

Evidence-based Practice Center Systematic Review Protocol

Project Title: Radiotherapy Treatments for Head and Neck Cancer Update

I. Background and Objectives for the Systematic Review

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). This CER examined evidence on the following radiotherapy (RT) interventions used in the treatment of head and neck cancers: conventional or two-dimensional RT (2DRT); three-dimensional conformal RT (3DRT), intensity-modulated RT (IMRT), and proton beam RT (PBRT). Key questions in the CER asked 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; 3) when used in certain anatomic locations or patient subpopulations; and, finally, 4) 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 xerostomia was reduced and QoL domains related to xerostomia were improved in patients treated with IMRT compared to those who received either 3DRT 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, 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 2011, AHRQ published a surveillance report that used methods developed by the RAND and Ottawa EPCs to assess whether an update of CER No. 20 was merited. The surveillance report evaluated an updated literature search, performed according to the original CER No. 20 Methods, and solicited input from clinical experts in the treatment of head and neck cancer. Its results suggested that several conclusions for Key Questions 1, 2, and 3 of the original CER are possibly out of date. The conclusions of the surveillance report were used by AHRQ to prioritize an update of AHRQ CER No. 20 in 2013.

In this update, we will systematically review and assess evidence on stereotactic body RT (SBRT), a newer RT modality that was not widely available when we prepared the original CER but has subsequently come into practice. We will exclude 2DRT from further review, as it is no longer widely used to treat head and neck cancer in the United

States. We will not seek evidence on brachytherapy, as this RT technique is not commonly used in definitive treatment of head and neck cancers. Thus, we will review and assess evidence on 3DRT, IMRT, PBRT and SBRT, addressing Key Questions as in the original work, using essentially the same Methods and search strategies modified to address the changes in the list of interventions. We will organize clinical evidence according to treatment, abstracted only from direct comparative studies (randomized or non-randomized) of RT methods used in definitive treatment for any head and neck cancer. The best evidence would be from comparative studies of RT modalities as sole interventions. However, if we do not identify comparative evidence on definitive primary radiotherapies, we will organize and analyze evidence according to treatment settings actually reported (e.g., concurrent chemoradiotherapy, adjuvant radiotherapy, etc.), as in the original CER.

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% of all head and neck cancers, and accounted for approximately 3% (about 50,000) of all new cancer cases and 2% (approximately 12,000) of all cancer deaths in 2010 in the United States.¹ While these cancers in total comprise a relatively small percentage of all cancers, together 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 2008.¹

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.² 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 United States has increased from 16.3% during the 1980s to 72.7% during the 2000s.^{3,4} Careful anatomic site stratification has shown that the age-adjusted incidence of oropharyngeal cancer is rising dramatically (estimated to be a 5% 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 disease and curable disease, whereas only a small percentage of these patients have demonstrable distant metastases. Treatment decisions are primarily determined by the size, location and aggressiveness traits of the primary tumor, the extent of nodal involvement, and the estimated functional

impact of therapy. Patient characteristics, which may include substantial co-morbidities and poor performance status, must also be considered in devising a comprehensive treatment plan.²

Aggressive multimodality treatments with curative intent may include surgery, radiotherapy and chemotherapy. Radiation therapy is the mainstay of treatment, offered to nearly 75% 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, and often with significant long term side effects. Curative surgical resection, when feasible without significant functional morbidity, is generally recommended for patients with early stage (I-II) SCCHN. Single-modality radiation therapy (RT) may be an alternative for these early-stage cases when functional concerns preclude the use of surgery. For patients with stage III SCCHN, surgery is considered generally appropriate in the absence of clinical nodal disease. For patients with N1–2 disease, a multi-modal approach may often be the preferred course of action, with resection followed by adjuvant RT or chemoradiotherapy (CRT) in order to decrease recurrence risk. Most recently, neoadjuvant chemotherapy (induction chemotherapy)^{5, 6} has also been used in some centers in these cases to decrease the risk of late distant recurrence. Depending on the expected post-surgical functional morbidity, non-surgical management with CRT may become the final treatment choice in cases where organ and functional preservation is a priority.

