Effective Health Care Program

Comparative Effectiveness Review
Number 144

Radiotherapy Treatments for Head and Neck Cancer Update

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Comparative Effectiveness Review

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Radiotherapy Treatments for Head and Neck Cancer Update

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

Contract No. 290-2007-10058

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AHRQ Publication No. 15-EHC001-EF
December 2014

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested 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.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Claudia Bonnell, R.N., M.L.S., Hussein Noorani, M.S., and Kathleen Ziegler, Pharm.D.

Key Informants

In preparing this update, the EPC did not consult Key Informants who represent the end-users of research. For Comparative Effectiveness Review No. 20, the earlier report, the EPC sought Key Informant input on the priority areas for research and synthesis. Key Informants were not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions did not necessarily represent the views of individual Key Informants.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Radiotherapy Treatments for Head and Neck Cancer Update

Structured Abstract

Objectives. This report is an update of a Comparative Effectiveness Review (CER) published in final form in May 2010 on the benefits and harms of radiotherapy (RT) to treat patients with head and neck cancer (CER No. 20). RT modalities included two-dimensional RT (2DRT), three-dimensional conformal RT (3DCRT), intensity-modulated RT (IMRT), and proton-beam RT (PBT).

In this CER update we included 3DCRT, IMRT, PBT, and stereotactic body RT (SBRT). We used the same Key Questions as for CER No. 20, asking whether any of these modalities is more effective than the others (1) in reducing normal tissue toxicity and adverse events, and improving quality of life (QOL); (2) in improving local tumor control, time to disease progression, and survival; or (3) when used in certain anatomic locations or patient subpopulations; and, finally, whether (4) there is more variation in patient outcomes with any modality secondary to user experience, treatment planning, or target volumes.

The main finding of CER No. 20 was that late xerostomia was reduced and QOL domains related to xerostomia were improved in patients treated with IMRT compared with those who received either 3DCRT or 2DRT. Evidence was insufficient to draw conclusions on survival or tumor control, adverse events other than late xerostomia (e.g., mucositis, dysphagia, skin toxicities, or osteoradionecrosis of the jaw), whether patient and tumor characteristics affected relative outcomes, or whether physician experience and treatment characteristics affected relative clinical outcomes such as survival or treatment-associated adverse events.

Data sources. A medical librarian searched MEDLINE®, Embase®, and the Cochrane Controlled Trials Registry for English-language articles. The overall search was performed for a period dating 12 months before the final literature search in CER No. 20 (September 28, 2009) through April 2013. For SBRT, the literature was searched for the period January 1, 1990, through April 2013. The search was updated May 1, 2014. A search of the gray literature included clinical trial registries and information from manufacturers if available.

Review methods. We sought only comparative studies that reported clinical outcomes and QOL among our populations of interest. In preparing CER No. 20, we found noncomparative studies to be uninformative due to substantial heterogeneity in methods and populations, so we excluded them from the update. Data were abstracted for each Key Question by one reviewer, with independent data verification. The study limitations of randomized controlled trials (RCTs) and other comparative studies were assessed using the U.S. Preventive Services Task Force (USPSTF) criteria. The strength of the body of evidence for specific outcomes was assessed according to the latest guidance in the Agency for Healthcare Research and Quality "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."

Results. In two searches, we identified 7,130 unique titles and screened 284 in full text. Of the latter, 14 unique studies (N=1,781) in 15 reports met the inclusion criteria, including one RCT (N=60). In the updated search, we identified a second citation to an RCT. However, the latter included the same patients as the previously identified RCT. Therefore, it was not double-

counted in the total number of patients; however, because it reported additional, different outcomes, it was reviewed. In 13 unique studies (14 reports, including the RCT), 3DCRT and IMRT were compared. One study compared 3DCRT and SBRT; none compared IMRT and SBRT. As in CER No. 20, no evidence was identified on PBT. Key outcomes of therapy included overall survival, local control, adverse effects, and QOL. According to USPSTF criteria, the RCT was deemed fair quality, whereas the other 13 studies were graded as poor quality.

Conclusions. New evidence on the comparative effectiveness of RT modalities for head and neck cancer is limited and heterogeneous for each comparison of 3DCRT versus IMRT or SBRT. We did not identify any evidence for PBT. New moderate-strength evidence enhances the CER No. 20 finding of reduced late xerostomia with IMRT compared with 3DCRT, with no relative change in other conclusions on adverse events or QOL. New evidence was insufficient to draw conclusions about the relative effects of IMRT and 3DCRT on overall survival or locoregional tumor control. New evidence is insufficient to draw conclusions on the comparative effectiveness of 3DCRT or IMRT versus SBRT or PBT.

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Executive Summary

Introduction

Objectives

In May 2010, the Agency for Healthcare Research and Quality (AHRQ) published the results of Comparative Effectiveness Review (CER) No. 20 "Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer" prepared by the Blue Cross and Blue Shield Association (BCBSA) Evidence-based Practice Center (EPC).[1] In CER No. 20 we reviewed evidence on the comparative effectiveness of various forms of radiotherapy (RT): two-dimensional radiotherapy (2DRT), three-dimensional conformal RT (3DCRT), intensity-modulated RT (IMRT), and proton-beam RT (PBT).

In 2012 a surveillance study prepared by the RAND and Ottawa EPCs suggested that new evidence relevant to CER No. 20 could alter some of its conclusions.[2] Based on the surveillance findings, AHRQ prioritized an update of CER No. 20 in 2013, to be undertaken by the BCBSA EPC. For this update, we reviewed and assessed new evidence on the comparative effectiveness of 3DCRT, IMRT, and PBT. We also systematically reviewed evidence on stereotactic body RT (SBRT), a newer RT modality that was not widely available when we prepared CER No. 20. However, we excluded opposed-beam 2DRT because it is considered obsolete in modern radiation oncology practice. We also excluded brachytherapy, as it has limited applicability in modern radiation oncology practice for head and neck cancer.

This CER update included the same Key Questions as in CER No. 20 and, for the most part, the same methods and search strategies, modified to address the changes in the list of interventions. We organized clinical evidence according to treatment(s) received, abstracted only from comparative studies (randomized or nonrandomized) of the conformal RT methods used in treatment for any head and neck cancer.

Epidemiology and Burden of Head and Neck Cancer

Head and neck cancer is a heterogeneous disease characterized by complex clinical and pathologic presentations. Squamous cell carcinoma of the head and neck (SCCHN) constitutes approximately 90 percent of all head and neck cancers, and accounted for approximately 3 percent (about 50,000) of all new cancer cases and 2 percent (approximately 12,000) of all cancer deaths in 2010 in the United States.[3] More than 600,000 people were diagnosed with SCCHN worldwide in 2008.[3]

Overview of Multimodal Clinical Management of Head and Neck Cancer

Aggressive multimodality treatments with curative intent may include surgery, RT, and chemotherapy. RT is a vital component of treatment, offered to nearly 75 percent of all head and neck cancer patients with either curative or palliative intent. RT may be used alone or as a part of a multimodality approach, often with significant long-term side effects.

Overview of RT in Head and Neck Cancer

Conformal RT refers to modalities in which radiation beams are "shaped" to cover the tumor volume plus surrounding tissue margin(s) to treat microscopic disease that may reside there.

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 and citations within that reference.[4]

Three-Dimensional Conformal Radiotherapy

Three-dimensional conformal RT allows for accurate and precise dose calculations that account for axial anatomy and complex tissue contours.5 Anatomic information in three dimensions is gathered from diagnostic computed tomography (CT) scans in a forward-planning process to deliver multiple highly focused beams of radiation that converge at the tumor site.

Intensity-Modulated Radiotherapy

IMRT is a newer, more complex, and resource-intensive form of 3DCRT that delivers ionizing radiation conformally to the target volume while sparing uninvolved healthy tissues.[5,6] An inverse-planned regime is designed that allows modulation of beam energies across conformally shaped radiation fields. Although IMRT theoretically reduces radiation dose to organs at risk (OAR), a greater volume of uninvolved tissue or OAR may receive irradiation than with non-IMRT conformal methods.

Stereotactic Body Radiotherapy

SBRT delivers doses of radiation in regimens that generally comprise a total dose similar to that delivered with 3DCRT or IMRT, but in fewer fractions than those techniques, typically eight for head and neck cancer.[7] In SBRT, the tumor location can be tracked in multiple dimensions using several CT imaging techniques that depend on the platform, tracking on bony structures or implanted fiducials.

Proton-Beam Radiotherapy

PBT is relatively rare, but has become increasingly available in the last few years. It has theoretical advantages over photon therapy because PBT lacks an "exit dose" due to the Bragg peak, potentially enabling physicians to deliver high-energy conformal doses to the tumor volume while almost completely sparing normal healthy tissue.

Summary

The optimal means of delivering external beam ionizing radiation in sufficient doses to cure a patient with SCCHN requires a fine balance between treatment effectiveness and associated toxicity. A surveillance study prepared in 2012 by the Ottawa and RAND EPCs suggested a rationale to update CER No. 20 based on signals of new evidence that could change several conclusions of that report. 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.

Key Questions

The following four Key Questions were addressed:

Key Question 1. What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding adverse events and QOL [quality of life]?

Key Question 2. What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding tumor control and patient survival?

Key Question 3. Are there differences in the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT for specific patient and tumor characteristics?

Key Question 4. Is there variation in the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT because of differences in user experience, treatment planning, treatment delivery, and target volume delineation?

Populations, Interventions, Comparators, Outcomes, and Timing (PICOTS)

Population(s)

Populations of interest (Key Questions 1–4) included patients with head and neck cancer. To define what constitutes head and neck cancer, we consulted clinical resources such as the National Cancer Institute's Physician Data Query Cancer Information Summary.[8] The definitions include cancer in these locations:

- Pharynx (hypopharynx, oropharynx, and nasopharynx)
- Larynx
- Lip and oral cavity
- Paranasal sinus and nasal cavity
- Salivary gland
- Head and neck (occult primary)

All therapeutic strategies were included. RT can be delivered as a primary (curative) intent therapy or as an adjunct to surgery. We sought direct evidence for one intervention compared with another, with or without chemotherapy or surgery.

Interventions

Interventions (Key Questions 1–4) were—

- 3DCRT
- IMRT
- SBRT
- PBT

Interventions may occur as part of a multimodal treatment strategy if the comparisons differ only with respect to the RT given.

Comparators

For comparators (Key Questions 1–4) all therapies were compared with each other as part of a continuum of treatment for patients with head and neck cancer.

Outcomes

Outcomes for Key Questions 1, 3, and 4 included—

- Final outcomes: QOL and adverse events, including radiation-induced xerostomia and dysphagia
- Intermediate outcomes: Salivary flow and probability of completing treatment according to protocol

We sought evidence related to user experience, treatment planning, and target volume delineation within the context of Key Question 4.

Outcomes for Key Questions 2–4 included—

- Final outcomes: Overall survival and cancer-specific survival
- Intermediate outcomes: Local control and time to recurrence

Timing

All durations of followup were considered.

Settings

Typically, settings were community based versus tertiary or academic medical centers.

Analytic Framework

Figure A provides an analytic framework illustrating the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis. It links the interventions of interest directly with final health outcomes (e.g., overall survival) and adverse events (e.g., xerostomia) as well as indirectly with final outcomes via intermediate outcomes (e.g., local control, disease-free survival).

Figure A. Analytic framework for comparative effectiveness of RT for head and neck cancer

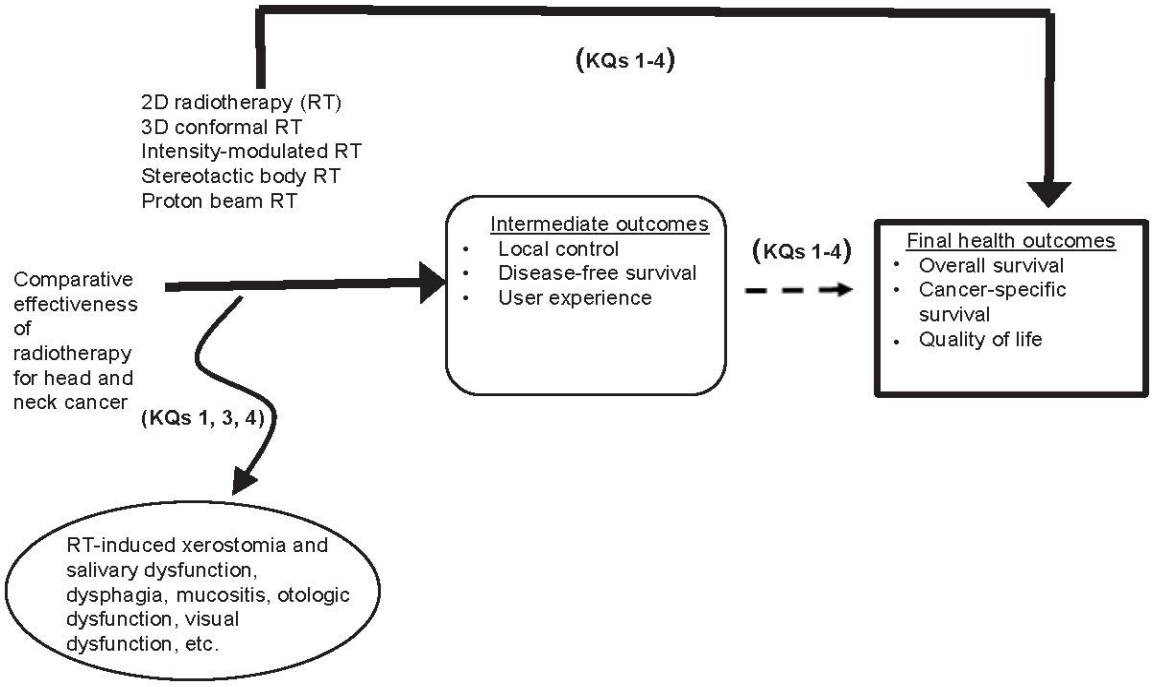


Figure A depicts the Key Questions (KQs) within the context of the PICOTS described in the previous section. In general, the figure illustrates how the interventions 3DCRT, IMRT, SBRT, and PBT may result in intermediate outcomes (e.g., local tumor control, disease-free survival) and final health outcomes (e.g., overall survival, cancer-specific survival, QOL). Also, adverse events (e.g., radiation-associated xerostomia and salivary dysfunction, dysphagia, mucositis, otologic dysfunction, visual dysfunction) may occur at any point after the treatment is received.
Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy; KQ = Key Question; PBT = proton-beam radiation therapy; QOL = quality of life; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Methods

Overview

This section describes the methods used to produce this CER update. The methodological practices we followed derived from the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide).[9] We also consulted the article published by Tsertsvadze et al. on methods to update CERs.[10]

Study Inclusion Criteria

We included only full-length reports that describe the final results of randomized controlled trials (RCTs) and nonrandomized comparative studies (observational, case-control, and cohort studies) that meet the PICOTS criteria (outlined above).

Literature Search Strategies

An experienced medical librarian designed and performed all searches for this CER update. The literature search for the update was backdated to 12 months before the final literature search for CER No. 20 (dated September 28, 2009). For SBRT, the literature was searched

electronically for citations from January 1, 1990, through April 2013. The entire search was updated May 1, 2014, after AHRQ posted the draft of this report for peer review. We searched the following databases:

- MEDLINE®
- EMBASE®
- Cochrane Controlled Trials Register

Data Abstraction and Data Management

Literature search results were transferred to EndNote® and subsequently into Distiller for study screening.

Review of Titles and Abstracts

We developed data collection forms for abstract review, full-text review, and data extraction. Two CER team members performed the initial title and abstract screen. To be excluded, a study must have been independently excluded by both team members.

Full-Text Review

Full-text articles were reviewed against the PICOTS to determine their inclusion in the systematic review. Two CER team members independently reviewed all articles, then met to resolve conflicts on inclusion, conferring with our clinical content expert if necessary. The reason for excluding each article retrieved in full text was recorded in the Distiller database.

Data Abstraction

We abstracted data into tables created in the Systematic Review Data Repository. Each article included was abstracted by a single reviewer. A second reviewer assessed the data extraction against the original articles for quality control.

The data elements abstracted included the following:

- Patient characteristics
- Treatment characteristics
- Outcome assessment (see PICOTS and Analytical Framework sections)

Evidence Tables

The same abstraction tables were used for all studies. The dimensions of each evidence table may vary by Key Question, but the tables contain common elements such as author, year of publication, sample size, study type, intervention(s), and comparator(s).

Methodological Risk of Bias (Quality or Limitations) of Individual Studies

In adherence to the Methods Guide,[9] the general approach to grading the quality or limitations of individual comparative studies was use of a U.S. Preventive Services Task Force (USPSTF) method.[11] Individual study quality assessment accounted for the following study elements:

- Number of participants and flow of participants through steps of study
- Treatment-allocation methods (including concealment)
- Use of blinding

- Study design (prospective vs. retrospective)
- Use of an independent outcome assessor

Data Synthesis

The qualitative synthesis emphasized comparative studies sorted by specific head-to-head comparisons of interventions, specific treatment regimens, patient characteristics, specific outcomes, and status relative to the evidence hierarchy and study quality assessment.

Grading the Strength of Evidence for Individual Comparisons and Outcomes

Studies were assessed for relevance against target populations, interventions of interest, and outcomes of interest. The system used for rating the strength of the overall body of evidence is outlined in the recently updated (2013) chapter from the Methods Guide[9] and is based on a system developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group.[12]

This system explicitly addresses the following domains: study limitations, directness, consistency, precision, and reporting bias.

The overall strength of evidence (SOE) grade is classified into four categories, as shown in Table A.

Table A. Overall strength-of-evidence categories and criteria for assignment

Grade	Definition	Criteria for Assignment
High	We are very confident that the estimate of effect lies close to the true effect for this outcome.	The body of evidence has few or no deficiencies. We believe that the findings are stable.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome.	The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome.	The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.	No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

Assessing Applicability

We assessed applicability of findings with the AHRQ Methods Guide using the PICOTS framework.[9,13] Included studies were assessed for relevance against target populations, interventions and comparators of interest, and outcomes of interest. We anticipated that results would be applicable only to the specialized populations of interest by Key Question.

Results

Overview

In this section, we first report our literature search results and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram, which depicts the flow of articles

through the review according to our screening and inclusion criteria. We provide an overview of the design, patients, and quality (risk of bias) of all included studies. Finally, we lay out a qualitative synthesis of the evidence focusing on key outcomes related to CER No. 20.

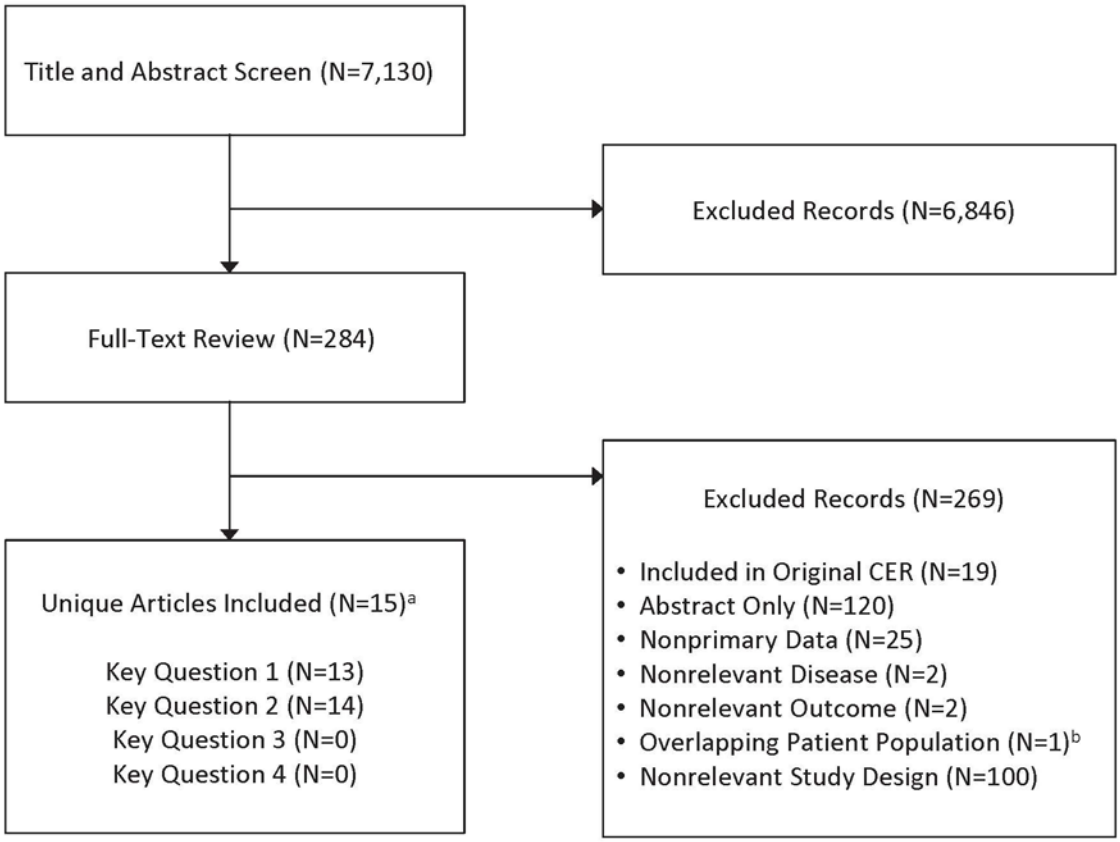
Results of Literature Searches

Electronic Search

In the original and postreview search for this CER we identified 7,130 unique titles and screened 284 in full text. Of the latter, 15 reports (14 unique studies; N=1,781) met the inclusion criteria, including one RCT (Gupta et al., 2012; N=60).[14] In the updated search, we identified a second citation to an RCT (Rathod et al., 2013).[15] Because the latter included the same patients as the previously identified RCT, it was not double-counted in the total number of patients; however, it reported additional, different outcomes that we reviewed and so is counted in that context. Thus, 3DCRT and IMRT were compared in 14 reports that contained unique data, including Rathod et al.'s RCT.[15] One study compared 3DCRT and SBRT;[16] none compared IMRT and SBRT. As in CER No. 20, no evidence was identified on PBT. The flow of articles through the screening and study selection process is shown in the PRISMA diagram (Figure B).

Although CER No. 20 was published in final form in 2010, we had obtained the final data for PARSPORT (Parotid-Sparing Intensity-Modulated versus Conventional Radiotherapy in Head and Neck Cancer),[17] a key phase 3 multicenter RCT, from the investigators at the time we updated the CER No. 20 literature search. Because the PARSPORT findings appeared in CER No. 20, they were not included in this report.

Figure B. PRISMA diagram for disposition of literature search results



[a]Twelve studies addressed both Key Questions 1 and 2.
[b]Overlapping patient population refers to the studies in which the same patients were included in more than 1 study. In this case, only 1 study was included to avoid oversampling. The decision to include a study was based on the clarity in reporting relevant patients and/or outcomes.
Abbreviations: CER = Comparative Effectiveness Review; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Gray Literature (Publication Bias)

We did not include any information based on comprehensive searches of meeting abstracts. We examined the bibliographies of all papers screened in full text to identify peer-reviewed articles the electronic search may have missed.

We accessed the Web site ClinicalTrials.gov to identify ongoing phase 3 RCTs that would meet the criteria for inclusion based on our protocol. After a MEDLINE search of the NCT (National Clinical Trial) number(s) and title(s), we did not find any published results; it is unknown whether any data have been reported. At submission of this final report, we had received Scientific Information Packets from one manufacturer of RT equipment. Information contained therein had no effect on our analysis.

Description of All Included Studies

Fifteen reports (14 unique studies) met the inclusion criteria for this CER update. They are generally described in this section; other details and results specific to a particular Key Question follow in the relevant subsections.

Study Limitations

We assigned a fair USPSTF rating to Gupta et al.'s RCT, primarily because the study was not double blinded, particularly its outcome assessments.[14] The investigators did not report an intention-to-treat analysis but did report a "modified intention-to-treat" analysis that was not further described. This is moot, however, because they reported a 97-percent followup rate in each of two study arms. Gupta et al. reported aggregated survival results in patients with tumors in different sites. However, the distribution of tumor sites and characteristics was similar between arms. Overall, the two study arms were statistically similar and comparable.

The 13 unique nonrandomized studies were retrospective database analyses, one of which used a historical comparator group. Overall, these studies were poorly designed, executed, and reported.

Study Design and Patient Characteristics

In total, 3DCRT and IMRT were compared in 13 studies (14 reports), including one small (N=60) RCT.

Overall, the body of studies in the update, similar to what we identified for CER No. 20, is heterogeneous in terms of tumor site and stage, treatment regimen, and treatment intent (e.g., curative vs. palliative or recurrent). Patients were generally in their midfifties, with males predominating across studies. Tumor sites included the hypopharynx, larynx, nasal sinus, nasopharynx, oral cavity, and oropharynx. Seven nonrandomized studies involved patients with single tumor sites.[16,18-23] The majority of patients across studies had locally advanced (stage III and IV) cancer, although small proportions of patients had stage I or II disease.

The treatment regimens included concurrent chemoradiotherapy (CCRT); RT with or without concurrent chemotherapy (CCT); CCRT with or without surgery; and adjuvant postoperative RT.

Key Question 1. 3DCRT, IMRT, SBRT, and PBT: Adverse Events and QOL

Overview

In this section we summarize evidence on comparative acute and late toxicities for different RT types. We focused this update, as we did CER No. 20, on grade 2 or higher toxicities prominently associated with RT in the head and neck and of high importance to patients: dysphagia, salivary gland function, and xerostomia. We did not seek evidence from other study designs (e.g., single-arm observational) that may report additional toxicities not captured in the comparative studies.

Our results show that toxicity outcomes were not collected consistently across studies. Only eight studies (53%) reported acute (<90 days post-treatment) toxicities.[14,16,20,22,24-27] Nine studies (60%) reported late (>90 days post-treatment) toxicities.[14,16,18-20,23-25,27] Only two studies, including the RCT by Rathod et al.,[15] reported QOL evidence according to RT modality.

Investigators did not adjust results to account for chemotherapy-associated toxicities independent of RT-associated toxicities, which complicates interpretation of toxicity evidence for many adverse events (e.g., mucositis). This is somewhat ameliorated by our focus on studies in which chemotherapy regimens are similar between study arms, thus potentially isolating the effect of the RT modality on such outcomes.

Key Points

Key points are—

- New comparative evidence assessed in this update strengthens the conclusion from CER No. 20 that the risk of grade 2 or higher late xerostomia is significantly lower in patients treated with IMRT than 3DCRT.
- Although we identified evidence on other key toxicities (e.g., mucositis, dysphagia, skin toxicities, osteoradionecrosis of the jaw) and QOL, the reported comparisons within modalities were inconsistent. Thus, evidence on adverse events other than late xerostomia remains insufficient to alter the conclusions of CER No. 20.
- Post-treatment toxicities were reported inconsistently across studies, precluding comparisons within the body of evidence. We are uncertain whether the limited evidence on RT-associated toxicities overall reflects their absence or whether the investigators either did not systematically collect them or chose not to report them.

Qualitative Synthesis

In Table B and below, we summarize new comparative evidence and the SOE related to Key Question 1 on QOL and toxicities actually reported in multiple studies according to the intervention comparison and timeframe (acute vs. long-term).

RT-Associated Toxicities

Three studies of IMRT compared with 3DCRT in the regimen of CCRT showed statistically significant reduction in late xerostomia with IMRT.[14,20,27] The rate of late xerostomia also was significantly lower with IMRT than 3DCRT in single studies in the regimen of RT with or without CCT[18] or postoperative RT.[19] The same set of studies reported inconsistent evidence on acute and late dysphagia.

RT-Associated QOL

One RCT reported QOL evidence on IMRT versus 3DCRT in the regimen of RT with CCT.[15] Rathod et al. reported on mean QOL scores using the European Organization for Research and Treatment of Cancer QOL questionnaire (QLQ-C30) and Head-Neck module (HN-35) validated self-administered tools at baseline (pretreatment) and periodically on followup (3, 6, 12, 18, and 24 months). The study reported that global QOL was not significantly affected by RT technique. Treatment with IMRT showed a benefit in some general QOL domains, as well as several domains specific to head and neck cancer, compared with 3DCRT. General domains in which IMRT demonstrated a significant benefit included emotional functioning at 12 months ($p=0.008$), role functioning at 12 months ($p = 0.008$), and social contact at 24 months ($p=0.03$). Symptoms specific to head and neck cancer for which IMRT demonstrated a significant benefit ($p <0.05$) compared with 3DCRT included scales and dry month (6, 12, and 18 months), as well as opening mouth (6 and 24 months). Sticky saliva, pain, swallowing, senses, sexuality, feeling ill, and insomnia tended to be ameliorated by the use of IMRT compared with 3DCRT and were all statistically significant for at least one timepoint. No QOL domains were worse with IMRT than 3DCRT at any timepoint. For both RT techniques, QOL domains generally experienced maximal deterioration after RT, followed by a trend toward gradual recovery over time.

A nonrandomized study reported QOL evidence on IMRT versus 3DCRT in the regimen of RT with or without CCT.[28] Chen et al. reported on mean QOL scores using the University of Washington Quality of Life validated self-administered tool. In this study, the salivary gland

domain was the only specific component of the score wherein significant differences were observed between the IMRT and the 3DCRT groups at both 1 and 2 years ($p < 0.001$ at both points). Other domains (pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood, anxiety) showed no differences according to RT modality. At 1 year after completion of RT, the global QOL was rated as "very good" or "outstanding" for 51 percent of patients treated with IMRT compared with 41 percent of those treated with 3DCRT ($p=0.11$). However, at 2 years, the corresponding percentages were 73 percent and 49 percent, respectively ($p < 0.001$), showing a benefit of IMRT. Multivariate analysis showed no effect on QOL scores by age, sex, radiation intent, radiation dose, T (tumor) stage, primary site, or use of CCT and neck dissection. The use of IMRT was the only variable associated with improved QOL ($p < 0.01$).

The qualitative evidence synthesis and SOE for QOL are summarized in Table B.

Table B. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL

Comparison	Outcome	Timeframe	Number of Studies (Number of Patients)	Individual Study Statistically Significant Results (p-Value)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
3DCRT vs. IMRT	Xerostomia	Late	Four studies[14,20,25,27] (N=576)	All 4 studies showed statistically significant benefit of IMRT vs. 3DCRT (p <0.05).	Moderate One fair-quality small RCT (N=60, Gupta, 2012[14]) plus 3 poor-quality nonrandomized studies result in a moderate study limitations rating.	Direct All 4 studies directly compared IMRT and 3DCRT.	Consistent All 4 studies showed a statistically significant reduction of late grade >2 xerostomia with IMRT compared with 3DCRT (p <0.05).	Precise	Moderate. The body of evidence comprises 1 RCT, for a provisional SOE of high. We downgraded the SOE 1 level based on the moderate risk of bias of the body of evidence. Although the Gupta trial[14] was relatively small, its statistically significant result, coupled with similar findings of the much larger nonrandomized evidence, merits an overall rating of precise. The overall SOE was rated as moderate due to limitations in the methodological quality of the studies. However, the findings of the 3 studies were consistent and indicated statistical significance.

Table B. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL (continued)

Comparison	Outcome	Timeframe	Number of Studies (Number of Patients)	Individual Study Statistically Significant Results (p-Value)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
3DCRT vs. IMRT (continued)	Dysphagia	Acute	Four studies[14,20,25,27] (N=576)	Only 1 study showed a statistically significant benefit of IMRT vs. 3DCRT (p <0.05).[20]	Moderate One fair-quality small RCT (N=60, Gupta 2012[14]) plus three poor-quality nonrandomized studies result in a moderate study limitations rating.	Direct	Inconsistent One nonrandomized study showed a statistically significant reduction with IMRT compared with 3DCRT (p <0.05).[20] The other non-RCTs showed a directionally same but nonsignificant effect that favored IMRT over 3DCRT. Gupta, 2012,[14] showed a lower but also nonsignificant rate difference for acute dysphagia with 3DCRT compared with IMRT.	Imprecise The Gupta RCT[14] included only 60 cases, compared with 516 for the other 3 studies. It was likely not sufficiently powered to detect slight changes in rates of adverse effects, particularly in the face of much larger, albeit poor-quality, non-RCT evidence.	Insufficient A high provisional SOE based on the Gupta RCT[14] was reduced 3 levels for 3 reasons: (1) rating was inconsistent; (2) rating was imprecise based on the small size of the Gupta RCT and its nonsignificant result; and (3) the 3 nonrandomized studies were of poor quality, heterogeneous, and subject to a high risk of bias, thus increasing the risk of bias to moderate for the body of evidence.

Table B. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL (continued)

Comparison	Outcome	Timeframe	Number of Studies (Number of Patients)	Individual Study Statistically Significant Results (p-Value)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
3DCRT vs. IMRT (continued)	Dysphagia (continued)	Late	Three studies[20,25,27] (N=774)	Two studies showed a statistically significant benefit of IMRT vs. 3DCRT (grade ≥2) (p <0.05)[20,25]	High Three poor-quality nonrandomized studies comprise the body of evidence.	Direct	Inconsistent Two studies showed a statistically significant effect of IMRT compared with 3DCRT (p <0.05), with the third study showing a reduction, albeit a nonsignificant reduction.	Precise	Insufficient The 3 nonrandomized studies were poor quality and heterogeneous, with high risk of bias that compromises the value of their results.

Table B. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL (continued)

Comparison	Outcome	Timeframe	Number of Studies (Number of Patients)	Individual Study Statistically Significant Results (p-Value)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
3DCRT vs. IMRT (continued)	QOL	Acute and late	Two studies[14,28] (N=215)	Rathod's RCT[15] showed statistically significant (p <0.05) benefit for IMRT in the domains specific to head and neck cancer of scales and dry mouth, sticky saliva, and swallowing for at least 1 timepoint. No QOL endpoints were worse with IMRT than with 3DCRT at any timepoint in the Rathod study. In the other study,[28] use of IMRT was the only variable associated with improved QOL (p <0.01).	Moderate One fair-quality small RCT (N=60, Rathod, 2013[15]) plus 1 poor-quality nonrandomized study result in a moderate study limitations rating.	Direct	Inconsistent One study showed a statistically significant benefit (p <0.001) of IMRT compared with 3DCRT for global QOL at 1 and 2 years,[28] while the second study reported no statistical difference based on radiotherapy technique.	Imprecise The Rathod RCT[15] included only 60 cases, compared with 155 for the second study. It was likely not sufficiently powered to detect slight changes in QOL, particularly in the face of much larger, albeit poor-quality, non-RCT evidence.	Insufficient A high provisional SOE based on the Rathod RCT[15] was reduced 3 levels for 3 reasons: (1) rating was inconsistent; (2) rating was imprecise based on the small size of the Rathod RCT and its nonsignificant result; and (3) the nonrandomized study was of poor quality, heterogeneous, and subject to a high risk of bias, thus increasing the risk of bias to moderate for the body of evidence.

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; QOL = quality of life; RCT = randomized controlled trial; SOE = strength of evidence.

Key Question 2. 3DCRT, IMRT, SBRT, and PBT: Tumor Control and Patient Survival

Overview

In this section we summarize evidence on comparative oncologic outcomes for different RT types. We did not seek evidence from other study designs (e.g., single-arm observational) that may report additional outcomes not captured in the comparative studies.

Overall, key oncologic outcomes were not reported consistently across studies, and not all outcomes were collected in each study. Data were most often reported on overall survival and locoregional control.

Key Points

Key points are—

- As we found in CER No. 20, comparative evidence assessed in this update was insufficient to draw relative conclusions on any oncologic outcomes.
- The key oncologic outcomes were not reported universally across studies, so we could not make comparisons across a larger body of evidence.

Qualitative Synthesis

In Table C, we summarize new comparative evidence and the SOE related to Key Question 2 on oncologic outcomes actually reported in multiple studies.

In general, evidence on tumor control and survival outcomes is sparse. Statistically significant differences were inconsistently reported for overall survival, local control, and locoregional control in studies of 3DCRT versus IMRT.

Table C. Key Question 2: Qualitative evidence synthesis for key reported comparative oncologic outcomes

Comparison	Outcome	Number of Studies (Number of Patients)	Individual Study Statistically Significant Results (p-Value)	Risk of Bias	Directness	Consistency	Precision	Overall SOE
3DCRT vs. IMRT	Overall survival	Eight studies (9 reports)[14,15,20-25,27] (N=1,080)	Only 1 study showed a statistically significant benefit of IMRT vs. 3DCRT (p <0.05)[21]	Moderate One fair-quality small RCT (2 reports; N=60, Gupta, 2012;[14] N=60, Rathod, 2013[15]) plus 7 poor-quality nonrandomized studies result in a moderate study limitations rating.	Direct All 8 studies directly compared IMRT and 3DCRT.	Inconsistent The retrospective Huang study[21] reports an overall survival benefit of IMRT compared with 3DCRT at 5 years. The remaining 7 studies showed no statistically significant difference between 3DCRT and IMRT in rate of overall survival at 2 or 5 years.	Imprecise The Gupta, 2012, RCT[14] was likely not sufficiently powered to detect slight changes in rates of overall survival with IMRT compared with 3DCRT, particularly in the face of much larger, albeit poor-quality, non-RCT evidence.	Insufficient A high provisional SOE based on the Gupta RCT[14] was reduced 3 levels for 3 reasons: (1) rating was imprecise based on the small size of the Gupta and Rathod RCT[14,15] and the nonsignificant result; (2) the 7 nonrandomized studies were of poor quality, heterogeneous, and subject to a high risk of bias, yielding an overall moderate risk of bias; and (3) the relatively larger size of these 7 studies compared with Gupta, accounting for over 94% of all patients in the body of evidence, obscures the findings of the latter, resulting in an overall SOE rating of insufficient.

Table C. Key Question 2: Qualitative evidence synthesis for key reported comparative oncologic outcomes (continued)

Comparison	Outcome	Number of Studies (Number of Patients)	Individual Study Statistically Significant Results (p-Value)	Risk of Bias	Directness	Consistency	Precision	Overall SOE
3DCRT vs. IMRT (continued)	Locoregional control	Six studies (7 reports)[14,15,20,21,23,25,27] (N=695)	Huang, 2013 (5-year),[21] Kong, 2013 (1- and 2-year),[25] and Mok, 2014 (3-year)[23] report a statistically significant benefit of IMRT vs. 3DCRT as it pertains to locoregional control ($p < 0.05$). The remaining 3 studies report no statistically significant difference in locoregional control.	Moderate One fair-quality RCT (Gupta, 2012;[14] Rathod, 2013[15]) and 5 much larger poor-quality nonrandomized studies result in a moderate study limitations rating.	Direct All studies directly compared IMRT and 3DCRT.	Inconsistent Three studies showed a statistically significant effect of IMRT compared with 3DCRT, while the remaining 3 showed no significant difference.	Imprecise Neither the Gupta, 2012,[14] nor Rathod, 2013,[15] RCT was likely sufficiently powered to detect slight changes in rates of locoregional control with IMRT compared with 3DCRT, particularly in the face of much larger, albeit poor-quality, non-RCT evidence.	Insufficient A high provisional SOE based on the Gupta[14] (and Rathod[15]) RCT was reduced 3 SOE levels, as outlined above, for overall survival. The patients in the nonrandomized studies comprised more than 91% of the evidence base, obscuring Gupta's and Rathod's results.

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; RCT = randomized controlled trial; SOE = strength of evidence.

Key Question 3. 3DCRT, IMRT, SBRT, or PBT: Specific Patient and Tumor Characteristics

In CER No. 20, no comparative studies addressed these issues. In this update, we did not identify any new evidence that specifically addressed Key Question 3.

Key Question 4. 3DCRT, IMRT, SBRT, or PBT: Differences in User Experience, Treatment Planning, Treatment Delivery, and Target Volume Delineation

In CER No. 20, no comparative studies addressed these issues. In this update, we did not identify any new evidence that specifically addressed Key Question 4.

Discussion

Strength of Evidence Relative to CER No. 20

Table D provides a summary of the conclusions we drew for the relevant RT comparisons for each Key Question in CER No. 20 and in this update. Because 2DRT was not addressed in the update, it is not included in Table D. Moderate-strength evidence from the update shows a reduction of the incidence of late grade 2 or higher xerostomia with IMRT compared with 3DCRT. This evidence increases the SOE on this toxicity from the SOE in CER No. 20, raising it to high based on a body of evidence including two RCTs that are in agreement on this outcome. Evidence in the update is insufficient to show a difference between IMRT and 3DCRT in overall survival or locoregional tumor control rates. We found no new evidence to alter any conclusions of CER No. 20 for any other toxicity, oncologic outcomes, or comparisons.

