Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer

Draft review available for public comment from July 24, 2009 to August 22, 2009.

Research Review Citation: Samson DJ, Ratko TA, Rothenberg BM, Brown HM, Bonnell CJ, Ziegler KM, Aronson N. Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer. Comparative Effectiveness Review No. 20. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality. May 2010. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Comment Section	Comment	Response
Introduction	This section provided a description of the toxicities associated with the treatment of head and neck cancer and some of the different toxicity grading and classification instruments. There was not any concerted effort, however, to describe the limitations of the systems themselves. A recognition and understanding of these limitations is important, because they too contribute to the difficulties in making comparative assessments of the toxicities associated with IMRT, 3D CRT and 2D RT. Unlike the ultimate measure of efficacy, survival, toxicity is a longitudinal, non-dichotomous endpoint. Most toxicity assessments simply report peak incidence and do not account for the temporal burden of toxicity incorporating both severity and duration (AUC assessment). Furthermore, the different classification systems often are at odds with one another , some emphasize anatomic effects while others focus on functional effects.. Finally, although all of the systems assign toxicity scores, a subjective component to assessment remains; thus, there can be significant inter-assessor variability unlike for assessment of toxicities such as absolute neutrophil count, which is completely quantitative.	A critique of the limitations of toxicity classification systems is beyond the scope of this report.
Introduction	1, 53: [with the exception of certain subsites stages (eg, nasopharynx, hypopharynx, advanced neck disease)]	Text added as suggested.
Introduction	2, 18: [in certain settings]	Text added as suggested.
Introduction	3, 39: [and pediatrics - brain tumors]	The text now reads as follows: "Although proton beam therapy has been used to treat tumors for more than 50 years, it has been used mostly in the treatment of prostate cancer, in addition to brain tumors, including those in children."
Methods	5, 42: [why not consider ASCO abstracts]	We reviewed the ASCO abstracts for the past five years and noted so in the Methods chapter.
Methods	10, 21: [concurrent is likely most relevant for local RT toxicity]	We did not limit the review to any particular treatment setting.
Methods	11, 20: [was addressed]	No action necessary.

Comment Section	Comment	Response
Methods	13, 23: [would consider cisplatin-based separately; local toxicity may differ by chemotherapy agent and mode of administration (eg, concurrent)]	Studies generally did not provide sufficient details about chemotherapeutic agents. The following bullet has been added to item 4 in the Future Research chapter: • Clear details are needed about timing, dose and specific chemotherapy agents given.
Methods	11, 7: [would consider IMRT vs 3D and 2D both alone and combined]	The topic as assigned was to address four individual modalities: IMRT, 3DCRT, 2DRT and proton beam therapy, not combinations.
Results	62, 18: [3D vs 2D but text refers to IMRT]	Text added as suggested.

Comment Section	Comment	Response
Results	**Comment:** There is no mention of the recent British randomized study comparing IMRT and 3DCRT for pharyngeal cancers and demonstrating significantly reduced xerostomia for IMRT. The reference is: First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer Meeting: 2009 ASCO Annual Meeting Abstract No: LBA6006 Citation: J Clin Oncol 27:18s, 2009 (suppl; abstr LBA6006) Author(s): C. Nutting, R. A'Hern, M. S. Rogers, M. A. Sydenham, F. Adab, K. Harrington, S. Jefferies, C. Scrase, B. K. Yap, E. Hall, On behalf of the PARSPORT Trial Management Group; Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; The Institute of Cancer Research, Sutton, Surrey, United Kingdom; University Hospital of North Staffordshire, Stoke on Trent, United Kingdom; Addenbrooke's Hospital NHS Foundation Trust, Cambridge, United Kingdom; The Ipswich Hospital NHS Trust, Ipswich, United Kingdom; The Christie NHS Foundation Trust, Manchester, United Kingdom	The PARSPORT randomized, controlled trial (Nutting et al., 2009) presented at the 2009 meeting of the American Society of Clinical Oncology has been incorporated into the CER, resulting in raising the strength of the evidence for IMRT vs 3DCRT or 2DRT on late xerostomia and quality of life from low to moderate.

