Comparative Effectiveness Review

Number 20

Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer

Agency for Healthcare Research and Quality

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

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

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Background

Head and neck cancers, specifically those arising in the oral cavity, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses/nasal cavity, salivary glands, and occult primaries, account for approximately 3 to 5 percent of cancers in the United States. According to the National Comprehensive Cancer Network, it was estimated that 47,560 new cases would occur in 2008, with an estimated 11,260 deaths.

The main challenge in radiation therapy for 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"). Radiation therapy designs have evolved over the past 20 years from being based on two-dimensional (2D) to three-dimensional (3D) images, incorporating increasingly complex computer algorithms. 2D radiotherapy consists of a single beam from one to four directions with the radiation fields designed on 2D fluoroscopic simulation images, whereas 3D conformal radiotherapy (CRT) employs computed tomography (CT) simulation. Intensity-modulated radiotherapy (IMRT) allows for the modulation of both the number of fields and the intensity of radiation within each field, allowing for greater control of the dose distribution to the target. Although proton beam therapy has been used to treat tumors for more than 50 years, it has been used mostly in the treatment of prostate cancer.

Radiation is associated with early and late toxicities, which can have a profound effect on a patient's quality of life, and chemoradiation may be associated with enhancement of these toxicities (particularly mucositis and xerostomia). Therapy-related toxicities are particularly relevant in the treatment of head and neck cancer because of the close proximity of many important dose-limiting normal tissues. Treatment effects can affect basic functions like chewing, swallowing, and breathing, and the senses (e.g., taste, smell, and hearing), and can significantly alter appearance and voice.

Key Questions

This Comparative Effectiveness Review addresses four key questions to compare alternative radiotherapy modalities in the treatment of head and neck cancer. Four alternative radiotherapy modalities will be reviewed: IMRT, 3DCRT, 2DRT, and proton beam.

1. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?
2. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?
3. Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?
4. Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?

Conclusions

When assessing a body of evidence, the AHRQ approach to grading its strength recommends that conclusions about comparative effects take into account the risk of bias,

consistency of findings, directness of evidence, precision, dose-response association, plausible influence of confounding, strength of association, and publication bias. For the body of evidence reviewed here, the quality of evidence was moderate in a few instances and was insufficient for the majority of key questions and outcomes addressed.

Comparison: IMRT Versus 3DCRT

- The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality-of-life domains related to xerostomia compared with 3DCRT. In a randomized, controlled trial presented at a conference but not yet published, the risk difference of late xerostomia grade 2 or higher was 35 percentage points with a 95 percent confidence interval between 12.6 and 55.5 percentage points. There is insufficient detail about methods used in the yet-to-be published randomized trial, so it is difficult to assess its quality and contribution to the overall body of evidence. The six observational studies that reported late xerostomia all favored IMRT. Of the five studies that reported frequencies, the reported range of differences is 7 to 79 percentage points. Quality of life was reported in three observational studies and generally favored IMRT in domains primarily related to xerostomia, such as dry mouth, swallowing, and sticky saliva.
- The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late osteoradionecrosis, and bone toxicity were reported in some and typically favored IMRT, but differences were not consistently statistically significant. Among studies of acute skin toxicity, neither the size of the difference nor the direction was consistent.
- No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. The single randomized, controlled trial had too small of a sample size and too short of a followup to ascertain differences in tumor control or survival. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias.
- No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions.

Comparison: 3DCRT Versus 2DRT

- The strength of evidence is insufficient to draw conclusions about the comparative adverse events or quality of life associated with 3DCRT and 2DRT. Among four studies reporting on late xerostomia, one reported a large statistically significant difference; all others were either nonsignificant or of unclear significance. One study compared quality-of-life outcomes between 3DCRT and 2DRT but did not report a statistical comparison. Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, acute skin toxicity, late skin toxicity, and late osteoradionecrosis and bone toxicity were reported in a few studies and differences between 3DCRT and 2DRT were small. The studies are of poor quality, and the results are not consistently statistically significant.
- No conclusions on tumor control or survival can be drawn from the body of evidence comparing 3DCRT versus 2DRT. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-

specific and overall survival is complex and requires greater controls for confounding and bias.

- No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions.

Comparison: IMRT Versus 2DRT

- The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality of life domains related to xerostomia compared with 2DRT. The direct evidence reviewed on IMRT versus 2DRT, although of limited quality, suggests a true effect in favor of IMRT. Indirect evidence from the comparison of IMRT versus 3DCRT shows that greater conformality of radiation reduces late xerostomia and improves quality-of-life domains related to xerostomia. Thus, inference from comparison of IMRT versus 3DCRT provides additional support for this conclusion.
- Nine studies reported on late xerostomia, and eight were statistically significant in favor of IMRT. Among the studies that reported frequency, the range of differences between IMRT and 2DRT was 43 to 62 percentage points. Quality of life was reported in one randomized, controlled trial and two observational studies and generally favored IMRT in domains primarily related to xerostomia.
- The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 2DRT for other adverse events. The quality of available studies is poor and no strongly consistent results were reported.
- No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 2DRT. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias.
- No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient, as no comparative studies addressed these key questions.

Proton Beam Therapy Versus Other Techniques

The strength of evidence is insufficient as there were no studies comparing proton beam therapy to any other radiotherapy modality. Therefore, no conclusions can be reached regarding the comparative effectiveness of proton beam therapy for any of the four key questions.

Remaining Issues

In principle, IMRT may offer advantages over 3DCRT and 2DRT because it is more conformal and has a steeper dose gradient. Dose planning studies have shown that IMRT can lower doses to normal tissues while maintaining or increasing the dose to the central tumor. In using IMRT to treat patients with head and neck cancer, theoretical dose delivery advantages must be translated into improved therapeutic outcomes. There is potential to introduce small errors at each step. It is precisely because there may be discrepancies between the planned dose and the amount delivered to a specific patient that treatment planning studies are not sufficient to demonstrate the comparative effectiveness of an approach. Differences in patient susceptibilities

to specific adverse events, e.g., xerostomia, are also an intervening variable. Therefore, comparative evidence on clinical outcomes is necessary to establish that the technical capabilities of IMRT do indeed benefit patients, not only by decreasing xerostomia, but also by achieving similar or improved tumor control and survival.

The capability of IMRT to deliver steep dose gradients around a tumor site may present a risk as well as potential benefit. If the planned dose does not align with the tumor contour and other anatomic attributes of the patient, the planned and actual dose may diverge substantially. As a result, the patient may be at risk of greater adverse effects from an inadvertently high dose to adjacent healthy tissues, or, conversely, be at risk of suboptimal tumor control because of an inadvertently low dose to the tumor. Thus, operator performance may prove to be critical in determining the outcomes of IMRT in clinical practice.

Xerostomia has a significant impact on quality of life. It appears to be common in patients with certain tumor sites, radiotherapy treatments, and chemotherapeutic regimens. Older age and certain therapies for chronic diseases may increase susceptibility for this adverse effect. Research to improve the management of xerostomia and to disseminate that knowledge to clinical practice could potentially improve morbidity and quality of life for cancer patients.

The challenges of conducting research in head and neck cancer need to be acknowledged. Head and neck cancers are not common, so the pace of patient accrual may be slow; this may be accompanied by changes in practices, both for the technology of radiotherapy itself and other aspects of management and treatment. On the other hand, the length of followup needed to study head and neck cancer treatments is relatively short compared to some common cancers, such as breast or colon cancer.

Future research should put high priority on multicenter trials to hasten patient accrual and trial completion. There are considerable obstacles to conducting randomized, controlled trials to ascertain tumor control and survival effects. These are: wide dissemination of IMRT, reluctance to randomize patients when effects on xerostomia are already known, the large patient numbers such trials would require, and other priorities for funding. Nonetheless, certainty about tumor control and survival outcomes can ideally be obtained through a robust randomized, controlled trial. Recognizing that observational studies will continue to be attractive to investigators, the usefulness and generalizability of such can be improved by conducting prospective studies that compare contemporaneous treatments. The patient groups being compared should be similar in terms of key variables, such as anatomic site, disease stage, and prior treatment. Multivariable regression analyses can be helpful in controlling for potential confounders and should adhere to good modeling practices.

Standardization in terminology and measurement would improve the quality of randomized controlled trials and observational studies. Standardization of tumor control and toxicity outcome terminology with common practices for data analysis and presentation would facilitate comparison among studies. Quality-of-life and patient-reported outcomes should be assessed with validated instruments for which clinically significant improvements have been quantified empirically.

Introduction

This is a comparative effectiveness review of alternative radiation therapy (RT) modalities in the treatment of head and neck cancer including: conventional or two-dimensional (2DRT), three-dimensional conformal (3DCRT), intensity-modulated (IMRT), and proton beam radiotherapy. Key questions that will be addressed are 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; (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.

Background

Burden of Illness

Head and neck cancers, specifically those arising in the oral cavity, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses/nasal cavity, salivary glands and occult primaries, account for approximately 3 to 5 percent of cancers in the U.S. According to the National Comprehensive Cancer Network, it was estimated that 47,560 new cases would occur in 2008, with an estimated 11,260 deaths.[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.[1] Viral etiologies have also been established, with human papillomavirus infection appearing to be a risk factor, particularly within the oropharynx, in younger people without a history of tobacco or alcohol abuse. In addition, an association has been made between Epstein-Barr virus and nasopharyngeal cancer.

Classification and Staging

The majority of head and neck cancers arise from a noninvasive precursor in surface squamous epithelium, progressing to a squamous carcinoma. Other less-common tumors arise from other structures, including the major and minor salivary glands, and give rise to a variety of other tumor types, like adenocarcinomas.

The staging of head and neck cancer varies slightly by anatomic site, but in general, early stage (stage I and II), which comprises approximately 40 percent of cases, defines a small primary tumor without lymph node involvement.[1] Locally advanced tumors (stage III and IV) include large primary tumors, which may invade adjacent structures and/or spread to regional lymph nodes, and represent approximately 60 percent of cases.[1] Metastatic disease is uncommon at the time of diagnosis of a head and neck cancer, with the exception of certain subsites (e.g., nasopharynx, hypopharynx, advanced neck disease).

Clinical Management

The management of head and neck cancer is complex, and usually involves a multidisciplinary team. In general, the approach to managing this type of cancer is dictated by the disease site and extent, as well as by the histologic type and grade of tumor. Early stage disease may be treated by a

single-modality (surgery or radiation), whereas patients with locally advanced disease are generally treated with combined modalities,[1] and depending upon the extent of disease spread, a cervical lymph node dissection may be performed.

Nearly all patients with locally advanced head and neck cancer receive chemotherapy in addition to radiation as a part of initial curative treatment.[2] The integration of chemotherapy into the treatment of head and neck cancer has resulted in improvements in overall survival and local-regional control, reduced the incidence of distant metastases, and has provided more opportunity for organ preservation in certain settings.[2]

Radiation Therapy

The main challenge in radiation therapy for 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).

Two-Dimensional and Three-Dimensional Conformal Radiation Therapy. Modern advances in computers have led to parallel advances in imaging technologies, allowing for higher levels of complexity in radiotherapy treatment planning systems.[3] Radiation therapy designs have evolved over the past 20 years from being based on two-dimensional (2D) to three-dimensional (3D) images, incorporating increasingly complex computer algorithms.

2DRT consists of a single beam from one to four directions with the radiation fields designed on 2D fluoroscopic simulation images, whereas 3D conformal radiotherapy (CRT) employs computed tomography (CT) simulation.[4] Three-dimensional radiotherapy represented a major advance over 2D, allowing for more accurate dose calculations by taking into account axial anatomy and complex tissue contours.

IMRT. IMRT, which has been implemented over the last decade, has further refined radiation dose delivery. IMRT allows for the modulation of both the number of fields and the intensity of radiation within each field, allowing for greater control of the dose distribution to the target.[3] Potential benefits include the ability to deliver higher doses to the tumor, while sparing normal, surrounding tissues, thereby decreasing toxicity. Reducing the radiation dose to normal structures offers potential benefits which include sparing of salivary gland tissue to reduce the severity of xerostomia (dryness of the mouth due to decreased salivary function), and reducing the dose to structures related to swallowing (e.g., pharyngeal constrictor muscles and the larynx).[5]

There are several disadvantages to IMRT. Patients receive a higher total body dose of radiation, there is decreased dose homogeneity, and increased risk of a marginal miss (in which case, the eradication of the tumor may be unsuccessful).[5] Compared to more conventional radiotherapy techniques, IMRT is more expensive and time consuming. Difficulties have arisen in set-up reproducibility and patient immobilization, and it has been shown that variations in daily patient positioning and changes in patient anatomy (e.g., weight loss, tumor shrinkage) may result in significant dose perturbations compared with the original treatment plan.[6] Finally, there has been concern about variations in prescribed doses versus what is actually delivered to the patient, and variations between medical institutions has raised concerns about the validity of comparing clinical outcomes for IMRT.

Radiation Treatment Planning. Both 2D and 3DCRT use forward planning to create radiation dose distributions, in which the radiation treatment fields are designated by a physician and a physicist then defines the number, direction, and shapes of the radiation beams. The treatment plan dose distribution shows how much dose is delivered to the tumor and normal structures.[4]

IMRT uses CT simulation images like 3DCRT; however, inverse planning is used to outline target volumes. Inverse planning requires the treatment planner to input the desired radiation dose to the tumor and the constraints for normal surrounding structures. Then, computer software is used to arrive at the radiation beam characteristics most likely to meet the requirements designated at the start of treatment planning.[4] Although repeat treatment planning may be chosen during the course of treatment, it is not typically performed.

In order to standardize image-based tumor volume definitions for three-dimensional radiation planning, the Internal Commission of Radiation Units and Measurements created terminology for use across institutions.[7] Definitions include gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV). 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/organ motion and day-to-day setup variation.[4]

Photons, Electrons, and Protons. The main form of treatment of deep tumors is with photons (as is used in 2D, 3D, and IMRT). Photons spare the skin and deposit dose along their entire path until the beam leaves the body.[8] As each beam continues on its path beyond the tumor, the use of multiple beams means that a significant volume of normal tissue receives a low dose.[8]

Electrons are the most widely used forms of radiation for superficial tumors, and because the depth of penetration can be well controlled by the energy of the beam, it is possible to spare underlying normal structures.[8]

Although proton beam therapy has been used to treat tumors for more than 50 years, it has been used mostly in the treatment of prostate cancer, as well as brain tumors, including those in children.[8] Charged particle beams like proton, differ from photons in that they interact only modestly with tissue until they reach the end of their path, where they deposit the majority of their energy and stop.[8] The ability to stop at a chosen depth offers the potential advantage of treating tumors close to critical structures, and with the potential to decrease regions of low dose, decreasing the chance of second malignancies. In the two- and three-dimensional era, proton therapy could deliver higher doses to the target than photon therapy because protons produce a more rapid falloff of dose between the target and normal tissues.[8] In the modern IMRT era, it is difficult to determine whether protons will allow a higher dose to be delivered to the target.[8] Another major issue is that proton beam facilities are substantially more expensive than a similar-sized photon facility.[8] The exact role of intensity-modulated proton therapy in the treatment of head and neck cancer is not well defined.

Adverse Effects of Radiation Therapy in Head and Neck Cancer

Radiation is associated with early and late toxicities, which can have a profound effect on a patient's quality of life, and chemoradiation may be associated with enhancement of these toxicities (particularly mucositis and xerostomia). Additionally, confounding factors may make it difficult to attribute all of the symptoms of an adverse event to treatment effect. For example, there are several other causes of xerostomia which include diseases that affect the salivary

glands, numerous medications and various others, that may be present in the population with head and neck cancer.

Therapy-related toxicities are particularly relevant in the treatment of head and neck cancer because of the close proximity of many important dose-limiting normal tissues. Treatment effects can impact basic functions like chewing, swallowing, and breathing; the senses (e.g., taste, smell and hearing), and significantly alter appearance and voice.

Traditionally, acute and late toxic effects are defined as occurring before and after 90 days, respectively. In an attempt to standardize the reporting of therapy-related acute and late toxicities, several grading instruments have been created, including the National Cancer Institute's 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 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).

Key Questions for this Comparative Effectiveness Review

This comparative effectiveness review addresses four key questions regarding the use of alternative radiotherapy modalities in the treatment of head and neck cancer. The radiotherapy modalities to be compared are intensity-modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3DCRT), two-dimensional radiation therapy (2DRT), and proton beam therapy.

1. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?
2. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?
3. Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT and proton beam therapy for specific patient and tumor characteristics?
4. Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?

Methods

Topic Development

The topic of this report and preliminary key questions were developed through a public process involving the public, the Scientific Resource Center (www.effectivehealthcare.ahrq.gov/aboutUS/contract.cfm) for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ), and various stakeholder groups. Additional study, patient, intervention, and eligibility criteria, as well as outcomes, were refined and agreed upon through discussions between the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC), the Technical Expert Panel (TEP) members, our AHRQ Task Order Officer, and comments received from the public.

Search Strategy

Electronic Databases

The following databases were searched for citations (search strategy can be found in Appendix A). The search was not limited to English-language references; however, foreign-language references to single-arm studies were not translated and abstracted.

- MEDLINE® (January 1, 1990, through September 28, 2009)
- EMBASE® (January 1, 1990, through September 28, 2009)
- Cochrane Controlled Trials Register (no date restriction)

Single-arm studies, which are not a main focus of this review, were selected from studies identified through the January 13, 2009 search result update. Comparative studies were identified through the latest search updates.

The TEP and individuals and organizations providing peer review were asked to inform the project team of any studies relevant to the key questions that were not included in the draft list of selected studies.

We examined the bibliographies of all retrieved articles for citations to any randomized, controlled trial or nonrandomized comparative study that was missed in the database searches. In addition, we searched abstracts for the past 5 years of meetings of the American Society of Therapeutic Radiation Oncology (ASTRO) and the American Society of Clinical Oncology (ASCO).

Search Screen

Search results were stored in a ProCite® database. The study selection process is outlined in Figure 1. Using the study selection criteria for screening titles and abstracts, a single reviewer marked each citation as either: (1) eligible for review as full-text articles; (2) ineligible for full-text review; or (3) uncertain. Citations marked as uncertain were reviewed by a second reviewer and resolved by consensus opinion, with a third reviewer to be consulted if necessary. Using the final study selection criteria, review of full-text articles was conducted in the same fashion to determine inclusion in the systematic review. Of 2,679 citations, 354 articles were retrieved and

108 selected for inclusion (Figure 2). Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, were kept in the ProCite® database (see Appendix B, Excluded Studies).

Figure 1. Study selection process

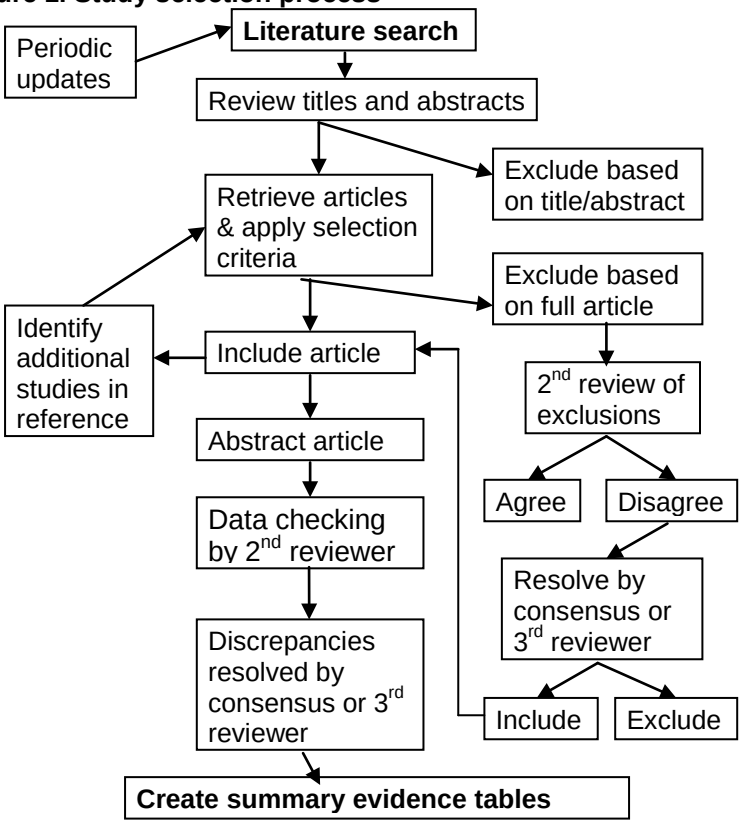
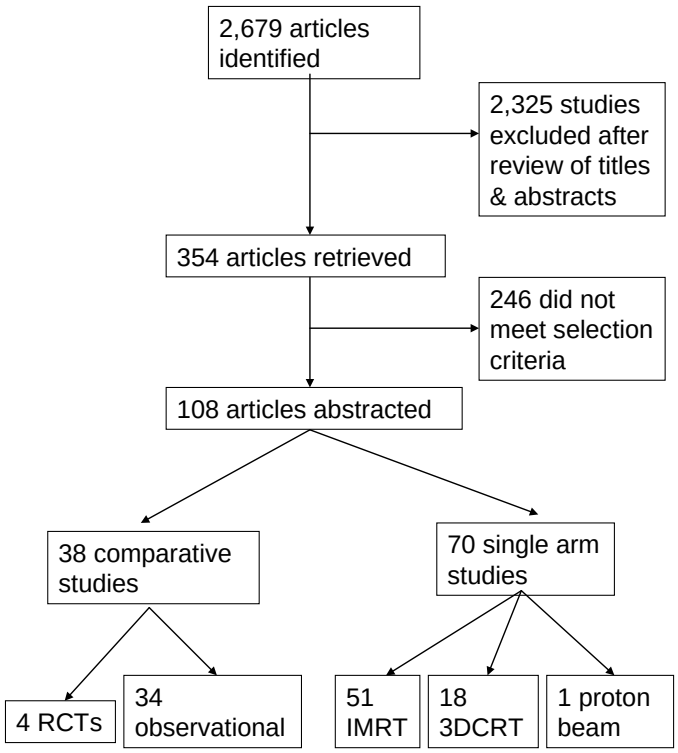


Figure 2. QUOROM flow diagram



Study Selection

This Evidence Report takes a two-tiered approach to evidence of the comparative effectiveness and safety of four types of radiotherapy. The primary focus is on comparative studies of these techniques to each other or to 2DRT, which was commonly used before the diffusion of IMRT and 3DCRT. The secondary focus is on reviewing single-arm studies on any of the technologies of interest for potential hypothesis generation.

The diagram in Figure 1 describes how we proceeded through this comparative effectiveness review, from conducting the literature search to applying the selection criteria. The complexity of the diagram stems from two factors: first, the need to insure that all relevant studies are included (hence the second review of excluded full-text articles, the review of bibliographies of abstracted articles, and the several updates performed while the review was being prepared) and second, the need for complete and accurate abstraction of the data from the included articles.

Further steps included data extraction and summary (see Data Extraction and Analysis, following), quality assessment (see Assessment of Study Quality, following), and finally evidence synthesis and interpretation. Assessment of the quality of the selected studies is an important part of how we conducted this review; however, interpretation of the body of evidence for a particular class of interventions entailed more than that. Quality assessment informed the critical appraisal of the results and conclusions of each type of study, but rating classes did not give a complete picture of the strength of the body of evidence.

Beyond quality ratings for each study, we explored the methodologic strengths and weaknesses of different study designs (randomized, controlled trials, nonrandomized comparative studies, and prospective or retrospective single-arm studies), to identify which can generate provide evidence on the efficacy and safety of the radiotherapy modalities and which can only help generate hypotheses that require later confirmation. All of these activities contributed to interpreting the overall strength of the evidence and determining whether conclusions could be drawn with respect to key questions.

Types of Studies

Studies were included for Key Question 1 and Key Question 2 if they were:

- Randomized trials, nonrandomized comparative studies, or single-arm intervention studies, that:
    - reported on an outcome of interest specifically among patients with head and neck cancer;
    - involved an intervention of interest, excluding noncomparative studies describing use of 2DRT (defined below) only;
    - reported results separately in individual patient groups according to radiation therapy modality received, except for proton beam therapy, where the results of photon and proton therapy may be combined;
    - reported tumor control data compiled separately according to tumor site, or included a multivariable analysis that controlled for anatomic location and evaluated the impact of type of radiotherapy on tumor control outcomes.
- Single-arm studies with 25 or more evaluable patients that adhere to all aforementioned criteria and provide descriptive information on tumor characteristics particularly location and histology. Single-arm (noncomparative) studies of 2DRT were excluded because this radiotherapy technique is currently little practiced. Studies had to use the same type of

radiotherapy for boost as for the planning treatment volume; 2DRT or electrons could be used in the lower neck.

The criteria allowing the use of a different type of therapy in the lower neck and the use of photons and protons combined were developed after the beginning of the project. These issues arose during the data abstraction process and were resolved with the assistance of the two members of the TEP who provided extended consultation.

Dose planning studies that did not report any outcome of interest were not included. While such studies may show apparently better dose distributions for IMRT or proton beam therapy over 3DCRT or 2DRT, this review emphasizes outcomes such as adverse events, quality of life, tumor control, and patient survival. Dose distribution is considered an intermediate outcome, which may be related to health outcomes, but by itself does not establish the comparative effectiveness of different radiotherapy techniques.

Studies were included for Key Question 3 if they met the selection criteria for Key Questions 1 and 2 and also:

- presented treatment outcome data associated with different categories or levels of:
    - tumor characteristics,
    - tumor anatomic locations, or
    - patient characteristics (e.g., older versus younger).

Studies were included for Key Question 4 if they met the selection criteria for Key Questions 1 and 2 and also:

- presented treatment outcome data associated with different categories or levels of:
    - user experience (years of experience with IMRT, number of patients treated with IMRT, formal training in IMRT),
    - target volume delineation (gross tumor volumes, clinical target volumes, planning target volumes, lymph node regions, organs at risk), or
    - dosimetric parameters (dose to targets, dose constraints for organs at risk).

Types of Participants

The populations of interest for all four Key Questions included patients with head and neck cancer. To define what constitutes head and neck cancer, we consulted with clinical resources such as the National Cancer Institute's Physician Data Query (PDQ) Cancer Information Summary (www.cancer.gov), the oncology textbook edited by DeVita, Hellman, and Rosenberg,[8] and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[1] The consensus definition of head and neck cancer includes tumors of:

- larynx;
- pharynx (hypopharynx, oropharyx, and nasopharynx);
- lip and oral cavity;
- paranasal sinus and nasal cavity;
- salivary gland; and
- occult primary of the head and neck

The following tumors were excluded:

- brain tumors;
- skull base tumors;

- uveal/choroidal melanoma, other ocular and eyelid tumors;
- otologic tumors;
- cutaneous tumors of the head and neck (including melanoma);
- thyroid cancer;
- parathyroid cancer;
- esophageal cancer; and
- tracheal tumors.

Tumor site was not necessarily defined as occurring in one anatomic location. For example, for purposes of data abstraction, "oral cavity" was considered as one site, although it technically involves multiple anatomic sites (e.g., buccal mucosa, the anterior two-thirds of the tongue, lips, etc.).

Treatment Setting

The original categories for therapeutic settings were refined after abstraction[*] to fit the mix of approaches used in the studies and to create meaningful categories for data synthesis. The final list follows:

- Primary (definitive): radiotherapy only (no surgery, with or without chemotherapy)
- Preoperative radiotherapy: radiotherapy before surgery.(with or without chemotherapy)
- Postoperative (adjuvant): radiotherapy after surgery (with or without chemotherapy)
- Reirradiation: radiotherapy after earlier radiotherapy (other treatments irrelevant)

Chemotherapy regimens given in conjunction with radiotherapy could be described in the following ways:

- Concurrent chemoradiotherapy: radiotherapy and chemotherapy at the same time (with or without surgery)
- Post-radiotherapy (adjuvant) chemoradiotherapy: chemotherapy given after radiotherapy (with or without surgery)
- Pre-radiotherapy (neoadjuvant) chemoradiotherapy: chemotherapy given before radiotherapy (with or without surgery)
- Split chemoradiotherapy: chemotherapy given both before and after radiotherapy (with or without surgery)

Initial review of studies revealed a wide variety of treatment settings defined by radiotherapy techniques in relation to both surgery and chemotherapy. Studies addressing only primary radiotherapy without surgery or chemotherapy were quite rare, so we included studies that addressed a single setting other than primary radiotherapy as well as studies that addressed a group of patients receiving a mix of settings. Evidence is reviewed first among studies that addressed a single setting, then among studies that included mixed settings.

[*] The original categories for therapeutic setting were definitive radiotherapy (primary, curative intent); postoperative (adjuvant); preoperative (neoadjuvant); chemoradiotherapy; postoperative chemoradiotherapy; metastatic; recurrent (reirradiation); and palliative.

The relevant practice settings were

- hospitals and
- outpatient radiotherapy facilities.

Subpopulations of interest included: age, race or ethnicity, sex, disease severity and duration, weight (body mass index), and prior treatments.

Types of Interventions

The interventions of interest were:

- intensity-modulated radiotherapy (IMRT), defined as any treatment plan where intensity-modulated radiation beams and computerized inverse treatment planning is used;
- three-dimensional conformal radiotherapy (3DCRT), defined as any treatment plan where CT-based treatment planning is used to delineate radiation beams and target volumes in three dimensions;
- proton beam therapy (PBT), defined as any treatment plan where proton beam radiation is used; and
- conventional two-dimensional radiotherapy (2DRT), defined as treatment planning where only 2D projection radiographs are used to delineate radiation beams and target volumes.

Studies were excluded when a mix of radiotherapy modalities was used, such as 2DRT plus IMRT boost or 3DCRT plus brachytherapy. Boost techniques were allowed if they were of the same modality as the main technique (e.g., IMRT with IMRT boost). Conventional 2DRT were addressed to the extent that comparative studies included groups of patients that received 2DRT. However, noncomparative studies of 2DRT were not sought. Data on other comparators such as stereotactic radiosurgery or similar modalities also were not sought.

Types of Outcomes

In general, outcomes should be standard, valid, reliable, and clinically meaningful.

Primary (health) outcomes included:

- radiation-induced toxicities;
- adverse events, both acute and chronic normal tissue toxicity, such as
    - xerostomia,
    - dysphagia;
    - mucositis,
    - skin toxicity,
    - osteoradionecrosis or bone toxicity, and
- effect on quality of life;
- clinical effectiveness, including
    - local and locoregional control,
    - time to any recurrence (disease-free survival), and
    - patient (disease-specific and overall) survival.

Secondary (intermediate) outcomes included:

- salivary flow and
- probability of completing treatment according to protocol.

Health outcomes were given greatest emphasis. Health outcomes may be defined as those directly related to length of life, quality of life, function, symptoms, or harms. Intermediate outcomes may reflect physiologic processes are important to the extent that they are related to health outcomes. The specific primary and secondary outcomes selected here were those for which more than five comparative studies provided data and clinical expert consensus indicated their importance.

Data Extraction and Analysis

Data Elements

The data elements following were abstracted, or recorded as not reported, from intervention studies. Data elements to be abstracted were defined in consultation with the TEP. They included the following:

- critical features of the study design:
  - patient inclusion/exclusion criteria
  - number of participants and flow of participants through steps of study
  - treatment allocation methods (including concealment)
  - use of blinding
- patient characteristics, including:
  - age
  - sex
  - race/ethnicity
  - disease and stage
  - tumor histology
  - tumor size
  - disease duration
  - other prognostic characteristics (history of tobacco use, etc.)
- treatment characteristics, including:
  - localization and staging methods
  - computerized treatment planning
  - radiation delivery source
  - regimen, schedule, dose, duration of treatment, fractionation, boosts
  - beam characteristics
  - immobilization and repositioning procedures
  - concurrent treatments and details
- outcome assessment details:
  - identified primary outcome
  - secondary outcomes
  - response criteria
  - use of independent outcome assessor
  - follow-up frequency and duration
- data analysis details:
  - statistical analyses (statistical test/estimation results)
    - test used
    - 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

The same abstraction tables were used for comparative and single-arm studies, although some elements did not apply to the latter (e.g., description of control group). A few studies were randomized on a treatment other than radiotherapy, e.g., type of chemotherapy. They were treated as single-arm studies for the purposes of this comparative effectiveness review.

Evidence Tables

Templates for evidence tables were created in Microsoft Excel® and Microsoft Word®. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer reviewed articles and evidence tables for accuracy. Disagreements were resolved by discussion, and if necessary, by consultation with a third reviewer. When small differences occurred in quantitative estimates of data from published figures, the values obtained by the two reviewers were averaged.

Assessment of Study Quality

Definition of Ratings Based on Criteria

In consultation with the AHRQ Task Order Officer and TEP, the general approach to grading individual comparative studies developed by the U.S. Preventive Services Task Force[9] (USPSTF) was applied to primary studies. The quality of the abstracted studies and the body of evidence was assessed by two independent reviewers. Discordant quality assessments were resolved with input from a third reviewer, if necessary.

The quality of studies was assessed on the basis of the following criteria:

- Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups
- Maintenance of comparable groups (includes attrition, crossovers, adherence, 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, intention-to-treat analysis

The rating of intervention studies encompasses the three quality categories described here.

- *Good:* Meets all criteria; comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); 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, for randomized, controlled trials, intention to treat analysis is used.
- *Fair:* Studies 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 question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and 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 is done for randomized, controlled trials.
- *Poor:* Studies 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 (including not masking outcome assessment); and key confounders are given little or no attention. For randomized, controlled trials, intention-to-treat analysis is lacking.

The quality of included nonrandomized comparative intervention studies was also assessed based on a selection of items proposed by Deeks et al.[10] to inform the USPSTF approach, as follows:

- Was sample definition and selection prospective or retrospective?
- Were inclusion/exclusion criteria clearly described?
- Were participants selected to be representative?
- Was there an attempt to balance groups by design?
- Were baseline prognostic characteristics clearly described and groups shown to be comparable?
- Were interventions clearly specified?
- Were participants in treatment groups recruited in the same time period?
- Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
- Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
- Were outcome measures clearly valid, reliable and equally applied to treatment groups?
- Were outcome assessors blinded?
- Was the length of follow-up adequate?
- Was attrition below an overall high level (less than 20 percent)?
- Was the difference in attrition between treatment groups below a high level (less than 15 percent)?

- Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

The quality of included single-arm intervention studies was assessed based on a set of study characteristics proposed by Carey and Boden[11] (Table 1), as follows:

- Clearly defined question
- Well-described study population
- Well-described intervention
- Use of validated outcome measures
- Appropriate statistical analyses
- Well-described results
- Discussion and conclusion supported by data
- Funding source acknowledged

The quality of included predictive studies was assessed based on an approach we applied to a systematic review of HER2 testing for breast cancer and other solid tumors.[12]

Table 2 shows the framework for evaluating how informative different designs and analytic strategies would be to predictions of outcomes according to different categories or levels of predictive factors. The most informative scenario would be a trial in which randomized assignment to treatment groups would be stratified by predictive factor level or patients were randomized to receive treatment guided by predictive factor or not.[13] An adequately powered stratified randomization would allow valid inferences of treatment by predictive factor interactions. Randomized trials generally are preferred because they convey the possibility of determining differences in the relative efficacy of two treatments, whereas single-arm studies can only assess the association between predictive factor and outcomes after a single treatment regimen. Subgroup analyses in randomized trials should ideally assess the significance of treatment effect interactions. Prespecified subgroups analyses guard against the problems of data dredging.

Table 1. Carey and Boden case series quality assessment tool

Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Funding/ Sponsorship Source Acknowledged
Question should be appropriate to study design; should not be stated in terms of effectiveness; best when focused;	Case definition (diagnostic criteria); type of criteria (clinical, radiographic); whether criteria used before (reference); explicit inclusion/ exclusion criteria; includes standard information (age; sex; socioeconomic status; stage and duration of disease; comorbidities; n; time to accrual; exclusions and reasons; loss to followup; refusal)	Sufficiently clear that another center could replicate study; if not identified in detail, should provide references; co-interventions should be described in reasonable detail	Reference to previous validation; ideally individual assessing patient's outcome should be masked to specific intervention; alternatively, assessor who is not in direct employ of clinical office; standardized length and intervals of observation and of sufficient duration to be clinically meaningful; justification for the duration of followup	Statistical tests and power calculations aimed at improvement over time; prepost analysis should take into account paired nature of data; comparisons with historical controls should take into account differences in co-interventions between time periods; attention to nonspecific effects and inability to distinguish procedure's effect from spontaneous improvement; avoids over-reliance on those variables showing improvement; analysis should address multiple comparisons	Utilize only validated outcome measures; description of adequacy of followup (number lost to followup, number who switch to another provider or pursue other treatments, number who die from other causes); [adaptation: inclusion of both potentially beneficial outcomes (symptom/ function/ quality of life) and adverse events]	Conclusion should be supported by the data in the article where other information is used to buttress conclusions, should be explicitly stated and referenced; limitations should be made explicit; description of specific next research steps (e.g., need for trial, details of trial) [adaptation: this element disregarded]	Funding source should be disclosed in addition to consulting or board relationship with manufacturer

Table 2. Hierarchy of study design and conduct for assessing prediction of outcome

More informative	Randomized trial, randomization stratified on predictive factor OR patients randomized to predictive factor-guided treatment or not
	Randomized trial, prespecified multivariable subgroup analysis
↑	Randomized trial, post-hoc multivariable subgroup analysis
	Randomized trial, treatment by predictive factor subgroup analysis
	Nonrandomized comparative study, prespecified multivariable subgroup analysis
Continuum	Nonrandomized comparative study, post-hoc multivariable subgroup analysis
	Nonrandomized comparative study, treatment by predictive factor subgroup analysis
↓	Single-arm study, prespecified multivariable analysis
	Single-arm study, post-hoc multivariable analysis
Less informative	Single-arm study, univariate analysis

Post-hoc subgroup analyses may generate hypotheses, but may not support strong inferences about differential effectiveness. Multivariable subgroup analyses in randomized trials may be useful if the subgroup variable introduces imbalances between different variable by treatment combinations, particularly when only a subset of patients have tumor or serum specimens available. An alternative to multivariable subgroup analysis is cross tabulation of treatment by predictive factor level results. The weakness of this approach is failure to control for imbalances in any important prognostic factors, particularly if the patients analyzed are a subset of those randomized. A formal test of interaction is preferred for any trial subgroup analysis. In single-arm (identically treated) studies, multivariable analyses may identify whether a variable is a significant independent predictor of treatment outcome while taking into account the separate influences of other predictors. The least informative situation would be a single-arm study which presents univariate comparisons of predictive factor groups.