Table D. Comparison of relevant CER No. 20 and update conclusions

Key Question	Comparison	Clinical Outcome	CER No. 20 Total Evidence Base	CER No. 20 Conclusions	CER No. 20 Update Total Evidence Base	CER No. 20 Update Conclusions	Cumulative Update Conclusions (Action Needed)
Key Question 1: What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding adverse events and QOL?	3DCRT vs. IMRT	Grade ≥2 late xerostomia	One good-quality RCT and 6 poor-quality non-RCTs	Moderate SOE shows significant reduction in incidence	One fair-quality RCT, 6 poor-quality non-RCTs	Moderate SOE shows significant reduction in incidence	Raises final SOE to high based on a body of evidence including 2 RCTs (no further study required)
	3DCRT vs. IMRT	Other RT-associated grade >2 toxicities (e.g., acute or late dysphagia, salivary gland dysfunction, swallowing function)	One good-quality RCT, 13 poor-quality non-RCTs	Insufficient evidence to draw conclusions	One good-quality RCT, 9 poor-quality non-RCTs	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
	3DCRT vs. IMRT	QOL	Three poor-quality non-RCTs	Insufficient evidence to draw conclusions	One fair-quality RCT, 1 poor-quality non-RCT	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. PBT	Any	No evidence identified	No evidence identified; insufficient	No evidence identified	No evidence identified; insufficient	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. SBRT	Any	Not applicable (SBRT not included)	Not applicable (SBRT not included)	One poor-quality non-RCT	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)

Table D. Comparison of relevant CER No. 20 and update conclusions (continued)

Key Question	Comparison	Clinical Outcome	CER No. 20 Total Evidence Base	CER No. 20 Conclusions	CER No. 20 Update Total Evidence Base	CER No. 20 Update Conclusions	Cumulative Update Conclusions (Action Needed)
Key Question 2: What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding tumor control and patient survival?	3DCRT vs. IMRT	Overall survival, local control, locoregional control, disease-free survival	One good-quality RCT, 6 poor-quality non-RCTs	Insufficient evidence to draw conclusions	One fair-quality RCT, 9 poor-quality non-RCTs	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. PBT	Any	No evidence identified	No evidence identified; insufficient	No evidence identified	No evidence identified; insufficient	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. SBRT	Any	Not applicable (SBRT not included)	Not applicable (SBRT not included)	One poor-quality non-RCT	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
Key Question 3: Are there differences in the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT for specific patient and tumor characteristics?	3DCRT or IMRT vs. PBT or SBRT	Any	No evidence identified	No evidence identified; insufficient	No evidence identified	No evidence identified; insufficient	Insufficient evidence to draw conclusions (further study required)
Key Question 4: Is there variation in the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT because of differences in user experience, treatment planning, treatment delivery, and target volume delineation?	3DCRT or IMRT vs. PBT or SBRT	Any	No evidence identified	No evidence identified; insufficient	No evidence identified	No evidence identified; insufficient	Insufficient evidence to draw conclusions (further study required)

Abbreviations: 3DCRT = 3-dimensional conformal radiotherapy; CER = Comparative Effectiveness Review; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; QOL = quality of life; RCT = randomized controlled trial; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SOE = strength of evidence.

Applicability of the Findings

In general, applicability assessment would depend on a body of evidence sufficient to form new conclusions about the comparative outcomes of 3DCRT, IMRT, SBRT, and PBT in treatment of head and neck cancer. However, comparative evidence that meets study selection criteria for this CER update is sparse for 3DCRT, IMRT, and SBRT, and nonexistent for PBT. In the absence of sufficient evidence, additional factors may be considered in making a treatment decision. Those could include relative convenience and cost, issues outside the scope of this CER.

In preparing this update, we discussed the interventions that we included in CER No. 20 and whether all remained applicable to current radiation oncology practice. In particular, we examined the role of opposed-beam 2DRT in modern radiation oncology practice and reexamined whether brachytherapy should be included. Based on the literature and input from our Technical Expert Panel members, we concluded that brachytherapy has a limited role in RT of head and neck cancer, so it was not included in this update. We also concluded that 2DRT is no longer used in the United States for definitive treatment of head and neck cancer; thus we excluded it from the update. We realize that, in doing so, we excluded evidence from an RCT performed in China that showed a statistically significant improvement in overall survival with IMRT compared with 2DRT, which to our knowledge is the only study that has shown a statistically significant survival benefit of one RT modality compared with another.[29] However, this did not alter our overall conclusion to exclude 2DRT from the current report.

We considered including dosimetry studies in CER No. 20 and this update. For both reports, our ultimate conclusion not to include dosimetry studies was agreed upon among our EPC team, among AHRQ personnel, and in discussion with our Technical Expert Panel. 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.

Key Questions 1 and 2

The degree to which the evidence presented in this report is applicable to clinical practice is a function of the similarity between populations in the included studies and the patient population that receives clinical care in diverse settings. It also is related to the relative availability of the interventions. Because of the overall weakness of evidence for Key Questions 1 and 2, we have primarily limited comments to the relevance of the PICOTS elements, a practical and useful structure to review the applicability in a systematic manner (Table E).

Table E. Summary of applicability of evidence for Key Questions 1 and 2

PICOTS Domain	Applicability of Evidence
Populations	• Overall, patients included in the evidence base of this CER update are typical of the head and neck cancer population treated with RT based on age, sex, and tumor characteristics.
Interventions	• 3DCRT, IMRT, and SBRT represent different technological approaches to the delivery of conformal photon RT. The major advantage of these interventions compared with traditional wide-field 2DRT is the ability to deliver tightly focused ionizing radiation by delineating the shape and size of the tumor using a CT-based or other imaging planning system. • 3DCRT represents a minimum technical standard for delivery of forward-planned conformal RT. It involves static fields with a fixed shape, modified by compensators (wedges and segments). 3DCRT is widely available. • IMRT offers beam strength attenuation through a multileaf collimator (tungsten), with dynamic field shapes for each beam angle. IMRT is as widely available as 3DCRT but requires labor-intensive inverse planning and a higher level of quality assurance. • SBRT is a hypofractionated technique to administer RT in far fewer fractions than 3DCRT and IMRT. • SBRT is not as widely available as 3DCRT or IMRT, but its use is growing in other diseases such as non–small-cell lung cancer. • The institutional programmatic requirements for SBRT differ from those of IMRT. • Comparative evidence for PBT is unavailable.
Comparators	• See above for Interventions.
Outcomes	• The major beneficial health outcomes in this CER are overall survival and late xerostomia. • Overall survival is the primary outcome of interest for any cancer intervention study. • Local control is of interest to patients because it measures the effectiveness of an intervention in disease control. On local failure, patients enter into a new category centered on systemic chemotherapy.
Timing	• The relevant periods occur from the time of treatment through followup over months (palliation) or years (overall survival).
Setting	• The evidence for Key Questions 1 and 2 is mostly international, primarily obtained in tertiary institutions. More sophisticated interventions such as IMRT and SBRT require an institutional commitment to quality assurance and ongoing training that may be difficult to achieve in smaller community-based centers. • We did not collect or analyze information to examine these issues.

Abbreviations: 2DRT = 2-dimensional radiotherapy; 3DCRT = 3-dimensional conformal radiotherapy; CER = Comparative Effectiveness Review; CT = computed tomography; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; PICOTS = populations, interventions, comparators, outcomes, timing and setting; RT = radiotherapy; SBRT = stereotactic body radiotherapy.

Key Questions 3 and 4

The current evidence base for Key Questions 3 and 4 is nonexistent based on our literature review. Therefore we cannot assess the applicability to clinical practice.

Findings in Relationship to What Is Already Known

Our updated systematic literature search and review revealed no relevant evidence-based guidelines we could compare with our findings for any of the Key Questions.

Limitations of the Current Review and Evidence Base

Although the body of evidence we identified was more substantial for 3DCRT and IMRT than SBRT, and nonexistent for PBT, we have significant concerns about interstudy heterogeneity, with variability in RT dose, schedule of treatment, concurrent treatments, patient selection criteria, tumor size and location, and so forth. As stated previously in this report, we are not sure whether the inconsistency in key reported RT-associated adverse events reflects a lack of systematic collection of this type of information by investigators or failure to consistently report it in publications. We acknowledge that our inclusion of comparative studies alone may have limited collection of additional RT-associated adverse events that may be revealed in larger observational studies. However, we believe our decision to focus on the key comparative outcomes of xerostomia, dysphagia, and salivary gland toxicity was merited based on our understanding of the literature and the importance of those toxicities to cancer patients.

We also are aware that a body of dosimetry evidence is available to suggest potential differences in the benefits and harms of different conformal RT types. Our exclusion of such evidence may be viewed by some readers as a limitation of this CER update. However, we maintain that because dosimetry modeling studies do not provide a clear link to clinical outcomes, they do not add critical information to assess the comparative effectiveness of RT in the treatment of head and neck cancer.

Research Gaps

The primary research gap we identified is a continuing lack of evidence from well-executed comparative studies (randomized or otherwise) to draw conclusions on the relative clinical benefits and harms of the RT interventions used in patients with head and neck cancer. We also identified some potential impediments to the type of rigorous comparative studies that we suggest are necessary to determine their comparative effectiveness. We urge that rigorous methods be used for the conduct of RCTs, particularly intention-to-treat analysis and adjustment of survival data to account for all patients based on their treatment plans.

Primary comparative oncologic outcomes that remain to be addressed in clinical studies include overall survival, cancer-specific survival, and local control. Prespecified systematic collection of adverse events using validated criteria (e.g., Common Terminology Criteria for Adverse Events) is necessary to permit accurate assessment of the relative benefits and risks of the interventions. In particular, given the evidence summarized in this report, we recognize dysphagia as a key adverse outcome of interest to patients to be included in comparative clinical studies of RT types.

The potential impact of tumor tissue human papilloma virus (HPV) positivity on oncologic outcomes and management of patients with HPV positivity has been increasing in importance. Studies are needed to identify reduced intensity-RT regimens that still yield satisfactory oncologic outcomes. To accomplish this, investigators will need to stratify patients according to HPV status and analyze data accordingly.

Potential Impediments to Comparative Studies of RT Interventions for Head and Neck Cancer

The general dissemination of advanced conformal RT technologies into community clinical practice is a theoretical impediment to comparative study of those technologies. Broad

availability of technologies previously available only in tertiary centers may dissuade referrals to tertiary centers in favor of a local provider. We also acknowledge that randomized studies of 3DCRT versus IMRT or PBT may be very difficult to recruit and conduct based on technical and potential ethical issues related to perceptions of unequal clinical benefit among the interventions. The cost of conducting rigorous RCTs is another potential impediment given current resource constraints in the United States.

Summary and Conclusions

The main finding of CER No. 20 was that late xerostomia was reduced and QOL domains related to xerostomia were improved in patients treated with IMRT compared with those who received either 3DCRT or 2DRT. Evidence was insufficient to draw relative conclusions on survival or tumor control; adverse events other than late xerostomia (e.g., mucositis, dysphagia, skin toxicities, osteoradionecrosis of the jaw); whether patient and tumor characteristics affected relative outcomes; or whether physician experience and treatment characteristics affected relative clinical outcomes such as survival or treatment-associated adverse events.

Moderate-strength evidence from the update shows a reduction of the incidence of late grade 2 or higher xerostomia with IMRT compared with 3DCRT. This increases the SOE on this toxicity from CER No. 20, raising it to "high" based on a body of evidence including two RCTs that are in agreement on this outcome. Evidence in the update is insufficient to show a difference between IMRT and 3DCRT in overall survival or locoregional tumor control rates. We found no new evidence to alter any conclusions of CER No. 20 for any other toxicity, oncologic outcomes, or comparisons.

References

1. Samson DJ, Ratko TA, Rothenberg BM, et al. Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer. Comparative Effectiveness Review No. 20 (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality; May 2010. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
2. Ahmadzai N, Tsertsvadze A, Skidmore B. AHRQ Comparative Effectiveness Review Surveillance Program: Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer. Agency for Healthcare Research and Quality; 2012. www.effectivehealthcare.ahrq.gov/ehc/products/19/1540/head-neck-cancer-surveillance-130613.pdf.
3. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69-90. PMID: 21296855.
4. National Cancer Institute. Radiation Therapy for Cancer. Fact Sheet. www.cancer.gov/cancertopics/factsheet/Therapy/radiation. Accessed August 13, 2014.
5. Bucci M, Bevan A, Roach M III. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin. 2005;55:117-34. PMID: 15761080.
6. Lee N, Puri DR, Blanco AI, et al. Intensity-modulated radiation therapy in head and neck cancers: an update. Head Neck. 2007;29(4):387-400. PMID: 16358297.
7. Siddiqui F, Raben D, Lu JJ, et al. Emerging applications of stereotactic body radiation therapy for head and neck cancer. Expert Rev Anticancer Ther. 2011 Sep;11(9):1429-36. PMID: 21929316.
8. Pfister DG, Ang K-K, Brizel DM, et al. Head and neck cancers. J Nat Compr Cancer Netw. 2011 Jun 1;9(6):596-650. PMID: 21636536.

9. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at www.effectivehealthcare.ahrq.gov.

10. Tsertsvadze A, Maglione M, Chou R, et al. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1208-15. PMID: 21684114.

11. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35. PMID: 11306229.

12. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010;63:513-23. PMID: 19595577.

13. Brown P, Brunnhuber K, Chalkidou K, et al. How to formulate research recommendations. BMJ. 2006 Oct 14;333(7572):804-6. PMID: 17038740.

14. Gupta T, Agarwal J, Jain S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. Radiother Oncol. 2012 Sep;104(3):343-8. PMID: 22853852.

15. Rathod S, Gupta T, Ghosh-Laskar S, et al. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. Oral Oncol. 2013 Jun;49(6):634-42. PMID: 23562564.

16. Ozyigit G, Cengiz M, Yazici G, et al. A retrospective comparison of robotic stereotactic body radiotherapy and three-dimensional conformal radiotherapy for the reirradiation of locally recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Physics. 2011;81(4):e263-8. PMID: 21514737.

17. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011 Feb;12(2):127-36. PMID: 21236730.

18. Al-Mamgani A, Mehilal R, van Rooij PH, et al. Toxicity, quality of life, and functional outcomes of 176 hypopharyngeal cancer patients treated by (chemo)radiation: the impact of treatment modality and radiation technique. Laryngoscope. 2012 Aug;122(8):1789-95. PMID: 22833307.

19. Al-Mamgani A, Monserez D, Rooij P, et al. Highly-conformal intensity-modulated radiotherapy reduced toxicity without jeopardizing outcome in patients with paranasal sinus cancer treated by surgery and radiotherapy or (chemo)radiation. Oral Oncol. 2012 Sep;48(9):905-11. PMID: 22584070.

20. Al-Mamgani A, van Rooij P, Verduijn GM, et al. The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. Laryngoscope. 2013 Feb;123(2):386-93. PMID: 23404489.

21. Huang HI, Chan KT, Shu CH, et al. T4-locally advanced nasopharyngeal carcinoma: prognostic influence of cranial nerve involvement in different radiotherapy techniques. Sci World J. 2013;2013:439073. PMID: 24385882.

22. Lohia S, Rajapurkar M, Nguyen SA, et al. A comparison of outcomes using intensity-modulated radiation therapy and 3-dimensional conformal radiation therapy in treatment of oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg. 2014 Apr 1;140(4):331-7. PMID: 24557509.

23. Mok G, Gauthier I, Jiang H, et al. Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head Neck. 2014 Mar 2. PMID: 24590756.

24. Dirix P, Vanstraelen B, Jorissen M, et al. Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. Int J Radiat Oncol Biol Physics. 2010;78(4):998-1004. PMID: 20338694.

25. Kong M, Hong SE, Choi J, et al. Comparison of survival rates between patients treated with conventional radiotherapy and helical tomotherapy for head and neck cancer. Radiat Oncol J. 2013;31(1):1-11. PMID: 2013256692.

26. Kruser TJ, Rice SR, Cleary KP, et al. Acute hematologic and mucosal toxicities in head and neck cancer patients undergoing chemoradiotherapy: a comparison of 3D-CRT, IMRT, and helical tomotherapy. Technol Cancer Res Treat. 2013;12(5):383-9. PMID: 2013256692.

27. Lambrecht M, Nevens D, Nuyts S. Intensity-modulated radiotherapy vs. parotid-sparing 3D conformal radiotherapy. Effect on outcome and toxicity in locally advanced head and neck cancer. Strahlenther Onkol. 2013 Mar;189(3):223-9. PMID: 23319256.

28. Chen AM, Farwell DG, Luu Q, et al. Intensity-modulated radiotherapy is associated with improved global quality of life among long-term survivors of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012 Sep 1;84(1):170-5. PMID: 22300572.

29. Peng G, Wang T, Yang KY, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol. 2012 Sep;104(3):286-93. PMID: 22995588.

Introduction

Objectives

In May 2010, the Agency for Healthcare Research and Quality (AHRQ) published the results of Comparative Effectiveness Review (CER) No. 20, "Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer," prepared by the Blue Cross and Blue Shield Association Evidence-based Practice Center (EPC).[1] CER No. 20 examined evidence on clinical outcomes achieved with two-dimensional radiotherapy (2DRT), three-dimensional conformal RT (3DCRT), intensity-modulated RT (IMRT), and proton-beam RT (PBT). The main finding of CER No. 20 was that late xerostomia was reduced and quality of life (QOL) domains related to xerostomia were improved in patients treated with IMRT compared with those who underwent 3DCRT or 2DRT. Evidence was insufficient to draw conclusions on overall survival or tumor control; adverse events other than late xerostomia (e.g., mucositis, dysphagia, skin toxicities, or osteoradionecrosis of the jaw); whether patient and tumor characteristics affected relative outcomes; or whether physician experience and treatment characteristics affected relative clinical outcomes such as survival or treatment-associated adverse events.

In 2012, AHRQ published a surveillance report that used methods developed by the RAND and Ottawa EPCs to prioritize an update of AHRQ CER No. 20 in 2013.[2] In preparing this update, we examined the applicability of opposed beam 2DRT and brachytherapy (BT) in modern radiation oncology practice. Our conclusion, based on the current literature and input from our Technical Expert Panel (TEP) members, was that 2DRT is no longer in routine use in the United States for definitive treatment of head and neck cancer, thus we excluded it from the update.

Brachytherapy is an invasive technique that was the first form of 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 BT over traditional opposed external beam 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., 3DCRT and IMRT) have become more prevalent in the past 2 decades, this advantage 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.[3,4] However, this practice has become uncommon because sufficient dose escalation can usually be achieved in these cases with a noninvasive approach (i.e., conformal RT). Brachytherapy alone is very rarely employed, except with small (T1) tumors of the nasal vestibule, lip, or oral cavity.[5-9] 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 BT 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.

For this update, we reviewed and assessed new evidence on the comparative effectiveness of 3DCRT, IMRT, and PBT. We also systematically reviewed and assessed evidence on stereotactic body RT (SBRT), a newer RT modality that was not widely available when we

prepared CER No. 20. This update used the same Key Questions as in CER No. 20 and, for the most part, the same methods and search strategies, modified to address the changes in the list of interventions. We organized clinical evidence according to treatment regimen, abstracted only from comparative studies (randomized or nonrandomized) of the conformal RT methods used in treatment for any head and neck cancer.

Epidemiology and Burden of Head and Neck Cancer

Head and neck cancer is a heterogeneous disease characterized by complex clinical and pathologic presentations. Squamous cell carcinoma of the head and neck (SCCHN) specifically arises in the squamous epithelium of the upper aerodigestive tract (oral cavity, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses/nasal cavity). SCCHN constitutes approximately 90 percent of all head and neck cancers, and accounted for approximately 3 percent (about 50,000) of all new cancer cases and 2 percent (approximately 12,000) of all cancer deaths in 2010 in the U.S.[10] While these cancers in total comprise a relatively small percentage of all cancers, cumulatively they are the sixth most common cancer worldwide, with notable exceptions of high nasopharyngeal cancer incidence in South Eastern China and South Eastern Asia and high oral cavity cancer incidence in Melanesia and South Central Asia. More than 600,000 people were diagnosed with SCCHN worldwide in 2008.[10]

Major risk factors for the development of head and neck cancer include tobacco and alcohol abuse, with other less common risk factors including occupational exposures, nutritional deficiencies, and poor oral health.[11] Viral etiologies have also been established, with human papillomavirus (HPV) infection appearing to be a risk factor, particularly within the oropharynx, in younger people without a history of tobacco or alcohol abuse. The reported proportion of oropharyngeal cancers attributable to HPV in the U.S. has increased from 16.3 percent during the 1980s to 72.7 percent during the 2000s.[12,13] Careful anatomic site stratification has shown that the age-adjusted incidence of oropharyngeal cancer is rising dramatically (estimated to be a 5 percent annual increase). In addition to HPV, an association has been made between Epstein-Barr virus and nasopharyngeal cancer.

Overview of Multimodal Clinical Management of Head and Neck Cancer

Most patients with SCCHN present with locally advanced but curable disease; only a small percentage of these patients have demonstrable distant metastases. Treatment decisions are primarily determined by the size, location, and grade of the primary tumor; the extent of nodal involvement; and the estimated functional impact of therapy. Patient characteristics may include substantial comorbidities and poor performance status that would be considered in devising a comprehensive treatment plan.[11]

Aggressive multimodality treatments with curative intent may include surgery, RT, and chemotherapy. Radiotherapy is a mainstay of treatment, offered to nearly 75 percent of all head and neck cancer patients with either curative or palliative intent. Radiotherapy may be used alone or as a part of multimodality approach, often with significant long-term side effects. In planning this CER, we sought to account for multimodal treatment strategies by organizing evidence according to treatments used in comparative studies of the RT modalities. Toxicities associated with RT represent important clinical outcomes that can substantially reduce QOL and the ability of cancer patients to tolerate and complete the entire planned course of treatment.

The main challenge in RT for any type of cancer is to attain the highest probability of tumor control or cure with the least amount of morbidity and toxicity. However, improved outcomes with aggressive RT regimes come at the cost of increased treatment toxicity, mainly due to the close proximity of critical organs and the often large irradiation fields necessary to effect local tumor control in head and neck cancer patients. For example, xerostomia is the most prevalent toxicity of RT to the head and neck and is a major cause of reduced QOL. In addition to patient perception of mouth dryness, it leads to impaired speech and swallow function, all of which also contribute to decreased QOL. Other prominent, RT-associated toxicities include salivary gland dysfunction, accelerated dental caries, and osteoradionecrosis.

Although RT-associated toxicities are highly problematic in any patient with head and neck cancer, such adverse events may assume greater importance in patients identified with HPV-positive compared with those with HPV-negative disease.[13] Patients with HPV-positive oropharynx cancer not only appear to have a different clinical phenotype from HPV-negative cancers, but they also have had better outcomes in multiple large studies, even when correcting for other known prognostic factors.[14] This trend has led investigators to research deintensification of treatment for patients with HPV-related head and neck cancers to limit toxicities, and alternatively intensification of treatment to improve tumor control in those with a significant HPV-negative cancer with a smoking history.[11,13] However, 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). In preparing this update, we sought to identify, where possible, HPV-positive patients as separate entities from HPV-negative patients.

RT in Head and Neck Cancer

Overview

We present a brief overview of the different types of RT modalities for those less familiar with the specific technologies. For those seeking further details on the different approaches, information is available from the National Cancer Institute and citations therein. [15]

Radiotherapy designs have evolved over the past 30 years from being based on two-dimensional (2D) to three-dimensional (3D) images, incorporating increasingly complex computer algorithms.[16] 2DRT consists of a single beam from one to four directions with the radiation fields designed on 2D fluoroscopic simulation images. A quest to improve on the survival rates and adverse effect profile of 2DRT led to widespread adoption and application of 3D imaging-based methods for definitive (curative) treatment of patients with SCCHN, with general abandonment of 2DRT in this role in the U.S.

Conformal RT refers to modalities in which radiation beams are “shaped” to cover the tumor volume plus a surrounding tissue margin to treat microscopic disease that may reside there. To standardize image-based tumor volume definitions for 3D radiation planning, the Internal Commission of Radiation Units and Measurements created terminology for use across institutions. Definitions include gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV).[17] The GTV pertains to gross disease identified by clinical workup (e.g., physical exam and imaging), CTV includes the GTV and any areas at risk for microscopic disease, and PTV is an expansion of the CTV by a margin (usually 3–5 mm in the head and neck patient) to account for patient or organ motion and day-to-day setup variation.

Conformal RT Modalities

Conformal external-beam photon-based RT modalities used to treat SCCHN include 3DCRT, IMRT, and SBRT, which is also known as stereotactic ablative RT.[16] For purposes of this update, we use the term *SBRT*. Charged particle-based conformal external-beam therapy such as PBT is also available. Here we briefly review each conformal RT modality in this CER update.

Three-Dimensional Conformal Radiotherapy

Three dimensional conformal RT uses 3D anatomic information from diagnostic computed tomography (CT) scans in a forward-planned process to deliver multiple, highly focused beams of radiation that converge at the tumor site. This allows accurate and precise conformity of the radiation to the typically irregular tumor volume, theoretically reducing exposure of surrounding tissues when compared with traditional opposed-beam 2DRT.[16]

Intensity-Modulated Radiotherapy

In the 1990s, technological and computer treatment planning advances led to the development of IMRT.[16,18] The technique of IMRT is more complex and resource-intensive than 3DCRT. It uses a CT-based inverse-planning process to deliver ionizing radiation conformally to the target. By altering the beam intensity using tungsten-based multileaf collimators, IMRT theoretically reduces radiation dose to adjacent organs or tissues at risk (e.g., the parotid glands). However, with IMRT a larger volume of uninvolved adjacent tissues may be exposed to ionizing radiation than 3DCRT. Standard IMRT techniques are referred to as sliding window, step and shoot, and volumetric modulated arcs; any of these was noted in this CER as IMRT.

Stereotactic Body Radiotherapy

Stereotactic body RT is a type of 3D conformal RT that is used to deliver tumoricidal doses of radiation in fewer treatment sessions than used in 3DCRT or IMRT regimens.[19] Regimens used in SBRT generally comprise a total dose equal to that delivered by 3DCRT or IMRT, but typically in eight fractions rather than 25 or more fractions. As a technique, SBRT 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, but especially in head and neck cancer therapy there is less tracking than for other sites, and 4D simulation is not used.

Proton-Beam Radiotherapy

Although PBT is not widely available in the U.S., it has become increasingly available in the last few years. Like IMRT or SBRT, PBT is a 3D conformal RT technique; however, it delivers charged particles at tumoricidal doses rather than photons. PBT has a physical advantage over photon therapy because it lacks an “exit dose” from tumor tissue. Unlike photons, which release energy along their path traversing tumors, protons deposit the majority of their energy at the end of their path through tissue, in the tumor volume, resulting in what is referred to as the Bragg peak.

Summary

The optimal means of delivering external beam ionizing radiation in sufficient doses to cure a patient with SCCHN requires a fine balance between treatment effectiveness and associated toxicity. In CER No. 20, the compiled evidence demonstrated an advantage for IMRT over

3DCRT and 2DRT in reducing late xerostomia and improving measures of xerostomia-related QOL. Evidence was insufficient to demonstrate any relative difference between modalities in measures such as overall survival or tumor control. Since CER No. 20 was published, a newer conformal technology—SBRT—has come into practice, whereas 2DRT has fallen out of use in the U.S. A surveillance study prepared in 2012 by the Ottawa and RAND EPCs suggested rationale to update CER No. 20, based on signals of new evidence that would change several conclusions of that report. Taken together, the emergence of new technology and evidence suggesting potential differences in some comparative outcomes prompted AHRQ to prioritize this update of CER No. 20.

Key Questions

The proposed Key Questions for CER No. 20, entitled "Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer," were posted for public comment for 4 weeks during its development. At that time, changes to the Key Questions and the PICOTS were made based on comments received and discussion with the TEP for the report. In the surveillance assessment used to determine the priority to update the 2010 report, the language of the Key Questions was modified slightly, but unchanged in meaning.

The Key Questions we used for this update follow below. In addition to 3DCRT, IMRT, and PBT, we included SBRT, which was not part of CER No. 20. Based on input from TEP discussions and a review of the literature, we excluded 2DRT from further consideration and did not include brachytherapy for reasons listed previously in the report. In response to TEP input, we also revised the language of Key Question 4 to expand the list of potential variables to consider.

Key Question 1.What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding adverse events and QOL?

Key Question 2.What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding tumor control and patient survival?

Key Question 3. Are there differences in the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT for specific patient and tumor characteristics?

Key Question 4. Is there variation in the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT because of differences in user experience, treatment planning, treatment delivery, and target volume delineation?

PICOTS

Population(s)

Key Questions 1–4

Populations of interest included patients with head and neck cancer. To define what constitutes head and neck cancer, we consulted clinical resources such as the National Cancer Institute's (NCI) Physician Data Query Cancer Information Summary and the National

Comprehensive Cancer Network (NCCN).[11] The consensus definition of head and neck cancer includes tumors of:

- Larynx
- Pharynx (hypopharynx, oropharynx, and nasopharynx)
- Lip and oral cavity
- Paranasal sinus and nasal cavity
- Salivary gland
- Occult primary of the head and neck

The following tumors were excluded:

- Brain tumors
- Skull base tumors
- Uveal/choroidal melanoma, other ocular and eyelid tumors
- Otologic tumors
- Cutaneous tumors of the head and neck (including melanoma)
- Thyroid cancer
- Parathyroid cancer
- Esophageal cancer
- Trachea tumors

All therapeutic strategies were included. RT can be delivered as a primary (curative) intent therapy or as an adjunct to surgery. Chemotherapy can also be given as an adjunct to RT, particularly in patients with more advanced cancer (i.e., stages III or IV). We sought direct evidence for one RT modality compared with another, with or without chemotherapy or surgery.

Interventions

Key Questions 1–4

- 3DCRT: defined as any treatment plan where CT-based forward treatment planning is used to delineate radiation beams and target volumes in three dimensions.
- IMRT: defined as any treatment plan using intensity-modulated radiation beams and computerized inverse treatment planning.
- SBRT: defined as conformal RT (forward- or reverse-planned) delivered in 3–5 relatively larger doses of ionizing radiation than typically delivered in a standard conformal schedule of 25–35 doses.
- PBT: defined as any treatment plan using proton-beam radiation.

RT may be delivered as part of a multimodal treatment strategy if the comparisons only differ with respect to the RT given.

Comparators

Key Questions 1–4

All therapies were compared with each other as part of a continuum of treatment for patients with head and neck cancer. Thus, we included studies in which an RT method was compared with a different method (e.g., with or without chemotherapy or surgery). We included all studies

in which we could be reasonably certain additional treatments were contemporary and similar, leaving the major comparison that between RT modalities; those that we could not ascertain from the publication would be excluded.

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 regimens in the strength of evidence (SOE) synthesis.

Outcomes

Key Questions 1, 3, and 4

Final outcomes: QOL and adverse events including: radiation-induced toxicities, xerostomia, mucositis, taste changes, dental problems, and dysphagia.

Intermediate outcomes: Salivary flow and probability of completing treatment according to protocol.

We sought evidence related to user experience, treatment planning, and target volume delineation within the context of Key Question 4.

Key Questions 2–4

Final outcomes: Overall survival and cancer-specific survival.

Intermediate outcomes: Local control and time to recurrence.

Timing

All durations of followup were considered.

Settings

Typically community-based versus tertiary or academic medical centers.

Analytic Framework

Figure 1 provides an analytic framework illustrating the population, RT modalities to be compared, outcomes, and adverse effects that guided our literature search and synthesis. It links the RT modalities of interest directly with final health outcomes (e.g., overall survival) and adverse events (e.g., xerostomia) as well as indirectly with final outcomes via intermediate outcomes (e.g., local control, disease-free survival).

Figure 1. Analytic framework for comparative effectiveness of RT for head and neck cancer

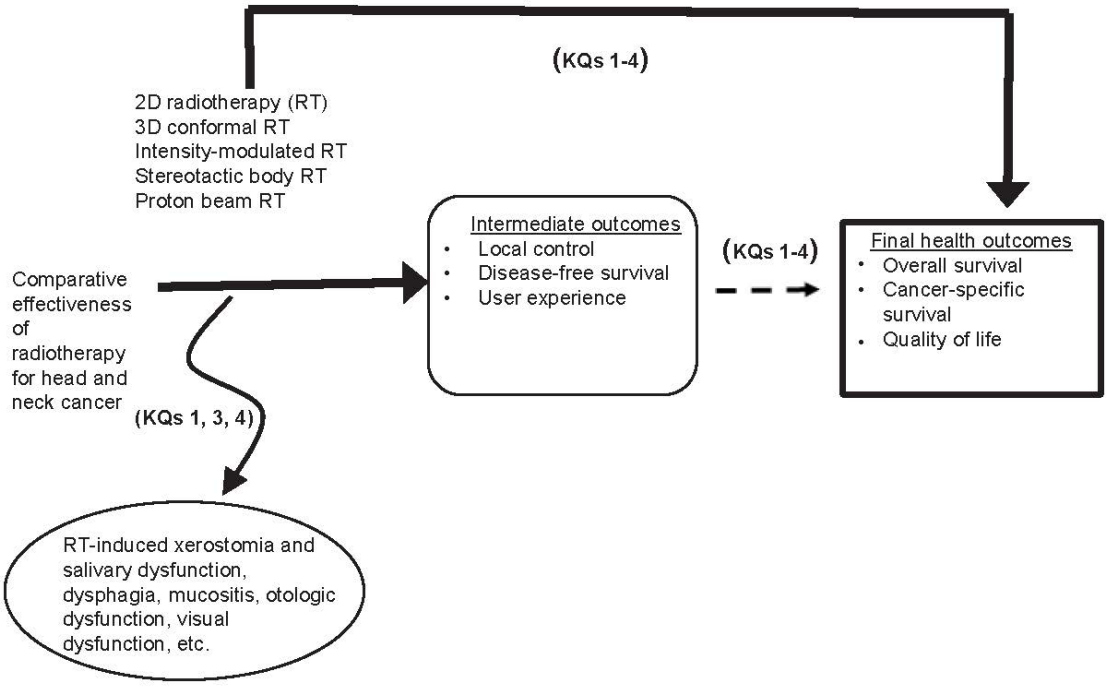


Figure 1 depicts the Key Questions (KQs) within the context of the PICOTS described in the previous section. In general, the figure illustrates how 3DCRT, IMRT, SBRT, or PBT may result in intermediate outcomes (e.g., local tumor control, disease-free survival) and final health outcomes (e.g., overall survival, cancer-specific survival, QOL). Also, adverse events (e.g., radiation-associated xerostomia and salivary dysfunction, dysphagia, mucositis, otologic dysfunction, visual dysfunction) may occur at any point after the treatment is received.

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy; KQ = Key Question; PBT = proton-beam radiation therapy; QOL = quality of life; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Organization of This Report

In the following sections of this CER update, we outline the methods used in its preparation, including literature search strategies, methods used to select studies for inclusion, data elements and their abstraction, tabulation of results, assessment of study quality and risk of bias, and how we evaluated the SOE. In the Results section, we provide an overview of the literature search results and study inclusion and exclusion. We then present evidence for each Key Question, using bulleted key points and a summary of the results and tabulature of such. The Discussion section contains our assessment of the SOE as related to the conclusions of CER No. 20. Finally, we discuss the applicability of the evidence to clinical decisionmaking and gaps in the evidence base in the Discussion section. The report concludes with an overall summary that ties it together to the CER No. 20 findings.

Methods

Overview

This section describes the methods used to produce this CER update. Methodological practices followed were derived from the Methods Guide and its subsequent updates.[20] We also consulted the article by Tsertsvadze et al. on methods to update CERs.[21] The main parts in this section reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Study Inclusion Criteria

We included only full-length reports that describe the final results of randomized controlled trials (RCTs) and nonrandomized comparative studies (observational, case-control, and cohort studies) of populations, interventions, comparisons, outcomes, treatment intervals, and settings that are part of the PICOTS (see above).

We excluded conference abstracts and other non-peer-reviewed sources as well as noncomparative (single-arm) studies from this CER update. In preparation of CER No. 20, we collected a substantial body of evidence from single-arm studies. In our analysis, we found that single-arm studies were very heterogeneous, with differences in patient populations, RT methods, treatment era, and adjunct treatments used, particularly cytotoxic chemotherapy regimens. As a consequence, we determined that the evidence was uninformative and not adequate for making valid comparisons or hypothesis generation.

We considered including dosimetry studies in CER No. 20, and this update. For both reports, our ultimate conclusion not to include dosimetry studies was agreed upon among our EPC team, among AHRQ personnel, and in discussion with our TEP. 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.

Literature Search

Search Strategies

An experienced medical librarian designed and performed all searches for this CER update. The literature search for the update was backdated to 12 months before the final literature search for CER No. 20 (dated September 28, 2009). For SBRT, the literature was searched electronically for citations from January 1, 1990, through April 2013. The entire search was updated May 1, 2014, after the draft was posted for peer review by AHRQ.

We searched the following databases:

- MEDLINE®
- EMBASE®
- Cochrane Controlled Trials Register

Data Abstraction and Data Management

Literature search results were transferred to EndNote® and subsequently into Distiller for study screening.

Review of Titles and Abstracts

We developed data collection forms for abstract review, full-text review, and data extraction. Using the study selection criteria for screening titles and abstracts, each citation was marked as eligible for review as full-text article or ineligible for full-text review. Two CER team members performed the initial title and abstract screen. A training set of 25–50 article selections were examined initially to assure uniform application of screening criteria. Full-text review was performed if it was unclear whether the study selection criteria were satisfied. Reasons for study exclusions at the title and abstract screening phase were not noted. To be excluded, a study must have been independently excluded by both team members. Discrepancies were decided by consensus opinion; a third reviewer was consulted if necessary.

Full-Text Review

Full-text articles were reviewed in the same fashion against the PICOTS to determine their inclusion in the systematic review. The reason for excluding an article retrieved in full-text was recorded in the Distiller database. Although an article could be excluded for multiple reasons, only the principal reason identified was noted.

Data Abstraction

For studies that met the inclusion criteria, we abstracted data into tables created in the Systematic Review Data Repository, with elements defined in an accompanying data dictionary. A training set of five articles was abstracted by one team member and reviewed by the Team Lead to ensure consistency. Each article included was abstracted by a single reviewer. A second reviewer assessed the data extraction against the original articles for quality control. Identified differences in data coding between the abstractor and reviewer were resolved by consensus.

The data elements abstracted included the following:

- Patient characteristics, including:
    - Age (excluding pediatric patients, 18 years or younger)
    - Sex
    - Race/ethnicity
    - Tumor location
    - Tumor stage
- Treatment characteristics, including:
    - Type of RT (e.g., photons, electrons, protons)
    - Total RT dose
    - Fractionation schedule
    - Imaging methods used to guide RT (e.g., CT, implanted fiducials, bony landmarks) and the frequency of imaging to assess therapy (e.g., daily, weekly, monthly)
    - Other prior or concurrent treatment modalities (e.g., systemic chemotherapy)
    - Number of prior lines of treatment
- Outcome assessment

- Identified final outcome (see PICOTS and Analytical Framework)
- Identified intermediate outcomes (see PICOTS and Analytical Framework)
- Adverse event response criteria
- Followup frequency and duration
- Data analysis details, including:
  - Statistical analyses (statistical test/estimation results)
  - Summary measures
  - Sample variability measures
  - Precision of estimate
  - p-values
- Regression modeling techniques
  - Model type
  - Candidate predictors and methods for identifying candidates
  - Univariate analysis results
  - Selected predictors and methods for selecting predictors
  - Testing of assumptions
  - Inclusion of interaction terms
  - Multivariable model results
  - Discrimination or validation methods and results
  - Calibration or "goodness-of-fit" results

Evidence Tables

The same abstraction tables were used for all studies. The dimensions of each evidence table may vary by Key Question, but the tables contain common elements such as author, year of publication, sample size, study type, intervention(s), and comparator(s). We report outcome data in strata according to prognostic or other patient-related factors (e.g., tumor stage) provided they were reported separately or could be inferred from the study in question.

Assessment of Methodological Risk of Bias (Quality or Limitations) of Individual Studies

In adherence to the Methods Guide,[20] the general approach to grading the quality or limitations of individual comparative studies was performed by using a United States Preventive Services Task Force (USPSTF) method (Appendix B).[22] Individual study quality assessment accounted for the following study elements:

- Number of participants and flow of participants through steps of study
- Treatment-allocation methods (including concealment)
- Use of blinding
- Study design (prospective vs. retrospective)
- Use of an independent outcome assessor

The quality of the abstracted studies was assessed independently by two investigators. Discordant quality assessments were resolved with input from a third reviewer, if necessary.