Comment Section	Comment	Response
Tables	17, 41: [3D vs 2D but footnote refers to IMRT]	No such footnote on C-17, line 41.
General Comment	This draft represents an extensive critical review of the literature related to the comparative effectiveness of IMRT, 2D, and 3D RT in the treatment of HN cancer. We acknowledge the thorough work performed by the authors and the comprehensive review of the literature on such an important topic. We understand that a large amount of work was put into this study and such a comprehensive document will be very useful for future studies to improve the quality of radiation therapy for head and neck cancers. We agree with to the decision to omit protons from this review as the data was too sparse. The study therefore focused on comparison between IMRT and 3D or 2D RT. The main conclusions were that overall the quality of the evidence is quite poor, however, taking into account consistent results, it can be concluded that some aspects related to xerostomia and some other domains of QOL are improved by IMRT compared with 2D or 3D. Our major Comments relate to the interpretation by the authors on the clinical relevance of major aspects in this large accumulated body of published clinical research.	No action necessary.

Comment Section	Comment	Response
General Comment	1. The authors examined separately the evidence related to IMRT vs 3D RT, IMRT vs 2D RT, and 3D vs 2D. These comparisons are largely redundant. In almost all cases the designation 3Dmeans simply 2D RT (lateral opposed beams, typically matched to an anterior low-neck field) using beams eye-views to help draw field edges to conform to the targets, without an intention to spare any organ. 3D represents an improvement in radiotherapy, mainly due to the benefit of CT-treatment planning: the radiotherapist has a higher certainty that the targets are being adequately irradiated. This technical improvement is not expected to yield measurable differences in tumor control, unless a very large number of patients with similar tumors are randomized. This is not likely to happen; one may argue that merely increasing the certainty of radiation delivery does not require more testing than, for example, delivering chemotherapy using accurate vs. non-accurate measurements of its delivered quantity. On the other hand, delivering 2D radiotherapy using the higher precision provided by 3D is not expected to change side effects or QOL, as no organ is spared. This includes the majority of the 3D RT papers, and excludes a small minority in which 3D techniques aimed specifically at sparing the parotid glands. Thus, IMRT should be compared to the literature dealing with both 2D and 3D RT. This literature is now very extensive. Such a comparison will now include 3 randomized studies (including C. Nutting et al, presented at ASCO 2009, J Clin Oncol 2009;27(18s):799). All three randomized studies, as well as all phase II-like and retrospective comparisons, report improved xerostomia using IMRT. We agree that all the randomized studies were small and that multivariate analyses for confounding factors could not be done. However, we do not agree that this body of experience can be regarded as having low strength.	No action necessary. While some readers may be more interested in comparisons between IMRT and either 3DCRT or 2DRT, the topic as assigned involved comparing any of the specified modalities, so we also reviewed 3DCRT vs. 2DRT. Regarding strength of evidence, the overall rating has been raised from low to moderate, incorporating the evidence from the PARSPORT trial.

Comment Section	Comment	Response
General Comment	2. We agree with the reviewers that there are trends for improvement in other domains of QOL in IMRT compared with 2D or 3D (see the randomized study of Pow et al and few retrospective studies: Graaf et al, Vergeer et al.), but additional good-quality studies are still necessary.	No action necessary.
General Comment	3. We agree that there is no evidence that IMRT increases tumor control rates. The superior dose distributions gained by IMRT may have an advantage in some patients with advanced tumors near critical organs, but this advantage needs to be balanced by the risk of marginal recurrences due to the steep dose gradients in the vicinity of the tumors. This issue requires more study.	No action necessary.
General Comment	4. Remaining Issues(p. ES-5): First paragraph: We agree that there are some differences between planned and delivered doses. These potential differences have been the subject of extensive research in recent years. We also agree that there are differences in patient susceptibility to specific side effect such as xerostomia. However, we strongly disagree with the statement that Therefore, comparative evidence on clinical outcome is necessary to establish that the technical capability of IMRT do indeed benefit patients. There is ample evidence, including 3 randomized studies and multiple non-randomized ones proving the benefit regarding xerostomia, as detailed above. The differences in patients susceptibility to xerostomia are dwarfed by the xerostomia caused by 2D or 3D RT and the proven benefits provided by IMRT. No further evidence is necessary to establish the benefit of IMRT regarding xersotomia. We agree that further study is required in order to document its benefits regarding other, non-xerostomia-related, aspects of QOL.	The CER concludes that relative to 3DCRT or 2DRT, IMRT reduces the frequency of late xerostomia and improves quality of life. This paragraph states that dose characteristics are insufficient alone to support conclusions about comparative effects for other outcomes, rather evidence for those particular outcomes is needed. We agree that additional evidence is no longer needed about late xerostomia and quality of life and the CER has been modified accordingly to make this clear.