To assess the quality of predictive studies, we adapted the "Reporting Recommendations for Tumor Marker Prognostic Studies" (REMARK) statement.[14] A checklist based on portions of REMARK and other sources[15-22] was developed. Table 2 identifies good quality characteristics that we looked for in predictive studies, including: prospective design; prespecified hypotheses about relation of predictive factor to outcome; large, well-defined, representative study population; predictive factor measurement methods well-described; blinded assessment of predictive factor in relation to outcome; homogeneous treatment(s), either randomized or rule-based selection; low rate of missing data (15 percent or less); sufficiently long follow-up; well-described, well-conducted multivariable analysis of outcome.

Assessment of Applicability

Applicability of findings in this review was assessed within the EPICOT[23] framework (Evidence, Population, Intervention, Comparison, Outcome, Timestamp). Selected studies were assessed for relevance against target populations, interventions of interest, and outcomes of interest.

Data Synthesis

Given that there are only three, quite clinically diverse, randomized trials involving the interventions of interest for treatment of head and neck cancer, this evidence review did not incorporate formal data synthesis using meta-analysis. Rather, the synthesis emphasized comparative studies sorted by specific head-to-head comparisons of interventions, specific patient characteristics, specific outcomes and status relative the evidence hierarchy/study quality assessment. Greater consideration was given to the studies that were more homogeneous in terms of treatment setting and tumor site.

Rating the Body of Evidence

The system used for rating the strength of the overall body of evidence was developed by AHRQ[24] for the EPC Methods Guide, based on a system developed by the GRADE Working Group.[25] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. Grade of evidence strength is classified into the following four categories:

High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence is either unavailable or does not permit estimation of an effect.

If concerns arose with the body of evidence, additional domains would be addressed, such as strength of association, publication bias, coherence, dose-response relationship, and residual confounding.

Quality of Life and Symptom Measurement

Quality of life (QOL) and the impact of symptoms resulting from both the cancer itself and therapy should be measured by instruments with established validity and reliability. Although results are frequently reported as mean change in the intervention compared to control arms, this is not the preferred method of measuring outcomes. More informative, is a comparison of response, that is the proportion of patients achieving an improvement that is established representing a minimum clinically important improvement.[26]

Three types of instruments may be used: generic QOL instruments, which measure wellbeing overall; disease-specific QOL instruments, which include items specific to the disease in question, e.g., swallowing and speaking, in the case of head and neck cancer; and symptom-specific instruments, which focus on a particular symptom, such as xerostomia. Table 3 lists and provides a brief description of the instruments used in the articles reviewed in this comparative effectiveness report. It also indicates whether studies were found assessing their internal consistency (measured by Cronbach's alpha), test-retest reliability, construct validity, criterion validity, and sensitivity to change. Internal consistency refers to whether the responses to similar

items are correlated; test-retest, to how stable a person's responses are if the instrument is readministered within a short period of time; construct validity, to the degree to which the instrument relates to the underlying concept to be measured (for example, a patient with more intense symptoms should score "worse" on a disease-specific QOL scale than a patient with less bothersome symptoms); and criterion validity, to the comparison of a scale to an existing, preferably well-validated scale.[27] Using ad hoc instruments or ones whose reliability and validity have not been thoroughly examined weakens confidence in the results. Apparent differences over time or between groups may be due to measurement issues rather than to variation in the underlying condition that the instrument is used to assess.

Peer Review and Public Commentary

As stated, a Technical Expert Panel (TEP) provided consultation for the comparative effectiveness review and reviewed the draft report. Two TEP members provided extended consultation, primarily for issues that needed to be addressed between the TEP meetings. The draft report was also posted to the Effective Health Care website (www.effectivehealthcare.ahrq.gov) for review by external reviewers, including invited clinical experts and stakeholders. Revisions were made to the draft report based on reviewers' comments.

Table 3. Summary of disease-specific quality-of-life instruments and symptom-specific instruments used in abstracted articles

Instrument	Articles Using Instrument	Domains Covered, # items	Scoring	Test-Retest Reliability	Internal Consistency	Construct Validity	Criterion Validity	Responsiveness to Change over Time
Generic and Global Quality of Life								
Short Form 36 (SF-36)	Pow et al. 2006[28]; McMillan et al. 2006[29]	Physical: Physical functioning, 10 Limitations of role functioning from physical limitations, 4 Bodily pain, 2 General perception of health, 5 Mental health: Vitality, 4 Role limitations from emotional problems, 3 Social functioning, 2 Mental health, 5 Self-reported health transition, 1	Two composite scores from 0 to 100 for physical and for mental health; higher scores= better functioning	Yes	Yes	Yes	Yes	Yes

Table 3. Summary of disease-specific quality-of-life instruments and symptom-specific instruments used in abstracted articles (continued)

Instrument	Articles Using Instrument	Domains Covered, # items	Scoring	Test-Retest Reliability	Internal Consistency	Construct Validity	Criterion Validity	Responsiveness to Change over Time
Disease-Specific Quality of Life								
Head and Neck Cancer-Specific Quality of Life (HNQOL)	Jabbari et al. 2005[30]; Feng et al. 2007[31]	Eating, 6 Communication, 4 Pain, 4 Emotion, 4	Lower scores= lower QOL	Yes	Yes	Yes	Uncertain	Yes
European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30)	Pow et al. 2006[28]; Fang et al. 2007[32]; McMillan et al. 2006[29]; Fang et al. 2008[33]; Vergeer et al. 2008[34]	Functioning --Physical, 5 --Role, 2 --Emotional, 4 --Cognitive, 2 --Social, 2 --Global QOL, 2 Fatigue, 3 Pain, 2 Nausea/ vomiting, 2 Dyspnea Insomnia Appetite loss Constipation Diarrhea Financial problems	0 to 100; high score=high level of symptoms or high level of functioning or global QOL	Yes	Yes	Yes	Yes	Yes

Table 3. Summary of disease-specific quality-of-life instruments and symptom-specific instruments used in abstracted articles (continued)

Instrument	Articles Using Instrument	Domains Covered, # items	Scoring	Test-Retest Reliability	Internal Consistency	Construct Validity	Criterion Validity	Responsiveness to Change over Time
Disease-Specific Quality of Life (continued)								
European Organization for Research and Treatment of Cancer QLQ-HN35 (EORTC QLQ-HN35 [1 of 10 modules to accompany EORTC QLQ-C30])	Pow et al. 2006[28]; Fang et al. 2007[31]; McMillan et al. 2006[29]; Fang et al. 2008[33]; Vergeer et al. 2008[34]; van Rij et al. 2008[35]	Pain, 4 Swallowing, 4 Senses, 2 Speech, 3 Social eating, 4 Social contact, 5 Sexuality, 2 Single items, 11	0 to 100; high score=high level of symptoms	Yes (Chinese translation)*	Yes	Yes	Yes	Yes
Head and Neck Cancer Inventory (HNCI)	Yao et al. 2007[36]; Dornfeld et al. 2007[37]	Speech, eating, aesthetics, social disruption; 30 items	0 to 100 for each domain; higher scores represent better outcomes	Yes	Yes	Yes	Yes	Yes

*Kappa low for some items, e.g., 0.38 for opening mouth; questionnaires administered 2 weeks apart.

Table 3. Summary of disease-specific quality-of-life instruments and symptom-specific instruments used in abstracted articles (continued)

Instrument	Articles Using Instrument	Domains Covered, # items	Scoring	Test-Retest Reliability	Internal Consistency	Construct Validity	Criterion Validity	Responsiveness to Change over Time
Disease-Specific Quality of Life (continued)								
University of Washington Quality of Life (UWQOL)	Feng et al. 2007[31]; Scrimger et al. 2007[38]	Version 4: Domain-specific (pain, appearance, activity level, recreation, swallowing, chewing, speech, shoulder function, taste, saliva function, depression, anxiety), 12 Generic QOL, Free text question, importance ranking	0 (worst) to 100 (best QOL) based on 12 domain-specific questions. Generic QOL reported separately	Yes (Brazilian Portuguese translation)	Yes	Yes (Brazilian Portuguese translation)	Yes	Yes

Table 3. Summary of disease-specific quality-of-life instruments and symptom-specific instruments used in abstracted articles (continued)

Instrument	Articles Using Instrument	Domains Covered, # items	Scoring	Test-Retest Reliability	Internal Consistency	Construct Validity	Criterion Validity	Responsiveness to Change over Time
Symptom-Specific								
Xerostomia questionnaire from #10300 Eisbruch et al. 2001 (XQ)	Jabbari et al. 2005[30]; Daly et al. 2007[39]; Pacholke et al. 2005[40]; van Rij et al. 2008[35]	Dryness while eating or chewing, 4 Dryness while not eating or chewing, 4	0 to 100; higher scores= greater xerostomia	Yes	Yes	Yes	Yes	Yes
Unnamed xerostomia questionnaire from Johnson et al. 1993	Kam et al. 2007[41]	6 items	No summary score reported; item response= increase ≥25 mm on visual analog scale	No studies of reliability and validity found.				
Unnamed xerostomia questionnaire	Braaksma et al. 2003[42]	3 yes/no questions and visual analog scale, all re: dry mouth	No summary score reported	No studies of reliability and validity found.				

Sources: 36,43–63

Results

Search Results

Of 2,679 records found in the electronic literature search, 354 articles were retrieved for further screening. Thirty-eight articles describing comparative studies were abstracted,[28,30,32-36,39,40,41,63-90] (Appendix D) in addition to 51 single-arm studies relating to IMRT,[29,31,37,38,91-137] 18 single-arm 3DCRT studies,[42,138-154] (Appendix E) and one proton beam therapy single-arm study.[155] This report will focus primarily on comparative studies. Of the 38 comparative studies, five were three-arm designs, so the total number of comparisons is 48. Interventions in comparative studies included IMRT, 3DCRT and 2DRT; none included proton beam therapy.

Organization of Results Chapter

- Comment on clinical diversity of the available evidence
- Synthesis of evidence across all four Key Questions, organized by specific comparison
- Summary of randomized, controlled trial evidence
- Summary of comparative study evidence base, emphasizing quantity of evidence by outcome and study quality concerns
- Applicability of evidence base
- Detailed description of evidence for Key Questions 1 and 2 organized by comparison, proceeding by site and setting
    - IMRT single-arm studies summary
    - 3DCRT single-arm studies summary
- Discussion of Key Question 3
- Discussion of Key Question 4
- Conclusions

A comprehensive listing of Abbreviations used throughout this review appears at the end of the document.

The Available Evidence is Clinically Diverse

The available evidence presented two main methodological challenges: clinical diversity and confounding. The evidence is highly diverse with respect to patient and treatment characteristics, both within and among studies. Clinical diversity refers to the mixing of patient groups with various characteristics such as different tumor histologies, tumor sites, stage of disease, age and treatment setting. Clinical diversity can be in measured or unmeasured characteristics and may reflect otherwise unmeasured prognostic factors. Clinical diversity contributes to confounding, which occurs when imbalances distort the estimates of treatment effects, leading to false conclusions. The distortion can overestimate or underestimate the presence, size and direction of the true treatment effect.

To provide greater clarity in synthesis of the evidence, this review sorts evidence first by comparison, then by site and by setting. This review emphasizes studies that selected participants with a single tumor site (such as nasopharyngeal, oropharyngeal, nasal cavity/paranasal sinuses, unknown primary and laryngeal), and a single setting (e.g., primary radiotherapy, primary

radiotherapy plus concurrent chemotherapy, postoperative radiotherapy, etc.). Studies that included participants with mixed sites or settings are considered weaker in design.

Synthesis of Evidence Across all Key Questions

Tables 4–6 provide a synthesis of the body of evidence according to the AHRQ/GRADE framework for the three main comparisons. There were no comparative studies involving proton beam therapy, therefore no table addresses this intervention.

IMRT Versus 3DCRT

Key Question 1: What is the comparative effectiveness of IMRT and 3DCRT regarding adverse events and quality of life?

The strength of the body of evidence showing IMRT reducing late xerostomia and improving quality of life domains related to xerostomia compared with 3DCRT was graded as moderate. One randomized, controlled trial[88] presented at a conference showed a large advantage for IMRT in the frequency of late xerostomia grade 2 or higher. That randomized, controlled trial was presented in a conference proceeding, but is not yet published. Since this trial has not yet been published in full manuscript form, its quality is rated as uncertain, as we lack sufficient details about its methods to clearly evaluate it. In addition, six observational studies found large statistically significant or moderate nonsignificant differences favoring IMRT.[33,34,71,79,81,83] All of the observational studies were of low quality; however, the reduction is unlikely the result of bias, as susceptibility to xerostomia is common in the head and neck cancer population and it is unlikely that between-group imbalances account for results. Thus, the evidence consistently shows that IMRT reduces the frequency of late xerostomia. Three observational studies[32-34] reported quality-of-life outcomes and all favored IMRT, especially in domains related to late xerostomia.

The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. One randomized, controlled trial[88] of uncertain quality presented at a conference was available and the quality of observational studies is poor, and no strongly consistent results are reported.

Key Question 2: What is the comparative effectiveness of IMRT and 3DCRT regarding tumor control and patient survival?

No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias.

Key Question 3: Patient and tumor characteristics affecting outcomes.

Key Question 4: Radiotherapy/physician characteristics affecting outcomes.

Table 4. Overall grade of strength of evidence, IMRT vs. 3DCRT

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
1. What is the comparative effectiveness of IMRT and 3DCRT regarding quality of life and adverse events?	Among 14 comparative studies addressing IMRT and 3DCRT, one was a randomized, controlled trials, the other 13 were observational, of which five were prospective designs.	The single randomized, controlled trial was presented at a conference and is not yet published, making rating of quality difficult. All other studies were rated as poor quality by the USPSTF framework and had an inherent risk of bias. Risk of bias in observational studies was due to: • uncertainty whether groups were comparable, • uncertainty regarding blinding of outcome assessors • noncontemp-oraneous treatment groups or unclear, and • lack of well-done multivariable analyses to adjust for confounding.	Consistent results were observed for two outcomes: • late xerostomia (7 studies); and • quality of life (3 studies), particularly domains most related to xerostomia Large statistically significant or nonsignificant differences favored IMRT. Although observational studies are not well designed to control for bias and confounding, it is unlikely that there was systematic imbalance of patients with a lower susceptibility to xerostomia in the IMRT groups. Susceptibility is common in the head/neck cancer population due to cancer site, prior and concurrent treatments, and sometimes older age and chronic medications Inconsistent results were observed for these outcomes: • acute xerostomia; • acute mucositis; • late mucositis; • acute dysphagia; • late skin toxicity; and • late osteoradionecrosis and bone toxicity. Results for these outcomes were reported in some studies and typically favored IMRT but differences were not consistently statistically significant. Among studies of acute skin toxicity neither the size of the difference nor the direction was consistent.	Direct evidence was available for all outcomes considered under this Key Question. There is direct evidence on late xerostomia from 7 studies	The single RCT shows a risk difference of grade 2 or higher xerostomia at 1 year of 35 percentage points with a 95% confidence interval from 12.6 to 55.4 percentage points. For observational studies, confidence intervals were not reported. Although we could not arrive at a pooled estimate or a confidence interval for the effect, the consistent direction and moderate-to-large differences favoring IMRT for frequency of late xerostomia, suggests a real effect.	The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality of life domains related to xerostomia compared with 3DCRT. One randomized, controlled trial and six observational studies found consistent results favoring IMRT. It was not possible to create a pooled effect estimate with a confidence interval. The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. In the future, well-designed studies may clarify the magnitude of effect for late xerostomia and quality of life, as well as whether there are between-group differences on other outcomes.

Table 4. Overall grade of strength of evidence, IMRT vs. 3DCRT (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
2. What is the comparative effectiveness of IMRT and 3DCRT regarding tumor control and patient survival?	Key Question 1 and Key Question 2 were addressed by a common set of studies.	The single randomized, controlled trial was presented at a conference and is not yet published, making rating of study quality difficult. Sample size is too small and followup is too short to ascertain any differences in tumor control or survival. All other studies were rated as poor quality by the USPSTF framework and therefore had an inherent risk of bias.	The evidence does not show consistently significant between-group differences for patient survival and tumor control. Of eight comparative studies reporting patient survival, one reported a statistically significant result; the difference was in the moderate range and favored IMRT Of the eight comparative studies reporting tumor control, none reported statistically significant differences between IMRT and 3DCRT.	Direct evidence is available for overall survival. Tumor control measures are intermediate outcomes, and are informative to the extent that they predict differences in disease-specific or overall survival.	Confidence intervals around observed treatment effects were not reported. Direction of effect cannot be determined.	The strength of the body of evidence is insufficient for tumor control and patient survival. No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. In the future, well-designed studies may clarify whether there are between-group differences on these outcomes.

Table 4. Overall grade of strength of evidence, IMRT vs. 3DCRT (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
2. What is the comparative effectiveness of IMRT and 3DCRT regarding tumor control and patient survival? (continued)	(See previous page)	Moreover, estimating between-group differences in disease-specific and overall survival is more complex than for adverse events. Observational studies can only be informative if there is detailed information about long-term losses to followup and well-done multivariable adjustment for confounding.	(See previous page)	(See previous page)	(See previous page)	(See previous page)
3. Patient and tumor characteristics affecting outcomes	No comparative studies addressed this Key Question.	NA	NA	NA	NA	The strength of evidence is insufficient, thus no conclusions can be reached.
4. Radiotherapy or physician characteristics affecting outcomes	No comparative studies addressed this Key Question.	NA	NA	NA	NA	The strength of evidence is insufficient, thus no conclusions can be reached.

Abbreviations: NA: not applicable; RCT: randomized, controlled trial

Table 5. Overall grade of strength of evidence, 3DCRT vs. 2DRT

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
1. What is the comparative effectiveness of 3DCRT and 2DRT regarding quality of life and adverse events?	Among 12 comparative studies addressing 3DCRT and 2DRT, one was an RCT and 11 were observational, including three prospective designs.	High risk of bias was observed throughout this set of studies. All were rated as poor quality by the USPSTF framework. Risk of bias was due to: • uncertainty whether groups were comparable, • uncertainty whether outcome assessors were blinded, • noncontemp-oraneous treatment groups or unclear, and • lack of well-done multivariable analyses to adjust for confounding among observational studies and • no intention-to-treat analysis in the RCT.	No consistent results were observed. Among four studies reporting on late xerostomia, one reported a large statistically significant difference; all others were either nonsignificant or of unclear significance. One study favored 2DRT by 10 percentage points; the others favored 3DCRT by 15 to 48 percentage points. Inconsistent results were observed for these outcomes: • acute xerostomia; • acute mucositis; • late mucositis; • acute dysphagia; • acute skin toxicity; • late skin toxicity; and • late osteoradionecrosis and bone toxicity. Results for these outcomes were reported in a few studies. Differences between 3DCRT and 2DRT were small and not statistically significant, not exceeding a difference of 9 percentage points. One study compared quality of life outcomes between 3DCRT and 2DRT but did not report a statistical comparison.	Direct evidence was available for all outcomes considered under this Key Question.	Confidence intervals around observed treatment effects were not reported. Direction of effect cannot be determined.	The strength of evidence is insufficient to draw conclusions about the comparative adverse events or quality of life associated with 3DCRT and 2DRT.

Table 5. Overall grade of strength of evidence, 3DCRT vs. 2DRT (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
2. What is the comparative effectiveness of 3DCRT and 2DRT regarding tumor control and patient survival?	Key Question 1 and Key Question 2 were addressed by a common set of studies.	As these are the same studies considered for Key Question 1, the risk of bias is high, as noted above. All studies were rated as poor quality by the USPSTF framework and therefore had an inherent risk of bias. Moreover, estimating between-group differences in disease-specific and overall survival is more complex than for adverse events. Observational studies can only be informative if there is detailed information about long-term losses to followup and well-done multivariable adjustment for confounding.	The evidence does not show consistently significant between-group differences for patient survival and tumor control. Of the eight comparative studies reporting tumor control, one reported a statistically significant difference in favor of 3DCRT. This RCT reported a large difference in tumor control at one year but did not report intent-to-treat analysis. Other differences were nonsignificant and/or negligible to moderate in size. Of seven comparative studies reporting patient survival, none reported a statistically significant result.	Direct evidence is available for disease-specific and overall survival. Tumor control measures are intermediate outcomes, and are informative to the extent that they predict differences in disease-specific or overall survival.	Confidence intervals around observed treatment effects were not reported. Direction of effect cannot be determined.	The strength of the body of evidence is insufficient for tumor control and patient survival. No conclusions on tumor control or survival can be drawn from the body of evidence comparing 3DCRT versus 2DRT.

Table 5. Overall grade of strength of evidence, 3DCRT vs. 2DRT (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
3. Patient and tumor characteristics affecting outcomes	No comparative studies addressed this Key Question.	NA	NA	NA	NA	The strength of evidence is insufficient, thus no conclusions can be reached.
4. Radiotherapy or physician characteristics affecting outcomes	No comparative studies addressed this Key Question.	NA	NA	NA	NA	The strength of evidence is insufficient, thus no conclusions can be reached.

Abbreviations: NA: not applicable; RCT: randomized, controlled trial

Table 6. Overall grade of strength of evidence, IMRT vs. 2DRT

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
1. What is the comparative effectiveness of IMRT and 2DRT regarding quality of life and adverse events?	Among 22 comparative studies addressing IMRT and 2DRT, 2 were RCTs, and 20 were observational, of which 5 were prospective designs.	A high risk of bias was observed throughout this set of studies. One RCT was rated as fair, while all other studies were rated as poor by the USPSTF framework. Risk of bias was due to: • uncertainty re: comparable groups • uncertainty re: blinding of outcome assessors noncontemp-oraneous treatment groups or unclear, • lack of well-done multivariable analyses to adjust for confounding among observational studies and • no ITT analysis in one RCT	Consistent results were observed for two outcomes: • quality of life (3 studies); and • late xerostomia (8 of 9 studies), particularly domains most related to xerostomia Statistically significant or otherwise moderate to large differences favored IMRT. Although the observational studies are not well designed to control for bias and confounding, it is unlikely that there was systematic imbalance of patients with a lower susceptibility to xerostomia in the IMRT groups. Susceptibility to xerostomia is common in the head/neck cancer population due to cancer site and prior and concurrent treatments, and sometimes due to older age and chronic medications Inconsistent results were observed for these outcomes: • acute xerostomia; • acute mucositis; • late mucositis; • acute dysphagia; • late dysphagia • acute skin toxicity; • late skin toxicity; and • late osteoradionecrosis and bone toxicity. Some of the strongest results were also found in studies with substantial methodological weaknesses.	Although direct evidence was available for all outcomes considered under this Key Question, complementary evidence from the comparison between IMRT and 3DCRT provides strong but indirect support for conclusions.	Confidence intervals around observed treatment effects were not reported. Although we could not arrive at a pooled estimate of the effect or a confidence interval for the effect, the consistent direction and moderate-to-large differences.	The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality of life domains related to xerostomia compared with 2DRT. The direct evidence reviewed on IMRT vs. 2DRT, although of limited quality, suggests a true effect in favor of IMRT. Indirect evidence, inference from comparison of IMRT vs. 3DCRT, provides additional support for this conclusion. The advantage of IMRT over 3DCRT is due to greater conformality of radiation delivery. Similarly, IMRT is inferred to be superior to 2DRT because 2DRT is less conformal than 3DCRT. The strength of evidence is insufficient to draw conclusions about the comparative impact of IMRT and 2DRT for other adverse events.

Table 6. Overall grade of strength of evidence, IMRT vs. 2DRT (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
1. What is the comparative effectiveness of IMRT and 2DRT regarding quality of life and adverse events? (continued)	(See previous page)	(See previous page)	Of six comparative studies reporting patient survival, one reported a statistically significant result; the difference was large and favored IMRT. Of the five comparative studies reporting tumor control, none reported statistically significant differences between IMRT and 2DRT.	(See previous page)	(See previous page)	(See previous page)
2. What is the comparative effectiveness of IMRT and 2DRT regarding tumor control and patient survival?	Key Question 1 and Key Question 2 were addressed by a common set of studies.	As these are the same studies considered for Key Question 1, the risk of bias is high, as noted above. Except for one fair quality randomized trial, all studies were rated as poor quality by the USPSTF framework and therefore had an inherent risk of bias.	The evidence does not show consistently significant between-group differences for patient survival and tumor control. Of six comparative studies reporting patient survival, one reported a statistically significant result; the difference was large and favored IMRT. Of five comparative studies reporting tumor control, none reported statistically significant differences between IMRT and 2DRT.	Direct evidence is available for overall survival. Tumor control measures are intermediate outcomes, and are informative to the extent that they predict differences in disease-specific or overall survival.	Confidence intervals around observed treatment effects were not reported. Direction of effect cannot be determined.	The strength of the body of evidence is insufficient for tumor control and patient survival.. No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 2DRT.

Table 6. Overall grade of strength of evidence, IMRT vs. 2DRT (continued)

Key Question	Study Design	Risk of Bias	Consistency	Directness	Precision	Overall Grade/Conclusion
2. What is the comparative effectiveness of IMRT and 2DRT regarding tumor control and patient survival? (continued)	(See previous page)	Moreover, estimating between-group differences in disease-specific and overall survival is more complex than for adverse events. Observational studies can only be informative if there is detailed information about long-term losses to followup and well-done multivariable adjustment for confounding.	(See previous page)	(See previous page)	(See previous page)	(See previous page)
3. Patient and tumor characteristics affecting outcomes	No comparative studies addressed this Key Question.	NA	NA	NA	NA	The strength of evidence is insufficient, thus no conclusions can be reached.
4. Radiotherapy or physician characteristics affecting outcomes	No comparative studies addressed this Key Question.	NA	NA	NA	NA	The strength of evidence is insufficient, thus no conclusions can be reached.

Abbreviations: ITT: intention to treat ; NA: not applicable; RCT: randomized, controlled trial

The strength of evidence is insufficient as no comparative studies addressed these key questions. Therefore, no conclusions can be reached.

3DCRT Versus 2DRT

Key Question 1: What is the comparative effectiveness of 3DCRT and 2DRT regarding adverse events and quality of life?

The strength of evidence is insufficient to draw conclusions about the comparative adverse events or quality of life associated with 3DCRT and 2DRT. The studies are of poor quality and the results are inconsistent.

Key Question 2: What is the comparative effectiveness of 3DCRT and 2DRT regarding tumor control and patient survival?

No conclusions on tumor control or survival can be drawn from the body of evidence comparing 3DCRT versus 2DRT. The strength of the body of evidence for tumor control and patient survival is insufficient.

Key Question 3: Patient and tumor characteristics affecting outcomes.

Key Question 4: Radiotherapy/physician characteristics affecting outcomes.

The strength of evidence is insufficient as no comparative studies addressed these key questions. Therefore, no conclusions can be reached.

IMRT Versus 2DRT

Key Question 1: What is the comparative effectiveness of IMRT and 2DRT regarding adverse events and quality of life?

The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality of life domains related to quality of life compared with 2DRT. The direct evidence reviewed on IMRT versus 2DRT, although of limited quality, suggests a true effect in favor of IMRT. Indirect evidence, inference from comparison of IMRT versus 3DCRT, provides additional support for this conclusion. The advantage of IMRT over 3DCRT is due to greater conformality of radiation delivery. Similarly, IMRT is inferred to be superior to 2DRT, because 2DRT is less conformal than 3DCRT.

The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 2DRT for other adverse events. The quality of available studies is poor and no strongly consistent results are reported.

Key Question 2: What is the comparative effectiveness of IMRT and 2DRT regarding tumor control and patient survival?

No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 2DRT. The strength of the body of evidence for tumor control and patient survival is insufficient.

Key Question 3: Patient and tumor characteristics affecting outcomes.

Key Question 4: Radiotherapy/physician characteristics affecting outcomes.

The strength of evidence is insufficient as no comparative studies addressed these key questions. Therefore, no conclusions can be reached.

Proton Beam Therapy Versus Other Techniques

The strength of evidence is insufficient as no comparative studies addressed any of the key questions. Therefore, no conclusions can be reached regarding the comparative effectiveness of proton beam therapy.

Summary of the Randomized, Controlled Trial Evidence

As shown in Table 7, four head-to-head randomized trials of IMRT, 3DCRT, and 2DRT have been published.[28,41,85,88] Three were studies of patients with nasopharyngeal cancer, while one selected patients with oropharyngeal or hypopharyngeal cancer. The most recent randomized trial, designated PARSPORT, was reported by Nutting et al.[88] at the 2009 annual meeting of the American Society of Clinical Oncology. Detailed slides from this unpublished study were available for review. Studies by Kam et al.[41] and Pow et al.[28] selected only patients with stage I/II disease and the Wu et al.[85] study selected only patients with stage III/IV. The proportion of patients with stage III/IV disease included by Nutting et al.[88] was 77 percent. Neither Kam et al.[41] nor Wu et al.[85] formally met study selection criteria, because patients were given a mix of radiotherapy modalities. They are presented in this review due to the limited number of randomized trials, otherwise. Kam et al.[41] compared primary IMRT and primary 2DRT, but both groups included some patients who did and did not receive intracavitary brachytherapy (ICBT). Wu et al.[85] split radiotherapy in the treatment group between early course 2DRT and late course 3DCRT, while the control group received only 2DRT. All patients in both groups received split chemotherapy.

Table 7. Head-to-head randomized trials of IMRT, 3DCRT, and 2DRT for nasopharyngeal cancer

Study	Patients	Treatment	Control	Randomization Method	Outcomes	ITT?
Nutting et al. 2009[88]	84, OPH/ HYP	Primary or postoperative IMRT ± preRT chemotherapy	Primary or postoperative 3DCRT ± preRT chemotherapy	Centralized	Xerostomia, dysphagia, mucositis, skin, mandible, locoregional control, overall survival, quality of life (not included in conference presentation), salivary flow (not included in conference presentation)	Unclear
Kam et al. 2007[41]	56, stage I/II NPC	Primary IMRT ± intracavitary brachytherapy	Primary 2DRT ± intracavitary brachytherapy	Centralized	Xerostomia, salivary flow	Yes
Pow et al. 2006[28]	45, stage I/II NPC	Primary IMRT	Primary 2DRT	Unclear	Quality of life, salivary flow	No
Wu et al. 2005[85]	96, stage III/IV NPC	Primary 2DRT/3DCRT + split chemo-therapy	Primary 2DRT + split chemo-therapy	Random draw from 20 numbers (treatment – odd, control – even)	Mucositis, local control, overall survival	Unclear

Abbreviations: HYP: hypopharynx; ITT: intention to treat; NPC: nasopharyngeal cancer; OPH: oropharyngral

Summary of the Comparative Study Evidence Base

The 38 comparative studies collectively included 5,061 participants. By comparison type, 14 comparisons involved IMRT versus 3DCRT, 12 involved 3DCRT versus 2DCRT and 22 involved IMRT versus 2DRT. None of the comparative studies addressed proton beam therapy.

Quality of study methods among these 38 comparative studies is summarized in Appendix Table C3. About three-fifths of studies were retrospective designs. Twenty-nine studies enrolled patient groups that were initially not comparable or of unclear comparability. More than three-fifths of studies either used historical controls or did not specify whether treatments were given in the same time period. Because treatment approaches often evolve over time, such historical comparisons may not be relevant to strategies presently in use. Only the Kam et al.[41] trial used a clearly random method for allocating patients to treatment groups. Of the other trials, Pow et al.[28] did not describe the randomization process in any detail and Wu et al.[85] noted a method that may have been biased. Two randomized trials[41,88] used intention-to-treat analysis, one did not,[28] and it was unclear for the fourth.[85]

Of the 34 nonrandomized studies, two[33,75] allocated patients based on equipment availability or physician preference, one study[81] based allocation on a waiting list, and two[30,69] studies based allocation on risk to sensitive areas. Outcome measures were generally valid and reliable, but only one study[28] stated that outcome assessors were blinded to treatment assignment. Sixteen studies did not conduct a multivariable analysis. None of the described

multivariable analyses could be rated as well conducted: 21 were either not done or clearly not well done and for 13, it is unclear if they were well done.

Using the USPSTF rating system, one[88] of these studies could not be clearly rated as a journal manuscript is not yet available, one[41] was rated as fair quality, and the remaining 36 studies were rated as poor quality. Of particular concern is the common finding of noncomparable groups or uncertain comparability and complete lack of clearly well-conducted multivariable analyses to adjust for potential confounders.

Applicability of the Evidence Base

The evidence appears to apply to a primarily middle-aged population with advanced head and neck cancer. Included studies were generally conducted at academic medical centers. Regarding study populations, the percentage of females in most studies was between 10 and 40 percent. Median age was in the 40s or 50s in all but five studies, consistent with ages when incidence of head and neck cancer increases considerably. One study enrolled pediatric patients with nasopharyngeal cancer, while the age ranges for the rest were quite close to 40 to 60 years. Table 8 shows how many studies enrolled different ranges of percentages for patients with stage III/IV disease. More studies included a large majority (≥75 percent) of patients with stage III/IV than any other category in this distribution. Nearly one-quarter of studies were very clinically diverse with respect to disease stage (25–74 percent stage III/IV). Three studies did not report stage information.

Prescribed dose (Table 9) was not reported in four studies. Eight studies gave a single value for prescribed dose for all patients or all patients in a given treatment group, ranging from 66 Gy to 75 Gy. In the 26 studies reporting a range of prescribed dose values, the minimum was at least 60 Gy in most studies and more than 70 Gy in most.

Table 8. Number of comparative studies reporting ranges of percentages of participants in American Joint Committee on Cancer stage III or IV

% Stage III or IV	Not Reported	0–24%	25–49%	50–74%	75–100%
No. of studies	3	5	5	4	21

Table 9. Number of comparative studies reporting different minimum and maximum prescribed doses

Range of Prescribed Dose Among 26 of 38 Comparative Studies	Minimum ≤49 Gy	Minimum 50–59 Gy	Minimum ≥60 Gy	Maximum ? Gy	Maximum ≤69 Gy	Maximum 70–74 Gy	Maximum ≥75 Gy
No. of studies	3	7	16	2	1	13	10

Gy: Gray

Key Question 1. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?

Key Question 2. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?

Comparative Studies, IMRT Versus 3DCRT

Overview

Of the three main comparisons that are addressed here, IMRT versus 3DCRT is the most relevant. Both take advantage of three-dimensional target delineation using CT or MRI and have been in frequent use in the past decade. In contrast, 2DRT relies on two-dimensional target localization and is currently little-used. This section compares IMRT and 3DCRT regarding evidence about quality of life, adverse events, tumor control and patient survival.

Fourteen studies provide comparative evidence on IMRT and 3DCRT. Table 10 shows that two comparisons included individuals with nasopharyngeal cancer, four with oropharyngeal patients, one with nasal cavity/paranasal sinus cancer and 6 with a mix of tumor sites. One randomized, controlled trial has addressed this comparison and the other 13 studies were observational designs. Seven studies were prospective designs and seven were retrospective.

The quality of all 13 observational studies was rated poor by USPSTF criteria, while the randomized, controlled trial could not be clearly rated as a manuscript is not available. None of these studies reported using blinded outcome assessors or well-done multivariable analyses to control for confounding. It was clear in two studies that groups were comparable on baseline characteristics and co-interventions. Six studies made clear that groups were treated during the same time period, while the periods were either unclear or different in the rest. Lack of concurrent treatment groups could mean that patients treated in an earlier era with 3DCRT may have received therapy that does not represent more current methods of 3DCRT. Furthermore, co-interventions given during different eras may have divergent effects.

Table 10. IMRT vs. 3DCRT: Summary of study design, quality, and key outcomes

Site	Studies	n	RCT	Prospective Observational	Assessor Blinded	Groups Comparable	Treatments in same time period	Well-done multi-variable analysis/ intention-to-treat	USPSTF Good/Fair
NPC	2	288	0	1	0	1	1	0	0/0
OPH	4	410	1	1	0	1	2	1	0/0
PNS	1	68	0	0	0	0	0	0	0/0
UNP	0	0	0	0	0	0	0	0	0/0
LAR	0	0	0	0	0	0	0	0	0/0
MIX	7	986	0	5	0	0	3	0	0/0
Total	14	1752	1	7	0	2	6	1	0/0

Outcome	Total No. studies	Large (>15 pctg pts) IMRT-3DCRT difference				Moderate (6-15 pctg pts) IMRT-3DCRT difference				Small (0-5 pctg pts) IMRT-3DCRT difference				Unquantifiable IMRT-3DCRT difference			
		No. Studies	Sig	NS	p NR	No. Studies	Sig	NS	p NR	No. Studies	Sig	NS	P NR	No. Studies	Sig	NS	p NR
Acute xerostomia	4	2	2+							2		1?	1+				
Late xerostomia	7	4	4+			2		2+						1			1+
Acute mucositis	6	1		1+		1		1+		4		3+	1-				
Late mucositis	2					1		1-		1			1+				
Acute dysphagia	2					1	1+			1			1?				
Late dysphagia	2					2	1-	1-									
Acute skin toxicity	5	2	2+			1	1-			2			1- 1?				
Late skin toxicity	3					1		1+		2			2+				
Acute osteoradionecrosis/ bone toxicity	0																
Late osteoradionecrosis/ bone toxicity	2					1			1+	1		1-					
Tumor control*	8	2		2+		2		2+		5		3+ 1? 1-					
Patient survival*	8	1		1+		4	1+	1+ 1-	1+	4		3+ 1?					

+: favors IMRT; -: favors 3DCRT; ?: unclear which group is favored; *Columns to the right may not sum to the total, because some studies reported more than one outcome for tumor control or patient survival, e.g., disease-specific survival and overall survival.

Abbreviations: NR: not reported; NS: not significant; pctg: percentage; pts: patients; RCT: randomized, controlled trial; sig: significant; USPSTF: U.S. Preventive Services Task force;

To conclude that outcomes differ between treatments, there should be predominantly moderate to large between-group differences favoring one treatment consistently. This level of consistency is needed to counteract uncertainty created by the risk of bias. Consistent results favoring IMRT were observed on later xerostomia and quality of life domains related to xerostomia.