Data Synthesis

Our experience with CER No. 20, for which we did not perform a quantitative data synthesis, led us to rule out a quantitative synthesis for this update. Our analysis of the literature indicated a substantial degree of interstudy heterogeneity; given the small numbers of studies, we concluded a qualitative synthesis would be appropriate. The qualitative synthesis emphasized comparative studies sorted by specific head-to-head comparisons of RT modalities, specific treatment regimens, patient characteristics, specific outcomes, and status relative the evidence hierarchy and study quality assessment.

Grading the SOE for Individual Comparisons and Outcomes

Studies were assessed for relevance against target populations, interventions of interest, and outcomes of interest. The system used for rating the strength of the overall body of evidence is outlined in the recently updated (2013) chapter from the "Methods Guide"[20] and is based on a system developed by the GRADE Working Group.[23]

This system explicitly addresses the following domains: study limitations, directness, consistency, precision, and reporting bias. Additional (optional) domains, including strength of association (magnitude of effect), dose-response association, and plausible confounding, could be addressed if appropriate. Table 1 describes the four required and three optional domains and their scores and applications.

Table 1. SOE rating domains: required and optional

Domain Name	Domain Type	Domain Definition and Elements	Domain Score and Application
Study limitations	Required	This domain reflects the degree to which included studies for a given outcome have high likelihood of protection against bias (i.e., good internal validity), assessed through two main elements: • Study design: Whether included studies are RCTs or other designs such as nonexperimental or observational studies. • Study conduct: Considers aggregation of ratings of risk of bias of the individual studies under consideration.	Score as one of three levels, separately by type of study design: • Low level of study limitations • Moderate level of study limitations • High level of study limitations

Table 1. SOE rating domains: required and optional (continued)

Domain Name	Domain Type	Domain Definition and Elements	Domain Score and Application
Directness	Required	Directness relates to: • Whether evidence links interventions directly to a health outcome of specific importance for the review, and • Whether the comparisons are based on head-to-head studies. The EPC should specify the comparison and outcome for which the SOE grade applies. Evidence may be indirect in several situations such as: • The outcome being graded is considered intermediate (i.e., laboratory test results) in a review that is focused on clinical health outcomes (i.e., morbidity, mortality). • Data do not come from head-to-head comparisons but rather from two or more bodies of evidence to compare interventions A and B (e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not direct studies of A vs. B). • Data are available only for proxy respondents (e.g., from family members or nurses) instead of directly from patients. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcome.	Score as one of two levels: • Direct • Indirect If the domain score is indirect, the EPC should specify what type of indirectness accounts for the rating.

Table 1. SOE rating domains: required and optional (continued)

Domain Name	Domain Type	Domain Definition and Elements	Domain Score and Application
Consistency	Required	Consistency is the degree to which included studies find either the same direction or similar magnitude of effect. The EPC can assess this through two main elements: • Direction of effect: Effect sizes have the same sign (i.e., are on the same side of no effect or a minimally important difference). • Magnitude of effect: The range of effect sizes is similar. The EPC may consider the overlap of confidence intervals when making this evaluation. The importance of direction vs. magnitude of effect will depend on the Key Question and EPC judgments.	Score as one of three levels: • Consistent • Inconsistent • Unknown (e.g., single study) Single-study evidence bases (including mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."

Table 1. SOE rating domains: required and optional (continued)

Domain Name	Domain Type	Domain Definition and Elements	Domain Score and Application
Precision	Required	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size and number of events. Several caveats must be considered in determining the precision of a body of evidence. • A body of evidence will generally be imprecise if the optimal information size is not met. Optimal information size refers to the minimum number of patients (and events when assessing dichotomous outcomes) needed for an evidence base to be considered adequately powered. • If an EPC performed a meta-analysis, then it may also consider whether the confidence interval crossed a threshold for a minimally important difference. • If meta-analysis is infeasible or inappropriate, the EPC may consider the narrowness of the range of confidence intervals or the significance level of p-values in the individual studies in the evidence base.	Score as one of two levels: • Precise • Imprecise A precise estimate is one that would allow users to reach a clinically useful conclusion (e.g., treatment A is more effective than treatment B).

Table 1. SOE rating domains: required and optional (continued)

Domain Name	Domain Type	Domain Definition and Elements	Domain Score and Application
Reporting bias	Required	Reporting bias results from selectively publishing or reporting research findings bases on the favorability of direction or magnitude of effect. It includes: • Study publication bias (i.e., nonreporting of the full study) • Selective outcome reporting bias (i.e., nonreporting or incomplete reporting of unplanned outcomes) • Selective analysis reporting bias (i.e., reporting one or more favorable analyses for a given outcome while not reporting other, less favorable analyses). Assessment of reporting bias for individual studies depends on many factors, including availability of study protocols, unpublished study documents, and patient-level data. Detecting such bias is likely with access to all relevant documentation and data pertaining to a journal publication, but such access is rare. Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies.	Score as one of two levels: • Suspected • Undetected Reporting bias is suspected when: • Testing for funnel plot asymmetry demonstrates a substantial likelihood of bias, and/or • A qualitative assessment suggests the likelihood of missing studies, analyses, or outcomes data that may alter the conclusions from the reported evidence. Undetected reporting bias includes all alternative scenarios.
Dose-response association	Optional	This association, either across or within studies, refers to a pattern of a larger effect with greater exposure (dose, duration, adherence)	This domain should be considered when studies in the evidence base have noted levels of exposure. Score as one of two levels: • Present: Dose-response pattern observed. • Undetected: No dose-response pattern observed (dose-response relationship not present or could not be determined).

Table 1. SOE rating domains: required and optional (continued)

Domain Name	Domain Type	Domain Definition and Elements	Domain Score and Application
Plausible confounding that would decrease observed effect	Optional	Occasionally, in an observational study, plausible confounding would work in the direction opposite that of the observed effect. Had these confounders not been present, the observed effect would have been even larger than the one observed.	This domain should be considered when plausible confounding exists that would decrease the observed effect. Score as one of two levels: • Present: Confounding factors that would decrease the observed effect may be present and have not been controlled for. • Absent: Confounding factors that would decrease the observed effect are not likely to be present or have been controlled for.
Strength of association (magnitude of effect)	Optional	Strength of association refers to the likelihood that the observed effect is large enough that it could not have occurred solely as a result of bias from potential confounding factors.	This additional domain should be considered when the effect size is particularly large. Score as one of two levels: • Strong: Large effect size that is unlikely to have occurred in the absence of a true effect of the intervention. • Weak: Small enough effect size that it could have occurred solely as a result of bias from confounding factors.

Abbreviations: RCT = randomized controlled trial; EPC = Evidence-based Practice Center; SOE = strength of evidence.

Grading a body of evidence involves consideration of the type of studies included in the review. For assessing a clinical outcome, RCT evidence is considered the best evidence, based purely on study design. In the EPC grading system, a body of evidence including RCTs is assigned a provisional SOE grade of "high." This may change, however, after assessment of study limitations based on how the RCTs were conducted, and other domains such as directness, consistency, and precision.

By contrast, evidence from nonrandomized comparative studies is assumed to pose a greater risk of having study limitations because of the typically higher risk of bias attributable to a lack of randomization and inability to control for critical confounding factors. This type of evidence is generally assigned a provisional initial SOE grade of "low." The latter may be moved up to "moderate" when study limitations are graded as low or moderate, based on controls for risk of bias through study conduct or analysis. The initial SOE for nonrandomized comparative study evidence may also be initially graded as "moderate" for certain outcomes such as important harms or for certain Key Questions when it is deemed at less risk for study limitations secondary to a lower risk of bias related to potential confounding.

A few real-world examples of grading evidence are illustrative of the literature encountered on this topic. In synthesizing a body of evidence represented by a single RCT rated as good quality and multiple nonrandomized comparative studies of lower quality (e.g., primarily poor), we would start with the findings from the "best available evidence" (the good quality RCT) and a high initial SOE. The study limitation domain in this instance would initially be rated as low. If the RCT and nonrandomized studies report results in opposite directions of effect, the body of evidence could be rated as having unknown consistency, thus reducing the overall strength by one level. Concluding unknown consistency is based on lack of confirmation for the direction and would be justified particularly if biases and confounding in nonrandomized studies do not have a predictable direction. However, if the differences are less dramatic and could be explained

by bias in a predictable direction, then it may be considered consistent. Direct head-to-head comparisons of an intervention and comparator that report on an important health outcome lead to a rating of direct on the directness domain. In a qualitative synthesis of this hypothetical body of evidence, insufficient size (compared with the optimal information size) of the RCT would render the aggregate results imprecise on the precision domain, reducing strength by at least one level. According to EPC convention, the path through all required domains would take the strength from high through two reductions to a final strength of low.

A second example would comprise a body of comparative evidence that included multiple, nonrandomized design studies. Even if direct results are consistent and precise, this example would have a starting study limitations grade of high and SOE of low. If all studies were deemed to be poor quality and poorly conducted, the body of evidence could be downgraded further to insufficient. However, application of the optional domains, particularly magnitude of effect in favor of an intervention, could raise the strength one level to low or, perhaps, moderate if sufficiently robust.

The overall SOE grade is classified into four categories, as shown in Table 2. Specific outcomes and comparisons to be rated depend on the evidence found in the literature review. The grade rating was made by independent reviewers, and disagreements were resolved by consensus adjudication.

We report a summary of key outcomes for each Key Question in a table that lists the major outcomes, the study design and number of studies of each type plus number of subjects, the findings, and the direction and magnitude of effect where applicable. The overall SOE grade for each outcome is specifically reported in this table.

Table 2. Overall strength-of-evidence categories and criteria for assignment

Grade	Definition	Criteria for Assignment
High	We are very confident that the estimate of effect lies close to the true effect for this outcome.	The body of evidence has few or no deficiencies. We believe that the findings are stable.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome.	The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome.	The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.	No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

Assessing Applicability

We assessed applicability of findings with the AHRQ Comparative Effectiveness "Methods Guide" using the PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting) framework.[20,24] Included studies were assessed for relevance against target populations, interventions and comparators of interest, and outcomes of interest. We anticipated that results would be applicable only to the specialized populations of interest by Key Question.

Results

Overview

In this section, we report our literature search results and PRISMA diagram, which depicts the flow of articles through the review according to our screening and inclusion criteria. We subsequently provide an overview of the design, patients, and study limitations (risk of bias) of all included studies, including relevant studies from CER No. 20. We lay out the results for each Key Question in order, starting with an overview of the relevant current studies, key bulleted points of information, and a synthesis of the evidence when possible. In the results, we did not incorporate formal data synthesis (e.g., meta-analysis) because there was only one randomized trial involving the interventions of interest for treatment of head and neck cancer and the nonrandomized studies were highly heterogeneous and of "poor" quality according to the USPSTF criteria. Finally, we lay out in tabular format the conclusions and evidence base from CER No. 20 and those from this update to qualitatively integrate the findings of both.

Results of Literature Searches

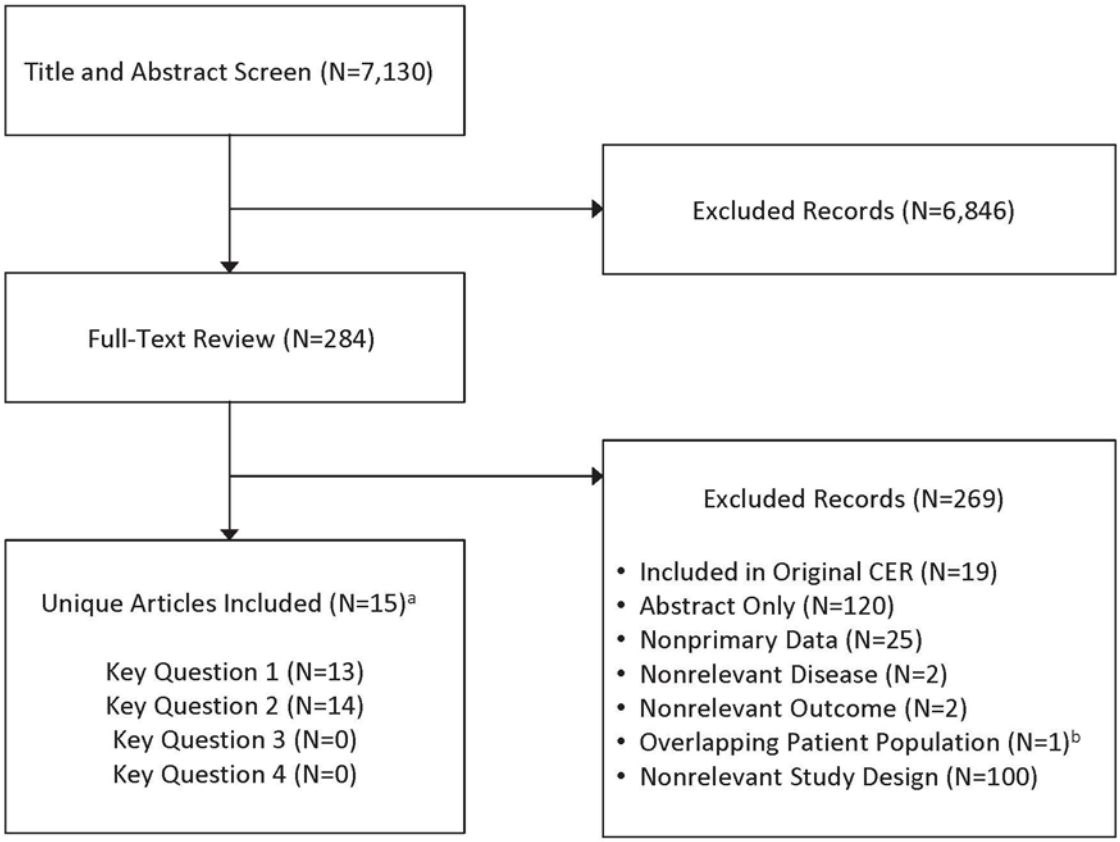
Electronic Search

A medical librarian searched MEDLINE®, EMBASE®, and the Cochrane Controlled Trials Registry for English-language articles. The overall search was performed for a period dating 12 months before the final literature search for CER No. 20 (September 28, 2009) through April 2013. For SBRT, the literature was searched for the period January 1, 1990, through April 2013. The entire search was updated May 1, 2014.

In both searches together, we identified 7,130 unique titles and screened 284 in full text. Of the latter, 15 (N=1,781) met the inclusion criteria, including one RCT (Gupta 2012, N=60).[25] In the updated search, we identified a second citation to an RCT (Rathod 2013).[26] Because the latter was the same study and included the same patients as the Gupta RCT, it was not double-counted in the total number of patients; however, it reported additional, different outcomes that were reviewed herein and so is counted in that context. Thus, in 14 studies that reported unique data, including the RCT of Rathod,[26] 3DCRT and IMRT were compared.[25,27-39] One study compared 3DCRT and SBRT[34]; none compared IMRT and SBRT. As in CER No. 20, no evidence was identified on PBT. The flow of articles through the screening and study selection process is shown in the PRISMA diagram (Figure 2).

We note that although CER No. 20 was published in final form in 2010, we had obtained the final data for PARSPORT,[40] a key RCT, from the investigators at the time we updated the CER No. 20 literature search. Because the PARSPORT findings appeared in CER No. 20, they were not included in this report.

Figure 2. PRISMA diagram for disposition of literature search results



[a]Twelve studies addressed both Key Questions 1 and 2.
[b]Overlapping patient population refers to the studies in which the same patients were included in more than one study. In this case, only one study was included to avoid oversampling. Decision to include a study was based on the clarity in reporting relevant patients and/or outcomes.
Abbreviations: CER = Comparative Effectiveness Review; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Gray Literature (Publication Bias)

The study selection criteria for this update stipulate exclusion of abstracts or other non-peer-reviewed or non-full-length studies. Therefore we did not include any information based on comprehensive searches of meeting abstracts. We examined the bibliographies of all papers screened in full text to identify peer-reviewed articles the electronic search may have missed.

We accessed the Web site ClinicalTrials.gov to identify ongoing phase 3 RCTs that would meet the criteria for inclusion based on our protocol. We identified two phase 3 RCTs of conformal RT in head and neck cancer that are recruiting patients. The first trial (National Clinical Trial [NCT] 01893307) is designed to compare IMRT and PBT in the treatment of oropharyngeal cancer. The primary outcome is the incidence of any late-onset (> 90 days) grade 3 toxicity during the 2 years after completion of RT. The second RCT (NCT01216800) is designed to compare the effects of IMRT and 3DCRT on auditory function (hearing) when used as adjuvant therapy in patients who have undergone surgical resection of parotid tumors. A MEDLINE search of the NCT number(s) and title(s) did not yield any published results; it is unknown whether any data have been reported. Examination of a Scientific Information Packet from one manufacturer of RT equipment did not yield published evidence to add to this update.

Description of All Included Studies

We identified 15 reports that met the inclusion criteria for this CER update. All are generally described in this section; other details and results specific to a particular Key Question are considered in the relevant subsections to follow.

Study Limitations

According to the USPSTF criteria for assessing the risk of bias of individual studies, the Gupta RCT was rated "fair," whereas the 13 nonrandomized studies were rated "poor." The rationale for the ratings is provided in Table B-1.

We assigned a "fair" USPSTF rating to the Gupta RCT, primarily because the study was not double-blinded, particularly its outcomes assessments. Furthermore, the investigators did not clarify the meaning of their reported "modified intention-to-treat" method. Although this point is for practical purposes moot, because they reported a 97 percent followup rate in each of two study arms, the USPSTF method stipulates assignment of this rating. Gupta reported aggregated survival results in patients with tumors in different sites. However, the distribution of tumor sites and characteristics between arms was similar. Overall, the two study arms were statistically similar and comparable. We note also the report of Rathod and colleagues, a RCT that included the same patients of Gupta but reported additional outcomes. [26] We include evidence from this report but do not double count it in the PRISMA diagram or summations of included evidence. Its risk of bias is identical to that of the Gupta study using the USPSTF system..

The 13 nonrandomized studies were retrospective database analyses, one of which used a historical comparator group. All of the included nonrandomized studies reported results in aggregate, mixing outcomes achieved in heterogeneous groups who may not have received the same treatment(s). Overall, we rated these studies as poor according to the USPSTF criteria.

Study Design and Patient Characteristics

Table 3 provides a high-level view of the studies included in this update. For comparative purposes, Table 3 also depicts the studies from CER No. 20 that compared 3DCRT and IMRT and reported on clinical outcomes covered herein. We address applicable evidence in more detail in the Discussion section, relating the results and conclusions to those of this update.

In total, for the update, 3DCRT and IMRT were compared in 13 studies, including one small (N=60) RCT.[25,26] One study compared 3DCRT and SBRT[34]; none compared IMRT and SBRT. As in CER No. 20, no evidence was identified on PBT. Study details are summarized in Table B-2.

Overall, similar to what we identified for CER No. 20, the body of studies in the update is heterogeneous in terms of tumor site and stage, treatment regimen, and treatment intent (e.g., curative vs. palliative or recurrent). Patients were generally in their mid-fifties, with males predominating across studies. Tumor sites included the hypopharynx, larynx, nasal sinus, nasopharynx, oral cavity, and oropharynx. Four studies involved patients with single tumor sites. The majority of patients across studies had locally advanced (stage III and IV) cancer, although small proportions of patients had stage I or II disease.

Treatment regimens included concurrent chemoradiotherapy (CCRT); RT with or without concurrent chemotherapy (CCT); CCRT with or without surgery; and adjuvant postoperative RT. Where it appears in all tables throughout this update, the term RT ± CCT refers to treatment regimens in which all patients received RT, but not all received CCT. This is distinct from

CCRT, in which all patients were reported to have received RT and chemotherapy concurrently. We did not abstract information on specific chemotherapy regimens or surgical procedures; they are beyond the scope of this update. As summarized in Table B-3, ionizing radiation was delivered by 3DCRT or IMRT to a total dose of 60–74 Gy using conventional fractionation schedules, which are typical of 3DCRT and IMRT (30–35 fractions, 2 Gy per fraction for 5–7 weeks); SBRT was delivered in a similar total dose but in five single fractions. We did not abstract or report on RT protocols in detail because they also are beyond the proposed scope of the review.

Table 3. Design and characteristics of studies included in the CER No. 20 Update and CER No. 20

Investigator (Year)	Comparison	Total No. Patients	RCT	Non-RCT	Mixed Tumor Sites	Single Tumor Site	CCRT	RT ± CCT	CCRT ± Surgery	Postop RT	RT ± CCT± Surgery	rRT ± CCT	USPSTF Study Quality
CER No. 20 Update													
Gupta (2012)[25]	3DCRT vs. IMRT	60	●		●		●						Fair
Rathod (2013)[26]		60	●		●		●						Fair
Al-Mamgani (2013)[29]		204		●		●	●						Poor
Lambrecht (2013) [33]		245		●	●		●						Poor
Al-Mamgani (2012)[27]		176		●		●		●					Poor
Chen (2012) [30]		155		●	●			●					Poor
Al-Mamgani (2012)[28]		82		●		●			●				Poor
Dirix (2010) [31]		81		●	●					●			Poor
Guan (2013)[32]		59		●	●						●		Poor
Mok (2014)[39]		181		●		●		●					Poor
Lohia (2014)[38]		159		●		●		●					Poor
Huang (2013)[35]		83		●		●		●					Poor
Kruser (2013)[37]		178		●	●				●				Poor
Kong (2013)[36]		67		●	●						●		Poor
Ozyigit (2011) [34]	3DCRT vs. SBRT	51		●		●						●	Poor

Table 3. Design and characteristics of studies included in the CER No. 20 Update and CER No. 20 (continued)

Investigator (Year)	Comparison	Total No. Patients	RCT	Non-RCT	Mixed Tumor Sites	Single Tumor Site	CCRT	RT ± CCT	CCRT ± Surgery	Postop RT	RT ± CCT± Surgery	rRT ± CCT	USPSTF Study Quality
CER No. 20													
Nutting (2011)[40]	3DCRT vs. IMRT	84	●			●		●					Good
Chao (2001)[41]		41		●	●						●		Poor
Marchal (2004)[42]		87		●	●						●		Poor
Chen (2007)[43]		68		●	●						●		Poor
Fang (2007)[44]		85		●		●		●					Poor
Golen (2007)[45]		40		●	●			●					Poor
Hodge (2007)[46]		195		●		●		●					Poor
Rades (2007)[47]		44		●		●					●		Poor
Fang (2008)[48]		203		●		●		●					Poor
Gomez (2008)[49]		42		●		●					●		Poor
Palazzi (2008)[50]		137		●		●					●		Poor
Rusthoven (2008)[51]		87		●		●		●					Poor
Vergeer (2009)[52]		141		●		●					●		Poor
Langendijk (2009)[53]		529		●		●					●		Poor

Abbreviations: CCRT = concurrent chemoradiotherapy; CCT = concurrent chemotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; RCT = randomized controlled trial; RT = radiotherapy; rRT = reirradiated radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

Key Question 1: Comparative Effectiveness of 3DCRT, IMRT, SBRT, and PBT Regarding Adverse Events and QOL

Overview

Tables 4 and 5 depict key comparative acute (< 90 days post-treatment) and late (> 90 days post-treatment) toxicity outcomes reported by each relevant study; a blank cell in any table means that the toxicity was not reported in that study. Acute and late toxicity outcomes were not collected consistently across studies. Only eight (53%) studies reported acute toxicities.[25,27,29,31,33,36-38] Nine (60%) studies reported late toxicities.[25,27-29,31,33,34,36,39] Only two studies reported QOL evidence according to RT modality, including the RCT by Rathod.[26]

Because toxicities were inconsistently reported, we focused this update, as we did CER No. 20, on those toxicities prominently associated with 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 or the NCI Common Terminology Criteria for Adverse Events. Grades greater than 2 are those that have direct impact on patient outcomes and can adversely affect treatment delivery.

Patients in all studies, except that of Dirix (2010),[31] received chemotherapy as part of treatment; those treated by Dirix received postoperative RT. In general, investigators did not adjust results to account for chemotherapy-associated toxicities independent of RT-associated toxicities, which complicates interpretation of toxicity evidence for many adverse events (e.g., mucositis). This is somewhat ameliorated by our focus on studies in which chemotherapy regimens are similar between study arms, thus potentially isolating the effect of the RT modality on such outcomes.

Table 4. Summary of key reported acute (<90 days post-treatment) comparative toxicity outcomes

Study (Year)	Study Design (USPSTF Rating)	RT Modalities (N)	Treatment Regimen	Tumor Site(s)	Dermatitis	Dysphagia	Mucositis	Nausea	Pain	Salivary Glands	Weight Loss	Other
Gupta (2012)[25]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	●	●	●			●	●	
Al-Mamgani (2013)[29]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx	●	●	●		●			
Lambrecht (2013)[33]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx		●	●					Erythema
Al-Mamgani (2012)[27]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx	●	●	●		●			Neutropenic fever Intercurrent infection Severe malaise
Dirix (2010)[31]	Comparative Prospective (IMRT) Retrospective (3DCRT) (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity Paranasal sinus	●	●	●		●	●		Smell Taste Fatigue Conjunctivitis Dry eye Tearing Alopecia Tinnitus Serous otitis Blurred vision
Kong (2013)[36]	Comparative Retrospective (poor)	3DCRT (37) IMRT (30)	RT ± CCT± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Paranasal sinus		●	●			●		
Lohia (2014)[38]	Comparative Retrospective (poor)	3DCRT (56) IMRT (103)	RT ± CCT	Oropharynx	●		●			●	●	Larynx Pharynx Death

Table 4. Summary of key reported acute (<90 days post-treatment) comparative toxicity outcomes (continued)

Study (Year)	Study Design (USPSTF Rating)	RT Modalities (N)	Treatment Regimen	Tumor Site(s)	Dermatitis	Dysphagia	Mucositis	Nausea	Pain	Salivary Glands	Weight Loss	Other
Kruser (2013)[37]	Comparative Prospective (poor)	3DCRT (41) IMRT (137)	CCRT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Unknown primary			•					Hematologic toxicities: hemoglobin, leukocyte & platelet counts

Abbreviations: CCRT = concurrent chemoradiotherapy; CCT = concurrent chemotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; RCT = randomized controlled trial; RT = radiotherapy; rRT = reirradiated radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

Table 5. Summary of key reported late (>90 days post-treatment) comparative toxicity outcomes

Study (Year)	Study Design (USPSTF Rating)	RT Modalities (N)	Treatment Regimen	Tumor Site(s)	Dysphagia	Mucositis	Pain	Skin	Salivary Glands	Subcutaneous	Xerostomia	Other
Gupta (2012)[25]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx					●	●	●	
Al-Mamgani (2013)[29]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx	●	●	●	●		●	●	
Lambrecht (2013)[33]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx	●						●	
Al-Mamgani (2012)[27]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx	●	●	●	●		●	●	Cartilage necrosis Esophagus
Al-Mamgani (2012)[28]	Comparative Retrospective (poor)	3DCRT (25) IMRT (57)	CCRT ± surgery	Paranasal sinus	●						●	Osteoradionecrosis Nasolacrimal duct Stenosis Ectropion Entropion Blindness Trismus Deafness
Dirix (2010)[31]	Comparative Prospective (IMRT) Retrospective (3DCRT) (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity Paranasal sinus		●	●	●	●		●	Dry eye syndrome Neuropathy
Kong (2013)[36]	Comparative Retrospective (poor)	3DCRT (37) IMRT (30)	RT ± CCT± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Paranasal sinus	●						●	

Table 5. Summary of key reported late (>90 days post-treatment) comparative toxicity outcomes (continued)

Study (Year)	Study Design (USPSTF Rating)	RT Modalities (N)	Treatment Regimen	Tumor Site(s)	Dysphagia	Mucositis	Pain	Skin	Salivary Glands	Subcutaneous	Xerostomia	Other
Lohia (2014)[38]	Comparative Retrospective (poor)	3DCRT (56) IMRT(103)	RT ± CCT	Oropharynx								PEG tube dependence
Mok (2014)[39]	Comparative Retrospective (poor)	3DCRT (90) IMRT (91)	RT ± CCT	Hypopharynx	•							Esophageal stenosis Larynx preservation PEG tube dependence

Abbreviations: CCRT = concurrent chemoradiotherapy; CCT = concurrent chemotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; PEG = percutaneous endoscopic gastrostomy; RCT = randomized controlled trial; RT = radiotherapy; rRT = reirradiated radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

[a]The study involved reirradiation of recurrent head-and-neck cancer tumors.

Key Points

- The results of primary interest for this Key Question comprise comparative acute (< 90 days) and late (> 90 days) radiation-associated dysphagia, salivary gland dysfunction, xerostomia, and QOL.
- New comparative evidence assessed in this update strengthens the conclusion from CER No. 20 that the risk of grade 2 or higher late xerostomia is significantly lower in patients treated with IMRT than with 3DCRT.
- Although we identified evidence on other key toxicities (e.g., mucositis, dysphagia, skin toxicities, osteoradionecrosis of the jaw) and QOL, the reported rates compared between modalities were inconsistent. Thus, evidence on adverse events other than late xerostomia remains insufficient to alter conclusions of CER No. 20.
- Post-treatment toxicities were reported inconsistently across studies, precluding comparisons within the body of evidence. We are uncertain whether the limited evidence on RT-associated toxicities overall reflects their absence or that the investigators did not systematically collect or chose not to report them.
- The best quality evidence comprises one small (N=60), fair quality RCT (Gupta, 2012) in which 3DCRT and IMRT were compared in a regimen of CCRT to treat patients with cancer of the hypopharynx, larynx, and oropharynx. Key findings of this study relevant to Key Question 1 pertained to late xerostomia and salivary gland dysfunction.
- One nonrandomized, poor quality study of 3DCRT versus SBRT did not report on primary outcomes for Key Question 1.
- One fair quality study and one poor quality nonrandomized study reported QOL outcomes related to treatment with 3DCRT or IMRT

Qualitative Synthesis

In Table 6, we aggregate new comparative evidence related to Key Question 1 on toxicities actually reported in studies according to the intervention comparison, treatment regimen, and timeframe (acute vs. long-term). We identified no evidence from patients stratified according to tumor site(s), so we did not include tumor information in this table. Although we collected evidence on lesser NCI Common Terminology Criteria for Adverse Events or Radiation Therapy Oncology Group grades, as shown in Tables B-4 and B-5, here we present grade 2 or higher toxicities, which are likely to adversely impact patient management, hospitalization, and survival outcomes. The last two columns of Table 6 show reported proportions for each toxicity and any statistically significant results by study if so achieved.

RT-Associated Toxicities

Results from one nonrandomized study show a statistically significant lower rate of acute dysphagia (49 percent vs. 84 percent, respectively, p=0.04) with IMRT compared with 3DCRT in a regimen of CCRT.[29] The Gupta[25] RCT showed a lower rate of acute dysphagia with 3DCRT (0 percent) than with IMRT (9.5 percent), although the difference was nonsignificant (p=0.21). Significantly reduced rates of late dysphagia were reported in single studies of IMRT compared with 3DCRT in a regimen of CCRT[29] or RT with or without CCT.[27] Two individual studies showed a reduced rate of acute salivary gland dysfunction with IMRT compared with 3DCRT in a regimen of CCRT[25] or postoperative RT,[31] respectively.

As shown in Table 6, all three studies of IMRT compared with 3DCRT in a regimen of CCRT showed statistically significant reduction in late xerostomia.[25,29,33] The rate of late xerostomia also was significantly lower with IMRT than with 3DCRT in single studies in a regimen of RT with or without CCT,[27] or postoperative RT,[28] respectively.

RT-Associated QOL

One RCT reported QOL evidence on IMRT versus 3DCRT in a regimen of RT with CCT.[26] Rathod et al. reported on mean QOL scores using the European Organization for Research and Treatment of Cancer QOL questionnaire (QLQ-C30) and Head-Neck module (HN-35) validated, self-administered tools at baseline (pretreatment) and periodically on follow-up (3, 6, 12, 18, and 24 months). The study reported global QOL was not significantly affected by RT technique. Treatment with IMRT showed a benefit to some general QOL domains, as well as several head and neck cancer-specific domains, as compared with 3DCRT. General domains toward which IMRT demonstrated a significant benefit included: emotional functioning at 12 months ($p=0.008$), role functioning at 12 months ($p=0.008$), and social contact at 24 months ($p=0.03$). Head and neck cancer-specific symptoms for which IMRT demonstrated a significant benefit ($p<0.05$) compared with 3DCRT included scales and dry month (6, 12, and 18 months), as well as opening mouth (6 and 24 months). Sticky saliva, pain, swallowing, senses, sexuality, feeling ill, and insomnia tended to be ameliorated by use of IMRT compared with 3DCRT, and were all statistically significant for at least one time point. No QOL domains were worse with IMRT than with 3DCRT at any time point. Among both RT techniques, QOL domains generally experienced maximal deterioration after RT, followed by a trend toward gradual recovery over time.

One nonrandomized study reported QOL evidence on IMRT versus 3DCRT in a regimen of RT with or without CCT. Chen et al. reported on mean QOL scores using the University of Washington Quality of Life validated, self-administered tool.[30] In this study, the salivary gland domain was the only specific component of this score wherein significant differences were observed between the IMRT and the 3DCRT groups at both 1 and 2 years ($p<0.001$ at both points). Other domains (pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood, anxiety) showed no differences according to RT modality. At 1 year after completion of RT, the global QOL was rated as “very good” or “outstanding” among 51 percent of patients treated with IMRT compared with 41 percent of those treated with 3DCRT ($p=0.11$). However, at 2 years, the corresponding percentages were 73 percent and 49 percent, respectively ($p<0.001$), showing a benefit of IMRT. Multivariate analysis showed no effect on QOL scores of age, sex, radiation intent, radiation dose, T stage, primary site, or use of CCT and neck dissection. Use of IMRT was the only variable associated with improved QOL ($p<0.01$).

Table 6. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL

Intervention	Comparator	Treatment Regimen	Outcome	Timeframe	Number of Studies (Number of Patients)	Reported Rates Across Studies (%)	Individual Study Statistically Significant Results (p-Value)
3DCRT	IMRT	CCRT	Dysphagia	Acute	Three studies[25,29,33] (N=509)	3DCRT: 0%–84% IMRT: 9.5%–76%	Only one study showed a statistically significant benefit of IMRT vs. 3DCRT (grade ≥ 2) 3DCRT: 84% IMRT: 49% (p=0.04)[29]
				Late	Two studies[29,33] (N=707)	3DCRT: 30%, 34% IMRT: 20%, 38%	Only one study showed a statistically significant benefit of IMRT vs. 3DCRT (grade ≥ 2) 3DCRT: 30% IMRT: 20% (p=0.04)[29]
		RT ± CCT	Dysphagia	Acute	One study[27] (N=176)	3DCRT: 47% IMRT: 36%	Not significant
				Late	Two studies[27,39] (N=357)	3DCRT: 10% IMRT: 1%	Only one study showed a statistically significant benefit of IMRT vs. 3DCRT (grade ≥ 2) 3DCRT: 10% IMRT: 1% (p=0.02)[27] The Mok 2014 study[39] does not present quantitative data pertaining to late dysphagia of 3DCRT vs. IMRT therapies other than to report there was no statistically significant difference between arms.
		CCRT ± surgery	Dysphagia	Late	One study[28] (N=82)	3DCRT: 12% IMRT: 5%	Not significant
		RT ± CCT± surgery	Dysphagia	Acute	One study[36] (N=67)	3DCRT: 84% IMRT: 80%	Not significant
				Late	One study[36] (N=67)	3DCRT: 23% IMRT: 54%	p=0.02
		Postoperative RT	Dysphagia	Acute	One study[31] (N=81)	3DCRT (any grade): 34% IMRT (grade 2): 7.5%	p=0.003

Table 6. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Timeframe	Number of Studies (Number of Patients)	Reported Rates Across Studies (%)	Individual Study Statistically Significant Results (p-Value)
3DCRT	IMRT	CCRT	Salivary glands	Acute	One study[25] (N=60)	3DCRT (grade 2): 89% IMRT (grade 2): 59%	p=0.03
		RT ± CCT	Salivary glands	Acute	One study[38] (N=159)	3DCRT: Not quantitated IMRT: Not quantitated	Not significant The Lohia 2014 study[38] does not present quantitative data pertaining to acute salivary glands toxicity of 3DCRT vs. IMRT therapies other than to report there was no statistically significant difference between arms
		Postoperative RT	Salivary glands	Acute	One study[31] (N=81)	3DCRT (any grade): 90% IMRT (grade 2): 0.0%	p<0.001

Table 6. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Timeframe	Number of Studies (Number of Patients)	Reported Rates Across Studies (%)	Individual Study Statistically Significant Results (p-Value)
3DCRT	IMRT	CCRT	Xerostomia	Late	Three studies[25,29,33] (N=509)	3DCRT (grade > 2): 49–77% IMRT (grade > 2): 23–33%	All three studies showed statistically significant benefit of IMRT vs. 3DCRT: p=0.001, p=0.002, p<0.001
		RT ± CCT	Xerostomia	Late	One study[27] (N=176)	3DCRT (grade 2): 24% IMRT (grade 2): 11%	p=0.009
		CCRT ± surgery	Xerostomia	Late	One study[28] (N=82)	3DCRT (grade > 2): 16% IMRT (grade > 2): 7%	Not significant
		RT ± CCT± surgery	Xerostomia	Acute	One study[36] (N=67)	3DCRT (grade ≥ 2): 46% IMRT (grade ≥ 2): 67%	Not significant
				Late	One study[36] (N=67)	3DCRT (grade ≥ 2): 94% IMRT (grade ≥ 2): 40%	p=0.004
		Postoperative RT	Xerostomia	Late	One study[31] (N=81)	3DCRT (any grade): 34% IMRT (grade 2): 0.0%	p=0.03

Table 6. Key Question 1: Qualitative evidence synthesis for key reported comparative grade 2 or higher toxicity outcomes and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Timeframe	Number of Studies (Number of Patients)	Reported Rates Across Studies (%)	Individual Study Statistically Significant Results (p-Value)
3DCRT	IMRT	CCRT	QOL	Acute and Late	Two studies[26,30] (N=215)	The RCT of Rathod[26] showed statistically significant benefit for IMRT in head and neck cancer specific domains of scales and dry mouth, sticky saliva, swallowing, for at least one time point. No QOL endpoints were worse with IMRT than with 3DCRT at any time point in the Rathod study. In the other study [30], use of IMRT was the only variable associated with improved QOL.	p<0.05 p<0.01

Abbreviations: CCRT = concurrent chemoradiotherapy; CCT = concurrent chemotherapy; IMRT = intensity-modulated radiotherapy; RT = radiotherapy; 3DCRT = three-dimensional conformal radiotherapy.

Strength of Evidence for Key Question 1

To evaluate the SOE, we used an approach specifically developed by the AHRQ EPC program and referenced in the "Methods Guide."[20] This approach is based on a system initially described by the GRADE Working Group. It explicitly addresses four required domains: risk of bias, directness, consistency, and precision, as outlined in the Methods section.

Table 7 shows the SOE for new evidence on the comparative effects on QOL and toxicities of 3DCRT, IMRT, SBRT, and PBT in the treatment of head and neck cancer patients.

The evidence we identified for this update supports an SOE rating of "moderate" for the comparison of 3DCRT and IMRT in a regimen of CCRT, showing a benefit of IMRT in significantly reducing the incidence of late grade 2 or higher xerostomia. Two other studies showed a statistically significant reduction in the incidence of late grade 2 or higher xerostomia in two other treatment regimens (RT with or without CCT, postoperative RT). New evidence on any other RT-associated toxicity is insufficient to form conclusions on a benefit or harm of 3DCRT compared with IMRT.

