Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Radiotherapy Treatments for Head and Neck Cancer Update

Draft review available for public comment from April 29, 2014 to May 27, 2014.

Research Review Citation: Ratko TA, Douglas GW, de Souza JA, Belinson SE, Aronson N. Radiotherapy Treatments for Head and Neck Cancer Update. Comparative Effectiveness Review No. 144. (Prepared by Blue Cross and Blue Shield Association Evidence-based Practice Center under Contract No. 290-2007-10058.) AHRQ Publication No. 15-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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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.

Commentator & Affiliation	Section	Comment	Response
TEP #1	Introduction	OK.	Thank you.
Peer Reviewer #1	Introduction	Concise.	Thank you.
Peer Reviewer #2	Introduction	The introduction nicely frames the issues studied and the goals of the meta-analysis.	Thank you. Note, though, we did not perform any quantitative synthesis of data.
TEP #2	Introduction	Thorough discussion of the background and purpose. May consider a separate statement in the first paragraph of the objectives to state that the purpose was to review effectiveness of RT techniques that are used alone as primary radiotherapeutic approach.	Added the following sentence to the first paragraph: "In particular, with the goal of reviewing the effectiveness of radiotherapy techniques that are used alone as the primary treatment modality."
TEP #3	Introduction	Some corrections and housekeeping issues: 1. It is stated through the report that stereotactic body RT (SBRT) delivers "ablative" doses of radiation. While this is sometimes the case for some anatomic sites (e.g. brain), it is not the case for head and neck RT as far as I know. Rather SBRT is used to give "tumoricidal" doses in short periods of time compared to standard IMRT delivery. 2. On page 4 lines 6 and 7 it is stated that the "PTV is an expansion of the PTV…" which should be changed to "PTV is an expansion of the CTV…"	1. Changed text to use the term "tumoricidal". 2. Changed to CTV 3. We revised to address this comment and correct the citation.

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		3. Also on Page 4 line 14 gives reference 13 in the context of definitions of 3DRT, IMRT, and SBRT. However ref 13 is Burri, *et al*. which includes no reference to SBRT in my search of that article. This should probably be a reference to Siddiqui, *et al*. which is #11 in the ES section. In addition, note that the correct name of the author in ref 13 is Bucci not Burri.	
TEP #4	Introduction	Concise, but see [general comments] re: PBRT	Thank you.
Peer Reviewer #3	Introduction	1. Well done overall. Radiation is a mainstay of treatment, but saying it is "the" mainstay some would say is an overstatement. Surgery is a central modality of therapy as well. Caution is appropriate regarding "deintensification" of treatment for HPV related disease. 2. While mentioning research in this area is fine, it should be noted that currently practice guidelines such as the NCCN do not recommend treatment differences based on HPV status (with perhaps the exception of HPV+ unknown primary cancers).	1. Changed from "the mainstay" to " a vital component of the treatment".. 2. Added on page 3: "In this regard, it is important to note that current practice guidelines, such as the National Comprehensive Cancer Network (NCCN) do not recommend treatment differences based on HPV status (with perhaps the exception of HPV+ unknown primary cancers)."
Peer Reviewer #4	Introduction	1. The distinctions between 3D-CRT, IMRT, and stereotactic body RT are vague and could be strengthened. This would be particularly helpful to	1. We agree that some distinctions were "high-level". However, we sought to make the introduction more accessible to lay healthcare

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		the physician but non-radiation oncologist readership. It would be useful to point out that the manner in which SBRT achieves dose conformality is the same as that used for IMRT, the only significant difference between the two being the dose per fraction. It is interesting the description of IMRT states that it is more conformal than "conventional therapy." 2. Conventional therapy is never defined, however, and the reader is left to wonder what conventional therapy actually is. Certainly it is not 2d radiotherapy, which the report rightfully labels as obsolete. It would be nice to define conventional therapy. I would argue that IMRT is now de facto conventional therapy	decision makers (as also suggested by Peer Reviewer #11). Nevertheless, the goal of this review is not to fully educate non-radiation oncologists on the different types of therapies, but to introduce the types of interventions we would be comparing in the analyses. We also added the following text to make sure readers are aware of our intent: "We present here a brief overview of the different types of conformal RT modalities for those who are less familiar with the specific technologies. For those seeking further details on the different approaches, information is available from the National Cancer Institute."[citation] 2. We removed the term "conventional" referring to 2DRT. We are not aware of a consensus definition of "conventional" RT so will avoid mention.
Peer Reviewer #5	Introduction	The description of radiation therapy modalities needs significant work.	We sought to make the introduction more accessible to lay healthcare decision makers (as also suggested by Peer Reviewer #11). The goal of this review is not to fully educate non-radiation oncologists on the different types of therapies, but to introduce the types of

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			interventions we would be comparing in the analyses. However, we have revised this section per comments received to accurately and succinctly reflect key differences among RT methods.
Peer Reviewer #6	Introduction	1. - p.7, L.7ff: The stronger recommendation regarding the lower incidence of xerostomia after IMRT as compared to 3DCRT would benefit from a discussion of two points: 1) was parotid sparing attempted in the 3DCRT arms of the reviewed trials? 2) a more careful consideration of case mix in terms of sites within the HN. This latter point is not trivial even if the distribution of tumors among sub-sites in the HN region is balanced between treatment arms. The concern is that the risk of xerostomia varies considerably from sub-site to sub-site, say, from vocal cord tumors to nasopharyngeal carcinomas. While ignoring this variability may be conservative in one sense, the problem arises when generalizing study findings to other populations. 2. - p.14, L.7: Definition of SBRT: "…generally compromise…by definition…" this statement is self-contradictory	1. We sought studies that specifically compared results between tumor subsites and specific organs, or that stratified for those. In CER No. 20, the PARSPORT trial, for example, only consisted of balanced oropharyngeal and hypopharynx tumors. Data on other subsites are indeed extrapolation of data, as it would not be possible to run Phase 3 trials for each subsite. 2. Changed to "generally consist of"

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		3. - p.14, L.21-23: "Taken together, the emergence of new technology and evidence suggesting potential differences between interventions in some outcomes prompted AHRQ to prioritize this update of CER No. 20." This statement is key in terms of justification for the update of CER No. 20. It should be substantiated and ideally a reference to the note (of published) should be included. 4. - p.15, L.5: Presumably the population was restricted to patients with a histopathological diagnosis of squamous cell carcinoma? This should be underlined. 5. - p.15, L.25: "intervention" should be replaced by "radiation therapy modality" 6. - p.15, L.42: "Comparator" perhaps better "Comparisons" - p.16, L.13: "Timing" – this is not satisfactory. It is necessary to distinguish between early and late effects. A study with a, say, 6-month median follow-up for reporting of late effects would not be acceptable.	3. Citation to CER no. 20 was added. 4. Added squamous cell carcinoma of the head and neck. 5. Added "radiation therapy modalities" 6. Added comparisons We acknowledge the importance of distinguishing early and late effects. However, for the purpose of this review, timing was placed in context with the study final and intermediate outcomes.
Peer Reviewer #6	Introduction (cont.)	1. - p.16, L.17: This should be more than just Inpatient v. Outpatient,	1. We revised this PICOT element to reflect the comment: "Typically

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		more like Academic Center v. Community Hospital. The distinction between inpatient and outpatient is not relevant in the context and gives the impression – probably not justified – that the writer is not familiar with the area of medicine reviewed. The explanation of the Setting is much better in Table E. 2. - p.17, Fig. A: I disagree that "user experience" is an outcome in CER. I also do not agree with the pairing of "intermediate vs. long-term" outcomes in the figure text. This is not a distinction in the time domain but a causal relationship. If this figure is cited from another source, a citation is needed. 3. - p.41, L.27: Please provide a reference to the AHRQ 2011 surveillance report. This report seems important in understanding the background of the current update and should be presented and discussed in a little more detail. It is remarkable to this reviewer that the surveillance report apparently predates the publication of the Gupta RCT (available online July 30, 2012).	community-based versus tertiary or academic medical centers". 2. "User experience" is a comparative parameter specified in Key Question 4. We acknowledge that it is not a clinical outcome, but it can be construed as an intermediate parameter that could have an impact on clinical outcomes. Thus, we left it in the analytical framework. We revised the figure legend by deleting "long-term" and substituting "final health" for that term. We created the figure so no citation is needed for it. 3. We added a citation for CER No. 20. The original surveillance report was released in 2011, predating the Gupta RCT.
Peer Reviewer #7	Introduction	The introduction was clear and concise without being obscure. As I mentioned in my	Edits were made throughout the text. However, we agree that lay language