Adverse event comparisons that report numerical differences in incidence are presented graphically in Appendix C, Figures C1–C9. Four studies found large (greater than 15 percentage points) significant differences favoring IMRT in the frequency of grade 2 or worse late xerostomia.[34,81,83,88] Two other studies found moderate differences between groups favoring IMRT on late xerostomia.[71,79] Vergeer et al.[34] found significant advantages for IMRT on most subscales of the EORTC QLQ-C30 and EORTC H&N-35 quality of life instruments (Table 11). Among the former's subscales were global health, fatigue and appetite loss and among the latter's subscales were dry mouth, pain, swallowing, social eating, teeth, opening mouth, and feeling ill. Fang et al.[33] observed a significant advantage for IMRT on the EORTC QLQ-C30 global health and fatigue subscales and on the EORTC H&N-35 dry mouth, taste/smell and feeling ill subscales. The smallest of three studies reporting quality of life data found no significant between-group differences on either instrument, but large, nonsignificant differences in favor of IMRT were seen on the EORTC QLQ-C30 pain and appetite loss subscales and the EORTC H&N-35 speech, social eating, teeth and opening mouth subscales.

It is unlikely that there was systematic imbalance of patients with a lower susceptibility to late xerostomia in the IMRT groups among observational studies. A susceptibility to xerostomia is common in the head and neck cancer population due to cancer site and prior and co-interventions and sometimes due to older age and chronic medications. Thus, the consistency of results suggests a treatment effect favoring IMRT.

Inconsistent results were observed for these outcomes: acute xerostomia; acute mucositis; late mucositis; acute dysphagia; late skin toxicity; and late osteoradionecrosis and bone toxicity. Results for these outcomes were reported in some studies and typically favored IMRT, but differences were not consistently moderate to large in size or statistically significant. Among studies of acute skin toxicity, neither the size of the difference nor the direction was consistent.

Among eight studies reporting tumor control outcomes, moderate to large differences favoring IMRT were not consistently reported. None of these results were statistically significant. Similarly inconsistent results were found among eight studies with evidence on patient survival. One study reported a statistically significant result; the difference was in the moderate range and favored IMRT. Compared with assessing a local adverse event like xerostomia, estimating between-group differences in disease-specific and overall survival is more complex and requires greater detail about long-term losses to followup and assurances that multivariable adjustment for confounding is well done.

Table 11. IMRT vs. 3DCRT: Summary of quality of life data

Study	EORTC QLQ-C30 (# domains)			EORTC H&N-35 (# domains)			SF-36 (# domains)			Other (HNCI, HNQOL) (# domains)		
	+	NS	—	+	NS	—	+	NS	—	+	NS	—
Fang et al. 2007[32]		15			12							
Fang et al. 2008[33]	2	12		3	12							
Vergeer et al. 2008[34]	8	7		9	3							

KEY:
+ statistically significant difference in favor of more conformal modality (listed first in comparison in 1st column)
NS difference not statistically significant
— statistically significant difference in favor of less conformal modality (listed second in comparison in 1st column)
*Between-group difference in total score, adjusted for baseline score.

Detailed results are presented in the following sections by site, then setting. Studies that were homogeneous by site and setting are described before clinically diverse studies. Recall that treatment setting refers to the presence and timing of combinations of these modalities for a given patient: surgery, radiation therapy, and chemotherapy. A homogeneous treatment setting within a study could mean that all patients in that study received, for example, postoperative radiotherapy with concurrent chemotherapy.

IMRT Versus 3DCRT: Nasopharyngeal Cancer, Mixed Settings. A retrospective study from 2007 by Fang and colleagues[32] (Table 12) included patients treated for nasopharyngeal cancer by primary radiotherapy with or without chemotherapy, although the timing of chemotherapy was unclear. Four treatment arms were included: 2DRT, 2DRT plus 3DCRT boost, 3DCRT, and IMRT. The second arm is not discussed here due to mixing of radiotherapy modalities, so this study is considered a three-arm design in this review. The key outcomes were QOL (EORTC QLQ-C30 and EORTC QLQ-H&N35) and late xerostomia. Multivariable analyses were conducted on global QOL and xerostomia, but they separated radiotherapy technique into two groups: 2DRT combined with 2DRT plus 3DCRT boost and 3DCRT combined with IMRT. Thus, these multivariable analyses are off-topic for the purposes of this review.

IMRT and 2DRT groups were mostly similar with respect to median age (49, 51 years), percentage female (29 percent and 24 percent) and percentage in stage III/IV (48 percent and 49 percent). Group proportions of patients given more than 70.2 Gy were 54 percent and 58 percent. Lack of multivariable analyses comparing IMRT and 3DCRT was largely responsible for the USPSTF rating of poor. Univariate comparisons found no statistically significant differences between IMRT and 3DCRT on any domains from the two QOL scales, including the EORTC QLQ-H&N35 xerostomia domain. It would be unwise to interpret these data as evidence of similar QOL for IMRT and 3DCRT.

The only other study comparing IMRT with 3DCRT was reported by Fang et al.[33] in 2008. This prospective study involved primary radiotherapy with or without chemotherapy. Groups appeared similar with regard to percentage of females (22 percent, 17 percent) and stage III/IV (53 percent, 56 percent), but IMRT has a lower percentage of individuals over age 60 (14 percent, 25 percent) and those with T4 tumors (11 percent, 25 percent). The prescribed dose was between 65 and 76 Gy for all patients. Treatments were allocated based on equipment availability and physician preference. It is unclear whether multivariable analyses were well done. Followup was conducted at 3, 12, and 24 months. Only isolated significant between-group differences were reported on the EORTC QLQ-C30 and EORTC QLQ-H&N35 QOL scales. Significant differences favoring IMRT were observed at three months on two QLQ-C30 domains

(Global Health and Fatigue) and three QLQ-H&N35 domains (Taste/Smell, Dry Mouth, and Feeling Ill). Note the lower proportion of IMRT participants over age 60 or with T4 tumors. Differences were not statistically significant for any other followup points and all other domains. Also, no differences were found between groups on locoregional control or overall survival. Taking these results with those of the 2007 Fang et al.[32] study, the relative effects of IMRT and 3DCRT are unclear with respect to QOL, xerostomia, tumor control, and patient survival.

Table 12. IMRT vs. 3DCRT: Summary of studies of nasopharyngeal cancer, mixed settings

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Fang et al. 2007[32]	Primary RT ± chemotherapy with unclear timing	Quality of life	85	24-36 mo, EORTC QLQ-C30 NS for all domains: Global Health, Physical Function, Role Function, Emotional Function, Cognitive Function, Social Function, Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial Difficulties EORTC QLQ-H&N35 NS for all domains: Pain, Swallowing, Taste/smell, Social eating, Social contract, Sexuality, Teeth, Opening mouth, Dry mouth, Sticky saliva, Coughing, Feeling ill		Retrospective	Yes	Yes	Off-topic	Poor

Table 12. IMRT vs. 3DCRT: Summary of studies of nasopharyngeal cancer, mixed settings (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Fang et al. 2008[33]	Primary RT ± concurrent chemotherapy	Quality of life	203	Post-RT/3/12/24 mo. EORTC QLQ-C30 Global health, 3 mo. IMRT+ <.05 (all other F/U NS) Fatigue, 3 mo. IMRT- <.05 (all other F/U NS) All other domains, all F/U NS: Physical Function, Role Function, Social Function, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial Difficulties, EORTC QLQ-H&N35 Taste/Smell, 3 mo. IMRT- <.05 (all other F/U NS) Dry Mouth, 3 mo. IMRT- <.05 (all other F/U NS) Feeling Ill , 3 mo. IMRT- <.05 (all other F/U NS) All other domains, all F/U NS: Pain, Swallowing, Social Eating, Social Contract, Sexuality, Teeth, Opening Mouth, Sticky Saliva, Coughing		Prospective	Yes	Yes	Unclear	Poor

Table 12. IMRT vs. 3DCRT: Summary of studies of nasopharyngeal cancer, mixed settings (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Fang et al. 2007[32]		Xerostomia	85	24-36 mo, EORTC QLQ-H&N35 Dry Mouth item NS		Retrospective			Off-topic	
Fang et al. 2008[33]		Xerostomia		Post-RT/3/12/24 mo, EORTC QLQ-H&N35 Dry Mouth item, 3 mo. IMRT- <.05 (all other F/U NS)		Prospective			Unclear	
Fang et al. 2008[33]		Locoregional control	203	3 yr., Δ+1, NS	NS				Unclear	
Fang et al. 2008[33]		Overall survival	203	3 yr., Δ+1, NS	NS				Unclear	

IMRT+: IMRT favored, IMRT-: IMRT not favored

IMRT Versus 3DCRT: Oropharyngeal Cancer, Primary Radiotherapy Plus Concurrent Chemotherapy. Rusthoven et al.[83] reported on primary IMRT or 3DCRT with concurrent chemotherapy (Table 13). This nonrandomized study found a significantly lower frequency of late xerostomia and acute skin toxicity with IMRT, but nonsignificant differences for mucositis, locoregional control, disease-free survival and overall survival.

Of the 87 patients with oropharyngeal cancer in the study,[83] the percentage female by group was 12 percent and 9 percent; all had stage III or IV cancer; and the prescribed dose to the primary tumor was 66–70 Gy for 3DCRT and 70–72 Gy for IMRT, respectively. Patients treated with IMRT were significantly less likely to experience acute xerostomia ($p<.001$) or acute skin toxicities ($p=.002$). At 6 months, 12 months, and 18 months, the differences in percentages with grade 2 or higher xerostomia favoring IMRT were 38 points, 79 points, and 87 points, respectively. Enrollment in this study occurred between 1998 and 2007 and the article does not make clear whether the two groups accrued equally over this period. If 3DCRT patients accrued mainly in the early study period, the reported difference may be greater than with current modalities. The reported higher prescribed dose range for IMRT suggests that the observed between-group difference is credible. The rates of mucositis appeared similar between IMRT and 3DCRT; statistical significance was not reported.

Two tumor control outcomes (locoregional control and disease-free survival) and overall patient survival were reported. Between-group comparisons appeared to favor IMRT for all three outcomes at four years, but no statistically significant differences were detected, using either univariate or multivariable analyses.

IMRT Versus 3DCRT: Oropharyngeal Cancer, Mixed Setting. Three studies compared IMRT and 3DCRT in patients with oropharyngeal cancer with mixed settings. A randomized trial by Nutting et al.[88] gave patients primary or postoperative radiotherapy with or without neoadjuvant chemotherapy. Of the two nonrandomized studies, Hodge et al.[71] included two sets 3DCRT controls: one from the IMRT era and the other from an earlier era (Table 13). Rades et al.[81] conducted a three-arm study, using postoperative radiotherapy with or without chemotherapy. Hodge et al.[71] delivered primary radiotherapy to all patients and Rades et al.[81] administered postoperative radiotherapy to all; both studies included a mix of patients who did and did not have concurrent chemotherapy.

The one-year rate of grade 2 or higher xerostomia was the primary outcome in the Nutting et al.[88] randomized trial; IMRT resulted in a 35 percentage point advantage ($p=.004$). The 95 percent confidence interval around this risk difference is between 12.6 percentage points and 55.5 percentage points. Significant xerostomia results also favored IMRT in the acute period and at 3, 6, and 18 months. Nutting et al.[88] also reported significant advantages for IMRT in acute dysphagia and acute skin toxicity and nonsignificant results for late dysphagia, late skin toxicity, late bone toxicity, and both acute and late mucositis. Rades et al.[81] observed a 56 percentage point reduction in the frequency of late grade 2–3 xerostomia ($p=.037$). Hodge et al.[71] did not find a statistically significant reduction in late xerostomia. For other outcomes, between-group differences in the two nonrandomized studies were either not statistically significant (e.g., acute mucositis,[71] local control,[81] overall survival,[71] multivariable analysis[81]) or p values were not reported (e.g., acute mucositis,[81] acute and late skin toxicity,[81] locoregional control,[71] disease-specific survival[71]).

The mean age reported by Nutting et al.[88] was 58 years, while neither nonrandomized study reported on patient age. Rades et al.[81] does not report on gender distribution, while the

sample selected by Nutting et al.[88] was 28 percent female and in Hodge et al.,[71] it was 5–29 percent female across treatment groups. The proportion of patients with stage III/IV disease included by Nutting et al.[88] was 77 percent. In the Hodge study,[71] the percentage of patients with stage III or IV disease was slightly lower in the IMRT group (86 percent) compared with the contemporaneous 3DCRT group (100%). Rades et al.[81] also had fewer patients with more advanced stage disease in the IMRT group (at least 50 percent versus at least 65 percent). The prescribed primary tumor dose was 60–70 for both treatments in the Rades et al.[81] study and 65–70 for IMRT, and 60–78 for 3DCRT in the Hodge et al. study.[71]

Comparing outcomes of 3DCRT before and after the introduction of IMRT in Hodge et al.[71] suggests 3DCRT may have improved over time. For example, four-year overall survival was 88 percent for IMRT, 81 percent for contemporaneous 3DCRT, and about 56 percent for pre-IMRT era 3DCRT, although IMRT was not a significant predictor of overall survival in a multivariable model that also included tumor stage. Fifty-six percent of IMRT patients had late xerostomia, compared 63 percent of 3DCRT patients treated during the same period (who also had a higher percentage of advanced cancer than either other group), and 67 percent of 3DCRT patients treated earlier. The statistical significance of differences in 3DCRT outcomes before and after the introduction of IMRT is not reported.

IMRT Versus 3DCRT: Nasal Cavity and Paranasal Sinuses, Mixed Settings. The study by Chen et al.[67] was limited to patients with cancer of the nasal cavity/paranasal sinuses and compared IMRT versus 3DCRT on toxicities, tumor control and patient survival outcomes (Table 14). Of the 68 of the patients receiving IMRT or 3DCRT, 40 percent were women; the median age was 61; and more than 85 percent had Stage III or IV cancer. The prescribed dose to the primary tumor fell in a broader range for 3DCRT (50–73 Gy) than for IMRT (66–72 Gy). Patients varied in the timing of radiotherapy and in both use and timing of chemotherapy. The frequency of late mucositis and skin toxicity was similar for IMRT and 3DCRT, while osteoradionecrosis or bone toxicity occurred slightly less often in the IMRT group. However, no statistical tests were reported for these comparisons. At five years, local control was similar for IMRT and 3DCRT, while overall survival was higher in the 3DCRT group; the magnitude of the difference for disease-free survival was not reported. None of these three comparisons was statistically significant. These results could be confounded by a number of factors, including treatment timing and potential baseline differences between groups.

Table 13. IMRT vs. 3DCRT: Summary data, oropharyngeal cancer

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Rusthoven et al. 2008[83]	Primary RT + concurrent chemotherapy	Xerostomia	87	6/12/18 mos., ≥ Gr 2, Δ-38/Δ-79/Δ-87, <.001		Retrospective	No	?	Not done	Poor
Hodge et al. 2007[71]	Primary RT ± concurrent chemotherapy	Xerostomia	195	Late, Gr mod, Δ-7, NS		Retrospective	Yes	Yes/No	Not done	Poor
Rades et al. 2007[81]	Postoperative RT ± concurrent chemotherapy	Xerostomia	44	Late, Gr 2-3, Δ-56, .037		Retrospective	Yes	Unclear	Not done	Poor
Nutting et al. 2009[88]	Primary or postoperative IMRT ± preRT chemotherapy	Xerostomia	84	Acute, Gr ≥ 2, Δ-20, .02 3/6/12/18 mos., Gr > 2, Δ-21/Δ-26/Δ-35/ Δ-42, ≤.05		Prospective	Yes	Yes	Not applicable	Good
Nutting et al. 2009[88]		Dysphagia	84	Acute, Gr ≥ 2, Δ-11, .05 Late, Gr ≥ 2, Δ-+7, NS					Not applicable	
Rusthoven et al. 2008[83]		Mucositis	87	Acute, ≥ Gr 3, Δ+3, p NR					Not done	
Hodge et al. 2007[71]		Mucositis	195	Acute, Gr 3, Δ-17, NS					Not done	
Rades et al. 2007[81]		Mucositis	44	Acute, Gr 2-3, Δ-4, p NR					Not done	
Nutting et al. 2009[88]		Mucositis	84	Acute, Gr ≥ 2, Δ-7, 0.18 Late, Gr ≥ 2, Δ+8, NS					Not applicable	

Table 13. IMRT vs. 3DCRT: Summary data, oropharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Rusthoven et al. 2008[83]		Skin toxicity	87	Acute, ≥ Gr 3, Δ-18, .002					Not done	
Rades et al. 2007[81]		Skin toxicity	44	Acute, Gr 2-3, Δ+5, p NR Late, Gr 2-3, Δ-5, p NR					Not done	
Nutting et al. 2009[88]		Skin toxicity	84	Acute, Gr ≥ 2, ∆--17, .02 Late, Gr ≥ 2, ∆-7, NS					Not applicable	
Nutting et al. 2009[88]		Osteoradio-necrosis or bone toxicity	84	Late, Gr ≥ 2, ∆-+1, NS						
Rades et al. 2007[81]		Local control	44	2 yr. Δ+10, NS	NS				Unclear	
Rusthoven et al. 2008[83]		Locoregional control	87	4 yr. Δ+15, NS	.075				Unclear	
Hodge et al. 2007[71]		Locoregional control	195	4 yr. Δ+18, p NR					Not done	
Nutting et al. 2009[88]		Locoregional control	84	1 yr. ∆-0.7, NS					Not applicable	
Rusthoven et al. 2008[83]		Disease-free survival	87	4 yr. Δ+18, NS	NS				Unclear	
Hodge et al. 2007[71]		Disease-free survival	195	4 yr. Δ+14, p NR					Not done	

Table 13. IMRT vs. 3DCRT: Summary data, oropharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Rusthoven et al. 2008[83]		Overall survival	87	4 yr. Δ+17, NS	NS				Unclear	
Hodge et al. 2007[71]		Overall survival	195	4 yr. Δ+7, .02	NS				Unclear	
Rades et al. 2007[81]		Overall survival	44	2 yr. Δ+6, NS	NS				Unclear	
Nutting et al. 2009[88]		Overall survival	84	1 yr. Δ+2.8, NS					Not applicable	

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

Table 14. IMRT vs. 3DCRT: Nasal cavity or paranasal cancer, mixed settings

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Chen et al. 2007[67]	Primary/ preoperative/ postoperative RT ± post-RT/ concurrent chemotherapy	Mucositis	68	Late, ≥ Gr 3, Δ-3, p NR		Retrospective	Unclear	No	Not done	Poor
Chen et al. 2007[67]		Skin toxicity	68	Late, ≥ Gr 3, Δ-5, p NR					Not done	
Chen et al. 2007[67]		Osteoradio-necrosis/ bone toxicity	68	Late, ≥ Gr 3, Δ-7, p NR					Not done	
Chen et al. 2007[67]		Local control	68	5 yr., Δ+3, NS					Not done	
Chen et al. 2007[67]		Disease-free survival	68	NS					Not done	
Chen et al. 2007[67]		Overall survival	68	5 yr., Δ-10, NS					Not done	

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

IMRT Versus 3DCRT: Mixed Tumor Sites, Primary Radiotherapy. Golen et al.[69] compared IMRT and 3DCRT among mixed head and neck cancer patients with a single treatment setting: primary radiotherapy and no chemotherapy (Table 15). The groups were described as similar for the single reported outcome—xerostomia—but no statistics were given. The lack of multiple settings is a positive attribute of this study, but is offset by uncertainty about whether groups were comparable at baseline. Of the 40 patients in this study,[69] 28 percent were women and 40 percent had stage III or IV cancer; age was not reported. The primary tumor prescribed dose was 62–72 Gy. Group means for xerostomia were reported at 3, 6, 12, 18, 24, and 30 months, but no statistical tests were reported. The groups were described as similar in the study. No multivariable analyses were performed to account for possible confounding factors; and no other outcomes were reported.

IMRT Versus 3DCRT: Mixed Tumor Sites, Mixed Settings. Six studies[34,65,70,79,80,89] (Table 16) with mixed tumor sites and mixed settings compared outcomes of IMRT and 3DCRT. Most of the studies treated patients with primary or postoperative radiotherapy, with or without chemotherapy. Of a total of 946 subjects, the majority were male in four[34,65,80,89] of the studies; one[79] did not report gender; the median age was in the 50s in three studies and the 60s in one (two studies[34,79] did not report age); and in three[34,65,80] of the studies, more than 60 percent of the patients had advanced cancer (stage III or IV). The prescribed dose to the primary tumor ranged from a minimum of 46 Gy to a maximum of 70 Gy; one study[79] did not report dose.

Vergeer et al.[34] reported on quality of life, using the validated EORTC QLQ-30. The IMRT group improved more than the 3DCRT group between 1.5 and 6 months after treatment for the following domains: global health; role, cognitive, and social function; fatigue; pain, insomnia; and appetite loss (all $p<.05$). Using the head and neck symptom-specific, validated EORTC QLQ-H&N35, also at 1.5 and 6 months, the IMRT group improved more than the 3DCRT group on the following domains: pain, swallowing, social eating, sexuality, teeth, opening mouth, dry mouth, sticky saliva, and feeling ill (all $p<.05$).

The IMRT group had statistically significantly fewer adverse events than the 3DCRT group. Frequency of xerostomia was similar or smaller for IMRT, but some results were statistically significant,[34] while others were not,[79,80] using salivary flow proxy.[65] One study[89] found a significantly higher frequency of late dysphagia among IMRT patients. Frequency differences between IMRT- and 3DCRT-treated patients were not statistically significant for acute dysphagia[80] and acute mucositis;[34,80] the results for acute skin toxicity were mixed.[34,80] The differences between treatment groups were not statistically significant for the only other outcomes reported: disease-free (at one year[79] or time not specified[70]) and overall survival (at one year[79] or time not specified[70]).

Table 15. IMRT vs. 3DCRT: Summary data on primary radiotherapy for mixed tumor sites

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Golen et al. 2007[69]	Primary RT	Xerostomia	40	3/6/12/18/24/30 months Group late Gr means presented at each F/U, but no statistical test results given, groups described as similar		Retrospective	Unclear	Yes, but allocation based on whether 3DCRT would deliver higher dose to parotids	Not done	Poor

Table 16. IMRT vs. 3DCRT: Summary data on mixed settings for mixed tumor sites

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Vergeer et al. 2008[34]	Primary/ postoperative RT ± concurrent chemotherapy	Quality of life	141	1.5/6 mo EORTC QLQ-C30, ANOVA with linear (l) and quadratic (q, changing effect sizes over time) time analyses Domains with statistically significant results: Global Health <.004-l, Role Function .042-l, Cognitive Function .033-l, Social Function <.001-l, Fatigue .026-l, Pain .042-q, Insomnia <.021-l, Appetite Loss .018-l Domains with NS results: Physical Function, Emotional Function, Nausea/ Vomiting, Dyspnea, Constipation, Diarrhea, Financial Difficulties 1.5/6 mo EORTC QLQ-H&N35 Domains with statistically significant results: Pain .03-l, .046-q; Swallowing .042-l, Social Eating .011-l, Sexuality .003-l, Teeth .015-l, Opening Mouth .026-q, Dry Mouth <.001-l, Sticky Saliva .001-l, Feeling Ill .0011-l Domains with NS results: Taste/Smell, Speech, Coughing		Prospective	No	No	Not done	Poor

Table 16. IMRT vs. 3DCRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Marchal et al. 2004[79]	Primary/ postoperative/ repeat RT ± pre-RT/post-RT/ concurrent chemotherapy	Xerostomia	87	Acute, ≥ Gr 2, Δ-1, p NR Late, ≥ Gr 2, Δ-8, .06		Prospective	Unclear	Yes	Not done	Poor
Palazzi et al. 2008[80]	Primary/ postoperative RT ± concurrent ± pre-RT chemotherapy	Xerostomia	137	Acute, > Gr 2	NS	Prospective	Unclear	No	Unclear	Poor
Vergeer et al. 2008[34]		Xerostomia	141	Acute, Gr 2, Δ-17, .014 Late, Gr mod-sev , Δ-26, <.001 Late mean xerostomia item from EORTC QLQ-H&N35, at 1.5/6/12 mo IMRT- ≤.002 Late, ≥ Gr 2, IMRT- .002	mod-sev, MV logistic regression adjusted OR (95% CI): 0.27 (0.13, 0.54) Gr 2-3, MV logistic regression adjusted OR (95% CI): 0.24 (0.12, 0.51)				Unclear	

Table 16. IMRT vs. 3DCRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Chao et al. 2001[65]	Primary/ postoperative RT ± post-RT/concurrent chemotherapy	Salivary flow	41	6 mos., stimulated whole salivary flow	NS	Prospective	Unclear	Yes	Unclear	Poor
Palazzi et al. 2008[80]		Dysphagia	137	Acute, > Gr 2	NS					
Langendijk et al. 2009[89]	Primary/ postoperative RT± chemotherapy with unclear timing	Dysphagia	529	Late, Gr 2-4, ∆+12, .043	Not reported	Prospective	Unclear	Yes	No	Poor
Palazzi et al. 2008[80]		Mucositis	137	Acute, > Gr 2	NS					
Vergeer et al. 2008[34]		Mucositis	141	Acute, ≥ Gr 3, Δ-4 NS						
Palazzi et al. 2008[80]		Skin toxicity	137	Acute, > Gr 2	NS					
Vergeer et al. 2008[34]		Skin toxicity	141	Acute, Gr 2, Δ+12, .03						
Marchal et al. 2004[79]		Disease-free survival	87	1 yr., Δ+3, NS						
Gomez et al. 2008[70]	Primary/ postoperative RT ± chemotherapy with unclear timing	Disease-free survival	42	NS	Not entered	Retrospective	Unclear	Yes	Unclear	Poor

Table 16. IMRT vs. 3DCRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Marchal et al. 2004[79]		Overall survival	87	1 yr., Δ+3, NS						
Gomez et al. 2008[70]		Overall survival	42	NS	Not entered					

Abbreviations: Δ: change; Gr: grade; mos.: months; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

Comparative Studies, 3DCRT Versus 2DRT

Overview

In the progression of development of new radiotherapy techniques used to treat head and neck cancer, 2DRT is the oldest included in this review; it was followed by 3DCRT and later IMRT. The previous section compared IMRT and 3DCRT, the two more recent techniques. This section compares the two older techniques to determine whether there is any evidence that 3DCRT, a conformal technique, provides better outcomes or fewer or less severe adverse events than 2DRT.

Twelve comparisons of 3DCRT versus 2DRT were reviewed. As Table 17 shows, three comparisons included only nasopharyngeal cancer patients; two nasal cavity/paranasal sinus cancer patients; one comparison each, for oropharyngeal, unknown primary, and laryngeal cancer patients; and four comparisons among patients with a mix of cancer sites. One randomized, controlled trial was included, and two comparisons were from prospective observational studies; the remainder were retrospective.

All of the studies were rated poor according to the USPSTF criteria. None reported blinded assessors or well-done multivariable analyses. It was unclear whether the randomized, controlled trial used an intention-to-treat approach. The groups were reported to be comparable in only one study. The alternative treatments were provided during different time periods or it was unclear in 9 comparisons. This could bias the results against the older technique, assuming that it continued to evolve over time so that a concurrent comparison might be more favorable.

No consistent between-group differences were found for any outcomes. The adverse event, tumor control, and survival outcomes are summarized in the second part of Table 17; adverse event comparisons that report numerical differences in incidence are presented graphically in Appendix C, Figures C10–C15. Between-group differences for two outcomes were statistically significant: one of four comparisons for the incidence of late xerostomia and one of two comparisons for tumor control. The significant late xerostomia result was in a retrospective study and the magnitude of the difference was more than twice as large as the differences for the other three studies. This comparison and two other nonsignificant comparisons of the proportion of patients with late xerostomia favored 3DCRT; the fourth comparison favored 2DRT. Because of the variation in the magnitude of the between-group differences and the inconsistency in the direction of the results, no conclusions can be drawn regarding the impact of 3DCRT versus 2DRT on late xerostomia incidence.

The second statistically significant, between-group difference was a univariate analysis of local control favoring 3DCRT in the single randomized, controlled trial. However, it was unclear whether the groups were comparable at baseline or whether an intention-to-treat approach was used in the analysis. Four other studies reported on local control, and none of the between-group differences were statistically significant (one univariate analysis, three multivariable analyses). Evidence from multiple, higher quality studies would be needed to determine whether local control is extended for patients receiving treatment with 3DCRT versus 2DRT.

Health-related quality of life using the EORTC QLQ-C30 and H&N-35 (see Table 3, Methods chapter, for a description of these instruments) was reported in one study; no statistical comparisons were reported (see Table 18).

Table 17. 3DCRT vs. 2DRT: Summary of study design, quality, and key outcomes

Site	Studies	n	RCT	Prospective Observational	Assessor Blinded	Groups Comparable	Treatments in same time period	Well-done multi-variable analysis/ intention-to-treat	USPSTF Good/Fair
NPC	3	370	1	1	0	0	1	0	0/0
OPH	1	130	0	0	0	0	0	0	0/0
PNS	2	231	0	0	0	0	0	0	0/0
UNP	1	87	0	0	0	0	0	0	0/0
LAR	1	122	0	0	0	0	0	0	0/0
MIX	4	557	0	2	0	1	2	0	0/0
Total	12	1497	1	3	0	1	3	0	0/0

Outcome	Total No. studies	Large (> 15 pctg pts) 3DCRT-2DRT difference				Moderate (6-15 pctg pts) 3DCRT-2DRT difference				Small (0-5 pctg pts) 3DCRT-2DRT difference				Unquantifiable 3DCRT-2DRT difference			
		No. Studies	Sig	NS	P NR	No. Studies	Sig	NS	p NR	No. Studies	Sig	NS	p NR	No. Studies	Sig	NS	p NR
Acute xerostomia	1									1		1?					
Late xerostomia	4	2	1+	1+		2		1+	1-								
Acute mucositis	4					1		1+		3		1?	1+ 1-				
Late mucositis	2									2		1?	1+				
Acute dysphagia	1									1		1?					
Late dysphagia	0																
Acute skin toxicity	3									3		1?	2+				
Late skin toxicity	3					1			1+	2			1+ 1=				
Acute osteoradionecrosis/ bone toxicity	0																
Late osteoradionecrosis/ bone toxicity	2									2			1- 1=				
Tumor control	8	2	1+	1+		2		2+		4		2+ 2?					
Patient survival	7	1		1+		2		2+		4		1+ 1- 2?					

+: favors IMRT; -: favors 3DCRT; ?: unclear which group is favored; =: same result for both groups
Statistical significance is based on multivariable analyses, where available; if only univariate results are reported, those are used.

Table 18. 3DCRT vs. 2DRT: Summary of quality of life data

Study	EORTC QLQ-C30 (# domains)			EORTC H&N-35 (# domains)			SF-36 (# domains)			Other (HNCI, HNQOL) (# domains)		
	+	NS	—	+	NS	—	+	NS	—	+	NS	—
Fang et al. 2007[32]	NR			NR								

KEY:
+ statistically significant difference in favor of more conformal modality (listed first in comparison in 1st column)
NS difference not statistically significant
— statistically significant difference in favor of less conformal modality (listed second in comparison in 1st column)

*Between-group difference in total score, adjusted for baseline score.

When none of the between-group differences were consistently moderate to large in size and statistically significant for an outcome, no conclusion can be drawn about the relative impact of these two types of radiotherapy. This situation occurred for the following outcomes: acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late osteoradionecrosis and bone toxicity, locoregional control, disease-free survival, disease-specific survival, and overall survival.

More detailed information on the 3DCRT-2DRT comparisons is presented in the following sections, grouped by cancer site (nasopharyngeal, oropharyngeal, nasal cavity/paranasal sinuses, unknown primary tumor, laryngeal, and mixed tumor sites) and then treatment setting. Setting refers to the order in which radiotherapy is given relative to surgery and chemotherapy and whether all patients in a given study followed the same sequence. Settings are not differentiated by the specific type of chemotherapy received.

3DCRT Versus 2DRT: Nasopharyngeal Cancer, Primary Radiotherapy. A single study by Jen et al.[73] (Table 19) compared 3DCRT and 2DRT in patients receiving primary radiotherapy for nasopharyngeal cancer. A multivariable analysis produced an odds ratio for the key outcome, severe xerostomia, with a value of 0.55 (p=.0053), a reduced risk for 3DCRT relative to 2DRT. The xerostomia odds ratio was adjusted for gender, but it is unclear why other patient covariates were not retained. Time of xerostomia had a significant main effect and there was a significant treatment group by time interaction, showing similar occurrence levels during and immediately after treatment, but increasing between-group differences in later periods. The prescribed dose for all patients was 70 Gy. Groups in this retrospective study were comparable by sex (15 percent female in the 3DCRT group; 18 percent female in the 2DRT group), age (median: 43 and 44 years, respectively), and disease stage (60 percent and 58 percent stage III/IV, respectively). However, the main quality concerns about this study are uncertainty about whether groups were treated in the same time period and use of poor quality multivariable analysis methods. Thus, this study provides weak evidence on the relative frequency of xerostomia for 3DCRT versus 2DRT.

Table 19. 3DCRT vs. 2DRT: Summary of studies of nasopharyngeal cancer

Study & Setting(s)	Outcome	n	Univariate p value	Multivariable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Jen et al. 2005[73] Primary radiotherapy	Xerostomia	180		Late, severe OR: 0.55, p=.0053 OR adjusted for gender RT technique by time interaction (p=.032), with larger between-group differences in later periods	Retrospective	Unclear	Unclear	No	Poor
Wu et al. 2005[85] RCT Primary radiotherapy plus split chemotherapy	Mucositis	96	Acute, Gr 3-4, Δ-6, NS		Prospective	Unclear	Yes	Unclear if intention-to-treat	Poor
	Local control	96	1 yr., Δ+20, .003						
	Overall survival	96	1 yr., Δ+4, NS						

Table 19. 3DCRT vs. 2DRT: Summary of studies of nasopharyngeal cancer (continued)

Study & Setting(s)	Outcome	n	Univariate p value	Multivariable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Fang et al. 2007[32] Mixed settings: Primary RT ± chemo-therapy with unclear timing	Quality of life	94	24-36 mos., EORTC QLQ-C30 Group means presented but no statistical test results given for all domains: Global Health, Physical Function, Role Function, Emotional Function, Cognitive Function, Social Function, Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial Difficulties EORTC QLQ-H&N35 Group means presented but no statistical test results given for all domains: Pain, Swallowing, Taste/smell, Social eating, Social contract, Sexuality, Teeth, Opening mouth, Dry mouth, Sticky saliva, Coughing, Feeling ill		Retrospective	Unclear	No	Off-topic	Poor
Fang et al. 2007[32]	Xerostomia	94	24-36 mos., EORTC QLQ-H&N35 Dry Mouth item Group means presented but no statistical test results given						

Abbreviations: Δ: change; Gr: grade; mos.: months; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

3DCRT Versus 2DRT: Nasopharyngeal Cancer, Primary Radiotherapy Plus Split Chemotherapy. A single randomized trial by Wu et al.[85] (Table 19) compared late-course 3DCRT and all-course 2DRT among patients with nasopharyngeal cancer receiving primary radiotherapy plus split chemotherapy. Each group received a course of platinum-based chemotherapy before and after radiotherapy. It is unclear whether allocation of patients to intervention groups was unbiased. The method involved drawing one of 20 numbers randomly for each patient; odd numbers were assigned to the treatment group and even numbers were assigned to the control group. While groups appeared similar with respect to sex (35 percent female for 3DCRT and 34 percent female for 2DRT), age (median: 45 and 44 years, respectively) and stage (all III/IV), uncertainty about the allocation method clouds whether groups are comparable on a sufficient range of prognostic factors. It is unclear if intention-to-treat analysis was conducted, a key quality metric in assessing randomized, controlled trials. The frequency of acute mucositis was slightly but nonsignificantly higher in the 3DCRT group. Local control was significantly better at one year in the 3DCRT group (.003). Overall survival at one year was similar in the two groups (p=NS). This single poor-quality trial provides very weak evidence on the comparative effects of 3DCRT and 2DCRT on nasopharyngeal cancer in the setting of primary radiotherapy plus split chemotherapy.

3DCRT Versus 2DRT: Nasopharyngeal Cancer, Mixed Settings. The only study addressing 3DCRT versus 2DRT for nasopharyngeal cancer in mixed settings is the three-arm design from 2007 described by Fang et al.[32] (Table 19). The proportions of patients who were female were 24 percent and 28 percent for the 3DCRT and 2DRT groups, respectively; media age in both groups was 51 years, and percentages in stage III or IV were 48 percent and 51 percent, respectively. The article provides group mean values for specific domains of two QOL scales: EORTC QLQ-C30 and EORTC QLQ-H&N35. No statistical tests were performed comparing 3DCRT and 2DRT. These authors compared two mixed groups: one consisting of a combination of those receiving 2DRT or 2DRT but 3DCRT boost and a second receiving either 3DCRT or IMRT. This mixing of patient groups does not address the questions of concern to this review.

3DCRT Versus 2DRT. Oropharyngeal Cancer, Mixed Settings. There was only one comparison of 3DCRT and 2DRT among patients with oropharyngeal cancer. The Rades et al.[81] three-arm study with mixed settings compared 3DCRT versus 2DRT in oropharyngeal cancer (Table 20). Outcomes were either comparable or nonsignificantly in favor of 3DCRT in this study. Age and gender distributions were not reported; cancer stage was III or IV in 65 percent or more in the 3DCRT group and 54 percent or more in the 2DRT group; and the prescribed primary tumor dose was 60–70 Gy in both groups.

No statistically significant differences in outcomes were reported for the single comparison of 3DRT and 2DRT: For adverse events (e.g., late xerostomia, acute mucositis, acute and late skin toxicities), no statistical tests were reported. For local control and overall survival, neither the univariate nor multivariable analyses produced statistically significant results.

This study provided insufficient evidence to draw any conclusions on the comparative effectiveness of 3DCRT and 2DRT among patients with oropharyngeal cancer.

Table 20. 3DCRT vs. 2DRT: Summary data for oropharyngeal cancer

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Rades et al. 2007[81]	Postoperative RT ± concurrent chemo-therapy	Xerostomia	130	Late, Gr 2-3, Δ+10, p NR		Retrospective	Yes	Yes, WL	Not done	Poor
Rades et al. 2007[81]		Mucositis		Acute, Gr 2-3, Δ+3, p NR					Not done	
Rades et al. 2007[81]		Skin toxicity		Acute, Gr 2-3, Δ-3, p NR Late, Gr 2-3, Δ-2, p NR					Not done	
Rades et al. 2007[81]		Local control		2 yr. Δ+1, NS	NS				Unclear	
Rades et al. 2007[81]		Overall survival		2 yr. Δ+8, NS	NS				Unclear	

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

3DCRT Versus 2DRT. Nasal Cavity and Paranasal Sinuses, Mixed Settings. There were two comparative studies[67,68] that included only patients with cancer of the nasal cavity and/or paranasal sinuses; neither was a randomized, controlled trial (Table 21). Both provide data comparing 3DCRT to 2DRT. The study by Chen et al.[67] had three arms, two of which compared 3DCRT to 2DRT; while the Dirix et al.[68] study had a 3DCRT arm and a 2DRT arm. Both studies have a mix of settings, with variations in the timing of radiotherapy within each study; Chen et al.[67] also includes chemotherapy for 15 percent of patients, some concurrent and some postradiotherapy. Chen et al.[67] reported no multivariable analysis, while Dirix et al.[68] described one that is flawed. No statistically significant between-group differences were reported.