In this CER, our analyses will account for multimodal treatment strategies by organizing evidence according to these strategies used in direct comparative studies of the radiotherapy approaches. In one approach, we would compile studies with multimodal approaches such as surgery and chemotherapy that are similar between groups compared according to accepted benchmarks, such as guidelines from the National Comprehensive Cancer Network (NCCN) or the National Cancer Institute (NCI), and only the radiotherapy interventions differ. A second method would allow studies in which additional treatments differed, for example types of chemotherapies or proportions of patients who received such treatments, but in which results were statistically adjusted to account for such. In these ways we can attempt to ensure we are reflecting the efficacy of the RT methods on clinical outcomes minus confounding due to adjunct treatment effects.

Acute and late toxicities of radiotherapy in cancer patients represent important clinical outcomes that can substantially reduce quality of life and the ability of individuals to complete the entire planned course of treatment. Toxic effects associated with cancer therapies have been traditionally defined as occurring fewer than 90, and more than 90 days posttreatment, respectively. Several grading instruments have been created to assess these, including the National Cancer Institute Common Toxicity Criteria (NCI CTC) and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system. Other tools used to assess adverse events include the Subjective, Objective, Management, Analytic (SOMA) system, subjective and objective questionnaires, including some that are tailored specifically for the head and neck (e.g., EORTC QLQ-H&N35) and visual analog scales (VAS).

Treatment-associated adverse events assume greater importance in patients identified with HPV as the causative agent of head and neck cancer, compared to those with HPV-negative disease.⁴ Patients with HPV-positive oropharynx cancer not only appear to have a different clinical phenotype than HPV-negative cancers, but multiple large studies have demonstrated a better outcome for these patients, even when correcting for other known prognostic factors.⁷ This trend has led investigators to research de-intensification of treatment for patients with HPV-related head and neck cancers in order to limit toxicities, and alternatively intensifying treatment to improve tumor control in those with a significant HPV-negative with a smoking history.^{2,4} In this report, when possible, we will address HPV-positive patients as a separate entity relative to HPV-negative patients.

Radiotherapy in Head and Neck Cancer

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 to normal surrounding tissues (sometimes referred to as “organs at risk”). Therefore, mainly due to the close proximity of critical organs and the often large irradiation fields, the improved outcomes in these aggressive RT regimes come at the cost of increased treatment toxicity. In this regard, xerostomia is the most prevalent toxicity of radiotherapy to the head and neck and a major cause of reduced QoL. In addition to patient perception of dryness, it leads to impaired speech and swallow function. Radiation therapy also can accelerate dental caries and may cause osteoradionecrosis.

Radiation therapy 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.⁸ 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 upon survival rates and the adverse effect profile of conventional 2DRT has led to widespread adoption and application of conformal radiotherapy methods for definitive (curative) treatment of patients with SCCHN, with general abandonment of 2DRT in this role in the United States. Therefore, two-dimensional RT will not be considered in this report.

Conformal radiotherapy refers to modalities in which cytotoxic 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 three-dimensional radiation planning, the International 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).⁹ 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 external beam photon-based RT modalities used to treat SCCHN include three-dimensional conformal radiation therapy (3DRT); intensity-modulated radiation therapy (IMRT); and, stereotactic body radiation therapy (SBRT), which is also known as stereotactic ablative radiotherapy.⁸ For purposes of this report, we will use the term “SBRT.” Charged particle-based conformal external beam therapy such as proton beam radiotherapy (PBRT) is also available.

Brachytherapy refers to treatment with ionizing radiation whose source is applied to the surface of the body or within the body a short distance from the area being treated. It has a very limited role in very specific settings for which surgery is not indicated due to resulting profound disability and disfigurement (e.g., deep base of the tongue) and for which external beam RT methods are not able to be used safely and effectively. Given this rationale, and that this technique was not included in the original CER, we will not consider brachytherapy in this update.

3-Dimensional Conformal Radiotherapy (3DRT)

3DRT allows for more accurate and precise dose calculations than achieved with 2DRT by taking into account axial anatomy and complex tissue contours.⁸ Three-dimensional anatomic information from diagnostic computed tomography (CT) scans is used 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 tumor volume, with very rapid dose fall-off in surrounding tissues. A 3DRT treatment protocol typically comprises 60-70 Gray (Gy) delivered in 25-40 fractions (usually 1.8-2 Gy) delivered over a period of 5-10 weeks.