Comment Section	Comment	Response
General Comment	5. The paragraph: Indeed, the capabilities of IMRT to deliver higher doses to the tumor site may in fact present a risk ..should be removed: There are small numbers of clinical studies examining tumor dose escalation. Besides careful phase I-II studies of dose escalation, a policy of delivering higher doses using IMRT is not practiced clinically off protocol and therefore should not be part of this report. This paragraph is completely speculative.	The original wording gave the mistaken impression that IMRT should be used routinely to escalate dose. This is not the meaning we intend to convey. This sentence has been modified to emphasize steep dose gradients: "The capability of IMRT to deliver steep dose gradients around a tumor site may present a risk as well as potential benefit."
General Comment	6. The overriding statement that xerostomia is common in patients with advanced cancers is highly speculative and needs supporting references. In addition, there is an increasing trend for younger patients being diagnosed with oropharygeal carcinoma from HPV-related causes both in the US and in Europe (Refs: Frisch M, Hjalgrim H, Jaeger AB, Biggar RJ. Changing patterns of tonsillar squamous cell carcinoma in the United States. Cancer Causes Control 2000; 11:489495, Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 2044 years. Cancer 2005; 103:18431849, Licitra L, Zigon G, Gatta G, et al. Human papillomavirus in HNSCC: a European epidemiologic perspective. Hematol Oncol Clin North Am 2008; 22:11431153). Most of these young patients do not have xerostomia at the time of diagnosis and are relatively healthy with minimal other medical co-morbidities. They also have a better prognosis and most are long term survivors after therapy. Therefore, preserving salivary function is even more critical in these patients. This fact needs to be acknowledged somewhere in this section.	We have corrected the impression that xerostomia is common in patients with advanced cancers. However, a young patients population is not represented in the comparative evidence we reveiwed. The statement about susceptibility to xerostomia has been modified as follows: "Xerostomia has a significant impact on quality of life. It appears to be common in patients with certain tumor sites, radiotherapy treatments and chemotherapeutic regimens. Older age and certain therapies for chronic diseases may increase susceptibility for this adverse effect. Research to improve the management of xerostomia and to disseminate that knowledge to clinical practice could potentially improve morbidity and quality of life for cancer patients."

Comment Section	Comment	Response
General Comment	7. Future research should put high priority on multicenter trials& randomized controlled trials are needed to assess survival outcomes... We believe that it will be very difficult enroll patients onto a randomized IMRT vs 2D or 3D RT trial if the same radiation fractionation and doses are used, considering the results of the 3 non-US randomized trials as mentioned above (bullet 1) and the unlikely impact of IMRT on local control when the same radiation dose are used (see bullet 3). Therefore, we believe that future directions should focus optimizing the dose/fraction schedule of IMRT while taking advantage of its ability for dose painting as well as integrating high dose IMRT with novel systemic treatment and targeted therapy. Such studies will be more likely to advance the field of head and neck cancer.	We have added acknowledgement of the challenges of conducting randomized, controlled trials of IMRT to address non-xerostomia adverse events, tumor control and survival: "There are considerable obstacles to conducting randomized, controlled trials to ascertain tumor control and survival effects. These are: wide dissemination of IMRT, reluctance to randomize patients when effects on xerostomia are already known, the large numbers such trials would require, and other priorities for funding. Nonetheless, certainty about tumor control and survival outcomes can ideally be obtained through a robust randomized, controlled trial." Regarding the relation between dose distribution and outcomes such as tumor control and survival, text has been added to explicitly identify dose distribution as an intermediate outcome: Dose distribution data is considered an intermediate outcome, which may be related to health outcomes, but by itself does not establish the comparative effectiveness of different radiotherapy techniques. The sentence appears in the Methods chapter under Study Selection, Types of Studies, 2nd paragraph between 2nd and 3rd bullet and in the Summary and Discussion chapter, after the summary table.

Comment Section	Comment	Response
General Comment	**Comparative Studies: IMRT vs. 3DCRT** . . . acknowledges that the primary concern raised in the report is the lack of randomized data to definitively demonstrate superior clinical outcomes with the use of IMRT, and the authors prioritize a need for randomized controlled trials (RCT). . . . notes, however, that the results of an RCT directly comparing IMRT to 3DCRT were presented at the 2009 ASCO Annual Meeting1 during the time this draft was being written and thus is not included in the draft. This multi-institutional trial from the United Kingdom randomized 94 patients with advanced head and neck cancer to IMRT vs. 3DCRT and demonstrated significant improvements in independently assessed subjective xerostomia by LENT SOM ($p = 0.003$) and RTOG criteria ($p < 0.001$), with no decrement in survival outcomes. This trial complements two earlier RCTs which document similar improvements in toxicity following use of IMRT compared to 2DRT (which would be expected to yield results very similar to 3DRT) for treatment of nasopharyngeal cancer2,3 which are cited by the AHRQ authors.	We noted above the addition of this new evidence. The PARSPORT randomized, controlled trial (Nutting et al., 2009) presented at the 2009 meeting of the American Society of Clinical Oncology has been incorporated into the CER**,** resulting in raising the strength of the evidence for IMRT vs 3DCRT or 2DRT on late xerostomia and quality of life from low to moderate.