The Dirix et al.[68] two-arm study had 127 subjects: 16 percent were women, the median age was 58, and more than 90 percent had stage III or stage IV cancer. The timing of radiotherapy was mixed; no chemotherapy was used. The primary tumor prescribed dose was 50–80 Gy. Fewer patients in the 3DCRT group had permanent xerostomia (p=.08, NS); the frequency of late mucositis was similar in both groups (p not reported). No late osteoradionecrosis was reported in either group. No statistically significant differences (magnitudes not reported) in local control, disease-specific survival, disease-free survival, or overall survival were found in this study.

The study population for the Chen three-arm study[67] is described above; 104 subjects were in the 3DCRT and 2DRT groups. The primary tumor prescribed dose was 50–74 Gy (versus 50–73 Gy for 3DCRT). The frequency of both late mucositis and osteoradionecrosis or bone toxicity was similar in the 3DCRT and 2DRT groups; late skin toxicity was slightly less common in the 3DCRT group. No statistical tests were reported for these three comparisons. The five-year local control rate was similar for 3DCRT and 2DRT, while overall survival was slightly higher with 3DCRT. Neither of these comparisons was statistically significant, nor was the comparison in disease-free survival between treatment groups.

These studies provided insufficient evidence to draw any conclusions on the comparative effectiveness of 3DCRT and 2DRT among patients with nasal cavity/paranasal sinus cancer.

Table 21. 3DCRT vs. 2DRT: Cancer of the nasal cavity/paranasal sinuses, mixed settings

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Dirix et al. 2007[68]	Primary/ preoperative/ postoperative RT	Xerostomia	127	Permanent, Δ-20, .08		Retrospective	Unclear	No	Not done	Poor
Dirix et al. 2007[68]		Mucositis	127	Late, Δ?, NS					Not done	
Chen et al. 2007[67]	Primary/ preoperative/ postoperative RT ± post-RT/ concurrent chemotherapy	Mucositis	104	Late, ≥ Gr 3, Δ-1, p NR		Retrospective	Unclear	No	Not done	Poor
Chen et al. 2007[67]		Skin toxicity	104	Late, ≥ Gr 3, Δ-8, p NR					Not done	
Dirix et al. 2007[68]		Osteoradio-necrosis/ bone toxicity	127	Late, ungraded, Δ=0, p NR					Not done	
Chen et al. 2007[67]		Osteoradio-necrosis/ bone toxicity	104	Late, ≥ Gr 3, Δ+1, p NR					Not done	
Dirix et al. 2007[68]		Local control	127	NS					No	
Chen et al. 2007[67]		Local control	104	5 yr., Δ+3, NS					Not done	

Table 21. 3DCRT vs. 2DRT: Cancer of the nasal cavity/paranasal sinuses, mixed settings (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Dirix et al. 2007[68]		Disease-free survival	127	NS					No	
Chen et al. 2007[67]		Disease-free survival	104	NS					Not done	
Dirix et al. 2007[68]		Disease-specific survival	127	NS					No	
Dirix et al. 2007[68]		Overall survival	127	NS					No	
Chen et al. 2007[67]		Overall survival	104	5 yr., Δ+6, NS					Not done	

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

3DCRT Versus 2DRT: Unknown Primary Cancers, Mixed Settings. A single study compared 3DCRT to 2DRT among patients with unknown primary tumors (Beldi et al.[63]). The retrospective study has a mix of treatment settings, and all 87 subjects have III or IV cancer (Table 22). Radiotherapy was primary or postoperative; some patients received chemotherapy before or with radiotherapy. The typical subject in this study was male (18 percent female) around 60 years of age (median: 59 years) and with advanced cancer. The primary tumor prescribed dose was 45–70 Gy. Two outcomes were reported: disease-free and overall survival at five years. For both, outcomes were significantly better for 3DCRT than for 2DRT group in a univariate analysis ($p<.01$), but the difference was not statistically significant in the multivariable analysis, which was flawed by use of arbitrary significance levels for inclusion in the model. Adverse events were not reported.

This study provided insufficient evidence to draw any conclusions on the comparative effectiveness of 3DCRT and 2DRT among patients with unknown primary cancer.

3DCRT Versus 2DRT: Laryngeal Cancers, Primary Radiotherapy. A single study compared 3DCRT with 2DRT in 122 patients with laryngeal cancer patients only (Zouhair et al.;[87] see Table 23). All patients were treated in a single setting, with primary radiotherapy. The typical study subject was male (percent female=13 percent), was late middle aged (median=62 years), and did not have advanced cancer (no stage III or IV). The prescribed dose to the primary tumor ranged from 60 to 74 Gy. No adverse event outcomes were reported. The single effectiveness outcome was local control: There was no statistically significant difference between 3DCRT and 2DRT at 5 years in univariate (86 percent versus 81 percent, $p=.55$) or multivariable analyses.

This study provided insufficient evidence to draw any conclusions on the comparative effectiveness of 3DCRT and 2DRT among patients with laryngeal cancer.

Table 22. 3DCRT vs. 2DRT: Summary data on mixed settings for unknown primary cancers

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Beldi et al. 2007[63]	Primary/ postoperative RT ± pre-RT/ concurrent chemotherapy	Disease-free survival	87	5 yr., Δ+33, <.01	NS	Retrospective	Unclear	No	No	Poor
		Overall survival	87	5 yr., Δ+43, <.01	NS					

Table 23. 3DCRT vs. 2DRT: Summary data on single setting for laryngeal cancers

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Zouhair et al. 2004[87]	Primary RT	Local control	122	5 yr., Δ+5, NS	NS	Retrospective	No	No	Unclear	Poor

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

3DCRT Versus 2DRT: Mixed Tumor Sites, Mixed Settings. Studies including patients with a variety of tumor sites are difficult to interpret, because the impact of radiotherapy modalities on outcomes may vary by tumor site, e.g., if the tumor is adjacent to a particular critical structure. Four studies[70,74,80,82] with mixed tumor sites compared outcomes of 3DCRT and 2DRT, and all had mixed settings (Table 24). None of the treatment group differences in outcomes was statistically significant.

Two of the comparisons came from two arms of a three-arm study (Gomez et al.,[70] Palazzi et al.[80]); the other two comparisons were from two-arm studies. Patients were treated with primary or postoperative radiotherapy, with or without chemotherapy. Of a total of 526 subjects, the majority were male in three of the studies;[74,80,82] the median age was 52–60 (one study[82] did not report age); and the percentage of patients with advanced cancer (stage III or IV) ranged from 47.4 percent or more[70] to 100 percent,[82] with one study[74] not reporting. The prescribed dose to the primary tumor ranged from a minimum of 52 Gy to a maximum of 72 Gy in three studies;[70,80,82] the dose in the fourth[74] was unclear.

None of these studies reported on QOL, and none of the treatment group difference in adverse effects was statistically significant. The adverse outcomes measured were acute xerostomia,[80] late xerostomia,[82] salivary flow at 10 weeks,[74] acute dysphagia,[80] acute mucositis[80] (p not reported in one study[82]), acute skin toxicity[80] (p not reported in one study[82]), and late skin toxicity[82] (p not reported). One tumor control outcome was reported—three-year locoregional control—and the treatment group difference was not statistically significant.[82] Differences in two patient survival outcomes were reported—disease-free survival[70] and overall survival (at three years for one study,[82] time not reported for another[70])—and none was statistically significant.

These studies provided insufficient evidence to draw any conclusions on the comparative effectiveness of 3DCRT and 2DRT among patients with mixed tumor sites, which are also inherently difficult to generalize.

Table 24. 3DCRT vs. 2DRT: Summary data on mixed settings for mixed tumor sites

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Rades et al. 2008[82]	Primary/ postoperative RT± concurrent chemotherapy	Xerostomia	345	Late, Gr 2-3, Δ-15, .06		Retrospective	Yes	Unclear	No	Poor
Palazzi et al. 2008[80]	Primary/ postoperative RT ± concurrent ± pre-RT chemotherapy	Xerostomia	116	Acute	NS	Prospective	Unclear	No	Unclear	Poor
Kuhnt et al. 2005[74]	Primary/ postoperative RT	Salivary flow	33	10 wks., salivary flow rate +, <0.1		Prospective	Unclear	Yes	Not done	Poor
Palazzi et al. 2008[80]		Dysphagia	116	Acute, > Gr 2	NS					
Rades et al. 2008[82]		Mucositis	345	Acute, Gr 2-3, Δ-5, p NR						
Palazzi et al. 2008[80]		Mucositis	116	Acute, > Gr 2	NS					
Rades et al. 2008[82]		Skin toxicity	345	Acute, Gr 2-3, Δ-4, p NR Late, Gr 2-3, Δ0, p NR						
Palazzi et al. 2008[80]		Skin toxicity	116	Acute, > Gr 2	NS					

Table 24. 3DCRT vs. 2DRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Rades et al. 2008[82]		Locogregional control	345	3 yr., Δ+3, NS						
Gomez et al. 2008[70]	Primary/ postoperative RT ± chemotherapy with unclear timing	Disease-free survival	32	NS	Not entered	Retrospective	Unclear	Yes	Unclear	Poor
Rades et al. 2008[82]		Overall survival	345	3 yr., Δ-5, NS						
Gomez et al. 2008[70]		Overall survival	32	NS	Not entered					

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; wks: weeks; yr: year;

Comparative Studies, IMRT Versus 2DRT

Overview

This section compares 2DRT, which is the oldest radiotherapy technique included in this review, to IMRT, which is the newest and is also conformal, to determine whether there is any evidence that IMRT provides better outcomes or fewer or less severe adverse events than 2DRT.

Twenty-two comparisons of IMRT versus 2DRT were reviewed. As Table 25 shows, 6 comparisons included only nasopharyngeal cancer patients; 4, oropharyngeal cancer patients; 1 comparison each, for nasal cavity/paranasal sinus and unknown primary cancer patients; and 10 comparisons, patients with a mix of cancer sites. There were no comparisons of IMRT versus 2DRT among laryngeal cancer patients alone. Two randomized, controlled trials were included, and five comparisons were from prospective observational studies; the remainder were retrospective.

All of the studies were rated poor according to the USPSTF criteria, except for one randomized, controlled trial on nasopharyngeal patients that was rated fair.[41] Only the latter reported using blinded assessors, had a well-done multivariable analysis, and the groups were comparable at baseline. It was rated fair because the treatment settings were mixed, making it difficult to separate the impact of IMRT or 2DRT from differences in timing of radiotherapy and the use of additional therapies. Furthermore, an unspecified number of patients also received brachytherapy. The second randomized, controlled trial was rated poor because it was unclear whether it used an intention-to-treat approach. In 18 of the comparisons, the alternative treatments were provided during different time periods or it was unclear. This could bias the results against the older technique, assuming that it continued to evolve over time so that a concurrent comparison might be more favorable.

Adverse events, tumor control, and survival outcomes are summarized in the second part of Table 25; adverse event comparisons that report numerical differences in incidence are presented graphically in Appendix C, Figures C16–C24. Consistent between-group differences were found for two outcomes: late xerostomia and health-related quality of life domains related to xerostomia. Nine studies reported on late xerostomia, and eight were statistically significant in favor of IMRT. Among the studies that reported frequency, the range of differences between IMRT and 2DRT was 43 to 62 percentage points (Figure C17 in Appendix C).

Health-related quality of life using the EORTC QLQ-C30 and H&N-35 (see Table 3, Methods chapter, for a description of these instruments) was reported in three studies; Pow et al.[28] reported statistically significant between-group comparisons favoring IMRT for 11 of 41 domains across three instruments; while Yao et al. [36] reported 1 of 4 statistically significant differences; the between-group differences in total scores in Jabbari et al. [30] was not statistically significant (see Table 26). Where domains addressed specific adverse events, such as reports on dry mouth and xerostomia, the results were combined with other measures discussed above. Overall, there is a low level of evidence from these studies that quality of life is greater in patients treated with IMRT compared to 2DRT.

Table 25. IMRT vs. 2DRT: Summary of study design, quality, and key outcomes

Site	Studies	n	RCT	Prospective Observational	Assessor Blind	Groups Comparable	Treatments in same time period	Well-done multivariable analysis/ intention-to-treat	USPSTF Good/Fair
NPC	6	662	2	3	1	3	3	1	0/1
OPH	4	717	0	1	0	0	0	0	0/0
PNS	1	82	0	0	0	0	0	0	0/0
UNP	1	41	0	0	0	0	0	0	0/0
LAR	0	0	0	0	0	0	0	0	0/0
MIX	10	939	0	3	0	0	2	0	0/0
Total	22	2441	2	7	1	3	5	1	0/1

Outcome	Total No. studies	Large (>15 pctg pts) IMRT-2DRT difference				Slight-moderate (6-15 pctg pts) IMRT-2DRT difference				Negligible (0-5 pctg pts) IMRT-2DRT difference				Unquantifiable IMRT-2DRT difference			
		No. Studies	Sig	NS	p NR	No. Studies	Sig	NS	p NR	No. Studies	Sig	NS	p NR	No. Studies	Sig	NS	p NR
Acute xerostomia	5	2	2+							3		2+ 1?					
Late xerostomia	9	5	5+											4	3+	1+	
Acute mucositis	6	1	1+			3		2+	1-	2		1?	1+				
Late mucositis	3	1			1+					2			2+				
Acute dysphagia	5	4	3+	1+						1		1?					
Late dysphagia	2	1	1+							1			1=				
Acute skin toxicity	6	3		2+	1+					3		1?	1+ 1-				
Late skin toxicity	5	2	2+			3			3+								
Acute osteoradionecrosis/ bone toxicity	0																
Late osteoradionecrosis/ bone toxicity	3					2			2+	1			1+				
Tumor control	6	1		1+		4		4+		1			1?				
Patient survival	7	2	1+	1+		3		3+		2		1- 1?					

+: favors IMRT; -: favors 3DCRT; ?: unclear which group is favored; =: same result for both groups

Table 26. IMRT vs. 2DRT: Summary of quality of life data

Study	EORTC QLQ-C30 (# domains)			EORTC H&N-35 (# domains)			SF-36 (# domains)			Other (HNCI, HNQOL) (# domains)		
	+	NS	—	+	NS	—	+	NS	—	+	NS	—
Pow et al. 2006[28]	2	14		7	11		2	5				
Yao et al. 2007[36]										1	3	
Jabbari et al. 2005[30]											1*	

KEY:
+ statistically significant difference in favor of more conformal modality (listed first in comparison in 1st column)
NS difference not statistically significant
— statistically significant difference in favor of less conformal modality (listed second in comparison in 1st column)

*Between-group difference in total score, adjusted for baseline score.

Additional between-group differences that had some statistically significant results are as follows: Two of five comparisons for the incidence of acute xerostomia, one of six comparisons for acute mucositis, two of five comparisons of acute dysphagia, one of two comparisons of late dysphagia, two of five comparisons for late skin toxicity, and none of seven for disease-free survival. Because of the variation in the proportion of studies with statistically significant between-group differences for each adverse event or outcome and the quality or limitations of the specific studies involved, conclusions can be drawn only regarding the impact of IMRT versus 2DRT on late xerostomia incidence and quality of life domains related to xerostomia. No between-group differences were statistically significant for the following outcomes: late mucositis, acute skin toxicity, late osteoradionecrosis and bone toxicity, and locoregional control.

More detailed information on the IMRT-2DRT comparisons is presented in the following sections, grouped by cancer site (nasopharyngeal, oropharyngeal, nasal cavity/paranasal sinuses, unknown primary tumor, and mixed tumor sites) and then treatment setting. Setting refers to the order in which radiotherapy is given relative to surgery and chemotherapy and whether all patients in a given study followed the same sequence. Settings are not differentiated by the specific type of chemotherapy received.

IMRT Versus 2DRT: Nasopharyngeal Cancer, Primary Radiotherapy. Of the two studies comparing IMRT and 2DRT among patients receiving primary radiotherapy for nasopharyngeal cancer (Table 27), the randomized trial by Pow et al.[28] provides suggestive evidence on quality of life, xerostomia, and salivary flow. Pow et al.[28] conducted a randomized trial in patients with stage I or II disease and excluded patients with local and/or distant failures. This trial did not analyze results using an intent-to-treat approach, thus it received a poor USPSTF rating. These authors administered three quality of life scales at 2, 6, and 12 months: SF-36, EORTC QLQ-C30, and EORTC QLQ-H&N35 (see Table 3 in the Methods chapter for descriptions of these instruments). Statistical tests were performed both at the individual followup points and for the entire series of points. Key statistically significant findings favoring IMRT for the entire followup series included these domains on the EORTC QLQ-H&N35: Dry Mouth, Sticky Saliva, Swallowing and Speech Problems. Other findings include statistically significant advantages for IMRT at 12 months for two SF-36 domains, Role-Physical and Bodily Pain. While these authors did not specifically quantify the clinical significance of their results, a small trial (n=45) that achieves statistical significance generally means the effect sizes are moderate to large.

A second study, by Wu et al.[86] was a retrospective design that did not show whether groups were comparable or were treated in the same time period and did not conduct a multivariable analysis. This nonrandomized study reported similar proportions of patients with acute xerostomia, but no statistical test results were provided. Wu et al. included a combined group of patients that was 32 percent female, had a median age of 38 years, and were mostly stage III/IV (86 percent). The prescribed dose was 75 Gy in the IMRT group and 70 Gy in the 2DRT group. The randomized trial and the nonrandomized study both reported significant advantages for IMRT with respect to salivary flow in the acute phase and in the late phase in the randomized trial.

IMRT Versus 2DRT: Pediatric Nasopharyngeal Cancer, Primary Radiotherapy Plus Split Chemotherapy. Laskar et al.[75] (Table 27) conducted a prospective, nonrandomized comparison of IMRT and 2DRT in 36 children with nasopharyngeal cancer. Allocation to treatment was based on physician preference and logistic factors. Multivariable analysis was conducted for tumor control outcomes and overall survival but details are lacking to confirm whether these analyses were well done. The overall USPSTF quality rating was poor. Groups were somewhat comparable. The percentages for IMRT and 2DRT recipients for these variables were: female participants, 26 percent and 18 percent; age over 14 years, 37 percent and 47 percent; larger tumors, 32 percent and 59 percent; and stage III/IV, 84 percent and 94 percent. All patients were given a prescribed dose of 70 Gy. Two cycles of platinum-based chemotherapy was given before radiotherapy and two cycles afterwards. Significantly lower proportions of IMRT patients experienced acute xerostomia, dysphagia, mucositis, and skin problems. However, multivariable analysis was not done for any of these adverse events, despite imbalances between groups. Tumor control (locoregional control and disease-free survival) was nonsignificantly higher at two years in the IMRT group; the same was observed for overall survival. Multivariable analyses were conducted for these three outcomes, but details were unclear. Radiotherapy technique was not entered into any of these analyses. Multivariable analysis for such small data sets is vulnerable to overfitting. A limitation in interpreting these results is that the baseline differences between groups on tumor size and stage somewhat favored the IMRT arm.

IMRT Versus 2DRT: Nasopharyngeal Cancer, Mixed Settings. Due to the clinical diversity of patient groups and treatment modalities, no clear conclusions can be reached from the three studies in Table 27 about the comparative effects of IMRT and 2DRT on quality of life and xerostomia. The randomized trial was reported by Kam et al.[41] in 2007, enrolling patients with stage I or II nasopharyngeal cancer. IMRT and 2DRT groups were mostly similar, by median age (46 and 51 years), and percentage female (25 percent and 32 percent). Intracavitary brachytherapy (ICBT) was given to some patients in each group, but the proportion receiving ICBT was not reported. Intention-to-treat analysis was performed and the overall USPSTF rating is fair. Physician-rated RTOG/EORTC xerostomia in grades 2 through 4 was significantly less frequent among IMRT in the acute period (6 weeks) and the late period (12 months). The absolute risk difference was 43 percentage points lower in the IMRT group with a 95 percent confidence interval between 20 and 66 percentage points. The University of Michigan Xerostomia Questionnaire (XQ; see Table 3 in the Methods chapter for further details on the instrument) was administered at 6 weeks, 6 months, and 12 months. No significant between-group differences in change in total XQ scores were observed at any followup. Stimulated whole and parotid salivary flow rates were significantly better in the IMRT group at all followup points.

Despite the salivary flow findings, the mixed results on xerostomia symptoms and the mixing of treatment modalities (use of ICBT) make these data difficult to interpret.

The 2007 Fang et al.[32] study presented mean quality of life data for IMRT and 2DRT, but again did not report statistical test results comparing these groups. The only other study comparing IMRT and 2DRT among patients treated with mixed settings for nasopharyngeal cancer was published by Hsiung et al.[72] in 2006. This retrospective study of 32 participants was imbalanced with respect to the percentage receiving concurrent chemotherapy (50 percent versus 75 percent) and proportion with stage III or IV disease (50 percent versus 38 percent), but the percentage of females was similar (31 percent and 25 percent) and the proportion older than age 50 was identical (31 percent). Late xerostomia was less frequent in the IMRT group. No multivariable analysis with adjustment of confounders was conducted. The group receiving 2DRT was a historical series and the USPSTF rating was poor.

Table 27. IMRT vs. 2DRT: Summary of studies of nasopharyngeal cancer

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Pow et al. 2006[28], RCT	Primary RT	Quality of life	45	2/6/12 mos. SF-36 Role-Physical, 12 mo IMRT+ <.05, all other F/U NS Bodily pain, 12 mo IMRT+ <.05, all other F/U NS All other domains, all F/U NS: Physical Function, Vitality, Social Functioning, Role-Emotional, Mental Health EORTC QLQ-C30 Role Function-Revised, 12 mos. IMRT+ <.05, all other F/U NS Diarrhea, 2 mos. IMRT- <.05, series IMRT- .009, other F/U NS All other domains, all F/U NS: Global Health, Global Health-Revised, Physical Function, Role Function, Emotional Function, Cognitive Function, Social Function, Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Financial Difficulties		Prospective	Yes	Yes	No ITT	Poor

Table 27. IMRT vs. 2DRT: Summary of studies of nasopharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Pow et al. 2006[28], RCT (continued)	(see previous page)	Quality of life (continued)		EORTC QLQ-H&N35 Swallowing, 12 mos. IMRT+ <.05, series IMRT+ .022, other F/U NS Taste/Smell, 2 mos. IMRT+ <.05, all other F/U NS Speech, 6 mos. IMRT+ <.05, 12 mos. IMRT+ <.05, series IMRT+ .053, 2 mos. NS Dry Mouth, series IMRT- .021, all other F/U NS Sticky Saliva, 2/6/12 mos. IMRT- <.05, series IMRT- <.001 Coughing, 6 mos. IMRT- <.05, all other F/U NS Weight Gain, 2 mos. IMRT- <.05, all other F/U NS All other domains, all F/U NS: Pain, Social Eating, Social Contact, Sexuality, Teeth, Opening Mouth, Feeling Ill, Pain Killers, Nutrition Supplement, Feeding Tube, Weight Loss		(see previous page)				

Table 27. IMRT vs. 2DRT: Summary of studies of nasopharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Wu et al. 2005[86] Primary radiotherapy		Xerostomia	380	Acute, Gr ?, Δ-3, p NR		Retrospective	Unclear	Unclear	Not done	Poor
Pow et al. 2006[28], RCT		Salivary flow	45	2/6/12 mo stimulated whole saliva flow ANOVA IMRT+ <.003 Stimulated parotid saliva flow ANOVA IMRT+ <.002		Prospective	Yes	Yes	No ITT	Poor
Wu et al. 2005[86]		Salivary flow	380	? mo, static secretion function, IMRT+ <.05						

Table 27. IMRT vs. 2DRT: Summary of studies of nasopharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Laskar et al. 2008[75]	Primary RT + split chemotherapy	Xerostomia	36	Acute, ≥ Gr 2, Δ-56, .002		Prospective	Yes	Yes	Not done	Poor
		Dysphagia	36	Acute, ≥ Gr 2, Δ-52, .01 Acute, ≥ Gr 3, Δ-30, .035					Not done	
		Mucositis	36	Acute, ≥ Gr 2, Δ-20, .066 Acute, ≥ Gr 3, Δ-37, .033					Not done	
		Skin toxicity	36	Acute, ≥ Gr 2, Δ-16, NS Acute, ≥ Gr 3, Δ-42, .006					Not done	
		Locoregional control	36	2 yr. Δ+16, NS	Not entered				Unclear	
		Disease-free survival	36	2 yr. Δ+12, NS	Not entered				Unclear	
		Overall survival	36	2 yr. Δ+14, NS	Not entered				Unclear	

Table 27. IMRT vs. 2DRT: Summary of studies of nasopharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Fang et al. 2007[32]	Primary RT ± chemotherapy with unclear timing	Quality of life	94	24-36 mos., EORTC QLQ-C30 Group means presented but no statistical test results given for all domains: Global Health, Physical Function, Role Function, Emotional Function, Cognitive Function, Social Function, Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial Difficulties EORTC QLQ-H&N35 Group means presented but no statistical test results given for all domains: Pain, Swallowing, Taste/smell, Social eating, Social contract, Sexuality, Teeth, Opening mouth, Dry mouth, Sticky saliva, Coughing, Feeling ill		Retrospective	Unclear	No	Off-topic	Poor
Fang et al. 2007[32]		Xerostomia	94	24-36 mos., EORTC QLQ-H&N35 Dry Mouth item Group means presented but no statistical test results given						

Table 27. IMRT vs. 2DRT: Summary of studies of nasopharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Kam et al. 2007[41] (RCT)	Primary RT ± intracavitary brachytherapy	Xerostomia	56	Acute, Gr 2-4, Δ-40, .002 Late, Gr 2-4, Δ-43, .001 1.5/6/12 mos., change in total from 6-item Xerostomia Scale, all F/U NS		Prospective	Yes	Yes	Yes ITT	Fair
Hsiung et al. 2006[72]	Primary RT± concurrent chemotherapy	Xerostomia	32	Late, Gr 2-4, Δ-50 <.001		Retrospective	No	No	Not done	Poor
Kam et al. 2007[41] (RCT)		Salivary flow	56	1.5/6/12 mos., stimulated whole saliva flow rate 12 mo IMRT+ <.01 Stimulated parotid saliva flow rate 1.5/6/12 mos. IMRT+ <.001						

Abbreviations: Δ: change; Gr: grade; mos.: months; NR: not reported; NS: not significant; RT: radiotherapy; wks: weeks; yr: year;

IMRT Versus 2DRT: Oropharyngeal Cancer, Primary Radiotherapy Plus Concurrent Chemotherapy. Lee et al.[76] compared IMRT to 2DRT among 112 patients with oropharyngeal cancer (Table 28). No statistically significant differences between groups were detected for the tumor control or patient survival outcomes. The IMRT group may have had fewer adverse events, although no multivariable analyses were reported that could control for any baseline between-group differences. As with the previous study, the quality was poor, due to the retrospective design, missing information about group comparability at baseline, and lack of blinded outcome assessors.

Less than 20 percent of the subjects were female, more than 95 percent had stage III or IV cancer, and the prescribed dose to the primary tumor was 66–70 Gy (IMRT) or 70–72 Gy (2DRT). The median age by group was 55 and 56 years. There was a significantly lower incidence of late xerostomia among the IMRT patients (12 percent) compared to those receiving 2DRT (67 percent; p=.002). Slightly fewer patients in the IMRT group had acute mucositis and acute skin toxicity (6 and 4 percentage point differences, respectively), but no statistical tests were reported. At five years, there was no statistically significant difference between the IMRT group and the 2DRT group on the three tumor control outcomes (local control, locoregional control, disease-free survival), and overall patient survival.

IMRT Versus 2DRT: Oropharyngeal Cancer, Mixed Settings. Three studies comparing IMRT and 2DRT in oropharyngeal cancer were clinically diverse studies in terms of whether and when surgery was given and the timing of and/or use of chemotherapy (Table 28). Chao et al.[66] provided separate comparisons between IMRT and 2DRT within definitive and postoperative settings. The 3-arm Rades et al.[81] study and the study by Yao et al.[36] were also in this group. The studies yielded few consistent, statistically significant differences in outcomes between treatment groups.

Late xerostomia appeared less common among patients treated with IMRT than for those treated with 2DRT in both studies[66,81] measuring this outcome; no p value was reported for acute xerostomia.[66] There was also a statistically significant improvement in the eating domain on a disease-specific quality of life instrument for IMRT versus 2DRT. Results were either statistically nonsignificant or statistical results were not reported for the remaining adverse effects measured (acute dysphagia,[66] acute or late mucositis[81] [acute only[66]], acute and late skin toxicity,[66,81] and late osteoradionecrosis or bone toxicity[66]).

The IMRT group appeared to have better overall survival than the 2DRT group, but the results were statistically significant in one study[66] (definitive radiotherapy, p=.001; postoperative radiotherapy, p=.003) and not in the other.[81] The difference was statistically significant for higher disease-free survival among both definitive (p=.002) and postoperative (p=.008) IMRT patients in one study.[66] There was no statistically significant difference for local control,[81] the one other outcome reported.

One study on oropharyngeal cancer measured quality of life. Yao et al.[36] used the Head and Neck Cancer Inventory (HNCI), an instrument whose reliability and validity has been assessed (see Table 3, Methods). In looking at four domains (eating, speech, aesthetics, and social disruption), there was statistically significant improvement in eating over time for IMRT compared to 2DRT (measured at 3, 6, and 12 months, p=.007). The authors characterized the change as of small or medium clinical significance. No other statistically significant differences were reported.

Table 28. IMRT vs. 2DRT: Summary data on primary radiotherapy plus concurrent chemotherapy for oropharyngeal cancer

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Lee et al. 2006[76]	Primary RT + concurrent chemotherapy	Xerostomia	112	Late, ≥ Gr 2, Δ-55, .002		Retrospective	Unclear	Unclear	Not done	Poor
		Mucositis		Acute, Δ-6, p NR					Not done	
		Skin toxicity		Acute, Δ-4, p NR					Not done	
		Local control		5 yr., Δ+10, NS					Not done	
		Locogregional control		5 yr., Δ+17, NS					Not done	
		Disease-free survival		5 yr., Δ+12, NS					Not done	
		Overall survival		5 yr., Δ+19, NS					Not done	
Yao et al. 2007[36]	Primary RT ± chemotherapy with unclear timing	Quality of life	53	12 mos., HNCI-Eating, IMRT+, .007; Speech, IMRT+, .059; Aesthetics, IMRT+, .069; Social Disruption, IMRT+ NS		Prospective	No	No	Not done	Poor

Table 28. IMRT vs. 2DRT: Summary data on primary radiotherapy plus concurrent chemotherapy for oropharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Rades et al. 2007[81]	Postoperative RT ± concurrent chemotherapy	Xerostomia	122	Late, Gr 2-3, Δ-46, .037		Retrospective	Yes	Yes, WL	Not done	Poor
Chao et al. 2001[66]	Primary/ preoperative/ postoperative RT ± concurrent chemotherapy	Xerostomia	430	Acute, Gr > 2, def/postop, Δ+6/Δ+1 p NR Late, Gr > 2, def/postop, Δ-54/ Δ-62, .0001		Retrospective	No	No	Not done	Poor
Chao et al. 2001[66]		Dysphagia	430	Acute, Gr 2-3, def/postop, Δ-16/ Δ-22, p NR					Not done	
Rades et al. 2007[81]		Mucositis	122	Acute, Gr 2-3, Δ-4, p NR					Not done	
Chao et al. 2001[66]		Mucositis	430	Acute, Gr 2-3, def/postop, Δ+8/ Δ+13, p NR Late, Gr 2-3, def/postop, Δ-2 / Δ-17, p NR					Not done	
Rades et al. 2007[81]		Skin toxicity	122	Acute, Gr 2-3, Δ+2, p NR Late, Δ-7, p NR					Not done	
Chao et al. 2001[66]		Skin toxicity	430	Acute, Gr 2-3, def/postop Δ-15/ Δ-1, p NR Late, Gr 2-3, def/postop Δ-7/Δ-8, p NR					Not done	

Table 28. IMRT vs. 2DRT: Summary data on primary radiotherapy plus concurrent chemotherapy for oropharyngeal cancer (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Chao et al. 2001[66]		Osteoradio-necrosis/bone toxicity	430	Late, def/postop Δ-6/Δ-3, p NR					Not done	
Rades et al. 2007[81]		Local control	122	2 yr., Δ+11, NS					Unclear	
Chao et al. 2001[66]		Locoregional control	430	2 yr., def/postop, Δ+20/Δ+24, NS					Not done	
Chao et al. 2001[66]		Disease-free survival	430	2 yr., def, Δ+22, .002; postop, Δ+18, .008					Not done	
Rades et al. 2007[81]		Overall survival	122	2 yr., Δ+12, NS					Unclear	
Chao et al. 2001[66]		Overall survival	430	2 yr., def, Δ+43, .001; postop, Δ+29, .003					Not done	

Abbreviations: Δ: change; Gr: grade; mos.: months; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

IMRT Versus 2DRT: Nasal Cavity and Paranasal Sinuses, Mixed Settings. There was one comparative study comparing IMRT versus 2DRT among only patients with cancer of the nasal cavity and/or paranasal sinuses, the three-arm study by Chen et al.[67] (Table 29). The study has a mix of settings, with variations in the timing of radiotherapy and chemotherapy for 15 percent of patients, some concurrent and some postradiotherapy. The study population, described above in the section comparing IMRT and 3DCRT, included 82 subjects in the IMRT and 2DRT groups.

Late mucositis was similar in the IMRT and 2DRT groups; late skin toxicity was less common with IMRT, and late osteoradionecrosis or bone toxicity was slightly less common in the IMRT group. The statistical significance of these IMRT-2DRT differences was not reported. Local control and overall survival was similar with IMRT and 2DCRT, while the magnitude of the difference for disease-free survival was not reported. However, none of these differences was statistically significant. No multivariable analysis was performed to account for potential confounders. This study provided insufficient evidence to draw any conclusions on the comparative effectiveness of IMRT and 2DRT among patients with nasal cavity/paranasal sinus cancer.

IMRT Versus 2DRT: Unknown Primary Cancers, Mixed Settings. A single study compared IMRT versus 2DRT among patients with unknown primary cancers. In a retrospective study Madani et al.[78] compared these radiotherapy techniques among 41 patients in mixed treatment settings (Table 30). Radiotherapy was primary or postoperative; some patients received chemotherapy but the timing was unclear. The typical subject in this study was male (22–26 percent female) around 60 years old (median: 58–61 years) with advanced cancer. The primary tumor prescribed dose was 56–69 Gy for IMRT and 66 Gy for 2DRT.

Acute grade 3 dysphagia was less common in the IMRT group (4.5%) than in the 2DRT group (50 percent, p=.003). Late grade 3 dysphagia was also significantly less common, with a between-group difference of 27 percentage points (p=.01). Acute grade 3 mucositis was slightly less frequent among IMRT patients; the difference was nonsignificant. Grade 3 acute skin toxicity was lower in the IMRT group (31.7 percent versus 66.7 percent, p=.08). Late skin toxicity was significantly less common with IMRT (0 percent versus 26.7 percent, p=.03). One-year overall survival was greater with IMRT, but the difference with 2DRT was not statistically significant. None of these results have been adjusted for potential confounding factors using a multivariable analysis. This study provided insufficient evidence to draw any conclusions on the comparative effectiveness of IMRT and 2DRT among patients with unknown primary cancers.

Table 29. IMRT vs. 2DRT: Cancer of the nasal cavity/paranasal sinuses, mixed settings

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Chen et al. 2007[67]	Primary/ preoperative/ postoperative RT ± post-RT/ concurrent chemotherapy	Mucositis	82	Late, ≥ Gr 3, Δ-4, p NR		Retrospective	Unclear	No	Not done	Poor
Chen et al. 2007[67]		Skin toxicity	82	Late, ≥ Gr 3, Δ-14, p NR					Not done	
Chen et al. 2007[67]		Osteoradio-necrosis/bone toxicity	82	Late, ≥ Gr 3, Δ-6, p NR					Not done	
Chen et al. 2007[67]		Local control	82	5 yr., Δ+6, NS					Not done	
Chen et al. 2007[67]		Disease-free survival	82	NS					Not done	
Chen et al. 2007[67]		Overall survival	82	5 yr., Δ-4, NS					Not done	

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

Table 30. IMRT vs. 2DRT: Summary data on mixed settings for unknown primary cancers

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Madani et al. 2008[78]	Primary/ postoperative RT ± chemotherapy with unclear timing	Dysphagia	41	Acute, Gr 3, Δ-45, .003 Late, Gr 3, Δ-27, .01		Retrospective	No	No	Not done	Poor
		Mucositis	41	Acute, Gr 3, Δ-9, NS					Not done	
		Skin toxicity	41	Acute, Gr 3, Δ-35, .08 Late, Gr 3, Δ-27, .03					Not done	
		Overall survival	41	1 yr., Δ+33, NS					Not done	

Abbreviations: Δ: change; Gr: grade; NR: not reported; NS: not significant; RT: radiotherapy; yr: year;

IMRT Versus 2DRT: Mixed Tumor Sites, Mixed Settings. Eight studies compared IMRT versus 2DRT among patients with mixed head and neck tumor sites and reported on one of the 12 key outcomes (Table 31). Gomez et al.[70] and Palazzi et al.[80] each had three arms, including IMRT to 2DRT. Six other studies[30,35,39,40,64,90] compared IMRT to 2DRT alone. Two studies reported data for outcomes that are not the central focus of this review and will not be discussed here further.[77,84]

These studies are difficult to interpret, because the impact of radiotherapy modalities on outcomes may vary by tumor site, e.g., if the tumor is adjacent to a particular critical structure. Multiple settings further complicate inferences about the data. Most did not have multivariable analyses, the analyses were not well done, or it was not clear whether they were well done. For four studies,[35,40,64,80] treatment for the comparison groups either was not performed during the same era or it was unclear.

