARS (ANTERIOR) (POSTERIOR)
146.3	MALIGNANT NEOPLASM OF VALLECULA EPIGLOTTICA
146.4	MALIGNANT NEOPLASM OF ANTERIOR ASPECT OF EPIGLOTTIS
146.5	MALIGNANT NEOPLASM OF JUNCTIONAL REGION OF OROPHARYNX
146.6	MALIGNANT NEOPLASM OF LATERAL WALL OF OROPHARYNX
146.7	MALIGNANT NEOPLASM OF POSTERIOR WALL OF OROPHARYNX
146.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF OROPHARYNX
146.9	MALIGNANT NEOPLASM OF OROPHARYNX, UNSPECIFIED SITE
147.0	MALIGNANT NEOPLASM OF SUPERIOR WALL OF NASOPHARYNX
147.1	MALIGNANT NEOPLASM OF POSTERIOR WALL OF

ICD-9 Code	Description
	NASOPHARYNX
147.2	MALIGNANT NEOPLASM OF LATERAL WALL OF NASOPHARYNX
147.3	MALIGNANT NEOPLASM OF ANTERIOR WALL OF NASOPHARYNX
147.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF NASOPHARYNX
147.9	MALIGNANT NEOPLASM OF NASOPHARYNX, UNSPECIFIED SITE
148.0	MALIGNANT NEOPLASM OF POSTCRICOID REGION OF HYPOPHARYNX
148.1	MALIGNANT NEOPLASM OF PYRIFORM SINUS
148.2	MALIGNANT NEOPLASM OF ARYEPIGLOTTIC FOLD, HYPOPHARYNGEAL ASPECT
148.3	MALIGNANT NEOPLASM OF POSTERIOR HYPOPHARYNGEAL WALL
148.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF HYPOPHARYNX
148.9	MALIGNANT NEOPLASM OF HYPOPHARYNX, UNSPECIFIED SITE
149.0	MALIGNANT NEOPLASM OF PHARYNX, UNSPECIFIED
149.1	MALIGNANT NEOPLASM OF WALDEYER'S RING
149.8	MALIGNANT NEOPLASM OF OTHER SITES WITHIN THE LIP AND ORAL CAVITY
149.9	MALIGNANT NEOPLASM OF ILL-DEFINED SITES WITHIN THE LIP AND ORAL CAVITY
150	MALIGNANT NEOPLASM OF ESOPHAGUS
150.0	MALIGNANT NEOPLASM OF CERVICAL ESOPHAGUS
150.1	MALIGNANT NEOPLASM OF THORACIC ESOPHAGUS
150.2	MALIGNANT NEOPLASM OF ABDOMINAL ESOPHAGUS
150.3	MALIGNANT NEOPLASM OF UPPER THIRD ESOPHAGUS
150.4	MALIGNANT NEOPLASM OF MIDDLE THIRD ESOPHAGUS
150.5	MALIGNANT NEOPLASM OF LOWER THIRD ESOPHAGUS
150.8	MALIGNANT NEOPLASM OF ESOPHAGUS, OTHER SPECIFIED PART
150.9	MALIGNANT NEOPLASM OF ESOPHAGUS UNSPECIFIED
151.0 – 151.9	MALIGNANT NEOPLASM OF CARDIA – MALIGNANT NEOPLASM OF STOMACH UNSPECIFIED SITE
153	MALIGNANT NEOPLASM OF COLON
153.0	MALIGNANT NEOPLASM OF HEPATIC FLEXURE
153.1	MALIGNANT NEOPLASM OF TRANSVERSE COLON
153.2	MALIGNANT NEOPLASM OF DESCENDING COLON
153.3	MALIGNANT NEOPLASM OF SIGMOID COLON
153.4	MALIGNANT NEOPLASM OF CECUM
153.5	MALIGNANT NEOPLASM OF APPENDIX
153.6	MALIGNANT NEOPLASM OF ASCENDING COLON
153.7	MALIGNANT NEOPLASM SPLENIC FLEXURE