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		general comments, I specifically wonder if plain language summary of this introductory information might make it more accessible to lay healthcare decision makers. However, I recognize the burden of trying to distill complex and nuanced information for a lay audience in such as way as avoids over-generalization and loss of critical detail.	would not make justice to such a topic, full of nuances.
TEP #5	Introduction	The overview of head and neck cancer, treatment modalities, and general approach to treatment are concisely presented and appropriate to the topic.	Thank you.
TEP #1	Methods	See my comment on inclusion/exclusion of studies in Results.	Acknowledged and addressed in Results.
Peer Reviewer #1	Methods	The logic was clear and reproducible.	Thank you.
Peer Reviewer #2	Methods	Methods described are straightforward.	Thank you.
TEP #2	Methods	Yes.	Unclear what this comment refers to.
TEP #3	Methods	1. As mentioned [elsewhere], it seems that perhaps the exclusion of "standard" a.k.a. "conventional" a.k.a. "2D treatment" methods compromised the number of studies analyzed and hence the usefulness of the results, especially as they related to QOL issue. 2. Additionally, it is not clear what some of the "reasons for exclusion" mean in Append C and this has compromised the	1. We understand that exclusion of 2DRT could compromise the numbers of studies we included. However, we determined a priori and in discussion with out TEP that 2DRT is no longer part of definitive RT for head and neck cancer. 2. We agree with the comment regarding reasons for exclusion, acknowledging that for example, the term "outdated

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		strength and acceptance of the conclusions. Some examples are: "outdated" study (Pow, *et al*., Pocholke, *et al*., Jabbari, *et al*.); "nonrelevant" study (Feng, *et al*.) and "invalid" treatment modalities (Yu, *et al*.). These terms need to be clearly defined in the context of this study and if they refer at all to the exclusion of any study that used 2D RT that is perhaps a serious flaw relative to the study goals. 3. While it would not be possible or relevant to incorporate 2D into Question 2, it does seem that studies comparing QOL issues to the standard of care (up to about 2005) can still shed light on questions 1, 3 and 4. 4. Finally, the exclusion of Nutting, *et al*. 2011 for the reason "included in the original CER" is very concerning since this is the 2011 published update on this very import CRT with long term FU – how could a 2011 publication have been included in the 2009 CER?	study" was an artifact of our screening protocol because of the publication date and that it may already have been in CER No. 20. We have revised this term. We did exclude any study that used 2DRT. 3. We understand that exclusion of 2DRT could compromise the numbers of studies we included. However, we determined a priori and in discussion with out TEP that 2DRT is no longer part of definitive RT for head and neck cancer. 4. We understand that PARSPORT was published in peer-reviewed form in 2011. However, we obtained the full data from Dr. Nutting in 2010 as the report went to press. We don't believe the longer F/U data alter our original conclusions. Hence, our exclusion of PARSPORT from the CER No. 20 update.
TEP #6	Methods	Appropriate and well done.	Thank you.
Peer Reviewer #3	Methods	Well done overall. As noted [in introduction comments], the identified studies focused on upper aerodigestive tracts cancers, not salivary gland cancers. It would have been appropriate to have some quantification	Thank you. We considered the role of chemotherapy very carefully in developing this CER update. In our internal discussions, review of the literature, and our TEP discussions, we

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		scheme for the administration of chemotherapy. This would have been relevant from a toxicity perspective (e.g. was compliance with chemotherapy affected?) and potentially for disease control outcomes (e.g. did one arm receive a different amount of concurrent chemotherapy?).	concluded that our most objective approach would be to examine CT regimens as to their current relevance, as well as issues such as compliance. The latter issue is a major reason why we decided to include only direct comparative studies that would minimize potential differences between study arms besides the RT modalities, allowing us to potentially "isolate" the RT effects.
Peer Reviewer #4	Methods	It is not clear what criteria were used to cull the manuscripts that were searched in full text from the original larger list of librarian identified titles. A more detailed description of this process would be helpful.	We clearly described our inclusion and exclusion criteria a priori in the Methods section of the CER. If a study met initial criteria including appropriate RT modalities in a direct comparative study of a defined head and neck cancer population, we retrieved it for full-text examination to ensure it met inclusion criteria.
Peer Reviewer #5	Methods	Please see the attached document. Methods were sufficient and nicely described.	Thank you.
Peer Reviewer #6	Methods	1. The search strategies are clearly described and appear reasonable, although the list of papers for full-text screening suggests that the filtering has not worked. 2. Regarding statistical methods, there are no attempts to synthesize or even compare quantitative estimates between studies, although in my view, that would have been	1. We cannot control issues that affect indexing of articles in MEDLINE or EMBASE and lead to larger takes than seem necessary. Our search strategies for the CER update were essentially identical to those used for CER No. 20 but broadened to include SBRT and PBT. 2. We believed based on our a priori

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		informative in the few instances where this would be have possible. See attached report for more detailed comments. 3. The assessment of consistency of findings across studies seems to be based on the significance of the P-value alone without appropriate consideration of effect sizes, see for example the discussion of Dysphagia in Table B on p. 26. This is not an appropriate criterion from a statistical point of view.	experience, and input from our TEP, that we would not have sufficiently homogeneous studies in sufficient number to perform rigorous quantitative syntheses, regardless of outcomes under consideration. This is stated in the Methods. 3. The "precision" domain of the GRADE SOE process is related to the effect sizes and confidence intervals (CI). The "consistency" domain does not consider CIs, but does consider the direction of change. Regardless, absent a statistically significant p-value for a relative effect size, one cannot ascribe an observed effect size to one intervention compared to the alternative in a trial.
Peer Reviewer #7	Methods	Overall, the methods were both appropriate and well presented. I appreciated use of schematics and effective application of tabular information. The inclusion and exclusion criteria were well delineated and appropriately structured. The definitions used are accepted and appropriate. The qualitative synthesis employed in the two questions for which there were evidence was appropriate. I felt that the authors reflected the state of the evidence fairly and clearly and without unnecessary judgment.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Methods	The methods are appropriate and clearly stated to address the goals of the investigation.	Thank you.

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TEP #1	Results	I am surprised at what was excluded. 1) The list of references (p. 96-) include many dating back to the 1980s, while the list of excluded papers has IMRT papers from as recently as 2005 whose reason for exclusion was "outdated study." Most of the papers in the references are graded "poor quality" by yourselves. I don't agree with the structured abstract conclusion that "evidence was insufficient to draw conclusions on… adverse events other than late xerostomia (e.g. dysphagia). My group has developed IMRT techniques aiming to spare the swallowing organs, and our published results of a Phase II study showed much lower dysphagia than expected after usual chemo-RT. These results have been published (Feng, FY, *et al*. JCO 2010, Eisbruch, A, *et al*. IJROBP 2011). These methods have in recent years been adopted by many other radiation oncologists. They suggest that judicious IMRT can reduce dysphagia substantially. I am surprised you have not included these papers, however, I am aware of my conflict of interest and if you decide they are not worth mentioning I will not protest. However, something needs to be said on the potential of IMRT to reduce dysphagia. It is a more important QOL issue than xerostomia (see Hunter, Ku, *et al.*, IJROBP 2013).	We used a strict set of study inclusion criteria. A major qualification was a study must be comparative to be included. Feng 2010, Eisbruch 2011, and Hunter 2013 are single-arm studies and so were excluded. We acknowledge that by excluding single-arm studies we may not have captured the universe of evidence on rates of RT-associated adverse events. However, we believe our focus on comparative studies is sound in reducing bias secondary to instudy heterogeneity that would complicate assessment of the evidence. We agree that dysphagia is an important patient-centered health outcome, but did not review its importance relative to others, such as xerostomia. Thus, we cannot address the reviewer's commment on that. Furthermore, we reported inconsistency in rates of dysphagia that conspired with poor study quality to render the body of evidence insufficient to form any conclusion as to the comparative effect of IMRT versus 3DCRT on that outcome.

Source: https://effectivehealthcare.ahrq.gov/topics/head-neck-cancer-update/research/
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Peer Reviewer #1	Results	I believe the results section is clear and appropriate.	Thank you.
Peer Reviewer #2	Results	No studies that I can see were excluded other than isolated smaller reviews.	Thank you.
TEP #2	Results	The tabular data is helpful.	Thank you.
TEP #3	Results	By and large all of these characteristics are adequately dealt with except as noted [elsewhere] in some of the excluded studies. Of particular note is the 2011 Nutting study which is a high-quality, long term FU of this RCT.	Thank you. We obtained the latest available data from Dr. Nutting and PARSPORT in 2010 when we updated the literature search for CER No. 20.
TEP #4	Results	A style point, but tables that continue to another page might have the headings that wrap to the next page (e.g. the first column in table B) be listed as "(heading), continued."	Thank you for your observation.
Peer Reviewer #3	Results	Well done. Exception is that chemotherapy data seems to have been considered in qualitative terms only. Another is that it would be helpful to quantitate how often discrepancies in study inclusion required a third reviewer; same for discordant quality assessments.	Thank you. We address the chemotherapy issue specifically in the Methods section of the CER. We didn't quantitate inclusion discrepancies because of the small numbers of articles involved. It was very clear to us whether or not to include a study based on rigorous selection criteria.
Peer Reviewer #4	Results	Ok as is.	Thank you.
Peer Reviewer #5	Results	Please see the attached document. Results were nicely described.	Thank you.