Intensity-Modulated Radiotherapy (IMRT)

In the 1990s, technological and computer treatment planning advances led to the development of intensity-modulated radiation therapy (IMRT).^{8, 10} Compared to 3DRT, IMRT is a newer, more complex, and resource-intensive form of radiation therapy that delivers a high dose of ionizing radiation conformally to the target volume while sparing uninvolved, normal tissues. A typical total dose of 60 to 70 Gy is usually delivered in 25-40 fractions over a period of 5-10 weeks. By varying the beam intensity across shaped radiation fields, IMRT holds the promise to reduce radiation dose to organs at risk, such as the parotid glands, potentially resulting in reduced xerostomia and improved QoL as compared with conventional radiotherapy. A number of technological advances within the general category of IMRT are available or under investigation, such as segmental, dynamic, combined dynamic and segmental in the same field, and conformal arc; these will be noted, but considered in this CER as “IMRT”.

Stereotactic Body Radiotherapy (SBRT)

SBRT delivers relatively large ablative doses of radiation in fewer treatment sessions than other conformal modalities.¹¹ Regimens generally comprise a total dose of 60 Gy at greater than 10 Gy per fraction, by definition in 5 or fewer fractions. The tumor location can be tracked in four dimensions (including time) using several CT imaging techniques

that depend on the platform, tracking on bony structures or implanted fiducials. SBRT can deliver very high biologically effective doses (BED) above 100 Gray equivalent (GyE) that are needed to ablate a tumor and sterilize the tumor margins, minimizing damage to adjacent normal tissues. Conventionally fractionated schemes, delivering a similar total dose in 25-40 fractions, typically do not reach a similar BED range.

Proton Beam Radiotherapy (PBRT)

Proton therapy has become increasingly available as a number of centers have been built in the last few years and several more are being planned or under construction. Proton beam radiotherapy (PBRT) has theoretical advantages over photon therapy due to a lack of “exit dose”, potentially enabling physicians to deliver high energy conformal doses to the tumor volume while almost completely sparing normal healthy tissue.

Summary

Radiation oncology is a continually evolving discipline, with new methods and delivery platforms in the therapeutic pipeline and under development. The optimal means of delivering external beam ionizing radiation in sufficient dosage to cure a patient with SCCHN requires a fine balance between treatment effectiveness and associated toxicity. In the original AHRQ CER No. 20, the compiled evidence demonstrated an advantage for IMRT over either 3DRT or 2DRT in reducing late xerostomia and improving measures of xerostomia-related QoL. Evidence was insufficient to demonstrate any relative difference between interventions in measures such as overall survival or tumor control. Since the time CER No. 20 was published, a newer conformal technology – SBRT – has come into practice, whereas 2DRT has fallen out of use in the United States. A surveillance study prepared in 2011 by the Ottawa and RAND EPCs suggested rationale to update the original CER, based on signals of new evidence that would change several conclusions of that report. Taken together, the emergence of new technology and new evidence suggesting potential differences between interventions in some outcomes, prompted AHRQ to prioritize this update of CER No. 20.

II. The Key Questions

The original proposed Key Questions (KQs) for the 2010 report entitled *Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer* were posted for public comment for 4 weeks during development of the original CER. At that time, changes to the original KQs and the PICOTS were made based on comments received and discussion with the Technical Expert Panel (TEP) for the original report. In the surveillance assessment used to determine the priority to update the 2010 report, the language of the original KQs was slightly modified, but unchanged in meaning.

The key questions we will use for this update follow below. In addition to 3DRT, IMRT, and PBRT, we will include Stereotactic Body Radiation Therapy (SBRT), which was not part of the original report. Based on input from TEP discussions, and knowledge of the literature, we have excluded 2DRT from further consideration, and will not include

brachytherapy. In response to TEP input we also revised the original language of Key Question 4 to expand the list of potential variables to consider.

Key Question 1

What is the comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT regarding adverse events and QoL?

Key Question 2

What is the comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT regarding tumor control and patient survival?

Key Question 3

Are there differences in comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT for specific patient and tumor characteristics?

Key Question 4

Is there variation in comparative effectiveness of 3DRT, IMRT, SBRT, and PBRT because of differences in user experience, treatment planning, treatment delivery, and target volume delineation?