ICD-9 Code	Description
153.8	MALIGNANT NEOPLASM OTHER SPECIFIED SITES OF LARGE INTESTINE
153.9	MALIGNANT NEOPLASM COLON, UNSPECIFIED
154	MALIGNANT NEOPLASM OF RECTUM, RECTOSIGMOID JUNCTION, AND ANUS
154.0	MALIGNANT NEOPLASM OF RECTOSIGMOID JUNCTION
154.1	MALIGNANT NEOPLASM OF RECTUM
154.2	MALIGNANT NEOPLASM OF ANAL CANAL
154.3	MALIGNANT NEOPLASM OF ANUS, UNSPECIFIED
154.8	MALIGNANT NEOPLASM OF RECTUM, RECTOSIGMOID JUNCTION, AND ANUS , OTHER
155	MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BILE DUCTS
155.0	MALIGNANT NEOPLASM OF LIVER, PRIMARY
155.1	MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS
155.2	MALIGNANT NEOPLASM OF GALLBLADDDER AND EXTRAHEPATIC BILE
156	MALIGNANT NEOPLASM OF GALLBLADDER AND EXTRAHEPATIC BILE DUCTS
156.0	MALIGNANT NEOPLASM OF GALLBLADDER
156.1	MALIGNANT NEOPLASM OF EXTRAHEPATIC BILE DUCTS
156.2	MALIGNANT NEOPLASM OF AMPULLA VATER
156.8	OTHER SPECIFIED SITES OF GALLBLADDER AND EXTRAHEPATIC BILE DUCTS
156.9	MALIGNANT NEOPLASM OF BILLIARY TRACT, PART UNSPECIFIED
157	MALIGNANT NEOPLASM OF PANCREAS
157.0	MALIGNANT NEOPLASM HEAD OF PANCREAS
157.1	MALIGNANT NEOPLASM BODY OF PANCREAS
157.2	MALIGNANT NEOPLASM TAIL OF PANCREAS
157.3	MALIGNANT NEOPLASM PANCREATIC DUCT
157.4	MALIGNANT NEOPLASM ISLETS OF LANGERHANS
157.8	MALIGNANT NEOPLASM OTHER SPECIFIED SITES OF PANCREAS
157.9	MALIGNANT NEOPLASM PANCREAS, PART UNSPECIFIED
158.0	MALIGNANT NEOPLASM OF RETROPERITONEUM
158.8	MALIGNANT NEOPLASM OF SPECIFIED PARTS OF PERITONEUM
158.9	MALIGNANT NEOPLASM OF PERITONEUM, UNSPECIFIED
160.0	MALIGNANT NEOPLASM OF NASAL CAVITIES
160.1	MALIGNANT NEOPLASM OF AUDITORY TUBE, MIDDLE EAR, AND MASTOID AIR CELLS
160.2	MALIGNANT NEOPLASM OF MAXILLARY SINUS
160.3	MALIGNANT NEOPLASM OF ETHMOIDAL SINUS
160.4	MALIGNANT NEOPLASM OF FRONTAL SINUS

ICD-9 Code	Description
160.5	MALIGNANT NEOPLASM OF SPHENOIDAL SINUS
160.8	MALIGNANT NEOPLASM OF OTHER ACCESSORY SINUSES
160.9	MALIGNANT NEOPLASM OF ACCESSORY SINUS, UNSPECIFIED
161.0 – 161.9	MALIGNANT NEOPLASM OF GLOTTIS – MALIGNANT NEOPLASM OF LARYNX UNSPECIFIED
162	MALIGNANT NEOPLASM OF TRACHEA, BRONCHUS, AND LUNG
162.0	MALIGNANT NEOPLASM TRACHEA
162.2	MALIGNANT NEOPLASM MAIN BRONCHUS
162.3	MALIGNANT NEOPLASM UPPER LOBE, BRONCHUS OR LUNG
162.4	MALIGNANT NEOPLASM MIDDLE LOBE, BRONCHUS OR LUNG
162.5	MALIGNANT NEOPLASM LOWER LOBE, BRONCHUS OR LUNG
162.8	MALIGNANT NEOPLASM OTHER PARTS OF BRONCHUS OR LUNG
162.9	BRONCHUS AND LUNG, UNSPECIFIED
163	MALIGNANT NEOPLASM OF PLEURA
163.0	MALIGNANT NEOPLSAM PARIETAL PLEURA
163.1	MALIGNANT NEOPLASM VISCERAL PLEURA
163.8	MALIGNANT NEOPLASM OTHER SPECIFIED SITES OF PLEURA
163.9	MALIGNANT NEOPLASM PLEURA UNSPECIFIED
164	MALIGNANT NEOPLASM OF THYMUS, HEART AND MEDIASTINUM
164.0	MALIGNANT NEOPLASM OF THYMUS
164.1	MALIGNANT NEOPLASM OF HEART
164.2	MALIGNANT NEOPLASM OF ANTERIOR MEDIASTINUM
164.3	MALIGNANT NEOPLASM OF POSTERIOR MEDIASTINUM
164.8	OTHER OF THYMUS, HEART MEDIASTINUM
164.9	MALIGNANT NEOPLASM MEDIASTINUM PART UNSPECIFIED
171.0	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE OF HEAD, FACE, AND NECK
171.2	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE OF UPPER LIMB, INCLUDING SHOULDER
171.3	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE OF LOWER LIMB, INCLUDING HIP
171.4	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE OF THORAX
171.5	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE OF ABDOMEN
171.6	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE OF PELVIS
171.7	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT TISSUE OF TRUNK, UNSPECIFIED
171.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF CONNECTIVE AND OTHER SOFT TISSUE
171.9	MALIGNANT NEOPLASM OF CONNECTIVE AND OTHER SOFT