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Peer Reviewer #6	Results	1. The results are presented in great detail and the tables are generally informative although I have specific issues with some of the included material (see attached report for examples). 2. The inclusion of the Ozyigit trial is controversial at the very least. This is the only SBRT v. IMRT comparison, but the setting is re-irradiation of patients after a local recurrence. The treatment aim, the spectrum of acceptable toxicities, the selected cases etc. are all very different from the primary situation. Where the CER update generally focuses on various planning and delivery technologies, the SBRT scenario compares two very different dose-fractionation regimens. They are not known to be equivalent in any simple sense, and I would argue that this comparison is not meaningful in the overall context of this report. 3. p.22, L.29: It in not correct that Gupta et al. did not report an intention-to-treat analysis, they did. But two patients were non-evaluable with respect to any of the study endpoints. This does not mean that the analysis was not intention-to-treat. See also below. 4. p.24, L.17: It is not sufficient that the chemotherapy is identical in the two groups treated with different RT modalities. It is conceivable that the benefit of one RT modality over another will vary with the use of chemotherapy, see for example Vogelius et al. Int J Radiat Oncol Biol Phys 2011 or Khuntia et al. Int J Radiat Oncol Biol Phys 2008. 72: S33.	1. Thank you. 2. We understand and acknowledge the issues raised about the Ozyigit trial. However, it was the only comparative study we identified for SBRT and included it as it met inclusion criteria. Our conclusions on SBRT would not be altered by exclusion of the Ozyigit study. 3. Gupta et al. report they performed a “modified intention-to-treat” analysis (p. 344, in the first paragraph under “Results”). This does not alter our view of the study. 4. We acknowledge that RT effects may indeed be differentially affected by chemotherapy agents. To ensure chemotherapy or other treatments were similar and contemporary, we consulted accepted guidelines such as those from NCCN or NCI. We did not extract details on chemotherapy dosages or schedules, but rather ascertained their degree of general similarity and the proportions of patients who receive and complete such regimens. We categorized and synthesized evidence according to overall treatment (e.g., concurrent chemoradiotherapy or adjuvant RT), not mixing these settings in the strength of evidence (SOE) synthesis. However, we had no way to quantitate this based on the studies we

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Peer Reviewer #10 (contd)	Results	5. p.24, L.21: "on those grade 2 or higher toxicities associated with RT in the head and neck: dysphagia, salivary gland function, and xerostomia." What does this mean? There are many other side effects in this population, e.g. sensorineural hearing loss, persistent laryngeal edema, hypothyroidism, myelopathy, cerebrovascular morbidity, changes in taste or smelling, fibrosis, strictures, telangiectasia, radio-osteonecrosis, fistula, trismus, etc. etc.	6. As we state in the report, toxicity outcomes were inconsistently reported across studies. For this reason, we focused this update, as we did CER No. 20, on those toxicities that are prominently associated with significant QoL decrements following RT in the head and neck: dysphagia, salivary gland function, and xerostomia. We also only consider toxicities of grade 2 or greater according to accepted criteria, such as those of the Radiation Therapy Oncology Group (RTOG) or the NCI Common Terminology Criteria for Adverse Events (CTCAE). This level and higher are associated with treatment interruption and hospitalization and thus substantially affect patient outcomes and perceptions.
Peer Reviewer #10	Results (cont.)	1. p.24, L.35: The sentence "We are uncertain…" sounds unreasonably naïve, there are late effects – and if they are not reported, it is because they are not reported! 2. p.26, L.25: I am surprised: so, the fact that a trial finds a significant P-value increases the SOE?? 3. p.26, Table B: Here and elsewhere in the report: It is a disservice to the reader	1. We make that statement because in our experience performing systematic reviews, adverse events are often relegated to secondary importance compared to clinical outcomes like OS. If adverse events are not reported in a paper, one cannot know whether the investigators actually sought to collect the data and didn't report it, or didn't even seek the data. 2. This SOE was arrived at using AHRQ methods that derive from the GRADE

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		that references are given as numeric in some instances and by first author and year in other instances. This means the reader will need to go back to the reference list to check the link between the various statements. 4. p.26, L.35ff: The discussion of "Precision" is confusing in so far that the two non-randomized studies did not reach the same conclusion. 5. p.29, Table C: Overall survival and locoregional control. It appears illogical (despite the description on p. 57) that a provisional SOE of "high" is lowered by the inclusion of two poor quality studies that agrees with the first one. In other words, if the strength of evidence on a given issue is high the publication of a very large, poor quality study in agreement with the previous studies would downgrade the SOE??	methodologists. The SOE increase is a result of the "precision" domain, due to the similar direction and effect sizes as well as the significant p-value of Gupta. 3. We use the AHRQ convention for citations and refer to author and date when highlighting a specific study. 4. The term "precision" as used in the AHRQ SOE rating system refers to statistical precision based on similar confidence intervals. However, when faced with a mixed evidence base that includes a fairly well executed RCT, the strongest evidence, and several poor quality non-RCTs, the fact that the RCT did not show a statistically significant result is sufficient to downgrade the domain. 5. One RCT does not provide sufficient evidence because it is not possible to grade the precision domain; the addition of 2 much larger, poor-quality studies will "overwhelm" the RCT evidence by increasing the risk of bias and resulting in a SOE downgrade.
Peer Reviewer #7	Results	I found the results section readable, logical, and effective. The update from CER 20 was easily apprehended. The level of detail was to my eye appropriate though again the issue of assimilation by lay readers came to mind. The key messages were both well stated and well formatted. I am not aware of	Thank you.

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		any studies that were overlooked. I believe the search strategy used in identification was well matched to this update.	
TEP #5	Results	The content and presentation of the results are concisely stated yet with adequate detail particularly with reference to the tables. The information is well-organized. Is it possible to add Table 3 (pp. 63 & 64) to the executive summary? This may provide meaningful information.	Thank you. The Executive Summary is not meant to be comprehensive given length limitations, so we did not include Table 3.
TEP #1	Discussion	See my comment on Results.	OK
Peer Reviewer #1	Discussion	I agree with the analysis and the conclusions.	Thank you.
Peer Reviewer #2	Discussion	A longer section on future work involving IMRT and its effects on dysphagia would be warranted since this is becoming an increasingly focused area of study, considering the important impact on quality of life that dysphagia entails.	We tried to focus on general areas that could be addressed given the scant amount of data that are available. We do mention dysphagia as a key health outcome in this section.
TEP #2	Discussion	Yes.	OK
TEP #3	Discussion	Findings are clearly stated as are the limitation of the studies covered, but again there seem to be a number of relevant studies that could/should have been included.	Which studies the reviewer refers to is not stated so we can't address the comment more specifically. However, we used a very specific set of inclusion criteria that we stated a priori and are confident we included all relevant publications.
TEP #4	Discussion	The statement about research gaps is pretty general. I recognize that this reflects the paucity of data. Good statement about the challenges of conducting comparative trials.	We intended the discussion on research gaps to reflect the large, general gap of a scant evidence base and how to go about addressing this through well-designed

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		You might make a stronger statement about the obligations to develop high quality CER in this area, perhaps suggesting the key comparisons and outcomes, which might support application for funding to study these questions.	clinical trials. We did address challenges, for example in terms of general dissemination of advanced RT technologies to the community and how that could impact clinical trial accrual.
Peer Reviewer #3	Discussion	Well done overall. However, on page 94 under impediments, there is only one paragraph. Given the limited extent and disappointing quality of the studies identified, it would be appropriate to expand this section. One issue not mentioned is that if payers are willing to reimburse for care associated with theoretical advantages but without (or with very limited) actual supporting clinical data, the development and accrual to the types of prospective clinical trials proposed in the prior section are undermined. In the absence of such clinical trials being done or planned, perhaps some type of registry program with required data reporting on these newer, typically expensive, RT techniques deserves consideration.	We intended the discussion on impediments to pertain to the RT modalities in the CER. Reimbursement is an issue that is outside the scope of a CER of this type.
Peer Reviewer #4	Discussion	These were somewhat vague and generic.	Ok.
Peer Reviewer #5	Discussion	Please see the attached document. Discussion was reasonable.	Thank you.
Peer Reviewer #6	Discussion	1. If this had been a scientific review submitted to a journal, I would have concluded that the insights added to CER No. 20 represents less than 1	1. The CER is intended to reflect the state of comparative evidence. It is not intended to comment or expound much beyond the

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		MPU (= minimum publishable unit). I am not impressed by the future research section which seems to state the obvious, i.e. that more RCT's are needed, but largely fails in defining the limitations to our current knowledge. 2. p.36, L.30: Please clarify the statement: "…perilous position for typically medically frail patients." 3. p.37, L.29: The statement on management of HPV-associated HNSCC should be related to the comparison of RT modalities or technologies that is the topic of this CER. 4. p.37, L.38: It is not clear why the "general dissemination of conformal RT technologies" is a problem in itself, but the wide uptake of IMRT and the associated financial implications are the real issues. The situation for PBRT is quite different and to lump them together in the same statement does not work.	evidence. 2. By "perilous position", we refer to a clinical state in which medically fragile patients could quickly spiral downward due to a combination of cancer recurrence and prior grueling therapy. 3. We revised the text to refer to RT modalities in the context of management of HPV-positive HNSCC. 4. We revised the text to reflect this comment, as follows: "The general dissemination of advanced conformal RT technologies into community clinical practice is a theoretical impediment to comparative study of those technologies. Thus, broad availability of technologies previously available only in the tertiary setting may dissuade referrals to the latter in favor of a local provider."
Peer Reviewer #7	Discussion	The authors stated the implications of their major findings clearly and acknowledge limitations. The use of PICOTS is effective and useful. I was glad to see CTCAE noted with regard to outcomes in the gap analysis.	Thank you for the compliments. We didn't consider the place of PROs as our charge in preparing a CER for AHRQ is to examine the published, peer-reviewed literature for comparative effectiveness