Identify for each key question:

a. Population(s):

KQs 1-4: Populations of interest include 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 (PDQ) Cancer Information Summary and the National Comprehensive Cancer Network.² 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; and
- occult primary of the head and neck

The following tumors are 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; and
- trachea tumors.

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

b. Interventions:

The primary interventions of interest in all therapeutic settings are:

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

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

c. Comparators:

KQ 1-4:

All therapies will be compared to each other as part of a continuum of treatment for patients with head and neck cancer. Thus, we will include studies in which a RT method was compared to a different method, for example with or without chemotherapy or surgery. We will include all studies from which we can be reasonably certain additional treatments are contemporary and similar, leaving the major comparison that between RT modalities; those that we cannot ascertain from the publication will be excluded. To ensure chemotherapy or other treatments are similar and contemporary, we will consult accepted guidelines such as those from NCCN or NCI. We will not extract details on chemotherapy dosages or schedules, but rather will ascertain their degree of general

similarity and the proportions of patients who receive and complete such regimens. We will categorize and synthesize evidence according to overall treatment, for example concurrent chemoradiotherapy, or adjuvant radiotherapy, not mixing these in the strength of evidence synthesis.

d. Outcomes:

KQ 1, 3 & 4:

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

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

We will search for evidence related to user experience, treatment planning, and target volume delineation within the context of KQ4. In the absence of an evidence-base on these measures, these issues will be addressed as appropriate in both the future research needs and discussion sections of the report.

Based on input received from the TEP, any outcomes not adequately addressed in the literature will be stated as evidence gaps for primary research in the future research needs section of the report.

KQ 2, 3 & 4:

Final outcomes: Overall survival and cancer specific survival

Intermediate outcomes: Local control, and time to recurrence

e. Timing:

All durations of follow-up will be considered

f. Settings:

Inpatient and outpatient

III. Analytic Framework

Figure 1 provides an analytic framework to illustrate the population, interventions, outcomes, and adverse effects that will guide the literature search and synthesis. It links the interventions of interest directly with final health outcomes (e.g., overall survival), or adverse events (e.g., xerostomia) as well as indirectly to final outcomes via intermediate outcomes (e.g., local control, disease-free survival).