ICD-9 Code	Description
	TISSUE, SITE UNSPECIFIED
174	MALIGNANT NEOPLASM OF FEMALE BREAST
174.0	MALIGNANT NEOPLASM NIPPLE AND AREOLA
174.1	MALIGNANT NEOPLASM CENTRAL PORTION
174.2	MALIGNANT NEOPLASM UPPER INNER QUADRANT
174.3	MALIGNANT NEOPLASM LOWER INNER QUADRANT
174.4	MALIGNANT NEOPLASM UPPER OUTER QUADRANT
174.5	MALIGNANT NEOPLASM LOWER OUTER QUADRANT
174.6	MALIGNANT NEOPLASM AXILLARY TAIL
174.8	OTHER SPECIFIED SITES OF FEMALE BREAST
175	MALIGNANT NEOPLASM OF MALE BREAST
175.0	MALIGNANT NEOPLASM OF NIPPLE AND AREOLA
175.9	OTHER AND UNSPECIFIED SITES OF MALE BREAST
179 -183.9	MALIGNANT NEOPLASM OF UTERUS-PART UNS – MALIGNANT NEOPLAMS OF UTERINE ADNEXA UNSPECIFIED SITE
184 – 184.9	MALIGNANT NEOPLASM OF OTHER AND UNSPECIFIED FEMALE GENITAL ORGANS
185	MALIGNANT NEOPLASM OF PROSTATE
188.0 – 188.9	MALIGNANT NEOPLASM OF TRIGONE OF URINARY BLADDER – MALIGNANT NEOPLASM OF BLADDER PART UNSPECIFIED
189.0 – 189.9	MALIGNANT NEOPLASM OF KIDNEY EXCEPT PELVIS – MALIGNANT NEOPLASM OF URINARY ORGAN SITE UNSPECIFIED
190.0	MALIGNANT NEOPLASM OF EYEBALL, EXCEPT CONJUNCTIVA, CORNEA, RETINA, AND CHOROID
190.1	MALIGNANT NEOPLASM OF ORBIT
190.2	MALIGNANT NEOPLASM OF LACRIMAL GLAND
190.3	MALIGNANT NEOPLASM OF CONJUNCTIVA
190.4	MALIGNANT NEOPLASM OF CORNEA
190.5	MALIGNANT NEOPLASM OF RETINA
190.6	MALIGNANT NEOPLASM OF CHOROID
190.7	MALIGNANT NEOPLASM OF LACRIMAL DUCT
190.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF EYE
190.9	MALIGNANT NEOPLASM OF EYE, PART UNSPECIFIED
191.0	MALIGNANT NEOPLASM OF CEREBRUM, EXCEPT LOBES AND VENTRICLES
191.1	MALIGNANT NEOPLASM OF FRONTAL LOBE
191.2	MALIGNANT NEOPLASM OF TEMPORAL LOBE
191.3	MALIGNANT NEOPLASM OF PARIETAL LOBE
191.4	MALIGNANT NEOPLASM OF OCCIPITAL LOBE
191.5	MALIGNANT NEOPLASM OF VENTRICLES
191.6	MALIGNANT NEOPLASM OF CEREBELLUM NOS
191.7	MALIGNANT NEOPLASM OF BRAIN STEM

ICD-9 Code	Description
191.8	MALIGNANT NEOPLASM OF OTHER PARTS OF BRAIN
191.9	MALIGNANT NEOPLASM OF BRAIN, UNSPECIFIED SITE
192.0	MALIGNANT NEOPLASM OF CRANIAL NERVES
192.1	MALIGNANT NEOPLASM OF CEREBRAL MENINGES
192.2	MALIGNANT NEOPLASM OF SPINAL CORD
192.3	MALIGNANT NEOPLASM OF SPINAL MENINGES
192.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF NERVOUS SYSTEM
192.9	MALIGNANT NEOPLASM OF NERVOUS SYSTEM, PART UNSPECIFIED
193	MALIGNANT NEOPLASM OF THYROID GLAND
194.0	MALIGNANT NEOPLASM OF ADRENAL GLAND
194.1	MALIGNANT NEOPLASM OF PITUITARY GLAND
194.5	OTHER ENDOCRINE GLANDS, CAROTID BODY
194.6	OTHER ENDOCRINCE GLANDS, AORTIC BODY AND OTHER PARAGANGLIA
195.0	MALIGNANT NEOPLASM OF HEAD, FACE, AND NECK
195.1	MALIGNANT NEOPLASM OF THORAX
195.2	MALIGNANT NEOPLASM OF ABDOMEN
195.3	MALIGNANT NEOPLASM OF PELVIS
195.4	MALIGNANT NEOPLASM OF UPPER LIMB
195.5	MALIGNANT NEOPLASM OF LOWER LIMB
195.8	MALIGNANT NEOPLASM OF HEAD, FACE, AND NECK - OTHER SPECIFIED SITES
196.0 – 196.9	SECONDARY AND UNSPECIFIED MALIGNANT NEOPLASM OF LYMPH NODES OF HEAD, FACE, AND NECK – SECONDARY AND UNSPECIFIED MALIGNANT NEOPLASM OF LYMPH NODES SITE UNSPECIFIED
197.0	SECONDARY MALIGNANT NEOPLASM OF LUNG
197.1	SECONDARY MALIGNANT NEOPLASM OF MEDIASTINUM
197.6	SECONDARY MALIGNANT NEOPLASM OF RETGROPERITONEUM AN DPERITONEUM
197.7	SECONDARY MALIGNANT NEOPLASM OF LIVER
197.8	SECONDARY MALIGNANT NEOPLASM OF OTHER DIGESTIVE ORGANS AND SPLEEN (e.g. pancreas, gallbladder, biliary tract)
198.0	SECONDARY MALIGNANT NEOPLASM OF KIDNEY
198.1	SECONDARY MALIGNANT NEOPLASM OF OTHER URINARY ORGANS
198.3	SECONDARY MALIGNANT NEOPLASM OF BRAIN AND SPINAL CORD
198.4	SECONDARY MALIGNANT NEOPLASM OF OTHER PARTS OF NERVOUS SYSTEM
198.5	SECONDARY MALIGNANT NEOPLASM OF BONE AND BONE