Table 7. SOE for Key Question 1: Adverse effects and QOL

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
3DCRT	IMRT	CCRT	Late xerostomia	Three studies including one RCT[25,29,33] (N=509)	Moderate One "fair" quality small RCT (N=60, Gupta[25]) plus two "poor" quality non-randomized studies result in a "moderate" study limitations rating	Direct All three studies directly compared IMRT and 3DCRT.	Consistent All three studies showed a statistically significant reduction of late grade > 2 xerostomia with IMRT compared with 3DCRT (p=0.001, p<0.002, p<0.001)	Precise	Moderate The body of evidence comprises one RCT, for a provisional SOE of "high". We downgraded the SOE one level based on the "moderate" risk of bias of the body of evidence. Although the Gupta trial[25] was relatively small, its statistically significant result coupled with similar findings of the much larger nonrandomized evidence merits an overall SOE rating of moderate. The overall SOE was rated as moderate due to limitations in the methodological quality of the studies. However, the findings of the three studies were consistent and indicated statistical significance.
		RT ± CCT	Late xerostomia	One study[27] (N=176)	High	Direct	Unknown	Imprecise	Insufficient
		CCRT ± surgery	Late xerostomia	One study[28] (N=82)	High	Direct	Unknown	Imprecise	Insufficient

Table 7. SOE for Key Question 1: Adverse effects and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
		RT ± CCT± surgery	Acute xerostomia	One study[36] (N=67)	High	Direct	Unknown	Imprecise	Insufficient
			Late xerostomia	One study[36] (N=67)	High	Direct	Unknown	Imprecise	Insufficient
		Postoperative RT	Late xerostomia	One study[31] (N=81)	High	Direct	Unknown	Imprecise	Insufficient

Table 7. SOE for Key Question 1: Adverse effects and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
		CCRT	Acute dysphagia	Three studies, including one RCT[25,29,33] (N=509)	Moderate One "fair" quality small RCT (N=60, Gupta[25]) plus two "poor" quality nonrandomized studies result in a "moderate" study limitations rating.	Direct	Inconsistent One non-randomized study showed a statistically significant reduction with IMRT (49%) compared with 3DCRT (84%).[29] The other non-RCT showed a directionally same but nonsignificant effect that favored IMRT over 3DCRT. The Gupta[25] RCT showed a lower but also nonsignificant rate difference of acute dysphagia with 3DCRT (0%) compared with IMRT (9.5%) (p=0.21).	Imprecise The Gupta RCT[25] only included 60 cases, compared with 449 for the other 2 studies. It was likely not sufficiently powered to detect slight changes in rates of adverse effects, particularly in the face of much larger, albeit "poor" quality non-RCT evidence.	Insufficient A "high" provisional SOE based on the Gupta RCT[25] was reduced three levels for three reasons: (1) inconsistent rating; (2) imprecise rating based on the small size of the Gupta RCT and its nonsignificant result; and (3) the two nonrandomized studies were of "poor" quality, heterogeneous, and subject to a high risk of bias, thus increasing the risk of bias to "moderate" for the body of evidence.

Table 7. SOE for Key Question 1: Adverse effects and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
			Late dysphagia	Two studies[29,33] (N=707)	High Two "poor" quality, nonrandomized studies comprise the body of evidence.	Direct	Inconsistent One study showed a statistically significant effect (p=0.03) of IMRT compared with 3DCRT, with the second study showing a reduction, albeit nonsignificant reduction.	Precise	Insufficient The two nonrandomized studies were "poor" quality and heterogeneous, with high risk of bias that compromises the value of their results.

Table 7. SOE for Key Question 1: Adverse effects and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
			QOL	Two studies[26,30] (N=215)	Moderate One "fair" quality small RCT (N=60, Rathod 2013[26]) plus one "poor" quality nonrandomized study result in a "moderate" study limitations rating.	Direct	Inconsistent One study showed a statistically significant benefit (p<0.001) of IMRT compared with 3DCRT as it pertains to global QOL at 1 and 2 years,[30] while the second study reports no statistical difference based on radiotherapy technique.	Imprecise The Rathod RCT[26] only included 60 cases, compared with 155 for the second study. It was likely not sufficiently powered to detect slight changes in QOL, particularly in the face of much larger, albeit "poor" quality non-RCT evidence.	Insufficient A "high" provisional SOE based on the Rathod RCT[26] was reduced three levels for three reasons: (1) inconsistent rating; (2) imprecise rating based on the small size of the Rathod RCT and its nonsignificant result; and (3) the nonrandomized study was of "poor" quality, heterogeneous, and subject to a high risk of bias, thus increasing the risk of bias to "moderate" for the body of evidence.
		RT ± CCT	Acute dysphagia	One study[27] (N=176)	High	Direct	Unknown	Imprecise	Insufficient

Table 7. SOE for Key Question 1: Adverse effects and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
			Late dysphagia	Two studies[27,39] (N=357)	High Two "poor" quality, nonrandomized studies comprise the body of evidence.	Direct	Inconsistent One study showed a statistically significant effect (p=0.02) of IMRT compared with 3DCRT, with the second study showing no statistically significant difference.	Imprecise	Insufficient The two nonrandomized studies were "poor" quality, heterogeneous, and with a high risk of bias that compromises the value of their results.
		CCRT ± surgery	Late dysphagia	One study[28] (N=82)	High	Direct	Unknown	Imprecise	Insufficient
		RT ± CCT± surgery	Acute dysphagia	One study[36] (N=67)	High	Direct	Unknown	Imprecise	Insufficient
			Late dysphagia	One study[36] (N=67)	High	Direct	Unknown	Imprecise	Insufficient
		Postoperative RT	Acute dysphagia	One study[31] (N=81)	High	Direct	Unknown	Imprecise	Insufficient
		CCRT	Acute salivary gland dysfunction	One study[25] (N=60)	High	Direct	Unknown	Imprecise	Insufficient
		RT ± CCT	Acute salivary gland dysfunction	One study[38] (N=159)	High	Direct	Unknown	Imprecise	Insufficient

Table 7. SOE for Key Question 1: Adverse effects and QOL (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Study Limitations (Risk of Bias)	Directness	Consistency	Precision	Overall SOE
		Postoperative RT	Acute salivary gland dysfunction	One study[31] (N=81)	High	Direct	Unknown	Imprecise	Insufficient
	SBRT PBT	Any regimen	Any outcome	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
IMRT	SBRT PBT	Any regimen	Any outcome	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence

Abbreviations: CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; RCT = randomized controlled trial; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SOE = strength of evidence; 3DCRT = three-dimensional conformal radiotherapy.

Key Question 2: Comparative Effectiveness of 3DCRT, IMRT, SBRT, and PBT Regarding Tumor Control and Patient Survival

Overview

In this section we summarize evidence on comparative oncologic outcomes for different RT types. As noted in the Methods section, we did not seek evidence from other study designs (e.g., single-arm observational) that may report additional outcomes not captured in the comparative studies.

Table 8 depicts key oncologic outcomes reported by each relevant study; a blank cell in each table means the outcome was not reported in that study. Not all outcomes were collected in each study. Outcomes of primary interest are overall survival, local control (no evidence of primary tumor), or locoregional control (no evidence of primary tumor or regional metastatic spread) among patients treated with IMRT compared with 3DCRT. Other oncologic outcomes were inconsistently reported across the body of studies, as shown in Table 8.

Table 8. Summary of key reported comparative oncologic outcomes

Study (Year)	Study Design (USPSTF Rating)	RT Modalities (N)	Treatment Regimen	Tumor Site(s)	Overall Survival	Cancer-Specific Survival	Disease-Free Survival	Local Control	Loco-regional Control	Distant Control	Other
Gupta (2012)[25]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	●				●		
Rathod (2013)[26]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	●				●		
Al-Mamgani (2013)[29]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx	●	●	●	●	●		
Lambrecht (2013)[33]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx	●				●		
Al-Mamgani (2012)[27]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx							●
Chen (2012)[30]	Comparative Retrospective (poor)	3DCRT (71) IMRT (84)	RT ± CCT	Hypopharynx Larynx Nasopharynx Oropharynx Unknown primary							●
Al-Mamgani (2012)[28]	Comparative Retrospective (poor)	3DCRT (25) IMRT (57)	CCRT ± surgery	Paranasal sinus				●			
Dirix (2010)[31]	Comparative Prospective (IMRT) Retrospective (3DCRT) (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity Paranasal sinus	●		●	●		●	
Mok (2014)[39]	Comparative Retrospective (poor)	3DCRT (90) IMRT (91)	RT ± CCT	Hypopharynx	●				●	●	

Table 8. Summary of key reported comparative oncologic outcomes (continued)

Study (Year)	Study Design (USPSTF Rating)	RT Modalities (N)	Treatment Regimen	Tumor Site(s)	Overall Survival	Cancer-Specific Survival	Disease-Free Survival	Local Control	Loco-regional Control	Distant Control	Other
Lohia (2014)[38]	Comparative Retrospective (poor)	3DCRT (56) IMRT (103)	RT ± CCT	Oropharynx	●		●				●
Huang (2013)[35]	Comparative Retrospective (poor)	3DCRT (53) IMRT (30)	RT ± CCT	Nasopharynx	●		●		●		
Guan (2013)[32]	Comparative Retrospective (poor)	3DCRT (16) IMRT (43)	RT ± CCT ± surgery	Nasal cavity Paranasal sinus					●		●
Kong (2013)[36]	Comparative Retrospective (poor)	3DCRT (37) IMRT (30)	RT ± CCT± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Paranasal sinus	●				●	●	
Ozyigit (2011)[34]	Comparative Retrospective (poor)	3DCRT (27) SBRT (24)	rRT ± CCT	Nasopharynx	●	●		●			

Abbreviations: 3DCRT = three-dimensional conformal radiotherapy; CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; IMRT = intensity-modulated radiotherapy; RCT = randomized controlled trial; RT = radiotherapy; rRT = reirradiated radiotherapy; SBRT = stereotactic body radiotherapy; USPSTF = United States Preventive Services Task Force.

Key Points

- The results of primary interest for this Key Question comprise overall survival, local control, and locoregional control.
- As we found in CER No. 20, comparative evidence assessed in this update was insufficient to draw relative conclusions on any oncologic outcomes.
- The key oncologic outcomes were not reported universally across studies, so we could not make comparisons across a larger body of evidence.
- The best quality evidence comprises one small (N=60), fair quality RCT (Gupta, 2012) in which 3DCRT and IMRT were compared in a regimen of CCRT to treat patients with cancer of the hypopharynx, larynx and oropharynx.
- Two additional nonrandomized, poor quality studies reported on the key oncologic outcomes with 3DCRT and IMRT in a regimen of CCRT among patients with cancer of the hypopharynx, larynx, oral cavity, nasopharynx, and oropharynx.
- One study of 3DCRT versus SBRT reported overall survival and local control in a regimen of RT with or without CCRT among patients with nasopharyngeal cancer. However, 22 percent of unidentified patients in the 3DCRT arm received concurrent high-dose rate brachytherapy so the oncologic outcomes are not included in this synthesis.

Qualitative Synthesis

In Table 9, we have aggregated new evidence related to Key Question 2 on comparative oncologic outcomes actually reported in studies according to the intervention comparison, treatment regimen, and timeframe. We identified no evidence from patients stratified according to tumor site(s), so we have not included tumor information in this table. Further, we did not identify any evidence on differences in oncologic outcomes related to the HPV status of patient tumors. The last two columns of Table 9 show reported proportions for each outcome and statistically significant results if attained.

In general, evidence on tumor control and survival outcomes is sparse. Table 9 shows that statistically significant differences were inconsistently reported for overall survival, local control, or locoregional control among studies of 3DCRT versus IMRT in any regimen compiled there. All abstracted data are shown in detail in Table B-6.

Table 9. Key Question 2: Qualitative evidence synthesis for key reported comparative oncologic outcomes

Intervention	Comparator	Treatment Regimen	Outcome	Number of Studies (Number of Patients)	Reported Rates Across Studies (%)	Individual Study Statistically Significant Results (p-Value)
3DCRT	IMRT	CCRT	Overall survival	Three studies (four reports)[25-27,33] (N=509)	3 years (2 studies) 3DCRT: 71%, 61% IMRT: 68%, 64% 5 years (1 study) 3DCRT: 43% IMRT: 47%	No statistically significant difference in overall survival was reported in any study.
			Local control	One study[29] (N=204)	5 years 3DCRT: 74% IMRT: 82%	No statistically significant difference in local control was reported.
			Locoregional control	Two studies (three reports)[25,26,33] (N=305)	3 years 3DCRT: 88%, 71% IMRT: 81%, 70%	No statistically significant difference in locoregional control was reported in either study.
			Disease-free survival	One study[29] (N=204)	5 years 3DCRT: 58% IMRT: 60%	No statistically significant difference in disease-free survival was reported.
		CCRT ± surgery	Local control	One study[28] (N=82)	5 years 3DCRT: 64% IMRT: 80%	No statistically significant difference in local control was reported.
		Postoperative RT	Overall survival	One study[31] (N=81)	2 years 3DCRT: 73% IMRT: 89%	No statistically significant difference in overall survival was reported.
			Local control	One study[31] (N=81)	2 years 3DCRT: 67% IMRT: 76%	No statistically significant difference in local control was reported.
			Disease-free survival	One study[31] (N=81)	2 years 3DCRT: 60% IMRT: 72%	p=0.02
		RT ± CCT ± surgery	Overall survival	One study[36] (N=67)	1 year 3DCRT: 94% IMRT: 97% 2 years 3DCRT: 87% IMRT: 97%	No statistically significant difference in overall survival was reported.

Table 9. Key Question 2: Qualitative evidence synthesis for key reported comparative oncologic outcomes (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Number of Studies (Number of Patients)	Reported Rates Across Studies (%)	Individual Study Statistically Significant Results (p-Value)
			Locoregional control	One study[36] (N=67)	1 year 3DCRT: 61% IMRT: 89% 2 years 3DCRT: 58% IMRT: 80%	p=0.029
			Distant metastasis-free survival	One study[31] (N=67)	1 year 3DCRT: 86% IMRT: 92% 2 years 3DCRT: 82% IMRT: 75%	No statistically significant difference in distant metastasis-free survival was reported.
		RT ± CCT	Overall survival	Three studies[35,38,39] (N=423)	2 years (1 study) 3DCRT: 58% IMRT: 35% 3 years (1 study) 3DCRT: 52% IMRT: 50% 5 years (1 study) 3DCRT: 50% IMRT: 89%	The Huang study[35] reports a statistically significant benefit of IMRT vs. 3DCRT as it pertains to 5-year overall survival (p=0.004). No statistically significant difference in overall survival was reported at 2- or 3-years in the other two studies.
			Locoregional control	Two studies[35,39] (N=264)	3 years (1 study) 3DCRT: 58% IMRT: 75% 5 years (1 study) 3DCRT: 54% IMRT: 75%	The Mok study[39] reports a statistically significant benefit of IMRT vs. 3DCRT as it pertains to 3-year locoregional control (p=0.003). The Huang study[35] reports a statistically significant benefit of IMRT vs. 3DCRT as it pertains to 5-year locoregional control (p=0.018).
			Distant relapse	One study[35,39] (N=181)	3 years 3DCRT: 20% IMRT: 23%	No statistically significant difference in distant relapse was reported.
			Disease-free survival	Two studies[35,38] (N=242)	2 years (1 study) 3DCRT: 66% IMRT: 59% 5 years (1 study) 3DCRT: 47% IMRT: 69%	No statistically significant difference in disease-free survival was reported by the Lohia study at 2 years.[38] The Huang study[35] reports a statistically significant benefit of IMRT vs. 3DCRT as it pertains to 5-year disease-free survival (p=0.046).

Abbreviations: CCRT = concurrent chemoradiotherapy; IMRT = intensity-modulated radiotherapy; RT = radiotherapy; 3DCRT = three-dimensional conformal radiotherapy.

Strength of Evidence for Key Question 2

To evaluate the SOE, we used an approach specifically developed by the AHRQ EPC program and referenced in the Methods Guide.[20] This approach is based on a system initially described by the GRADE Working Group. It explicitly addresses four required domains: risk of bias, directness, consistency, and precision, as outlined in the Methods section.

Table 10 shows the SOE for the comparative effects of 3DCRT, IMRT, SBRT, and PBT on oncologic outcomes in the treatment of head and neck cancer patients. The criteria we used to arrive at the SOE ratings are outlined in the Methods section of the update. Details on how the SOE ratings were determined are summarized in Table 10.

We determined that new evidence, including one "fair" quality RCT (Gupta, 2012),[25] is insufficient to support a conclusion on the relative effect of IMRT and 3DCRT on overall survival or locoregional control rates in a regimen of CCRT. New evidence is insufficient to form conclusions on the effect of any other RT modality comparison for any oncologic outcome in any other regimen we identified in this update.

Table 10. SOE for Key Question 2: Oncologic outcomes

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Risk of Bias	Directness	Consistency	Precision	Overall SOE
3DCRT	IMRT	CCRT	Overall survival	Three studies (four reports) including the Gupta (2012) and Rathod (2013) RCTs[25,26,29,33] (N=509)	Moderate One "fair" quality small RCT (N=60, Gupta, 2012; N=60, Rathod, 2013) plus two "poor" quality non-randomized studies result in a provisional "moderate" study limitations rating.	Direct All three studies (four reports) directly compared IMRT and 3DCRT.	Consistent All three studies (four reports) showed no statistically significant difference between 3DCRT and IMRT in rate of overall survival at 2 or 5 years.	Imprecise The Gupta RCT[25] was likely not sufficiently powered to detect slight changes in rates of overall survival with IMRT compared with 3DCRT, particularly in the face of much larger, albeit "poor" quality non-RCT evidence.	Insufficient A "high" provisional SOE based on the Gupta RCT[25] was reduced three levels for three reasons: (1) imprecise rating based on the small size of the Gupta RCT and its nonsignificant result; (2) the two nonrandomized studies were of "poor" quality, heterogeneous, and subject to a high risk of bias, thus increasing the risk of bias to "moderate" for the body of evidence; and, (3) the relative larger size of these 2 studies compared to Gupta accounting for 88% of all patients in the body of evidence, obscure the findings of the latter, resulting in an overall SOE rating of "insufficient".

Table 10. SOE for Key Question 2: Oncologic outcomes (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Risk of Bias	Directness	Consistency	Precision	Overall SOE
			Locoregional control	Two studies (three reports) including the Gupta (2012) and Rathod (2013) RCTs[25,26,33] (N=305)	Moderate One "fair" quality RCT (N=60, Gupta, 2012; N=60, Rathod, 2013) and a much larger "poor" quality nonrandomized study result in a "moderate" study limitations rating.	Direct Both studies (three reports) directly compared IMRT and 3DCRT.	Consistent Both studies (three reports) showed no statistically significant difference between 3DCRT and IMRT in rate of overall survival at 2 or 5 years.	Imprecise The Gupta RCT[25] was likely not sufficiently powered to detect slight changes in rates of locoregional control with IMRT compared with 3DCRT, particularly in the face of much larger, albeit "poor" quality non-RCT evidence.	Insufficient A "high" provisional SOE based on the Gupta RCT[25] was reduced three SOE levels as outlined above for overall survival. Note the patients in the nonrandomized study comprised more than 80% of the evidence base, obscuring Gupta's results.
			Local control	One study[29] (N=204)	High	Direct	Unknown	Imprecise	Insufficient
			Disease-free survival	One study[29] (N=204)	High	Direct	Unknown	Imprecise	Insufficient
		CCRT ± surgery	Local control	One study[28] (N=82)	High	Direct	Unknown	Imprecise	Insufficient
		Postoperative RT	Overall survival	One study[31] (N=81)	High	Direct	Unknown	Imprecise	Insufficient
			Local control	One study[31] (N=81)	High	Direct	Unknown	Imprecise	Insufficient
			Disease-free survival	One study[31] (N=81)	High	Direct	Unknown	Imprecise	Insufficient
		RT ± CCT ± surgery	Overall survival	One study[36] (N=67)	High	Direct	Unknown	Imprecise	Insufficient
			Locoregional control	One study[36] (N=67)	High	Direct	Unknown	Imprecise	Insufficient
			Distant metastasis-free survival	One study[36] (N=67)	High	Direct	Unknown	Imprecise	Insufficient

Table 10. SOE for Key Question 2: Oncologic outcomes (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Risk of Bias	Directness	Consistency	Precision	Overall SOE
		RT ± CCT	Overall survival	Three studies[35,38,39] (N=423)	High Three "poor" quality nonrandomized studies result in a "high" study limitations rating.	Direct All three studies directly compared IMRT and 3DCRT.	Inconsistent The Huang 2013 study[35] showed a statistically significant benefit (p=0.004) of IMRT compared with 3DCRT as it pertains to overall survival at 5 years, while the remaining two studies report no statistical difference based on RT technique at 2 or 3 years.	Imprecise The "poor" quality, nonrandomized Huang 2013 study[35] was likely not sufficiently powered to detect slight changes in rates of overall survival of IMRT compared with 3DCRT, particularly in the face of the much larger, "poor" quality nonrandomized studies which report no benefit of IMRT.	Insufficient The three nonrandomized studies were "poor" quality and heterogeneous, with high risk of bias that compromises the value of their results.
			Locoregional control	Two studies[35,39] (N=264)	High Two "poor" quality nonrandomized studies result in a "high" study limitations rating.	Direct Both studies directly compared IMRT and 3DCRT.	Consistent Both studies report a statistically significant difference between 3DCRT and IMRT in rate of locoregional control at 3 or 5 years.	Imprecise Due to the "poor" quality, nonrandomized design of these studies, it is likely that they were not sufficiently powered to detect slight changes in the rates locoregional control with IMRT as compared with 3DCRT.	Insufficient The two nonrandomized studies were "poor" quality and heterogeneous, with high risk of bias that compromises the value of their results.

Table 10. SOE for Key Question 2: Oncologic outcomes (continued)

Intervention	Comparator	Treatment Regimen	Outcome	Evidence Base (Number of Patients)	Risk of Bias	Directness	Consistency	Precision	Overall SOE
			Distant relapse	One study[35,39] (N=181)	High	Direct	Unknown	Imprecise	Insufficient
			Disease-free survival	Two studies[35,38] (N=242)	High Two "poor" quality nonrandomized studies result in a "high" study limitations rating	Direct Both studies directly compared IMRT and 3DCRT	Inconsistent The Huang 2013 study[35] reports a statistically significant benefit (p=0.046) of IMRT compared with 3DCRT as it pertains to disease-free survival at 5 years, while the Lohia 2014 study[38] reports a directionally opposite and statistically nonsignificant benefit of 3DCRT over IMRT at 2 years.	Imprecise Due to the "poor" quality, nonrandomized design of these studies, it is likely that they were not sufficiently powered to detect slight changes in the rates of disease-free survival with IMRT as compared with 3DCRT.	Insufficient The two nonrandomized studies were "poor" quality and heterogeneous, with high risk of bias that compromises the value of their results.
	SBRT PBT	Any regimen	Any outcome	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
IMRT	SBRT PBT	Any regimen	Any outcome	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence

Abbreviations: CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; RCT = randomized controlled trial; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SOE = strength of evidence; 3DCRT = three-dimensional conformal radiotherapy.

Key Question 3: Comparative Effectiveness of 3DCRT, IMRT, SBRT, or PBT for Specific Patient and Tumor Characteristics

Key Points

- In CER No. 20, no comparative studies addressed these issues. In this update, we did not identify any new evidence that specifically addressed Key Question 3.
- Therefore insufficient evidence exists to form conclusions about the comparative effects or SOE on 3DCRT, IMRT, SBRT, or PBT based on specific patient and tumor characteristics.

Key Question 4: Comparative Effectiveness of 3DCRT, IMRT, SBRT, or PBT Because of Differences in User Experience, Treatment Planning, Treatment Delivery, and Target Volume Delineation

Key Points

- In CER No. 20, no comparative studies addressed these issues. In this update, we did not identify any new evidence that specifically addressed Key Question 4.
- Therefore insufficient evidence exists to form conclusions about the comparative effects or SOE on 3DCRT, IMRT, SBRT, or PBT based on specific patient and tumor characteristics.

Discussion

CER Update Strength of Evidence Relative to CER No. 20 Findings

Table 11 provides a summary of the conclusions we drew for the relevant interventional comparisons for each Key Question in CER No. 20 and in this update. Because 2DRT and SBRT are not commonly addressed in CER No. 20 and the update, they are not included in Table 11. Moderate strength evidence from the update shows a reduction of the incidence of late grade 2 or higher xerostomia with IMRT compared with 3DCRT. This increases the SOE on this toxicity from CER No. 20, raising it to "high" based on a body of evidence including 2 RCTs and observational studies that are in agreement on this outcome. Evidence in the update is insufficient to show a difference between IMRT and 3DCRT in overall survival or locoregional tumor control rates. We found no new evidence to alter any conclusions of CER No. 20 for any other toxicity, oncologic outcomes, or comparisons.

Table 11. Comparison of relevant CER No. 20 and update conclusions

Key Question	Comparison	Clinical Outcome	CER No. 20 Total Evidence Base	CER No. 20 Conclusions	CER No. 20 Update Total Evidence Base	CER No. 20 Update Conclusions	Cumulative Update Conclusions (Action Needed)
Key Question 1: What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding adverse events and QOL?	3DCRT vs. IMRT	Grade ≥ 2 late xerostomia	One good quality RCT and six poor quality non-RCTs	Moderate SOE shows significant reduction in incidence	One fair quality RCT, six poor quality non-RCTs	Moderate SOE shows significant reduction in incidence	Raises final SOE to "high" based on a body of evidence including 2 RCTs (no further study required)
	3DCRT vs. IMRT	Other RT-associated grade > 2 toxicities (e.g., acute or late dysphagia, salivary gland dysfunction, swallowing function)	Variously, one good quality RCT, 13 poor quality non-RCTs	Insufficient evidence to draw conclusions	Variously, one good quality RCT, nine poor quality non-RCTs	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
	3DCRT vs. IMRT	QOL	Three poor quality non-RCTs	Insufficient evidence to draw conclusions	One fair quality RCT, one poor quality non-RCT	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. PBT	Any	No evidence identified	No evidence identified, insufficient	No evidence identified	No evidence identified, insufficient	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. SBRT	Any	Not applicable (SBRT not included)	Not applicable (SBRT not included)	One poor quality non-RCT	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)

Table 11. Comparison of relevant CER No. 20 and update conclusions (continued)

Key Question	Comparison	Clinical Outcome	CER No. 20 Total Evidence Base	CER No. 20 Conclusions	CER No. 20 Update Total Evidence Base	CER No. 20 Update Conclusions	Cumulative Update Conclusions (Action Needed)
Key Question 2: What is the comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT regarding tumor control and patient survival?	3DCRT vs. IMRT	Overall survival, local control, locoregional control, disease-free survival	Variously, one good quality RCT, six poor quality non-RCTs	Insufficient evidence to draw conclusions	One fair quality RCT, nine poor quality non-RCTs	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. PBT	Any	No evidence identified	No evidence identified, insufficient	No evidence identified	No evidence identified, insufficient	Insufficient evidence to draw conclusions (further study required)
	3DCRT or IMRT vs. SBRT	Any	Not applicable (SBRT not included)	Not applicable (SBRT not included)	One poor quality non-RCT	Insufficient evidence to draw conclusions	Insufficient evidence to draw conclusions (further study required)
Key Question 3: Are there differences in comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT for specific patient and tumor characteristics?	3DCRT or IMRT vs. PBT or SBRT	Any	No evidence identified	No evidence identified, insufficient	No evidence identified	No evidence identified, insufficient	Insufficient evidence to draw conclusions (further study required)

Table 11. Comparison of relevant CER No. 20 and update conclusions (continued)

Key Question	Comparison	Clinical Outcome	CER No. 20 Total Evidence Base	CER No. 20 Conclusions	CER No. 20 Update Total Evidence Base	CER No. 20 Update Conclusions	Cumulative Update Conclusions (Action Needed)
Key Question 4: Is there variation in comparative effectiveness of 3DCRT, IMRT, SBRT, and PBT because of differences in user experience, treatment planning, treatment delivery, and target volume delineation?	3DCRT or IMRT vs. PBT or SBRT	Any	No evidence identified	No evidence identified, insufficient	No evidence identified	No evidence identified, insufficient	Insufficient evidence to draw conclusions (further study required)

Abbreviations: CER = Comparative Effectiveness Review; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; QOL = quality of life; RCT = randomized controlled trial; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SOE = strength of evidence; 3DCRT = three-dimensional conformal radiotherapy.

Applicability of the Findings

In general, applicability assessment would depend on a body of evidence sufficient to form new conclusions about the comparative outcomes of 3DCRT, IMRT, SBRT, and PBT in treatment of head and neck cancer. However, comparative evidence that meets study selection criteria for this CER update is sparse for 3DCRT, IMRT, and SBRT, and nonexistent for PBT. In the absence of sufficient evidence, additional factors may be considered in making a treatment decision. Those could include relative convenience and cost, issues outside the scope of this CER.

In preparing this update, we reconsidered the RT modalities included in CER No. 20 and whether all remained applicable to current radiation oncology practice. In particular, we examined the role of opposed beam 2DRT in modern radiation oncology practice. Based on the current literature and input from our TEP members, we concluded 2DRT is no longer used in the U.S. for definitive treatment of head and neck cancer, thus we excluded it from the update. We realize in doing so we excluded evidence from a RCT performed in China that showed a statistically significant improvement in overall survival with IMRT compared to 2DRT, which to our knowledge is the only study that has shown a statistically significant survival benefit of one RT modality compared to another.[54] However, this did not alter our overall conclusion to exclude 2DRT from the current report.

We also re-examined whether to include brachytherapy in this update; it was not part of CER No. 20. Although brachytherapy can be used in select cases as a means of dose escalation in conjunction with external beam irradiation for head and neck cancer,[3,4] this practice has become uncommon because sufficient dose escalation can often be achieved in these cases with a noninvasive approach (e.g., conformal RT). Brachytherapy alone is very rarely employed, except in small (T1) tumors of the nasal vestibule, lip, or oral cavity, which are relatively uncommon (1 percent to perhaps 5 percent of all cases).[5-9] Therefore, because use of brachytherapy alone for primary management of head and neck malignancies has limited applicability in modern head and neck radiation oncology practice, we did not seek evidence of it for this CER; we focused instead on RT modalities that are used as the sole RT modality for a given presentation of head and neck cancer.

We considered including dosimetry studies in CER No. 20, and this update. For both reports, our ultimate conclusion not to include dosimetry studies was agreed upon among our EPC team, among AHRQ personnel, and in discussion with our TEP. 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.

Key Questions 1 and 2

The degree to which the evidence presented in this update is applicable to clinical practice is a function of the similarity between populations in the included studies and the patient population that receives clinical care in diverse settings. It also is related to the relative availability of the modalities. Because of the overall weakness of evidence for Key Questions 1 and 2, we have primarily limited comments to the relevance of the PICOTS elements, a practical and useful structure to review the applicability in a systematic manner (Table 12).

Table 12. Summary of applicability of evidence for Key Questions 1 and 2

PICOTS Domain	Applicability of Evidence
Populations	• Overall patients included in the evidence base of this CER update are typical of the head and neck cancer population treated with RT based on age, sex, and tumor characteristics.
Interventions	• 3DCRT, IMRT, and SBRT represent different technological approaches to the delivery of conformal photon RT. The major advantage of these interventions compared with traditional wide-field 2DRT is the ability to deliver tightly focused ionizing radiation by delineating the shape and size of the tumor using a CT-based or other imaging planning system. • 3DCRT represents a minimum technical standard for delivery of forward-planned conformal RT. It involves static fields with a fixed shape, modified by compensators (wedges and segments). 3DCRT is widely available. • IMRT offers beam strength attenuation through a multileaf collimator (tungsten), with dynamic field shapes for each beam angle. IMRT is as widely available as 3DCRT, but requires labor-intensive inverse planning and a higher level of quality assurance. • SBRT is a hypofractionated technique to administer RT in far fewer fractions than 3DCRT and IMRT. • SBRT is not as widely available as 3DCRT or IMRT, but its use is growing in other diseases such as non-small-cell lung cancer. • The institutional programmatic requirements for SBRT differ from those of IMRT. • Comparative evidence for PBT is unavailable.
Comparators	• See above for Interventions.
Outcomes	• The major beneficial health outcomes in this CER are overall survival and late xerostomia. • Overall survival is the primary outcome of interest for any cancer intervention study. • Local control is of interest to patients because it measures the effectiveness of an intervention in disease control. On local failure, patients enter into a new category centered on systemic chemotherapy.
Timing	• The relevant periods occur from the time of treatment through followup over months (palliation) or years (overall survival).
Setting	• The evidence for Key Questions 1 and 2 is mostly international, primarily obtained in tertiary institutions. More sophisticated interventions such as IMRT and SBRT require an institutional commitment to quality assurance and ongoing training that may be difficult to achieve in smaller community-based centers. • We did not collect or analyze information to examine these issues.

Abbreviations: CER = Comparative Effectiveness Review; CT = computed tomography; IMRT = intensity-modulated radiotherapy; PBT = proton-beam radiotherapy; RCT = randomized controlled trial; RT = radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy.

Key Questions 3 and 4

The current evidence base for Key Questions 3 and 4 is nonexistent based on our literature review. Therefore we cannot assess the applicability to clinical practice.

Findings in Relationship to What Is Already Known

Our updated systematic literature search and review revealed no relevant evidence-based guidelines we could compare with our findings for any of the Key Questions.

Limitations of Current Review and Evidence Base

The primary limitation for all Key Questions here is lack of well-designed and conducted comparative trials. Although the body of evidence we identified was more substantial for 3DCRT and IMRT than SBRT, and nonexistent for PBT, we have significant concerns about interstudy heterogeneity, with variability in RT dose, schedule of treatment, concurrent treatments, patient selection criteria, tumor size and location, and so forth.

We acknowledge that our inclusion of comparative studies alone may have limited collection of RT-associated adverse events that may be revealed in larger observational studies. However, we believe our decision to focus on key comparative outcomes xerostomia, dysphagia, and salivary gland toxicity was merited based on our understanding of the literature and the importance of those toxicities to cancer patients.

As stated previously in this report, we are not sure whether the inconsistency we observed in comparative RT-associated adverse events reflects a lack of systematic collection of this type of information by investigators, or failure to consistently report it in publications. In a systematic review in general, a heterogeneous evidence base makes it very difficult to assess the relative benefits and harms of any modality, particularly evidence drawn from nonrandomized trials, and to assess the SOE of a body of evidence. In this CER update, the sparse new evidence we identified limited additional comparative assessment among the modalities. We therefore believe further careful study of the RT methods compared in this CER is needed, particularly in the regimens of Key Question 1 or 2 to establish optimal technical protocols and patient selection criteria, perhaps standardizing and comparing them across institutions. These data and methods could, in theory, be applied to the design and conduct of comparative studies, as outlined in the Research Gaps section below.

We are aware that a body of dosimetry evidence is available to suggest potential differences in the benefits and harms of different conformal RT types. Our exclusion of such evidence may be viewed by some readers as a limitation of this CER update. However, we maintain that because dosimetry modeling studies do not provide a clear link to clinical outcomes, they do not add critical information to assess the comparative effectiveness of RT in the treatment of head and neck cancer.

Research Gaps

The primary research gap we identified is a continuing lack of evidence from well-executed comparative studies (randomized or otherwise) to draw conclusions on the relative clinical benefits and harms of the RT methods used in patients with head and neck cancer. We also identified some feasibility issues associated with the RT methods that are potential impediments to the type of rigorous comparative studies we suggest are necessary to determine their comparative effectiveness. In this section, we first describe characteristics of ideal comparative studies we believe are needed to compare these technologies. Some potential impediments to such studies are discussed subsequently in this section.

Lack of Clinical Trial Evidence on RT Interventions for Head and Neck Cancer

We suggest that further prospective studies are needed to properly evaluate the relative clinical benefits and harms of the technologies assessed in this CER, taking into account the potential impediments we discuss below. Ideally, comparative studies would incorporate the following:

- To assure comparability of patients and to minimize bias, standardized patient selection criteria would be used that involve consultation, including a head and neck surgeon, medical oncologist, and radiation oncology specialist. Key factors to consider include comorbidity status, age, performance status, tumor size, and tumor location.

- Standardized intervention protocols with training and quality assurance programs within and across participating institutions are necessary for the best study. For RT, key factors would include the imaging and planning method, immobilization method, dose, and fractionation schedule for comparisons of different modalities (e.g., 3DCRT, IMRT, SBRT, PBT).
- Prespecified followup criteria and methods—in particular, notation of systemic therapy—are key considerations in study design. Systemic therapy is a key concern because it is difficult to discern the effects of an intervention with systemic therapy from that achieved with the intervention alone. Is the effectiveness a function of the systemic therapy, the intervention, or the combination?
- Rigorous and standardized reporting is needed to account for all patients and treatments received. We urge that rigorous methods be used to conduct RCTs, particularly intention-to-treat analysis and adjustment of survival data to account for all patients based on their treatment plans.
- Primary outcomes would include overall survival, cancer-specific survival, and local control. Prespecified systematic collection of adverse events using validated criteria (e.g., Common Terminology Criteria for Adverse Events) is necessary to permit accurate assessment of relative benefits and risks of the interventions.
- As alluded to in the Introduction of this update, the potential impact of tumor tissue HPV positivity on oncologic outcomes and management of such patients has been increasing in importance. Studies are needed to identify reduced intensity therapies that still yield satisfactory oncologic outcomes in HPV-positive cases. This will require investigators to stratify patients by HPV status and analyze data accordingly.

Potential Impediments to Comparative Studies of RT Interventions for Head and Neck Cancer

The general dissemination of conformal RT technologies into community clinical practice is a potential impediment to comparative study of those technologies. We acknowledge that randomized studies of 3DCRT versus IMRT or PBT may be very difficult to recruit and conduct, based on technical and potential ethical issues related to perceptions of unequal clinical benefit among the interventions. We also recognize that the cost of conducting rigorous RCTs may pose a significant impediment given the resource limitations that exist in the United States. This CER supports a conclusion that RT-associated adverse events—in particular late xerostomia—are lessened with IMRT compared with 3DCRT. However, we maintain that current evidence is insufficient to support a view that clinical oncologic outcomes achieved with any of the technologies are relatively superior or inferior. Clinical evidence from comparative studies is needed to establish the standard of care for head and neck cancer patients.

Summary and Conclusions

Key Questions in CER No. 20 asked whether any of the RT modalities under consideration (2DRT, 3DCRT, IMRT, PBT) is more effective than the others:

- in reducing normal tissue toxicity and adverse events, and improving QOL
- in improving local tumor control, time to disease progression, and survival
- when used in certain anatomic locations or patient subpopulations

- whether there is more variation in patient outcomes with any modality secondary to user experience, treatment planning, or target volumes

The main finding of CER No. 20 was that late grade 2 or higher xerostomia was reduced and QOL domains related to xerostomia were improved in patients treated with IMRT compared with those who received either 3DCRT or 2DRT. Evidence was insufficient to draw relative conclusions on survival or tumor control; adverse events other than late xerostomia (e.g., mucositis, dysphagia, skin toxicities, osteoradionecrosis of the jaw); whether patient and tumor characteristics affected relative outcomes; or whether physician experience and treatment characteristics affected relative clinical outcomes such as survival or treatment-associated adverse events.

Moderate strength evidence from the update shows a reduction of the incidence of late grade 2 or higher xerostomia with IMRT compared with 3DCRT, which strengthens the conclusion on this toxicity from CER No. 20. Evidence in the update is insufficient to show a difference between IMRT and 3DCRT in overall survival or locoregional tumor control rates. We found no new evidence to alter any conclusions of CER No. 20 for any other toxicity, oncologic outcomes, or comparisons.

References

1. Samson DJ RT, Rothenberg BM, et al. Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer. Comparative Effectiveness Review No. 20 (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality, 2009; May 2010.
2. Tsertsvadze A AN, Skidmore B et al. . AHRQ Comparative Effectiveness Review Surveillance Program: Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer. AHRQ Website 2012.
3. Erickson BA, Wilson JF. Nasopharyngeal brachytherapy. Am J Clin Oncol. Oct 1993;16(5):424-443. PMID 82136264.
4. Esche BA, Haie CM, Gerbaulet AP, Eschwege F, Richard JM, Chassagne D. Interstitial and external radiotherapy in carcinoma of the soft palate and uvula. Int J Radiat Oncol Biol Phys. Sep 1988;15(3):619-625. PMID 31382135.
5. Jorgensen K, Elbrond O, Andersen AP. Carcinoma of the lip. A series of 869 cases. Acta Radiol Ther Phys Biol. Jun 1973;12(3):177-190. PMID 4749173
6. Marchese MJ, Nori D, Anderson LL, Hilaris BS. A versatile permanent planar implant technique utilizing iodine-125 seeds imbedded in gelfoam. Int J Radiat Oncol Biol Phys. May 1984;10(5):747-751. PMID 6735761
7. Marcus RB, Jr., Million RR, Mitchell TP. A preloaded, custom-designed implantation device for stage T1-T2 carcinoma of the floor of mouth. Int J Radiat Oncol Biol Phys. Jan 1980;6(1):111-113. PMID 73646008.
8. Mendenhall NP, Parsons JT, Cassisi NJ, Million RR. Carcinoma of the nasal vestibule. Int J Radiat Oncol Biol Phys. May 1984;10(5):627-637. PMID 6429094
9. Mendenhall NP, Parsons JT, Cassisi NJ, Million RR. Carcinoma of the nasal vestibule treated with radiation therapy. Laryngoscope. May 1987;97(5):626-632. PMID 3573913
10. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians. 2011;61(2):69-90. PMID 21296855
11. Pfister DG, Ang K-K, Brizel DM, et al. Head and Neck Cancers. Journal of the National Comprehensive Cancer Network. June 1, 2011 2011;9(6):596-650. PMID 21636536
12. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of Clinical Oncology. November 10, 2011 2011;29(32):4294-4301. PMID 21969503.
13. Sturgis EM, Ang KK. The epidemic of HVP-associated oropharyngeal cancer is here: Is it time to change our treatment paradigms? Journal of the National Comprehensive Cancer Network. 2011;9(6):665-673. PMID 21636538
14. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. Jul 1 2010;363(1):24-35. PMID 20530316
15. National Cancer Institute Fact Sheet: Radiation Therapy for Cancer (www.cancer.gov/cancertopics/factsheet/Therapy/radiation). Accessed August 13, 2014.
16. Bucci M, Bevan A, Roach III, M. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin. 2005;55:117-134. PMID 15761080
17. Chavaudra J, Bridier A. [Definition of volumes in external radiotherapy: ICRU reports 50 and 62]. Cancer Radiother. Oct 2001;5(5):472-478. PMID 11715299
18. Lee N, Puri DR, Blanco AI, et al. Intensity-modulated radiation therapy in head and neck cancers: An update. Head & Neck. 2007;29(4):387-400. PMID 16358297
19. Siddiqui F, Raben D, Lu JJ, et al. Emerging applications of stereotactic body radiation therapy for head and neck cancer. Expert Rev Anticancer Ther. Sep 2011;11(9):1429-1436. PMID 21929316

20. Helfand M, Balshem H. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. August 2009. Rockville, MD. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at www.effectivehealthcare.ahrq.gov.