Comment Section	Comment	Response
General Comment	. . . is concerned that if the size, design, and consistent results of these multiple RCTs do not satisfy AHRQ's threshold for significance, then a number of important issues require clarification. We question who would be interested in financing follow-up RCTs so long after widespread adoption of the technology, based on the volume and consistency of literature supporting the use of IMRT. If AHRQ believes further RCTs are necessary in this area, we urge you to advocate for government funding for RTOG trials through the National Cancer Institute or to conduct additional study through AHRQ's comparative effectiveness mechanisms.	We have added acknowledgement of the challenges of conducting randomized, controlled trials of IMRT to address non-xerostomia adverse events, tumor control and survival: "There are considerable obstacles to conducting randomized, controlled trials to ascertain tumor control and survival effects. These are: wide dissemination of IMRT, reluctance to randomize patients when effects on xerostomia are already known, the large numbers such trials would require, and other priorities for funding. Nonetheless, certainty about tumor control and survival outcomes can ideally be obtained through a robust randomized, controlled trial." We do not comment on whether such randomized, controlled trials are a high funding priority.
General Comment	Another important question is what the appropriate endpoints are. It is critical to recognize that with anticipated local disease control rates of ~90% in the modern era, it will take an extremely large sample size to show any difference in treatment efficacy between IMRT and older techniques. Unlike other disease sites such as prostate cancer, the emphasis of head and neck IMRT studies has been on reducing toxicity (e.g., xerostomia) while maintaining equivalent disease control. A phase III trial to demonstrate reduced toxicity with IMRT would need to be powered for non-inferiority, again requiring a very large study cohort. We would be interested to know if AHRQ is willing to work with NCI to fund, staff and advise on such a trial.	As noted above, we acknowledge the challenges of conducting randomized, controlled trials of IMRT to address non-xerostomia adverse events tumor control and survival: We do not commen on whether such randomized, controlled trials are a high funding priority.

Comment Section	Comment	Response
General Comment	The intersection between coverage and accrual to clinical trials is significant in radiation oncology. We are concerned that private insurers may drop IMRT coverage in response to this draft report. One of the unintended consequences would likely be that without private insurer coverage, it would be more difficult to accrue patients outside of the Medicare-age population. This would be particularly unfortunate as these under-65 year old patients are those who stand to benefit most from the dose sparing benefits of IMRT. We urge AHRQ to be mindful of such unintended consequences to our patients when it issues its final paper.	The potential impact of this CER's conclusions on coverage decisions is beyond the scope of this report. The conclusions were based on faithful application of clearly described systematic review methods.
General Comment	Another hurdle is that culturally, it is difficult to imagine the acceptance for randomization of patients away from IMRT. If the issue of equipoise is at play in the eyes of first degree stakeholders, would such a trial be considered ethical? Additionally, we are concerned that any marginal benefit from such a future trial would be outweighed as it would divert resources away from other pressing cancer treatment questions and delay deployment of technologies which may further improve IMRT.	As noted above, we acknowledge the challenges of conducting randomized, controlled trials of IMRT.
General Comment	**Data Supporting Head &Neck (H&N) IMRT** Radiation oncology is a data-driven specialty which has been committed to generating and adapting clear standards of care from randomized, prospective, multi-institutional trials and detailed consensus technical recommendations. The history and accomplishments of . . . testify to this fact. The field frequently relies upon institutional observational series to assess efficacy and safety of emerging technologies due to unavoidable limitations in patient numbers and financial resources.	No action necessary.