ICD-9 Code	Description
	MARROW
198.6	SECONDARY MALIGNANT NEOPLASM OF OVARY
198.82	SECONDARY MALIGNANT NEOPLASM OF GENITAL ORGANS
198.89	SECONDARY MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES
201	HODGKIN'S DISEASE
201.0	HODGKIN'S PARAGRANULOMA
201.1	HODGKIN'S GRANULOMA
201.2	HODGKIN'S SARCOMA
201.4	LYMPHOCYTIC-HISTIOCYTIC PREDOMINANCE
201.5	NODULAR SCLEROSIS
201.6	MIXED CELLULARITY
201.7	LYMPHOCYTIC DEPLETION
201.9	HODGKIN'S DISEASE, UNSPECIFIED
202	OTHER MALIGNANT NEOPLASMS OF LYMPHOID AND HISTIOCYTIC TISSUE
202.0	NODULAR LYMPHOMA
202.8	OTHER LYMPHOMAS
202.80	UNSPECIFIED SITE, EXTRANODAL AND SOLID ORGAN SITES
202.81	LYMPH NODES OF HEAD, FACE, AND NECK
202.82	INTRATHORACIC LYMPH NODES
202.83	INTRA-ABDOMINAL LYMPH NODES
202.84	LYMPH NODES OF THE AXILLA AND UPPER LIMB
202.85	LYMPH NODES OF INGUINAL REGION AND LOWER LIMB
202.86	INTRAPELVIC LYMPH NODES
202.87	SPLEEN
202.88	LYMPH NODES OF MULTIPLE SITES
202.9	OTHER AND UNSPECIFIED MALIGNANT NEOPLASMS OF LYMPHOID AND HISTIOCYTIC TISSUE
208.8	OTHER LEUKEMIA OF UNSPECIFIED CELL TYPE
213	BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE
213.0	BONES OF SKULL AND FACE
213.1	LOWER JAW BONE
213.2	VERTEBRAL COLUMN, EXCLUDING SACRUM AND COCCYX
213.3	RIBS, STERNUM, AND CLAVICLE
213.4	SCAPULA AND LONG BONES OF UPPER LIMB
213.5	SHORT BONES OF UPPER LIMB
213.6	PELVIC BONES, SACRUM, AND COCCYX
213.7	LONG BONES OF LOWER LIMB
213.8	SHORT BONES OF LOWER LIMB
213.9	BONE AND ARTICULAR CARTILAGE, SITE UNSPECIFIED
225.1	BENIGN NEOPLASM OF CRANIAL NERVES

ICD-9 Code	Description
225.2	BENIGN NEOPLASM OF CEREBRAL MENINGES
227.3	BENIGN NEOPLASM OF PITUITARY GLAND AND CRANIOPHARYNGEAL DUCT
227.4	BENIGN NEOPLASM OF PINEAL GLAND
227.6	BENIGN NEOPLASM OF AORTIC BODY AND OTHER PARAGANGLIA
228.1	LYMPHANGIOMA, ANY SITE
336.9	UNSPECIFIED DISEASE OF SPINAL CORD
459.2	COMPRESSION OF VEIN /STRICTURE OF VEIN/ VENA CAVA SYNDROME (INFERIOR) (SUPERIOR)
747.81	CONGENITAL ANOMALIES OF CEREBROVASCULAR SYSTEM

DIAGNOSES THAT SUPPORT MEDICAL NECESSITY:
Codes that indicate primary tumors or metastases as listed in the "Indications" section and the "ICD-9-CM Codes That Support Medical Necessity" section of this policy.

ICD-9-CM CODES THAT DO NOT SUPPORT MEDICAL NECESSITY:
ICD-9-CM Codes not listed under the "ICD-9 Codes That Support Medical Necessity" section of this policy are typically not covered. However, clinical circumstances rather than specific diagnoses may be the most important determinants for using IMRT.

REASONS FOR DENIAL:
IMRT is not considered reasonable and necessary when none of the criteria listed in the "Indications" of coverage section and none of the diagnosis listed in the "ICD-9-CM Codes That Support Medical Necessity" section of this policy are present.

DOCUMENTATION REQUIREMENTS:
Documentation in the patient's medical records must support:

1. The reasonable and necessary requirements as outlined under the "Coverage and Limitations" sections of this policy and must be available to the Contractor for review upon request.
2. The prescription must define the dose to the target and the dose constraints to the nearby critical structures.
3. A note of medical necessity for IMRT, by the treating physician.
4. Signed IMRT inverse plan that meets prescribed dose constraints for the planning target volume (PTV) and surrounding normal tissue.
5. The target verification methodology must include the following:
    a. Documentation of the clinical treatment volume (CTV) and the planning target volume (PTV).
    b. Documentation of immobilization and patient positioning.
6. Independent basic dose calculations of monitor units have been performed for each beam before the patient's first treatment.
7. Documentation of fluence distributions (re-computed and measured in a phantom or dosimetry measuring device) is required.

8. Identification of structures that traverse high-and low-dose regions created by respiration is indicated. Voluntary breath-holding alone is not a satisfactory solution for accounting for organ motion.

CODING GUIDELINES:

The following CPT codes were used as *building blocks* during the development of the IMRT planning CPT code. They are components of CPT code 77301 and therefore should not be separately coded or billed on the same day of service.