21. Tsertsvadze A, Maglione M, Chou R, et al. Updating comparative effectiveness reviews: current efforts in AHRQ's Effective Health Care Program. J Clin Epidemiol. Nov 2011;64(11):1208-1215. PMID 21684114

22. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35. PMID 11306229

23. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010;63:513-523. PMID 19595577

24. Brown P, Brunnhuber K, Chalkidou K, et al. How to formulate research recommendations. BMJ. Oct 14 2006;333(7572):804-806. PMID 17038740

25. Gupta T, Agarwal J, Jain S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. Radiother Oncol. Sep 2012;104(3):343-348. PMID 22853852

26. Rathod S, Gupta T, Ghosh-Laskar S, Murthy V, Budrukkar A, Agarwal J. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. Oral Oncol. Jun 2013;49(6):634-642. PMID 23562564

27. Al-Mamgani A, Mehilal R, van Rooij PH, Tans L, Sewnaik A, Levendag PC. Toxicity, quality of life, and functional outcomes of 176 hypopharyngeal cancer patients treated by (chemo)radiation: the impact of treatment modality and radiation technique. Laryngoscope. Aug 2012;122(8):1789-1795. PMID 22833307

28. Al-Mamgani A, Monserez D, Rooij P, Verduijn GM, Hardillo JA, Levendag PC. Highly-conformal intensity-modulated radiotherapy reduced toxicity without jeopardizing outcome in patients with paranasal sinus cancer treated by surgery and radiotherapy or (chemo)radiation. Oral Oncol. Sep 2012;48(9):905-911. PMID 22584070

29. Al-Mamgani A, van Rooij P, Verduijn GM, Mehilal R, Kerrebijn JD, Levendag PC. The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. Laryngoscope. Feb 2013;123(2):386-393. PMID 23404489

30. Chen AM, Farwell DG, Luu Q, Vazquez EG, Lau DH, Purdy JA. Intensity-modulated radiotherapy is associated with improved global quality of life among long-term survivors of head-and-neck cancer. Int J Radiat Oncol Biol Phys. Sep 1 2012;84(1):170-175. PMID 22300572

31. Dirix P, Vanstraelen B, Jorissen M, Vander Poorten V, Nuyts S. Intensity-modulated radiotherapy for sinonasal cancer: Improved outcome compared to conventional radiotherapy. International Journal of Radiation Oncology Biology Physics. 2010;78(4):998-1004. PMID 20338694

32. Guan X, Wang X, Liu Y, Hu C, Zhu G. Lymph node metastasis in sinonasal squamous cell carcinoma treated with IMRT/3D-CRT. Oral Oncology. 2013;49(1):60-65. PMID 22884302

33. Lambrecht M, Nevens D, Nuyts S. Intensity-modulated radiotherapy vs. parotid-sparing 3D conformal radiotherapy. Effect on outcome and toxicity in locally advanced head and neck cancer. Strahlenther Onkol. Mar 2013;189(3):223-229. PMID 23319256

34. Ozyigit G, Cengiz M, Yazici G, et al. A retrospective comparison of robotic stereotactic body radiotherapy and three-dimensional conformal radiotherapy for the reirradiation of locally recurrent nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics. 2011;81(4):e263-e268. PMID 21514737

35. Huang HI, Chan KT, Shu CH, Ho CY. T4-locally advanced nasopharyngeal carcinoma: prognostic influence of cranial nerve involvement in different radiotherapy techniques. Scientific World Journal. 2013;2013:439073. PMID 24385882

36. Kong M, Hong SE, Choi J, Kim Y. Comparison of survival rates between patients treated with conventional radiotherapy and helical tomotherapy for head and neck cancer. Radiation Oncology Journal. 2013;31(1):1-11. PMID 23620863

37. Kruser TJ, Rice SR, Cleary KP, et al. Acute hematologic and mucosal toxicities in head and neck cancer patients undergoing chemoradiotherapy: A comparison of 3D-CRT, IMRT, and helical tomotherapy. Technology in Cancer Research and Treatment. 2013;12(5):383-389. PMID

38. Lohia S, Rajapurkar M, Nguyen SA, Sharma AK, Gillespie MB, Day TA. A comparison of outcomes using intensity-modulated radiation therapy and 3-dimensional conformal radiation therapy in treatment of oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg. Apr 1 2014;140(4):331-337. PMID 24557509

39. Mok G, Gauthier I, Jiang H, et al. Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head Neck. Mar 2 2014. PMID 24590756

40. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. Feb 2011;12(2):127-136. PMID 21236730

41. Chao KS, Deasy JO, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys. Mar 15 2001;49(4):907-916. PMID 11240231

42. Marchal C, Lapeyre M, Beckendorf V, et al. [Preliminary results of the assessment of intensity modulated radiotherapy (IMRT) for prostatic and head and neck tumors (STIC 2001)]. Cancer Radiother. Nov 2004;8 Suppl 1:S121-127. PMID 15679257

43. Chen AM, Daly ME, Bucci MK, et al. Carcinomas of the paranasal sinuses and nasal cavity treated with radiotherapy at a single institution over five decades: are we making improvement? Int J Radiat Oncol Biol Phys. Sep 1 2007;69(1):141-147. PMID 17459609

44. Fang FM, Tsai WL, Chen HC, et al. Intensity-modulated or conformal radiotherapy improves the quality of life of patients with nasopharyngeal carcinoma: comparisons of four radiotherapy techniques. Cancer. Jan 15 2007;109(2):313-321. PMID 17154159

45. Golen M SK, Wygoda A, et al. The influence of radiation technique on xerostomia in head and neck cancer patients: prospective study. Rep Pract Oncol Radiother. 2007;12(5):253-260.

46. Hodge CW, Bentzen SM, Wong G, et al. Are we influencing outcome in oropharynx cancer with intensity-modulated radiotherapy? An inter-era comparison. Int J Radiat Oncol Biol Phys. Nov 15 2007;69(4):1032-1041. PMID 17967300

47. Rades D, Fehlauer F, Wroblesky J, Albers D, Schild SE, Schmidt R. Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol. Jul 2007;43(6):535-543. PMID 17005437

48. Fang FM, Chien CY, Tsai WL, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy-a longitudinal study. Int J Radiat Oncol Biol Phys. Oct 1 2008;72(2):356-364. PMID 18355980

49. Gomez DR, Hoppe BS, Wolden SL, et al. Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. Int J Radiat Oncol Biol Phys. Apr 1 2008;70(5):1365-1372. PMID 18029108

50. Palazzi M, Tomatis S, Orlandi E, et al. Effects of treatment intensification on acute local toxicity during radiotherapy for head and neck cancer: prospective observational study validating CTCAE, version 3.0, scoring system. Int J Radiat Oncol Biol Phys. Feb 1 2008;70(2):330-337. PMID 17881148

51. Rusthoven KE, Raben D, Ballonoff A, Kane M, Song JI, Chen C. Effect of radiation techniques in treatment of oropharynx cancer. Laryngoscope. Apr 2008;118(4):635-639. PMID 18176348

52. Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys. May 1 2009;74(1):1-8. PMID 19111400

53. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol. Feb 2009;90(2):189-195. PMID 19167120

54. Peng G, Wang T, Yang KY, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol. Sep 2012;104(3):286-293. PMID 22995588

Summary of Protocol Amendments

Protocol amendments are summarized in Table 13.

Table 13. Protocol amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
January 10, 2014	IV. Methods: Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes	Please refer to section IV(F), p. 14: Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes	Please refer to section IV(F), p. 14: Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes	We performed a total rewrite based on input from the Task Order Officer and AHRQ personnel to make explicit the process to be used for grading the SOE, based on the updated chapter in the Methods Guide (2013).
January 10, 2014	IV. Methods: p. 10	"We will include only randomized controlled trials (RCTs) and nonrandomized comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that are part of the PICOTS (see above). We will exclude noncomparative studies from this CER,"…	"We will include only full-length reports—excluding conference abstracts and other non-peer reviewed articles— describing final results of randomized controlled trials (RCTs) and non-randomized comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that are part of the PICOTS (see above). We will exclude non-comparative studies from this CER,"…	To make explicit study selection criteria that include only full-length, peer-reviewed evidence

Review of Key Questions

For all EPC reviews, Key Questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel to assure that the questions were specific and explicit about what information is being reviewed. In addition, the Key Questions were posted for public comment and finalized by the EPC after review of the comments.

EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

Role of the Funder

This project was funded under Contract No. 290-2007-10058 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Search Strategy

PubMed Search Strategy

("Head and Neck Neoplasms"[Mesh]
OR
(("Neoplasms"[Mesh] OR neoplasms [TIAB] OR tumor [TIAB] OR tumors [TIAB] OR tumour [TIAB] OR tumours [TIAB] OR cancer [TIAB] OR cancers [TIAB] OR adenocarcinoma [TIAB] OR carcinoma [TIAB])
AND
(larynx [TIAB] OR laryngeal [TIAB] OR supraglottic [TIAB] OR glottic [TIAB] OR subglottic [TIAB] OR pharynx [TIAB] OR pharyngeal [TIAB] OR hypopharynx [TIAB] OR hypopharyngeal [TIAB] OR hypo-pharynx [TIAB] OR hypo-pharyngeal [TIAB] OR oropharynx [TIAB] OR oropharyngeal [TIAB] OR oro-pharynx [TIAB] OR oro-pharyngeal [TIAB] OR nasopharynx [TIAB] OR nasopharyngeal [TIAB] OR naso-pharynx [TIAB] OR naso-pharyngeal [TIAB] OR lip [TIAB] OR lips [TIAB] OR oral [TIAB] OR paranasal [TIAB] OR para-nasal [TIAB] OR nasal [TIAB] OR sinus [TIAB] OR salivary [TIAB] OR parotid [TIAB]))
OR
"Neoplasms, Unknown Primary"[Mesh] OR "occult primary" [TIAB] OR "unknown primary" [TIAB])
AND
(("Radiotherapy, Conformal"[Mesh] OR "Radiotherapy, Intensity-Modulated"[Mesh] OR "Protons"[Mesh] OR IMRT [TIAB] OR 3dcrt [TIAB] OR "3D-CRT" [TIAB] OR "3-D CRT" [TIAB] OR "3D CRT" [TIAB] OR (intensity [TIAB] AND modulated [TIAB]) OR conformal [TIAB] OR proton [TIAB] OR protons [TIAB]) OR (("Radiotherapy"[Mesh] OR "radiotherapy" [Subheading]) AND (3dcrt [TIAB] OR "3D-CRT" [TIAB] OR "3-D CRT" [TIAB] OR "3D CRT" [TIAB] OR (intensity [TIAB] AND modulated [TIAB]) OR conformal [TIAB] OR proton [TIAB] OR protons [TIAB])))
AND
Publication date from 2008/09/28 to 2013/04/04; Humans; English
("Head and Neck Neoplasms"[Mesh]
OR
(("Neoplasms"[Mesh] OR neoplasms [TIAB] OR tumor [TIAB] OR tumors [TIAB] OR tumour [TIAB] OR tumours [TIAB] OR cancer [TIAB] OR cancers [TIAB] OR adenocarcinoma [TIAB] OR carcinoma [TIAB])
AND
(larynx [TIAB] OR laryngeal [TIAB] OR supraglottic [TIAB] OR glottic [TIAB] OR subglottic [TIAB] OR pharynx [TIAB] OR pharyngeal [TIAB] OR hypopharynx [TIAB] OR hypopharyngeal [TIAB] OR hypo-pharynx [TIAB] OR hypo-pharyngeal [TIAB] OR oropharynx [TIAB] OR oropharyngeal [TIAB] OR oro-pharynx [TIAB] OR oro-pharyngeal [TIAB] OR nasopharynx [TIAB] OR nasopharyngeal [TIAB] OR naso-pharynx [TIAB] OR naso-pharyngeal [TIAB] OR lip [TIAB] OR lips [TIAB] OR oral [TIAB] OR paranasal [TIAB] OR para-nasal [TIAB] OR nasal [TIAB] OR sinus [TIAB] OR salivary [TIAB] OR parotid [TIAB]))
OR
"Neoplasms, Unknown Primary"[Mesh] OR "occult primary" [TIAB] OR "unknown primary" [TIAB])

AND
"Brachytherapy"[Mesh] OR brachytherapy OR ((interstitial OR intracavitary OR implant OR surface) AND radiotherapy)
AND
Publication date from 1990/01/01 to 2013/04/04; Humans; English
("Head and Neck Neoplasms"[Mesh]
OR
(("Neoplasms"[Mesh] OR neoplasms [TIAB] OR tumor [TIAB] OR tumors [TIAB] OR tumour [TIAB] OR tumours [TIAB] OR cancer [TIAB] OR cancers [TIAB] OR adenocarcinoma [TIAB] OR carcinoma [TIAB])
AND
(larynx [TIAB] OR laryngeal [TIAB] OR supraglottic [TIAB] OR glottic [TIAB] OR subglottic [TIAB] OR pharynx [TIAB] OR pharyngeal [TIAB] OR hypopharynx [TIAB] OR hypopharyngeal [TIAB] OR hypo-pharynx [TIAB] OR hypo-pharyngeal [TIAB] OR oropharynx [TIAB] OR oropharyngeal [TIAB] OR oro-pharynx [TIAB] OR oro-pharyngeal [TIAB] OR nasopharynx [TIAB] OR nasopharyngeal [TIAB] OR naso-pharynx [TIAB] OR naso-pharyngeal [TIAB] OR lip [TIAB] OR lips [TIAB] OR oral [TIAB] OR paranasal [TIAB] OR para-nasal [TIAB] OR nasal [TIAB] OR sinus [TIAB] OR salivary [TIAB] OR parotid [TIAB]))
OR
"Neoplasms, Unknown Primary"[Mesh] OR "occult primary" [TIAB] OR "unknown primary" [TIAB])
AND
(((("Radiosurgery"[Mesh]) OR "Stereotaxic Techniques"[Mesh] OR (stereotactic AND (radiosurgery OR radiotherapy)) OR SBRT OR tomotherapy OR tomotherapies))
AND
Publication date from 1990/01/01 to 2013/04/04; Humans; English

EMBASE Search Strategy

(neoplasms:ti,ab OR tumor:ti,ab OR tumors:ti,ab OR tumour:ti,ab OR tumours:ti,ab OR cancer:ti,ab OR cancers:ti,ab OR adenocarcinoma:ti,ab OR carcinoma*:ti,ab)
AND
(larynx:ab,ti OR laryngeal:ab,ti OR supraglottic:ab,ti OR glottic:ab,ti OR subglottic:ab,ti OR pharynx:ab,ti OR pharyngeal:ab,ti OR hypopharynx:ab,ti OR hypopharyngeal:ab,ti OR 'hypo pharynx':ab,ti OR 'hypo pharyngeal':ab,ti OR oropharynx:ab,ti OR oropharyngeal:ab,ti OR 'oro pharynx':ab,ti OR 'oro pharyngeal':ab,ti OR nasopharynx:ab,ti OR nasopharyngeal:ab,ti OR 'naso pharynx':ab,ti OR 'naso pharyngeal':ab,ti OR lip:ab,ti OR lips:ab,ti OR oral:ab,ti OR paranasal:ab,ti OR 'para nasal':ab,ti OR nasal:ab,ti OR sinus:ab,ti OR 'naso sinus':ab,ti OR salivary:ab,ti OR parotid:ab,ti OR 'occult primary':ab,ti OR 'unknown primary':ab,ti) OR ('head and neck' AND (neoplasms:ab,ti OR tumor:ab,ti OR tumors:ab,ti OR tumour:ab,ti OR tumours:ab,ti OR cancer:ab,ti OR cancers:ab,ti OR adenocarcinoma:ab,ti OR carcinoma:ab,ti)
AND
('radiotherapy'/exp AND (3dcrt:ab,ti OR '3d-crt':ab,ti OR '3-d crt':ab,ti OR '3d crt':ab,ti OR (intensity:ab,ti AND modulated:ab,ti) OR conformal:ab,ti OR proton:ab,ti OR protons:ab,ti) OR imrt:ab,ti OR 3dcrt:ab,ti OR '3d-crt':ab,ti OR '3-d crt':ab,ti OR '3d crt':ab,ti OR (intensity:ab,ti AND modulated:ab,ti) OR conformal:ab,ti OR proton:ab,ti OR protons:ab,ti)
AND

[humans]/lim AND [english]/lim AND [embase]/lim AND [2008-2013]/py
(neoplasms:ti,ab OR tumor:ti,ab OR tumors:ti,ab OR tumour:ti,ab OR tumours:ti,ab OR cancer:ti,ab OR cancers:ti,ab OR adenocarcinoma:ti,ab OR carcinoma*:ti,ab)
AND
(larynx:ab,ti OR laryngeal:ab,ti OR supraglottic:ab,ti OR glottic:ab,ti OR subglottic:ab,ti OR pharynx:ab,ti OR pharyngeal:ab,ti OR hypopharynx:ab,ti OR hypopharyngeal:ab,ti OR 'hypo pharynx':ab,ti OR 'hypo pharyngeal':ab,ti OR oropharynx:ab,ti OR oropharyngeal:ab,ti OR 'oro pharynx':ab,ti OR 'oro pharyngeal':ab,ti OR nasopharynx:ab,ti OR nasopharyngeal:ab,ti OR 'naso pharynx':ab,ti OR 'naso pharyngeal':ab,ti OR lip:ab,ti OR lips:ab,ti OR oral:ab,ti OR paranasal:ab,ti OR 'para nasal':ab,ti OR nasal:ab,ti OR sinus:ab,ti OR 'naso sinus':ab,ti OR salivary:ab,ti OR parotid:ab,ti OR 'occult primary':ab,ti OR 'unknown primary':ab,ti) OR ('head and neck' AND (neoplasms:ab,ti OR tumor:ab,ti OR tumors:ab,ti OR tumour:ab,ti OR tumours:ab,ti OR cancer:ab,ti OR cancers:ab,ti OR adenocarcinoma:ab,ti OR carcinoma:ab,ti)
AND
'brachytherapy'/exp OR ((interstitial OR intracavitary OR 'implant'/exp OR 'surface'/exp) AND 'radiotherapy'/exp)
AND
[humans]/lim AND [english]/lim AND [embase]/lim AND [1990-2013]/py
(neoplasms:ti,ab OR tumor:ti,ab OR tumors:ti,ab OR tumour:ti,ab OR tumours:ti,ab OR cancer:ti,ab OR cancers:ti,ab OR adenocarcinoma:ti,ab OR carcinoma*:ti,ab)

AND
(larynx:ab,ti OR laryngeal:ab,ti OR supraglottic:ab,ti OR glottic:ab,ti OR subglottic:ab,ti OR pharynx:ab,ti OR pharyngeal:ab,ti OR hypopharynx:ab,ti OR hypopharyngeal:ab,ti OR 'hypo pharynx':ab,ti OR 'hypo pharyngeal':ab,ti OR oropharynx:ab,ti OR oropharyngeal:ab,ti OR 'oro pharynx':ab,ti OR 'oro pharyngeal':ab,ti OR nasopharynx:ab,ti OR nasopharyngeal:ab,ti OR 'naso pharynx':ab,ti OR 'naso pharyngeal':ab,ti OR lip:ab,ti OR lips:ab,ti OR oral:ab,ti OR paranasal:ab,ti OR 'para nasal':ab,ti OR nasal:ab,ti OR sinus:ab,ti OR 'naso sinus':ab,ti OR salivary:ab,ti OR parotid:ab,ti OR 'occult primary':ab,ti OR 'unknown primary':ab,ti) OR ('head and neck' AND (neoplasms:ab,ti OR tumor:ab,ti OR tumors:ab,ti OR tumour:ab,ti OR tumours:ab,ti OR cancer:ab,ti OR cancers:ab,ti OR adenocarcinoma:ab,ti OR carcinoma:ab,ti)
AND
'stereotaxic techniques'/exp OR (stereotactic AND ('radiosurgery'/exp OR 'radiotherapy'/exp)) OR 'sbrt'/exp OR 'tomotherapy'/exp
AND
[humans]/lim AND [english]/lim AND [embase]/lim AND [1990-2013]/py

Appendix B. UPSTF Study Quality Ratings

- The quality of studies was assessed on the basis of the following criteria:
    - Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups.
    - Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).
    - Important differential loss to followup or overall high loss to followup.
    - Measurements: equal, reliable, and valid (includes masking of outcome assessment).
    - Clear definition of interventions.
    - All important outcomes considered.
    - Analysis: adjustment for potential confounders and intention-to-treat analysis.
- The rating of intervention studies were rated according to one of three quality categories:

Good. Meets all criteria; comparable groups were assembled initially and maintained throughout the study (followup at least 80 percent); reliable and valid measurement instruments were used and applied equally to the groups; interventions were spelled out clearly; all important outcomes were considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair. Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: In general, comparable groups were assembled initially, but some questions remain about whether some (although not major) differences occurred with followup; measurement instruments were acceptable (although not the best) and were generally applied equally; some but not all important outcomes were considered; and some but not all potential confounders were accounted for. Intention-to-treat analysis has been done for RCTs.

Poor. Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially were not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments were used or not applied at all equally among groups; and key confounders were given little or no attention; lack of masked outcome assessment; and for RCTs, intention-to-treat analysis is lacking.

Table B-1. USPSTF study limitations ratings

Study (year)	Initial assembly of comparable groups?	Maintenance of comparable groups?	Important differential loss to followup?	Measurements equal, reliable, and valid?	Interventions clear and well-defined?	All important outcomes considered?	Appropriate analysis and adjustment for confounders?	Overall rating
Gupta (2012)[1]	Yes RCT Groups well matched for tumor site and TNM status Allocation concealment not reported	Yes	No 28 of 29 (97%) in 3DCRT and 32 of 33 (97%) IMRT group evaluated	No Study was not double-blinded nor was outcome assessment	Yes	Yes	Yes Did not use ITT but this was unnecessary given good followup numbers	Fair
Rathod (2013)[2]	Yes RCT Groups well matched for tumor site and TNM status Allocation concealment not reported	Yes	No 58 of 60 (97%) of all study patients completed at least on QoL questionnaire, while 18 (64%) in the 3DCRT group and 18 (56%) in the IMRT completed the QoL questionnaire at 24 months	No Study was not double-blinded nor was outcome assessment	Yes RT methods are detailed and extensive	Yes Although this report does not provide toxicity outcomes, toxicity events from this same cohort was previously presented in the Gupta [20] report	Yes Did not use ITT but this was unnecessary given good followup numbers	Fair
Al-Mamgani (2013)[3]	No Retrospective study Different groups not described	Unclear Groups were not described	Unclear Groups were not described	Unclear No masking of outcome assessment reported	Yes	Yes	Yes	Poor

Table B-1. USPSTF study limitations ratings (continued)

Study (year)	Initial assembly of comparable groups?	Maintenance of comparable groups?	Important differential loss to followup?	Measurements equal, reliable, and valid?	Interventions clear and well-defined?	All important outcomes considered?	Appropriate analysis and adjustment for confounders?	Overall rating
Lambrecht (2013)[4]	No Not an RCT Significant differences reported in tumor locations and N stage	No For xerostomia, 18% loss of patients 3DCRT group, 21% loss to followup in IMRT group For overall survival, numbers of patients per group not reported	Yes For xerostomia, 18% loss of patients 3DCRT group, 21% loss to followup in IMRT group For overall survival, numbers of patients per group not reported	Unclear No masking of outcome assessment reported	Yes	Yes	No	Poor
Al-Mamgani (2012)[5]	No Retrospective study Individual groups not reported by RT type	Unclear	No	Unclear No masking of outcome assessment reported	Yes	Yes	No Although they performed logistic regression to evaluate effect of clinical parameters on local failure and late toxicity, they did not use this to assess effects according to RT modality	Poor
Chen (2012)[6]	Yes Groups appear similar with no statistical differences but this is a retrospective study	Unclear Numbers of patients at follow-up were not reported by intervention or outcome	Unclear	Unclear No masking of outcome assessment reported	Yes	Yes	Yes	Poor

Table B-1. USPSTF study limitations ratings (continued)

Study (year)	Initial assembly of comparable groups?	Maintenance of comparable groups?	Important differential loss to followup?	Measurements equal, reliable, and valid?	Interventions clear and well-defined?	All important outcomes considered?	Appropriate analysis and adjustment for confounders?	Overall rating
Al-Mamgani (2012)[7]	No Retrospective study Individual groups not reported by RT type	Unclear	No	Unclear No masking of outcome assessment reported	Yes	Yes	No Although they performed logistic regression to evaluate effect of clinical parameters on local failure and late toxicity, they did not use this to assess effects according to RT modality	Poor
Kruser (2013)[8]	No Retrospective study Patients were unbalanced with regards to primary clinical endpoints	Unclear Numbers of patients at follow-up were not reported by intervention or outcome	Unclear Groups were not described	Unclear No masking of outcome assessment reported	No IMRT well described, 3DCRT details not provided beyond aggregate dose rate and fractionation	No No oncological outcomes were considered	No Imbalanced baseline clinical characteristics and lack of assessment of complete blood count characteristics on enrollment	Poor
Dirix (2010)[9]	No Retrospective study with historical control cohort	Unclear Historical comparators preclude analysis	Unclear	Unclear No masking of outcome assessment reported	No IMRT well described, 3DCRT details not provided beyond noting use of the same fractionation schedule	Yes	No	Poor

Table B-1. USPSTF study limitations ratings (continued)

Study (year)	Initial assembly of comparable groups?	Maintenance of comparable groups?	Important differential loss to followup?	Measurements equal, reliable, and valid?	Interventions clear and well-defined?	All important outcomes considered?	Appropriate analysis and adjustment for confounders?	Overall rating
Guan (2013)[10]	No Retrospective study Individual groups not reported by RT type	Unclear Numbers of patients at follow-up were not reported by intervention or outcome	Unclear	Unclear No masking of outcome assessment reported	Yes	Yes	Yes	Poor
Kong (2013)[11]	No Retrospective study Significant differences reported in RT dose and rate of use of RT as definitive treatment between groups	Unclear	Unclear Groups were not described in terms of baseline characteristics	Unclear No masking of outcome assessment reported	Yes	Yes	No No effort to adjust for the studies many limitations (small sample size; heterogeneous population; discretionary rather than protocol prescription of RT dose)	Poor
Huang (2013)[12]	No Retrospective study Significant differences reported in use of concurrent chemotherapy and cranial nerve involvement	Unclear	Unclear Patients lost to follow-up were not described in terms of baseline characteristics	Unclear No masking of outcome assessment reported	No No information is reported which pertains to radiation dose, fractionation schedule, or treatment delivery times	Yes	No	Poor

Table B-1. USPSTF study limitations ratings (continued)

Study (year)	Initial assembly of comparable groups?	Maintenance of comparable groups?	Important differential loss to followup?	Measurements equal, reliable, and valid?	Interventions clear and well-defined?	All important outcomes considered?	Appropriate analysis and adjustment for confounders?	Overall rating
Lohia (2014)[13]	Yes There was not a significant variation between the two groups in regards to baseline characteristics; however, this was a retrospective study	Yes However, follow-up was poor (75% for the 3DCRT group at 24-months versus 78% for IMRT)	Unclear Groups were not described	Unclear No masking of outcome assessment reported	Yes	Yes	No Great variation in the use and nature of concurrent chemotherapy	Poor
Mok (2014)[14]	No Not an RCT Significant differences reported in tumor N stage and group ages	Unclear Numbers of patients at followup were not reported by intervention or outcome	Unclear	Unclear No masking of outcome assessment reported	Yes	Yes	Yes Log-rank test was used to compare oncological outcomes between 3DCRT and IMRT arms	Poor
Ozyigit (2011)[15]	Yes Groups appear similar with no statistical differences, but this is a retrospective study	Yes	No	Yes No masking of outcome assessment reported	Yes	Yes	No Survival outcomes include six patients in the 3DCRT arm who also received brachytherapy	Poor

Abbreviations: IMRT = intensity-modulated radiotherapy; ITT= intention-to-treat; PBT = proton-beam radiotherapy; RCT = randomized clinical trial; RT = radiotherapy; 3DCRT = three-dimensional conformal radiotherapy.

Table B-2. Comparative study design and patient characteristics

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Age	Sex	AJCC stage	T classification	N classification
Gupta (2012)[1]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx 3DCRT: 29% IMRT: 28% Larynx 3DCRT: 18% IMRT: 19% Oropharynx 3DCRT: 53% IMRT: 53%	3DCRT Median 55 years (range 33-65 years) IMRT Median 51 years (range 31-65 years)	3DCRT 89% Male 11% Female IMRT 91% Male 9% Female	3DCRT 18% I-II 50% III 32% IV IMRT 22% I-II 50% III 28% IV	3DCRT 43% T1-T2 57% T3 IMRT 44% T1-T2 56% T3	3DCRT 68% N0-N1 32% N2a-b IMRT 66% N0-N1 34% N2a-b
Rathod (2013)[2]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx 3DCRT: 29% IMRT: 28% Larynx 3DCRT: 18% IMRT: 19% Oropharynx 3DCRT: 53% IMRT: 53%	3DCRT Median 55 years (range 33-65 years) IMRT Median 51 years (range 31-65 years)	3DCRT 89% Male 11% Female IMRT 91% Male 9% Female	3DCRT 18% I-II 50% III 32% IV IMRT 22% I-II 50% III 28% IV	3DRT 43% T1-T2 57% T3 IMRT 44% T1-T2 56% T3	3DCRT 68% N0-N1 32% N2a-b IMRT 66% N0-N1 34% N2a-b
Al-Mamgani (2013)[3]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx 100%	Median 54 years[a] (range 40-84 years)	69% Male[a] 31% Female	34% III[a] 59% IVA 7% IVB	62% T3[a] 33% T4a 5% T4b	34% N0[a] 14% N1 4% N2a 31% N2b 12% N2c 5% N3

Table B-2. Comparative study design and patient characteristics (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Age	Sex	AJCC stage	T classification	N classification
Lambrecht (2013)[4]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx 3DCRT: 16% IMRT: 3% Larynx 3DCRT: 21% IMRT: 25% Nasopharynx 3DCRT: 2% IMRT: 4% Oral cavity 3DCRT: 4% IMRT: 4% Oropharynx 3DCRT: 56% IMRT: 40%	3DCRT Mean 57 years Median 56 years (SD 9 years) IMRT Mean 61 years Median 60 years (SD 9 years)	3DCRT 86% Male 14% Female IMRT 85% Male 15% Female	3DCRT 24% III 76% IV IMRT 18% III 82% IV	3DCRT 7% T1 21% T2 33% T3 39% T4 IMRT 5% T1 17% T2 36% T3 42% T4	3DCRT 14% N0 24% N1 4% N2a 30% N2b 26% N2c 2% N3 IMRT 14% N0 10% N1 3% N2a 30% N2b 38% N2c 5% N3
Al-Mamgani (2012)[5]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx 100%	Median 60 years[a] (range 36-87 years)	79% Male[a] 21% Female	Not reported	10% T1[a] 31% T2 32% T3 20% T4a 7% T4b	24 % N0[a] 17% N1 4% N2a 30% N2b 15% N2c 10% N3
Chen (2012)[6]	Comparative Retrospective (poor)	3DCRT (71) IMRT (84)	RT ± CCT	Hypopharynx 3DCRT: 12% IMRT: 13% Larynx 3DCRT: 12% IMRT: 13% Nasopharynx 3DCRT: 7% IMRT: 10% Oropharynx 3DCRT: 41% IMRT: 38% Unknown primary 3DCRT: 10% IMRT: 12%	Median 56 years (range 21-93 years) 3DCRT 51% < 56 years 49% > 56 years IMRT 45% < 56 years 55% > 56 years	59% Male[a] 41% Female	Not reported	3DCRT 10% T0 17% T1 20% T2 25% T3 28% T4 IMRT 12% T0 18% T1 19% T2 23% T3 29% T4	Not reported

Table B-2. Comparative study design and patient characteristics (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Age	Sex	AJCC stage	T classification	N classification
Al-Mamgani (2012)[7]	Comparative Retrospective (poor)	3DCRT (25) IMRT (57)	CCRT ± surgery	Paranasal sinus 100%	Median 62 years[a] (range 28-86 years)	67% Male[a] 33% Female	Not reported	9% T2[a] 27% T3 37% T4a 27% T4b	87 % N0[a] 13% N+
Kruser (2013)[8]	Comparative Prospective (poor)	3DCRT (41) IMRT (137)	CCRT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Unknown primary	3DCRT Median 54 years (range 39-78 years) IMRT LINAC-IMRT: Median 53 years (range 36-77 years) Tomotherapy: Median 57 years (39-77 years)	3DCRT 75.6% Male 24.4% Female IMRT 78.8% Male 22.2% Female	11.8% III[c] 88.2% IVa-b	6.7% T0[c] 16.3% T1 32.6% T2 25.3% T3 19.1% T4	Not reported
Dirix (2010)[9]	Comparative Prospective IMRT Retrospective 3DCRT (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity 3DCRT: 5% IMRT: 15% Paranasal sinus 3DCRT: 95% IMRT: 85%	3DCRT Median 61 years (range 37-85 years) IMRT Median 63 years (range 37-84 years)	3DCRT 82.9% Male 17.1% Female IMRT 85.0% Male 15.0% Female	Not reported	3DCRT 24.4% T2 56.1% T3 12.2% T4a 7.3% T4b IMRT 22.5% T2 47.5% T3 17.5% T4a 12.5% T4b	3DCRT 100.0% N0 IMRT Not reported
Guan (2013)[10]	Comparative Retrospective (poor)	3DCRT (16) IMRT (43)	RT ± CCT ± surgery	Nasal cavity 68% Paranasal sinus 32%	Median 56 years[a] (range 19-83 years) 63.7% ≤ 60 years 37.3% > 60 years	69.5% Male[a] 30.5% Female	5.1% I[a] 6.8% II 16.9% III 45.8% IVa 28.8% IVb	6.8% T1[a] 10.2% T2 18.6% T3 40.7% T4a 23.7% T4b	69.4% N0[a] 15.3% N1 11.9% N2 3.4% N3

Table B-2. Comparative study design and patient characteristics (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Age	Sex	AJCC stage	T classification	N classification
Kong (2013)[11]	Comparative Retrospective (poor)	3DCRT (30) IMRT (37)	RT ± CCT ± surgery	Hypopharynx 3DCRT: 16.2% IMRT: 3.3% Larynx 3DCRT: 13.5% IMRT: 13.3% Nasopharynx 3DCRT: 8.1% IMRT: 33.3% Oral Cavity 3DCRT: 40.5% IMRT: 33.3% Oropharynx 3DCRT: 13.5% IMRT: 13.3% Paranasal sinus 3DCRT: 8.1% IMRT: 3.3%	3DCRT Median 63 years (range 20-84 years) IMRT Median 56 years (range 29-84 years)	3DCRT 70.3% Male 29.7% Female IMRT 73.3% Male 26.7% Female	3DCRT 35.1% ≤ III 64.9% ≥ IVA IMRT 60.0% ≤ III 40.0% ≥ IVA	3DCRT 8.2% T1 35.1% T2 29.7% T3 27.0% T4 IMRT 20.0% T1 56.7% T2 10.0% T3 13.3% T4	3DCRT 40.5% N0 8.1% N1 48.6% N2 2.8% N3 IMRT 30.0% N0 23.3% N1 46.7% N2 0.0% N3
Huang (2013)[12]	Comparative Retrospective (poor)	3DCRT (53) IMRT (30)	RT ± CCT	Nasopharynx 100%	3DCRT Mean 52.3 ± 13.9 years (range 18-78 years) IMRT Mean 48.2 ± 14.0 years (range 19-78 years)	3DCRT 83% Male 17% Female IMRT 83.3% Male 16.7% Female	Not reported	All included patients were enrolled with Nonmetastatic T4 lesions	3DCRT 22.6% N0 32.1% N1 43.4% N2 1.9% N3 IMRT 10.0% N0 23.3% N1 63.3% N2 3.3% N3

Table B-2. Comparative study design and patient characteristics (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Age	Sex	AJCC stage	T classification	N classification
Lohia (2014)[13]	Comparative Retrospective (poor)	3DCRT (56) IMRT (103)	RT ± CCT	Oropharynx 100%	3DCRT Median 58.5 years (range 33-78 years) IMRT Median 58.5 years (range 37-82 years)	3DCRT 80.4% Male 19.6% Female IMRT 85.4% Male 14.6% Female	3DCRT 0% I 5% II 30% III 21% IV IMRT 0% I 11% II 65% III 27% IV	3DCRT 8.9% T1 35.7% T2 19.6% T3 28.6% T4a 7.1% T4b IMRT 10.7% T1 47.6% T2 21.4% T3 12.6% T4a 7.8% T4b	3DCRT 7.1% N0 19.6% N1 17.9% N2a 21.4% N2b 32.1% N2c 1.8% N3 IMRT 9.7% N0 9.7% N1 9.7% N2a 37.9% N2b 27.2% N2c 5.8% N3
Mok (2014)[14]	Comparative Retrospective (poor)	3DCRT (90) IMRT (91)	RT ± CCT	Hypopharynx 100%	3DCRT Median 62 years (range 43-84 years) IMRT Median 67 years (range 35-85 years)	3DCRT 84.0% Male 16.0% Female IMRT 81.0% Male 19.0% Female	Not reported	3DCRT 46% T1-T2 54% T3-T4 IMRT 38% T1-T2 62% T3-T4	3DCRT 58% N0-N2a 42% N2b-N3 IMRT 37% N0-N2a 63% N2b-N3

Table B-2. Comparative study design and patient characteristics (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Age	Sex	AJCC stage	T classification	N classification
Ozyigit (2011)[15]	Comparative Retrospective (poor)	3DCRT (27) SBRT (24)	rRT ± CCT	Nasopharynx 100%	Median 46 years (range 13-70 years) 3DCRT[b] 52% < 46 years 48% ≥ 46 years SBRT 42% < 46 years 58% ≥ 46 years	3DCRT[b] 78% Male 22% Female SBRT 63% Male 37% Female	3DCRT[b] 7% I (11% rI) 30% II (11% rII) 30% III (37% rIII) 33% IV (41% rIV) SBRT 8% I (21% rI) 17% II (8% rII) 46% III (25% rIII) 29% IV (46% rIV)	3DCRT[b] 30% TI (15% rT2) 18% T2 (7% rT2) 26% T3 (37% rT3) 26% T4 (41% rT4) SBRT 29% TI (21% rT1) 17% T2 (8% rT2) 29% T3 (25% rT3) 25% T4 (46% rT4)	Not reported

Abbreviations: AJCC = American Joint Commission on Cancer; CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; IMRT = intensity-modulated radiotherapy; RCT = randomized clinical trial; RT = radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

[a]No breakdown of the characteristic between treatment arms was provided.

[b]Six (22.2%) of patients in the 3DCRT treatment arm also received high-dose rate brachytherapy. As reported, these data do not reflect a discrimination between positive brachytherapy and negative brachytherapy subjects.

[c]No breakdown of the characteristic between RT regimen was provided, however, it was reported that there was no significant difference between treatment arms.