Patients were treated with primary or postoperative radiotherapy, with or without chemotherapy. Of a total of 758 subjects, the majority were male in six of the studies (one exception[70] and not reported in one[40]); the median age was 52–59 (age not reported in one[40]); and the percentage of patients with advanced cancer (stage III or IV) was 80 percent or greater in six studies ($\geq$47.4 percent in one[70] and not reported in one[40]). The prescribed dose to the primary tumor ranged from a minimum of 52 Gy to a maximum of 79 Gy in all studies, except for 2DRT dose not reported in one study.[39]

One study[30] reported quality of life, using HNQOL at 1, 3, 6, 12, 18, and 24 months (for more information on quality of life and xerostomia instruments, see Table 3 in the Methods chapter). There was a significant improvement trend for IMRT, but not for 2DRT; however, the between-group difference for the total score, adjusted for the baseline value, was not statistically significant. The University of Michigan Xerostomia Questionnaire (XQ) was used to gauge xerostomia in three studies[30,39,40] and a blend of EORTC QLQ-H&N35 and XQ in one.[35] Acute xerostomia was also reported for another study.[80] The results were mixed, with statistically significant differences between treatment groups for some items (with IMRT results better than 2DRT) but not others. No statistically significant differences in the frequency of adverse events between IMRT and 2DRT were found for dysphagia,[64,80] acute mucositis,[80,90] or acute skin toxicity.[80] Only one study[70] reported patient survival outcomes, and the treatment group differences for disease-free and overall survival were not statistically significant in the univariate analysis; type of radiotherapy was not included as a factor in the multivariable analysis.

These studies of mixed head and neck cancer sites provided insufficient evidence to draw any conclusions on the comparative effectiveness of IMRT and 2DRT among these patients.

Table 31. IMRT vs. 2DRT: Summary data on mixed settings for mixed tumor sites

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable ?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Jabbari et al. 2005[30]	Primary/ postoperative RT ± chemotherapy with unclear timing	Quality of life	106	1/3/6/12/18/24 mos., HNQOL, total and 4 domains IMRT: all F/U, trend for improvement: total .04, Communication NS, Eating .07, Emotion .04, Pain .05 2DRT: all F/U, trend for improvement, total and all domains NS 12-month between-group difference in total HNQOL, adjusted for baseline score NS		Prospective	Unclear	Yes	Not done	Poor

Table 31. IMRT vs. 2DRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable ?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Daly et al. 2007[39]	Primary/ postoperative RT ± concurrent/ chemotherapy with unclear timing	Xerostomia	69	> 6 mos., U Michigan Xerostomia Questionnaire (XQ), item means Items with statistically significant results: Talking Difficulty IMRT- .003, Chewing Difficulty IMRT- .03, Dryness with Eating IMRT- .02, Dryness without Eating IMRT- .03, Frequent Sipping when Eating IMRT- .002, Frequent Sipping when no Eating IMRT- .0006, Total IMRT- .006 Items with statistically NS results: Swallowing Difficulty, Sleeping Problems		Retrospective	Yes	Yes	Not done	Poor
Jabbari et al. 2005[30]			106	1/3/6/12/18/24 mos., XQ item medians IMRT: 6-12 mo trend for improvement .08 2DRT: trend for improvement NS 12-month between-group difference in XQ, adjusted for baseline score NS						

Table 31. IMRT vs. 2DRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable ?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Pacholke et al. 2005[40]	Primary/ postoperative RT ± chemotherapy with unclear timing	Xerostomia	210	> 1 yr. XQ total means RT technique was significant at <.001 on multivariable analysis		Retrospective	Unclear	Unclear	Unclear	Poor
Palazzi et al. 2008[80]	Primary/ postoperative RT ± concurrent ± pre-RT chemotherapy	Xerostomia	45	Acute	NS	Prospective	Unclear	No	Unclear	Poor

Table 31. IMRT vs. 2DRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable ?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
van Rij et al. 2008[35]	Primary/ postoperative RT ± concurrent chemotherapy	Xerostomia	162	Median F/U 2.6 yr, blend of EORTC QLQ-H&N35 and XQ in rest and during meals	.008	Retrospective	Unclear	Unclear	Unclear	Poor
				Less/much less saliva IMRT-, .07	NS					
				Less/much less change in saliva NS	.001					
				Freq/always dry not eating IMRT-, .004	NS					
				Freq/always probs w/ gums NS	<.001					
				Freq/always probs speak IMRT-, <.0001	.001					
				Freq/always drink day IMRT-, .001	NS					
				Freq/always trouble sleeping NS	.03					
				Freq/always drink night IMRT-, .05	<.001					
				Freq/always probs solid food IMRT-, <.001	.001					
				Freq/always probs grnd food IMRT-, <.001	<.001					
				Freq/always probs swallow solid IMRT-, <.001	.02					
				Freq/always probs swallow grnd IMRT-, .007	<.001					
				Freq/always dry during meals IMRT-, <.001	<.001					
				Freq/always water to swallow IMRT-, <.001	.02					
				Freq/always difficult social eating IMRT-, .006	NS					
				Ground/liquid diet .03						
				Swallow more freq NS						

Table 31. IMRT vs. 2DRT: Summary data on mixed settings for mixed tumor sites (continued)

Study	Setting	Outcome	n	Univariate p value	Multi-variable p value	Study design	Initial groups comp-arable ?	Treat-ments in same time period?	Well-done multivariable analysis?	Study quality rating
Palazzi et al. 2008[80]		Dysphagia	45	Acute, > Gr 2	NS					
Caudell et al. 2009[64]	Primary RT ± pre-RT and/or concurrent chemotherapy	Dysphagia	122	Long-term PEG dependence/aspiration pneumonia/pharyngeal-esophageal stricture/stenosis, ≈ NS	NS	Retrospective	Unclear	Unclear	No	Poor
Palazzi et al. 2008[80]		Mucositis	45	Acute, > Gr 2	NS					
Murphy et al. 2009[90]		Mucositis	75	Acute, > mod Gr, Δ-25, NS		Prospective	Unclear	Yes	No	Poor
Palazzi et al. 2008[80]		Skin toxicity	45	Acute, > Gr 2	NS					
Gomez et al. 2008[70]		Disease-free survival	44	NS	Not entered	Retrospective	Unclear	Yes	Unclear	Poor
Gomez et al. 2008[70]		Overall survival	44	NS	Not entered					

Abbreviations: Δ: change; Gr: grade; mos.: months; NR: not reported; NS: not significant; RT: radiotherapy; wks: weeks; yr: year;

IMRT Single-Arm Studies Summary

Study Overview

Two-thirds of 51 studies (total 2,292 patients) involved full-field IMRT, 33 percent (996 patients) used a split-field technique. Enrollee numbers ranged from 25 patients[127] to 409,[124] with median (or mean) ages from 43 years[105] to 65 years.[99] Males represented 42 to 90 percent of patients by study. Patients had tumors at a single site in 41 percent of studies, including nasopharyngeal (n=seven studies[29,105,108,110,111,131,133]); oropharyngeal (n=six studies[95,97,101,118,125,137]); paranasal sinuses (n=4 studies[98–100,103]); oral cavity/lip (n=two studies[93,134]); hypopharynx (n=one study[122]); and base of tongue (n=one study[107]). Eight studies[31,106,109,112,119,130,132,135] (16 percent) included 100 percent stage III/IV, and four studies[94,108,111,121] (8 percent) included recurrent disease. Two studies[29,105] (4 percent) included 100 percent early stage (I/II) nasopharyngeal cases. Among the remaining 37 studies, case mixtures included 50–96 percent stage III/IV disease.

Concurrent chemoradiotherapy in 37 studies ranged from 5 percent[93,134] to 100 percent[31,94,102,107,109] of patients; one of the latter[107] involved patients with a single tumor location (base of tongue). Primary radiotherapy was used in eight studies[29,95,104,105,111,118,126,133] (16 percent), six of which[29,95,105,111,118,133] involved patients with a single tumor location. Postoperative radiotherapy was used in three studies[99,100,127] (6 percent), two of which[99,100] involved a single tumor site (nasal cavity/paranasal sinuses). The prescribed radiotherapy dose to the primary tumor ranged from 30 Gy to 77 Gy, with a prescribed 70 Gy in 55 percent of studies. Median follow-up ranged from 9 months[111] to 64 months.[132]

Key Question 1. QOL questionnaire outcomes were reported in four studies[29,31,37,38] (8 percent; total n=142) with a mixture of tumor locations and stages. No two studies used the same QOL scoring instrument. Xerostomia was reported in 21 studies (41 percent) studies (total n=1,072). No grade 4 xerostomia was reported. Nine studies[91,102,114,115,117,119,120,128,133] (18 percent) reported grade 3 xerostomia; the balance of studies reported xerostomia grades 0, 1, or 2. Salivary gland function was assessed in six studies[29,38,95,105,113,117] (12 percent).

Dysphagia was scored in 16 studies (31 percent) including a total of 820 patients. Most patients reported grades 1–3 dysphagia. No dysphagia was reported in one study[133] (n=75) of primary radiotherapy for nasopharyngeal cancer. Grade 3–4 acute dysphagia was reported in one highly clinically diverse study.[112] Grades 0–4 mucositis was reported in 28 (55 percent) studies (n=1,471). Grade 4 acute mucositis was reported in five studies[94,96,97,117,132] (10 percent), all of which also involved chemotherapy.

Skin-related toxicities were reported in 21 studies (41 percent) (n=1,089), the majority grades 1 and 2. One study[97] reported grade 4 acute skin-related toxicity in 5 percent of patients with mostly advanced (93 percent stage III/IV) oropharyngeal cancer. Acute grade 3–4 skin-related toxicity was reported in one study[112] involving 100 percent advanced cancers.

Osteoradionecrosis and bone-related adverse events were reported in seven studies (14 percent; n=516). One grade 4 late toxicity (mandibular fracture) was reported in a single study[114] of patients (n=48) with a mix of cancers; late grade 3 osteoradionecrosis was reported in another study[125] of patients (n=73) with oropharyngeal cancer.

Key Question 2. Local tumor control rates were reported in 22 studies[98–101,103,105,107,109,112,114,118,120–124,131,133–137] (43 percent; n=1,717). Locoregional tumor control rates were reported in 12 studies[97,106,108,109,119,123,125,128,133–135,137] (24 percent; n=948). Disease-free survival (DFS) was reported in 12 studies[94,97–100,106,110,121,124,125,128,137] (24 percent; n=1,006). Overall survival (OS) was reported in 27 studies[94,97–101,103,105–110,112,114,119,120,124,128,131–133,135–137] (53 percent; n=1,943). Disease-specific survival (DSS) was reported in seven studies[100,110,112,120,121,132,134] (14 percent; n=384).

3DCRT Single-Arm Studies Summary

There were 18 single-arm studies involving a total of 1,761 patients, which reported outcomes using 3DCRT, 12 studies[42,140,142,145–152,154] using full field and six studies[138,139,141,143,144,153] using split field. Enrollment ranged from 24 patients[145] to 630 patients[138]; the majority of studies involved less than 60 patients. Patient age ranged from 17 years[153] to 99 years of age[139] and the majority of participants were male. Eight studies reported outcomes for a single tumor site, including nasopharyngeal,[138,141,145,153,154] oral cavity,[140] paranasal sinuses,[147] and larynx[42]; the remaining studies involved patients with tumors in mixed sites. Five studies[140,141,144,147,150] involved patients with stage 3 or 4 disease; the remainder of the studies but one included a mix of stages or it was not clear what the stage was for all patients. One study[145] involved only patients with stage 2 disease.

Treatment settings were variable, with two studies using primary radiotherapy for 100% of patients.[42,144] The remaining studies used chemotherapy in variable proportions, including concurrently and pre- or post-radiation. Three studies[150, 152,154] involved reirradiation with 3DCRT.

Reporting of patient outcomes included adverse events, tumor control and survival. For adverse events, xerostomia was reported in six studies,[42,142,145,149,151,154] salivary flow in two studies,[42,139] dysphagia in three studies,[143,146,149] mucositis in nine studies,[140–142,144–147,150,152,154] skin-related events in seven studies,[140,142,143,145,147,149,154] and osteoradionecrosis in one study.[154] No study reported quality of life measures.

Reporting of tumor control included local control rates in three studies[145,153,154] and locoregional control in five studies.[138,141,143,146,149] Survival outcomes included disease-free survival in four studies,[42,141,143,145] overall survival in 12 studies,[42,141,143–147,149,150,152–,154] and disease-specific survival in one study.[143]

Key Question 3. Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT and proton beam therapy for specific patient and tumor characteristics?

The best way methodologically to answer Key Question 3 is to include interaction terms between radiotherapy modality and patient characteristics in a multivariable analysis of data from a randomized, controlled trial. A statistically significant interaction term would indicate that the impact of treatment varies with that patient characteristic. Performing this analysis in the context of a randomized controlled trial would ensure that other potential confounding factors have been taken into account and would provide the strongest evidence (level 1). The second best approach is to include such interaction terms in a well-conducted multivariable analysis of data from a nonrandomized comparative study, also accounting for potential baseline differences in treatment groups in the multivariable analysis (level 2).

The final approach, used to generate hypotheses to be confirmed in studies with stronger research designs, is to conduct multivariable analyses of single arms studies to identify factors that may influence outcomes (level 3). The drawback of this last approach is that such results cannot separate the influence of factors on outcomes regardless of treatment from any differential impact of treatment associated with specific patient characteristics. For example, advanced disease is often associated with a poorer prognosis, independent of other factors. If, hypothetically, a treatment were less effective among patients with advanced disease, patients in the study with advanced disease would have poorer outcomes from the treatment itself. Without a comparison to another treatment modality, one cannot separate whether poorer outcomes among patients with advanced disease are due to the underlying disease process or to the relative lack of effectiveness of the treatment among those patients.

Unfortunately, of the 38 comparative studies included in this review, including three randomized controlled trials, none address the issue of the interaction between radiotherapy modality and patient/disease-specific characteristics. Therefore, there are insufficient data to answer Key Question 3.

Several single-arm studies analyzed the impact of patient characteristics on outcomes; the results, summarized below, can be used for hypothesis generation.

Single-Arm IMRT Studies. Relevant univariate or multivariable analyses of prognostic factors for locoregional control, disease-free survival, overall survival, and disease-specific survival, including age, treatment, radiotherapy dose, and tumor site, stage and histology were variously reported in five[97,108,110,132,134] single-arm studies (10 percent) of IMRT (n=779; Table 32). All of these analyses reported on tumor control or patient survival outcomes as the dependent variable; none evaluated factors associated with frequency of adverse events. Among the patient or tumor characteristics found to be associated with these outcomes were age, tumor site and volume, and histology. However, these analyses do not address comparative benefit of radiotherapy techniques. Further comparative studies are needed to determine whether treatment effects vary by these factors or whether these factors are prognostic regardless of radiotherapy modality.

Single-Arm 3DCRT Studies. Relevant univariate and multivariable analyses of prognostic factors for local control, locoregional control, disease-specific survival, and overall survival, including age, gender, histologic type, mean radiation dose to primary tumor, volume of tumor irradiated, tumor stage, treatment interval, lymph node metastases, and primary tumor site were variously reported in five studies[138,140,143,153,154] of 3DCRT (Table 33). All of these analyses reported on tumor control or patient survival outcomes as the dependent variable; none evaluated factors associated with frequency of adverse events. Among the patient or tumor characteristics found to be associated with these outcomes were age, stage, tumor site and volume, lactate dehydrogenase (LDH) level, and histology. However, these analyses do not address comparative benefit of radiotherapy techniques. Further comparative studies are needed to determine whether treatment effects vary by these factors or whether these factors are prognostic regardless of radiotherapy modality.

Table 32. Summary of multivariable analyses in single-arm studies of IMRT

Study	No. Pts	Setting	Site	% Stage 0/I/II	% Stage III/IV	Outcome	Univariate Predictors	p Value	Multivariable Predictors	p Value
Lee et al., 2007[108] (07/1996-09/2005)	105	ReRT: 100	MIX		Recurrent: 100	LRPFS	IMRT vs. non-IMRT RT dose ≥ 50 Gy vs. < 50 Gy chemotherapy vs. no chemotherapy	<.001 .001 .031	IMRT vs. non-IMRT	.006
						OS	Age Multiple recurrences prior to re-RT vs. single chemotherapy vs. no chemotherapy IMRT vs. non-IMRT PHX vs. non-NPH tumor SCC vs. other histology	.003 .016 .046 .026 <.001 .006	RT dose ≥ 50 Gy vs. < 50 Gy PHX vs. NPH tumor Other tumor vs. NPH SCC vs. other histology	.043 .001 .04 .027
Yao et al., 2007[134] (05/2001-07/2005)	55	Primary RT: 4 Postop RT: 85 PreopRT: 2 CCRTx: 5 PreRT chemo-therapy: 2 adjuvant chemo-therapy: 2	OCL	9	91	LRC	Extracapsular extension vs. not	.0277	NR	

Table 32. Summary of multivariable analyses in single-arm studies of IMRT (continued)

Study	No. Pts	Setting	Site	% Stage 0/I/II	% Stage III/IV	Outcome	Univariate Predictors	p Value	Multivariable Predictors	p Value
Worden et al., 2008[132] (01/2000-11/2002)	53	PreRT chemo-therapy: 100	MIX		100	OS	Female sex Lower KPS Higher T class Lower N class Current smoking HPV-negative tumor BOT site	< .005 < .05 < .05 < .05 < .05 < .05 < .05	Female sex Higher T class Lower N class Current smoking HPV-negative tumor BOT site	.008,
						DSS	Female sex Higher T class Lower N class Current smoking HPV-negative tumor BOT site	< .005 < .005 < .05 < .005 < .05 < .05		.004
Chao et al., 2004[97] (02/1997-09/2001)	74	Primary RT: 19 Postop RT: 58 CCRTx: 23	OPH	7	93	DFS	Definitive IMRT vs. postop IMRT	.02	NR	
						LRC	Definitive IMRT vs. postop IMRT		GTV nGTV	.03 .05
						DMFS	Definitive IMRT vs. postop IMRT		GTV nGTV GTV	.03 .01 .03
Liu et al., 2003[110] (06/1999-04/2003)	83	Primary RT: 24 CCRTx: 76	NPH	37	63	OS	Stage I/II vs. III/IV N0 vs. other RT dose > 76 Gy	.007 .046 .046	Stage I/II vs. III/IV N0 vs. other R dose > 76 Gy	.041 .023 .029
						DFS DSS	T1/2 vs. T3/4 RT dose > 76 Gy	.04 .01	NR RT dose > 76 Gy	 .020

Table 33. Summary of multivariable analyses in single-arm studies of 3DCRT

Study	No. Pts	Setting	Site	% Stage 0/I/II	% Stage III/IV	Outcome	Univariate Predictors	p Value	Multivariable Predictors	p Value
Zheng et al. 2005[154] (07/97-03/03)	86	ReRT (100) chemo-therapy unclear (53)	NPH		≥51 (?balance)	OS LFF MLT	Age Gender Histologic type Mean dose primary tx Volume of primary tx irradiated T stage of recurrence GTV volume of recurrence Interval from completion of first course of RT to dx of recurrence Pre-existing late toxicities from previous RT, CT, simultaneous regional recurrence and dose conformity index.	T stage and GTV for OS (p<.01), LFF (p<.01 and p=.03), and MLT (p<.01). Advanced T stage and large GTV volume were associated with poor OS and LFF and high risk of MLT.	T stage and GTV volume	T stage significant for OS (p<.01) and LFF (p=.01). GTV volume significant for MLT (p=.04).
Ikushima et al. 2008[140] (1999-2002)	40	Concur-rent chemo-therapy (100)	OC		100	Survival	Age Sex Stage Local response to tx Mode of tumor invasion LN mets	.32 .53 .86 .04 .03 .01	Age Sex Local response to tx Mode of tumor invasion LN mets	0.39 0.79 0.12 0.14 0.15

Table 33. Summary of multivariable analyses in single-arm studies of 3DCRT (continued)

Study	No. Pts	Setting	Site	% Stage 0/I/II	% Stage III/IV	Outcome	Univariate Predictors	p Value	Multivariable Predictors	p Value
Cheng et al. 2006[138] (04/90-12/02)	630	Primary RT (#NR) Concur-rent chemo-therapy (93) Adju-vant chemo-therapy (76)	NPH		≥65.2 (?balance)	Risk of LR recurrence	T stage T3 vs. T1–T2 T4 vs. T1–T2 Primary tumor size ≥4 cm Parapharyngeal space extension Sphenoid floor invasion Clivus marrow infiltration Clivus cortex invasion Prevertebral muscles invasion Petrous bone invasion Sphenoid sinus invasion Foramen lacerum invasion Foramen ovale invasion Cavernous sinus invasion Intracranial invasion Infratemporal fossa invasion Ethmoid sinus invasion Hard palate invasion Anatomic grouping #2 with two or more anatomic sites involved Anatomic grouping #3 with one or more anatomic sites involved Anatomic grouping #5 with one or more anatomic sites involved	 .02 .0002 .002 .01 <.0001 .002 <.0001 <.0001 .01 .001 .001 .0003 .0004 .002 .005 .006 .02 <.0001 .0001 .02	Age >40 vs. ≤40 LDH ≥410 vs. <410 Histology (WHO type I-II vs. III) Anatomic site involved ≥2 vs. <2	.03 .002 .002 .0004

Table 33. Summary of multivariable analyses in single-arm studies of 3DCRT (continued)

Study	No. Pts	Setting	Site	% Stage 0/I/II	% Stage III/IV	Outcome	Univariate Predictors	p Value	Multivariable Predictors	p Value
Lau et al. 2006[143] (09/00-12/02)	56	Adju-vant chemo-therapy (100)	MIX	7.1	92.8	OS	Age at dx	Significant	Amount of CT received	Significant
							Initial Hb	"	N classification	
							Karnofsky PS	"		
							Receiving <50% planned chemotherapy	"		
							T and N stage	"		
							Overall stage	NS		
							Primary tumor site	"		
						DSS				
							Age at dx	Significant		
							Initial Hb	"		
							Karnofsky PS	"		
							T and N stage	"		
							Amount of chemotherapy received	NS		
							Overall stage	"		
						LRRFS	Primary site	"		
							Age at dx	Significant		
							Karnofsky PS	"		
							Amount of chemotherapy received	"		
							T and N stage	"		
							Initial Hb	NS		
							Overall stage	"		
							Primary site	"		

Table 33. Summary of multivariable analyses in single-arm studies of 3DCRT (continued)

Study	No. Pts	Setting	Site	% Stage 0/I/II	% Stage III/IV	Outcome	Univariate Predictors	p Value	Multivariable Predictors	p Value
Sze et al. 2004[153] (11/98-06/01)	308	Primary RT (58.4) Concur-rent chemo-therapy (37.7) Neoad-juvant chemo-therapy (3.9)	NPH		≥56.5 (?balance)	LFFR PFS OS	GTV-P (using T stage [T1-2 vs. T3-4] as a covariate, GTV-P remained an independent prognostic factor for LFFR. When adjusted for group stage, age, gender, CT and fractionation scheme=NS)	<.05 <.05 <.05		

Key Question 4: Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?

As with Key Question 3, Key Question 4 would best be addressed by evaluating treatment effect interactions with respect to user experience, target volume delineation, or dosimetric parameters, ideally using data from randomized controlled trials or secondarily, from nonrandomized comparative studies while controlling for potential differences between treatment groups at baseline. Alternatively, analyses of the impact of these factors on treatment outcomes using data from single arm studies could generate hypotheses. Unfortunately, no comparative studies were found that look at the impact of user experience, target volume delineation, or dosimetric parameters on treatment outcomes.

Two single-arm studies included radiotherapy dose as one factor in a multivariable analysis to identify factors associated with tumor control or patient survival. Lee et al.[108] reported that radiotherapy dose greater than 50 Gy was associated with longer overall survival in a study of treatment for patients with recurrent disease. Liu et al.[110] reported that radiotherapy dose greater than 76 Gy is a predictor of overall survival as well. However, these analyses do not address predictors of variability in radiotherapy outcomes. No other studies were found that evaluated the relationship between outcomes and user experience, target volume delineation, or dosimetric parameters. Therefore, Key Question 4 cannot be answered with the evidence available at this time.

Proton Beam Therapy

Initial review of literature search results yielded no articles on proton beam therapy that met selection criteria. Additional efforts were undertaken to identify studies, included a focused search of the literature search result, scrutiny of review article reference lists, and request for and review of bibliography compiled for the AHRQ Technical Brief, "Particle Beam Radiation Therapies for Cancer" (published September 2009 at www.effectivehealthcare.ahrq.gov/ehc/products/58/173/2009_0915_PBRT_tech_brief.pdf).

The only relevant studies identified used a combination of proton and photon therapy, which were initially excluded because they involved more than one type of radiotherapy. The selection criteria were amended to include these studies, based on expert advice from two members of TEP providing extended consultation. Despite this change, only one single-arm study met the revised selection criteria; no comparative studies were identified.

Most studies on proton beam therapy that were characterized as dealing with head and neck cancer evaluated cancers that did not meet the consensus definition of head and neck cancer used in this review. Specifically, many of these studies dealt with skull-base tumors. A number of others were treatment planning studies that did not provide data on outcomes or adverse events. The single study abstracted[155] reported on 29 patients with stage II–IV squamous cell carcinoma or lymphoepithelioma oropharyngeal cancer who received accelerated photon and proton therapy. Tumor location was mixed, comprised of 55 percent base of tongue, 34 percent tonsillar, 7 percent anterior faucial pillar-retromolar trigone, and 3 percent pharyngeal wall. Total dose was 75.9 Gy, with 50.4 Gy from photons and a 25.5 Gy boost using protons. Locoregional control was 96 percent at 2 years and 88 percent at 5 years, while disease-free survival was 81 percent and 65 percent at 2 and 5 years, respectively. Fourteen percent of subjects developed

metastatic disease. Severe acute mucositis was mentioned but no numbers were reported. One case each of the following grade 3 adverse events was reported: subcutaneous fibrosis, vocal cord paralysis, and epiglottitis.

Single-arm studies can at best suggest hypotheses to be tested in comparative studies, ideally randomized, controlled trials. The available evidence on proton beam therapy in head and neck cancer is further weakened by the small sample size and mix of tumor locations in the single study that met the revised selection criteria, and by the lack of additional studies. Thus, insufficient data are available on combined photon-proton treatment of head and neck cancer to draw any conclusions regarding its effectiveness or likely adverse effects.

Summary and Discussion

The results of the comparative effectiveness review of four types of radiotherapy (IMRT, 3DCRT, 2DRT, and proton beam therapy) are summarized in the following table. A small body of randomized, controlled trials is accompanied by a larger body of poor quality observational, nonrandomized studies. Study quality was assessed according to principles described in a reference guide for conducting comparative effectiveness reviews produced by AHRQ.[156] The observational studies reviewed here are clinically diverse with respect to patient characteristics and treatment setting, creating uncertainty about whether results should be attributed to confounding rather than treatment differences. Details were often lacking among observational studies about patient characteristics and treatments and it was not clear for any study whether well-done multivariable analyses were performed to adjust for differences.

The main conclusion is that there is moderate evidence that IMRT, compared with 3DCRT, reduces late xerostomia and improves quality of life, particularly quality of life domains most related to xerostomia. This conclusion is based primarily on the consistency of large differences favoring IMRT in 6 observational studies. A recent randomized, controlled trial also found results supporting this conclusion, but full details of this study are unavailable, so it is difficult to assess its quality and contribution to the overall body of evidence. There was also moderate evidence that IMRT, compared with 2DRT, reduces late xerostomia and improves quality of life domains related to xerostomia. However, the comparison of IMRT versus 2DRT relies greatly on inferences drawn from evidence comparing IMRT versus 3DCRT, which demonstrate the relationship between radiation dose conformality in the treatment of head and neck cancers and reduction in the frequency of late xerostomia. Inconsistent and nonsignificant results were observed between IMRT and comparators on other adverse events, overall quality of life, tumor control, and survival outcomes. Thus, the evidence is insufficient to support conclusions in these areas.

Key Question	Level of Evidence	Conclusion
1. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT and proton beam therapy regarding quality of life and adverse events?		• There were 38 comparative studies. Of these, four were randomized, controlled trials. One randomized, controlled trial could not be clearly rated because a manuscript was unavailable, one was rated fair and two were rated poor due to lack of intention-to-treat analysis. • The remaining 34 studies were observational, with significant flaws such as lack of comparable groups at baseline; comparing radiotherapy technologies at different points in time, that is, the study arms were not contemporaneous; and poorly done multivariable analyses.

Key Question	Level of Evidence	Conclusion
1a. IMRT versus 3DCRT	Moderate (late xerostomia, quality of life) Insufficient (other outcomes)	• One randomized, controlled trial presented at a conference showed a large advantage for IMRT in the frequency of late xerostomia grade 2 or higher. The risk difference was 35 percentage points with a 95% confidence interval between 12.6 and 55.5 percentage points. • Six observational studies favored IMRT. Of the five studies that reported frequencies, the reported range of differences is 7 to 79 percentage points. • Quality of life was reported in three observational studies and generally favored IMRT, although not all domains measured were statistically significant. Significant advantages for IMRT included these domains: dry mouth, sticky saliva, taste/smell, fatigue and feeling ill. • Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late osteoradionecrosis and bone toxicity were reported in some and typically favored IMRT but differences were not consistently statistically significant. Among studies of acute skin toxicity neither the size of the difference nor the direction was consistent.
1b. 3DCRT versus 2DRT	Insufficient (all outcomes)	• Four studies reported on late xerostomia with a range of differences between 3DCRT and 2DRT of 15 to 48 percentage points, except one study that favored 2DRT by 10 percentage points. Only one result was statistically significant. • One study compared quality of life outcomes between 3DCRT and 2DRT but did not report a statistical comparison. • Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, acute skin toxicity, late skin toxicity, and late osteoradionecrosis and bone toxicity were reported in a few studies and differences between 3DCRT and 2DRT were small and not statistically significant, not exceeding a difference of 9 percentage points. • The available literature is of insufficient quantity and quality and to ascertain whether there are differences in quality of life or adverse events between 3DCRT and 2DRT.

Key Question	Level of Evidence	Conclusion
1c. IMRT versus 2DRT	Moderate (late xerostomia, quality of life) Insufficient (other outcomes)	• Nine studies reported on late xerostomia, and eight were statistically significant in favor of IMRT. Among the studies that reported frequency, the range of differences between IMRT and 2DRT was 43 to 62 percentage points.. • Quality of life was reported in one randomized, controlled trial and two observational studies and generally favored IMRT although not all domains measured were statistically significant. Domains significantly favoring IMRT included dry mouth and sticky saliva. • Indirect evidence from the comparison of IMRT vs. 3DCRT shows that greater conformality of radiation reduces late xerostomia and improves quality of life. Thus, inference from comparison of IMRT vs. 3DCRT, provides additional support for this conclusion. • Acute and late mucositis, acute and late dysphagia, acute and late skin toxicity, and late osteoradionecrosis and bone toxicity were reported in some studies. Few studies reported significant results. These tended to be small studies or the 2DRT data were from an earlier time period than IMRT.
1d. Proton beam versus other techniques	Insufficient	• There were no comparative studies.
2. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT and proton beam therapy regarding tumor control and patient survival?		• The body of evidence was the same as for Question 1 .
2a. IMRT versus 3DRCT	Insufficient (all outcomes)	• In the single randomized, controlled trial presented at a conference, the sample size is too small and followup is too short to ascertain any differences in tumor control or survival. • Of the seven comparative observational studies reporting tumor control, none reported statistically significant differences between IMRT and 3DCRT. • Of seven comparative studies reporting patient survival, one reported a statistically significant result; the difference was in the slight-to-moderate range and favors IMRT. • No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT.

Key Question	Level of Evidence	Conclusion
2b. 3DCRT versus 2DRT	Insufficient (all outcomes)	• Of the eight comparative studies reporting tumor control, one reported a statistically significant difference in favor of 3DCRT. This randomized, controlled trial reported a large difference in tumor control at one year but did not report intent-to-treat analysis. • Of seven comparative studies reporting patient survival, none reported a statistically significant result. • No conclusions on tumor control or survival can be drawn from the body of evidence comparing 3DCRT versus 2DRT.
2c. IMRT versus 2DRT	Insufficient (all outcomes)	• Of the six comparative observational studies reporting tumor control, none reported a statistically significant difference. • Of seven comparative observational studies reporting patient survival, one reported a large, statistically significant result in favor of IMRT. • No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 2DRT.
2d. Proton beam versus other techniques	Insufficient	• There were no comparative studies.
3. Patient and tumor characteristics affecting outcomes	Insufficient	• No comparative studies addressed this issue.
4. Radiotherapy/physician characteristics affecting outcomes	Insufficient	• No studies addressed this issue.

Compared to either 3DCRT or 2DRT, IMRT produces a more conformal dose distribution and a steeper dose gradient between the tumor target and adjacent uninvolved tissues or organs at risk. Dose distribution is considered an intermediate outcome, which may be related to health outcomes, but by itself does not establish the comparative effectiveness of different radiotherapy techniques. It was hypothesized that these technical differences would result in improved tumor control while reducing the incidence and severity of radiation toxicities, particularly in head and neck cancer patients treated with IMRT compared to 3DCRT or 2DRT.[157,158]

In using IMRT to treat head and neck cancer patients, theoretical dose delivery advantages must be translated into improved therapeutic outcomes. There is potential to introduce small errors or inconsistencies at each step in the process of inverse treatment planning and its ultimate delivery. Thus, accurate delineation of the tumor, surrounding areas at risk for subclinical disease, and normal tissues or organs at risk for radiation toxicities rely on the accuracy of computed tomography. Subsequent conversion of the physician-prescribed doses to a radiotherapy plan by one of several available inverse treatment planning systems also is subject to variability based on the type of system used.[159] Because there are often clear discrepancies between the prescribed dose and the amount of radiation ultimately delivered to a specific patient, treatment planning studies are not sufficient to demonstrate the comparative effectiveness of different radiotherapy modalities. Furthermore, differences among patients in susceptibilities to specific adverse events, for example xerostomia, preclude the use of dose

planning studies to compare techniques.[160] Comparative evidence on clinical outcomes is necessary to establish that the technical advantages of IMRT do indeed benefit patients, not only by decreasing xerostomia, but also by achieving similar or improved tumor control and survival.

The capability of IMRT to deliver steep dose gradients around a tumor site may present a risk as well as potential benefit.[161] Because the dose gradient (i.e., the difference in dose between the tumor and adjacent healthy areas) is greater for IMRT than for other modalities, patient positioning becomes critical. If the planned dose does not align with the tumor contour and other anatomic attributes of the patient, the planned and actual dose may diverge substantially. It is possible for part of the tumor to receive a much lower dose than needed if it inadvertently receives the dose intended for the adjacent healthy tissue and vice versa. A few millimeters of margin is built into the treatment plan (i.e., planning target volume) to account for this, but it may not be uniformly the right amount and can detract from the precision of IMRT. Tumor shrinkage and differences in patient habitus due to weight loss during treatment also may alter the relation of the planned dose distribution to the intended target.[157,158]

Most of the studies in this review were based on the results of patients treated at academic medical centers. However, an informal survey estimates that 30 to 60 percent of all cancer patients in the U.S. are treated with IMRT.[159] Whether similar results will be achieved as the technology diffuses to less-experienced settings[162] has not been addressed in the comparative studies available for this review.

Future Research

The available literature to assess the relative effectiveness of different techniques of radiotherapy in head and neck cancer on the whole consisted of poor-quality studies and, with the exception of late xerostomia and quality of life, a low or insufficient level of evidence. The challenges of conducting research in head and neck cancer need to be acknowledged. Head and neck cancers are not common, so the pace of patient accrual may be slow; this may be accompanied by changes in practices, both for the technology of radiotherapy itself and other aspects of management and treatment. Also, head and neck cancer patients are likely to be clinically diverse in terms of tumor site, histology, stage, prior and co-interventions, and other factors. On the other hand, the length of followup needed to study head and neck cancer treatments is relatively short compared to some common cancers, such as breast or colon cancer. A further challenge to evaluating radiotherapy techniques for head and neck cancer concerns the rapid pace at which these technologies are evolving.

Specific recommendations for future research:

1. Promote multicenter trials to hasten patient accrual and trial completion.

2. There are considerable obstacles to conducting randomized, controlled trials to ascertain tumor control and survival effects. These are: wide dissemination of IMRT, reluctance to randomize patients when effects on xerostomia are already known, the large numbers such trials would require, and other priorities for funding. Nonetheless, certainty about tumor control and survival outcomes can ideally be obtained through a robust randomized, controlled trial. Both treatment characteristics, including adjunctive treatments such as chemotherapy, and patient characteristics, e.g., prognostic factors such as age, stage, and comorbidities, can be confounding factors.
    - While trial recruiting challenges may limit statistical power to test for effects among subgroups, trial protocols should prespecify subgroup analyses on prognostic variables such as patient age, site, stage, and tumor grade as well as user variables such as treatment experience, target volume parameters and dosimetric parameters.
    - Statistical analysis should be conducted in accordance with preferred methods.[163]
    - Trials should be designed, conducted and published with attention to reporting and quality domains noted in the CONSORT statement[164] and USPSTF framework.[9]

3. Recognizing that observational studies, including case series, will continue to be attractive to investigators, recommendations to improve the usefulness and generalizability of such comparative studies are:
    - Conduct prospective studies with contemporaneous treatments being compared.
    - Comparison groups should be comparable in terms of key variables, such as anatomic site, disease stage, and prior treatment.
    - Multivariable regression analyses can be helpful in controlling for potential confounders and should adhere to good modeling practices.[14-21]

- Guidance for study quality in observational studies has been addressed by Deeks et al.[10]

4. Additional features that would improve the quality of randomized, controlled trials, observational studies, and case series are:
    - To facilitate comparisons between studies, outcome measures need to be standardized, such as the Common Terminology Criteria for Adverse Events.[165]
    - Key outcome measures include tumor control, type and extent of toxicity and functional/quality of life status..
    - Outcome measures should be valid and reliable, and their assessment should be blinded or otherwise be performed by an independent assessor well-trained in toxicity assessment.
    - Quality-of-life and patient-reported outcomes should be assessed with validated instruments for which clinically significant improvements have been quantified empirically.
    - Standardized radiotherapy delivery terminology should be adopted (e.g., the use and meaning of gross tumor volume [GTV], clinical target volume [CTV], planning target volume [PTV]) to permit evaluation of outcomes relative to modality.
    - Clear details are needed about timing, dose and specific chemotherapy agents given.
    - Consistently conduct and report rigorous multivariable adjustment for confounding. Among other factors, this will require sample sizes sufficient to support multivariable analysis, consistent and thorough measurement of potential confounders, and good modeling techniques.
    - Among the variables of interest are patient and tumor characteristics that may affect outcomes.
    - Operator and performance characteristics should also be assessed for effect on outcomes. Characteristics of interest include experience and success in delivering prescribed doses.