CPT® Code	CPT® Code Descriptor
76370 / 77014 (deleted/current)	Computerized axial tomography guidance for placement of radiation therapy fields
76375/ 76376 (deleted/current)	Coronal, sagittal, multiplanar, oblique, three-dimensional and/or holographic reconstruction of computerized axial tomography, magnetic resonance imaging, or other tomography modality
77295	Therapeutic radiology simulation-aided field setting; Three-dimensional simulation
77331	Special radiation dosimetry

The following list of codes should also not be reported on the *same date of service* as IMRT planning (77301). They may, however, correctly be used, as needed, for medically necessary simulation and treatment planning during the course of IMRT treatment (i.e. with code 77418.).

CPT® Code	CPT® Code Descriptor
77280	Therapeutic radiology simulation-aided field setting, simple
77285	Therapeutic radiology simulation-aided field setting, intermediate
77290	Therapeutic radiology simulation-aided field setting, complex
77305	Teletherapy, isodose plan (whether had or computer calculated); simple (one or two parallel opposed unmodified ports directed to a single area of interest
77310	Teletherapy, isodose plan (whether had or computer calculated); intermediate (three or more treatment ports directed to a single area of interest)
77315	Teletherapy, isodose plan (whether had or computer calculated); Complex (mantle or inverted Y, tangential ports, the use of wedges, compensators, complex blocking, rotational beam, or special beam considerations).

UTILIZATION GUIDELINES:

AMA CPT COPYRIGHT STATEMENT:

GENERAL IMRT REFERENCES:

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APPENDIX B.REFERENCES AND ATTACHMENTS SUBMITTED BY VARIAN MEDICAL SYSTEMS

A Review of Intensity Modulated Radiation Therapy (IMRT): A Cost Effective, Personalized Form of Radiation Therapy

Radiation therapy (RT) is used to treat approximately 67% of cancer patients in the US, one or more times during the course of their treatment, or about 1 million patients per year (ASTRO fact sheet, 2009).

In the early 1990s, the standard of care was to deliver RT using a set of intersecting beams, each shaped in two dimensions to the contour of the cancer. Called 3-D conformal radiation therapy (3-D CRT), the combination of two dimensionally shaped beams produces a three dimensional high dose region that approximates the shape of the cancer.

In the late 1990s, the use of a more sculpted beam of RT became common: Intensity Modulated Radiation Therapy, or IMRT. Each IMRT beam does more than simply conform to the shape of the cancer in two dimensions. It actually varies the intensity of the RT according to the dimensions of the cancer in three dimensions. A single IMRT beam is composed of many small "beamlets"; each can be a different intensity. Very complicated cancer shapes can be created, with rapid fall-off of dose immediately outside the cancer. IMRT improves the dosimetry of 3-D CRT, and is often compared with 3-D CRT in clinical studies.

Due to the increase in the utilization of IMRT over the last decade, the complexity of IMRT to plan and administer, and because at first, there was limited published clinical data, some have criticized IMRT as expensive medicine with uncertain benefit. This handout provides an overview of recent data related to the clinical effectiveness of IMRT and describes studies that are currently underway so the reader will understand the reasons for increased adoption of IMRT.

The goal of IMRT is to escalate the dose delivered to the target in order to achieve higher local cancer control rates, without a corresponding increase in normal tissue toxicity. The results are sufficiently encouraging to stimulate further clinical development (see Tables 1 & 2). Initial data indicate that cancer control after IMRT is superior to results from 3-D CRT and randomized controlled phase III trials are underway. The beam shaping and variation in dose intensity of IMRT is done specifically for each cancer patient and is "personalized" RT.

CLINICAL RESULTS SINCE THE INTRODUCTION OF IMRT

This handout reports comparisons between 3-D CRT and IMRT in terms of toxicity, quality of life (QOL) and cancer control outcomes for several different cancers, based on both published data and on clinical trial data not yet published. (It takes an average of 6.75 years for a data set to go from treatment to publication—see Figure 1). For each data set described, the dates of the patient treatments are given. Data have not yet been reported for patients treated after 2006. This handout covers the types of cancer treatments for which the most IMRT data exist. There is no study or data set where patients treated with IMRT have a worse outcome than 3-D CRT with respect to tumor control as measured by local control, disease free survival or overall survival. Not reviewed are data for brain, gastrointestinal, gynecological, sarcoma, and other cancer sites for which there are limited studies.

Extensive data are published on the dosimetric and physics advantages of IMRT compared to 3-D CRT (Braaksma, 2003; Luxton, 2004).

Breast Cancer

RT is well established as a treatment for early breast cancer patients. Studies report that RT results in both increased local control of the cancer and increased survival rates (Yang, 2009, Poortmans, 2007). IMRT has had a major role in limiting acute and chronic toxicity and improving the quality of life for women who receive RT (Table 3).

Head & Neck Cancer – Nasopharynx

Nasopharyngeal cancer is endemic in China and Southeast Asia. The standard of care is a combination of chemotherapy and RT (Lu, 2009). The toxicities of RT and concurrent chemotherapy are often severe, causing delays or dose reductions during chemotherapy, interruptions of RT, and diminished QOL for patients. When toxicities force alterations in the planned therapy, this can lead to decreased cancer control. The use of IMRT has substantially decreased these toxicities, and decreased interruptions in planned therapy.