Commentator & Affiliation	Section	Comment	Response
		However, I wonder if the authors might also consider reflecting on the place of PROs in this analysis. The place of the CTCAE-PRO and the relation to healthcare decision makers is a valuable matter on which to comment if we are to move the science forward. The anatomic site variation and relative rarity of head and neck cancer underscores this point for me. I hope it is useful to the authors as well. Issues of inconsistent measurement and of outcomes reporting are important in this realm of cancer treatment both for intensity of treatment and treatment outcomes. I read the discussion and gap analysis carefully, coming to the conclusion that the authors might want to emphasize the directions for future research a bit more strongly. I worry that the heterogeneity that limits this science presently will continue without somewhat sharp reminders to improve the quality of future investigations. As this is a CER update, I am not confident about the suitability of my suggestion for this particular report. However, given my practice and research in the domain, I think that somewhat more pointed direction for future research is important to consider if substantive change is to occur.	evidence on relative outcomes associated with conformal RT modalities. Although patient-reported outcomes may indeed accurately reflect a specific patient's condition(s), compilation from a database may provide an inaccurate picture of AEs. We acknowledge that AEs observed in clinical studies and reported in the literature also are often limited in scope and hence information value. In this work, we attempt to minimize bias by specifically delimiting the allowed evidence base and not admixing it with non-peer reviewed evidence.
TEP #5	Discussion	I am not aware of any relevant literature that has not been included in the analysis. The discussion is thorough without being overly redundant with the earlier content. The	Thank you.

Commentator & Affiliation	Section	Comment	Response
		findings are supported and the limitations clearly stated for each of the 4 key questions.	
TEP #1	Conclusion	Yes.	Ok.
Peer Reviewer #1	Conclusion	I agree with the analysis and the conclusions.	Thank you.
Peer Reviewer #2	Conclusion	Since the study confirms a prior one, I don't see how any major influence on policy decisions can ensue.	We agree to an extent, but we also believe our update strengthens the original findings in the specific area of xerostomia.
TEP #2	Conclusion	Yes, it is well organized. Yes, it can be used to inform practice/policy with most of the limits to that being exerted by the lack of data not the structure of the report.	Thank you.
TEP #3	Conclusion	Yes to structure, organization and clarity. However, the conclusions are not very useful since they do not extend those presented in the 2009 report. This reviewer feels that this is perhaps misleading since it seems some excluded studies would have added to the conclusions in a meaningful way for both providers and payers.	Thank you for the compliments. We specifically limited inclusion criteria to direct comparative studies of patients with HNSCC who received treatment with conformal RT. We are confident our a priori methods are sound and based on acceptable CER principles.
TEP #4	Conclusion	Yes to the limits of the available data.	Thank you.
Peer Reviewer #3	Conclusion	Yes – caveats as outlined [elsewhere].	Thank you.
Peer Reviewer #4	Conclusion	They are usable with respect to the assertion that IMRT represents the optimal approach to prevention and/or reduction of radiation induced xerostomia.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Conclusion	Please see the attached document. The description of radiation therapy needs significant work.	We did not attempt to provide a detailed description of the RT methods that would necessarily educate non-RT oncologists. Our intent was to succinctly describe the RT methods we would include and highlight key differences among them that may be relevant to differential outcomes.
Peer Reviewer #6	Conclusion	I have to be absolutely honest: I felt that the finish on this report was not what I would have expected at the time a report is sent out for external review. There is a lack of attention to detail that bothers me. The text is of highly variable quality and does not seem to be aimed at a defined target audience. The section on epidemiology of HNSC is largely irrelevant for the topic of the report. The mention of HPV associated HNSCC is superficial and appears more like a token acknowledgement of a currently hot topic in HN oncology. HPV+ HNSCC could potentially be relevant for a discussion of the relative merits of various RT modalities, but the authors of the report apparently have nothing to say about this issue.	The CER update is meant to be a reflection of the state of published comparative evidence and how it fits in with the prior CER. We did not attempt to be highly detailed in our discussions of the RT modalities or epidemiology of HNSCC. Furthermore, we did not investigate HPV-positive HNSCC and RT specifically and so would not be expected to comment on this area.
Peer Reviewer #7	Conclusion	I enjoyed reading this report update. I thought it was well written, nicely formatted, and actually rather visually interesting (not a common experience in reading academic and clinical science materials). Aside from my comments about accessibility for lay healthcare decision makers and future research, I have no further comments to offer the authors for improvement. Thank	Thank you.

Commentator & Affiliation	Section	Comment	Response
		you.	
TEP #5	Conclusion	The report is well structured and organized. The conclusions are clearly presented. The findings should be important to clinical practice but the impact is minor as the technology of IMRT has already gained substantial adoption across the country. To me, the findings of insufficient data to conclude that quality of life or toxicities of dysphagia, and mucositis (acute and late) are less with IMRT highlights an important gap in the evidence as well as the lack of data for SBRT and proton therapy.	Thank you.
Peer Reviewer #6	Appendix	- Appendix C: As the search strategy included a filter on publication date, it is not clear how the 40 "outdated" studies ended up on the list of papers for full-text screening? And why was it necessary to screen the full text even if for some reason these references had passed the first screen?	We don't understand why the filter allowed "outdated" studies through. It may be a vagary of indexing for MEDLINE or EMBASE. We screened all articles for which we were unclear due to, for example, absence of an abstract or lack of clarity in the abstract.
TEP #1	General	The report is moderately clinically meaningful. My impression is that you try to isolate RT technique as a single factor which affects tumor outcome. You compare IMRT to 3D and you rightly conclude that there is no evidence IMRT improves tumor outcome. I agree. A confounding factor in such analyses is the biological changes in HN cancer: In the past 10-15 years we are faced with an "epidemic" of HPV-related oropharyngeal cancer, which have a better prognosis than smoking related cancer.	Thank you for the compliments. We did not analyze outcomes of patients with HPV-positive cancers treated with RT as we identified no specific evidence.

Commentator & Affiliation	Section	Comment	Response
		IMRT series likely contain many more such patients than 3DRT patients treated in the 80's and 90's. I suggest to add this point to the inability to assess if IMRT changed tumor control rates.	
Peer Reviewer #1	General	Yes, the data is limited but the conclusions are solid. They are also consistent with general consensus. The report gives the target population as well as appropriate background.	Thank you.
Peer Reviewer #2	General	This report confirms the prior one and is a good review of existing literature.	Thank you.
TEP #2	General	This is a thorough review of the topic of radiotherapy for head and neck cancer. Methods are well described. Key questions are explicitly stated and appropriately answered.	Thank you.
TEP #3	General	Yes this report seems to be quite clear in intent and conclusions. It should be helpful to the community including the payers. It is unfortunate that there was not enough high quality data to allow further conclusions around questions 2 through 4. In retrospect, it seems the decision to exclude 2D treatments perhaps compromised the gathering of some additional useful data since there were a number of studies excluded which were published after the 2010 report and which compared for example IMRT to "conventional" RT which was likely 2D therapy. This would still have comprised useful information at least in terms of questions 1, 3 and 4. This point is addressed further in the Methods section.	Thank you for the compliments. We used a very specific set of a priori inclusion and exclusion criteria, based on our look at the literature, as well as input from our TEP, to decide not to include 2DRT. Our intent was to use only direct comparative evidence that would minimize bias in making comparisons. As such, we did not allow comparisons of individual study arms drawn from different reports.

Commentator & Affiliation	Section	Comment	Response
TEP #4	General	This is very well written, concise and useful. I note that in your description of PBRT you give no references. I recall and agree with the general dismissal of PBRT as a modality when we had the TEP discussion. However, perhaps a richer discussion of this modality would counterbalance the "evidence non-existent" in the remainder of the document. This would help practitioners appropriately counsel patients on the modality. Imagine what you might want a non-radiation oncologists to tell patients about PBRT beyond "there is no CER."	We sought to make the introduction more accessible to lay healthcare decision makers (as also suggested by Peer Reviewer #11). The goal of this review is not to fully educate non-radiation oncologists on the different types of therapies, but to introduce the types of interventions we would be comparing in the analyses. However, we have revised this section per comments received to accurately and succinctly reflect key differences among RT methods.
Peer Reviewer #3	General	The report is clinically meaningful. Questions are appropriate and understandable. Listing patients with salivary gland cancers as head and neck cancers is understandable since they are in that body region, but the study data presented focus on upper aerodigestive tract cancers (typically squamous or a variant) and different from salivary gland cancers (typically variants of adenocarcinoma). The toxicity data is likely relevant; the efficacy data is not.	Thank you. We agree toxicity data are relevant and oncologic outcomes are less informative for clinical practice..
Peer Reviewer #4	General	Unclear as to why a radiation oncologist was not included as one of the co-authors but a medical oncologist was. Inclusion of a radiation oncologist, specifically one with expertise in head and neck cancer, would bolster the significance of this report in the radiation oncology community.	We had radiation oncologists as part of our Technical Expert Panel. Our medical oncologist co-author was able to consult radiation oncologists at his institution.
Peer Reviewer #5	General	1. Please see the attached document for further comments, especially about the utility of asking KQ 3 and 4, as well as the rationale for including PBT and	1. We could not know the utility of KQ 3 or 4 unless we performed a systematic review of the literature.