Table B-3. Summary of radiotherapy techniques

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Total RT dose	Fractionation schedule
Gupta (2012)[1]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	3DCRT 70 Gy IMRT 66 Gy GTV + margins 60 Gy HREV 54 Gy LREV	3DCRT 35 fx 2 Gy/fx 5 daily fx/week IMRT 30 fx 2.2 Gy/fx GTV 2.0 Gy/fx HREV 1.8 Gy/fx LREV 5 daily fx/week
Rathod (2013)[2]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	3DCRT 70 Gy IMRT 66 Gy GTV + margins 60 Gy HREV 54 Gy LREV	3DCRT 35 fx 2 Gy/fx 5 daily fx/week IMRT 30 fx 2.2 Gy/fx GTV 2.0 Gy/fx HREV 1.8 Gy/fx LREV 5 daily fx/week
Al-Mamgani (2013)[3]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx	70 Gy primary 70 Gy involved neck levels 46 Gy bilateral neck	3DCRT Not reported IMRT 46 Gy primary + bilateral neck 23 fx 2 Gy/fx 6 fx/week 24 Gy boost primary + involved neck 12 fx 2 Gy/fx 6 fx/week

Table B-3. Summary of radiotherapy techniques (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Total RT dose	Fractionation schedule
Lambrecht (2013)[4]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx	70 or 72 Gy >26 Gy parotid-sparing >50 Gy spinal cord <u>Median doses</u> 65 Gy (IQR 50-69 Gy) ipsilateral parotid 40 Gy (IQR 21-51 Gy) contralateral parotid	70 Gy conventional <u>72 Gy hybrid</u> 40 Gy - 20 fx - 2 Gy/fx/day + 32 Gy - 20 fx bid - 1.6 Gy/fx
Al-Mamgani (2012)[5]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx	70 Gy 46 Gy bilateral ENI to levels II, III, and IV if N0 <u>IMRT planning aim</u> >26 Gy parotid-sparing >39 Gy submandibular glands > 50 Gy constrictor muscles > 50 Gy spinal cord	35 fx 2 Gy/fx 6 fx/week

Table B-3. Summary of radiotherapy techniques (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Total RT dose	Fractionation schedule
Chen (2012)[6]	Comparative Retrospective (poor)	3DCRT (71) IMRT (84)	RT ± CCT	Hypopharynx Larynx Nasopharynx Oropharynx Unknown primary	66 Gy primary median (range 60-74 Gy) 60 Gy postoperative median (range 54-66 Gy) 70 Gy definitive median (range 66-74 Gy) <u>IMRT planning aim</u> >54 Gy brainstem/optic nerves >45 Gy spinal cord/optic chiasm >60 Gy temporal lobes >30 Gy 50% of contralateral parotid	Not reported
Al-Mamgani (2012)[7]	Comparative Retrospective (poor)	3DCRT (25) IMRT (57)	CCRT ± surgery	Paranasal sinus	66 Gy median (range 56-74 Gy) <u>3DCRT</u> 60-70 Gy <u>IMRT</u> 60-74 Gy	2 Gy/fx/day
Kruser (2013)[8]	Comparative Prospective (poor)	3DCRT (41) IMRT (137)	CCRT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Unknown primary	<u>3DCRT</u> Mean 69.8 Gy <u>IMRT</u> LINAC-IMRT: mean 69.2 Gy Tomotherapy: mean 68.4 Gy 70 Gy primary 60 Gy high-risk nodal PTV 54 Gy lower-risk PTV 50 Gy lowest-risk PTV	<u>3DCRT</u> Mean 39.2 fx <u>LINAC-IMRT</u> Mean 33.0 fx <u>Tomotherapy</u> Mean 32.4 fx

Table B-3. Summary of radiotherapy techniques (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Total RT dose	Fractionation schedule
Dirix (2010)[9]	Comparative Prospective IMRT Retrospective 3DCRT (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity Paranasal sinus	3DCRT 60 Gy (65.9%) or 66 Gy (34.1%) IMRT 60 Gy (52.5%) or 66 Gy (47.5%)	60 Gy 30 daily fx 2 Gy/fx 5 fx/week 66 Gy if + margins 30 daily fx 2 Gy/fx 5 fx/week + 2 Gy/fx/tid X 1 IMRT Underdosage tolerated for optic structures
Guan (2013)[10]	Comparative Retrospective (poor)	3DCRT (16) IMRT (43)	RT ± CCT ± surgery	Nasal cavity Paranasal sinus	66-70 Gy GTV 60-63 Gy CTV 66 Gy median for N+ patients (range 65-70 Gy) 60 Gy ENI median dose (range 60-66 Gy)	46 patients[a] 2 Gy/fx 5 fx/week 12 patients 2.2 Gy/fx 5 fx/week 1 patient 1.8 Gy/fx 5 daily fx/week
Kong (2013)[11]	Comparative Retrospective (poor)	3DCRT (30) IMRT (37)	RT ± CCT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Paranasal sinus	3DCRT 72.0 Gy median (range 72.0-84.0 Gy) IMRT 80.5 Gy median (range 67.1-88.9 Gy)	3DCRT Definitive RT • PTV1: 2 Gy/fx; 33-35 fx; 5 fx/week • PTV2: 2 Gy/fx; 25 fx Postoperative RT • PTV1: 2 Gy/fx; 30 fx[b] • PTV2: 2 Gy/fx; 25 fx IMRT Definitive RT • 1.8-2.25 Gy/fx/od • Total dose: 66-73.5 Gy Postoperative RT • PTV1: 1.8-2.2Gy/fx; 5 fx/week; total dose: 55.72.6 Gy • PTV2: 1.65-2.1 Gy/fx; total dose: 45-63 Gy

Table B-3. Summary of radiotherapy techniques (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Total RT dose	Fractionation schedule
Huang (2013)[12]	Comparative Retrospective (poor)	3DCRT (53) IMRT (30)	RT ± CCT	Nasopharynx	Not reported	Not reported
Lohia (2014)[13]	Comparative Retrospective (poor)	3DCRT (56) IMRT (103)	RT ± CCT	Oropharynx	3DCRT 50 Gy + 20 Gy boost IMRT 70 Gy (primary tumor and involved nodes) 56.0 to 58.1 Gy (at-risk nodes)	3DCRT 2 Gy/fx 1 fx/day 5 days/week IMRT 2 Gy/fx 1 fx/day X 35 5 days/week

Table B-3. Summary of radiotherapy techniques (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Total RT dose	Fractionation schedule
Mok (2014)[14]	Comparative Retrospective (poor)	3DCRT (90) IMRT (91)	RT ± CCT	Hypopharynx	3DCRT Conventional fractionation • 70 Gy CTV-HD • 60 Gy CTV-ID • 50 Gy CTV-ED Accelerated hyperfractionation • 64 Gy CTV-HD • 57.6 Gy CTV-ID • 44.8 Gy CTV-ED Hypofractionation • 60 Gy CTV-HD • 55.2 Gy CTV-ID • 43.2 Gy CTV-ED IMRT Conventional fractionation • 70 Gy CTV-HD • 63 Gy CTV-ID • 56 Gy CTV-ED Accelerated hyperfractionation • 64 Gy CTV-HD • 56 Gy CTV-ID • 46 Gy CTV-ED Hypofractionation • 60 Gy CTV-HD • 56 Gy CTV-ID • 50 Gy CTV-ED	Conventional fractionation 2 Gy/fx 5-6fx/week Accelerated hyperfractionation 1.6 Gy/fx/bid 10 fx/week Hypofractionation 2.4 Gy/fx X 25

Table B-3. Summary of radiotherapy techniques (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Total RT dose	Fractionation schedule
Ozyigit (2011)[15]	Comparative Retrospective (poor)	3DCRT (27) SBRT (24)	rRT ± CCT	Nasopharynx	3DCRT 67.4 Gy primary median (range 59.4-70 Gy) 57 Gy rRT median (range 30-61 Gy) 3DCRT + brachytherapy 67.4 Gy primary median (range 59.4-70 Gy) 57 Gy rRT median (range 30-61 Gy) 16 Gy brachytherapy SBRT 70 Gy primary median (range 48-70 Gy) 39 Gy rRT median (range 36-50 Gy)	3DCRT 2 Gy/fx/day 3DCRT + brachytherapy 2 Gy/fx/day 4 Gy daily Brachytherapy fx × 4 days SBRT 30 Gy over 5 consecutive days Remaining dose fractionation not reported

Abbreviations: CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; CTV = clinical target volume; ED = elective dose; ENI = elective neck irradiation; GTV = gross tumor volume; HD = high-dose; HREV = high-risk elective volume; ID = intermediate-dose; IMRT = intensity-modulated radiotherapy; IQR = interquartile range; LREV = low-risk elective volume; PTV = planning treatment volume; RCT = randomized clinical trial; rRT = reirradiation; RT = radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

[a]Differentiation between patients according to treatment arm is not reported.

[b]In the case of residual disease, 66-70 Gy was given 2 Gy/fx, 33-35 fx.

Table B-4. Key acute (< 90 days posttreatment) toxicities

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dermatitis	Dysphagia	Mucositis	Nausea	Pain	Salivary glands	Weight loss
Gupta (2012)[1]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	Grade 2 3DCRT:78.5% IMRT: 88% Grade 3 3DCRT: 18% IMRT: 6% p=0.35	Grade 2 3DCRT:71.5% IMRT: 50% Grade 3 3DCRT: 0% IMRT: 9.5% p=0.21	Grade 2 3DCRT: 78.5% IMRT: 71% Grade 3 3DCRT:14.5% IMRT: 6% p=0.20	Not reported	Not reported	Grade 2 3DCRT: 89% IMRT: 59% p=0.03	No loss 3DCRT: 7% IMRT: 9.5% < 10% Loss 3DCRT: 57% IMRT: 75% ≥ 10% Loss 3DCRT: 36% IMRT:15.5% p=0.2
Rathod (2013)[2]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Al-Mamgani (2013)[3]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx	Grade ≥ 2 3DCRT: 52% IMRT: 50% p=0.8 Grade 3 3DCRT: 51% IMRT: 45% p=0.5	Grade ≥ 2 3DCRT: 100% IMRT: 90% p=0.008 Grade 3 3DCRT: 72% IMRT: 49% p=0.04	Grade ≥ 2 3DCRT: 88% IMRT: 80% p=0.4 Grade 3 3DCRT: 82% IMRT: 68% p=0.07	Not reported	Grade ≥ 2 3DCRT: 60% IMRT: 45% p=0.04 Grade 3 3DCRT: 52% IMRT: 32% p=0.007	Not reported	Not reported
Lambrecht (2013)[4]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx	Not reported	Grade ≥ 3 3DCRT: 78% IMRT: 73% p=*ns*	Grade ≥ 3 3DCRT: 44% IMRT: 32% p=0.03	Not reported	Not reported	Not reported	Not reported

Table B-4. Key acute (< 90 days posttreatment) toxicities (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dermatitis	Dysphagia	Mucositis	Nausea	Pain	Salivary glands	Weight loss
Al-Mamgani (2012)[5]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx	Grade 2 3DCRT: 37% IMRT: 43% p= 0.4 Grade 3 3DCRT: 63% IMRT: 42% p=0.008	Grade 2 3DCRT: 42% IMRT: 52% p=0.1 Grade 3 3DCRT: 47% IMRT: 36% p=0.06	Grade 2 3DCRT: 40% IMRT: 46% p=0.4 Grade 3 3DCRT: 56% IMRT: 39% p=002	Not reported	Grade 2 3DCRT: 32% IMRT: 35% p=0.7 Grade 3 3DCRT: 50% IMRT: 32% p=0.01	Not reported	Not reported
Chen (2012)[6]	Comparative Retrospective (poor)	3DCRT (71) IMRT (84)	RT ± CCT	Hypopharynx Larynx Nasopharynx Oropharynx Unknown primary	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Al-Mamgani (2012)[7]	Comparative Retrospective (poor)	3DCRT (25) IMRT (57)	CCRT ± surgery	Paranasal sinus	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table B-4. Key acute (< 90 days posttreatment) toxicities (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dermatitis	Dysphagia	Mucositis	Nausea	Pain	Salivary glands	Weight loss
Kruser (2013)[8]	Comparative Prospective (poor)	3DCRT (41) IMRT (137)	CCRT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Unknown primary	Not reported	Not reported	3DCRT Mean grade: 2.7 IMRT Mean grade: 2.55 p=0.20 Oropharynx patients 3DCRT Grade 2: 12.5% 3DCRT Grade 3: 83.3% IMRT Grade 2: 34% IMRT Grade 3: 65% p=0.149	Not reported	Not reported	Not reported	Not reported
Dirix (2010)[9]	Comparative Prospective IMRT Retrospective 3DCRT (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity Paranasal sinus	3DCRT Any grade: 97.6% IMRT Grade 2:7.5% p=0.003	3DCRT Any grade: 34.1% IMRT Grade 2: 2.5% p=0.25	3DCRT Any grade: 97.6% IMRT Grade 2: 12.5% p<0.001	Not reported	3DCRT Any grade: 82.9% IMRT Grade 2: 10.0% p=0.02	3DCRT Any grade: 90.2% IMRT Grade 2: 0.0% p<0.001	Not reported
Guan (2013)[10]	Comparative Retrospective (poor)	3DCRT (16) IMRT (43)	RT ± CCT ± surgery	Nasal cavity Paranasal sinus	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table B-4. Key acute (< 90 days posttreatment) toxicities (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dermatitis	Dysphagia	Mucositis	Nausea	Pain	Salivary glands	Weight loss
Kong (2013)[11]	Comparative Retrospective (poor)	3DCRT (30) IMRT (37)	RT ± CCT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Paranasal sinus	Not reported	3DCRT Grade 1: 16% Grade 2: 41% Grade 3: 43% IMRT Grade 0: 3% Grade 1: 17% Grade 2: 40% Grade 3: 40%	3DCRT Grade 1: 16% Grade 2: 32% Grade 3: 51% IMRT Grade 1: 13% Grade 2: 37% Grade 3: 50%	Not reported	Not reported	3DCRT Grade 1: 54% Grade 2: 32% Grade 3: 14% IMRT Grade 0: 3% Grade 1: 30% Grade 2: 50% Grade 3: 17%	Not reported
Huang (2013)[12]	Comparative Retrospective (poor)	3DCRT (53) IMRT (30)	RT ± CCT	Nasopharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Lohia (2014)[13]	Comparative Retrospective (poor)	3DCRT (56) IMRT (103)	RT ± CCT	Oropharynx	Grade ≥ 3 3DCRT: 23% IMRT: 7% p=0.02	Not reported	Grade ≥ 3 3DCRT: 76% IMRT: 37% p<0.001	Not reported	Not reported	*ns*	Mean (kg) 3DCRT: 8.4 IMRT: 8.1 p=0.86
Mok (2014)[14]	Comparative Retrospective (poor)	3DCRT (90) IMRT (91)	RT ± CCT	Hypopharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Ozyigit (2011)[15]	Comparative Retrospective (poor)	3DCRT (27) SBRT (24)	rRT ± CCT	Nasopharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Abbreviations: CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; kg = kilogram; IMRT = intensity-modulated radiotherapy; *ns* = not significant; RCT = randomized clinical trial; rRT = reirradiation; RT = radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

Table B-5. Key late toxicities

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dysphagia	Mucosal	Pain	Skin	Subcutaneous	Xerostomia
Gupta (2012)[1]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	Not reported	Not reported	Not reported	Not reported	Grade ≥ 2 at 6 months 3DCRT: 64% IMRT: 17% p<0.001 Grade ≥ 2 at 12 months 3DCRT: 67% IMRT: 11% P<0.001 Grade ≥ 2 at 18 months 3DCRT: 53% IMRT: 13% p=0.004 Grade ≥ 2 at 24 months 3DCRT: 59% IMRT: 14% p=0.005 Grade ≥ 2 at 30 months 3DCRT: 50% IMRT: 0% p=0.001 Grade ≥ 2 at 36 months 3DCRT: 45% IMRT: 15% p=0.079	Grade ≥ 2 at 6 months 3DCRT: 77% IMRT: 33% p=0.001 Grade ≥ 2 at 12 months 3DCRT: 75% IMRT: 31% p=0.001 Grade ≥ 2 at 18 months 3DCRT: 69% IMRT: 19% p=0.001 Grade ≥ 2 at 24 months 3DCRT: 59% IMRT: 22% p=0.014 Grade ≥ 2 at 30 months 3DCRT: 65% IMRT: 6% p=0.003 Grade ≥ 2 at 36 months 3DCRT: 60% IMRT: 0% p=0.003
Rathod (2013)[2]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table B-5. Key late toxicities (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dysphagia	Mucosal	Pain	Skin	Subcutaneous	Xerostomia
Al-Mamgani (2013)[3]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx	Grade ≥ 2 3DCRT: 30% IMRT: 20% p=0.04 Grade 3 3DCRT: 20% IMRT: 10% p=0.03	Grade ≥ 2 3DCRT: 20% IMRT: 10% p=0.04 Grade 3 3DCRT: 11% IMRT: 2% p=0.04	Grade ≥ 2 3DCRT: 11% IMRT: 11% p=0.6 Grade 3 3DCRT: 3% IMRT: 5% p=0.9	Grade ≥ 2 3DCRT:8% IMRT: 6% p=0.6 Grade 3 3DCRT:5% IMRT: 2% p=0.3	Grade ≥ 2 3DCRT: 2% IMRT: 7% p=0.1 Grade 3 3DCRT: 2% IMRT: 1% p=0.7	Grade ≥ 2 3DCRT: 49% IMRT: 26% p=0.001 Grade 3 3DCRT: 23% IMRT: 7% p=0.002
Lambrecht (2013)[4]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx	Grade ≥ 2 at 6 months 3DCRT: 34% IMRT: 38% p=0.3 Grade ≥ 2 at 12 months 3DCRT: 28% IMRT: 21% p=*ns* Grade ≥ 2 at 18 months 3DCRT: 22% IMRT: 13% p=*ns* Grade ≥ 2 at 24 months 3DCRT: 21% IMRT: 11% p=0.08	Not reported	Not reported	Not reported	Not reported	Grade ≥ 2 3DCRT: 68% IMRT: 23% p<0.001
Al-Mamgani (2012)[5]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx	Grade 2 3DCRT: 23% IMRT: 14% p=0.1 Grade 3 3DCRT: 10% IMRT: 1% p=0.02	Grade 2 3DCRT: 13% IMRT: 10% p=0.5 Grade 3 3DCRT: 8% IMRT: 1% p=0.02	Grade 2 3DCRT: 10% IMRT: 4% p=0.09 Grade 3 3DCRT: 3% IMRT: 0% p=0.1	Grade 2 3DCRT: 10% IMRT: 10% p=0.9 Grade 3 3DCRT: 6% IMRT: 1% p=0.06	Grade 2 3DCRT: 21% IMRT: 10% p=0.03 Grade 3 3DCRT: 8% IMRT: 2% p=0.09	Grade 2 3DCRT: 24% IMRT: 11% p=0.009 Grade 3 3DCRT: 8% IMRT: 2% p=0.02

Table B-5. Key late toxicities (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dysphagia	Mucosal	Pain	Skin	Subcutaneous	Xerostomia
Chen (2012)[6]	Comparative Retrospective (poor)	3DCRT (71) IMRT (84)	RT ± CCT	Hypopharynx Larynx Nasopharynx Oropharynx Unknown primary	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Al-Mamgani (2012)[7]	Comparative Retrospective (poor)	3DCRT (25) IMRT (57)	CCRT ± surgery	Paranasal sinus	Grade ≥ 2 3DCRT: 12% IMRT: 5.3%	Not reported	Not reported	Not reported	Not reported	Grade ≥ 2 3DCRT: 16% IMRT: 7%
Kruser (2013)[8]	Comparative Prospective (poor)	3DCRT (41) IMRT (137)	CCRT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Unknown primary	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Dirix (2010)[9]	Comparative Prospective IMRT Retrospective 3DCRT (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity Paranasal sinus		3DCRT Any grade: 73.7% IMRT Grade 0: 69.2% Grade 1: 25.6% Grade 2: 5.1% p<0.001	HEADACHE 3DCRT Not scored IMRT Grade 0: 64.1% Grade 1: 28.2% Grade 2: 7.7%	3DCRT Any grade: 73.7% IMRT Grade 0: 92.3% Grade 1: 5.1% Grade 2: 2.6% p=0.05		3DCRT Any grade: 34.2% IMRT Grade 0: 87.2% Grade 1: 12.8% Grade : 0% p=0.03
Guan (2013)[10]	Comparative Retrospective (poor)	3DCRT (16) IMRT (43)	RT ± CCT ± surgery	Nasal cavity Paranasal sinus	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table B-5. Key late toxicities (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Dysphagia	Mucosal	Pain	Skin	Subcutaneous	Xerostomia
Kong (2013)[11]	Comparative Retrospective (poor)	3DCRT (30) IMRT (37)	RT ± CCT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Paranasal sinus	3DCRT Grade 0: 35% Grade 1: 11% Grade 2: 43% Grade 3: 11% IMRT Grade 0: 43% Grade 1: 33% Grade 2: 13% Grade 3: 10%	Not reported	Not reported	Not reported	Not reported	3DCRT Grade 1: 5% Grade 2: 70% Grade 3: 24% IMRT Grade 1: 60% Grade 2: 30% Grade 3: 10%
Huang (2013)[12]	Comparative Retrospective (poor)	3DCRT (53) IMRT (30)	RT ± CCT	Nasopharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Lohia (2014)[13]	Comparative Retrospective (poor)	3DCRT (56) IMRT (103)	RT ± CCT	Oropharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Mok (2014)[14]	Comparative Retrospective (poor)	3DCRT (90) IMRT (91)	RT ± CCT	Hypopharynx	Not reported[a]	Not reported	Not reported	Not reported	Not reported	Not reported
Ozyigit (2011)[15]	Comparative Retrospective (poor)	3DCRT (27) SBRT (24)	rRT ± CCT	Nasopharynx	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Abbreviations: CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; IMRT = intensity-modulated radiotherapy; RCT = randomized clinical trial; rRT = reirradiation; RT = radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

[a]Late toxicities were reported in aggregate, with no distinction between specific toxicities. There was no statistical difference between arms as it pertains to ≥ grade 3 toxicity (p=.174)

Table B-6. Key oncologic outcomes

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Overall survival	Disease-free survival	Local control	Loco-regional control	Distant control
Gupta (2012)[1]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	3-year Kaplan-Meier estimate 3DCRT: 88.2% (95% CI 75.4 to 100%) IMRT: 80.5% (95% CI 66.1 to 94.9%) p=0.45	Not reported	Not reported	3-year Kaplan-Meier estimate 3DCRT: 70.6% (95% CI 53 to 88.2%) IMRT: 68% (95% CI 51.2 to 84.8%) p=0.81	Not reported
Rathod (2013)[2]	RCT (fair)	3DCRT (28) IMRT (32)	CCRT	Hypopharynx Larynx Oropharynx	3-year Kaplan-Meier estimate 3DCRT: 88.2% (95% CI 75.4 to 100%) IMRT: 80.5% (95% CI 66.1 to 94.9%) p=0.45	Not reported	Not reported	3-year Kaplan-Meier estimate 3DCRT: 70.6% (95% CI 53 to 88.2%) IMRT: 68% (95% CI 51.2 to 84.8%) p=0.81	Not reported
Al-Mamgani (2013)[3]	Comparative Retrospective (poor)	3DCRT (65) IMRT (139)	CCRT	Oropharynx	5-year Kaplan-Meier estimate 3DCRT: 43% IMRT: 47% p=0.40	5-year Kaplan-Meier estimate 3DCRT: 58% IMRT: 60% p=0.73	5-year Kaplan-Meier estimate 3DCRT: 74% IMRT: 82% p=0.19	Not reported	Not reported
Lambrecht (2013)[4]	Comparative Retrospective (poor)	3DCRT (135) IMRT (110)	CCRT	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx	3-year Kaplan-Meier estimate 3DCRT: 61% IMRT: 64% p=0.5	Not reported	Not reported	3-year Kaplan-Meier estimate 3DCRT: 71% IMRT: 70% p=0.7	Not reported
Al-Mamgani (2012)[5]	Comparative Retrospective (poor)	3DCRT (62) IMRT (114)	RT ± CCT	Hypopharynx	Not reported	Not reported	Not reported	Not reported	Not reported

Table B-6. Key oncologic outcomes (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Overall survival	Disease-free survival	Local control	Loco-regional control	Distant control
Chen (2012)[6]	Comparative Retrospective (poor)	3DCRT (71) IMRT (84)	RT ± CCT	Hypopharynx Larynx Nasopharynx Oropharynx Unknown primary	Not reported	Not reported	Not reported	Not reported	Not reported
Al-Mamgani (2012)[7]	Comparative Retrospective (poor)	3DCRT (25) IMRT (57)	CCRT ± surgery	Paranasal sinus	Not reported	Not reported	IMRT vs. 3DCRT local failure p=0.2 Median time to recurrence = 12 months (range 5-112)	Not reported	Not reported
Kruser (2013)[8]	Comparative Prospective (poor)	3DCRT (41) IMRT (137)	CCRT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Unknown primary	Not reported	Not reported	Not reported	Not reported	Not reported
Dirix (2010)[9]	Comparative Prospective IMRT Retrospective 3DCRT (poor)	3DCRT (41) IMRT (40)	Postoperative RT	Nasal cavity Paranasal sinus	2-year Kaplan-Meier estimate 3DCRT: 73% IMRT: 89% p=0.07	2-year Kaplan-Meier estimate 3DCRT: 60% IMRT: 72% p=0.02	2-year Kaplan-Meier estimate 3DCRT: 67% IMRT: 76% p=0.06	Not reported	2-year Kaplan-Meier estimate 3DCRT: 89% IMRT: 89% p=0.68
Guan (2013)[10]	Comparative Retrospective (poor)	3DCRT (16) IMRT (43)	RT ± CCT ± surgery	Nasal cavity Paranasal sinus	Not reported	Not reported	Not reported	Regional relapse 3DCRT: 15.4% IMRT: 16.1% Neck recurrence in N0 necks 3DCRT: 7.7% IMRT: 16.1% p=0.109	Not reported

Table B-6. Key oncologic outcomes (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Overall survival	Disease-free survival	Local control	Loco-regional control	Distant control
Kong (2013)[11]	Comparative Retrospective (poor)	3DCRT (30) IMRT (37)	RT ± CCT ± surgery	Hypopharynx Larynx Nasopharynx Oral cavity Oropharynx Paranasal sinus	Kaplan-Meier estimate 3DCRT 1-year: 94% 2-year: 87% IMRT 1-year: 97% 2-year: 97% p=0.095	Not reported	Not reported	Kaplan-Meier estimate 3DCRT 1-year: 61% 2-year: 58% IMRT 1-year: 89% 2-year: 80% p=0.029	Kaplan-Meier estimate 3DCRT 1-year: 86% 2-year: 82% IMRT 1-year: 92% 2-year: 75% p=0.994
Huang (2013)[12]	Comparative Retrospective (poor)	3DCRT (53) IMRT (30)	RT ± CCT	Nasopharynx	5-year Kaplan-Meier estimate 3DCRT: 58.2% IMRT: 88.9% p=0.004	5-year Kaplan-Meier estimate 3DCRT: 47.2% IMRT: 69.2% p=0.046	Not reported	5-year Kaplan-Meier estimate 3DCRT: 54.4% IMRT: 75.2% p=0.018	Not reported
Lohia (2014)[13]	Comparative Retrospective (poor)	3DCRT (56) IMRT (103)	RT ± CCT	Oropharynx	2-year Kaplan-Meier estimate 3DCRT: 58% IMRT: 35% p=0.45	2-year Kaplan-Meier estimate 3DCRT: 66% IMRT: 59% *ns* Comparative disease recurrence Hazard ratio: 0.82 (95% CI 0.47-1.41)	Not reported	Not reported	Not reported

Table B-6. Key oncologic outcomes (continued)

Study (year)	Study design (USPSTF rating)	RT modalities (n)	Treatment setting	Tumor setting	Overall survival	Disease-free survival	Local control	Loco-regional control	Distant control
Mok (2014)[14]	Comparative Retrospective (poor)	3DCRT (90) IMRT (91)	RT ± CCT	Hypopharynx	3-year Kaplan-Meier estimate 3DCRT: 52% (95% CI 41 to 62%) IMRT: 50% (95% CI 40 to 60%) p=0.99	Not reported	Not reported	3-year cumulative incidence proportion 3DCRT: 58% (95% CI 48 to 68%) IMRT: 75% (95% CI 65 to 84%) p=0.003	3-year cumulative incidence proportion 3DCRT: 80% IMRT: 77% p=0.79
Ozyigit (2011)[15]	Comparative Retrospective (poor)	3DCRT (27) SBRT (24)	rRT ± CCT	Nasopharynx	Not reported 22% of patients in the 3DCRT arm received concurrent brachytherapy	Not reported 22% of patients in the 3DCRT arm received concurrent brachytherapy	Not reported 22% of patients in the 3DCRT arm received concurrent brachytherapy	Not reported 22% of patients in the 3DCRT arm received concurrent brachytherapy	Not reported 22% of patients in the 3DCRT arm received concurrent brachytherapy

Abbreviations: CCT = concurrent chemotherapy; CCRT = concurrent chemoradiotherapy; IMRT = intensity-modulated radiotherapy; RCT = randomized clinical trial; rRT = reirradiation; RT = radiotherapy; SBRT = stereotactic body radiotherapy; 3DCRT = three-dimensional conformal radiotherapy; USPSTF = United States Preventive Services Task Force.

References Cited in Appendix B

1. Gupta, T., et al., Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. Radiother Oncol, 2012. 104(3): p. 343-8.
2. Rathod, S., et al., Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. Oral Oncol, 2013. 49(6): p. 634-42.
3. Al-Mamgani, A., et al., The impact of treatment modality and radiation technique on outcomes and toxicity of patients with locally advanced oropharyngeal cancer. Laryngoscope, 2013. 123(2): p. 386-93.
4. Lambrecht, M., D. Nevens, and S. Nuyts, Intensity-modulated radiotherapy vs. parotid-sparing 3D conformal radiotherapy. Effect on outcome and toxicity in locally advanced head and neck cancer. Strahlenther Onkol, 2013. 189(3): p. 223-9.
5. Al-Mamgani, A., et al., Toxicity, quality of life, and functional outcomes of 176 hypopharyngeal cancer patients treated by (chemo)radiation: the impact of treatment modality and radiation technique. Laryngoscope, 2012. 122(8): p. 1789-95.
6. Chen, A.M., et al., Intensity-modulated radiotherapy is associated with improved global quality of life among long-term survivors of head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2012. 84(1): p. 170-5.
7. Al-Mamgani, A., et al., Highly-conformal intensity-modulated radiotherapy reduced toxicity without jeopardizing outcome in patients with paranasal sinus cancer treated by surgery and radiotherapy or (chemo)radiation. Oral Oncol, 2012. 48(9): p. 905-11.
8. Kruser, T.J., et al., Acute hematologic and mucosal toxicities in head and neck cancer patients undergoing chemoradiotherapy: A comparison of 3D-CRT, IMRT, and helical tomotherapy. Technology in Cancer Research and Treatment, 2013. 12(5): p. 383-389.
9. Dirix, P., et al., Intensity-modulated radiotherapy for sinonasal cancer: Improved outcome compared to conventional radiotherapy. International Journal of Radiation Oncology Biology Physics, 2010. 78(4): p. 998-1004.
10. Guan, X., et al., Lymph node metastasis in sinonasal squamous cell carcinoma treated with IMRT/3D-CRT. Oral Oncology, 2013. 49(1): p. 60-65.
11. Kong, M., et al., Comparison of survival rates between patients treated with conventional radiotherapy and helical tomotherapy for head and neck cancer. Radiation Oncology Journal, 2013. 31(1): p. 1-11.
12. Huang, H.I., et al., T4-locally advanced nasopharyngeal carcinoma: prognostic influence of cranial nerve involvement in different radiotherapy techniques. ScientificWorldJournal, 2013. 2013: p. 439073.
13. Lohia, S., et al., A comparison of outcomes using intensity-modulated radiation therapy and 3-dimensional conformal radiation therapy in treatment of oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg, 2014. 140(4): p. 331-7.
14. Mok, G., et al., Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head Neck, 2014.
15. Ozyigit, G., et al., A retrospective comparison of robotic stereotactic body radiotherapy and three-dimensional conformal radiotherapy for the reirradiation of locally recurrent nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics, 2011. 81(4): p. e263-e268.

Appendix C. Summary of Reasons for Study Exclusion at the Level of Full-Text Review

Citation	Reason for exclusion
A. Al-Mamgani, P. Van Rooij, L. Tans, D. N. Teguh and P. C. Levendag. Toxicity and outcome of intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy for oropharyngeal cancer: a matched-pair analysis. Technol Cancer Res Treat. 2013. 12:123-30	Nonrelevant Study Design
A. Al-Mamgani, P. Van Rooij, R. Mehilal, L. Tans and P. C. Levendag. Combined-modality treatment improved outcome in sinonasal undifferentiated carcinoma: Single-institutional experience of 21 patients and review of the literature. European Archives of Oto-Rhino-Laryngology. 2013. 270:293-299	Nonrelevant Study Design
A. B. Miah, S. L. Gulliford, C. H. Clark, S. A. Bhide, S. H. Zaidi, K. L. Newbold, K. J. Harrington and C. M. Nutting. Does-response of parotid gland function Dose-response analysis of parotid gland function: What is the best measure of xerostomia?. Radiotherapy and Oncology. 2013. 106:341-345	Nonrelevant Study Design
A. Birnbaum, T. Dipetrillo, R. Rathore, E. Anderson, H. Wanebo, Y. Puthwala, D. Joyce, H. Safran, D. Henderson, T. Kennedy, N. Ready and T. T. W. Sio. Cetuximab, paclitaxel, carboplatin, and radiation for head and neck cancer: A toxicity analysis. American Journal of Clinical Oncology: Cancer Clinical Trials. 2010. 33:144-147	Nonrelevant Study Design
A. C. Houweling, M. E. P. Philippens, T. Dijkema, J. M. Roesink, C. H. J. Terhaard, C. Schilstra, R. K. Ten Haken, A. Eisbruch and C. P. J. Raaijmakers. A Comparison of Dose-Response Models for the Parotid Gland in a Large Group of Head-and-Neck Cancer Patients. International Journal of Radiation Oncology Biology Physics. 2010. 76:1259-1265	Nonrelevant Study Design
A. C. Tiong, S. Huang, B. O'Sullivan, W. Xu, J. Kim, L. A. Dawson, J. Cho, R. Gilbert, S. Breen and J. N. Waldron. Outcomes For T2N0M0 glottic squamous cell carcinoma treated with IMRT compared with conventional parallel opposed fields. International Journal of Radiation Oncology Biology Physics. 2011. 81:S106-S107	Abstract Only
A. D. Jensen, J. Krauss, W. Weichert, Z. P. Bergmann, K. Freier, J. Debus and M. W. Munter. Disease control and functional outcome in three modern combined organ preserving regimens for locally advanced squamous cell carcinoma of the head and neck (SCCHN). Radiation Oncology. 2011. 6:#pages#	Nonrelevant Study Design
A. Eisbruch, H. M. Kim, F. Y. Feng, T. H. Lyden, M. J. Haxer, M. Feng, F. P. Worden, C. R. Bradford, M. E. Prince, J. S. Moyer, G. T. Wolf, D. B. Chepeha and R. K. Ten Haken. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: Swallowing organs later complication probabilities and dosimetric correlates. Dysphagia. 2012. 27:439	Abstract Only
A. Eisbruch, H. M. Kim, J. E. Terrell, L. H. Marsh, L. A. Dawson and J. A. Ship. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001. 50:695-704	Included in Original CER
A. Eisbruch, J. A. Ship, L. A. Dawson, H. M. Kim, C. R. Bradford, J. E. Terrell, D. B. Chepeha, T. N. Teknos, N. D. Hogikyan, Y. Anzai, L. H. Marsh, R. K. Ten Haken and G. T. Wolf. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. World J Surg. 2003. 27:832-7	Nonrelevant Study Design
A. Eisbruch, L. A. Dawson, H. M. Kim, C. R. Bradford, J. E. Terrell, D. B. Chepeha, T. N. Teknos, Y. Anzai, L. H. Marsh, M. K. Martel, R. K. Ten Haken, G. T. Wolf and J. A. Ship. Conformal and intensity modulated irradiation of head and neck cancer: the potential for improved target irradiation, salivary gland function, and quality of life. Acta Otorhinolaryngol Belg. 1999. 53:271-5	Nonrelevant Study Design
A. Eisbruch, L. H. Marsh, L. A. Dawson, C. R. Bradford, T. N. Teknos, D. B. Chepeha, F. P. Worden, S. Urba, A. Lin, M. J. Schipper and G. T. Wolf. Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol Biol Phys. 2004. 59:28-42	Nonrelevant Disease

Citation	Reason for exclusion
A. Eisbruch, P. C. Levendag, F. Y. Feng, D. Teguh, T. Lyden, P. I. Schmitz, M. Haxer, I. Noever, D. B. Chepeha and B. J. Heijmen. Can IMRT or brachytherapy reduce dysphagia associated with chemoradiotherapy of head and neck cancer? The Michigan and Rotterdam experiences. Int J Radiat Oncol Biol Phys. 2007. 69:S40-2	Nonprimary Data
A. Eisbruch, R. K. Ten Haken, H. M. Kim, L. H. Marsh and J. A. Ship. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys. 1999. 45:577-87	Nonrelevant Study Design
A. Eisbruch. Intensity-modulated radiotherapy of head-and-neck cancer: encouraging early results. Int J Radiat Oncol Biol Phys. 2002. 53:1-3	Nonprimary Data
A. I. Blanco, K. S. Chao, I. El Naqa, G. E. Franklin, K. Zakarian, M. Vicic and J. O. Deasy. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. Int J Radiat Oncol Biol Phys. 2005. 62:1055-69	Nonrelevant Study Design
A. Kovacs, G. Antal, C. S. Glavak, J. Hadjiev, G. Liposits, C. S. Vandulek, F. Lakosi, R. C. Colen and I. Repa. Treatment of head-neck cancer patients using conpas technique. 2 years follow up results. Radiotherapy and Oncology. 2012. 103:S455-S456	Abstract Only
A. Kumar, E. Shih, N. Woody, S. A. Koyfman, J. P. Saxton, C. P. Rodriguez, D. J. Adelstein, P. Xia and J. F. Greskovich. A dosimetric correlation of radiation dose and early grade 3 dysphagia in oropharyngeal cancer patients: A comparison of conventional and IMRT plans. International Journal of Radiation Oncology Biology Physics. 2011. 81:S499	Abstract Only
A. Kumar, T. Bledsoe, A. Noble, Q. Shang, J. P. Saxton, C. Rodriguez, D. J. Adelstein, S. A. Koyfman, P. Xia and J. F. Greskovich. A dosimetric analysis of imrt versus 3D planning and its impact on acute grade 3 dysphagia and xerostomia in oropharyngeal cancer patients treated with chemoradiation therapy. International Journal of Radiation Oncology Biology Physics. 2012. 84:S477	Abstract Only
A. Lee. The battle against nasopharyngeal cancer. Radiotherapy and Oncology. 2012. 103:S198	Abstract Only
A. Ligey, J. Gentil, G. Crehange, X. Montbarbon, P. Pommier, K. Peignaux, G. Truc and P. Maingon. Impact of target volumes and radiation technique on loco-regional control and survival for patients with unilateral cervical lymph node metastases from an unknown primary. Radiotherapy and Oncology. 2009. 93:483-487	Nonrelevant Disease
A. M. Allen, T. Pawlicki, L. Dong, E. Fourkal, M. Buyyounouski, K. Cengel, J. Plastaras, M. K. Bucci, T. I. Yock, L. Bonilla, R. Price, E. E. Harris and A. A. Konski. An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee. Radiotherapy and Oncology. 2012. 103:8-11	Nonprimary Data
A. M. Chen, B. Q. Li, D. G. Farwell, J. Marsano, S. Vijayakumar and J. A. Purdy. Improved dosimetric and clinical outcomes with intensity-modulated radiotherapy for head-and-neck cancer of unknown primary origin. International Journal of Radiation Oncology Biology Physics. 2011. 79:756-762	Nonrelevant Study Design
A. M. Chen, D. G. Farwell, D. H. Lau, B. Q. Li, Q. Luu and P. J. Donald. Radiation therapy in the management of head-and-neck cancer of unknown primary origin: How does the addition of concurrent chemotherapy affect the therapeutic ratio?. International Journal of Radiation Oncology Biology Physics. 2011. 81:346-352	Nonrelevant Study Design
A. M. Chen, D. G. Farwell, Q. Luu, L. M. Chen, S. Vijayakumar and J. A. Purdy. Misses and near-misses after postoperative radiation therapy for head and neck cancer: Comparison of IMRT and non-IMRT techniques in the CT-simulation era. Head and Neck. 2010. 32:1452-1459	Nonrelevant Study Design
A. M. Chen, W. H. Hall, J. Li, L. Beckett, D. G. Farwell, D. H. Lau and J. A. Purdy. Brachial plexus-associated neuropathy after high-dose radiation therapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012. 84:165-9	Nonrelevant Study Design
A. Miah, S. Gulliford, S. Bhide, K. Newbold, K. Harrington and C. Nutting. Dose volume histogram atlases of xerostomia incidence: An alternative predictor of recovery of salivary function. Radiotherapy and Oncology. 2011. 98:S27-S28	Abstract Only
A. Miah, S. Gulllford, K. Harrington, S. Bhlde, K. Newbold and C. Nutting. Recovery of salivary gland toxicity: Contralateral parotid gland (PG) versus bilateral superficial lobes parotid sparing IMRT (parsport versus parsport II). Radiotherapy and Oncology. 2011. 99:S211	Abstract Only