Comment Section	Comment	Response
General Comment	. . . is concerned that there is more data to support use of H&N IMRT than has been cited in this report. The report cites none of the prospective assessment of H&N IMRT by RTOG. RTOG 00224 and 02255 are just now being reported, and RTOG 0625 has just completed enrollment. All of these phase II multi-institutional trials have confirmed the feasibility and safety of IMRT across institutions. Both RTOG 0022 and 0225 have demonstrated preliminary survival (89-91% 2-year locoregional disease control in oropharyngeal and nasopharyngeal sites) and parotid toxicity outcomes (13.5-25% grade >2 late xerostomia, with continued improvement at later time points) which compare favorably to results from older 3DRT series. In addition, two phase III RTOG trials (0522 and 0234) have 3DRT and IMRT treatment populations which could be compared to provide exploratory health technology assessment (HTA) analysis of high quality, RCT-derived data. . . . would be pleased to work with AHRQ to formally compare the historical RTOG 3DRT morbidity and survival data with this emerging RTOG IMRT outcomes data.	The primary focus of this CER was comparative studies using any of the key radiotherapy modalities: IMRT, 3DCRT, 2DRT or proton beam therapy. None of the studies cited were comparative studies of the relevant radiotherapy modalities. Specifically, RTOG 00224 and 02255 are single-arm studies, not comparative. RTOG 0522 and 0234 are not randomized comparisons of IMRT and 3DCRT. Comparative studies, randomized or nonrandomized had to compare any of the four specific radiotherapy techniques of interest.
General Comment	. . . is concerned that the AHRQ report retroactively assigns standards to this literature which it would not be expected to meet without foreknowledge, while discounting the longitudinal consistency of clinical results across reports. The criteria for rating evidence listed on pages13-18 are not readily familiar to the field. It is interesting to note that the IMRT literature (vs. 3DCRT/2DRT) has grown in volume and has randomized data missing from the older 3DCRT vs. 2DRT literature. This reflects a widely accepted recognition of the larger dosimetric and clinical impact from using IMRT compared to either of the older techniques as well as a trend toward increased formal assessment of emerging H&N treatment technologies by investigators. Thus, previous studies were not tasked and, therefore, were not designed to directly address the research quality standards used by AHRQ. This could be effectively and rapidly addressed by direct, cooperative efforts between AHRQ and . . . to draft, disseminate, and adopt new HTA research standards for future trial design and publication. Further, . . . continues to independently and aggressively engage the issue of IMRT terminology and measurement standardization6 highlighted by the AHRQ.	Standards we applied for assessing the quality of individual studies and bodies of evidence have evolved over the past 10-15 years and are widely disseminated. These standards apply to assessing studies of any therapeutic interventions, not just radiotherapy techniques. Further educational efforts to present standards are beyond the duties of the BCBSA-TEC EPC, but may be pursued by AHRQ.

Comment Section	Comment	Response
General Comment	**AHRQ's Analysis of the Literature** . . . believes that the accessibility and scientific rigor of the AHRQ's analysis of the literature is itself subject to critique. The report does not attempt to demonstrate any relationship between individual or group-wide study quality to outcome differences between modalities. This is undoubtedly due to the fact that 104 out of 105 selected articles were rated as "poor" by the report according to the 3-point ordinal rating system described on page14. Without denying deficiencies in the literature, such a grading system discourages detection and comparison of relative stronger data/sub-analyses within individual trials and remains incongruent with the report's assessment that the consistency of presented data suggests "a true effect in favor of IMRT, but not precise enough to quantify the magnitude of effect" (page ES-2). Although a detailed literature search strategy and flow diagram is shown, the report provides no listing of the 246 retrieved references excluded from review. Further, while the draft report exhaustively details and references its individual procedural steps, no evidence is presented to support the overall quality or validity of the report itself.	The key system used to assess the quality of individual studies was the USPSTF approach, which is widely used and accepted. The CER was focused on identifying the strongest evidence available. The consistency of results or late xerostomia was considered in relation to risk of bias. We concluded that risk of bias was not so great as to cancel out the pattern of findings favoring IMRT. The list of excluded studies will be an appendix of the final version of the CER. The overall quality of the CER was assessed via peer review.
General Comment	To conclude, . . . and the radiation oncology community at-large are well positioned to move forward to rectify legitimate shortcomings in the available literature and to meet all current and future technology assessment requirements. The point taken in the Executive Summary and on page 108 of the AHRQ report that "the capability of IMRT to deliver higher doses to a tumor site may in fact present a risk as well as potential benefit" is well taken and well appreciated by our field. . . . recommends, however, that in lieu of any emphasis on resource-intensive RCTs, . . . and AHRQ directly engage in dialogue to find alternative, cost-effective means to streamline development of improved standards for future HTA publications which would improve institutional observational reports and prospective multi-institutional trials.	No action necessary.