Commentator & Affiliation	Section	Comment	Response
		SBRT here. 2. The authors have constructed an excellent review of the clinical data supporting the comparative effectiveness of radiotherapy modalities for head and neck cancer. In comparison to the original report, ultimately this update boils down to a strengthening of the SOE showing a clear xerostomia benefit with IMRT. 3. I honestly do not see the need to include proton beam therapy in this review. It is well known that there are virtually no clinical data supporting its use in the management of the vast majority of head and neck malignancies (namely, in nasopharynx, oropharynx, larynx and hypopharynx cancers). Thus I do not feel that it is worth including them in this report. 4. Similarly, SBRT has only been studied in the reirradiation setting, which is a distinctly different clinical scenario than the vast majority of patients treated with radiotherapy. There are no meaningful comparative data in this scenario, so why include this modality in this review?	2. Thank you. 3. We understand confusion about including PBT, but because it was in CER No. 20 we decided it merited inclusions. Without actually performing a systematic review, how can one state that there are no data on PBT? 4. We understand confusion about including SBRT. Without actually performing a systematic review, how can one state that there are no data on this technology?

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General (cont.)	1) ES-2, RT in Head and Neck Cancer. I found this section to be inadequate. The authors need to better articulate the differences between the radiotherapy modalities. 2D radiation is also shaped to cover a tumor volume plus a margin. This is not what distinguishes 2D from conformal radiotherapy. The fundamental difference between 2D and 3D radiation therapy is the use of CT planning to define targets on axial imaging and then calculate the dose to those targets and normal tissues. This process is very powerful and allows for much better plans – better blocks, better beam angles, and thus better dose distributions to tumor and normal tissue, neither of which was calculable before. 2) Additionally, the following line is simply incorrect: "3DRT allows for… very rapid dose fall-off in surrounding tissues than with 2DRT because 3DRT takes into account axial anatomy and complex tissue contours." The dose gradient is not necessarily different between 2D and 3D-RT, especially in head and neck radiotherapy. In fact, 3D radiation in HN is essentially the same as 2D, just with better target delineation. The dose gradients are virtually the same, because the beams themselves are almost identical. 3) The IMRT description needs to be much better. IMRT is defined not only by intensity modulation but also inverse planning, which is an absolutely critical component of the modality. Also, describing the radiation as "high dose" is deceptive, because it's actually the same dose as in conventional radiation.	1. We sought to make the introduction more accessible to lay healthcare decision makers (as also suggested by Peer Reviewer #11). The goal of this review is not to fully educate non-radiation oncologists on the different types of therapies, but to introduce the types of interventions we would be comparing in the analyses. However, we have revised the introduction per comments received to accurately and succinctly reflect key differences among RT methods. 2. We revised the draft to reflect this comment. 3. We revised the draft to reflect this comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General (cont.)	1. The SBRT description should be much better. The term “ablative” is loaded, actually, since conventional radiation is also ablative (i.e. it sterilizes tumor). The line “Regimens generally comprise a total dose by definition in five or fewer fractions” does not make sense grammatically but also in principle. The 5 or fewer fractions piece is an artifact of US reimbursement, not the technique itself. SBRT as a technique is defined by robust immobilization, highly precise, image- guided patient setup, and high dose-per-fraction irradiation focused on gross disease with a minimal margin for setup error. There are many different platforms for SBRT, as indicated, but especially in head and neck there is less tracking, and 4D simulation is never done. That line is more suitable for a lung manuscript, not HN. 2. The proton section should briefly mention the Bragg peak, which is why there’s no exit dose. Also the term “high-energy” should be avoided, since the prescribed dose is the same in protons and photons. 3. Is it really worth asking Key	1. We revised the draft to reflect this comment. 2. We revised the draft to reflect this comment. 3. The KQs were initially proposed back in 2009 when we developed CER No. 20. To maintain continuity, and to ensure we didn’t mistakenly overlook new evidence pertaining to those KQs, we retained them in the update.

Commentator & Affiliation	Section	Comment	Response
		Questions 3 and 4 when there are no studies that apply to them? It seems unreasonable to include these KQ in the paper.	
Peer Reviewer #5	General (cont.)	1. Table E, Interventions. This needs work, and I would recommend contacting a radiation oncologist for input (similar issues as above). For HN cancer, 3D-RT and 2D-RT are nearly the same; both use a 3-field, and frankly the beams look very similar however they are planned. Also, the following line is actually very difficult to follow: "IMRT offers beam strength attenuation through a multileaf collimator (tungsten), with dynamic field shapes for each beam angle." The beam "strength" (not sure what that means… maybe energy?) is not attenuated… it's the same… it's the MLC's that drive the intensity modulation. Secondly, the comment "IMRT is not as widely available as 3DRT is probably not accurate in 2014. Almost everyone who has 3D is going to have IMRT. 2. Regarding SBRT, IMRT is often used for SBRT, and 3D is also often used for SBRT. 3D and IMRT refer to the planning and delivery of the treatment. SBRT adds the precise setup, tight margins without a CTV, and hypofractionation. Also, the line "the institutional programmatic requirements	1. We revised the text and table to reflect this comment. 2. We revised the draft to reflect this comment.

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		for SBRT are similar to those for IMRT" is not true. Most departments have separate stereotactic groups and/or stereotactic physicists. The requirements, particularly regarding setup, imaging, and beam QA, are different.	
Peer Reviewer #5	General (cont.)	3. Paper page 3, under RT in Head and Neck Cancer. I would ask the authors to consider showing this section to a radiation oncologist to ensure accuracy. Under 3D-CRT, would not use the term "highly focused." Line 40, 25 fractions is not a common regimen. Line 45. "segmental, dynamic etc." is confusing and not that accurate. The standard IMRT techniques are sliding window, step and shoot, and volumetric modulated arcs.	4. We revised the draft to reflect this comment.
Peer Reviewer #5	General (cont.)	1. The SBRT description is completely wrong. That text describes lung SBRT. Head and neck SBRT is a different beast. The maximum dose used is generally 8 Gy x5, which is far less than 100 BED. One criticism of HN SBRT is actually that the dose is not that high relative to SBRT in other body sites, due to risk of late toxicity. 2. Page 7, "SBRT: defined as conformal RT (forward- or reverse-planned) delivered in 3-5 relatively larger doses of	1. The piece on SBRT was revised to reflect this comment as follows: "SBRT is a type of 3D conformal RT that is used to deliver tumoricidal doses of radiation in fewer treatment sessions than used in conventional 3DRT or IMRT regimens. Regimens generally comprise a total dose equal to that delivered by 3DRT or IMRT, but typically in 8 fractions rather than 25 or more fractions. As a technique, SBRT is defined by robust immobilization, highly precise, image-

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		ionizing radiation than typically delivered in a standard conformal schedule of 25-35 doses." Again, not true. For example, BED (10), 8 Gy x 5 = 72. BED (10), 2 Gy x 35 = 84! The repopulation factor isn't included, but you get the point. 3. It would be helpful to better articulate the decision of going from SOE moderate to high for xerostomia. Two moderates = high? Reasonable but should be better described. 4. The acronym PBRT is not used for proton beam therapy. Use PBT instead, which is the accepted acronym (for better or worse). 5. I would recommend not starting sentences with an abbreviation. So use Radiotherapy instead of RT. 6. Page ES-2 (under RT in Head and Neck Cancer). Line 32. All radiation is cytotoxic. No reason to add that adjective.	guided patient setup, and high dose-per-fraction irradiation focused on gross disease with a minimal margin for setup error. There are many different platforms for SBRT, but especially in head and neck cancer therapy there is less than for other sites, and 4D simulation is not used." 2. We revised the text to reflect this comment. 3. The "high" SOE was the result of new RCT evidence added to existing RCT evidence from CER No. 20. 4. Text was revised throughout to reflect this change. 5. We revised to reflect this comment. 6. The term "cytotoxic" was removed as a qualifier for radiation.
Peer Reviewer #6	General	1. The current draft report reviews the minimal new evidence published after the completion of CER No. 20. The report seems unnecessarily lengthy for a very limited return in terms of updated insights. The target audience is not completely clear. The text is clearly aimed at a radiation oncology	1. We acknowledge your general commentary. The length of the draft is partly a function of the AHRQ-mandated structure to ensure consistency across reviews. The target audience is not specifically described because the report is aimed

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		or even a cancer specialist audience. Many explanations of technical and medical terms are superficial or even naïve. An interested reader would be better off with the average Wikipedia definition of the same terms. The key questions are clear but not very specific. It is unlikely that these delivery technologies are associated with the same differential benefit irrespective of the tumor sub-site within the head and neck region. The possible role of systemic therapy is very relevant and definitely a gap in our current knowledge. The inclusion of SBRT is debatable to say the least. This opens a completely different can of worms, way beyond the scope of the current report. Please see attached report for more details. 2. I read this report with interest and clearly a good deal of work has gone into preparing it. Still, I have a feeling that it was not ready for external review. In addition, I have several concerns regarding the quality of this report. 3. The language and terminology is imprecise in many places. I appreciate that this is an early draft but the whole tone of the report and an apparent lack of attention to detail concern me.	more generally to encompass providers, payers, and other interested readers. We expect radiation oncologists to be interested, of course, but our intent is to reach a wide readership. The background is not meant to be highly detailed but rather to introduce key concepts and the interventions of concern. The Key Questions were provided to us in their basic form when we prepared CER No. 20, and have been revised to maintain consistency. We identified no evidence specifically aimed at differential outcomes according to tumor sub-sites, nor did we investigate the role of systemic therapy in the context of RT. We included SBRT because it is an emerging modality. 2. We appreciate your review. 3. This was indeed a draft version; it has been revised to reflect numerous comments. We appreciate your review.
Peer Reviewer #6	General (contd)	4. In view of the extremely limited amount of new evidence since the 2010 report, I find the current report much too long and unfocused. The need and justification for	4. This was indeed a draft; it has been revised to reflect numerous comments. We appreciate your review.