5. Xerostomia has a significant impact on quality of life. It appears to be common in patients with certain tumor sites, radiotherapy treatments and chemotherapeutic regimens. Older age and certain therapies for chronic diseases may increase susceptibility for this adverse effect. Research to improve the management of xerostomia and to disseminate that knowledge to clinical practice could potentially improve morbidity and quality of life for cancer patients.

References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers (V.1.2009). Available at: http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf. Accessed October 2009.

2. Forastiere AA. Chemotherapy in the treatment of locally advanced head and neck cancer. J Surg Oncol 2008;97:701-707.

3. Burri MK, Bevan A, Roach III M. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin 2005;55:117-134.

4. Lee NY, Terezakis SA. Intensity-modulated radiation therapy. J Surg Oncol 2008;97:691-696.

5. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. J Clin Oncol 2006;24:2618-2623.

6. Ballivy O, Santamaria RG, Borbalas AL, et al. Clinical application of intensity-modulated radiotherapy for head and neck cancer. Clin Transl Oncol 2008;10:407-414.

7. Chavaudra J, Bridler A. Definition of volumes in external radiotherapy: ICRU reports 50 and 62. Cancer Radiother 2001;5:472-478.

8. Lawrence TS, Ten Haken RK, Giaccia A. Principles of radiation oncology. Chapter 21. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Cancer. Principles and Practice of Oncology. (8th ed.). Philadelphia: Lippincott Williams and Wilkins; 2008.

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

10. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7(27):iii-x, 1-173.

11. Carey TS, Boden SD. A critical guide to case series reports. Spine 2003;28(15):1631-1634.

12. Seidenfeld J, Samson DJ, Rothenberg BM, et al. HER2 testing to manage patients with breast cancer or other solid tumors. Evidence Report/Technology Assessment No. 172. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026.) AHRQ Publication No. 09-E001. Rockville, MD: Agency for Healthcare Research and Quality. November 2008.

13. Conley BA, Taube SE. Prognostic and predictive markers in cancer. Dis Markers 2004;20(2):35-43.

14. McShane LM, Altman DG, Sauerbrei W, et al. for the Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. Reporting recommendations for tumor marker prognostic studies (REMARK) J Natl Cancer Inst 2005;97:(16)1180-1184.

15. Altman DG. Systematic reviews of evaluations of prognostic variables BMJ 2001a; 323:(7306)224-228.

16. Altman DG. Systematic reviews of evaluations of prognostic variables. In: Egger M, Davey Smith G, Altman DG, eds. Systematic reviews in health care: Meta-analysis in context. 2nd ed. London: BMJ Books 2001b:228-247.

17. Altman DG, Lyman GH. Methodological challenges in the evaluation of prognostic factors in breast cancer Breast Cancer Res Treat 1998;52:289-303.

18. Altman DG, Riley RD. Primer: an evidence-based approach to prognostic markers. Nat Clin Pract Oncol 2005;2(9):466-472.

19. Gould Rothberg BE, Bracken MB. E-cadherin immunohistochemical expression as a prognostic factor in infiltrating ductal carcinoma of the breast: a systematic review and meta-analysis Breast Cancer Res Treat 2006;100(2):139-148.

20. Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis Br J Obstet Gynaecol 1998;105:836-848.

21. Simon R, Altman DG. Statistical aspects of prognostic factor studies in oncology Br J Cancer 1994;69:979-985.

22. Ransohoff DF. How to improve reliability and efficiency of research about molecular markers: roles of phases, guidelines, and study design. J Clin Epidemiol 2007;60(12):1205-1219.

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

24. Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol [In press].

25. Guyatt GH, Oxman AD, Vist GE, et al. for the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-926.

26. Tubach F, Wells GA, Ravaud P, et al. Minimal clinically important difference, low disease activity state, and patient acceptable symptom state: methodological issues. J Rheumatol 2005;32(10):2025-2029.

27. Streiner DL, Norman GR. Health Measurement Scales: A Practical Guide to their Development and Use. 4th ed. New York: Oxford University Press, 2008.

28. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006;66(4):981-991.

29. McMillan AS, Pow EH, Kwong DL, et al. Preservation of quality of life after intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: results of a prospective longitudinal study. Head Neck 2006;28(8):712-722.

30. Jabbari S, Kim HM, Feng M, et al. Matched case-control study of quality of life and xerostomia after intensity-modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. Int J Radiat Oncol Biol Phys 2005;63(3):725-731.

31. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2007;68(5):1289-1298.

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

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

34. Vergeer MR, Doornaert PA, Rietveld DH, et al. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys 2009;74(1):1-8.

35. van Rij CM, Oughlane-Heemsbergen WD, Ackerstaff AH, et al. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. Radiat Oncol 2008;3:41.

36. Yao M, Karnell LH, Funk GF, et al. Health-related quality-of-life outcomes following IMRT versus conventional radiotherapy for oropharyngeal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2007;69(5):1354-1360.

37. Dornfeld K, Simmons JR, Karnell L, et al. Radiation doses to structures within and adjacent to the larynx are correlated with long-term diet- and speech-related quality of life. Int J Radiat Oncol Biol Phys 2007;68(3):750-757.

38. Scrimger R, Kanji A, Parliament M, et al. Correlation between saliva production and quality of life measurements in head and neck cancer patients treated with intensity-modulated radiotherapy. Am J Clin Oncol 2007; 30(3):271-277.

39. Daly ME, Lieskovsky Y, Pawlicki T, et al. Evaluation of patterns of failure and subjective salivary function in patients treated with intensity modulated radiotherapy for head and neck squamous cell carcinoma. Head Neck 2007;29(3):211-220.

40. Pacholke HD, Amdur RJ, Morris CG, et al. Late xerostomia after intensity-modulated radiation therapy versus conventional radiotherapy. Am J Clin Oncol 2005;28(4):351-358.

41. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 2007;25(31):4873-4879.

42. Braaksma MM, Wijers OB, van Sornsen de Koste JR, et al. Optimisation of conformal radiation therapy by intensity modulation: cancer of the larynx and salivary gland function. Radiother Oncol 2003;66(3):291-302.

43. University of Washington Department of Otolaryngology/Head and Neck Surgery. University of Washington Quality of Life Scale. Available at: http://depts.washington.edu/otoweb/research/head_neck_cancer/uw_qol_scoring_instructions.pdf. Accessed October 2009.

44. European Organisation for Research and Treatment of Cancer (EORTC) Group for Research into Quality of Life. Bibliography. Available at: http://groups.eortc.be/qol/documentation_bibliography.htm. Accessed October 2009.

45. Ware Jr JE. SF-36® Health Survey Update. Available at: http://www.sf-36.org/tools/SF36.shtml. Accessed October 2009.

46. Bjordal K, Ahlner-Elmqvist M, Tollesson E, et al. Development of a European Organization for Research and Treatment of Cancer quality of life questionnaire-H&N 35. J Clin Oncol 1999;17:1008-1019.

47. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. Eur J Cancer 2000;36:1976-1807.

48. Chandu A, Smith ACH, Rogers SN. Health-related quality of life in oral cancer: A review. J Oral Maxillofac Surg 2006;64:495-502.

49. Chie W-C, Hong R-L, Lai C-C, et al. Quality of life in patient of nasopharyngeal carcinoma: Validation of the Taiwan Chinese version of the EORTC QLQ-C30 and the EORTC QLQ-H&N35. Qual Life Res 2003;12(1):93-98.

50. Eisbruch A, Kim HM, Terrell JE, et al. Xerostomia and its predictors following parotid-sparing irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 2001;50:695-704.

51. El-Deiry M, Funk GF, Nalwa S, et al. Long-term quality of life for surgical and nonsurgical treatment of head and neck cancer. Arch Otolaryngol Head Neck Surg 2005;131:879-885.

52. Jameson MJ, Hynds Karnell L, et al. First-year trends in self-reported general health predict survival in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2008;134(9):958-964.

53. Funk GF, Karnell LH, Christensen AJ, et al. Comprehensive head and neck oncology health status assessment. Head Neck 2003;25(7):561-575.

54. Hjermstad MJ, Fossa SD, Bjordal K, et al. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. J Clin Oncol 1995;13(5):1249-1254.

55. Johnson JT, Ferretti GA, Nethery WJ, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. N Engl J Med 1993;329:390-395.

56. Kaasa S, Bjordal K, Aaronson N, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. Eur J Cancer 1995;31A(13-14):2260-2263.

57. Rogers SN, Gwanne S, Lowe D, et al. The addition of mood and anxiety domains to the University of Washington quality of life scale. Head Neck 2002;24(6):521-529.

58. Ronis DL, Duffy SA, Fowler KE, et al. Changes in quality of life over 1 year in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2008; 134:241-8.

59. Terrell JE. Quality of life assessment in head and neck cancer patients. Hematol Oncol Clin N Am 1999;13(4):49-65.

60. Terrell JE, Nanavati KA, Esclamado RM, et al. Head and neck cancer-specific quality of life: Instrument validation. Arch Otolaryngol Head Neck Surg 1997;123:1125-1132.

61. Vartanian JG, Carvalho AL, Yueh B, et al. Brazilian-Portuguese validation of the University of Washington Quality of Life questionnaire for patients with head and neck cancer. Head Neck 2006;28(12):1115-1121.

62. Weymuller Jr EA, Alsarraf A, Yueh B, et al. Analysis of the performance characteristics of the University of Washington Quality of Life instrument and its modification (UW-QOL-R). Arch Otolaryngol Head Neck Surg 2001;127:489-493.

63. Beldi D, Jereczek-Fossa BA, D'Onofrio A, et al. Role of radiotherapy in the treatment of cervical lymph node metastases from an unknown primary site: retrospective analysis of 113 patients. Int J Radiat Oncol Biol Phys 2007;69(4):1051-1058.

64. Caudell JJ, Schaner PE, Meredith RF, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;73(2):410-415.

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

66. Chao KS, Majhail N, Huang CJ, et al. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol 2001;61(3):275-280.

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

68. Dirix P, Nuyts S, Geussens Y, et al. Malignancies of the nasal cavity and paranasal sinuses: long-term outcome with conventional or three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 2007;9(4):1042-1050.

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

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

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

72. Hsiung CY, Ting HM, Huang HY, et al. Parotid-sparing intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma: preserved parotid function after IMRT on quantitative salivary scintigraphy, and comparison with historical data after conventional radiotherapy. Int J Radiat Oncol Biol Phys 2006;66(2):454-461.

73. Jen YM, Shih R, Lin YS, et al. Parotid gland-sparing 3-dimensional conformal radiotherapy results in less severe dry mouth in nasopharyngeal cancer patients: a dosimetric and clinical comparison with conventional radiotherapy. Radiother Oncol 2005;75(2):204-209.

74. Kuhnt T, Jirsak N, Muller AC, et al. [Quantitative and qualitative investigations of salivary gland function in dependence on irradiation dose and volume for reduction of xerostomia in patients with head-and-neck cancer]. Strahlenther Onkol 2005;181(8):520-528.

75. Laskar S, Bahl G, Muckaden M, et al. Nasopharyngeal carcinoma in children: comparison of conventional and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2008;72(3):728-736.

76. Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;66(4):966-974.

77. Louise Kent M, Brennan MT, Noll JL, et al. Radiation-induced trismus in head and neck cancer patients. Supportive Care Cancer 2008;16(3):305-309.

78. Madani I, Vakaet L, Bonte K, et al. Intensity-modulated radiotherapy for cervical lymph node metastases from unknown primary cancer. Int J Radiat Oncol Biol Phys 2008;71(4):1158-1166.

79. Marchal C, Lapeyre M, Beckendorf V, et al. [Preliminary results of the assessment of intensity modulated radiotherapy (IMRT) for prostatic and head and neck tumors (STIC 2001)]. Cancer Radiother 2004;8 (Suppl 1):S121-S127.

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

81. Rades D, Fehlauer F, Wroblesky J, et al. Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol 2007;43(6):535-543.

82. Rades D, Stoehr M, Meyners T, et al. Evaluation of prognostic factors and two radiation techniques in patients treated with surgery followed by radio(chemo)therapy or definitive radio(chemo)therapy for locally advanced head-and-neck cancer. Strahlenther Onkol 2008;184(4):198-205.

83. Rusthoven KE, Raben D, Ballonoff A, et al. Effect of radiation techniques in treatment of oropharynx cancer. Laryngoscope 2008;118(4):635-639.

84. Sanguineti G, Adapala P, Endres EJ, et al. Dosimetric predictors of laryngeal edema. Int J Radiat Oncol Biol Phys 2007;68(3):741-749.

85. Wu H, Lin Q, Yu ZH, et al. [Late course conformal radiotherapy combined with chemotherapy for stage III and IV a nasopharyngeal carcinoma]. Zhonghua Yi Xue Za Zhi 2005;85(25):1778-1780.

86. Wu Y, Chen SB, Cai CQ. [Parotid dysfunction after various methods of radiotherapy for nasopharyngeal carcinoma]. Zhonghua Zhong Liu Za Zhi 2005;27(7):432-434.

87. Zouhair A, Azria D, Coucke P, et al. Decreased local control following radiation therapy alone in early-stage glottic carcinoma with anterior commissure extension. Strahlenther Onkol 2004;180(2):84-90.

88. Nutting C, A'Hern R, Rogers MS, et al. First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005, abstract and presentation). Proc Am Soc Clin Oncol 2009;27:302s.

89. Langendijk JA , Doornaert P, Rietveld DH, et al. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol 2009;90(2):189-195.

90. Murphy BA, Beaumont JL, Isitt J, et al. Mucositis-related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy. J Pain Symptom Manage 2009;38(4):522-532.

91. Amosson CM, Teh BS, Van TJ, et al. Dosimetric predictors of xerostomia for head-and-neck cancer patients treated with the smart (simultaneous modulated accelerated radiation therapy) boost technique. Int J Radiat Oncol Biol Phys 2003; 56(1):136-144.

92. Anand AK, Chaudhoory AR, Shukla A, et al. Favourable impact of intensity-modulated radiation therapy on chronic dysphagia in patients with head and neck cancer. Br J Radiol 2008;81(971):865-871.

93. Ben-David MA, Diamante M, Radawski JD, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. Int J Radiat Oncol Biol Phys 2007;68(2):396-402.

94. Biagioli MC, Harvey M, Roman E, et al. Intensity-modulated radiotherapy with concurrent chemotherapy for previously irradiated, recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69(4):1067-1073.

95. Braam PM, Terhaard CH, Roesink JM, et al. Intensity-modulated radiotherapy significantly reduces xerostomia compared with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2006;66(4):975-980.

96. Caglar HB, Tishler RB, Othus M, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2008;72(4):1110-1118.

97. Chao KS, Ozyigit G, Blanco AI, et al. Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. Int J Radiat Oncol Biol Phys 2004;59(1):43-50.

98. Daly ME, Chen AM, Bucci MK, et al. Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses. Int J Radiat Oncol Biol Phys 2007;67(1):151-157.

99. Dirix P, Nuyts S, Vanstraelen B, et al. Post-operative intensity-modulated radiotherapy for malignancies of the nasal cavity and paranasal sinuses. Radiother Oncol 2007;85(3):385-391.

100. Duthoy W, Boterberg T, Claus F, et al. Postoperative intensity-modulated radiotherapy in sinonasal carcinoma: clinical results in 39 patients. Cancer 2005;104(1):71-82.

101. Garden AS, Morrison WH, Wong PF, et al. Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2007;67(2):438-444.

102. Guerrero Urbano T, Clark CH, et al. A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. Radiother Oncol 2007;85(1):36-41.

103. Hoppe BS, Wolden SL, Zelefsky MJ, et al. Postoperative intensity-modulated radiation therapy for cancers of the paranasal sinuses, nasal cavity, and lacrimal glands: Technique, early outcomes, and toxicity. Head Neck 2008;30(7):925-932.

104. Kuppersmith RB, Greco SC, Teh BS, et al. Intensity-modulated radiotherapy: first results with this new technology on neoplasms of the head and neck. Ear Nose Throat J 1999;78(4):238, 241-246, 248 passim.

105. Kwong DL, Pow EH, Sham JS, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. Cancer 2004;101(7):1584-1593.

106. Kwong DL, Sham JS, Leung LH, et al. Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;64(2):374-381.

107. Lawson JD, Otto K, Chen A, et al. Concurrent platinum-based chemotherapy and simultaneous modulated accelerated radiation therapy for locally advanced squamous cell carcinoma of the tongue base. Head Neck 2008; 30(3):327-335.

108. Lee N, Chan K, Bekelman JE, et al. Salvage re-irradiation for recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 2007;68(3):731-740.

109. Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. Int J Radiat Oncol Biol Phys 2007;69(2):459-468.

110. Liu MT, Hsieh CY, Chang TH, et al. Prognostic factors affecting the outcome of nasopharyngeal carcinoma. Jpn J Clin Oncol 2003;33(10):501-508.

111. Lu TX, Mai WY, Teh BS, et al. Initial experience using intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2004;58(3):682-687.

112. Madani I, Duthoy W, Derie C, et al. Positron emission tomography-guided, focal-dose escalation using intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2007;68(1):126-135.

113. Meirovitz A, Murdoch-Kinch CA, Schipper M, et al. Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2006;66(2):445-453.

114. Munter MW, Thilmann C, Hof H, et al. Stereotactic intensity modulated radiation therapy and inverse treatment planning for tumors of the head and neck region: clinical implementation of the step and shoot approach and first clinical results. Radiother Oncol 2003;66(3):313-321.

115. Nishimura Y, Nakamatsu K, Shibata T, et al. Importance of the initial volume of parotid glands in xerostomia for patients with head and neck cancers treated with IMRT. Jpn J Clin Oncol 2005;35(7):375-379.

116. Rosenthal DI, Chambers MS, Fuller CD, et al. Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;72(3):747-755.

117. Saarilahti K, Kouri M, Collan J, et al. Sparing of the submandibular glands by intensity modulated radiotherapy in the treatment of head and neck cancer. Radiother Oncol 2006;78(3):270-275.

118. Sanguineti G, Gunn GB, Endres EJ, et al. Patterns of locoregional failure after exclusive IMRT for oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2008;72(3):737-746.

119. Schwartz M, Vuong T, Ballivy O, et al. Accelerated radiotherapy with simultaneous integrated boost fractionation and intensity-modulated radiotherapy for advanced head and neck cancer. Otolaryngol Head Neck Surg 2007;136(4):549-555.

120. Seung S, Bae J, Solhjem M, et al. Intensity-modulated radiotherapy for head-and-neck cancer in the community setting. Int J Radiat Oncol Biol Phys 2008;72(4):1075-1081.

121. Studer G, Graetz KW, Glanzmann C. Outcome in recurrent head neck cancer treated with salvage-IMRT. Radiat Oncol 2008;3(1):43.

122. Studer G, Lutolf UM, Davis JB, et al. IMRT in hypopharyngeal tumors. Strahlenther Onkol 2006;182(6):331-335.

123. Studer G, Lutolf UM, El-Bassiouni M et al. Volumetric staging (VS) is superior to TNM and AJCC staging in predicting outcome of head and neck cancer treated with IMRT. Acta Oncol 2007;46(3):386-394.

124. Studer G, Seifert B, Glanzmann C. Prediction of distant metastasis in head neck cancer patients: Implications for induction chemotherapy and pre-treatment staging? Strahlenther Onkol 2008;184(11):580-585.

125. Studer G, Studer SP, Zwahlen RA, et al. Osteoradionecrosis of the mandible: minimized risk profile following intensity-modulated radiation therapy (IMRT). Strahlenther Onkol 2006;182(5):283-288.

126. Teh BS, Mai WY, Grant 3rd WH, et al. Intensity modulated radiotherapy (IMRT) decreases treatment-related morbidity and potentially enhances tumor control. Cancer Invest 2002;20(4):437-451.

127. Thorstad WL, Chao KS, Haughey B. Toxicity and compliance of subcutaneous amifostine in patients undergoing postoperative intensity-modulated radiation therapy for head and neck cancer. Semin Oncol 2004; 31(6 Suppl 18):8-12.

128. Vosmik M, Kordac P, Paluska P, et al. IMRT using simultaneous integrated boost (66 Gy in 6 weeks) with and without concurrent chemotherapy in head and neck cancer: toxicity evaluation. Rep Pract Oncol Radiother 2008; 13(2):86-95.

129. Vosmik M, Odrazka K, Dolezel M, et al. IMRT with the use of simultaneous integrated boost in treatment of head and neck cancer: acute toxicity evaluation. Acta Medica (Hradec Kralove) 2006;49(3):167-173.

130. Wendt TG, Abbasi-Senger N, Salz H, et al. 3D-conformal-intensity modulated radiotherapy with compensators for head and neck cancer: clinical results of normal tissue sparing. Radiat Oncol 2006;1:18.

131. Wolden SL, Chen WC, Pfister DG, et al. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 2006;64(1):57-62.

132. Worden FP, Kumar B, Lee JS, et al. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. J Clin Oncol 2008;26(19):3138-3146.

133. Wu S, Xie C, Jin X, et al. Simultaneous modulated accelerated radiation therapy in the treatment of nasopharyngeal cancer: a local center's experience. Int J Radiat Oncol Biol Phys 2006;66(4 Suppl.):S40-S46.

134. Yao M, Chang K, Funk GF, et al. The failure patterns of oral cavity squamous cell carcinoma after intensity-modulated radiotherapy-the University of Iowa experience. Int J Radiat Oncol Biol Phys 2007a;67(5):1332-1341.

135. Yao M, Dornfeld KJ, Buatti JM, et al. Intensity-modulated radiation treatment for head-and-neck squamous cell carcinoma--the University of Iowa experience. Int J Radiat Oncol Biol Phys 2005;63(2):410-421.

136. Yao M, Hoffman HT, Chang K, et al. Is planned neck dissection necessary for head and neck cancer after intensity-modulated radiotherapy? Int J Radiat Oncol Biol Phys 2007b;68(3):707-713.

137. Yao M, Nguyen T, Buatti JM, et al. Changing failure patterns in oropharyngeal squamous cell carcinoma treated with intensity modulated radiotherapy and implications for future research. Am J Clin Oncol 2006;29(6):606-612.

138. Cheng SH, Tsai SY, Horng CF, et al. A prognostic scoring system for locoregional control in nasopharyngeal carcinoma following conformal radiotherapy. Int J Radiat Oncol Biol Phys 2006;66(4):992-1003.

139. Dijkema T, Terhaard CHJ, Roesink JM, et al. Large cohort dose-volume response analysis of parotid gland function after radiotherapy: intensity-modulated versus conventional radiotherapy. Int J Radiat Oncol Biol Phys 2008;72(4):1101-1109.

140. Ikushima I, Korogi Y, Ishii A, et al. Superselective intra-arterial infusion chemotherapy for stage III/IV squamous cell carcinomas of the oral cavity: midterm results. Eur J Radiol 2008;66(1):7-12.

141. Jian JJ, Cheng SH, Tsai SY, et al. Improvement of local control of T3 and T4 nasopharyngeal carcinoma by hyperfractionated radiotherapy and concomitant chemotherapy. Int J Radiat Oncol Biol Phys 2002;53(2):344-352.

142. Kovacs AF, Schiemann M, Turowski B. Combined modality treatment of oral and oropharyngeal cancer including neoadjuvant intraarterial cisplatin and radical surgery followed by concurrent radiation and chemotherapy with weekly docetaxel—three year results of a pilot study. J Craniomaxillofac Surg 2002;30(2):112-120.

143. Lau H, Brar S, Hao D, et al. Concomitant low-dose cisplatin and three-dimensional conformal radiotherapy for locally advanced squamous cell carcinoma of the head and neck: analysis of survival and toxicity. Head Neck 2006;28(3):189-196.

144. Levendag P, Braaksma M, Coche E, et al. Rotterdam and Brussels CT-based neck nodal delineation compared with the surgical levels as defined by the American Academy of Otolaryngology-Head and Neck Surgery. Int J Radiat Oncol Biol Phys 2004; 58(1):113-23.

145. Lu JJ, Shakespeare TP, Thiagarajan A, et al. Prospective phase II trial of concomitant boost radiotherapy for stage II nasopharyngeal carcinoma: an evaluation of response and toxicity. Laryngoscope 2005;115(5):806-810.

146. Ozsahin M, Betz M, Matzinger O, et al. Feasibility and efficacy of subcutaneous amifostine therapy in patients with head and neck cancer treated with curative accelerated concomitant-boost radiation therapy. Arch Otolaryngol Head Neck Surg 2006;132(2):141-145.

147. Padovani L, Pommier P, Clippe SS, et al. Three-dimensional conformal radiotherapy for paranasal sinus carcinoma: clinical results for 25 patients. Int J Radiat Oncol Biol Phys 2003;56(1):169-176.

148. Pan CC, Eisbruch A, Lee JS, et al. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 2005;61(5):1393-1402.

149. Pfreundner L, Hoppe F, Willner J, et al. Induction chemotherapy with paclitaxel and cisplatin and CT-based 3D radiotherapy in patients with advanced laryngeal and hypopharyngeal carcinomas—a possibility for organ preservation. Radiother Oncol 2003;68(2):163-170.

150. Pommier P, Ginestet C, Sunyach M, et al. Conformal radiotherapy for paranasal sinus and nasal cavity tumors: three-dimensional treatment planning and preliminary results in 40 patients. Int J Radiat Oncol Biol Phys 2000;48(2):485-493.

151. Portaluri M, Fucilli FI, Castagna R, et al. Three-dimensional conformal radiotherapy for locally advanced (Stage II and worse) head-and-neck cancer: dosimetric and clinical evaluation. Int J Radiat Oncol Biol Phys 2006;66(4):1036-1043.

152. Scorsetti M, Cerreta V, Mattana F, et al. Stereotactic and conformal radiotherapy (STRT and CFRT) as rescue treatment of relapsing head and neck carcinomas. Tumori 2001;87(4 Suppl 1):S67-S68.

153. Sze WM, Lee AW, Yau TK, et al. Primary tumor volume of nasopharyngeal carcinoma: prognostic significance for local control. Int J Radiat Oncol Biol Phys 2004;59(1):21-27.

154. Zheng XK, Ma J, Chen LH, et al. Dosimetric and clinical results of three-dimensional conformal radiotherapy for locally recurrent nasopharyngeal carcinoma. Radiother Oncol 2005;75(2):197-203.

155. Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. Int J Radiat Oncol Biol Phys 2005;62(2):494-500.

156. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 [Draft posted Oct. 2007]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf. Accessed December 2009.

157. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. J Clin Oncol 2006;24(17):2618-2623.

158. Gregoire V, De Neve W, Eisbruch A, et al. Intensity-modulated radiation therapy for head and neck carcinoma. Oncologist 2007;12(5):555-564.

159. Das IJ, Cheng CW, Chopra KL, et al. Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems. J Natl Cancer Inst 2008;100(5):300-307.

160. Davies AN, Broadley K, Beighton D. Salivary gland hypofunction in patients with advanced cancer. Oral Oncol 2002;38(7):680-685.

161. Randall ME, Ibbott GS. Intensity-modulated radiation therapy for gynecologic cancers: pitfalls, hazards, and cautions to be considered. Semin Radiat Oncol 2006;16(3):138-143.

162. Willins J, Kachnic L. Clinically relevant standards for intensity-modulated radiation therapy dose prescription. J Natl Cancer Inst 2008;100(5):288-290.

163. Pocock SJ, Assmann SE, Enos LE, et al. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: Current practice and problems. Statist Med 2002;21:2917-2930.

164. Moher D, Schulz KF, Altman D. The CONSORT Statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285(15):1987-1991.

165. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS March 31, 2003. Available at: http://ctep.cancer.gov. Publish Date: August 9, 2006.

Abbreviations

Δ	change
~	approximately
1^{o}	primary
2.5D	2 ½ D RT
2D	two-dimensional
2DRT	2D conventional RT
3D	three dimensional
3DC	3D conformal RT
3DCRT	3D conformal radiotherapy
ACC	accelerated fractionation
AdjCtx	adjuvant chemoradiotherapy
AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society of Clinical Oncology
ASTRO	American Society of Therapeutic Radiation Oncology
AUD	auditory acuity
BON	bone
BOT	base of tongue
BRA	brachytherapy
BRN	brain AEs
BST	boost dose
CCRTx	concurrent chemoradiotherapy
CER	comparative effectiveness review
CHT	chemotherapy only
CNT	central nervous system tumor (including spine)
CRN	cranial nerve tumors
CRT	chemoradiotherapy
CT	computed tomography
CTP	cytoprotective agent
CTV	clinical target volume
CUT	cutaneous tumors (melanoma, etc.)
def	definitive
DFR	definitive RT
DFS	disease-free survival
DNT	dental AEs
DS?	disease unclear
DSS	(cancer) disease-specific survival
DYS	dysphagia
Dx	diagnosis
EAR	ear tumors
EORTC	European Organization for Research and Treatment of Cancer
EPC	Evidence-based Practice Center
EPICOT	Evidence, Population, Intervention, Comparators, Outcome, Time stamp
ESO	esophagus AEs
EST	esophageal or precursors
ETH	ethmoid sinus
EYE	eye tumors
F/U	followup
F/U?	followup uncertain
freq	frequency
Gr	grade
grnd	ground
GTV	gross tumor volume
Gy	Gray
Hb	hemoglobin
HEM	hematologic tumor (including lymphoma
HN	head and neck
HNCI	Head and Neck Cancer Inventory
HNQOL	Head and Neck Cancer-Specific Quality of Life
HNU	head & neck unspecified
HPV	human papillomavirus
HRT	heart AEs
HYF	hyperfractionation
HYP	hypopharyngeal
ICBT	intracavitary brachytherapy
IMM	with immobilization
IMR	IMRT
IMRT	intensity modulated radiotherapy
ITT	intention to treat
LAR	laryngeal
LC	local control
LDH	lactate dehydrogenase
LFF	local failure free
LFFR	local freedom from recurrence
LN	lymph node
LNG	lung AEs
LR	locoregional
LRC	locoregional control
LRPFS	locoregional progression-free survival
LRRFS	locoregional recurrence-free survival
LX	larynx AEs
MAX	maxillary sinus
MET	metastatic
mets	metastases
MFS	(distant) metastasis-free survival
MIX	mixed head and neck

MLT	major late toxicities
mod	moderate
mo(s).	month(s)
MUC	mucous membrane AEs
MVA	multivariable analysis
NA	not applicable
NBT	neutron beam therapy
NCCN	National Comprehensive Cancer Network
NCI CTC	National Cancer Institute's Common Toxicity Criteria
NeoadjCtx	neoadjuvant chemoradiotherapy
NPC	nasopharyngeal cancer
NPH	nasopharyngeal
NR	not reported
NRD	not relevant disease
NRO	not relevant outcome (or no follow-up)
NRT	not relevant treatment
NS	not significant
NV	nausea/vomiting
O?	outcome unclear
OAE	other AE
OCL	oral cavity/lip
OCU	ocular AEs
OHN	other head and neck tumor
OLF	olfactory AEs
OPH	oropharyngeal
ORN	osteoradionecrosis
OS	overall survival
OST	other non-head and neck solid tumor
OTE	other time-to-event outcome
OTO	otologic/auditory AEs
PAL	palliative
PAR	paraganglioma
PBT	proton beam therapy
PCR	postoperative CRT
pctg	percentage
PDQ	Physician Data Query
PFS	progression-free survival
PHR	pharyngeal
PHX	pharynx
PNS	paranasal sinus/nasal cavity
postop	postoperative
postopRT	postoperative radiotherapy
postRT	after radiotherapy
PRE	preoperative (neoadjuvant)
preop	preoperative
preopRT	preoperative radiotherapy
preRT	before radiotherapy
Pro	prospective
prob(s)	probability(ies)
PS	performance status
PST	postoperative (adjuvant)
PTH	parathyroid
PTV	planning target volume
Q#?	unclear if relevant to any key question
QLQ	Quality of Life Questionnaire
QOL	quality of life
RCT	randomized, controlled trial
REC	recurrent (reirradiation)
ReRT	reirradiation
Retro	retrospective
RSE	radiosensitizing agent
RSP	tumor response
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SAL	salivary gland, including parotid
SB	skull base tumors
SCC	small cell cancer
sev	severity
SF-36	Short Form-36
SIN	sinus unspecified
SKN	skin AEs
SLF	salivary flow
SOMA	Subjective, Objective, Management, Analytic
SPN	spinal cord AEs
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
SUB	subcutaneous tissue AEs
SUR	surgery only
Sx	symptoms
T?	treatment unclear
TAE	toxicity/adverse events (not specified)
TEP	Technical Expert Panel
THY	thyroid
TR	tracheal tumors
TRD	treatment-related death
TTR	time-to-recurrence
Tx	treatment
UA	univariate analysis
UCF	unspecified conformal RT
UNP	unknown/occult primary
URT	unspecified radiotherapy
USPSTF	U.S. Preventive Services Task Force
UWQOL	University of Washington Quality of Life
VAS	visual analog scale
VSA	visual acuity
XQ	xerostomia questionnaire
XST	xerostomia
yr(s)	years

Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer

Appendixes

Appendix A: Exact Search Strings

- MEDLINE® (January 1, 1990, through September 28, 2009)
- EMBASE® (January 1, 1990, through September 28, 2009)
- Cochrane Controlled Trials Register (no date restriction)

Single-arm studies, which are not a main focus of this review, were selected from studies identified through the January 13, 2009 search result update. Comparative studies were identified through the latest search updates.

In addition to electronic databases, abstracts for the past 5 years of meetings of the American Society of Therapeutic Radiation Oncology (ASTRO) and American Society of Clinical Oncology (ASCO) were searched.