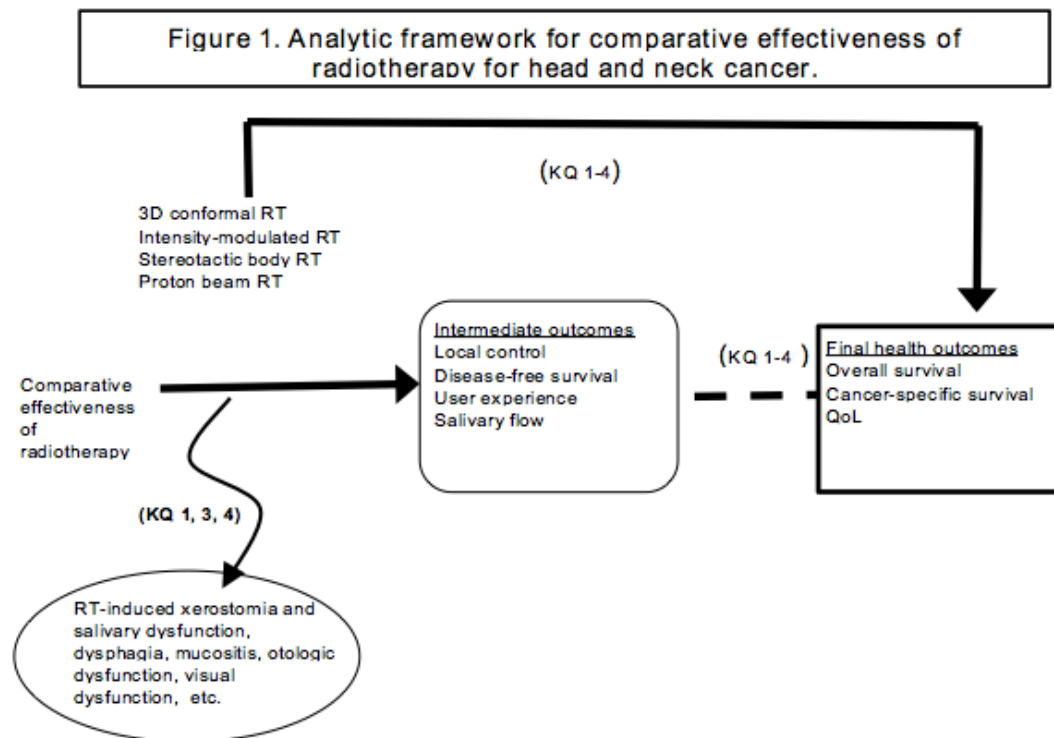


Figure 1: This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how the interventions 3DRT, IMRT, SBRT, or PBRT may result in intermediate outcomes such as local tumor control or disease-free survival and long-term outcomes such as overall survival, cancer-specific survival and QoL. Also, adverse events such as radiation-associated xerostomia and salivary dysfunction, dysphagia, mucositis, otologic dysfunction, or visual dysfunction, may occur at any point after the treatment is received.

IV. Methods

Methodological practices to be followed in this review will be derived from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*) and its subsequent updates.¹²

A. Criteria for Inclusion/Exclusion of Studies in the Review

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 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 non-comparative studies from this CER, based on the following reasoning. We collected a substantial body of evidence from single-arm

studies in preparation of the original CER No. 20. In our analysis, we found that the 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, not adequate for making valid comparisons or hypothesis generation.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Search strategies

The literature search will be updated going back 12 months before the final literature search in the original report, dated September 28, 2009. For SBRT (and any other new interventions we subsequently determine merit inclusion) the literature will be searched electronically by a medical librarian for citations from January 1, 1990 through April 2013. The search will be updated at the time the draft is posted for peer review by AHRQ. We will search the following databases:

- MEDLINE[®]
- EMBASE[®]
- Cochrane Controlled Trials Register

The search will be limited to English-language studies based on evidence that suggests language restrictions do not change results of systematic review for conventional medical interventions.¹³ Our search strategy will use the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE[®] and adapted for use in other databases. The searches will be limited to studies of human subjects, published in English, as shown in Appendix A.

Grey literature

Grey literature will be sought by searching for clinical trials (Clinicaltrials.gov), FDA website, and American Society for Therapeutic Radiation Oncology (ASTRO) conference abstracts for data pertaining to the interventions under consideration used to treat head and neck cancer. We will review Scientific Information Packets from the Scientific Resource Center.

C. Data Abstraction and Data Management

Literature search results will be transferred to EndNote[®] and subsequently into Distiller for study screening.

Review of titles and abstracts

We will develop data collection forms for abstract review, full-text review and data extraction. Using the study-selection criteria for screening titles and abstracts, each citation will be marked as: 1) eligible for review as full-text articles or as 2) ineligible for full-text review. Reasons for study exclusions will not be noted. The title and abstract screening will be performed by two senior team members. To be excluded, a study must be independently excluded by both team members. Discrepancies will be decided by consensus opinion; a third reviewer will be consulted if necessary. A training set of 25 to 50 will be examined initially to assure uniform application of screening criteria. Full-text review will be performed when it is unclear whether the study-selection criteria have been satisfied.

Full-text review

Full-text articles will be reviewed in the same fashion to determine their inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, will be kept in the Access database. While a paper may be excluded for multiple reasons, the first reason identified will be recorded.

Data abstraction

For studies that meet the conditions for inclusion, data abstraction will be performed directly into tables created in the Systematic Review Data Repository (SRDR) with elements defined in an accompanying data dictionary. A training set of five articles will be abstracted by two team members to ensure consistency. Each included article will be abstracted by a single reviewer. A second reviewer will review the data extraction against the original articles for quality control. Identified differences in data coding between the abstractor and reviewer will be resolved by consensus.