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General Comment	IMRT—especially with an increased dose per fraction to specific target volumes—provides for far better local control than previously reported in patients with head and neck cancer. These come at a higher risk of esophageal toxicity, and of need for tube feedings. Attachments refer…	Studies were included in the synthesis of comparative evidence only if the article described data for outcomes of interest for at least two groups treated by different radiotherapy techniques among patients with head and neck cancer. The included studies are not comparative.
General Comment	The work demonstrates (nicely) the poor quality of the data supporting the widespread adoption of IMRT in the treatment of head & neck cancer. While treatment toxicity and side affects may be ameliorated to a degree, there is no evidence to substantiate improved tumor control. I was disappointed to find little, or no, reference to this in the conclusions. IMRT is expensive to deliver, and costs associated with its administration are high.	Discussion of cost was beyond the scope of this CER.
General Comment	A costly approach has been adopted by the radiation oncology community. Do the benefits experienced by patients justify the increased expenditure? Is a conversation concerning the "cost/benefit ratio" for IMRT in comparison to CT treatment planning appropriate to this review? If so, it is absent.	Discussion of cost-effectiveness was beyond the scope of this CER.
General Comment	This draft represents an extensive critical review of the literature related to the comparative effectiveness of IMRT, 2D, and 3D RT in the treatment of HN cancer. We acknowledge the thorough work performed by the authors. The data related to protons was too sparse and therefore was omitted; we agree with this decision. The main conclusions were that overall the quality of the evidence is quite poor, however, taking into account consistent results, it can be concluded that some aspects related to xerostomia and some other domains of QOL are improved by IMRT compared with 2D or 3D.	No action necessary.

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General Comment	Our Major Comments relate to the interpretation by the authors of the clinical relevance of major aspects in this large accumulated body of published clinical research. 1. The authors examined separately the evidence related to IMRT vs 3D RT, IMRT vs 2D RT, and 3D vs 2D. These comparisons are largely redundant. In almost all cases the designation "3D" means simply 2D RT (lateral opposed beams, typically matched to an anterior low-neck field) using beam's eye-views to help draw field edges to conform to the targets, without an intention to spare any organ. 3D represents an improvement in radiotherapy, mainly due to the benefit of CT- treatment planning: the radiotherapist has a higher certainty that the targets are being adequately irradiated. This technical improvement is not expected to yield measurable differences in tumor control, unless a very large number of patients with similar tumors are randomized. This is not likely to happen; one may argue that merely increasing the certainty of radiation delivery does not require more testing than, for example, delivering chemotherapy using accurate vs. non-accurate measurements of its delivered quantity. On the other hand, delivering 2D radiotherapy using the higher precision provided by 3D is not expected to change side effects or QOL, as no organ is spared. This includes the majority of the 3D RT papers, and excludes a small minority in which 3D techniques aimed specifically at sparing the parotid glands. Thus, IMRT should be compared to the literature dealing with both 2D and 3D RT. This literature is now very extensive. Such a comparison will now include 3 randomized studies (including C. Nutting et al, presented at ASCO 2009, J Clin Oncol 2009;27(18s):799). All three randomized studies, as well as all phase II-like and retrospective comparisons, report improved xerostomia using IMRT. We agree that all the randomized studies were small and that multivariate analyses for confounding factors could not be done. However, we do not agree that this body of experience can be regarded as having "low strength".	No action necessary. While some readers may be more interested in comparisons between IMRT and either 3DCRT or 2DRT, the topic as assigned involved comparing any of the specified modalities, so we also reviewed 3DCRT vs. 2DRT. Regarding strength of evidence, the overall rating has been raised from low to moderate, incorporating the evidence from the PARSPORT trial.

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General Comment	2. We agree with the reviewers that there are trends for improvement in other domains of QOL in IMRT compared with 2D or 3D (see the randomized study of Pow et al and few retrospective studies: Graaf et al, Vergeer et al.), but additional good-quality studies are still necessary.	No action necessary.
General Comment	3. We agree that there is no evidence that IMRT increases tumor control rates. The superior dose distributions gained by IMRT may have an advantage in some patients with advanced tumors near critical organs, but this advantage needs to be balanced by the risk of marginal recurrences due to the steep dose gradients in the vicinity of the tumors. This issue requires more study.	No action necessary.
General Comment	4. "Remaining Issues"(p. ES-5): First paragraph: We agree that there are some differences between planned and delivered doses. These potential differences have been the subject of extensive research in recent years. We also agree that there are differences in patient susceptibility to specific side effect such as xerostomia. However, **we strongly disagree with the statement that "Therefore, comparative evidence on clinical outcome is necessary to establish that the technical capability of IMRT do indeed benefit patients"**. There is ample evidence, including 3 randomized studies and multiple non-randomized ones proving the benefit regarding xerostomia, as detailed above. The differences in patients susceptibility to xerostomia are dwarfed by the xerostomia caused by 2D or 3D RT and the proven benefits provided by IMRT. No further evidence is necessary to establish the benefit of IMRT regarding xersotomia. We agree that further study is required in order to document its benefits regarding other, non-xerostomia-related, aspects of QOL.	The CER concludes that relative to 3DCRT or 2DRT, IMRT reduces the frequency of late xerostomia and improves quality of life. This paragraph states that dose characteristics are insufficient alone to support conclusions about comparative effects for other outcomes, rather evidence for those particular outcomes is needed. We agree that additional evidence is no longer needed about late xerostomia and quality of life and the CER has been modified accordingly to make this clear.