Database Search Strategy:

(head and neck neoplasms [MH] OR ((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])

AND

(neoplasm [TIAB] 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])

OR

"occult primary" [TIAB] OR "unknown primary" [TIAB]

AND

(radiotherapy, conformal [MH] 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 protons [MH]))

AND

humans [MH]

Appendix B: Excluded Studies

Full Review Codes

Key Question Codes

NRQ	not relevant question (note if ANM, NDE, NRD, NRO, NRT)
Q#?	unclear if relevant to any key question

Study Design Codes

ADB	administrative database
ANM	animal study
CEA	cost/cost-effectiveness analysis
CCS	case-control study
COH	cohort study
COM	commentary
CR	case report (n≤5)
CS	case series
D?	design unclear/possibly relevant
DAC	diagnostic accuracy study
DPC	dose planning study, comparative
DPN	dose planning study, noncomparative
EDT	editorial
GUI	guideline
INV	in vitro
LTR	letter
MA	meta-analysis
NAB	no abstract
NDE	not relevant design
NPD	no primary data
NRA	narrative review article
PI	phase I trial
PII	phase II trial
PHY	physics study
PHN	phantom study
POS	patient positioning study
PRG	prognostic study
PRO	prospective single-arm study
QEX	quasi-experimental study (nonrandomized comparative)
RAD	radiology/imaging study
RCT	randomized controlled trial
REG	registry
RET	retrospective study
SR	systematic review
STG	disease staging study
XSL	cross-sectional study

Sample Size Code (single-arm only)

FEW	n < 10
N10	10 ≤ n < 25
N25	25 ≤ n < 50
N50	50 ≤ n < 100
N100	n ≥ 100
N?	n unclear

Disease Codes

CNT	central nervous system tumor (including spine)
CRN	cranial nerve tumors
CUT	cutaneous tumors (melanoma, etc.)
DS?	disease unclear
EAR	ear tumors
EST	esophageal or precursors
ETH	ethmoid sinus
EYE	eye tumors
HEM	hematologic tumor (including lymphoma
HNU	head & neck unspecified
HYP	hypopharyngeal
LAR	laryngeal
MAX	maxillary sinus
MIX	mixed head and neck
NRD	not relevant disease
NPH	nasopharyngeal
OCL	oral cavity/lip
OHN	other head and neck tumor
OPH	oropharyngeal
OST	other non-head and neck solid tumor
PAR	paraganglioma
PHR	pharyngeal
PNS	paranasal sinus/nasal cavity
PTH	parathyroid
SAL	salivary gland, including parotid
SB	skull base tumors
SIN	sinus unspecified
THY	thyroid
TR	tracheal tumors
UNP	unknown/occult primary

Intervention Codes

3DC	3D conformal RT
2.5D	2 ½ D RT
2DR	2D conventional RT
ACC	accelerated fractionation
BST	boost dose
BRA	brachytherapy
CHT	chemotherapy only
CRT	chemoradiotherapy
CTP	cytoprotective agent
DFR	definitive RT
HYF	hyperfractionation
IMR	IMRT
IMM	with immobilization
MET	metastatic
NBT	neutron beam therapy
NRT	not relevant treatment
PAL	palliative
PBT	proton beam therapy
PCR	postoperative CRT
PST	postoperative (adjuvant)
PRE	preoperative (neoadjuvant)
REC	recurrent (reirradiation)
RSE	radiosensitizing agent
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
SUR	surgery only
T?	treatment unclear
UCF	unspecified conformal RT
URT	unspecified radiotherapy

[No author]. RTOG 0522: a randomized phase III trial of concurrent accelerated radiation and cisplatin versus concurrent accelerated radiation, cisplatin, and cetuximab [followed by surgery for selected patients] for Stage III and IV head and neck carcinomas. Clin Adv Hematol Oncol 2007;5(2):79-81.
Rec #: 1840
Reprint: EXC NPD

[No author]. AstraZeneca. Formulary 1999;34(10 SUPPL):13-18.
Rec #: 27340
Reprint: EXC NRD

Aarstad AK, Aarstad HJ, Bru E, et al. Psychological coping style versus disease extent, tumour treatment and quality of life in successfully treated head and neck squamous cell carcinoma patients. Clin Otolaryngol 2005;30(6):530-538.
Rec #: 3920
Reprint: EXC URT, MIXED

Abayomi OK. Pathogenesis of cognitive decline following therapeutic irradiation for head and neck tumors. Acta Oncol 2002;41(4):346-351.
Rec #: 8970
Reprint: EXC NRA

Al-Nawas B, Al-Nawas K, Kunkel M, et al. Quantifying radioxerostomia: salivary flow rate, examiner's score, and quality of life questionnaire. Strahlenther Onkol 2006;182(6):336-341.
Rec #: 3330
Reprint: EXC T? URT

Allen AM, Tishler RB. Commentary: IMRT for head and neck cancer: many chapters left to write. Oncologist 2007;12(5):565-568.
Rec #: 1460
Reprint: EXC COM

Amosson CM, Teh BS, Mai WY, et al. Using technology to decrease xerostomia for head and neck cancer patients treated with radiation therapy. Semin Oncol 2002;29(6 Suppl 19):71-79.
Rec #: 8600
Reprint: EXC DPN

Anand AK, Jain J, Negi PS, et al. Can dose reduction to one parotid gland prevent xerostomia?--A feasibility study for locally advanced head and neck cancer patients treated with intensity-modulated radiotherapy. Clin Oncol (R Coll Radiol) 2006;18(6):497-504.
Rec #: 2880
Reprint: EXC N10

Ang KK. Altered fractionation trials in head and neck cancer. Semin Radiat Oncol 1998;8(4):230-236.
Rec #: 36730
Reprint: EXC MA

Ask A, Bjork-Eriksson T, Zackrisson B, et al. The potential of proton beam radiation therapy in head and neck cancer. Acta Oncol 2005;44(8):876-880.
Rec #: 4110
Reprint: EXC NRA

Astreinidou E, Dehnad H, Terhaard CH, et al. Level II lymph nodes and radiation-induced xerostomia. Int J Radiat Oncol Biol Phys 2004;58(1):124-131.
Rec #: 7560
Reprint: EXC N10

Back M, Oliver L, Bromley R, et al. Multicentre quality assurance of intensity-modulated radiotherapy planning: beware the benchmarker. J Med Imaging Radiat Oncol 2008;52(2):197.
Rec #: 28870
Reprint: EXC NRQ

Baker SR, Pankhurst CL, Robinson PG. Testing relationships between clinical and non-clinical variables in xerostomia: a structural equation model of oral health-related quality of life. Qual Life Res 2007;16(2):297-308.
Rec #: 37460
Reprint: EXC NRQ

Bangalore M, Matthews S, Suntharalingam M. Recent advances in radiation therapy for head and neck cancer. ORL J Otorhinolaryngol Relat Spec 2007;69(1):1-12.
Rec #: 2490
Reprint: EXC NRA

Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. J Clin Oncol 2007;25(26):4096-4103.
Rec #: 37680
Reprint: EXC NRA

Bentzen SM, Wasserman TH. Balancing on a knife's edge: evidence-based medicine and the marketing of health technology. Int J Radiat Oncol Biol Phys 2008;72(1):12-14.
Rec #: 39250
Reprint: EXC COM

Bhatnagar A, Deutsch M. The Role for intensity modulated radiation therapy (IMRT) in pediatric population. Technol Cancer Res Treat 2006;(6):591-595.
Rec #: 2410
Reprint: EXC N10, NRD

Blanco AI, Chao C. Management of radiation-induced head and neck injury. Cancer Treat Res 2006;128:23-41.
Rec #: 4080
Reprint: EXC NRA

Blanco AI, Chao KS, El Naqa I, et al. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. Int J Radiat Oncol Biol Phys 2005;62(4):1055-1069.
Rec #: 4970
Reprint: EXC NRT, MIXED

Bourhis J, Guigay J, Temam S, et al. Chemo-radiotherapy in head and neck cancer. Ann Oncol 2006;17(SUPPL. 10):x39-x41.
Rec #: 17030
Reprint: EXC NRA

Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368(9538):843-854.
Rec #: 30800
Reprint: EXC MA

Braaksma M, Levendag P. Tools for optimal tissue sparing in concomitant chemoradiation of advanced head and neck cancer: subcutaneous amifostine and computed tomography-based target delineation. Semin Oncol 2002;29(6 Suppl 19):63-70.
Rec #: 8610
Reprint: EXC NRT, MIXED

Braam PM, Roesink JM, Raaijmakers CP, et al. Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy. Radiat Oncol 2007;2:3.
Rec #: 37610
Reprint: EXC 2DR CS

Brada M, Pijls-Johannesma M, De Ruysscher D. Proton therapy in clinical practice: current clinical evidence. J Clin Oncol 2007;25(8):965-970.
Rec #: 1830
Reprint: EXC NRA

Brizel DM. Radiotherapy and concurrent chemotherapy for the treatment of locally advanced head and neck squamous cell carcinoma. Semin Radiat Oncol 1998;8(4):237-246.
Rec #: 37470
Reprint: EXC MA

Budach W, Hehr T, Budach V, et al. A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer 2006;6:28.
Rec #: 37480
Reprint: EXC MA

Bussels B, Maes A, Flamen P, et al. Dose-response relationships within the parotid gland after radiotherapy for head and neck cancer. Radiother Oncol 2004;73(3):297-306.
Rec #: 6110
Reprint: EXC N10

Bussels B, Maes A, Hermans R, et al. Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer. Radiother Oncol 2004;72(2):119-127.
Rec #: 6620
Reprint: EXC NRT, MIXED

Butler EB, Teh BS, Grant 3rd WH, et al. Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 1999;45(1):21-32.
Rec #: 11480
Reprint: EXC N10 IMR

Caglar HB, Allen AM. Intensity-modulated radiotherapy for head and neck cancer. Clin Adv Hematol Oncol 2007;5(6):425-431.
Rec #: 15090
Reprint: EXC NRA

Calais G, Le Floch O. [Concomitant radiotherapy and chemotherapy in the treatment of cancers of the upper respiratory and digestive tracts]. Bull Cancer Radiother 1996;83(4):321-329.
Rec #: 37490
Reprint: EXC MA

Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;70(3):660-665.
Rec #: 350
Reprint: EXC CS

Castro JR, Linstadt DE, Bahary J-P, et al. Experience in charged particle irradiation of tumors of the skull base: 1977-1992. Int J Radiat Oncol Biol Phys 1994;29(4):647-655.
Rec #: 28540
Reprint: EXC NRD NRT

Cattaneo GM, Ceresoli GL. Optimisation of conformal radiotherapy for lung and nasopharynx cancers: Literature review and clinical experience at HS Raffaele Phys Med 2001;17(SUPPL 2):93-102.
Rec #: 26310
Reprint: EXC NRA

Chambers MS, Garden AS, Kies MS, et al. Radiation-induced xerostomia in patients with head and neck cancer: pathogenesis, impact on quality of life, and management. Head Neck 2004;26(9):796-807.
Rec #: 6470
Reprint: EXC NRA

Chambers MS, Garden AS, Rosenthal D, et al. Intensity-modulated radiotherapy: is xerostomia still prevalent? Curr Oncol Rep 2005;7(2):131-136.
Rec #: 5780
Reprint: EXC NRA

Chambers MS, Rosenthal DI, Weber RS. Radiation-induced xerostomia. Head Neck 2007;29(1):58-63.
Rec #: 2900
Reprint: EXC NRA

Chambers MS, Weber RS, Garden AS. Intensity-modulated radiation therapy and xerostomia. J Calif Dent Assoc 2006;34(9):743-748.
Rec #: 2640
Reprint: EXC NRA

Chan ATC. Head and neck cancer: Treatment of nasopharyngeal cancer. Ann Oncol 2005;16(SUPPL 2):ii265-ii268.
Rec #: 20040
Reprint: EXC NRA

Chang JT, See LC, Liao CT, et al. Locally recurrent nasopharyngeal carcinoma. Radiother Oncol 2000;54(2):135-142.
Rec #: 11090
Reprint: EXC T?

Chao KS. Protection of salivary function by intensity-modulated radiation therapy in patients with head and neck cancer. Semin Radiat Oncol 2002;2(1 Suppl 1):20-25.
Rec #: 9670
Reprint: EXC NRA

Chao KS, Bhide S, Chen H, et al. Reduce in variation and improve efficiency of target volume delineation by a computer-assisted system using a deformable image registration approach. Int J Radiat Oncol Biol Phys 2007;68(5):1512-1521.
Rec #: 1190
Reprint: EXC DPN

Chao KS, Low DA, Perez CA, et al. Intensity-modulated radiation therapy in head and neck cancers: The Mallinckrodt experience. Int J Cancer 2000;90(2):92-103.
Rec #: 11010
Reprint: EXC N10 IMR

Chao KS, Ozyigit G, Tran BN, et al. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2003;55(2):312-321.
Rec #: 8720
Reprint: EXC NRT, MIXED

Chao KS, Wippold FJ, Ozyigit G, et al. Determination and delineation of nodal target volumes for head-and-neck cancer based on patterns of failure in patients receiving definitive and postoperative IMRT. Int J Radiat Oncol Biol Phys 2002;53(5):1174-1184.
Rec #: 9140
Reprint: EXC DPN NRO

Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 2006;106(4):820-829.
Rec #: 3870
Reprint: EXC N10 NRO

Chen YJ, Kuo JV, Ramsinghani NS, et al. Intensity-modulated radiotherapy for previously irradiated, recurrent head-and-neck cancer. Med Dosim 2002;27(2):171-176.
Rec #: 9320
Reprint: EXC N10 IMR

Chua DT, Ma J, Sham JS, et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. J Clin Oncol 2005;23(6):1118-1124.
Rec #: 37500
Reprint: EXC 2DR MA

Chua DT, Sham JS, Au GK. Induction chemotherapy with cisplatin and gemcitabine followed by reirradiation for locally recurrent nasopharyngeal carcinoma. Am J Clin Oncol 2005;28(5):464-471.
Rec #: 4460
Reprint: EXC N10 NRT, MIXED

Chua DT, Sham JS, Leung LH, et al. Re-irradiation of nasopharyngeal carcinoma with intensity-modulated radiotherapy. Radiother Oncol 2005;77(3):290-294.
Rec #: 4190
Reprint: EXC NRT, MIXED

Chua DTT, Tian Y, Wei WI. Late oral complications following radiotherapy for head and neck cancers. Expert Rev Anticancer Ther 2007; 7(9):1215-1224.
Rec #: 14540

Claus F, Duthoy W, Boterberg T, et al. Intensity modulated radiation therapy for oropharyngeal and oral cavity tumors: clinical use and experience. Oral Oncol 2002;38(6):597-604.
Rec #: 9050
Reprint: EXC N10 IMR

Cohen SM, Garrett CG, Dupont WD, et al. Voice-related quality of life in T1 glottic cancer: irradiation versus endoscopic excision. Ann Otol Rhinol Laryngol 2006;115(8):581-586.
Rec #: 37510
Reprint: EXC NDE NRT

Combs SE, Behnisch W, Kulozik AE, et al. Intensity Modulated Radiotherapy (IMRT) and Fractionated Stereotactic Radiotherapy (FSRT) for children with head-and-neck-rhabdomyosarcoma. BMC Cancer 2007;7:177.
Rec #: 880
Reprint: EXC NRD

Corry J, Hornby C, Fisher R, et al. 'Boomerang' technique: an improved method for conformal treatment of locally advanced nasopharyngeal cancer. Australas Radiol 2004;48(2):170-180.
Rec #: 6730
Reprint: EXC N10 IMR

Corvo R. Evidence-based radiation oncology in head and neck squamous cell carcinoma. Radiother Oncol 2007;85(1):156-70.
Rec #: 1510
Reprint: EXC SR

Cox JD, Fu KK, Pajak TF, et al. Radiation Therapy Oncology Group (RTOG) trials for head and neck cancer. Rays 2000;25(3):321-323.
Rec #: 35850
Reprint: EXC NRA

Das IJ, Cheng CW, Chopra KL, et al. Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems. J Natl Cancer Inst 2008;100(5):300-307.
Rec #: 70
Reprint: EXC DPN

Davies AN, Broadley K, Beighton D. Salivary gland hypofunction in patients with advanced cancer. Oral Oncol. 2002;38(7):680-685.
Rec #: 25250
Reprint: EXC T?

Davies AN, Broadley K, Beighton D. Xerostomia in patients with advanced cancer. J Pain Symptom Manage 2001;22(4):820-825.
Rec #: 26240
Reprint: EXC T? NRD

Dawson LA, Anzai Y, Marsh L, et al. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2000;46(5):1117-1126.
Rec #: 11050
Reprint: EXC T?, MIXED

Dawson LA, Myers LL, Bradford CR, et al. Conformal re-irradiation of recurrent and new primary head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50(2):377-385.
Rec #: 10320
Reprint: EXC NRT, MIXED

de Arruda FF, Puri DR, Zhung J, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 2006;64(2):363-373.
Rec #: 5150
Reprint: EXC NRT, MIXED

de Castro Jr G, Federico MH. Evaluation, prevention and management of radiotherapy-induced xerostomia in head and neck cancer patients. Curr Opin Oncol 2006;18(3):266-270.
Rec #: 3620
Reprint: EXC NRA

DeLaney TF. Clinical proton radiation therapy research at the Francis H. Burr Proton Therapy Center Technol Cancer Res Treat 2007;6(4 Suppl):61-66.
Rec #: 1020
Reprint: EXC NRA

Ding Y, Wu DH, Chen LH. [Value of 18F-fluorodeoxyglucose positron emission tomography in three-dimensional conformal radiotherapy for locally persistent or recurrent nasopharyngeal carcinoma]. Di Yi Jun Yi Da Xue Xue Bao 2005;25(12):1568-1570.
Rec #: 4000
Reprint: EXC FLA CS

Dinshaw KA, Agarwal JP, Ghosh-Laskar S, et al. Radical radiotherapy in head and neck squamous cell carcinoma: an analysis of prognostic and therapeutic factors. Clin Oncol (R Coll Radiol) 2006;18(5):383-389.
Rec #: 3110
Reprint: EXC NRT, MIXED

Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. Cancer 2006;107(11):2525-2534.
Rec #: 2510
Reprint: EXC NRA

Douglas JG, Einck J, Austin-Seymour M, et al. Neutron radiotherapy for recurrent pleomorphic adenomas of major salivary glands. Head Neck 2001;23(12):1037-1042.
Rec #: 9860
Reprint: EXC NRT

Dulguerov P, Jacobsen MS, Allal AS, et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. Cancer 2001;92(12):3012-3029.
Rec #: 37520
Reprint: EXC 2DR CS

Eisbruch A. Reducing xerostomia by IMRT: what may, and may not, be achieved. J Clin Oncol 2007;25(31):4863-4864.
Rec #: 540
Reprint: EXC COM

Eisbruch A. Intensity-modulated radiation therapy in the treatment of head and neck cancer. Nat Clin Pract Oncol 2005;2(1):34-39.
Rec #: 4300
Reprint: EXC NRA

Eisbruch A, Kim HM, Terrell JE, et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50(3):695-704.
Rec #: 10300
Reprint: EXC T?, MIXED

Eisbruch A, Levendag PC, Feng FY, et al. Can IMRT or brachytherapy reduce dysphagia associated with chemoradiotherapy of head and neck cancer? The Michigan and Rotterdam experiences. Int J Radiat Oncol Biol Phys 2007;69(2 Suppl):S40-S42.
Rec #: 630
Reprint: EXC NRT

Eisbruch A, Marsh LH, Dawson LA, et al. Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol Biol Phys 2004; 59(1):28-42.
Rec #: 7100
Reprint: EXC NRT, MIXED

Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 2004;60(5):1425-1439.
Rec #: 6070
Reprint: EXC NRO DPN

Eisbruch A, Ship JA, Dawson LA, et al. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. World J Surg 2003;27(7):832-837.
Rec #: 7920
Reprint: EXC N10 IMR 3DC

Eisbruch A, Ship JA, Martel MK, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. Int J Radiat Oncol Biol Phys 1996;36(2):469-480.
Rec #: 12230
Reprint: EXC N10 3DC

Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45(3):577-587.
Rec #: 11400
Reprint: EXC T?, MIXED

Eisbruch A, Terrell JE, Logemann JA, et al. Letters to the Editor (multiple letters). Head Neck 2003;25(12):1082-1083.
Rec #: 24760
Reprint: EXC LTR

Ernst-Stecken A, Grabenbauer G, Iro H, et al. Phase II trial of hyperfractionated accelerated split-course radiochemotherapy with 5-FU and Cis-DDP in advanced head and neck cancer: results and toxicity. Strahlenther Onkol 2004;80(12):805-810.
Rec #: 6030
Reprint: EXC NRT 2DR CS

Feng J, Coppes RP. Can we rescue salivary gland function after irradiation? TheScientificWorld Journal 2008;8(-):959-962.
Rec #: 38890
Reprint: EXC COM

Feng M, Eisbruch A. Future issues in highly conformal radiotherapy for head and neck cancer. J Clin Oncol 2007;25(8):1009-1013.
Rec #: 1820
Reprint: EXC NRA

Feng M, Jabbari S, Lin A, et al . Predictive factors of local-regional recurrences following parotid sparing intensity modulated or 3D conformal radiotherapy for head and neck cancer. Radiother Oncol 2005;77(1):32-38.
Rec #: 4680
Reprint: EXC NRT, MIXED

Fischer M, Pottgen C, Wechsler S, et al. [Accelerated hyperfractionated radiotherapy with concurrent chemotherapy in locally advanced nasopharyngeal carcinomas]. HNO 2007;55(12):950-955.
Rec #: 1810
Reprint: EXC FLA, CS

Fitzek MM, Thornton AF, Varvares M, et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. Cancer 2002; 94(10):2623-2634.
Rec #: 9040
Reprint: EXC NRT, MIXED

Foote RL. Radiotherapy Alone for Early-Stage Squamous Cell Carcinoma of the Larynx and Hypopharynx. Int J Radiat Oncol Biol Phys 2007;69(2 SUPPL):S31-S36.
Rec #: 14900
Reprint: EXC GUI NRA

Fu KK. Combined radiotherapy and chemotherapy for nasopharyngeal carcinoma. Semin Radiat Oncol 1998;8(4):247-253.
Rec #: 37530
Reprint: EXC MA

Fua TF, Corry J, Milner AD, et al. Intensity-modulated radiotherapy for nasopharyngeal carcinoma: clinical correlation of dose to the pharyngo-esophageal axis and dysphagia. Int J Radiat Oncol Biol Phys 2007;67(4):976-981.
Rec #: 2070
Reprint: EXC N10

Garden AS, Lewin JS, Chambers MS. How to reduce radiation-related toxicity in patients with cancer of the head and neck. Curr Oncol Rep 2006;8(2):140-145.
Rec #: 3740
Reprint: EXC NRA

Goitein M, Cox JD. Should randomized clinical trials be required for proton radiotherapy? J Clin Oncol 2008;26(2):175-176.
Rec #: 250
Reprint: EXC COM

Graff P, Lapeyre M, Desandes E, et al. Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: matched-pair comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2007;67(5):1309-1317.
Rec #: 1960
Reprint: EXC NRT, MIXED

Gregoire V, De Neve W, Eisbruch A, et al. Intensity-modulated radiation therapy for head and neck carcinoma. Oncologist 2007;12(5):555-564.
Rec #: 1470
Reprint: EXC NRA

Guerrero Urbano MT, Nutting CM. Clinical use of intensity-modulated radiotherapy: part I. Br J Radiol 2004;77(914):88-96.
Rec #: 7300
Reprint: EXC NRA

Guerrero Urbano MT, Nutting CM. Clinical use of intensity-modulated radiotherapy: part II. Br J Radiol 2004;77(915):177-182.
Rec #: 37620
Reprint: EXC NRA

Harari PM. Promising new advances in head and neck radiotherapy. Ann Oncol 2005;16 Suppl 6:vi13-vi19.
Rec #: 4980
Reprint: EXC NRA

Herrmann F, Dorr W, Muller R, et al. A prospective study on radiation-induced changes in hearing function. Int J Radiat Oncol Biol Phys 2006;65(5):1338-1344.
Rec #: 3040
Reprint: EXC NRO

Hoppe BS, Nelson CJ, Gomez DR, et al. Unresectable Carcinoma of the Paranasal Sinuses: Outcomes and Toxicities. Int J Radiat Oncol Biol Phys 2008;72(3):763-769.
Rec #: 39040
Reprint: EXC T?

Hoppe BS, Stegman LD, Zelefsky MJ, et al. Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting--the MSKCC experience. Int J Radiat Oncol Biol Phys 2007;67(3):691-702.
Rec #: 2240
Reprint: EXC T? 2DR 3DC IMR

Huang K, Xia P, Chuang C, et al. Intensity-modulated chemoradiation for treatment of stage III and IV oropharyngeal carcinoma: The University of California-San Francisco experience. Cancer 2008;113(3):497-507.
Rec #: 39270
Reprint: EXC NRT, MIXED

Hutcheson KA, Barringer DA, Rosenthal DI, et al. Swallowing outcomes after radiotherapy for laryngeal carcinoma. Arch Otolaryngol Head Neck Surg 2008;134(2):178-183.
Rec #: 37810
Reprint: EXC T?

Ishii A, Korogi Y, Hirai T, et al. Intraarterial infusion chemotherapy and conformal radiotherapy for cancer of the mouth: prediction of the histological response to therapy with magnetic resonance imaging. Acta Radiol 2007;48(8):900-906.
Rec #: 680
Reprint: EXC T?

Jensen K. Measuring side effects after radiotherapy for pharynx cancer. Acta Oncol 2007;46(8):1051-1063.
Rec #: 780
Reprint: EXC NRA

Jensen K, Lambertsen K, Torkov P, et al. Patient assessed symptoms are poor predictors of objective findings. Results from a cross sectional study in patients treated with radiotherapy for pharyngeal cancer. Acta Oncol 2007;46(8):1159-1168.
Rec #: 890
Reprint: EXC URT

Jereczek-Fossa BA, Garibaldi C, Catalano G, et al. Analysis of mandibular dose distribution in radiotherapy for oropharyngeal cancer: dosimetric and clinical results in 18 patients. Radiother Oncol 2003;66(1):49-56.
Rec #: 8670
Reprint: EXC N10 2DR

Jereczek-Fossa BA, Krengli M, Orecchia R. Particle beam radiotherapy for head and neck tumors: radiobiological basis and clinical experience. Head Neck 2006;28(8):750-760.
Rec #: 3120
Reprint: EXC NRA

Kagei K, Tokuuye K, Sugahara S, et al. [Initial experience of proton beam therapy at the new facility of the University of Tsukuba]. Nippon Igaku Hoshasen Gakkai Zasshi 2004;64(4):225-230.
Rec #: 6760
Reprint: EXC FLA CS PBT

Kahn ST, Johnstone PA. Management of xerostomia related to radiotherapy for head and neck cancer. Oncology (Williston Park) 2005;19(14):1827-1832;discussion 1832-1834, 1837-1839.
Rec #: 3750
Reprint: EXC NRA

Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. Int J Radiat Oncol Biol Phys 2004;60(5):1440-1450.
Rec #: 6060
Reprint: EXC NRT, MIXED

Kassir RR, Rassekh CH, Kinsella JB, et al. Osteosarcoma of the head and neck: meta-analysis of nonrandomized studies. Laryngoscope 1997;107(1):56-61.
Rec #: 37540
Reprint: EXC MA NRD

Kawamorita R, Yamada K, Nakajima T, et al. Changes in regional body volume and gross tumor volume affect dose distribution during IMRT for head and neck cancer. J JASTRO 2006;18(4):199-207.
Rec #: 18660
Reprint: EXC DPN

Kearvell R, Kuan R, Preston R, et al. Acute radiation toxicity assessment of a 3-D conformal head and neck radiation treatment technique. Australas Radiol 2004;48(3):358-363.
Rec #: 6500
Reprint: EXC N10 IMR

Kim GE, Lim J, Park HC, et al. A feasibility study using three-dimensional conformal boost technique in locally advanced carcinoma of the nasopharynx. Acta Oncol 2001;40(5):582-587.
Rec #: 10040
Reprint: EXC N10 NRT

King AD, Ahuja AT, Yeung DK, et al. Delayed complications of radiotherapy treatment for nasopharyngeal carcinoma: imaging findings. Clin Radiol 2007;62(3):195-203.
Rec #: 16060
Reprint: EXC NRA

Kinoshita R, Tsuchiya K, Ohmori K, et al. Intensity-Modulated Radiation Therapy (IMRT) for head and neck region. J JASTRO 2006;18(4):191-197.
Rec #: 18650
Reprint: EXC N10 IMR

Kitamoto Y, Akimoto T, Ishikawa H, et al. Acute toxicity and preliminary clinical outcomes of concurrent radiation therapy and weekly docetaxel and daily cisplatin for head and neck cancer. Jpn J Clin Oncol 2005;35(11):639-644.
Rec #: 4210
Reprint: EXC NRT, MIXED

Kitano M, Nishiguchi I, Aoki Y, et al. [Relation between overall treatment time and local control of early glottic laryngeal cancer: comparison of six versus five times per week]. Nippon Igaku Hoshasen Gakkai Zasshi 2002;62(7):366-369.
Rec #: 9100
Reprint: EXC FLA CS

Klem ML, Mechalakos JG, Wolden SL, et al. Intensity-modulated radiotherapy for head and neck cancer of unknown primary: toxicity and preliminary efficacy. Int J Radiat Oncol Biol Phys 2008;70(4):1100-1107.
Rec #: 510
Reprint: EXC N10

Koom WS, Kim TH, Shin KH, et al. SMART (simultaneous modulated accelerated radiotherapy) for locally advanced nasopharyngeal carcinomas. Head Neck 2008;30(2):159-169.
Rec #: 950
Reprint: EXC N10

Koukourakis MI, Danielidis V. Preventing radiation induced xerostomia. Cancer Treat Rev 2005;31(7):546-554.
Rec #: 4340
Reprint: EXC NRA

Kristensen CA, Kjaer-Kristoffersen F, Sapru W, et al. Nasopharyngeal carcinoma. Treatment planning with IMRT and 3D conformal radiotherapy. Acta Oncol 2007;46(2):214-220.
Rec #: 1580
Reprint: EXC DPN, N10

Lalami Y, Vereecken P, Dequanter D, et al. Salivary gland carcinomas, paranasal sinus cancers and melanoma of the head and neck: an update about rare but challenging tumors. Curr Opin Oncol 2006;18(3):258-265.
Rec #: 3630
Reprint: EXC NRA

Langendijk JA. New developments in radiotherapy of head and neck cancer: Higher precision with less patient discomfort? Radiother Oncol 2007;85(1):1-6.
Rec #: 16310
Reprint: EXC NRA

Langendijk JA, Leemans CR, Buter J, et al. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. J Clin Oncol 2004;22(22):4604-4612.
Rec #: 37550
Reprint: EXC MA

Langer CJ, Duffy K, Horwitz EM, et al. Phase I trial of concurrent hyperfractionated split course radiotherapy (HFx RT), cisplatin (cDDP), and paclitaxel in patients with recurrent, previously irradiated, or treatment-naive locally advanced upper aerodigestive malignancy. Cancer Invest 2006;24(2):164-173.
Rec #: 3690
Reprint: EXC NRT, MIXED

Laskar SG, Agarwal JP, Srinivas C, et al. Radiotherapeutic management of locally advanced head and neck cancer. Expert Rev Anticancer Ther 2006;6(3):405-417.
Rec #: 3760
Reprint: EXC NRA

Lauve A, Morris M, Schmidt-Ullrich R, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II--clinical results. Int J Radiat Oncol Biol Phys 2004;60(2):374-387.
Rec #: 6420
Reprint: EXC N10 IMR

Le QT. Nasopharyngeal and oropharyngeal carcinomas: target delineation, therapy delivery and stereotactic boost procedures with intensity-modulated/ image-guided radiation therapy. Front Radiat Ther Oncol 2007;40:208-231.
Rec #: 1270
Reprint: EXC NRA

Lee AW, Yau TK, Wong DH, et al. Treatment of stage IV(A-B) nasopharyngeal carcinoma by induction-concurrent chemoradiotherapy and accelerated fractionation. Int J Radiat Oncol Biol Phys 2005;63(5):1331-1338.
Rec #: 4580
Reprint: EXC NRT, MIXED

Lee N, Puri DR, Blanco AI, et al. Intensity-modulated radiation therapy in head and neck cancers: an update. Head Neck 2007;29(4):387-400.
Rec #: 4030
Reprint: EXC NRA

Lee N, Xia P, Fischbein NJ, et al. Intensity-modulated radiation therapy for head-and-neck cancer: the UCSF experience focusing on target volume delineation. Int J Radiat Oncol Biol Phys 2003;57(1):49-60.
Rec #: 8040
Reprint: EXC NRT, MIXED

Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 2002;53(1):12-22.
Rec #: 9540
Reprint: EXC NRT, MIXED

Lee NY, Le QT. New developments in radiation therapy for head and neck cancer: intensity-modulated radiation therapy and hypoxia targeting. Semin Oncol 2008; 35(3):236-250.
Rec #: 37760
Reprint: EXC NRA

Lee SW, Back GM, Yi BY, et al. Preliminary results of a phase I/II study of simultaneous modulated accelerated radiotherapy for nondisseminated nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;65(1):152-160.
Rec #: 3830
Reprint: EXC N10

Levendag P, Nijdam W, Noever I, et al. Brachytherapy versus surgery in carcinoma of tonsillar fossa and/or soft palate: late adverse sequelae and performance status: can we be more selective and obtain better tissue sparing? Int J Radiat Oncol Biol Phys 2004;59(3):713-724.
Rec #: 6820
Reprint: EXC NRT, MIXED

Levendag PC, Teguh DN, Voet P, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol 2007;85(1):64-73.
Rec #: 1000
Reprint: EXC T?

Li Y, Taylor JM, Ten Haken RK, et al. The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy. Int J Radiat Oncol Biol Phys 2007;67(3):660-669.
Rec #: 2360
Reprint: EXC T? NRO

Liauw SL, Mancuso AA, Morris CG, et al. Definitive radiotherapy for head-and-neck cancer with radiographically positive retropharyngeal nodes: incomplete radiographic response does not necessarily indicate failure. Int J Radiat Oncol Biol Phys 2006;66(4):1017-1021.
Rec #: 2320
Reprint: EXC N10

Licitra L. Chemoradiation therapy in locally advanced nasopharyngeal cancer: Which kind of cooperation? Ann Oncol 2003;14(4):508-509.
Rec #: 23550
Reprint: EXC EDT

Licitra L, Locati LD, Bossi P. Head and neck cancer. Ann. Oncol. 2004;15(SUPPL 4):iv267-iv273.
Rec #: 21450
Reprint: EXC NRA

Lin OS, Mannava S, Hwang KL, et al. Reasons for current practices in managing Barrett's esophagus. Dis Esophagus 2002;15(1):39-45.
Rec #: 9440
Reprint: EXC NRD

Lin R, Slater JD, Yonemoto LT, et al. Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy--dose-volume histogram analysis. Radiology 1999;213(2):489-494.
Rec #: 11340
Reprint: EXC N10 PBT

Liu WS, Kuo HC, Lin JC, et al. Assessment of salivary function change in nasopharyngeal carcinoma treated by parotid-sparing radiotherapy. Cancer J 2006;12(6):494-500.
Rec #: 2170
Reprint: EXC NRT, MIXED

Liu WS, Lee SP, Lee JK, et al. Factors influencing the parotid function in nasopharyngeal carcinoma treated with parotid-sparing radiotherapy. Jpn J Clin Oncol 2006;36(10):626-631.
Rec #: 2680
Reprint: EXC T?, MIXED

Liu WS, Su MC, Wu MF, et al. Nasopharyngeal carcinoma treated with precision-oriented radiation therapy techniques including intensity-modulated radiotherapy: preliminary results. Kaohsiung J Med Sci 2004;20(2):49-55.
Rec #: 6310
Reprint: EXC N10 IMR

Logemann JA, Pauloski BR, Rademaker AW, et al. Swallowing disorders in the first year after radiation and chemoradiation. Head Neck 2008;30(2):148-158.
Rec #: 13610
Reprint: EXC URT

Lu H, Yao M. The current status of intensity-modulated radiation therapy in the treatment of nasopharyngeal carcinoma. Cancer Treat Rev 2008;34(1):27-36.
Rec #: 710
Reprint: EXC NRA

Macbeth FR, Williams MV. Proton therapy should be tested in randomized trials. J Clin Oncol 2008;26(15):2590-2591.
Rec #: 39120
Reprint: EXC LTR

MacDonald SM, DeLaney TF, Loeffler JS. Proton beam radiation therapy. Cancer Invest 2006;24(2):199-208.
Rec #: 18480
Reprint: EXC NRA PBT

Maes A, Weltens C, Flamen P, et al. Preservation of parotid function with uncomplicated conformal radiotherapy. Radiother Oncol 2002;63(2):203-211.
Rec #: 9380
Reprint: EXC NRT, MIXED

McLean JN, Nunley SR, Klass C, et al. Combined modality therapy of esthesioneuroblastoma. Otolaryngol Head Neck Surg 2007;136(6):998-1002.
Rec #: 1440
Reprint: EXC N10

McMillan AS. Oral health and quality of life following radiotherapy for nasopharyngeal carcinoma. J HK Coll Radiol 2003;6(2):75-77.
Rec #: 24650
Reprint: EXC 2DR CS

Mendenhall WM. In Reply to Drs. Studer and Glanzmann. Int J Radiat Oncol Biol Phys 2008;72(4):1272.
Rec #: 38810
Reprint: EXC LTR

Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. J Clin Oncol 2006;24(17):2618-2623.
Rec #: 3180
Reprint: EXC NRA

Mendenhall WM, Mancuso AA, Hinerman RW, et al. Multidisciplinary management of laryngeal carcinoma. Int J Radiat Oncol Biol Phys 2007;69(2 SUPPL):S12-S14.
Rec #: 14880
Reprint: EXC NRA

Mendenhall WM, Morris CG, Amdur RJ, et al. Definitive radiotherapy for tonsillar squamous cell carcinoma. Am J Clin Oncol 2006;29(3):290-297.
Rec #: 3190
Reprint: EXC NRT, MIXED

Mendenhall WM, Morris CG, Hinerman RW, et al. Definitive radiotherapy for nasopharyngeal carcinoma. Am J Clin Oncol 2006;29(6):622-627.
Rec #: 2280
Reprint: EXC T? URT IMR

Meyer J, Hummel SM, Cho PS, et al. Automatic selection of non-coplanar beam directions for three-dimensional conformal radiotherapy. Br J Radiol 2005;78(928):316-327.
Rec #: 20700
Reprint: EXC PHY

Meyer JL, Eisbruch A, Le QT. A discussion of the clinical use of advanced technologies in head and neck radiotherapy. Front Radiat Ther Oncol 2007;40:232-238.
Rec #: 1260
Reprint: EXC COM

Milano MT, Haraf DJ, Stenson KM, et al. Phase I study of concomitant chemoradiotherapy with paclitaxel, fluorouracil, gemcitabine, and twice-daily radiation in patients with poor-prognosis cancer of the head and neck. Clin Cancer Res 2004;10(15):4922-4932.
Rec #: 6600
Reprint: EXC 2DR CS

Milano MT, Vokes EE, Kao J, et al . Intensity-modulated radiation therapy in advanced head and neck patients treated with intensive chemoradiotherapy: preliminary experience and future directions. Int J Oncol 2006;28(5):1141-1151.
Rec #: 3520
Reprint: EXC NRT, MIXED

Munter MW, Hoffner S, Hof H, et al . Changes in salivary gland function after radiotherapy of head and neck tumors measured by quantitative pertechnetate scintigraphy: comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without Amifostine. Int J Radiat Oncol Biol Phys 2007;67(3):651-659.
Rec #: 2230
Reprint: EXC NRO

Munter MW, Karger CP, Hoffner SG, et al. Evaluation of salivary gland function after treatment of head-and-neck tumors with intensity-modulated radiotherapy by quantitative pertechnetate scintigraphy. Int J Radiat Oncol Biol Phys 2004;58(1):175-184.
Rec #: 7540
Reprint: EXC N10 IMR

Murata Y, Zhang L, Ishida R, et al. Maintained salivary function after brachytherapy in patients with head and neck carcinomas--evaluation using quantitative salivary gland scintigraphy. Acta Oncol 2002;41(7-8):684-688.
Rec #: 7640
Reprint: EXC NRT BRA

Murayama S, Fuji H, Yamashita H, et al. [Initial clinical experience of proton therapy at Shizuoka Cancer Center]. Nippon Igaku Hoshasen Gakkai Zasshi 2005;65(4):424-431.
Rec #: 4090
Reprint: EXC FLA CS PBT

Murdoch-Kinch C-A, Kim HM, Vineberg KA, et al. Dose-Effect Relationships for the Submandibular Salivary Glands and Implications for Their Sparing by Intensity Modulated Radiotherapy. Int J Radiat Oncol Biol Phys 2008;72(2):373-382.
Rec #: 39100
Reprint: EXC T?

Nangia S, Chufal KS, Arivazhagan V, et al. Compensator-based intensity-modulated radiotherapy in head and neck cancer: our experience in achieving dosimetric parameters and their clinical correlation. Clin Oncol (R Coll Radiol) 2006;18(6):485-492.
Rec #: 2890
Reprint: EXC N10

Ng MK, Porceddu SV, Milner AD, et al. Parotid-sparing radiotherapy: does it really reduce xerostomia? Clin Oncol (R Coll Radiol) 2005;17(8):610-617.
Rec #: 3980
Reprint: EXC NRT, MIXED

Ng WT, Chan SH, Lee AWM, et al. Parapharyngeal extension of nasopharyngeal carcinoma: still a significant factor in era of modern radiotherapy? Int J Radiat Oncol Biol Phys 2008;72(4):1082-1089.
Rec #: 38880
Reprint: EXC NRT, MIXED

Nishioka T, Shirato H, Kagei K, et al. Three-dimensional small-volume irradiation for residual or recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2000;48(2):495-500.
Rec #: 10730
Reprint: EXC N10 3DC

Nutting C. Intensity-modulated radiotherapy (IMRT): The most important advance in radiotherapy since the linear accelerator? Br J Radiol 2003;76(910):673.
Rec #: 23480
Reprint: EXC EDT

O'Meara WP, Lee N. Advances in nasopharyngeal carcinoma. Curr Opin Oncol 2005;17(3):225-230.
Rec #: 5390
Reprint: EXC NRA

Ohizumi Y, Tamai Y, Imamiya S, et al. Prediction of tumor control by tumor regression at 40 Gy/4 weeks of external beam irradiation for oropharyngeal carcinoma . Radiat Med Med Imaging Radiat Oncol 2004;22(5):324-331.
Rec #: 21610
Reprint: EXC 2DR CS

Ozyigit G, Chao KS. Clinical experience of head-and-neck cancer IMRT with serial tomotherapy. Med Dosim 2002;27(2):91-98.
Rec #: 9310
Reprint: EXC NRO

Pan JJ, Wu JX, Zhang XC, et al. High dose rate conformal brachytherapy for nasopharyngeal carcinoma: A preliminary study. Curr Oncol 1998;5(1):28-32.
Rec #: 27810
Reprint: EXC NRT

Parliament MB, Scrimger RA, Anderson SG, et al. Preservation of oral health-related quality of life and salivary flow rates after inverse-planned intensity-modulated radiotherapy (IMRT) for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2004;58(3):663-673.
Rec #: 7380
Reprint: EXC N10 IMR

Paulino AC, Koshy M. Patterns of failure after IMRT for head-and- neck cancer: let's not count the chickens before the eggs hatch. Int J Radiat Oncol Biol Phys 2003;56(5):1508; author reply 1508.
Rec #: 8110
Reprint: EXC COM

Paulsen F, Belka C, Alber M, et al. Intensity - Modulated radiotherapy: INTENSITATSMODULIERTE STRAHLENTHERAPIE. Onkologe 2003;9(3):315-325.
Rec #: 24050
Reprint: EXC FLA D?