The data elements to be abstracted will include 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 radiotherapy (e.g., photons, electrons, protons)
 - Total radiotherapy dose
 - Fractionation schedule

- Imaging methods used to guide radiotherapy (e.g., CT, implanted fiducials, bony landmarks, etc.) and the frequency of imaging to assess therapy (e.g., daily, weekly, monthly, etc)
- Other prior or concurrent treatment modalities (e.g., systemic chemotherapy)
- Number of prior lines of treatment
- Outcome Assessment
 - Identified final outcome (see Analytical Frameworks and PICOTS above)
 - Identified intermediate outcomes (see Analytical Frameworks and PICOTS above)
 - Adverse event response criteria
 - Follow-up 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 will be used for all studies. The dimensions of each evidence table may vary by KQ, but, the tables will contain common elements such as author, year of publication, sample size, study type, intervention(s), and comparator(s). We will only report outcome data in strata according to prognostic or other patient- related factors such as tumor stage, providing they are reported separately or can be inferred from the study in question.

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

In adherence with the *Methods Guide*,¹² the general approach to grading the quality or limitations of individual comparative studies will be performed by using a method used by the U.S. Preventive Services Task Force.¹⁴ (Appendix

B) Individual study quality assessment takes into account 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 versus retrospective)
- Use of an independent outcome assessor

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

E. Data Synthesis

Whether or not our evidence review will incorporate formal data synthesis (e.g., meta-analysis) will be determined after completing the formal literature search. However, based on our original CER, we do not anticipate performing a quantitative synthesis for this update. A decision to pool studies would be based on the following:

- 1) the studies address a common question; and,
- 2) they are fairly homogeneous with respect to population, methods, and interventions.

If a meta-analysis can be performed, subgroup and sensitivity analyses will be based on assessment of clinical diversity in available studies. The standard variables for subgroup/sensitivity analyses are study size, study quality, and treatment and patient characteristics that vary on the study level. Indirect quantitative comparisons may be used where indicated. We will not use network meta-analysis due to the heterogeneity of the populations and treatments in the non-randomized studies that we expect to dominate the evidence base as in the original CER. Network meta-analyses require strong assumptions of exchangeability such that studies are similar in all respects other than the intervention of interest.

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes

Studies will be 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*¹² and is based on a system developed by the GRADE Working Group.¹⁵

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 will be addressed if appropriate. Table 1 describes the four required and three optional domains and their score and application.

Table 1. Strength of evidence rating domains: required and optional

Domain Name	Domain Type	Domain Definition and Elements	Domain Score and Application
Study limitations	Required	<p>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:</p> <ul style="list-style-type: none"> • 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. 	<p>Score as one of three levels, separately by type of study design:</p> <ul style="list-style-type: none"> • Low level of study limitations • Medium level of study limitations • High level of study limitations
Directness	Required	<p>Directness relates to:</p> <ul style="list-style-type: none"> • 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. <p>The EPC should specify the comparison and outcome for which the SOE grade applies.</p> <p>Evidence may be indirect in several situations such as:</p> <ul style="list-style-type: none"> • The outcome being graded is 	<p>Score as one of two levels:</p> <ul style="list-style-type: none"> • Direct • Indirect <p>If the domain score is indirect, the EPC should specify what type of indirectness accounts for the rating.</p>

		<p>considered intermediate (i.e., laboratory test results) in a review that is focused on clinical health outcomes (i.e., morbidity, mortality).</p> <ul style="list-style-type: none"> • 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. <p>Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcome.</p>	
Consistency	Required	<p>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:</p> <ul style="list-style-type: none"> • Direction of effect: Effect sizes have the same sign (that is, are on the same side of no effect or a minimally important difference [MID]). • Magnitude of effect: The range of effect sizes is similar. The EPC may consider the overlap of CIs when making this evaluation. <p>The importance of direction vs. magnitude of effect will depend on the key question and EPC judgments.</p>	<p>Score as one of three levels:</p> <ul style="list-style-type: none"> • Consistent • Inconsistent • Unknown (e.g., single study) <p>Single-study evidence bases (including meta-trials) cannot be judged with respect to consistency. In that instance, use “Consistency unknown (single study).”</p>
Precision	Required	<p>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.</p> <ul style="list-style-type: none"> • A body of evidence will generally be imprecise if the optimal 	<p>Score as one of two levels:</p> <ul style="list-style-type: none"> • Precise • Imprecise <p>A precise estimate is one that would allow users to reach a clinically useful</p>