Citation	Reason for exclusion
A. Popovtzer, I. Gluck, D. B. Chepeha, T. N. Teknos, J. S. Moyer, M. E. Prince, C. R. Bradford and A. Eisbruch. The Pattern of Failure After Reirradiation of Recurrent Squamous Cell Head and Neck Cancer: Implications for Defining the Targets. International Journal of Radiation Oncology Biology Physics. 2009. 74:1342-1347	Nonrelevant Study Design
A. Ruiz, R. D'Ambrosi, A. Castano, R. De Juan, P. Cotrina, P. Sarandeses, S. Guardado, J. Perez-Regadera, M. Colmenero and E. Lanzos. Prediction of early response to radiation therapy using FDG-PET standard uptake value. Radiotherapy and Oncology. 2012. 103:S462-S463	Abstract Only
A. Turaka, L. Tianyu, A. D. Cohen, B. Pro, M. Millenson, V. Robu, T. I. Al-Saleem and M. R. Smith. Results of radiation therapy for primary extranodal lymphoma of the head and neck: A report of case series. Blood. 2011. 118:#pages#	Abstract Only
A. Turaka, T. Li, M. M. Millenson and M. R. Smith. Results of radiation therapy for primary extranodal lymphoma of the head and neck: A report of case series. International Journal of Radiation Oncology Biology Physics. 2012. 84:S621	Abstract Only
A. Turaka, T. Li, N. Nicolaou, M. N. Lango, B. Burtness, E. M. Horwitz, J. A. Ridge and S. J. Feigenberg. Use of a conventional Low Neck Field (LNF) and intensity-modulated radiotherapy (IMRT): No clinical detriment of IMRT to an anterior LNF during the treatment of Head-and neck-cancer. International Journal of Radiation Oncology Biology Physics. 2011. 79:65-70	Nonrelevant Study Design
A. W. Chan, S. M. McBride, M. Cianchetti, P. M. Busse, N. N. Ali and J. J. Wang. Tobacco smoking during radiation treatment predicts for decreased survival in patients with oropharyngeal Carcinoma. International Journal of Radiation Oncology Biology Physics. 2011. 81:S487	Abstract Only
A. W. Lee, W. T. Ng, L. L. Chan, W. M. Hung, C. C. Chan, H. C. Sze, O. S. Chan, A. T. Chang and R. M. Yeung. Evolution of treatment for nasopharyngeal cancer - Success and setback in the intensity-modulated radiotherapy era. Radiother Oncol. 2014. 110:377-84	Nonrelevant Study Design
A. W. M. Lee, W. T. Ng, L. K. Chan, O. S. H. Chan, W. M. Hung, C. C. Chan, P. T. C. Cheng, H. Sze, T. S. Lam and T. K. Yau. The strength/weakness of the AJCC/UICC staging system (7th edition) for nasopharyngeal cancer and suggestions for future improvement. Oral Oncology. 2012. 48:1007-1013	Nonrelevant Study Design
B. A. Jereczek-Fossa, A. Kowalczyk, A. D'Onofrio, G. Catalano, C. Garibaldi, G. Boboc, V. Vitolo, M. C. Leonardi, R. Cambria and R. Orecchia. Three-dimensional conformal or stereotactic reirradiation of recurrent, metastatic or new primary tumors: Analysis of 108 patients. Strahlentherapie und Onkologie. 2008. 184:36-40	Nonrelevant Study Design
B. A. Murphy, J. L. Beaumont, J. Isitt, A. S. Garden, C. K. Gwede, A. M. Trotti, R. F. Meredith, J. B. Epstein, Q. T. Le, D. M. Brizel, L. A. Bellm, N. Wells and D. Cella. Mucositis-Related Morbidity and Resource Utilization in Head and Neck Cancer Patients Receiving Radiation Therapy With or Without Chemotherapy. Journal of Pain and Symptom Management. 2009. 38:522-532	Nonrelevant Study Design
B. Bussels, A. Maes, R. Hermans, S. Nuyts, C. Weltens and W. Van den Bogaert. Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer. Radiother Oncol. 2004. 72:119-27	Nonrelevant Study Design
B. L. T. Ramaekers, M. Pijls-Johannesma, M. A. Joore, P. van den Ende, J. A. Langendijk, P. Lambin, A. G. H. Kessels and J. P. C. Grutters. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: Comparing photons, carbon-ions and protons. Cancer Treatment Reviews. 2011. 37:185-201	Nonprimary Data
B. M. Beadle, K. P. Liao, L. S. Elting, T. A. Buchholz, K. K. Ang, A. S. Garden and B. A. Guadagnolo. Improved survival using intensity-modulated radiation therapy in head and neck cancers: A SEER-medicare analysis. Cancer. 2014. 120:702-710	Nonrelevant Study Design
B. Pehlivan, F. Luthi, O. Matzinger, M. Betz, D. Dragusanu, S. Bulling, L. Bron, P. Pasche, W. Seelentag, R. O. Mirimanoff, A. Zouhair and M. Ozsahin. Feasibility and efficacy of accelerated weekly concomitant boost postoperative radiation therapy combined with concomitant chemotherapy in patients with locally advanced head and neck cancer. Annals of Surgical Oncology. 2009. 16:1337-1343	Nonrelevant Study Design
B. S. Hoppe, C. J. Nelson, D. R. Gomez, L. D. Stegman, A. J. Wu, S. L. Wolden, D. G. Pfister, M. J. Zelefsky, J. P. Shah, D. H. Kraus and N. Y. Lee. Unresectable Carcinoma of the Paranasal Sinuses: Outcomes and Toxicities. International Journal of Radiation Oncology Biology Physics. 2008. 72:763-769	Nonrelevant Study Design

Citation	Reason for exclusion
B. S. Hoppe, L. D. Stegman, M. J. Zelefsky, K. E. Rosenzweig, S. L. Wolden, S. G. Patel, J. P. Shah, D. H. Kraus and N. Y. Lee. Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting--the MSKCC experience. Int J Radiat Oncol Biol Phys. 2007. 67:691-702	Nonrelevant Study Design
C. A. Kristensen, F. Kjaer-Kristoffersen, W. Sapru, A. K. Berthelsen, A. Loft and L. Specht. Nasopharyngeal carcinoma. Treatment planning with IMRT and 3D conformal radiotherapy. Acta Oncol. 2007. 46:214-20	Nonrelevant Study Design
C. B. Hess and A. M. Chen. Global and health-related quality of life after intensity-modulated radiation therapy for head and neck cancer. Expert Review of Anticancer Therapy. 2012. 12:1469-1477	Nonprimary Data
C. Chen, W. Yi, J. Gao, X. H. Li, L. J. Shen, B. F. Li, Z. W. Tu, Y. L. Tao, C. B. Jiang and Y. F. Xia. Alternative endpoints to the 5-year overall survival and locoregional control for nasopharyngeal carcinoma: A retrospective analysis of 2,450 patients. Mol Clin Oncol. 2014. 2:385-392	Nonrelevant Study Design
C. Chin, N. Riaz, F. Ho, M. Hu, J. Hong, E. Sherman, R. Wong, S. Wolden, S. Rao and N. Lee. Can meaningful and durable locoregional control be achieved for oral cavity squamous cell carcinoma (OCSCC) treated with definitive radiation therapy (RT)?. International Journal of Radiation Oncology Biology Physics. 2012. 84:S464-S465	Abstract Only
C. Chin, N. Riaz, F. Ho, M. Hu, J. Hong, E. Sherman, R. Wong, S. Wolden, S. Rao and N. Lee. Surgery improves outcome in recurrent squamous cell carcinoma of the oral cavity. International Journal of Radiation Oncology Biology Physics. 2012. 84:S466	Abstract Only
C. H. Clark, E. A. Miles, M. T. Guerrero Urbano, S. A. Bhide, A. M. Bidmead, K. J. Harrington and C. M. Nutting. Pre-trial quality assurance processes for an intensity-modulated radiation therapy (IMRT) trial: PARSPORT, a UK multicentre Phase III trial comparing conventional radiotherapy and parotid-sparing IMRT for locally advanced head and neck cancer. British Journal of Radiology. 2009. 82:585-594	Nonprimary Data
C. Huang, E. Huang, C. Wang, H. Chen, H. Hsu, Y. Huang, Y. Wang and F. Fang. Treatment outcome and prognostic factors for nasopharyngeal carcinoma with cranial nerve palsy treated by conventional or conformal radiotherapy. International Journal of Radiation Oncology Biology Physics. 2011. 81:S509	Abstract Only
C. Lertbutsayanukul, K. Shotelersuk, C. Khorprasert, T. Sanghangthum, S. Oonsiri, Ayuthaya, II, C. Jumpangern, S. Suriyapee and P. Rojpornpradit. A two-year experience of implementing 3 dimensional radiation therapy and intensity-modulated radiation therapy for 925 patients in King Chulalongkorn Memorial Hospital. J Med Assoc Thai. 2008. 91:215-24	Nonprimary Data
C. Liberatoscioli, J. A. Langendijk, C. Van Herpen, L. Collette, E. M. Ozsahin, R. Karra Gurunath, D. A. Lacombe, A. Gulyban, N. Gosselin and W. Budach. EORTC 22071-24071: Randomized, phase III trial of EGFR-antibody combined with adjuvant chemoradiation for patients with head and neck squamous cell carcinoma (HNSCC) at high risk of recurrence. Journal of Clinical Oncology. 2011. 29:#pages#	Abstract Only
C. M. Lim, D. A. Clump, D. E. Heron and R. L. Ferris. Stereotactic Body Radiotherapy (SBRT) for primary and recurrent head and neck tumors. Oral Oncology. 2013. #volume#:#pages#	Nonprimary Data
C. M. Nutting, J. P. Morden, K. J. Harrington, T. G. Urbano, S. A. Bhide, C. Clark, E. A. Miles, A. B. Miah, K. Newbold, M. Tanay, F. Adab, S. J. Jefferies, C. Scrase, B. K. Yap, R. P. A'Hern, M. A. Sydenham, M. Emson and E. Hall. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. The Lancet Oncology. 2011. 12:127-136	Included in Original CER
C. M. Van Rij, W. D. Oughlane-Heemsbergen, A. H. Ackerstaff, E. A. Lamers, A. J. M. Balm and C. R. N. Rasch. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. Radiation Oncology. 2008. 3:#pages#	Nonrelevant Study Design
C. Makita, T. Nakamura, A. Takada, K. Takayama, T. Katou and N. Fuwa. Proton beam therapy for patients with Stage T4 and/or N3 nasopharyngeal carcinoma. Radiotherapy and Oncology. 2012. 103:S452-S453	Abstract Only

Citation	Reason for exclusion
C. S. Lin, Y. M. Jen, W. Y. Kao, C. L. Ho, M. S. Dai, C. L. Shih, J. C. Cheng, P. Y. Chang, W. Y. Huang and Y. F. Su. Improved outcomes in buccal squamous cell carcinoma. Head and Neck. 2013. 35:65-71	Nonrelevant Study Design
C. W. Hodge, S. M. Bentzen, G. Wong, K. L. Palazzi-Churas, P. A. Wiederholt, V. Gondi, G. M. Richards, G. K. Hartig and P. M. Harari. Are we influencing outcome in oropharynx cancer with intensity-modulated radiotherapy? An inter-era comparison. Int J Radiat Oncol Biol Phys. 2007. 69:1032-41	Included in Original CER
C. Y. Hsiung, H. M. Ting, H. Y. Huang, C. H. Lee, E. Y. Huang and H. C. Hsu. Parotid-sparing intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma: preserved parotid function after IMRT on quantitative salivary scintigraphy, and comparison with historical data after conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2006. 66:454-61	Included in Original CER
D. B. Shultz, J. D. Murphy, M. E. Daly, W. Hara, Q. T. Le and D. T. Chang. Radiotherapy for adenoid cystic carcinomas of the head and neck: Clinical outcomes and patterns of failure. International Journal of Radiation Oncology Biology Physics. 2011. 81:S528	Abstract Only
D. Chua, P. Ho, V. Lee and J. Sham. A randomized phase II study of external beam reirradiation versus external beam reirradiation plus radiosurgery boost in recurrent nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics. 2011. 81:S506	Abstract Only
D. E. Peterson, W. Doerr, A. Hovan, A. Pinto, D. Saunders, L. S. Elting, F. K. L. Spijkervet and M. T. Brennan. Osteoradionecrosis in cancer patients: The evidence base for treatment-dependent frequency, current management strategies, and future studies. Supportive Care in Cancer. 2010. 18:1089-1098	Nonprimary Data
D. E. Soto, M. L. Kessler, M. Piert and A. Eisbruch. Correlation between pretreatment FDG-PET biological target volume and anatomical location of failure after radiation therapy for head and neck cancers. Radiotherapy and Oncology. 2008. 89:13-18	Nonrelevant Study Design
D. F. Lee, M. Davis, M. Rajaraman, H. Hollenhorst and D. Wilke. Impact of intensity modulated radiotherapy on weight loss and percutaneous gastrostomy tube placement rates in advanced head and neck cancer patients. International Journal of Radiation Oncology Biology Physics. 2011. 81:S520	Abstract Only
D. Fried, A. Khandani, C. Shores, M. Weissler, N. Hayes, T. Hackman, J. Rosenman and B. Chera. Matched cohort analysis of the effect of pre-treatment positron emission tomography on clinical outcomes of head and neck cancer patients treated with definitive chemoradiotherapy. International Journal of Radiation Oncology Biology Physics. 2011. 81:S537	Abstract Only
D. Fried, J. Rosenman, M. Varia, D. Morris, C. Shores, M. Weissler, T. Hackman and B. Chera. A matched cohort comparison of head and neck squamous cell carcinoma patients treated with intensity modulated radiation therapy versus conventional radiotherapy. International Journal of Radiation Oncology Biology Physics. 2011. 81:S545	Abstract Only
D. Fried, M. Lawrence, A. Khandani, J. Rosenman, T. Cullip and B. Chera. Is image registration of FDG-PET for head and neck treatment planning necessary?. International Journal of Radiation Oncology Biology Physics. 2011. 81:S539-S540	Abstract Only
D. I. Rosenthal, G. B. Gunn, T. R. Mendoza, A. S. Garden, B. M. Beadle, W. H. Morrison, X. S. Wang, S. J. Frank, R. S. Weber, K. K. Ang and C. S. Cleeland. Long-term symptom burden after radiation treatment for oropharynx cancer: A comparison of 3D and IMRT techniques. Journal of Clinical Oncology. 2011. 29:#pages#	Abstract Only
D. I. Rosenthal, M. S. Chambers, C. D. Fuller, N. C. S. Rebueno, J. Garcia, M. S. Kies, W. H. Morrison, K. K. Ang and A. S. Garden. Beam Path Toxicities to Non-Target Structures During Intensity-Modulated Radiation Therapy for Head and Neck Cancer. International Journal of Radiation Oncology Biology Physics. 2008. 72:747-755	Nonrelevant Study Design
D. J. Givens, L. H. Karnell, A. K. Gupta, G. H. Clamon, N. A. Pagedar, K. E. Chang, D. J. Van Daele and G. F. Funk. Adverse events associated with concurrent chemoradiation therapy in patients with head and neck cancer. Archives of Otolaryngology - Head and Neck Surgery. 2009. 135:1209-1217	Nonrelevant Study Design

Citation	Reason for exclusion
D. Rades, F. Fehlauer, J. Wroblesky, D. Albers, S. E. Schild and R. Schmidt. Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol. 2007. 43:535-43	Included in Original CER
D. S. Lin, Y. M. Jen, J. C. Lee, S. C. Liu and Y. S. Lin. Recurrence of nasopharyngeal carcinoma in the parotid region after parotid-gland-sparing radiotherapy. J Formos Med Assoc. 2011. 110:655-60	Nonrelevant Study Design
D. W. Golden, M. Witt, S. R. Rudra, T. I. Nwizu, E. E. Cohen, E. Blair, K. M. Stenson, E. E. Vokes and D. J. Haraf. Outcomes of induction chemotherapy and concurrent chemoradiation for nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics. 2012. 84:S485-S486	Abstract Only
E. A. Klein, M. Guiou, D. G. Farwell, Q. Luu, D. H. Lau, K. Stuart, A. Vaughan, S. Vijayakumar and A. M. Chen. Primary radiation therapy for head-and-neck cancer in the setting of human immunodeficiency virus. International Journal of Radiation Oncology Biology Physics. 2011. 79:60-64	Nonrelevant Study Design
E. Bragantini, S. Girlando, V. Vanoni, A. Bolner, F. Valduga, R. Carella, M. Barbareschi, M. Silvestrini, C. Grandi and P. Dalla Palma. Oropharynx cancer: Evaluation of clinical outcome according to HPV status and radiotherapy technique. Virchows Archiv. 2011. 459:S106-S107	Abstract Only
E. H. Pow, D. L. Kwong, A. S. McMillan, M. C. Wong, J. S. Sham, L. H. Leung and W. K. Leung. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys. 2006. 66:981-91	Included in Original CER
E. Katsoulakis, M. Hu, N. Riaz, S. Wolden, S. Rao and N. Lee. Outcomes of radiation therapy for hypopharyngeal squamous cell carcinoma: A single institution experience. International Journal of Radiation Oncology Biology Physics. 2012. 84:S494	Abstract Only
F. Bekiroglu, N. Ghazali, R. Laycock, C. Katre, D. Lowe and S. N. Rogers. Adjuvant radiotherapy and health-related quality of life of patients at intermediate risk of recurrence following primary surgery for oral squamous cell carcinoma. Oral Oncology. 2011. 47:967-973	Nonrelevant Study Design
F. Caparrotti, V. Vinh-Hung, N. Mach, P. Dulguerov, R. Miralbell and M. Betz. Concomitant radiotherapy and cetuximab for head and neck cancer: Late toxicity and outcomes. Strahlentherapie und Onkologie. 2011. 187:536	Abstract Only
F. Dionisi, F. Bracco, D. Asnaghi, A. Cocchi, E. Iannacone and M. F. Palazzi. Quality of life of head neck cancer patients 1 year after radiotherapy with the use of EORTC QLQ-C30 and HN-35 modules. Radiotherapy and Oncology. 2012. 103:S454-S455	Abstract Only
F. Ho, N. Riaz, C. Chin, M. Hu, J. Hong, E. Sherman, R. Wong, S. Wolden, S. Rao and N. Lee. IMRT versus conventional radiation therapy for postoperative treatment of oral cavity squamous cell carcinoma (OCSCC). International Journal of Radiation Oncology Biology Physics. 2012. 84:S465-S466	Abstract Only
F. Liu and J. Xiao. Evaluation of fractionated stereotactic radiotherapy with vagina carotica protection for residual nasopharyngeal carcinoma. Radiotherapy and Oncology. 2011. 99:S324	Abstract Only
F. Liu, J. P. Xiao, Y. J. Xu, Y. Zhang, G. Z. Xu, L. Gao, J. L. Yi, J. W. Luo, X. D. Huang, F. K. Huan, H. Fang, B. Wan and Y. X. Li. Fractionated stereotactic radiotherapy with vagina carotica protection technique for local residual nasopharyngeal carcinoma after primary radiotherapy. Chin Med J (Engl). 2012. 125:2525-9	Nonrelevant Study Design
F. M. Fang, C. Y. Chien, W. L. Tsai, H. C. Chen, H. C. Hsu, C. C. Lui, T. L. Huang and H. Y. Huang. Quality of Life and Survival Outcome for Patients With Nasopharyngeal Carcinoma Receiving Three-Dimensional Conformal Radiotherapy vs. Intensity-Modulated Radiotherapy-A Longitudinal Study. International Journal of Radiation Oncology Biology Physics. 2008. 72:356-364	Included in Original CER
F. M. Fang, W. L. Tsai, H. C. Chen, H. C. Hsu, C. Y. Hsiung, C. Y. Chien and S. F. Ko. Intensity-modulated or conformal radiotherapy improves the quality of life of patients with nasopharyngeal carcinoma: comparisons of four radiotherapy techniques. Cancer. 2007. 109:313-21	Included in Original CER

Citation	Reason for exclusion
F. M. Fang, W. L. Tsai, T. F. Lee, K. C. Liao, H. C. Chen and H. C. Hsu. Multivariate analysis of quality of life outcome for nasopharyngeal carcinoma patients after treatment. Radiotherapy and Oncology. 2010. 97:263-269	Nonrelevant Study Design
F. Moretto, M. Rampino, F. Munoz, M. G. Ruo Redda, A. Reali, V. Balcet, S. Badellino, C. Piva, M. Schena, M. Airoldi, O. Ostellino, G. Pecorari, R. Ragona and U. Ricardi. Conventional 2D (2DRT) and 3D conformal radiotherapy (3DCRT) versus intensity-modulated radiotherapy (IMRT) for nasopharyngeal cancer treatment. Radiol Med. 2014. #volume#:#pages#	Nonrelevant Study Design
F. Roeder, F. Zwicker, L. Saleh-Ebrahimi, C. Timke, C. Thieke, M. Bischof, J. Debus and P. E. Huber. Intensity modulated or fractionated stereotactic reirradiation in patients with recurrent nasopharyngeal cancer. Radiation Oncology. 2011. 6:#pages#	Nonrelevant Study Design
F. Y. Feng, H. M. Kim, T. H. Lyden, M. J. Haxer, F. P. Worden, M. Feng, J. S. Moyer, M. E. Prince, T. E. Carey, G. T. Wolf, C. R. Bradford, D. B. Chepeha and A. Eisbruch. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: Clinical and functional results. Dysphagia. 2011. 26:206-207	Nonrelevant Study Design
G. A. Hobeika, Y. Zia, G. Walker, M. Samuels, M. Abramowitz and N. Elsayyad. Definitive radiation therapy for locally advanced oropharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics. 2012. 84:S474	Abstract Only
G. B. Gunn, G. M. Chronowski, A. S. Garden, S. J. Frank, W. H. Morrison, B. M. Beadle, C. M. Lewis, T. R. Mendoza, C. S. Cleeland and D. I. Rosenthal. Symptom-free cure following unilateral radiation therapy for tonsil cancer: A patient-reported outcomes (PRO) benchmark. International Journal of Radiation Oncology Biology Physics. 2012. 84:S467	Abstract Only
G. B. Gunn, T. R. Mendoza, A. S. Garden, X. S. Wang, W. H. Morrison, S. J. Frank, E. Y. Hanna, C. Lu, B. M. Beadle, K. K. Ang, C. S. Cleeland and D. I. Rosenthal. Patient-reported fatigue in head and neck cancer survivors. Journal of Clinical Oncology. 2011. 29:#pages#	Abstract Only
G. Dickie, K. Choma, P. Dwyer, C. Lin, B. Higgs and L. Kenny. Head and neck cancer treated with helical IMRT; Initial results and acute toxicity. Journal of Medical Imaging and Radiation Oncology. 2012. 56:252	Abstract Only
G. F. Huber, C. Gengler, C. Walter, T. Roth, A. Huber and D. Holzmann. Adenocarcinoma of the nasal cavity and paranasal sinuses: Single-institution review of diagnosis, histology, and outcome. Journal of Otolaryngology - Head and Neck Surgery. 2011. 40:34-39	Nonrelevant Study Design
G. Mok, I. Gauthier, H. Jiang, S. Huang, K. Chan, I. Witterick, J. J. Kim, J. N. Waldron, B. O'Sullivan and J. Ringash. Does IMRT for hypopharyngeal cancer improve locoregional control? A comparison to 3D conformal radiation therapy. International Journal of Radiation Oncology Biology Physics. 2012. 84:S492	Abstract Only
G. Studer, K. Furrer, B. J. Davis, S. S. Stoeckli, R. A. Zwahlen, U. M. Luetolf and C. Glanzmann. Postoperative IMRT in head and neck cancer. Radiat Oncol. 2006. 1:40	Nonrelevant Study Design
G. Studer, R. A. Zwahlen, K. W. Graetz, B. J. Davis and C. Glanzmann. IMRT in oral cavity cancer. Radiat Oncol. 2007. 2:16	Nonrelevant Study Design
H. D. Pacholke, R. J. Amdur, C. G. Morris, J. G. Li, J. F. Dempsey, R. W. Hinerman and W. M. Mendenhall. Late xerostomia after intensity-modulated radiation therapy versus conventional radiotherapy. Am J Clin Oncol. 2005. 28:351-8	Included in Original CER
H. Hojo, S. Zenda, M. Kawashima, S. Arahira, M. Tahara, R. Hayashi and K. Sasai. The response evaluation using CT/MRI for nasal cavity and paranasal sinuses malignancies treated with radiotherapy or proton beam therapy. European Journal of Cancer. 2011. 47:S567	Abstract Only
H. Inokuchi, T. Nakamura, T. Tomoda, A. Takada, K. Takayama, C. Makita, M. Shiomi, T. Kato and N. Fuwa. Assessment of acute cervical skin toxicity due to fractionated proton beam therapy for head-and-neck cancer. International Journal of Radiation Oncology Biology Physics. 2012. 84:S836-S837	Abstract Only
H. Langendijk, R. Steenbakkers, O. Hoegen-Choevalova and H. P. Bijl. Late functional outcome in chemo-radiation. European Journal of Cancer. 2011. 47:S12	Abstract Only
H. Lee, Y. Ahn, H. Nam, D. Oh, B. Kim, H. Park, J. Park and S. Park. Tumor volume reduction rate during definitive radiation therapy: A potential prognosticator in oropharynx cancer. International Journal of Radiation Oncology Biology Physics. 2012. 84:S470-S471	Abstract Only

Citation	Reason for exclusion
H. P. Van Der Laan, T. Van De Water, H. Van Herpt, M. Christianen, H. P. Bijl, C. Schilstra and H. Langendijk. Dysphagia reduction with optimized photon and proton intensity-modulated radiotherapy for head and neck cancer. Radiotherapy and Oncology. 2011. 99:S72	Abstract Only
I. Beetz, C. Schilstra, A. Visink, A. van der Schaaf, H. P. Bijl, B. F. van der Laan, R. J. Steenbakkers and J. A. Langendijk. Role of minor salivary glands in developing patient-rated xerostomia and sticky saliva during day and night. Radiother Oncol. 2013. 109:311-6	Nonrelevant Study Design
I. Beetz, C. Schilstra, P. Luijk'van, M. E. M. C. Christianen, H. P. Bijl, O. Chouvalova, P. Doornaert, E. R. Van Den Heuvel, D. Van, R. J. H. M. Steenbakkers and J. A. Langendijk. 3D-CRT based predictive models for patient-rated xerostomia and sticky saliva are not valid among patients treated with IMRT. International Journal of Radiation Oncology Biology Physics. 2011. 81:S174-S175	Abstract Only
I. Beetz, R. J. Steenbakkers, O. Chouvalova, C. R. Leemans, P. Doornaert, B. F. van der Laan, M. E. Christianen, A. Vissink, H. P. Bijl, P. van Luijk and J. A. Langendijk. The QUANTEC criteria for parotid gland dose and their efficacy to prevent moderate to severe patient-rated xerostomia. Acta Oncol. 2014. 53:597-604	Nonrelevant Study Design
I. Mallick, S. K. Gupta, R. Ray, T. Sinha, S. Sinha, R. Achari and S. Chatterjee. Predictors of weight loss during conformal radiotherapy for head and neck cancers - how important are planning target volumes?. Clin Oncol (R Coll Radiol). 2013. 25:557-63	Nonprimary Data
J. A. Dorth and D. M. Brizel. Incidence of asymptomatic carotid artery stenosis in survivors of head and neck radiation. International Journal of Radiation Oncology Biology Physics. 2011. 81:S76	Abstract Only
J. Agarwal, S. Rathod, V. Murthy, S. Ghosh-laskar, A. Budrukkar, K. Dinshaw, P. Chaturvedi, K. Prabhash, A. D'Cruz and T. Gupta. Improved quality of life (QOL) outcomes in patients with head-and-neck squamous cell carcinoma (HNSCC) treated with intensity modulated radiation therapy (IMRT) compared to 3-dimensional conformal radiation therapy (3D-CRT): Evidence from a prospective randomized study. International Journal of Radiation Oncology Biology Physics. 2012. 84:S211	Abstract Only
J. B. Yu, P. R. Soulos, R. Sharma, D. V. Makarov, R. H. Decker, B. D. Smith, R. A. Desai, L. D. Cramer and C. P. Gross. Patterns of care and outcomes associated with intensity-modulated radiation therapy versus conventional radiation therapy for older patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012. 83:e101-7	Nonrelevant Study Design
J. Buntzel, M. Glatzel, R. Mucke, O. Micke and F. Bruns. Influence of amifostine on late radiation-toxicity in head and neck cancer--a follow-up study. Anticancer Res. 2007. 27:1953-6	Nonrelevant Study Design
J. Caudell, W. Carroll, J. Locher and J. Bonner. Factors associated with long term dysphagia following treatment of locally advanced head and neck cancer with surgery and post-operative radiotherapy. Dysphagia. 2011. 26:450-451	Abstract Only
J. Hey, J. Setz, R. Gerlach, M. Janich, G. Hildebrandt, D. Vordermark, C. R. Gernhardt and T. Kuhnt. Parotid gland-recovery after radiotherapy in the head and neck region--36 months follow-up of a prospective clinical study. Radiat Oncol. 2011. 6:125	Nonrelevant Study Design
J. J. Beitler, Q. Zhang, K. K. Fu, A. Trotti, S. A. Spencer, C. U. Jones, A. S. Garden, G. Shenouda, J. Harris and K. K. Ang. Rtog 90-03: Final report. International Journal of Radiation Oncology Biology Physics. 2012. 84:S6	Abstract Only
J. J. Wang, T. A. Goldsmith, A. S. Holman, M. Cianchetti and A. W. Chan. Pharyngoesophageal stricture after treatment for head and neck cancer. Head and Neck. 2012. 34:967-973	Nonprimary Data
J. Kharofa, N. Choong, D. Wang, S. Firat, C. Schultz, C. Sadasiwan and S. Wong. Continuous-course reirradiation with concurrent carboplatin and paclitaxel for locally recurrent, nonmetastatic squamous cell carcinoma of the head-and-neck. Int J Radiat Oncol Biol Phys. 2012. 83:690-5	Nonrelevant Study Design
J. Kubes, J. Cvek, V. Vondracek, M. Pala and D. Feltl. Accelerated radiotherapy with concomitant boost technique (69.5 Gy/5 weeks): An alternative in the treatment of locally advanced head and neck cancer. Strahlentherapie und Onkologie. 2011. 187:651-655	Nonrelevant Study Design

Citation	Reason for exclusion
J. L. Yi, L. Gao, X. D. Huang, S. Y. Li, J. W. Luo, W. M. Cai, J. P. Xiao and G. Z. Xu. Nasopharyngeal carcinoma treated by radical radiotherapy alone: Ten-year experience of a single institution. Int J Radiat Oncol Biol Phys. 2006. 65:161-8	Nonrelevant Study Design
J. Mundi and M. St. John. Evaluation of trends in use of IMRT in head and neck cancer. Otolaryngology - Head and Neck Surgery. 2011. 145:166	Abstract Only
J. Petsuksiri, A. Sermsree, K. Thephamongkhol, P. Keskool, K. Thongyai, Y. Chansilpa and P. Pattaranutaporn. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. Radiation Oncology. 2011. 6:#pages#	Nonrelevant Study Design
J. S. Kornerup, N. Brodin, C. Birk Christiansen, M. Aznar, T. Bjork- Eriksson, A. Kiil Berthelsen, E. Markova, A. Loft Jacobsen, L. Borgwardt and P. Munck af Rosenschold. Influence of pet data on the radiation therapy planning of pediatric cancer. International Journal of Radiation Oncology Biology Physics. 2012. 84:S639-S640	Abstract Only
J. Staffurth. A review of the clinical evidence for intensity-modulated radiotherapy. Clinical Oncology. 2010. 22:643-657	Nonprimary Data
J. T. Chang, C. Y. Lin, K. H. Fan, H. M. Wang, C. T. Liao, K. Kang and S. F. Hung. The treatment result of advanced stage oropharyngeal cancer by radiotherapy with or without chemotherapy - The impact of intensity modulation radiotherapy and FDG-PET. European Journal of Cancer. 2011. 47:S555	Abstract Only
J. Vargo, D. E. Heron, R. L. Ferris, J. M. Rwigema, R. E. Wegner, R. Kalash, J. Ohr, G. J. Kubicek and S. Burton. Treatment duration>2 weeks negatively impacts disease control following SBRT for locally recurrent, previously irradiated headand-neck cancers. International Journal of Radiation Oncology Biology Physics. 2012. 84:S510	Abstract Only
J. W. G. Roe, P. N. Carding, R. C. Dwivedi, R. A. Kazi, P. H. Rhys-Evans, K. J. Harrington and C. M. Nutting. Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer - A systematic review. Oral Oncology. 2010. 46:727-733	Nonprimary Data
J. W. Jang, R. J. Parambi, T. A. Goldsmith, A. S. Holman, L. J. Wirth, J. R. Clark, P. M. Busse and A. W. Chan. Factors associated with prolonged gastrostomy tube usage in patients with oropharyngeal cancer treated with chemoradiation. International Journal of Radiation Oncology Biology Physics. 2012. 84:S479	Abstract Only
J. W. Roe, P. N. Carding, R. C. Dwivedi, R. A. Kazi, P. H. Rhys-Evans, K. J. Harrington and C. M. Nutting. Swallowing outcomes following intensity modulated radiation therapy (IMRT) for head and neck cancer - A systematic review. Dysphagia. 2011. 26:428	Abstract Only
J. Waldron, S. Huang, W. Xu, H. Zhao, D. Chen, J. Kim, A. Bayley, K. Chan, R. Gilbert and B. O'Sullivan. Neck-specific outcome of N2-N3 head-and-neck cancer treated with radiation (plus or minus) chemotherapy. International Journal of Radiation Oncology Biology Physics. 2012. 84:S206	Abstract Only
K. E. Rusthoven, D. Raben, A. Ballonoff, M. Kane, J. I. Song and C. Chen. Effect of radiation techniques in treatment of oropharynx cancer. Laryngoscope. 2008. 118:635-9	Included in Original CER
K. Hu, L. B. Harrison, R. A. Shourbaji, B. Culliney, Z. Li and W. Fouad Mourad. Outcomes of occult primary (OP) of the head and neck squamous cell carcinoma (HNSCC) treated with oropharynx (OPX)-targeted radiotherapy (RT) and concurrent chemotherapy (CCRT). Journal of Clinical Oncology. 2012. 30:#pages#	Abstract Only
K. Hu, M. Kumar, S. Sura, B. Culliney, T. Tran, A. Jacobson, M. Perksy, M. Urken, P. Costantino and L. Harrison. Can stage III-IV head and neck cancer patients be treated with unilateral radiotherapy?. International Journal of Radiation Oncology Biology Physics. 2011. 81:S486-S487	Abstract Only
K. Hu, W. F. Mourad, R. Shourbaji, W. Lin, B. Culliney, A. Jacobson, T. Tran, M. Urken, M. Persky and L. B. Harrison. Five-year outcomes of oropharynx (OPX) targeted radiation therapy (RT) for metastatic squamous cell carcinoma of unknown primary (MUP) in the head and neck. International Journal of Radiation Oncology Biology Physics. 2012. 84:S22	Abstract Only

Citation	Reason for exclusion
K. Jingu, K. Abe, M. Koto, K. Fujimoto, H. Matsushita, T. Sugawara, R. Umezawa, N. Kadoya, K. Takeda and S. Yamada. Does IMRT increase loco-regional failure in patients with nasopharyngeal cancer? A first report. Radiotherapy and Oncology. 2012. 103:S447-S448	Abstract Only
K. S. Chao, J. O. Deasy, J. Markman, J. Haynie, C. A. Perez, J. A. Purdy and D. A. Low. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys. 2001. 49:907-16	Included in Original CER
K. S. Chao, N. Majhail, C. J. Huang, J. R. Simpson, C. A. Perez, B. Haughey and G. Spector. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol. 2001. 61:275-80	Included in Original CER
K. Tsuchiya, K. Yasuda, Y. Nishikawa, R. Kinoshita, R. Onimaru and H. Shirato. Retrospective comparison between cisplatin plus fluorouracil and weekly cisplatin in concurrent chemoradiation therapy setting for stage II-IV nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics. 2012. 84:S484-S485	Abstract Only
L. B. Harrison, K. Hu, R. A. Shourbaji, B. Culliney, Z. Li, M. Urken, M. Persky and W. F. Mourad. The role of postoperative radiotherapy (PORT) in the management of parotid gland malignancy (PGM). Journal of Clinical Oncology. 2012. 30:#pages#	Abstract Only
L. Costa, M. Buglione, N. Pasinetti, E. Castrezzati, R. Cavagnini, S. Tonoli and S. M. Magrini. Oropharynx cancer (OC): Acute/sub-acute toxicity in pts treated with 3D-conformal radiotherapy and IMRT. Radiotherapy and Oncology. 2012. 103:S448	Abstract Only
L. Kong, Y. W. Zhang, C. S. Hu and Y. Guo. Neoadjuvant chemotherapy followed by concurrent chemoradiation for locally advanced nasopharyngeal carcinoma. Chinese Journal of Cancer. 2010. 29:551-555	Nonrelevant Study Design
L. Ma, L. Du, L. Feng, X. Zhang, F. Li, G. Zhou, B. Qu, S. Xu and C. Xie. Treatment of nasopharyngeal carcinoma with helical tomotherapy: A retrospective study of 121 cases. International Journal of Radiation Oncology Biology Physics. 2012. 84:S485	Abstract Only
L. Ma, Q. Guo, Y. Zhang, X. Kong, L. Yang, S. Lin, C. Huang, J. Pan and J. Lu. The effect of intensity-modulated radiotherapy versus conventional radiotherapy on quality of life in patients with nasopharyngeal cancer: a cross-sectional study. Head Neck Oncol. 2013. 5:8	Nonrelevant Study Design
L. Veldeman, I. Madani, F. Hulstaert, G. De Meerleer, M. Mareel and W. De Neve. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. The Lancet Oncology. 2008. 9:367-375	Nonprimary Data
M. Abdel-Wahab, A. Abitbol, I. Elattar, O. Mahmoud, M. Troner and A. Lewin. Does radiation technique influence peg dependence? A comparison between intensity modulated radiation therapy and 3-dimensional conformal techniques. International Journal of Radiation Oncology Biology Physics. 2012. 84:S652	Abstract Only
M. Boomsma-Van Holten, H. P. Bijl, M. Christianen, I. Beetz, O. Chouvalova, R. Steenbakkers, B. Van Der Laan, S. Oostinq, C. Schilstra and H. Langendijk. A NTCP model for radiation-induced hypothyroidism based on a prospective cohort study. Radiotherapy and Oncology. 2011. 98:S25-S26	Abstract Only
M. E. Daly, Y. Lieskovsky, T. Pawlicki, J. Yau, H. Pinto, M. Kaplan, W. E. Fee, A. Koong, D. R. Goffinet, L. Xing and Q. T. Le. Evaluation of patterns of failure and subjective salivary function in patients treated with intensity modulated radiotherapy for head and neck squamous cell carcinoma. Head Neck. 2007. 29:211-20	Included in Original CER
M. F. Roenjom, C. Brink, L. Hegedus, J. Overgaard and J. Johansen. Dose-response of hypothyroidism after primary radiotherapy in carcinoma of the head and neck (HNSCC). Radiotherapy and Oncology. 2012. 103:S202	Abstract Only
M. Feng, S. Jabbari, A. Lin, C. R. Bradford, D. B. Chepeha, T. N. Teknos, F. P. Worden, C. Tsien, M. J. Schipper, G. T. Wolf, L. A. Dawson and A. Eisbruch. Predictive factors of local-regional recurrences following parotid sparing intensity modulated or 3D conformal radiotherapy for head and neck cancer. Radiother Oncol. 2005. 77:32-8	Nonrelevant Study Design
M. Hu, E. Katsoulakis, N. Riaz, S. Jaffery, S. Rao and N. Lee. Excellent laryngeal preservation can be achieved with imrt for locoregionally advanced laryngeal cancer. International Journal of Radiation Oncology Biology Physics. 2012. 84:S495-S496	Nonrelevant Study Design