Commentator & Affiliation	Section	Comment	Response
		updating the 2010 report seems weak to me. What is the minimal amount of new evidence that is required before the current report is updated in, say, four years' time? Is this an efficient use of AHRQ funds? 5. The report appears to be a lot of words adding very little to CER No. 20 in terms of new knowledge or new recommendations. It seems that a much condensed update with the more extensive tables published as an online appendix, would have been a service to potential readers.	5. This update was undertaken as a result of an AHRQ surveillance report that suggested new evidence had emerged that could alter the conclusions of CER No. 20. We don't know whether there is a "minimal" amount of new evidence required to stimulate an update. The subject of efficient use of AHRQ funding is a topic for AHRQ to consider. AHRQ will ultimately prepare a plain-language condensed summary of this report to public use.
Peer Reviewer #6	General (cont.)	1. p.42-42: While the decision to exclude evidence relating to 2DRT is debatable, in view of the world-wide perspective on the burden of HNSCC on p.42, excluding brachytherapy makes sense to this reviewer. However, did the panel advice to include SBRT in this report? And if so, what is the argument? 2. p.43, L.37: The remark on HPV-associated disease raises false expectations, as the only further mention of HPV is on p.81 where – in a single sentence – it is noted that "… we did not identify any evidence on differences in oncologic outcomes related to HPV status…" Fair enough, but did the reader have to wait 38 pages to read this	1. The Technical Expert Panel provided input on inclusion or exclusion of RT interventions that was considered by us in the context of our views based on emerging literature. The use of SBRT is increasing rapidly in a number of tumors, so we concluded that we would be justified in seeking evidence on it; the TEP concurred. Similarly, for BT we decided to not include it based on our view of the literature and TEP input as to its current role in treatment of head and neck cancer. 2. We didn't expound on HPV further

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		simple conclusion? 3. p.45, L.6: The remark that "Conventionally fractionated schemes, delivering a similar total dose in 25-40 fractions, typically do not reach a similar biologically effective dose range" is pure speculation. This presumes the, as yet unproven, validity of the linear-quadratic model also at dose per fraction exceeding 10 Gy and the absence of a competing biological effects such as reduced re-oxygenation in short, intensive schedules. 4. p.45, L.10ff: The description of PBRT is very superficial and appears naïve.	as we had no need to based on the evidence. 3. We have struck from the text all mention of BED. 4. Thank you for your opinion. We have revised the SBRT piece per comments received from you and others.
Peer Reviewer #6	General (cont.)	1. p.108, Tab. B1 and p.61: The quality score for the Gupta trial does not seem completely fair to this reviewer. Blinding of RT trials is generally impossible, and should really not detract from the quality score, although the assessor of treatment outcome could have been blinded. It is, however, a laudable feature of the Gupta trial, that all contouring of targets and organs at risk was completed prior to randomization. This deserves mentioning. The trial is actually analyzed according to ITT, with two	3. We acknowledge the difficulty in masking outcomes assessment in RT RCTs. Further, Gupta et al. report they performed a "modified intention-to-treat" analysis (p. 344, in the first paragraph under "Results"). This does not alter our view of the study. 4. Thank you for your review. We have attempted to satisfactorily revise the draft per comments received from you and others.

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		cases not being evaluable but there is no way the investigators could help that. The loss to follow-up rate is mentioned, but it would also be relevant to note that all cases were evaluated with respect to the early endpoints. In comparison, CER No. 20 scored the study quality of the Nutting trial as "good," although this was also not blinded, did not blind assessors, and had a much higher rate of non-evaluable patients. What's the difference? 2. The list of specific issues above is by no means exhaustive. Many issues occur throughout the report and I have in general only noted one occurrence. The report in its current version includes a number of typos and imprecise wordings.	
Peer Reviewer #7	General	Thank you for the opportunity to review this update on CER 20. The resulting report is both clinically meaningful and a call to investigators to address the state of the science. The authors nicely outline the target population and clearly define the audience as healthcare decision makers. I found the report highly intelligible and accessible. However, I practice in head and neck oncology. I worry that what I found lucid might still confound most lay people including experienced patients and caregivers as well as some healthcare administrators and policy makers. Head and neck cancer care is	Thank you for the compliments. The AHRQ typically prepares a plain-language summary of reviews prepared by its contractors.

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		increasingly a high technology/high complexity realm of healthcare. I wonder if a plain language summary of key findings and recommendations for clinical practice and future research might be a helpful addition. The key questions are both useful and appropriate.	
TEP #5	General	This report is an update of the 2010 CER No. 20 report on radiotherapy in head and neck cancer. The findings strengthen the findings of the last report but do not break new ground. This is due to insufficient data from a paucity of well-designed and conducted trials in the radiotherapy literature and specifically with respect to head and neck cancer for IMRT vs. 3D conformal and proton beam therapy. One can hope that this sends a message to the research community. The key questions are appropriate and clearly stated.	Thank you for your comments.
Public Reviewer #1 (American Brachytherapy Society (ABS))	General	1. The reviewer feels that the CER should have included brachytherapy in its review because brachytherapy is an established and cost effective radiotherapy modality in head and neck cancers. One of the stated reasons for excluding brachytherapy from the report is that it is used as a boost to external beam radiation. While brachytherapy is often used as a boost to EBRT, brachytherapy alone is often used preferentially over surgery to treat smaller tumor in accessible areas of the head and neck preserving cosmesis and function at locations including lip, buccal mucosa, tongue, floor of the mouth,	We considered including brachytherapy (BT) in CER No. 20, as well as in this update. We examined literature reviews, consulted our Technical Expert Panel, and AHRQ personnel. Our conclusion remains that BT, an invasive procedure, is not widely used in RT for head and neck cancer in the US. We added the following text to the Introduction of this report to clarify our decision: "Brachytherapy is an invasive technique that was the first form of radiotherapy (RT) in clinical use, dating back to 1901. Historically, it has been used extensively in many tumor types, including head and

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		tonsil, nasopharynx, neck nodes etc. where surgery would result in poor cosmesis or function. Brachytherapy alone is also useful for the salvage of recurrent tumors that have failed EBRT. 2. Another reason given for the exclusion of brachytherapy was the limited use. This is certainly not true. While the radiation oncologists in the panel may have had limited information about the use of brachytherapy in head and neck tumors, it is very widely used in the primary treatment of head and neck cancers especially in Europe.	neck cancer. The primary advantage of brachytherapy over traditional opposed external beam two-dimensional radiotherapy (2DRT) has been its capability to conform a high, localized radiation dose to the implanted tumor, limiting exposure to noninvolved tissues. However, as conformal external beam RT methods (e.g., three-dimensional conformal RT [3DRT], intensity-modulated RT [IMRT]) have become more prevalent in the past 2 decades, this advantage of brachytherapy has been mitigated.

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Public Reviewer #1 (American Brachytherapy Society (ABS))	General (contd)	3. Brachytherapy, especially using manually after loaded 192Ir, has been widely used to treat head and neck cancers. Van Limberbergen reported the GEC-ESTRO (European) experience on 2794 lip cancer patients treated with Ir-192 with an overall 5 year local control of 94%. For T1 tumors the 5, 10, and 15 year disease free survival were 95%, 91% and 90%, respectively. (13) Similarly, Mazeron et al reported on 1896 lip cancer patients treated with Ir-192 with an overall 5 year local control of 94%. (8)	Brachytherapy can be used in select head and neck cancer cases as a means of dose escalation in conjunction with external beam irradiation. However, this practice has become uncommon because sufficient dose escalation can usually be achieved in these cases with a noninvasive approach (conformal RT). Brachytherapy alone is very rarely employed, except with small (T1) tumors of the nasal vestibule, lip, or oral cavity. These presentations of head and neck cancers are relatively uncommon (1 percent to perhaps 5 percent of all cases), and RT is typically not first-line treatment in many cases. Therefore, because use of brachytherapy alone for primary management of head and neck malignancies has limited applicability in modern radiation oncology practice, we did not seek evidence of it for this current CER; we focused instead on RT modalities that are used as the sole RT intervention for a given presentation of head and neck cancer.