		<p>information size (OIS) is not met. OIS refers to the minimum number of patients (and events when assessing dichotomous outcomes) needed for an evidence base to be considered adequately powered.</p> <ul style="list-style-type: none"> • If an EPC performed a meta-analysis, then it may also consider whether the CI crossed a threshold for an MID. • If meta-analysis is infeasible or inappropriate, the EPC may consider the narrowness of the range of CIs or the significance level of p-values in the individual studies in the evidence base. 	<p>conclusion (e.g., treatment A is more effective than treatment B).</p>
Reporting bias	Required	<p>Reporting bias results from selectively publishing or reporting research findings bases on the favorability of direction or magnitude of effect. It includes:</p> <ul style="list-style-type: none"> • 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 of one or more favorable analyses for a given outcome while not reporting other, less favorable analyses. <p>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.</p> <p>Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies.</p>	<p>Score as one of two levels:</p> <ul style="list-style-type: none"> • Suspected • Undetected <p>Reporting bias is suspected when:</p> <ul style="list-style-type: none"> • 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. <p>Undetected reporting bias includes all alternative scenarios.</p>
Dose-response association	Optional	<p>This association, either across or within studies, refers to a pattern of a larger effect with greater exposure (dose,</p>	<p>This domain should be considered when studies in the evidence base</p>

		duration, adherence)	<p>have noted levels of exposure.</p> <p>Score as one of two levels:</p> <ul style="list-style-type: none"> • Present: Dose-response pattern observed. • Undetected: No dose-response pattern observed (dose-response relationship not present or could not be determined).
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.	<p>This domain should be considered when plausible confounding exists that would decrease the observed effect.</p> <p>Score as one of two levels:</p> <ul style="list-style-type: none"> • 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 cannot have occurred solely as a result of bias from potential confounding factors.	<p>This additional domain should be considered when the effect size is particularly large.</p> <p>Score as one of two levels:</p>

			<ul style="list-style-type: none"> • 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.
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The process for grading a body of evidence begins with the type of studies that are 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 observational 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 medium, based on controls for risk of bias through study conduct or analysis. The initial SOE for observational 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.

The process of grading a body of evidence can be illustrated with real-world examples typical of the literature encountered in the initial CER of this topic. In synthesizing a body of evidence represented by a single RCT rated as good quality and multiple non-randomized 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 start with a high initial SOE. The study limitation domain in this instance would initially be rated as low. If the RCT and non-randomized studies report very different 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 non-randomized 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 (as compared to the OIS) of the RCT would render the aggregate results imprecise on the precision domain, reducing strength by at least one level. According to the 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 observational (nonrandomized) comparative evidence that included multiple studies. Even if direct results are consistent and precise, this example would have a starting study limitations grade of high, and thus starting SOE of low. If all the 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 will depend on the evidence found in the literature review. The grade rating will be made by independent reviewers, and disagreements will be resolved by consensus adjudication.

We will 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 direction and magnitude of effect where applicable. The overall SOE grade for each outcome will be 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	No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

	outcome.	
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G. Assessing Applicability

Applicability of findings in this review will be assessed according to the AHRQ Comparative Effectiveness Methods Guide using the PICOS (Population, Intervention, Comparator, Outcome, Setting) framework.^{12, 16} Included studies will be assessed for relevance against target populations, interventions and comparators of interest, and outcomes of interest. These variables are listed in this protocol above in Section C. It is anticipated that results will be applicable only to the specialized populations of interest by Key Question.

V. References

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<http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=318>.
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VI. Definition of Terms

If not applicable, simply make a note to that effect.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale. Changes made to the protocol should not be incorporated throughout various sections of the protocol. Instead, protocol amendments should only be noted in section VII of the protocol preferably in a tabular format (please see example below) and the date of the amendment noted at the top of the protocol. Example table below:

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 TOO 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: (A)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 non-comparative 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 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 non-comparative studies from this CER,”...	To make explicit study selection criteria that include only full-length, peer-reviewed evidence
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VIII. 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 (TEP) to assure that the questions are 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.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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 are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. 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.

XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx 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.

XIV. Appendix A

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 nasopharynx [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 nasopharynx [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

XV. Appendix B.

- The quality of studies will be 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 follow-up or overall high loss to follow-up.
 - 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 will be rated according to one of three quality categories:

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

Fair. Studies are 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 are assembled initially, but some questions remain about whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and are generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis has been done for RCTs.

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