Citation	Reason for exclusion
M. K. Bhayani, K. A. Hutcheson, D. Barringer, A. Lisec, D. Roberts, S. Y. Lai and J. S. Lewin. Identification and management of oropharyngeal carcinoma patients with risk factors for gastrostomy tube placement and dependence. International Journal of Radiation Oncology Biology Physics. 2011. 81:S495	Abstract Only
M. Lambrecht, D. Nevens and S. Nuyts. The effect of IMRT on outcome and toxicity compared to 3DCRT. A mono-centric, retrospective analysis. Radiotherapy and Oncology. 2012. 103:S456	Abstract Only
M. Leclerc, E. Lartigau, T. Lacornerie, J. Daisne and V. Gregoire. Target volume delineation based on 18FDG PET for locally advanced head and neck cancer treated by chemo-radiotherapy. Radiotherapy and Oncology. 2012. 103:S175-S176	Abstract Only
M. Lopez-Valcarcel, R. Moleron, E. Amaya, A. Sanz, P. Tavera, M. Hernandez, M. A. Cobo, J. Romero, C. Ispizua and A. De La Torre. Helical tomotherapy and 3D-conformal radiotherapy in nasopharyngeal cancer: Dosimetric and toxicity comparison. Radiotherapy and Oncology. 2012. 103:S445	Abstract Only
M. Louise Kent, M. T. Brennan, J. L. Noll, P. C. Fox, S. H. Burri, J. C. Hunter and P. B. Lockhart. Radiation-induced trismus in head and neck cancer patients. Support Care Cancer. 2008. 16:305-9	Nonrelevant Study Design
M. M. Qureshi, P. B. Romesser, L. T. Chatburn, R. M. Subramaniam and M. Truong. Determining the optimal prognostic volumetric threshold of gross tumor volume in head and neck cancer treated by radiotherapy. International Journal of Radiation Oncology Biology Physics. 2011. 81:S536	Abstract Only
M. Palazzi, E. Orlandi, P. Bossi, E. Pignoli, P. Potepan, M. Guzzo, M. Franceschini, G. Scaramellini, G. Cantu, L. Licitra, P. Olmi and S. Tomatis. Further Improvement in Outcomes of Nasopharyngeal Carcinoma With Optimized Radiotherapy and Induction Plus Concomitant Chemotherapy: An Update of the Milan Experience. International Journal of Radiation Oncology Biology Physics. 2009. 74:774-780	Nonrelevant Study Design
M. Qureshi, P. B. Romesser, A. Ajani, L. A. Kachnic and M. Truong. Gross tumor volume presentation in different race/ethnic groups as a determinant of treatment outcome in head-and-neck cancer patients treated with definitive radiation therapy. International Journal of Radiation Oncology Biology Physics. 2012. 84:S539	Abstract Only
M. R. Vergeer, P. A. H. Doornaert, D. H. F. Rietveld, C. R. Leemans, B. J. Slotman and J. A. Langendijk. Intensity-Modulated Radiotherapy Reduces Radiation-Induced Morbidity and Improves Health-Related Quality of Life: Results of a Nonrandomized Prospective Study Using a Standardized Follow-Up Program. International Journal of Radiation Oncology Biology Physics. 2009. 74:1-8	Included in Original CER
M. Roenjom, C. Brink, L. Hegedu s, J. Overgaard and J. Johansen. Hypothyroidism after primary radiation therapy in squamous cell carcinoma of the head and neck (HNSCC). International Journal of Radiation Oncology Biology Physics. 2012. 84:S61	Abstract Only
M. Sujith Kumar, S. Chakraborty, M. Geetha, E. P. Greeshma, M. Kumar and B. Sateeshan. Geriatric radiation oncology practice in a tertiary care center in India: Cure sometimes, comfort always. Journal of Cancer Research and Therapeutics. 2012. 8:S176-S177	Abstract Only
M. Suntharalingam, Y. Kwok, O. Goloubeva, A. Parekh, R. Taylor, J. Wolf, A. Zimrin, S. Strome, R. Ord and K. J. Cullen. Phase II study evaluating the addition of cetuximab to the concurrent delivery of weekly carboplatin, paclitaxel, and daily radiotherapy for patients with locally advanced squamous cell carcinomas of the head and neck. International Journal of Radiation Oncology Biology Physics. 2012. 82:1845-1850	Nonrelevant Study Design
M. T. Milano, E. E. Vokes, J. Kao, W. Jackson, M. A. List, K. M. Stenson, M. E. Witt, A. Dekker, E. MacCracken, M. C. Garofalo, S. J. Chmura, R. R. Weichselbaum and D. J. Haraf. Intensity-modulated radiation therapy in advanced head and neck patients treated with intensive chemoradiotherapy: preliminary experience and future directions. Int J Oncol. 2006. 28:1141-51	Nonrelevant Study Design
M. Vergeer, P. Doornaert, D. Rietveld, C. R. Leemans, J. A. Langendijk and B. Slotman. IMRT in head and neck cancer: Prognostic factors and patterns of recurrence. Radiotherapy and Oncology. 2012. 103:S279-S280	Abstract Only

Citation	Reason for exclusion
M. W. Munter, S. Hoffner, H. Hof, K. K. Herfarth, U. Haberkorn, V. Rudat, P. Huber, J. Debus and C. P. Karger. Changes in salivary gland function after radiotherapy of head and neck tumors measured by quantitative pertechnetate scintigraphy: comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without Amifostine. Int J Radiat Oncol Biol Phys. 2007. 67:651-9	Nonprimary Data
M. Y. Chen and R. Jiang. Endoscopic surgery and IMRT are effective in recurrent NPC. Otolaryngology - Head and Neck Surgery. 2011. 145:65	Abstract Only
M. Yao, L. H. Karnell, G. F. Funk, H. Lu, K. Dornfeld and J. M. Buatti. Health-related quality-of-life outcomes following IMRT versus conventional radiotherapy for oropharyngeal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2007. 69:1354-60	Included in Original CER
N. C. Sheets, S. B. Wheeler, R. E. Kohler, D. V. Fried, P. M. Brown and B. S. Chera. Costs of care in a matched pair comparison of intensity-modulated radiation therapy (IMRT) versus conventional radiation therapy (CRT) for the treatment of head and neck cancer. American Journal of Clinical Oncology: Cancer Clin. 2013. #volume#:#pages#	Nonrelevant Study Design
N. Galanopoulos, M. Yao, P. Lavertu, A. Argiris, J. Greskovich, P. Fu, J. Wasman, R. Rezaee, M. Machtay and P. Savvides. Phase II study of concurrent chemoradiation with bevacizumab and docetaxel for treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN). International Journal of Radiation Oncology Biology Physics. 2011. 81:S77	Abstract Only
N. Joshi, S. Mallick, A. Gandhi, S. Pandit, B. Mohanti, G. Rath, D. Sharma and P. Julka. Reirradiation in head-and-neck cancers: An indian tertiary cancer center experience. International Journal of Radiation Oncology Biology Physics. 2012. 84:S476	Abstract Only
N. Lee, C. Akazawa, P. Akazawa, J. M. Quivey, C. Tang, L. J. Verhey and P. Xia. A forward-planned treatment technique using multisegments in the treatment of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2004. 59:584-94	Nonrelevant Study Design
N. Riaz, S. Jaffery, M. Hu, S. Wolden, S. Rao and N. Lee. Is IMRT associated with inferior outcomes for T1-2N0 squamous cell carcinoma of the larynx?. International Journal of Radiation Oncology Biology Physics. 2012. 84:S495	Abstract Only
N. Wiedenmann, S. Bucher, M. Mix, M. Hentschel, M. I. Bittner, S. Adebahr, C. Offermann, U. Nestle, W. Weber and A. Grosu. Tumor hypoxia in head and neck cancer during radiochemotherapy evaluated with serial [18f]-fluoromisonidazole pet. Radiotherapy and Oncology. 2012. 102:S163-S164	Abstract Only
N. Y. Lee, F. F. de Arruda, D. R. Puri, S. L. Wolden, A. Narayana, J. Mechalakos, E. S. Venkatraman, D. Kraus, A. Shaha, J. P. Shah, D. G. Pfister and M. J. Zelefsky. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2006. 66:966-74	Included in Original CER
O. Ardenfors, D. Josefsson and A. Dasu. Are IMRT treatments in the H&N region increasing the risk of secondary cancers?. Radiotherapy and Oncology. 2012. 103:S569-S570	Abstract Only
O. K. Jilani, P. Singh, A. G. Wernicke, D. I. Kutler, W. Kuhel, P. Christos, D. Nori, A. Sabbas, K. S. C. Chao and B. Parashar. Radiation therapy is well tolerated and produces excellent control rates in elderly patients with locally advanced head and neck cancers. Journal of Geriatric Oncology. 2012. 3:337-343	Nonrelevant Study Design
P. A. Paximadis, M. Christensen, D. Kamdar, G. Dyson, A. Sukari, H. Lin, H. Kim and G. Yoo. Up-front neck dissection followed by definitive chemoradiation in patients with regionally advanced head and neck cancer. International Journal of Radiation Oncology Biology Physics. 2011. 81:S546	Abstract Only
P. B. Romesser, M. M. Qureshi, L. A. Kachnic and M. Truong. Non-english speaking language rather than non-white race predicts treatment outcomes in patients treated with radiotherapy (RT) for head and neck cancer (HNC). International Journal of Radiation Oncology Biology Physics. 2011. 81:S556-S557	Abstract Only
P. B. Romesser, M. M. Qureshi, R. M. Subramaniam, O. Sakai, S. Jalisi and M. T. Truong. A prognostic volumetric threshold of gross tumor volume in head and neck cancer patients treated with radiotherapy. American Journal of Clinical Oncology: Cancer Clin. 2012. #volume#:#pages#	Nonrelevant Study Design

Citation	Reason for exclusion
P. C. Levendag, D. N. Teguh, F. Keskin-Cambay, A. Al-Mamgani, P. Van Rooij, E. Astreinidou, S. L. S. Kwa, B. Heijmen, D. A. Monserez and S. O. S. Osman. Single vocal cord irradiation: A competitive treatment strategy in early glottic cancer. Radiotherapy and Oncology. 2011. 101:415-419	Nonrelevant Study Design
P. C. Levendag, D. N. Teguh, P. Voet, H. van der Est, I. Noever, W. J. de Kruijf, I. K. Kolkman-Deurloo, J. B. Prevost, J. Poll, P. I. Schmitz and B. J. Heijmen. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol. 2007. 85:64-73	Nonrelevant Study Design
P. C. Levendag, F. J. Lagerwaard, C. de Pan, I. Noever, A. van Nimwegen, O. Wijers and P. J. Nowak. High-dose, high-precision treatment options for boosting cancer of the nasopharynx. Radiother Oncol. 2002. 63:67-74	Nonrelevant Study Design
P. Dirix and S. Nuyts. Value of intensity-modulated radiotherapy in stage IV head-and-neck squamous cell carcinoma. *International Journal of Radiation Oncology Biology Physics.* 2010. 78:1373-1380	Overlapping Patient Population
P. Graff, M. Lapeyre, E. Desandes, C. Ortholan, R. J. Bensadoun, M. Alfonsi, P. Maingon, P. Giraud, J. Bourhis, V. Marchesi, A. Mege and D. Peiffert. Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: matched-pair comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2007. 67:1309-17	Nonrelevant Study Design
P. Levendag, D. N. Teguh, F. Keskin-Cambay, S. L. S. Kwa, P. Rooij Van, A. Al-Mamgani, E. Astreinidou, B. Heijmen, M. Hoogeman and S. O. S. Osman. Single vocal cord irradiation - A competitive treatment strategy in early glottic cancer. European Journal of Cancer. 2011. 47:S561	Abstract Only
P. M. Braam, C. H. Terhaard, J. M. Roesink and C. P. Raaijmakers. Intensity-modulated radiotherapy significantly reduces xerostomia compared with conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2006. 66:975-80	Nonrelevant Study Design
P. Mohindra, P. A. Wiederholt, H. M. Geye, D. Khuntia, T. Hoang, A. M. Traynor, T. Speer, T. M. McCulloch, G. K. Hartig and P. M. Harari. Squamous cell carcinoma of the oropharynx: 20-year outcome results. International Journal of Radiation Oncology Biology Physics. 2012. 84:S481	Abstract Only
P. Paximadis, G. Yoo, H. S. Lin, J. Jacobs, A. Sukari, G. Dyson, M. Christensen and H. Kim. Concurrent chemoradiotherapy improves survival in patients with hypopharyngeal cancer. International Journal of Radiation Oncology Biology Physics. 2012. 82:1515-1521	Nonrelevant Study Design
P. R. Patel, J. Lee, D. Kundu, K. Temple, R. May, W. Lee, D. Yoo and D. Brizel. Postoperative radiation therapy for salivary gland tumors: Factors associated with treatment failure and toxicity. International Journal of Radiation Oncology Biology Physics. 2012. 84:S502-S503	Abstract Only
P. Y. Chen, H. H. Chen, J. R. Hsiao, M. W. Yang, W. T. Hsueh, S. T. Tasi, F. C. Lin and Y. H. Wu. Intensity-modulated radiotherapy improves outcomes in postoperative patients with squamous cell carcinoma of the oral cavity. Oral Oncol. 2012. 48:747-52	Nonrelevant Study Design
Q. Guo, W. Jiang, S. Lin, L. Yang, C. Chen, L. Xu, J. Wu and J. Pan. Radiation therapy for locoregionally advanced nasopharyngeal carcinoma in elderly patients. Journal of Radiation Oncology. 2012. 1:323-332	Nonrelevant Study Design
R. Banner, S. Gwynne, N. Palaniappan, J. Mathlin, S. Beachus, T. Rackley, L. Moss and M. Evans. Acute toxicity of chemo-IMRT for oropharyngeal cancer (OPC). A prospective audit compared with published data. Radiotherapy and Oncology. 2012. 103:S453-S454	Abstract Only
R. Beesley, J. Rieger, S. Compton, M. Parliament, H. Seikaly and J. Wolfaardt. Comparison of tooth loss between intensity-modulated and conventional radiotherapy in head and neck cancer patients. Journal of Otolaryngology - Head and Neck Surgery. 2012. 41:389-395	Nonrelevant Study Design
R. C. Miller, M. Lodge, M. H. Murad and B. Jones. Controversies in clinical trials in proton radiotherapy: The present and the future. Seminars in Radiation Oncology. 2013. 23:127-133	Nonprimary Data

Citation	Reason for exclusion
R. I. Smee, N. S. Meagher, K. Broadley, T. Ho, J. R. Williams and G. P. Bridger. Recurrent nasopharyngeal carcinoma: current management approaches. Am J Clin Oncol. 2010. 33:469-73	Nonrelevant Study Design
R. J. Bensadoun, D. Riesenbeck, P. B. Lockhart, L. S. Elting, F. K. L. Spijkervet and M. T. Brennan. A systematic review of trismus induced by cancer therapies in head and neck cancer patients. Supportive Care in Cancer. 2010. 18:1033-1038	Nonprimary Data
R. J. H. M. Steenbakkers, I. Beetz, O. Chouvalova, P. Doornaert, D. Rietveld, B. F. A. M. Van Der Laan, A. Vissink, H. P. Bijl, P. Van Luijk and J. A. Langendijk. Quantec dose volume constraints for parotid glands are feasible only in a minority of H&N patients treated with IMRT. Radiotherapy and Oncology. 2012. 103:S202-S203	Abstract Only
R. Rahmati, N. Lee, G. Linkov, A. Mohebati and D. Kraus. Outcomes in recurrent head and neck cancer after salvage surgery and flap reconstruction with postoperative reirradiation (RE-RT). International Journal of Radiation Oncology Biology Physics. 2011. 81:S548	Abstract Only
S. B. Jensen, A. M. L. Pedersen, A. Vissink, E. Andersen, C. G. Brown, A. N. Davies, J. Dutilh, J. S. Fulton, L. Jankovic, N. N. F. Lopes, A. L. S. Mello, L. V. Muniz, C. A. Murdoch-Kinch, R. G. Nair, J. J. Napenas, A. Nogueira-Rodrigues, D. Saunders, B. Stirling, I. Von Bultzingslowen, D. S. Weikel, L. S. Elting, F. K. L. Spijkervet and M. T. Brennan. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: Management strategies and economic impact. Supportive Care in Cancer. 2010. 18:1061-1079	Nonprimary Data
S. B. Jensen, A. M. L. Pedersen, A. Vissink, E. Andersen, C. G. Brown, A. N. Davies, J. Dutilh, J. S. Fulton, L. Jankovic, N. N. F. Lopes, A. L. S. Mello, L. V. Muniz, C. A. Murdoch-Kinch, R. G. Nair, J. J. Napenas, A. Nogueira-Rodrigues, D. Saunders, B. Stirling, I. Von Bultzingslowen, D. S. Weikel, L. S. Elting, F. K. L. Spijkervet and M. T. Brennan. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: Prevalence, severity and impact on quality of life. Supportive Care in Cancer. 2010. 18:1039-1060	Nonprimary Data
S. Chopra, D. Kamdar, O. E. Tulunay Ugur, G. Chen, B. Peshek, M. Marunick, H. Kim, H. S. Lin and J. Jacobs. Factors predictive of severity of osteoradionecrosis of the mandible. Head and Neck. 2011. 33:1600-1605	Nonrelevant Study Design
S. Clavel, D. H. A. Nguyen, B. Fortin, P. Despres, N. Khaouam, D. Donath, D. Soulires, L. Guertin and P. F. Nguyen-Tan. Simultaneous integrated boost using intensity-modulated radiotherapy compared with conventional radiotherapy in patients treated with concurrent carboplatin and 5-fluorouracil for locally advanced oropharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics. 2012. 82:582-589	Nonrelevant Study Design
S. Colbert, M. Algholmy, M. Gray, S. Walji and J. Davies. Management of the cervical lymph node metastasis of unknown origin. British Journal of Oral and Maxillofacial Surgery. 2011. 49:S43	Abstract Only
S. Das, S. G. Laskar, D. Gupta, T. Gupta, V. Murthy, A. Budrukkar and J. P. Agarwal. Hearing loss after conformal radiotherapy in non-nasopharyngeal head and neck cancer-A prospective study. Journal of Cancer Research and Therapeutics. 2012. 8:S186-S187	Abstract Only
S. E. Mowry, C. Tang, A. Sadeghi and M. B. Wang. Standard chemoradiation versus intensity-modulated chemoradiation: A quality of life assessment in oropharyngeal cancer patients. European Archives of Oto-Rhino-Laryngology. 2010. 267:1111-1116	Nonrelevant Study Design
S. F. Qiu, J. D. J. Lu, S. J. Lin, I. W. K. Tham, J. Lu and J. J. Pan. Three-dimensional conformal radiation therapy in the salvage of 212 locally recurrent nasopharyngeal carcinoma cases. International Journal of Radiation Oncology Biology Physics. 2011. 81:S508-S509	Abstract Only
S. Ghosh-Laskar, D. A. Chaukar, J. P. Agarwal, T. Gupta, A. Budrukkar and V. Murthy. Comparison of early quality of life (QOL) in patients with squamous cell carcinoma of the head and neck (HNSCC) treated with 3-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiotherapy (IMRT). Oral Oncology. 2011. 47:S56	Abstract Only

Citation	Reason for exclusion
S. Guha, C. G. Kelly, R. Guha, R. Achari, I. Mallick, V. Paleri, A. J. Munro and S. Chatterjee. Intensity modulated radiation therapy (IMRT) in the treatment of squamous carcinoma of the oropharynx: An overview. Journal of Cancer Science and Therapy. 2012. 4:77-83	Nonprimary Data
S. Gulliford, A. Miah, S. Brennan, M. Partridge, K. Harrington and C. Nutting. The dose-volume response of posterior fossa and brainstem with respect to acute fatigue. Radiotherapy and Oncology. 2011. 99:S428	Abstract Only
S. Gulliford, A. Miah, S. Brennan, M. Partridqe, K. Harrinqton and C. Nutting. Dose-volume atlases of complication incidence for acute fatigue: Data from the parsport trial. Radiotherapy and Oncology. 2011. 98:S28	Abstract Only
S. H. Chan, W. T. Ng, K. L. Kam, M. C. H. Lee, C. W. Choi, T. K. Yau, A. W. M. Lee and S. K. Chow. Sensorineural Hearing Loss After Treatment of Nasopharyngeal Carcinoma: A Longitudinal Analysis. International Journal of Radiation Oncology Biology Physics. 2009. 73:1335-1342	Nonrelevant Study Design
S. H. Kataoka, F. C. Setzer, E. R. Fregnani, O. F. Pessoa, E. Gondim, Jr. and C. L. Caldeira. Effects of 3-dimensional conformal or intensity-modulated radiotherapy on dental pulp sensitivity during and after the treatment of oral or oropharyngeal malignancies. J Endod. 2012. 38:148-52	Nonrelevant Outcome
S. Iganej, G. L. Buchschacher and I. A. Abdalla. Triweekly carboplatin alone in the treatment of oropharyngeal carcinoma with definitive concurrent chemoradiation: Outcomes of 120 unselected patients and a comparison to the RTOG 0129 regimen results. Journal of Clinical Oncology. 2012. 30:#pages#	Abstract Only
S. Jabbari, H. M. Kim, M. Feng, A. Lin, C. Tsien, M. Elshaikh, J. E. Terrel, C. Murdoch-Kinch and A. Eisbruch. Matched case-control study of quality of life and xerostomia after intensity-modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. Int J Radiat Oncol Biol Phys. 2005. 63:725-31	Included in Original CER
S. K. Gupta, R. Ray, S. Chatterjee, T. Sinha, S. Sinha, D. Gowardhanan, R. Achari and I. Mallick. Predictors of weight loss during conformal radiotherapy for head and neck cancers-How important are PTV volumes?. Journal of Cancer Research and Therapeutics. 2012. 8:S192-S193	Abstract Only
S. K. Mullapally, B. K. Mohanti, M. A. Laviraj, S. Thulkar, V. Subramani, A. Sharma, S. Bhasker, R. M. Pandey, A. Thakkar and G. K. Rath. Image guided adaptive radiotherapy (IGART) of head and neck cancer: Volumetric and clinical evidence. Radiotherapy and Oncology. 2012. 103:S284	Abstract Only
S. L. Gulliford, A. B. Miah, S. Brennan, D. McQuaid, C. H. Clark, M. Partridge, K. J. Harrington, J. P. Morden, E. Hall and C. M. Nutting. Dosimetric explanations of fatigue in head and neck radiotherapy: an analysis from the PARSPORT Phase III trial. #journal#. 2013. #volume#:205-12	Nonprimary Data
S. L. Shiao, J. M. Quivey, V. K. Weinberg, D. W. Eisele, C. M. Glastonbury and S. S. Yom. Radiotherapy for carcinoma of the hypopharynx over four decades: Experience at the university of california san francisco. International Journal of Radiation Oncology Biology Physics. 2011. 81:S514-S515	Abstract Only
S. L. Wolden, W. C. Chen, D. G. Pfister, D. H. Kraus, S. L. Berry and M. J. Zelefsky. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys. 2006. 64:57-62	Included in Original CER
S. Laskar, G. Bahl, M. Muckaden, S. K. Pai, T. Gupta, S. Banavali, B. Arora, D. Sharma, P. A. Kurkure, M. Ramadwar, S. Viswanathan, V. Rangarajan, S. Qureshi, D. D. Deshpande, S. K. Shrivastava and K. A. Dinshaw. Nasopharyngeal Carcinoma in Children: Comparison of Conventional and Intensity-Modulated Radiotherapy. International Journal of Radiation Oncology Biology Physics. 2008. 72:728-736	Nonrelevant Study Design
S. M. Karandikar, K. Bokil, S. P. Deshmukh, S. Basu, B. Shinde, H. Patil and N. Gupta. Retrospective analysis of head and neck cancer patients successfully treated with chemoradiation plus nimotuzumab. Journal of Clinical Oncology. 2011. 29:#pages#	Abstract Only
S. M. Magrini, S. Tonoli, L. Costa, N. Pasinetti, F. Paiar, L. Livi, G. Simontacchi, I. Meattini, L. Pegurri, P. Borghetti, P. Frata, P. Ponticelli, M. Buglione and G. Biti. A benchmark study on 883 nasopharyngeal cancer patients treated in two Italian centres from 1977 to 2000. Part II: Evolving technical choices and toxicity patterns. Radiol Med. 2012. 117:715-24	Nonrelevant Study Design

Citation	Reason for exclusion
S. M. McBride, R. J. Parambi, J. W. Jang, T. Goldsmith, P. M. Busse and A. W. Chan. Intensity-modulated versus conventional radiation therapy for oropharyngeal carcinoma: long-term dysphagia and tumor control outcomes. Head Neck. 2014. 36:492-8	Nonrelevant Study Design
S. McBride, J. J. Wang, P. M. Busse and A. W. Chan. Predictors of distant metastasis in locally advanced oropharyngeal squamous cell carcinoma. International Journal of Radiation Oncology Biology Physics. 2011. 81:S489-S490	Abstract Only
S. Rathod, T. Gupta, S. Laskar, V. Murthy, A. Budrukkar, K. Prabhash, P. Chaturvedi and J. Agarwal. Change in health-related quality of life scores predict survival in head-and-neck squamous cell carcinoma treated with definitive high precision radiation therapy: Evidence from a prospective study. International Journal of Radiation Oncology Biology Physics. 2012. 84:S649	Abstract Only
S. Tonoli, D. Alterio, O. Caspiani, A. Bacigalupo, F. Bunkheila, M. Cianciulli, A. Merlotti, A. Podhrdska, M. Rampino and D. Cante. Nasopharyngeal cancer: Treatment technique, dose homogeneity and acute toxicity in an Italian prospective study. Radiotherapy and Oncology. 2012. 103:S277-S278	Abstract Only
S. Tonoli, S. M. Magrini, L. Costa, F. Paiar, G. Simontacchi, V. Scotti, N. Pasinetti, R. Barca, D. Barbieri, A. De Stefani, E. Cellai, M. Buglione and G. Biti. A benchmark study on 883 nasopharyngeal cancer patients treated in two Italian centres from 1977 to 2000. Part I: Evolving technical choices and survival. Radiol Med. 2012. 117:690-714	Nonrelevant Study Design
S. Tribius and C. Bergelt. Intensity-modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: Is there a worthwhile quality of life gain?. Cancer Treatment Reviews. 2011. 37:511-519	Nonprimary Data
S. W. Loo, K. Geropantas, C. Beadsmoore, P. Q. Montgomery, W. M. C. Martin and T. W. Roques. Neck dissection can be avoided after sequential chemoradiotherapy and negative post-treatment positron emission tomography-computed tomography in N2 Head and neck squamous cell carcinoma. Clinical Oncology. 2011. 23:512-517	Nonrelevant Study Design
S. Wan Leung, T. F. Lee, C. Y. Chien, P. J. Chao, W. L. Tsai and F. M. Fang. Health-related Quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. BMC Cancer. 2011. 11:#pages#	Nonrelevant Study Design
T. Bledsoe, A. Noble, G. Hunter, L. Rybicki, A. Hoschar, D. Chute, J. P. Saxton, J. F. Greskovich, D. J. Adelstein and S. A. Koyfman. Oropharyngeal squamous cell carcinoma (OPSCC) with known human papillomavirus (HPV) status treated with definitive chemoradiation therapy: Patterns of failure and toxicity outcomes. International Journal of Radiation Oncology Biology Physics. 2012. 84:S478	Abstract Only
T. Dijkema, C. P. J. Raaijmakers, R. K. Ten Haken, J. M. Roesink, P. M. Braam, A. C. Houweling, M. A. Moerland, A. Eisbruch and C. H. J. Terhaard. Parotid gland function after radiotherapy: The combined Michigan and Utrecht experience. International Journal of Radiation Oncology Biology Physics. 2010. 78:449-453	Nonrelevant Study Design
T. Goldsmith, J. Wang, A. Holman and A. W. Chan. Risk of Cervical Esophageal Stricture with Intensity Modulated vs. Conventional Radiation Therapy for Head and Neck Cancer: A Systemic Review. International Journal of Radiation Oncology Biology Physics. 2010. 78:S453-S454	Abstract Only
T. Gupta, S. Jain, J. P. Agarwal, S. Ghosh-Laskar, R. Phurailatpam, R. Pai-Shetty and K. A. Dinshaw. Prospective assessment of patterns of failure after high-precision definitive (chemo)radiation in head-and-neck squamous cell carcinoma. International Journal of Radiation Oncology Biology Physics. 2011. 80:522-531	Nonrelevant Study Design
T. Hoang, C. Zhang, H. M. Geye, T. Speer, M. Yu, P. A. Wiederholt, J. C. Kakuske, A. M. Traynor, J. F. Cleary, S. H. Dailey, C. N. Ford, T. M. McCulloch, G. K. Hartig and P. M. Harari. Gender associations in head and neck squamous cell carcinoma (HNSCC). Journal of Clinical Oncology. 2012. 30:#pages#	Abstract Only
T. Kodaira, H. Tachibana, N. Tomita, Y. Oshima, K. Hirata, J. Ito, Y. Goto and N. Fuwa. Clinical efficacy of helical tomotherapy for nasopharyngeal cancer treated with definite concurrent chemoradiation therapy. International Journal of Radiation Oncology Biology Physics. 2012. 84:S483	Abstract Only

Citation	Reason for exclusion
T. R. Koo, H. G. Wu, K. H. Kim, M. W. Sung and C. I. Park. Treatment outcomes of radiotherapy for tonsillar carcinoma in the era of intensity-modulated radiotherapy. European Journal of Cancer. 2011. 47:S565-S566	Abstract Only
T. Shahid, M. S. Chowdhury, G. S. Bhattacharya, S. Murshed, S. Poddar and K. Bhattacharya. Quality of life in head and neck cancer patients after treatment with radical radiotherapy alone or in combination with concurrent chemoradiation. Journal of Cancer Research and Therapeutics. 2012. 8:S169	Abstract Only
T. Terasawa, T. Dvorak, S. Ip, G. Raman, J. Lau and T. A. Trikalinos. Systematic review: Charged-particle radiation therapy for cancer. Annals of Internal Medicine. 2009. 151:556-565	Nonprimary Data
T. W. Leung, S. Y. Tung, W. K. Sze, F. C. Wong, K. K. Yuen, C. M. Lui, S. H. Lo, T. Y. Ng and S. K. O. Treatment results of 1070 patients with nasopharyngeal carcinoma: an analysis of survival and failure patterns. Head Neck. 2005. 27:555-65	Nonrelevant Study Design
T. W. Roques, S. W. Loo, K. Geropantas, C. Beadsmoore, I. Worthington, J. Harrowven and C. Martin. Response assessment with FDG-PET/CT following definitive radiochemotherapy in head and neck cancer. Radiotherapy and Oncology. 2012. 103:S279	Abstract Only
U. Schick, M. Betz, P. Ghadjar, J. H. A. M. Kaanders and M. Ozsahin. Outcome and prognostic factors in adenosquamous carcinoma of the head and neck: A multi center rare cancer network study. International Journal of Radiation Oncology Biology Physics. 2011. 81:S541-S542	Abstract Only
U. Schick, M. Betz, P. Ghadjar, J. H. A. M. Kaanders, C. Demiroz and M. Ozsahin. Outcome and prognostic factors in adenosquamous carcinoma of the head and neck - A multicenter rare cancer network study. European Journal of Cancer. 2011. 47:S555	Abstract Only
V. Budach, C. H. Cho, B. Sedlmaier, M. Wittlinger, H. Iro, E. C. Rita, M. Hautmann, J. Strutz, M. Flentje, B. Hueltenschmidt, L. Moser, M. Bleif, W. Budach, S. Staar, G. Becker, S. Tribius, P. C. Feyer, K. D. Wernecke and J. Werner. Five years' results of the German ARO 04-01 trial of concurrent 72 Gy hyperfractionated accelerated radiation therapy (HART) plus once weekly cisplatinum/5-FU versus mitomycin C/5-FU in stage IV head and neck cancer. Journal of Clinical Oncology. 2012. 30:#pages#	Abstract Only
V. Gregoire, P. Mamgon, S. Nuyts, G. Calais, N. Grosso, U. Thalin, P. Sorensen, T. Nielsen and E. Brun. An open-label, phase I/II dose-escalation trial investigating zalutumumab, a human monoclonal EGF receptor (EGFR) antibody. In combination with chemoradiation as first line treatment of patients with locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN). Radiotherapy and Oncology. 2010. 96:S309-S310	Abstract Only
V. Lau, L. M. Chen, D. G. Farwell, Q. Luu, P. Donald and A. M. Chen. Postoperative radiation therapy for head and neck cancer in the setting of orocutaneous and pharyngocutaneous fistula. American Journal of Clinical Oncology: Cancer Clinical Trials. 2011. 34:276-280	Nonrelevant Study Design
V. M. Duarte, Y. F. Liu, S. Rafizadeh, T. Tajima, V. Nabili and M. B. Wang. Comparison of dental health of patients with head and neck cancer receiving IMRT vs conventional radiation. Otolaryngol Head Neck Surg. 2014. 150:81-6	Nonrelevant Study Design
V. Murthy, K. Narang, J. P. Agarwal, S. Ghosh-Laskar, T. Gupta and A. Budrukkar. Hypothyroidism after head and neck 3DCRT and IMRT: Prospective data from two randomized trials. Radiotherapy and Oncology. 2012. 103:S176	Abstract Only
V. Murthy, K. Narang, S. Ghosh-Laskar, T. Gupta, A. Budrukkar and J. P. Agrawal. Hypothyroidism after 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy for head and neck cancers: Prospective data from 2 randomized controlled trials. Head Neck. 2013. #volume#:#pages#	Nonprimary Data
W. C. Chen, T. Z. Hwang, W. H. Wang, C. H. Lu, C. C. Chen, C. M. Chen, H. H. Weng, C. H. Lai and M. F. Chen. Comparison between conventional and intensity-modulated post-operative radiotherapy for stage III and IV oral cavity cancer in terms of treatment results and toxicity. Oral Oncology. 2009. 45:505-510	Nonrelevant Study Design

Citation	Reason for exclusion
W. Duthoy, T. Boterberg, F. Claus, P. Ost, L. Vakaet, S. Bral, F. Duprez, M. Van Landuyt, H. Vermeersch and W. De Neve. Postoperative intensity-modulated radiotherapy in sinonasal carcinoma: clinical results in 39 patients. Cancer. 2005. 104:71-82	Included in Original CER
W. F. Mourad, K. S. Hu, R. A. Shourbaji, D. Berlach, W. Lin, E. Kaplan-Marans, M. Urken, B. Culliney, M. Persky and L. B. Harrison. Outcomes of parotid gland tumors treated with surgery and postoperative radiation therapy. International Journal of Radiation Oncology Biology Physics. 2012. 84:S499	Abstract Only
W. F. Mourad, K. S. Hu, R. A. Shourbaji, W. Lin, E. Kaplan-Marans, S. Manolidis, B. Culliney, M. Urken, M. Persky and L. B. Harrison. Pattern of failure of head and neck malignancy (HNM) with perineural invasion (PNI). International Journal of Radiation Oncology Biology Physics. 2012. 84:S506-S507	Abstract Only
W. L. Kuang, Q. Zhou and L. F. Shen. Outcomes and prognostic factors of conformal radiotherapy versus intensity-modulated radiotherapy for nasopharyngeal carcinoma. Clin Transl Oncol. 2012. 14:783-90	Nonrelevant Study Design
W. Nijdam, P. Levendag, I. Noever, C. U. Groot and M. Agthoven. Cancer in the oropharynx: cost calculation of different treatment modalities for controlled primaries, relapses and grade III/IV complications. Radiother Oncol. 2005. 77:65-72	Nonrelevant Study Design
W. S. Liu, H. C. Kuo, J. C. Lin, M. C. Su, J. K. Lee, M. J. Chou, M. C. Chou and H. Lee. Assessment of salivary function change in nasopharyngeal carcinoma treated by parotid-sparing radiotherapy. Cancer J. 2006. 12:494-500	Nonrelevant Study Design
W. S. Liu, S. P. Lee, J. K. Lee, M. C. Su, G. D. Chen, H. S. Lee and H. Lee. Factors influencing the parotid function in nasopharyngeal carcinoma treated with parotid-sparing radiotherapy. Jpn J Clin Oncol. 2006. 36:626-31	Nonrelevant Study Design
X. Ou, C. Shen, L. Kong, X. Wang, J. Ding, Y. Gao, T. Xu and C. Hu. Treatment outcome of nasopharyngeal carcinoma with retropharyngeal lymph nodes metastasis only and the feasibility of elective neck irradiation. Oral Oncol. 2012. 48:1045-50	Nonrelevant Study Design
Y. C. Ahn, K. C. Lee, D. Y. Kim, S. J. Huh, I. H. Yeo, D. H. Lim, M. K. Kim, K. H. Shin, S. Park and S. H. Chang. Fractionated stereotactic radiation therapy for extracranial head and neck tumors. Int J Radiat Oncol Biol Phys. 2000. 48:501-5	Nonrelevant Study Design
Y. Doi, M. Kenjyo, I. Takahashi, Y. Takeuti, S. Takahashi, I. Nishibuti, Y. Kaneyasu, Y. Murakami, T. Kimura and Y. Nagata. The frequency of adverse events by radiation therapy for atomic bomb survivors with cancer. International Journal of Radiation Oncology Biology Physics. 2012. 84:S538	Abstract Only
Y. H. Wu, H. M. Wang, H. H. W. Chen, C. Y. Lin, E. Y. C. Chen, K. H. Fan, S. F. Huang, I. H. Chen, C. T. Liao, A. J. Cheng and J. T. C. Chang. Hypothyroidism After Radiotherapy for Nasopharyngeal Cancer Patients. International Journal of Radiation Oncology Biology Physics. 2010. 76:1133-1139	Nonrelevant Study Design
Y. Li, J. M. Taylor, R. K. Ten Haken and A. Eisbruch. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. Int J Radiat Oncol Biol Phys. 2007. 67:660-9	Nonprimary Data
Y. Shibamoto, M. Okamoto, M. Kobayashi, S. Ayakawa, H. Iwata, C. Sugie, Y. Mitsuishi and H. Takahashi. Imax (immunity-maximized) cancer therapy: Combination of dendritic cell-based vaccine and intensity modulated radiation. International Journal of Radiation Oncology Biology Physics. 2012. 84:S74-S75	Abstract Only
Y. Shibamoto, M. Okamoto, M. Kobayashi, S. Ayakawa, H. Iwata, C. Sugie, Y. Mitsuishi and H. Takahashi. Immune-maximizing (IMAX) therapy for cancer: Combination of dendritic cell vaccine and intensity-modulated radiation. Mol Clin Oncol. 2013. 1:649-654	Nonrelevant Study Design
Y. Sun and B. Zheng. The clinical outcomes of radiation therapy with VMAT in locoregionally advanced nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics. 2012. 84:S489	Abstract Only
Y. Wu. Postoperative IMRT improved outcome in patients with oral cavity squamous cell carcinoma. Radiotherapy and Oncology. 2012. 103:S447	Abstract Only
Y. Zeidan, J. D. Murphy, C. Chan, Y. An, M. Kaplan, A. Colevas, C. Kong and Q. Le. Postoperative radiation therapy for minor salivary gland carcinomas of the head and neck: Long-term outcomes. International Journal of Radiation Oncology Biology Physics. 2012. 84:S500	Abstract Only

Citation	Reason for exclusion
Y. Zhang, Z. A. Lin, J. J. Pan, Z. Zheng, L. Yang, S. J. Lin and F. Zheng. Concurrent control study of different radiotherapy for primary nasopharyngeal carcinoma: Intensity-modulated radiotherapy versus conventional radiotherapy. Chinese Journal of Cancer. 2009. 28:21-26	Nonrelevant Study Design
Z. H. Wang, C. Yan, Z. Y. Zhang, C. P. Zhang, H. S. Hu, W. Y. Tu, J. Kirwan and W. M. Mendenhall. Outcomes and xerostomia after postoperative radiotherapy for oral and oropharyngeal carcinoma. Head Neck. 2013. #volume#:#pages#	Nonrelevant Study Design
Z. Y. Shao, Z. S. Tang, C. Yan, Y. T. Jiang, R. Ma, Z. Liu and Z. W. Huang. Effects of intensity-modulated radiotherapy on human oral microflora. J Radiat Res. 2011. 52:834-9	Nonrelevant Outcome