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Public Reviewer #1 (American Brachytherapy Society (ABS))	General (cont.)	1. Brachytherapy in the head and neck area was traditionally given by low dose rate (LDR) brachytherapy. Due to concerns about radiation hazard to the care givers, and the ability to easily permit dosimetry optimization, most of the recent reports have used pulsed dose rate (PDR) or, more commonly, high dose rate (HDR) brachytherapy (184-199, 101). Both the ABS and GEC-ESTRO have separately published general recommendations of utilizing HDR brachytherapy in the various sites of head and neck cancer (10, 200). 2. The nasopharynx is a site within the head and neck area that is easily accessed by an intracavitary HDR applicator. Levendag et al have reported their extensive experience in treating nasopharyngeal lesions with HDR brachytherapy using a special nasopharynx applicator (201-203). 3. The use of HDR brachytherapy catheters incorporated in removable dental molds allows repeated, highly reproducible, fractionated outpatient brachytherapy of superficial (<0.5-cm thick) tumors without requiring repeated catheter insertion into the tumor (204). Suitable sites for mold therapy include the scalp, face, pinna, lip, buccal mucosa, maxillary antrum, hard palate, oral cavity, external auditory canal, and the orbital cavity after exenteration. A total HDR dose equivalent to about 60 Gy LDR (prescribed at 0.5-cm depth) is recommended when used as the sole modality (10).	We considered including brachytherapy (BT) in CER No. 20, as well as in this update. We examined literature reviews, consulted our Technical Expert Panel, and AHRQ personnel. Our conclusion remains that BT, an invasive procedure, is not widely used in RT for head and neck cancer in the US. We added the following text to the Introduction of this report to clarify our decision: "Brachytherapy is an invasive technique that was the first form of radiotherapy (RT) in clinical use, dating back to 1901. Historically, it has been used extensively in many tumor types, including head and neck cancer. The primary advantage of brachytherapy over traditional opposed external beam two-dimensional radiotherapy (2DRT) has been its capability to conform a high, localized radiation dose to the implanted tumor, limiting exposure to noninvolved tissues. However, as conformal external beam RT methods (e.g., three-dimensional conformal RT [3DRT], intensity-modulated RT [IMRT]) have become more prevalent in the past 2 decades, this advantage of brachytherapy has been mitigated. Brachytherapy can be used in select head and neck cancer cases as a means of dose escalation in conjunction with external beam irradiation. However, this practice has become uncommon because sufficient dose escalation can usually be achieved in these cases with a noninvasive approach (conformal RT).

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Public Reviewer #1 (American Brachytherapy Society (ABS))	General (cont.)	4. Surgical salvage is generally the preferred treatment for locoregional recurrences after failure of external beam radiation in head and neck cancers, however, surgery is not possible in all cases. Brachytherapy is useful for salvage of recurrent disease in previously irradiated patients with results comparable to other modalities (205-209).	Brachytherapy alone is very rarely employed, except with small (T1) tumors of the nasal vestibule, lip, or oral cavity. These presentations of head and neck cancers are relatively uncommon (1 percent to perhaps 5 percent of all cases), and RT is typically not first-line treatment in many cases. Therefore, because use of brachytherapy alone for primary management of head and neck malignancies has limited applicability in modern radiation oncology practice, we did not seek evidence of it for this current CER; we focused instead on RT modalities that are used as the sole RT intervention for a given presentation of head and neck cancer."
Public Reviewer #1 (American Brachytherapy Society (ABS))	General (cont.)	1. Another innovative approach is the use of intraoperative HDR brachytherapy, which permits normal tissues to be retracted or shielded during brachytherapy. Intraoperative HDR brachytherapy can reach many sites in the head and neck area that are difficult to treat or are inaccessible by either LDR brachytherapy or intraoperative electron beam radiation. The catheters are removed immediately after the single dose of radiation, hence, minimizing inconvenience and permitting the use of brachytherapy in areas such as the base of skull. In recurrent tumors where no further EBRT can be given, a single	We considered including brachytherapy (BT) in CER No. 20, as well as in this update. We examined literature reviews, consulted our Technical Expert Panel, and AHRQ personnel. Our conclusion remains that BT, an invasive procedure, is not widely used in RT for head and neck cancer in the US. We added the following text to the Introduction of this report to clarify our decision: "Brachytherapy is an invasive technique that was the first form of radiotherapy (RT) in clinical use, dating back to 1901. Historically, it has been used extensively in many tumor types, including head and

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		intraoperative dose of 15 to 20 Gy is generally given (194, 195). 2. In brief, published literature shows that brachytherapy has a more well-defined, cost effective role in the primary management of select head & neck cancer than do either, The role of brachytherapy is well established but excluded from your report while protons and SBRT, whose role in head and neck cancer may well be considered investigational, is included in your report. 3. The reviewer is concerned that the exclusion of proven and well established modality of brachytherapy from the AHRQ report just perpetuates the role of "new" and highly expensive technologies to treat tumors for which proven and highly cost-effective modalities exist.	neck cancer. The primary advantage of brachytherapy over traditional opposed external beam two-dimensional radiotherapy (2DRT) has been its capability to conform a high, localized radiation dose to the implanted tumor, limiting exposure to noninvolved tissues. However, as conformal external beam RT methods (e.g., three-dimensional conformal RT [3DRT], intensity-modulated RT [IMRT]) have become more prevalent in the past 2 decades, this advantage of brachytherapy has been mitigated. Brachytherapy can be used in select head and neck cancer cases as a means of dose escalation in conjunction with external beam irradiation. However, this practice has become uncommon because sufficient dose escalation can usually be achieved in these cases with a noninvasive approach (conformal RT). Brachytherapy alone is very rarely employed, except with small (T1) tumors of the nasal vestibule, lip, or oral cavity.
Public Reviewer #1 (American Brachytherapy Society (ABS))	General (cont.)		These presentations of head and neck cancers are relatively uncommon (1 percent to perhaps 5 percent of all cases), and RT is typically not first-line treatment in many cases. Therefore, because use of brachytherapy alone for primary management of head and neck malignancies has limited applicability in

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			modern radiation oncology practice, we did not seek evidence of it for this current CER; we focused instead on RT modalities that are used as the sole RT intervention for a given presentation of head and neck cancer."
Public Reviewer #2 (American Society for Radiation Oncology (ASTRO))	General	1. We appreciate that AHRQ is updating the initial report on this topic. We also agree that the potential impact of human papilloma virus positive tumor tissue plays into outcomes and patient management. As the report notes, studies are needed to identify reduced intensity therapies that continue to yield satisfactory outcomes. We believe these factors will continue to make this topic important for the years to come. 2. We are pleased that this review has found the evidence strengthening the previous comparative effectiveness review's finding of a significant reduction in late xerostomia with IMRT compared with 3DRT. 3. We agree with the decision to exclude brachytherapy alone for primary management of head and neck malignancies because of its limited applicability in modern	1. Thank you for your comment. 2. Thank you for your comment. 3. Thank you for your comment.

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		radiation oncology practice to a small subset of head and neck cancers.	
Public Reviewer #2 (American Society for Radiation Oncology (ASTRO))	General (cont.)	We are, however, concerned by some of the other decisions that were made to guide this update. 1. For example, by deciding to not consider conventional 2D radiation therapy, this review has overlooked a large randomized study showing a survival advantage and significant toxicity reduction of IMRT compared to 2DCRT in nasopharynx cancer (1). The conclusion of this study is that IMRT provides improved local-recurrence free survival, especially in late-stage nasopharynx cancer patients and is associated with a lower incidence of toxicities. Additionally, we are surprised that the report states that there is no evidence IMRT improves any other toxicities besides xerostomia. There is now published data suggesting improvements in dysphagia in patients receiving chemo-IMRT compared with what we expect using previous techniques (2). This prospective study of 73 patients found that on average, long-term patient-reported, observer-rated, and objective measures of swallowing were only slightly worse than pretherapy measures. We believe the findings from this prospective study are significant and should be considered rather than	1. We used a strict set of study inclusion and exclusion criteria that we developed a priori for this report. We came to the conclusion that 2DRT is no longer relevant to this report as its use has become obsolete in the US, so we would not include comparative studies in which this modality was compared with 3D conformal RT methods. 2. We checked and corrected the

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		discarded as non-relevant. 2. Please note, we believe this study is listed in the Appendix on page 28 with a "nonrelevant study design" designation; however the citation - Dysphagia. 2011. 26:206-207- is incorrect.)	citation in question.
Public Reviewer #2 (American Society for Radiation Oncology (ASTRO))	General (cont.)	3. Under Interventions (Table E, page ES-25), we do not understand why the draft review makes comments on the availability of IMRT and SBRT. According to our membership survey, in 2013 over 95% of US radiation oncology practices offered both IMRT and SBRT. We do not believe that the comments about the availability of these two treatment options are accurate and recommend that this commentary be removed.	4. We revised the text in the table to reflect this comment.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	Our comments address the fact that the Draft Report fails to apply the most appropriate evidentiary thresholds and endpoints for evaluating technologies in the radiation therapy sector. Our comments are divided into the following three sections: (1) Evidentiary thresholds and endpoints should reflect the cancer care paradigm;	1. In preparing this report, and its predecessor, CER No. 20, we used accepted methods for conducting systematic reviews that were approved by AHRQ. We laid out our evidence criteria a priori and adhered to them to ensure we minimized bias in the results. A main criterion was that we would include only direct, comparative evidence, to reduce potential bias due to interstudy heterogeneity among single-arm