The principle results of studies that looked at IMRT as compared with earlier forms of RT for nasopharyngeal cancer patients showed decreased normal tissue toxicity and improved local control of cancers. These results are not likely to be unique to nasopharyngeal cancer patients (Table 4).

Head & Neck Cancer – Oropharynx

A phase III multicenter trial (PARSPORT) in the United Kingdom compared IMRT to 3-D CRT in the treatment of pharyngeal cancer patients (Nutting et al. 2009). The percentage of 3-D CRT patients experiencing grade 2 or worse xerostomia was 64%, compared with 41% from the IMRT group – a statistically significant difference.

A retrospective study (Clavel, 2009) compared the toxicity and the efficacy of 3-D CRT and IMRT administered to patients who were also receiving chemotherapy for locally advanced cancer of the oropharynx. The results after three years of follow-up give significantly improved overall survival, disease free survival, and locoregional control of the tumor with IMRT (Table 5).

French physicians did a matched pair analysis of head and neck patients treated with IMRT vs. 3-D CRT (Graff et al. 2007). They studied 67 pairs of patients. Using validated QOL questionnaires, they reported statistically significant improvements in QOL for patients treated with IMRT, including less dry mouth, sticky saliva, mouth pain, jaw pain, and swallowing and eating difficulties. Xerostomia greater than grade 2 occurred in 67% of the 3-D CRT patients and in only 12% of the IMRT patients. There were no differences in cancer control outcomes.

Lung Cancer

Several physics and dosimetry studies have compared 3-D CRT and IMRT treatment plans for the treatment of locally advanced lung cancer (i.e. stages III and IV). The resulting dose distributions and dose volume histograms show better sparing of normal tissues with IMRT. The IMRT plans, delivered lower doses to the healthy lung, esophagus, heart, and spinal cord (Christian, 2006; Liu, 2003; Grills, 2003).

Several clinical studies report that higher doses of RT delivered to the cancer result in improved local cancer control (Kong, 2005; Rengan, 2004). Since IMRT makes it possible for physicians to deliver higher doses without causing commensurate levels of toxicity in healthy tissues, future studies may show greater treatment efficacy with IMRT. Current clinical trials are designed to evaluate whether IMRT can deliver higher doses while holding toxicity to acceptable levels. The outcomes that these studies are designed to measure include local cancer control, toxicity, and QOL (Table 6).

Prostate Cancer

The studies reported to date comparing 3-D CRT with IMRT in the treatment of prostate cancer are not controlled trials, but are retrospective comparisons of 2 cohorts of patients treated in different years. Some studies use a "matched pair" form of analysis.

All of these studies concern "early stage" patients. The definition of early stage varies, and involves age, tumor stage, PSA value and Gleason score. Because of these differences, the studies can be somewhat difficult to directly compare. Some also use different criteria for evaluating PSA control as an endpoint.

IMRT in the treatment of prostate cancer is used for two clinical aims: reduction of treatment toxicity and improvement in disease free survival (DFS). In the quest for higher rates of DFS, some centers have used IMRT to escalate the dose to the prostate, delivering doses that would produce unacceptable levels of toxicity using 3-D CRT. Other centers choose to stay with lower doses, and use IMRT only to reduce toxicity. Some level of urinary toxicity from RT to the prostatic urethra, which runs through the center of the prostate, is unavoidable.

Several randomized trials demonstrate that higher doses of 3-D CRT produce a better DFS rate (Goldner, 2009; Zelefsky, 2008). The Fox Chase Cancer Center experience with prostate cancer patients shows a dose response for doses from less than 72 Gy to greater than 76 Gy (Pollack, 2004). IMRT makes it possible to deliver doses that are higher (≥80 Gy), and there is evidence that these higher doses produce even longer DFS, especially in low and intermediate risk patients.

Patients in the Memorial Sloan-Kettering Cancer Center (MSKCC) study (Cahlon, 2008) attained a higher PSA

control rate and a much lower rectal toxicity rate than patients in the M.D. Anderson Cancer Center (MDACC) study (Kuban, 2008). This is likely because the MSKCC physicians used IMRT and the MDACC physicians did not (Table 7).

RTOG sponsored a phase III trial (0126) comparing different RT doses in the treatment of prostate cancer. The study, which opened in March 2002 and closed in August 2008, involved 1,532 patients. The participating institutions chose whether to use 3-D CRT or IMRT based on technical capability. Patients were randomly assigned to the 70.2 Gy or 79.2 Gy dose groups after the RT treatment modality was selected. About one-third of the patients received IMRT. The study is in the follow up period, and will report on toxicity levels, QOL, PSA failure rates, disease free survival, and overall survival.

The current RTOG trial (0415) for early stage prostate cancer patients compares two other treatment regimens: delivery of 70 Gy delivered over 28 fractions as compared with 73.8 Gy delivered over 41 fractions. Again, the choice of 3-D CRT or IMRT is made by each institution, prior to the randomly assigned dose regimen. The outcomes measured are the same as in the previous trial described above.

These two RTOG trials will allow for a comparison of 3-D CRT and IMRT.

Ongoing Clinical Trials

A search of the NCI clinical trials database for IMRT trials, conducted in August 2009, yielded 169 results; 55 were not pertinent or had been withdrawn. Table 1 gives a listing by cancer type and study phase. The 21 phase III trials, which are ongoing, will yield more data on the value of IMRT in the ensuing years.