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General Comment	5. The paragraph: "Indeed, the capabilities of IMRT to deliver higher doses to the tumor site may in fact present a risk .." should be removed: There are small numbers of clinical studies examining tumor dose escalation. Besides careful phase I-II studies of dose escalation, a policy of delivering higher doses using IMRT is not practiced clinically off protocol and therefore should not be part of this report. This paragraph is completely speculative.	The original wording gave the mistaken impression that IMRT should be used routinely to escalate dose. This is not the meaning we intend to convey. This sentence has been modified to emphasize steep dose gradients: **"**The capability of IMRT to deliver steep dose gradients around a tumor site may present a risk as well as potential benefit."
General Comment	6. The overriding statement that xerostomia is common in patients with advanced cancers is highly speculative and needs supporting references. In addition, there is an increasing trend for younger patients being diagnosed with oropharygeal carcinoma from HPV-related causes both in the US and in Europe (Refs: Frisch M, Hjalgrim H, Jaeger AB, Biggar RJ. Changing patterns of tonsillar squamous cell carcinoma in the United States. Cancer Causes Control 2000; 11:489–495, Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20–44 years. Cancer 2005; 103:1843–1849, Licitra L, Zigon G, Gatta G, et al. Human papillomavirus in HNSCC: a European epidemiologic perspective. Hematol Oncol Clin North Am 2008; 22:1143–1153). Most of these young patients do not have xerostomia at the time of diagnosis and are relatively healthy with minimal other medical co-morbidities. They also have a better prognosis and most are long term survivors after therapy. Therefore, preserving salivary function is even more critical in these patients. This fact needs to be acknowledged somewhere in this section.	We have corrected the impression that xerostomia is common in patients with advanced cancers. However, a young patients population is not represented in the comparative evidence we reveiwed. The statement about susceptibility to xerostomia has been modified as follows: "Xerostomia has a significant impact on quality of life. It appears to be common in patients with certain tumor sites, radiotherapy treatments and chemotherapeutic regimens. Older age and certain therapies for chronic diseases may increase susceptibility for this adverse effect. Research to improve the management of xerostomia and to disseminate that knowledge to clinical practice could potentially improve morbidity and quality of life for cancer patients."

Comment Section	Comment	Response
General Comment	7. "Future research should put high priority on multicenter trials… randomized controlled trials are needed to asses survival outcomes..". We object to this proposal. There is no further need for randomized studies comparing IMRT with 2D or 3D. None of us would agree to participate in such a study if we were to be diagnosed with HN cancer, nor would we agree to submit any of our patients to such a study: In our view, the proven benefits of IMRT regarding xerostomia, and the emerging data suggesting improvements in other aspects of QOL, would make such a study a non-ethical one.	We have added acknowledgement of the challenges of conducting randomized, controlled trials of IMRT to address non-xerostomia adverse events, tumor control and survival: "There are considerable obstacles to conducting randomized, controlled trials to ascertain tumor control and survival effects. These are: wide dissemination of IMRT, reluctance to randomize patients when effects on xerostomia are already known, the large numbers such trials would require, and other priorities for funding. Nonetheless, certainty about tumor control and survival outcomes can ideally be obtained through a robust randomized, controlled trial." Regarding the relation between dose distribution and outcomes such as tumor control and survival, text has been added to explicitly identify dose distribution as an intermediate outcome: Dose distribution data is considered an intermediate outcome, which may be related to health outcomes, but by itself does not establish the comparative effectiveness of different radiotherapy techniques. The sentence appears in the Methods chapter under Study Selection, Types of Studies, 2nd paragraph between 2nd and 3rd bullet and in the Summary and Discussion chapter, after the summary table.

