Comparative Effectiveness Review
Number 144

Effective Health Care Program

Radiotherapy Treatments for Head and Neck Cancer Update

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

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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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

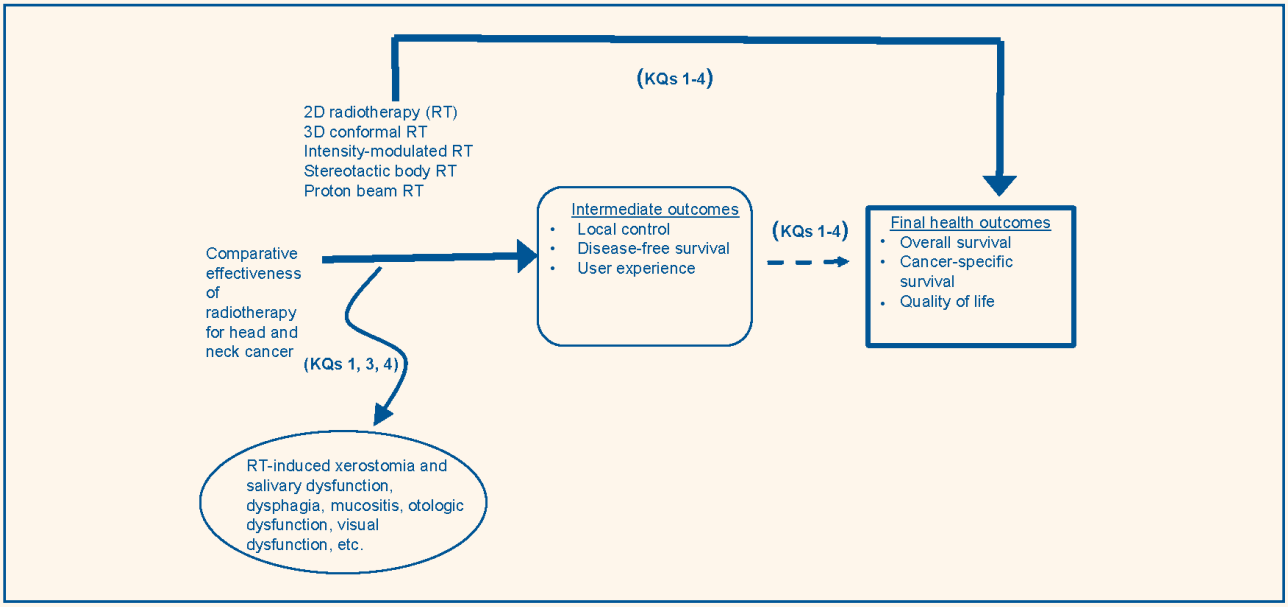


Figure A depicts the Key Questions (KQs) within the context of the PICOTS described in the previous section. In general, the figure illustrates how the interventions 3DCRT, IMRT, SBRT, and PBT may result in intermediate outcomes (e.g., local tumor control, disease-free survival) and final health outcomes (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.

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.

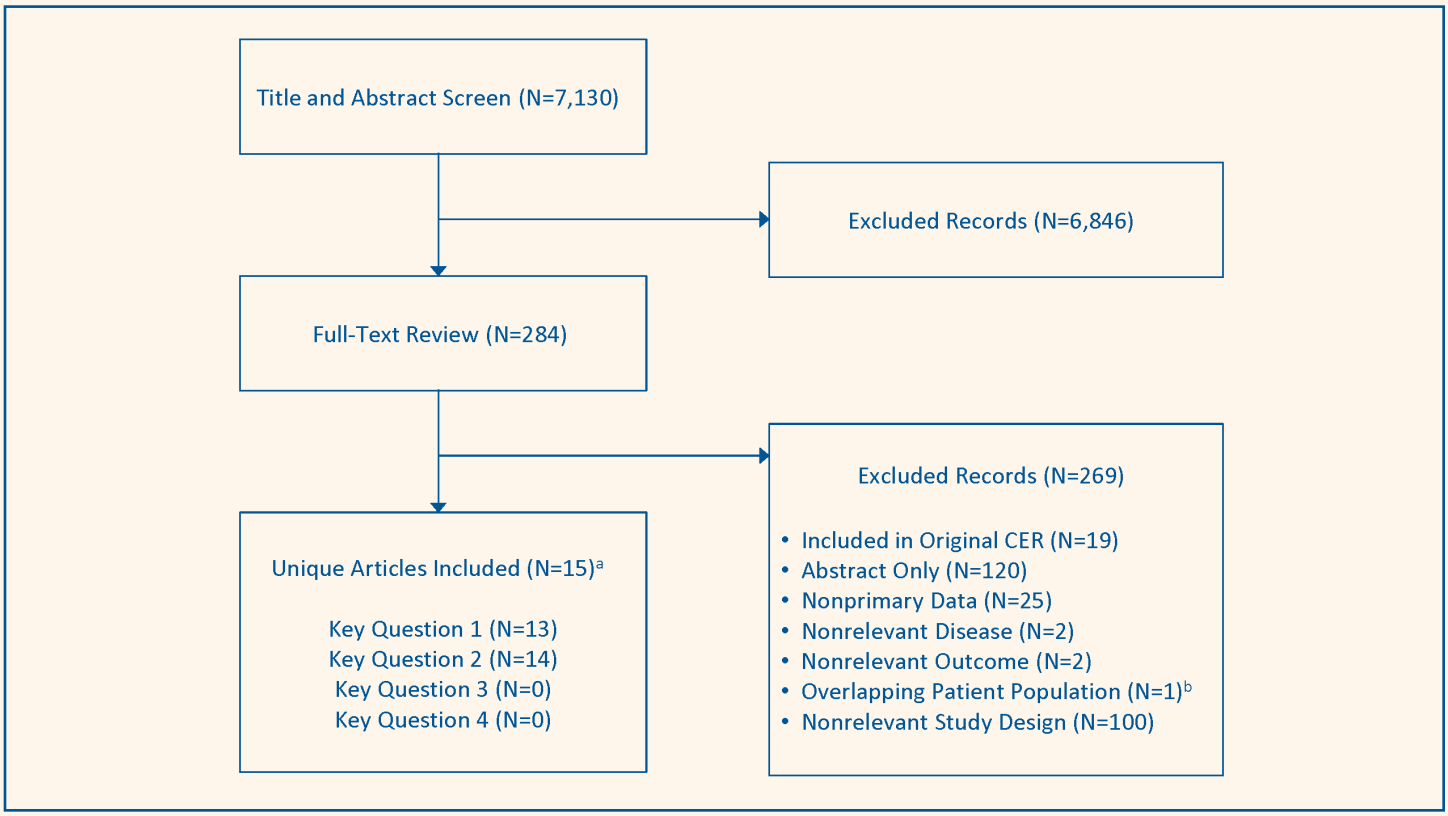
Results of Literature Searches

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.

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, 201214) 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 trial14 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
	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 RCT14 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 RCT14 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
		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	

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
	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, 201315) 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 RCT15 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 RCT15 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.

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
	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 Rathod15) 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.

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)

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.

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.

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Full Report

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