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			studies. For comparison between RT interventions, RCTs provide the reference standard for efficacy outcomes; direct comparative studies of non-randomized design provide good evidence as well, although not the same quality as RCTs. We believe our transparent methods meet proper standards for this type of evidence review.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	1. By failing to include high quality reproducible dosimetric studies, the literature referenced in the Draft Report is inappropriately limited. 2. Randomized controlled trials should not be the sole evidentiary threshold for radiation therapy. 3. In its current form, the Draft Report provides misleading information regarding the critical role that advanced radiation therapy technologies play in ameliorating head and neck cancers. The omission of numerous high quality studies could have dramatic, adverse impacts on patient access in the future to the most appropriate forms of radiation therapy. We urge AHRQ and the authors to amend the report consistent with the observations and recommendation described below.	1. We indeed considered including dosimetry studies in CER No. 20, and this update. For both reports, our ultimate conclusion was agreed upon in-house, among AHRQ personnel, and in discussion with our TEP – not to include dosimetry studies. The primary rationale for this conclusion is that dosimetry studies do not provide a link to actual clinical outcomes that are realized by patients. Dosimetry modeling is clearly needed to advance research in RT methods, but it does not provide evidence for clinical efficacy per se. 2. We agree RCTs should not be the sole evidentiary threshold for RT. However, we made an a priori decision to include only direct comparative evidence among RT methods as a means to reduce

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			heterogeneity and thus enhance internal and external validity of our results. All but 2 of the studies included were observational studies. 3. We disagree on this point. We agree RCTs should not be the sole evidentiary threshold for RT. However, we made an a priori decision to include only direct comparative evidence among RT methods as a means to reduce heterogeneity and thus enhance internal and external validity of our results. All but 2 of the studies included were observational studies.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	4. The treatment of head and neck cancer has evolved considerably over the last decade. This is partly related to our improved understanding of the disease, as well as improvements in the reduction of adverse events and increase in quality of life regarding novel radiotherapy techniques. Head and neck cancer is unique in that target volumes are often in very close proximity to several normal structures that must be avoided, and as a result advanced radiotherapy techniques, such as IMRT, may add significant value in the management of head and neck cancer. Patient quality of life is an acceptable study endpoint, and	4. Thank you for your comment.

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		therefore IMRT is the standard of care for most advanced head and neck cancer and the preferred treatment over 3DRT.	
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	1. Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT) have shown value in certain settings and Intensity Modulated Proton Therapy (IMPT) technologies may further enhance the ability to improve head and neck cancer therapy, but additional data is needed. 2. We are concerned that the Draft Report draws conclusions based on only nine of the 6,661 items identified in the literature search. There are many valuable and clinically relevant studies within the more than 6,000 items identified by the reviewers, but not considered in the conclusions. For example, high quality reproducible dosimetric studies are valuable in evaluating and establishing clinical standards in the area of radiation oncology. It is well-established that even modest differences in dosimetry are clinically significant, and dosimetry provides an important surrogate for toxicity. Such studies provide a timely and robust approach to evaluating technologies in the rapidly evolving area of radiation oncology in which incremental improvements in technology	1. We agree with your comment and have called for further comparative studies of these modalities. 2. We address dosimetry studies in the revised document. In general, because dosimetry studies per se do not link to clinical outcomes in patients, we do not view them as relevant to a comparative effectiveness review.

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		occur frequently. 3. As a result, the Draft Report is fundamentally flawed in its current form. Completely ignoring high quality dosimetric studies misrepresents the existing body of scientific evidence that plays a valuable role in guiding clinical treatment decisions in radiation oncology.	3. We address dosimetry studies in the revised document. In general, because dosimetry studies per se do not link to clinical outcomes in patients, we do not view them as relevant to a comparative effectiveness review.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	Inappropriate scaling back of the studies used resulted in limitations related to the Key Questions: *1. Key Question 1 - What is the comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT regarding adverse events and quality of life?* The three studies that were utilized to draw conclusions support that IMRT shows a benefit in the statistically significant reduction of late grade > xerostomia. One of the three studies showed a statistically significant reduction in dysphagia with IMRT as compared to 3D. While not considered statistically significant, two other studies supported the reduction in dysphagia and this fact should not be discounted.	1. We assessed the strength of available evidence on dysphagia according to validate methods used by AHRQ in conducting systematic reviews. As such, we conclude what the methods allow us to conclude based on the relevant evidence only. 2. We assessed the strength of

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		2. *Key Question 2 - What is the comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT regarding tumor control and patient survival?* The studies were found to show insufficient proof for both overall survival and locoregional control, but we do not feel that this discounts the adverse events and quality of life benefits addressed in the first question.	available evidence on oncologic outcomes according to validate methods used by AHRQ in conducting systematic reviews. As such, we conclude what the methods allow us to conclude based on the relevant evidence only.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	3. *Key Questions 3 and 4 - Are there differences in the comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT for specific patient and tumor characteristics? Is there variation in the comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT because of differences in user experience, treatment planning, treatment delivery, and target volume delineation?* There were no studies included to address the measures. While we certainly understand the need for additional randomized controlled trials to address all four of the measures in this draft, it should be noted that the difficulty of conducting randomized controlled trials in radiation oncology, which we outline further in this letter.	3. We agree, and have addressed issues and impediments relevant to conduct of clinical trials in a later section of the report.

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Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	There are several challenges with relying on radiation therapy randomized controlled trials as the main or sole evidentiary threshold. *1. Ethical Considerations* More technologically advanced radiotherapy techniques deliver therapeutic radiation doses more precisely than older forms of radiation treatment. When conducting randomized trials comparing older and newer radiotherapy technologies, it may be unethical to subject a cancer patient to a notably inferior dosimetry in certain situations where the dosimetric advantages are clear and the trade-offs are minimal. As stated by investigators, "The treatment options being compared must look at acceptable trade-offs between risks and benefits, perhaps for different reasons – and this is what will ultimately make a trial ethically acceptable to the participating investigators and eventually lead an informed patient to volunteer as a trial participant (4)."	1. We agree there are impediments to conduct of clinical trials of RT modalities, and allude to possible ethical constraints. However, we did not seek or review evidence on these concerns and so did not address them substantively in the draft.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	*2. Patient Choice and Education* Patients do not want to be enrolled in clinical trials when there is a chance that they will receive	2. We agree there are impediments to conduct of clinical trials of RT modalities, and allude to possible constraints. However, we did not seek or review evidence on these

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		an inferior radiation treatment option. Data suggest that patients are less likely to consent to randomization if they get more detailed information on trial arms (5,6) and also that the willingness to volunteer seems to be inversely correlated with the level of education of the research subject or their medical legal proxy (7). In addition, there is a significant amount of data available through a variety of resources for patients regarding the best and/or latest technologies for cancer care. Though these data may not have met the criteria for inclusion in the Draft Report, they are relevant as patients and their families will consider this information; those patients not at a terminal stage are likely unwilling to risk being assigned to a treatment technique that their research has led them to believe is substandard.	concerns and so did not address them substantively in the draft.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	1. *Costs* Randomized controlled trials are extremely expensive to conduct. On average, excluding overhead expenses, it cost slightly more than $6,094 (range, $2,098 to $19,285) per enrolled subject for an industry-sponsored trial, including $1,999 devoted to nonclinical costs (8). In addition, due to significant costs associated with	1. The costs of randomized trials do indeed pose an impediment to research in the United States. We acknowledge the cost of RCTs in the research gaps section. In general costs and cost-effectiveness are outside the purview of an AHRQ systematic review of this type. We did not review any evidence related to

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		radiation therapy capital equipment, randomized clinical trials are typically the domain of academic institutions. This fact limits opportunities to conduct randomized controlled trials. Furthermore, radiation technologies evolve incrementally. Isolating each development and performing randomized controlled trials is simply impractical. Such an approach would place an unsustainable drain on the nation's resources for research. 2. Traditional randomized controlled trials should be used to address a limited number of high impact questions in the field of radiation oncology that are not reasonably addressed through alternative, more cost-effective research approaches. In radiation oncology, high quality dosimetry studies often provide the preferred option for addressing clinically important questions in a timely, cost-effective manner.	this area. 2. We address dosimetry studies in the revised document. In general, because dosimetry studies per se do not link to clinical outcomes in patients, we do not view them as relevant to a comparative effectiveness review.
Public Reviewer #3 (Medical Imaging & Technology Alliance (MITA))	General (cont.)	*1. Duration and Medical Innovation* Diseases with prolonged natural history such as prostate cancer demonstrate an additional challenge with randomized controlled trials. In particular, radiation therapy techniques and dosing schemes evolve during the long periods of follow up that may be required in these cancers. By	1. We agree with this comment, which is one reason why this report was commissioned by AHRQ.

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		the time the results of a trial are known, if ever, the technology will have progressed. 2. In finalizing the Draft Report, we urge AHRQ and the authors to reflect the positive findings arising from the large number of high-quality studies initially excluded from the current draft. As described above, there are valid rationales in the field of radiation oncology for considering high-quality dosimetric studies and other types of research. Unfortunately, the current version of the Draft Report is likely to confuse policymakers and undermine patient access to the most appropriate radiation therapies by failing to report on the positive findings arising in a large number of important, clinically-relevant studies.	2. We address dosimetry studies in the revised document. In general, because dosimetry studies per se do not link to clinical outcomes in patients, we do not view them as relevant to a comparative effectiveness review.