Specific RTOG trials using IMRT are listed in Table 2.

Conclusions

A key question regarding IMRT is whether IMRT is cost effective. The cost is higher than other forms of RT, mostly due to increased physician and other staff time. The additional time spent in planning and delivering IMRT is now a necessary part of maintaining accuracy.

With time, more of the processes involved in planning and delivering IMRT treatments will be computer controlled, so staff time will decrease. Manufacturers of RT equipment and software have made significant progress in producing tools that make IMRT easier and faster to plan and deliver. As clinicians perform more IMRT, their speed and proficiency has improved. New, faster forms of IMRT are now available, which speed up delivery, and thereby increase the throughput and reduce the cost per patient.

The effectiveness is initially evidenced by better treatment plans designed to deliver more dose to the cancer and less to surrounding healthy tissues. This allows for less normal tissue toxicity, which maintains the patients QOL. Toxicity prevention is cost effective when compared to the cost of administering treatments for such toxicities.

Better cancer control occurs when higher doses of RT or better combinations of RT and chemotherapy are possible. This is supported by data in the treatment of head & neck, lung and prostate cancer. No data set reports worse outcomes for IMRT patients (Table 8).

The broad use of IMRT will lead to more clinical studies and opportunities to demonstrate lower cost and increased effectiveness. IMRT use started in 1994 and 15 years later the data on IMRT is starting to mature. Within 5 years the number of studies involving IMRT treatments and their outcomes will double. IMRT is not a treatment offered only in academic medical centers, but is used daily in community-based cancer care settings around the world.

Figure 1 – Date Timetable in Months

It takes an average of 6.75 years for a data set to go from treatment to publication

Treatment	Follow Up	Data Analysis	Time to Publication	Overall Time →
24 – 36 months	24 – 36 months	1 – 3 months	12 – 24 months	61 – 99 months (average 81 months or 6.75 years)

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Table 1 – Clinical Trials of IMRT from the NCI Clinical Trials Data System as of August 2009

Cancer Site	Phase I	Phase II	Phase III	Total
Breast	2	10	4	16
Head & Neck	5	28	4	37
Head & Neck Nasopharyngeal		5	1	6
Lung	3	4	2	9
Prostate	5	13	9	27
Anal		2		2
Rectal	2			2
Pancreatic		2		2
Glioblastoma	1			1
Brain Mets	4	3		7
Cervical	1	1		2
Sarcoma		2	1	3
Total	23	70	21	114

Table 2 – Radiation Therapy Oncology Group (RTOG) Trials Involving IMRT (N=14) as of December 2009

RTOG #	Phase	Cancer Site	Therapy	# Patients	Date Started – Completed
0615	II	Head & Neck Nasopharynx	Chemo + 3-D CRT or IMRT	46	12/06 – 12/09
0522	III	Head & Neck	Accelerated RT or IMRT + chemo +/- C225	942	11/05 – 3/09
0920	III	Head & Neck	Pre op IMRT +/- C225	0 / 700	11/09 –
0538 CALGB	III	Small Cell Lung	RT + chemo 3 RT schema		3/08 –
0126	III	Prostate	70.2 vs 79.2 Gy 3-D CRT or IMRT	1,532	3/02 – 8/08
0415	III	Prostate	70 Gy in 28 fxs vs 73.8 Gy in 41 fxs 3-D CRT or IMRT	1,067	4/06 – 11/09
0521	III	Prostate	72-75.6 Gy 3-D CRT or IMRT	603	12/05 – 8/09
0621	II	Prostate	Post op RT 3-D CRT or IMRT	46 / 76	4/08 –
0622	II	Prostate	Post op 3-D CRT or IMRT + Samarium 153	9 / 76	4/08 –
0529	II	Anal	Dose painted IMRT & chemo	63	12/06 – 3/08
0822	II	Rectum	IMRT & chemo	75	4/08 – 11/09
0630	II	Extremity Sarcomas	Pre op RT 3-D CRT or IMRT +/- chemo	50 / 102	3/08 –
0921	II	Uterus	IMRT + Cisplatin + Bevacizumab	0 / 34	11/09 –
0418	II	Cervix, Uterus	IMRT +/- chemo Post op	48 / 58	3/06 – 10/08

Table 3 – IMRT Clinical Data
Breast Cancer – 4 Studies

Reference	Institution	Years Patient Treated	# of Patients	Therapy	Outcomes	Comments
Barnett, 2009	Cambridge England	4/06-6/07	404 411	2D Wedged Pair vs. IMRT		Randomized study Improved dose distribution Final results pending
Pignol, 2008	Canada	7/03-3/05	161 170	2D RT or IMRT	Moist desquamation 48% 31%	Correlates with pain and QOL
McDonald, 2008	Emory	1/99-12/03	124 121	3DCRT or IMRT	Skin Toxicity 52% 39%	No differences in tumor control or survival Retrospective comparison
Freedman, 2008	Fox Chase Cancer Center	2001-2006	405 399	2D RT or IMRT	Skin Toxicity 75% 52%	Retrospective comparison