Comment Section	Comment	Response
General Comment	109, 24: Feasibility of RCTs comparing IMRT to older technology given current patterns of practice and xerostomia data.	We noted above the addition of this new evidence. The PARSPORT randomized, controlled trial (Nutting et al., 2009) presented at the 2009 meeting of the American Society of Clinical Oncology has been incorporated into the CER, resulting in raising the strength of the evidence for IMRT vs 3DCRT or 2DRT on late xerostomia and quality of life from low to moderate.
General Comment	110, 21: [How might management strategies for xerostomia affect IMRT effect on this endpoint.]	The focus of this CER was on comparative effects of different radiotherapy modalities and future improvements in management of xerostomia would affect patients treatment by any modality, but would not necessarily affect comparative effects of different modalities on xerostomia.
General Comment	Overall, I think the report is very thorough and reasonable in conclusions and reccomendations. I hope this report prompts more organized efforts to fund and conduct comparative effectiveness research. I noted that IOM report lists management of localized prostate cancer in the top quartile priority for comparative effectiveness research needs. I would point out that it may be easier to document outcomes and benefits in H&N cancer than in prostate where disease outcomes take > 10 years, and only minor differences in toxicity are likely to be seen.	No action necessary.

Comment Section	Comment	Response
General Comment	One thing I don't think was well noted in the report is that FDA regulation of technology does not require a new technology to be more effective, only operationally safe and similar to previous technology. This is partly why little comparative research has been done. Also, technology changes so fast that by the time one plans a study, the technology has moved on and the question may be moot.	FDA regulation is beyond the scope of this CER
General Comment	I believe one should view IMRT as a part of a stepwise evolution for more precise radiation and that mostly does not need comparison to past technology. Although clear benefits will be demonstrable in selected areas, it is reasonable to extrapolate to other sites and assume some degree of benefit (even though the magnitude may be small), or perhaps no clinical benefit, but there is a overall benefit when this becomes a standard part of routine care by providing the new more advanced platform for all new technology (e.g, data transfer for planning and delivery and QA process). The cost of delivery should come down as this becomes the new standard.	No action necessary.
General Comment	Protons are a somewhat different leap in technology and in my opinion need a stronger level of scrutiny, not only for cost but also to document safety regarding marginal miss recurrences. This technology is almost "too precise" or conformal for most solid tumors, with outcomes more likely to be operator dependent.	No action necessary.
General Comment	There are now 3 randomized controlled trials comparing 2d with IMRT showing benefit in terms of xerostomia. It is not possible to do blinded studies of such technology. As noted in the report, the magnitude of benefit and use of multiple measures supports IMRT benefit as true.	The newest randomized, controlled trial, PARSPORT (Nutting et al., 2009) presented at the 2009 meeting of the American Society of Clinical Oncology has been incorporated into the CER, resulting in raising the strength of the evidence for IMRT vs 3DCRT or 2DRT on late xerostomia and quality of life from low to moderate

Comment Section	Comment	Response
General Comment	Dose escalation trials can be done, but few have been launched. One trial of IMRT is now ongoing in France (GORTEC). Most efforts are aimed at combining drugs with radiation, not simply escalating radiation alone. This may be a fertile ground for protons.	The original wording gave the mistaken impression that IMRT should be used to routinely to escalate dose. This is not the meaning we intend to convey. This sentence has been modified to emphasize steep dose gradients: "The capability of IMRT to deliver steep dose gradients around a tumor site may present a risk as well as potential benefit."
General Comment	The suggestion of future well designed observational studies is a good one. This is best done via real time registries or retrospective review/secondary analysis of cooperative group data (RTOG). Funds for such analysis should be made available.	No action necessary.

Comment Section	Comment	Response
General Comment	A number of efforts to develop the "standards", as suggested, are under way: • QUANTEC is an ASTRO/AAPM (medical physics society) collaboration to set standards and quantify normal tissue injury. Joe Deasy and Soren Bentzen are leading. First set of publications are coming out soon. • NCI H&N Steering Committee has a working group developing standards for definitions for measuring H&N cancer outcomes (eg, locoregional progression, PFS, OS). Report should be available in 2010. • CTCAE is a broad dictionary of adverse event terms and grades. It is not designed to serve as primary endpoints in CER studies or toxicity interventions. It must be supplemented with a plan for site and organ specific objective tools and patient reported outcome measures. • RTOG sets standards for technology certification and QA of individual cases for dose planning and outcomes. • RTOG protocol 0522 is an example of prospectively building in site specific AEs to improve clinical relevance and specificity of reporting.	The following text has been added to item 4 of the Future Research chapter: To facilitate comparisons between studies, outcome measure need to be standardized, such as the Common Terminology Criteria for Adverse Events