Table 4 – IMRT Clinical Data
Nasopharynx Cancer – 5 Studies

Reference	Institution	Years Patient Treated	# of Patients	Therapy	Outcomes	Comments
Pow, 2006	University of Hong Kong	6/00-7/04	21 46	2D RT vs. IMRT	Improved salivary function and QOL scores with IMRT	Stage II
Kam, 2007	Hong King	11/01-12/03	28 28	2D RT vs. IMRT	Xerostomia grade ≥ 2 at 1 yr 82% 39%	Better saliva flow rates and QOL with IMRT
Lee, 2009	RTOG	2/03-11/05	68	IMRT + Chemo	92% 2 yr local control	
Tham, 2009	Singapore	2002-2005	195	IMRT +/- Chemo	3% Xerostomia (grade 3) 90% 3 yr local control 94% 3 yr survival	
Wong, 2009	China	6/04-12/05	175	IMRT +/- Chemo	94% local control 87% regional control 87% 3 yr survival	

Table 5 – IMRT Clinical Data
Oropharynx and Other Head and Neck Cancers – 5 Studies

Reference	Institution	Years Patient Treated	# of Patients	Therapy	Outcomes			Comments
Nutting, 2009	United Kingdom Group (Parsport)	2003-2007	47 47	3DCRT vs. IMRT	Xerostomia grade ≥ 2 64% 41% p < .05			Oropharynx
Clavel, 2009	Montreal	1/00-12/07	149 100	3DCRT or IMRT RT + Chemo	3 yr survival 3 yr NED survival 3 yr local control	3DCRT 76% 72% 85%	IMRT 95% 89% 92%	Stage III or IV oropharynx
Lee, 2006	Memorial Cancer Center	9/98-6/04	71 41	3DCRT or IMRT	2 yr. feeding tube Xerostomia grade ≥ 2	3DCRT 21% 64%	IMRT 4% 41%	
van Rij, 2008	Netherlands	1/99-12/03	88 75	3DCRT or IMRT	IMRT QOL better scores			
Graff, 2006	France	1/01-1/05	67 67	3DCRT or IMRT	Xerostomia grade ≥ 2 67% 12%			QOL matched pair analysis

Table 6 – IMRT Clinical Data
Lung Cancer – 1 Study

Reference	Institution	Years Patient Treated	# of Patients	Therapy	Outcomes	Comments
Yom, 2007	MD Anderson	8/02-8/05	222 68	3D CRT + Chemo IMRT + Chemo	Pneumonitis at 1 year 32% 8%	Stage III, IMRT had larger lung vols.

Table 7 – Prostate Cancer Therapy for Early Stage Disease

Treatment	Author	Center	Year Pub.	# of Patients	Median Follow-Up (Months)	Dose (Gy) / # Fx	Prostate BED [a/B=1.5] (Gy)	% PSA Relapse	Late Normal Tissue BED [a/B=3]	% Grade 2 + 3 Chronic Urinary Toxicity	% Grade 2 + 3 Chronic Rectal Toxicity	% Chronic Erectile Dysfunction
3D Conformal Radiotherapy	Kuban, 2008	M.D. Anderson Cancer Center	2008	151	104	78 / 39	182	22	130	7+3	19+7	ND
High Dose IMRT	Cahlon, 2008	Memorial Sloan-Kettering	2008	478	53	86.4 / 48	190	15	138	13+3	2+1	34
Prostatectomy	Walsh, 1994	Johns Hopkins	1994	995	4	NA	NA	18	NA	8	1	32
Robotic Prostatectomy	Badani, 2007	Henry Ford	2007	2766	22	NA	NA	16	NA	ND	ND	21

NA = Not Applicable
ND = No Data Reported

Table 8 – IMRT Clinical Value

Cancer Type	Decreased Local Toxicity	Increased Tumor Dose	Increased Local Control	Increased Disease Free Survival
Nasopharynx	Yes	NE	Yes	Yes
Oropharynx	Yes	NE	Yes	Yes
Other Head & Neck	Yes	NE	Yes	NE
Breast	Yes	NE	NE	NE
Lung	Yes	Yes	NE	NE
Prostate	Yes	Yes	Yes	NE

NE = Not Evaluable

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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Head and Neck Cancers

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Discussion

RADIATION TECHNIQUES[1-8]

Target delineation and optimal dose distribution require experience in head and neck imaging, and a thorough understanding of patterns of disease spread. Standards for target definition, dose specification, 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.[9]

Intensity-Modulated Radiotherapy (IMRT)

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 (eg, oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians.

IMRT and Fractionation[10,11]

A number of ways exist to integrate IMRT, target volume dosing, and fractionation. The Simultaneous Integrated Boost (SIB) technique uses differential "dose painting" (66-74 Gy to gross disease; 50-60 Gy to subclinical disease) for each fraction of treatment throughout the entire course of radiation.[4] SIB is commonly used in conventional (5 fractions/week) and the "6 fractions/week accelerated" schedule.[5] The Sequential (SEQ) IMRT technique typically delivers the initial (lower dose) phase (weeks 1-5) followed by the high-dose boost volume phase (weeks 6-7) using 2-3 separate dose plans, and is commonly applied in standard fractionation and hyperfractionation. The Concomitant Boost Accelerated schedule may utilize a "Modified SEQ" dose plan by delivering the dose to the subclinical targets once a day for 6 weeks, and a separate boost dose plan as a second daily fraction for the last 12 treatment days.[6]

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