Perez CA, Purdy JA, Harms W, et al. Three-dimensional treatment planning and conformal radiation therapy: preliminary evaluation. Radiother Oncol 1995;36(1):32-43.
Rec #: 12490
Reprint: EXC NRO

Pignon JP, Baujat B, Bourhis J. [Individual patient data meta-analyses in head and neck carcinoma: what have we learnt?]. Cancer Radiother 2005;9(1):31-36.
Rec #: 37560
Reprint: EXC FLA MA

Pigott K, Dische S, Saunders MI. Where exactly does failure occur after radiation in head and neck cancer? Radiother Oncol 1995; 37(1):17-19.
Rec #: 12470
Reprint: EXC NRT URT

Ploquin N, Lau H, Dunscombe P. Intensity modulated and three-dimensional conformal radiation therapy plans for oropharyngeal cancer: A comparison of their sensitivity to set-up errors and uncertainties. Curr Oncol 2006;13(2):61-66.
Rec #: 18160
Reprint: EXC DPC IMR 3DC

Popovtzer A, Eisbruch A. Advances in radiation therapy of head and neck cancer. Expert Rev Anticancer Ther 2008;8(4):633-644.
Rec #: 28850
Reprint: EXC NRA

Posner MR. IMRT bests standard RT in long-term QOL in head and neck cancer patients. Oncol Rep 2005;-(SPRING):69-70.
Rec #: 20730
Reprint: EXC CR

Posner MR. Early postop chemo/chemoradiation feasible in high-risk head and neck cancer. Oncol Rep 2005; -(SPRING):77-78.
Rec #: 20750
Reprint: EXC CR

Puri DR, Chou W, Lee N. Intensity-modulated radiation therapy in head and neck cancers: dosimetric advantages and update of clinical results. Am J Clin Oncol 2005;28(4):415-423.
Rec #: 4820
Reprint: EXC NRA

Qadeer MA, Lopez R, Wood BG, et al. Does acid suppressive therapy reduce the risk of laryngeal cancer recurrence? Laryngoscope 2005;115(10 I):1877-1881.
Rec #: 19360
Reprint: EXC NRQ

Rabbani A, Amdur RJ, Mancuso AA, et al. Definitive radiotherapy for T1-T2 squamous cell carcinoma of pyriform sinus. Int J Radiat Oncol Biol Phys 2008;72(2):351-355.
Rec #: 39080
Reprint: EXC 2DR T?

Redda MGR, Succo G, Guarneri A, et al. Radiotherapy after surgery for advanced adenoid cystic carcinoma of paranasal sinus. Lancet Oncol 2005;6(12):994-996.
Rec #: 19060
Reprint: EXC CR

Robinson MH. Radiotherapy: technical aspects. Medicine (GBR) 2008;36(1):9-14.
Rec #: 13900
Reprint: EXC NRA

Ronis DL, Duffy SA, Fowler KE, et al. Changes in quality of life over 1 year in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2008;134(3):241-248.
Rec #: 37800
Reprint: EXC T?

Rudat V, Munter M, Rades D, et al. The effect of amifostine or IMRT to preserve the parotid function after radiotherapy of the head and neck region measured by quantitative salivary gland scintigraphy. Radiother Oncol 2008;89(1):71-80.
Rec #: 38910
Reprint: EXC NRO

Saarilahti K, Kouri M, Collan J, et al. Intensity modulated radiotherapy for head and neck cancer: evidence for preserved salivary gland function. Radiother Oncol 2005;74(3):251-258.
Rec #: 5600
Reprint: EXC N10 IMR

Salama JK, Haraf DJ, Stenson K, et al. Phase I study of concomitant chemoradiotherapy with irinotecan, 5-FU, and hydroxyurea for patients with advanced and/or recurrent head and neck cancer. Cancer J 2005;11(2):140-146.
Rec #: 5060
Reprint: EXC NRT, MIXED

Salama JK, Stenson KM, List MA, et al. Characteristics associated with swallowing changes after concurrent chemotherapy and radiotherapy in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2008;134(10):1060-1065.
Rec #: 38300
Reprint: EXC T?

Sanderson RJ, Ironside JAD. Squamous cell carcinomas of the head and neck. Br Med J 2002;325(7368):822-827.
Rec #: 25080
Reprint: EXC NRA

Schulz-Ertner D, Nikoghosyan A, Jakel O, et al. Feasibility and toxicity of combined photon and carbon ion radiotherapy for locally advanced adenoid cystic carcinomas. Int J Radiat Oncol Biol Phys 2003;56(2):391-398.
Rec #: 8320
Reprint: EXC NRT, MIXED

Scrimger RA, Stavrev P, Parliament MB, et al. Phenomenologic model describing flow reduction for parotid gland irradiation with intensity-modulated radiotherapy: evidence of significant recovery effect. Int J Radiat Oncol Biol Phys 2004;60(1):178-185.
Rec #: 6520
Reprint: EXC N10 IMR

Selek U, Garden AS, Morrison WH, et al. Radiation therapy for early-stage carcinoma of the oropharynx. Int J Radiat Oncol Biol Phys 2004;59(3):743-751.
Rec #: 33430
Reprint: EXC URT

Shin SS, Ahn YC, Lim DH, et al. High dose 3-dimensional re-irradiation for locally recurrent nasopharyngeal cancer. Yonsei Med J 2004;45(1):100-106.
Rec #: 7310
Reprint: EXC N10 3DC

Slater JD. Clinical applications of proton radiation treatment at Loma Linda University: Review of a fifteen-year experience. Technol Cancer Res Treat 2006;5(2):81-89.
Rec #: 17950
Reprint: EXC NRA PBT

Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. Int J Radiat Oncol Biol Phys 2005;62(2):494-500.
Rec #: 5270
Reprint: EXC NRT, MIXED

Smith A, Goitein M, Flanz J, et al. The Northeast Proton Therapy center at Massachusetts General Hospital. J Brachytherapy Int 1997;13(1):137-139.
Rec #: 27930
Reprint: EXC NRA

Smith AR. Against the proposition. Med Phys 1999;26(7):1187.
Rec #: 27550
Reprint: EXC NRD NRQ

Stokman MA, Spijkervet FK, Boezen HM, et al. Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. J Dent Res 2006;85(8):690-700.
Rec #: 37570
Reprint: EXC NRQ MA

Studer G, Luetolf UM, Glanzmann C. Locoregional failure analysis in head-and-neck cancer patients treated with IMRT. Strahlenther Onkol 2007;183(8):417-423; discussion 424-425.
Rec #: 1140
Reprint: EXC precursor study to rec#38640

Studer GM, Glanzmann C. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer: in regard to Schoenfeld et al. (Int J Radiat Oncol Biol Phys 2008;71:377-385). Int J Radiat Oncol Biol Phys 2008;72(4):1271-1272; author reply 1272.
Rec #: 38270
Reprint: EXC COM

Stuschke M, Thames HD. Hyperfractionated radiotherapy of human tumors: overview of the randomized clinical trials. Int J Radiat Oncol Biol Phys 1997;37(2):259-267.
Rec #: 37580
Reprint: EXC MA

Sultanem K, Shu HK, Xia P, et al. Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: the University of California-San Francisco experience. Int J Radiat Oncol Biol Phys 2000;48(3):711-722.
Rec #: 10700
Reprint: EXC NRT, MIXED

Suzuki G, Hayabuchi N, Kojima K, et al. Treatment outcome of nasopharynx cancer: Dose presence of MR findings of extracapsular spread in cervical node metastasis influence distant metastasis? J JASTRO 2004;16(2):95-100.
Rec #: 22050
Reprint: EXC T?

Tang YQ, Luo W, He ZC, et al. [Three-dimensional conformal radiotherapy for primary nasopharyngeal carcinoma and analysis of locoregional recurrence]. Ai Zheng 2006;25(3):330-334.
Rec #: 3700
Reprint: EXC FLA CS

Taylor A, Powell ME. Intensity-modulated radiotherapy - what is it? Cancer Imaging 2004;4(2):68-73.
Rec #: 37630
Reprint: EXC NRA

Teguh DN, Levendag PC, Noever I, et al. Treatment Techniques and Site Considerations Regarding Dysphagia-Related Quality of Life in Cancer of the Oropharynx and Nasopharynx. Int J Radiat Oncol Biol Phys 2008;72(4):1119-1127.
Rec #: 38860
Reprint: EXC NRT, MIXED

Teo PM, Ma BB, Chan AT. Radiotherapy for nasopharyngeal carcinoma--transition from two-dimensional to three-dimensional methods. Radiother Oncol 2004;73(2):163-172.
Rec #: 6220
Reprint: EXC NRA

Terezakis SA, Bohle 3rd GC, Lee NY. Fistula formation after postoperative radiation treatment for paranasal sinus cancer. Am J Clin Oncol 2008;31(2):199-204.
Rec #: 10
Reprint: EXC NRA

Terhaard CHJ. Postoperative and Primary Radiotherapy for Salivary Gland Carcinomas: Indications, Techniques, and Results. Int J Radiat Oncol Biol Phys 2007;69(2 SUPPL):S52-S55.
Rec #: 14890
Reprint: EXC NRA

Thariat J, Ahamad A, El-Naggar AK, et al. Outcomes after radiotherapy for basaloid squamous cell carcinoma of the head and neck: A case-control study. Cancer 2008;112(12):2698-2709.
Rec #: 39220
Reprint: EXC T?

Thorstad WL, Haughey B, Chao KS. Pilot study of subcutaneous amifostine in patients undergoing postoperative intensity modulated radiation therapy for head and neck cancer: preliminary data. Semin Oncol 2003;30(6 Suppl 18):96-100.
Rec #: 7460
Reprint: EXC N10 IMR

Tokuuye K, Akine Y, Kagei K, et al. Proton therapy for head and neck malignancies at Tsukuba. Strahlenther Onkol 2004;180(2):96-101.
Rec #: 7390
Reprint: EXC NRT, MIXED

Trotti A, Colevas AD, Setser A, et al. Patient-reported outcomes and the evolution of adverse event reporting in oncology. J Clin Oncol 2007;25(32):5121-5127.
Rec #: 37690
Reprint: EXC NRA

Tsao AS, Garden AS, Kies MS, et al. Phase I/II study of docetaxel, cisplatin, and concomitant boost radiation for locally advanced squamous cell cancer of the head and neck. J Clin Oncol 2006;24(25):4163-4169.
Rec #: 30810
Reprint: EXC 2DR CS

Uchida D, Shirato H, Onimaru R, et al. Long-term results of ethmoid squamous cell or undifferentiated carcinoma treated with radiotherapy with or without surgery. Cancer J 2005;11(2):152-156.
Rec #: 5050
Reprint: EXC NRT, MIXED

Veldeman L, Madani I, Hulstaert F, et al. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol 2008;9(4):367-375.
Rec #: 13370
Reprint: EXC MA

Vernon MR, Maheshwari M, Schultz CJ, et al. Clinical outcomes of patients receiving integrated PET/CT-guided radiotherapy for head and neck carcinoma. Int J Radiat Oncol Biol Phys 2008;70(3):678-684.
Rec #: 110
Reprint: EXC Q?

Vissink A, Burlage FR, Spijkervet FK, et al. Prevention and treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Biol Med 2003;14(3):213-225.
Rec #: 37640
Reprint: EXC NRA

Vissink A, Jansma J, Spijkervet FK, et al. Oral sequelae of head and neck radiotherapy. Crit Rev Oral Biol Med 2003;14(3):199-212.
Rec #: 37650
Reprint: EXC NRA

Wadsley JC, Bentzen SM. Investigation of relationship between change in locoregional control and change in overall survival in randomized controlled trials of modified radiotherapy in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2004;60(5):1405-1409.
Rec #: 37590
Reprint: EXC MA

Waldron J, Tin MM, Keller A, et al. Limitation of conventional two dimensional radiation therapy planning in nasopharyngeal carcinoma. Radiother Oncol 2003;68(2):153-161.
Rec #: 7950
Reprint: EXC 2DR CS

Warde P. Radiotherapy: practical applications and clinical aspects. Medicine (GBR) 2008;36(1):15-18.
Rec #: 13910
Reprint: EXC NRA

Weber DC, Chan AW, Lessell S, et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. Radiother Oncol 2006;81(3):243-249.
Rec #: 2620
Reprint: EXC NRT, MIXED

Wijers OB, Levendag PC, Luyten GPM, et al. Radiation-induced bilateral optic neuropathy in cancer of the nasopharynx: Case failure analysis and a review of the literature. Strahlenther Onkol 1999;175(1):21-27.
Rec #: 27650
Reprint: EXC CR NRA

Willins J, Kachnic L. Clinically relevant standards for intensity-modulated radiation therapy dose prescription. J Natl Cancer Inst 2008;100(5):288-290.
Rec #: 37670
Reprint: EXC COM

Withers HR, Peters LJ. Comment on Editorial "Magical Protons" by Dr. Michael Goitein (Int J Radiat Oncol Biol Phys 2008;70:654-656) and in Reply to Dr. Fowler. Int J Radiat Oncol Biol Phys 2008;72(4):1271.
Rec #: 38830
Reprint: EXC COM

Wolden SL, Zelefsky MJ, Hunt MA, et al. Failure of a 3D conformal boost to improve radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2001;49(5):1229-1234.
Rec #: 10420
Reprint: EXC NRT, MIXED

Wu DH, Chen LH. [Therapeutic effects of three-dimensional conformal radiation therapy for locally recurrent nasopharyngeal carcinoma]. Di Yi Jun Yi Da Xue Xue Bao 2002;22(11):1028-1029.
Rec #: 8860
Reprint: EXC FLA 3DC

Wu Q, Mohan R, Morris M, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas. I: dosimetric results. Int J Radiat Oncol Biol Phys 2003;56(2):573-585.
Rec #: 8310
Reprint: EXC N10 IMR

Wu VWC, Kwong DWL, Sham JST, et al. Auto-optimisation for three-dimensional conformal radiotherapy of nasopharyngeal carcinoma. Radiography 2003;9(3):201-210.
Rec #: 23240
Reprint: EXC DPN

Yao M, Graham MM, Smith RB, et al. Value of FDG PET in assessment of treatment response and surveillance in head-and-neck cancer patients after intensity modulated radiation treatment: a preliminary report. Int J Radiat Oncol Biol Phys 2004;60(5):1410-1418.
Rec #: 6090
Reprint: EXC NRO RAD

Yau TK, Lee AW, Wong DH, et al. Treatment of Stage IV(A-B) nasopharyngeal carcinoma by induction-concurrent chemoradiotherapy and accelerated fractionation: impact of chemotherapy schemes. Int J Radiat Oncol Biol Phys 2006;66(4):1004-1010.
Rec #: 2330
Reprint: EXC O?

Yi JL, Gao L, Huang XD, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: Ten-year experience of a single institution. Int J Radiat Oncol Biol Phys 2006;65(1):161-168.
Rec #: 3680
Reprint: EXC NRT, MIXED

Zackrisson B, Mercke C, Strander H, et al. A systematic overview of radiation therapy effects in head and neck cancer. Acta Oncol 2003;42(5-6):443-461.
Rec #: 37600
Reprint: EXC SR

Zhang X-C, Shi M, Xiao F, et al. Clinical study of 73 local-advanced nasopharyngeal carcinoma patients treated with chemoradiotherapy. Chin J Cancer Prev Treat 2007;14(22):1710-1713.
Rec #: 14410
Reprint: INC QEX 2DR IMR

Zhang Y, Pan J-J, Zheng Z, et al. Analysis of recurrent cases after IMRT in nasopharyngeal carcinoma. Chin J Cancer Prev Treat 2007;14(13):1011-1013.
Rec #: 15060
Reprint: EXC FLA CS IMR

Zhao C, Han F, Lu LX, et al. [Intensity modulated radiotherapy for local-regional advanced nasopharyngeal carcinoma]. Ai Zheng 2004;23(11 Suppl):1532-1537.
Rec #: 6150
Reprint: EXC FLA CS IMR

Zheng XK, Chen LH, Chen YQ, et al. Three-dimensional conformal radiotherapy versus intracavitary brachytherapy for salvage treatment of locally persistent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2004;60(1):165-170.
Rec #: 6530
Reprint: EXC NRT, MIXED

Zheng X-K, Ma J, Xia Y-F, et al. Three-dimensional conformal radiation therapy for locally recurrent nasopharyngeal carcinoma. Chin J Cancer Res 2001;13(3):221-225.
Rec #: 26180
Reprint: EXC NRT, MIXED

Appendix C: Summary Tables and Figures

Appendix Table C1. Numbers of comparative studies and participants by single setting and site

	All	One Setting	One Site	NPC	OPH	PNS	UNP	LAR	MIX
IMRT vs. 3DCRT									
Comparisons	14	2	7	2	4	1	0	0	7
Total n	1752	127	766	288	410	68	0	0	986
3DCRT vs. 2DRT									
Comparisons	12	3	8	3	1	2	1	1	4
Total n	1497	398	940	373	130	231	87	122	526
IMRT vs. 2DRT									
Comparisons	22	4	12	6	4	1	1	0	10
Total n	2441	573	1502	662	717	82	41	0	939
All comparisons									
Total comparisons	48	9	27	11	9	4	2	1	21
Total studies	38	9	21	9	7	2	2	1	17
Grand total n	5061	1098	2787	1174	1109	254	128	122	2274

Appendix Table C2. Numbers of comparisons, studies and participants by outcome

		QOL/Adverse Events							Tumor Control			Patient Survival	
		QOL	XST	SF	DYS	MUC	SKN	ORH or BON	LC	LRC	DFS	DSS	OS
IMRT vs. 3DCRT													
Comparisons	14	3	9	1	3	7	6	2	2	4	4	1	8
Total n	1752	429	879	41	729	735	540	152	112	569	274	195	800
3DCRT vs. 2DRT													
Comparisons	12	1	6	1	1	6	4	2	5	1	4	1	7
Total n	1497	94	1013	33	137	939	716	231	579	345	360	127	931
IMRT vs. 2DRT													
Comparisons	22	4	13	3	5	8	7	2	3	2	5	0	7
Total n	2441	317	1873	481	674	943	868	512	316	466	704	0	867
All comparisons													
Total comparisons	48	8	28	5	9	21	17	6	10	7	13	2	22
Total studies	38	6	22	5	7	15	11	4	6	7	9	2	16
Grand total n	5061	694	3322	555	1391	2193	1700	768	732	1380	1152	322	2264

Appendix Table C3. Summary of study quality characteristics: comparative studies

Selection Prospective/ Retrospective	Inclusion/ Exclusion Criteria Clear	Representative Selection	Initial Groups Comparable	Balanced by Design (Random/ Matched)	Baseline Characteristics Clearly Comparable
Pro 15	Yes 31	Yes 25	Yes 10	Yes 5	Yes 17
Retro 23	No 7	Unclear 8	Unclear 21	No 33	Unclear 17
		No 5	No 7		No 4

Treatments Given During Same Time Period	Unbiased Treatment Allocation	Other Treatments Equal	Maintenance of Comparable Groups
Yes 13	Clearly Random 2	NA 3	NA 25
Unclear 11	Unclear 18	Yes 12	Yes 3
Yes and No 1	Unclear/Era 1	Unclear 16	Unclear 9
No 13	Era 12	No 7	No 1
	Availability/Preference 2		
	Waiting List 1		
	Risk to Sensitive Areas 2		

Outcomes Valid, Reliable, Equal	Outcome Assessors Blind	Treatments Clearly Described	Multivariable Analysis (MVA) Conducted?	Well-done MVA or Intention-to-Treat Analysis (ITT)	USPSTF
Yes 38	Yes 1	Yes 32	NA 2	2 ITT	Good 1
Unclear 0	Unclear 13	No 6	Yes 20	1 unclear if ITT 13 unclear if well-done MVA	Fair 1
No 0	No 24		No 16	1 not ITT 21 not well-done MVA	Poor 36

Appendix Table C4. Summary of results for tumor control outcomes

Comparison	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:3DCRT	OPH	1^{o} RT + CCTx	Rustoven, 2008	87	LRC DFS	4yr ↑ NS 4yr ↑ NS	0.075 NS	Retro	Poor
	NPH	MIX: 1^{o} RT ± CCTx	Fang, 2008	203	LRC	3yr, ≈ NS	NS	Pro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	44	LC	2yr ↑ NS	NS	Retro	Poor
	OPH	MIX: 1^{o} RT ± CCTx	Hodge, 2005	195	LRC	4yr ↑ p NR		Retro	Poor
	OPH	MIX: 1^{o}/postop RT ± preRT CTx	Nutting, 2009 (RCT)	84	LRC	1yr ≈ NS		Pro	Good
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	68	LC DFS	5yr, ≈ NS NS		Retro	Poor
	MIX	MIX: 1^{o}/postop/repeat RT ± pre/post RT CTx/CCTx	Marchal, 2004	87	DFS	1yr, ≈ NS		Pro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	42	DFS	NS	RT not in MVA	Retro	Poor
3DCRT:2DRT	NPH	1^{o} RT + split CTx	Wu, 2005 (RCT)	96	LC	1yr, ↑ 0.003		Pro	Poor
	LAR	1^{o} RT	Zouhair, 2004	122	LC	5yr, ≈ NS	NS	Retro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	130	LC	2yr ≈ NS	NS	Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	104	LC DFS	5yr, ≈ NS NS		Retro	Poor
	NC/PNS	1^{o}/preop/postop RT	Dirix, 2007	127	LC DFS	NS NS		Retro	Poor
	UNK	1^{o}/postop RT± preRT CTx/CCTx	Beldi, 2007	87	DFS	5yr, ↑ <0.01	NS	Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	32	DFS	NS	RT not in MVA	Retro	Poor
	MIX	MIX: 1^{o}/postop RT± CCTx	Rades, 2008	345	LRC	3yr, ≈ NS		Retro	Poor

Appendix Table C4. Summary of results for tumor control outcomes (continued)

Comparison	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:2DRT	NPH	1^{o} RT + split CTx	Laskar, 2008	36	LRC DFS	2yr ↑ NS 2yr ↑ NS	RT not in MVA	Pro	Poor
	OPH	1^{o} RT + CCTx	Lee, 2006	112	LC LRC DFS	5yr, ↑ NS 5yr, ↑ NS 5yr, ↑ NS		Retro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	122	LC	2yr, ↑ NS		Retro	Poor
	OPH	MIX: 1^{o}/pre/postop RT ± CCTx	Chao, 2001	430	LRC DFS	2yr, def, ↑ NS; postop, ↑ NS 2yr, def, ↑ 0.002; postop, ↑ 0.008		Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	82	LC DFS	5yr, ≈ NS NS		Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	44	DFS	NS	RT not in MVA	Retro	Poor

Appendix Table C5. Summary of results for patient survival outcomes

Study	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:3DCRT	OPH	1^{o} RT + CCTx	Rustoven, 2008	87	OS	4yr ↑ NS	NS	Retro	Poor
	NPH	MIX: 1^{o} RT ± CCTx	Fang, 2008	203	OS	3yr, ≈ NS	NS	Pro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	44	OS	2yr ~↑ NS	NS	Retro	Poor
	OPH	MIX: 1^{o} RT ± CCTx	Hodge, 2005	195	DSS OS	4yr ↑ p NR 4yr ↑ 0.02	 NS	Retro	Poor
	OPH	MIX: 1^{o}/postop RT ± preRT CTx	Nutting, 2009 (RCT)	84	OS	1yr, ≈ NS		Pro	Good
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	68	OS	5yr, ↓ NS		Retro	Poor
	MIX	MIX: 1^{o}/postop/repeat RT ± pre/post RT CTx/CCTx	Marchal, 2004	87	OS	1yr, ≈ NS		Pro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	42	OS	NS	RT not in MVA	Retro	Poor
3DCRT:2DRT	NPH	MIX: 1^{o} RT ± CTx (t?)	Wu, 2005 (RCT)	96	OS	1yr, ≈ NS		Pro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	130	OS	2yr ~↑ NS	NS	Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	104	OS	5yr, ~↑ NS		Retro	Poor
	NC/PNS	1^{o}/preop/postop RT	Dirix, 2007	127	OS DSS	NS NS		Retro	Poor
	UNK	1^{o}/postop RT± preRT CTx/CCTx	Beldi, 2007	87	OS	5yr, ↑ <0.01	NS	Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	32	OS	NS	RT not in MVA	Retro	Poor
	MIX	MIX: 1^{o}/postop RT± CCTx	Rades, 2008	345	OS	3yr, ≈ NS		Retro	Poor

Appendix Table C5. Summary of results for patient survival outcomes (continued)

Study	Tumor Site	Setting	Study	n	Outcome	UV p	MV p	Pro/ Retro	USPSTF
IMRT:2DRT	NPH	1^{o} RT + split CTx	Laskar, 2008	36	OS	2yr ↑ NS	RT not in MVA	Pro	Poor
	OPH	1^{o} RT + CCTx	Lee, 2006	112	OS	5yr, ↑ NS		Retro	Poor
	OPH	MIX: Postop RT ± CCTx	Rades, 2007	122	OS	2yr, ↑ NS		Retro	Poor
	OPH	MIX: 1^{o}/pre/postop RT ± CCTx	Chao, 2001	430	OS	2yr, def, ↑ 0.001; postop, ↑ 0.003		Retro	Poor
	NC/PNS	MIX: Primary/preop/postop RT with or without postRT CTx or concurrent CTx (1o/preop/postop RT ± postRT CTx/CCTx)	Chen, 2007	82	OS	5yr, ≈ NS		Retro	Poor
	UNK	1^{o}/postop RT ± CTx (t?)	Madani, 2008	41	OS	1yr, ↑ NS		Retro	Poor
	MIX	MIX: 1^{o}/postop RT ± CTx (t?)	Gomez, 2008	44	OS	NS	RT not in MVA	Retro	Poor

Figure C1. Acute xerostomia, IMRT vs. 3DRCT

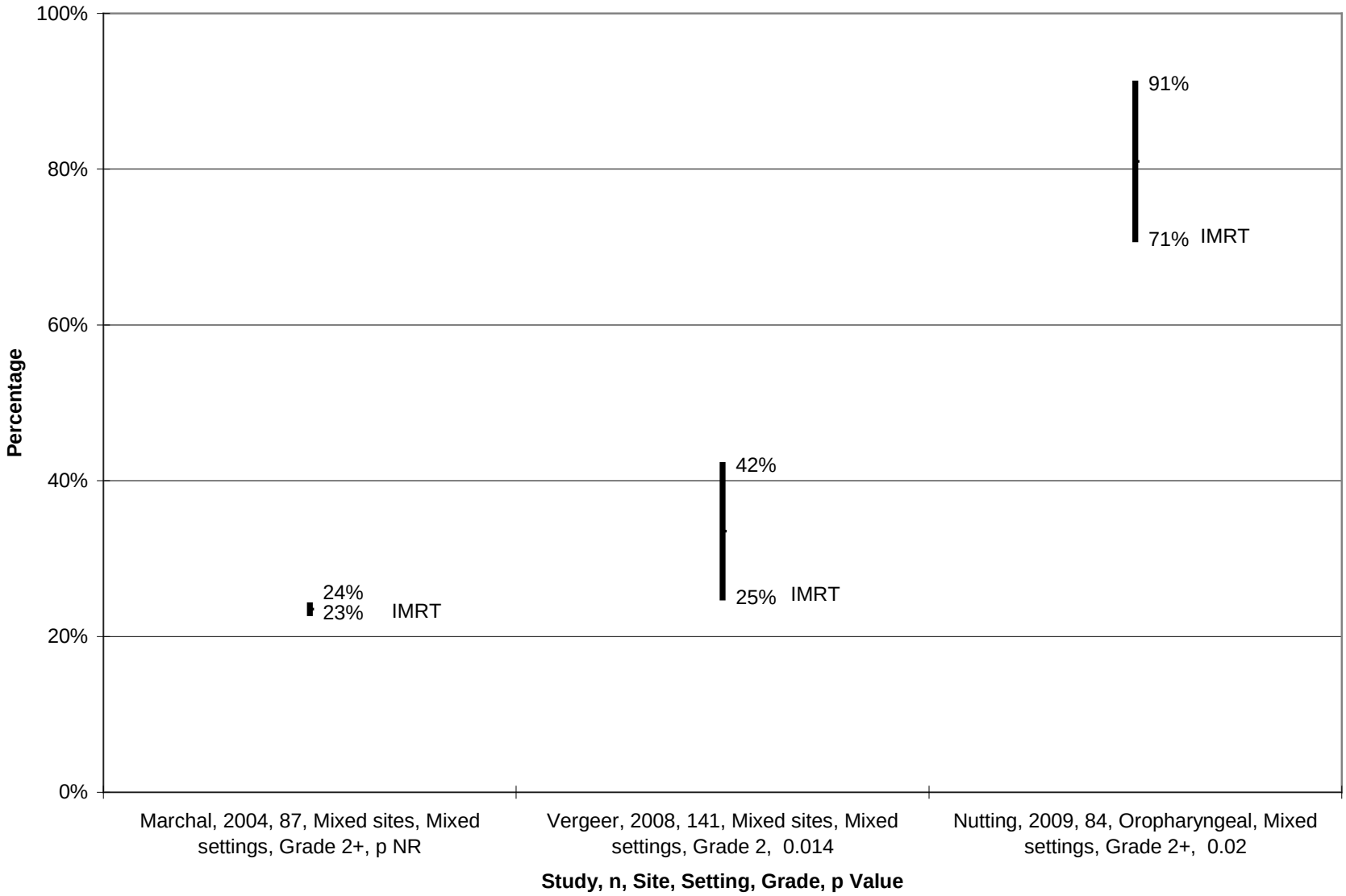


Figure C2. Late xerostomia, IMRT vs. 3DCRT

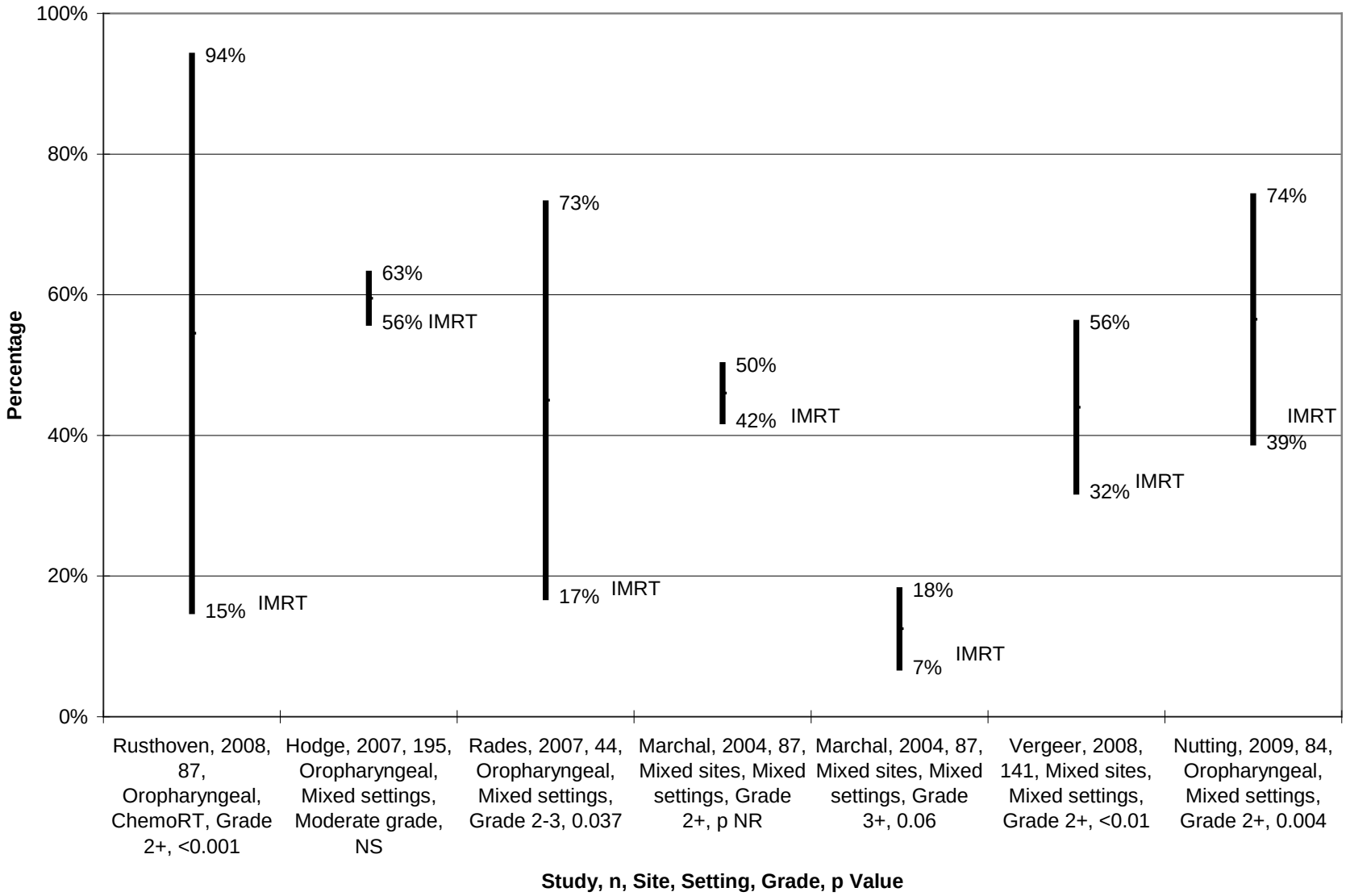


Figure C3. Acute mucositis, IMRT vs. 3DCRT

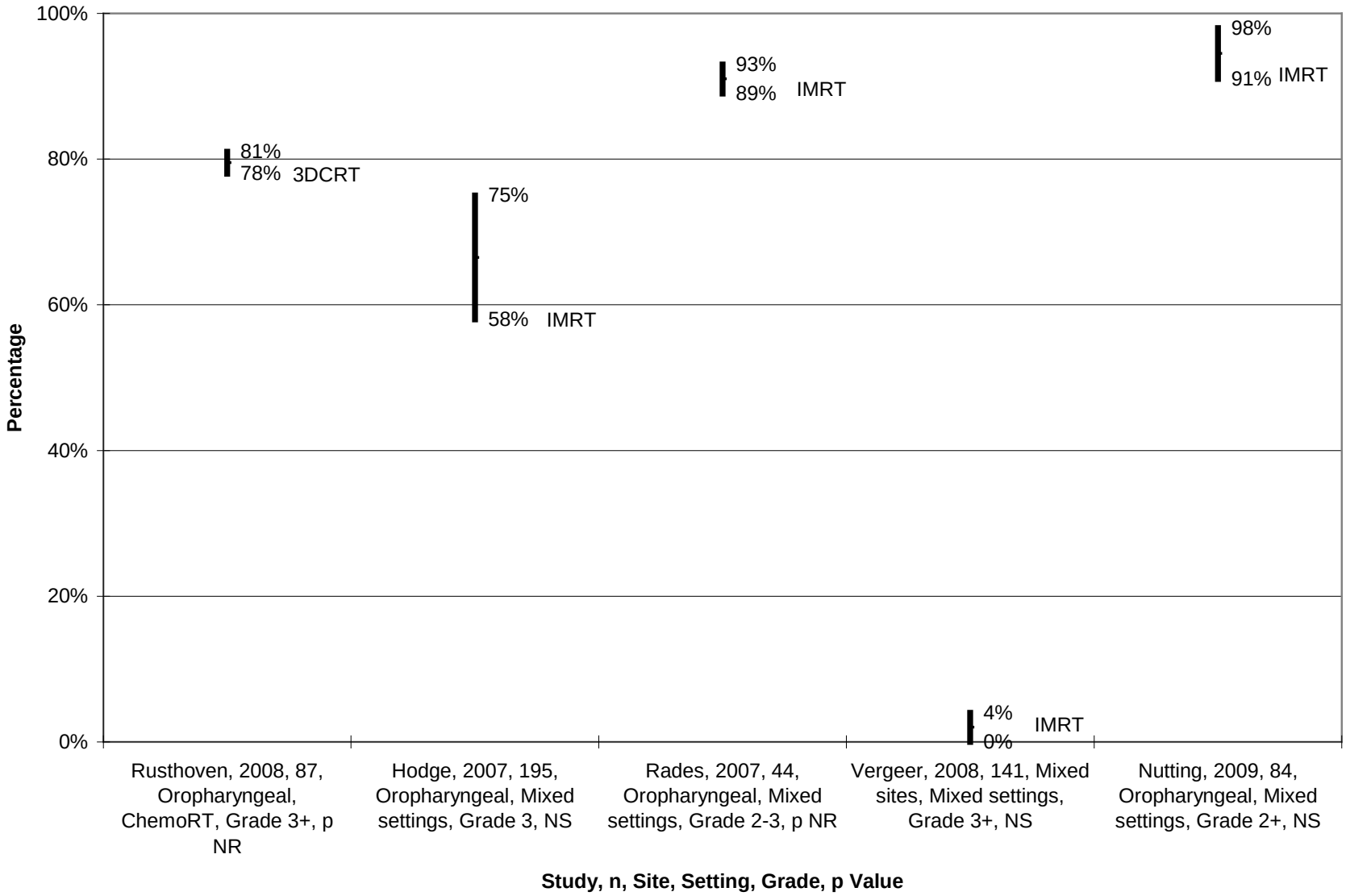


Figure C4. Late mucositis, IMRT vs. 3DCRT

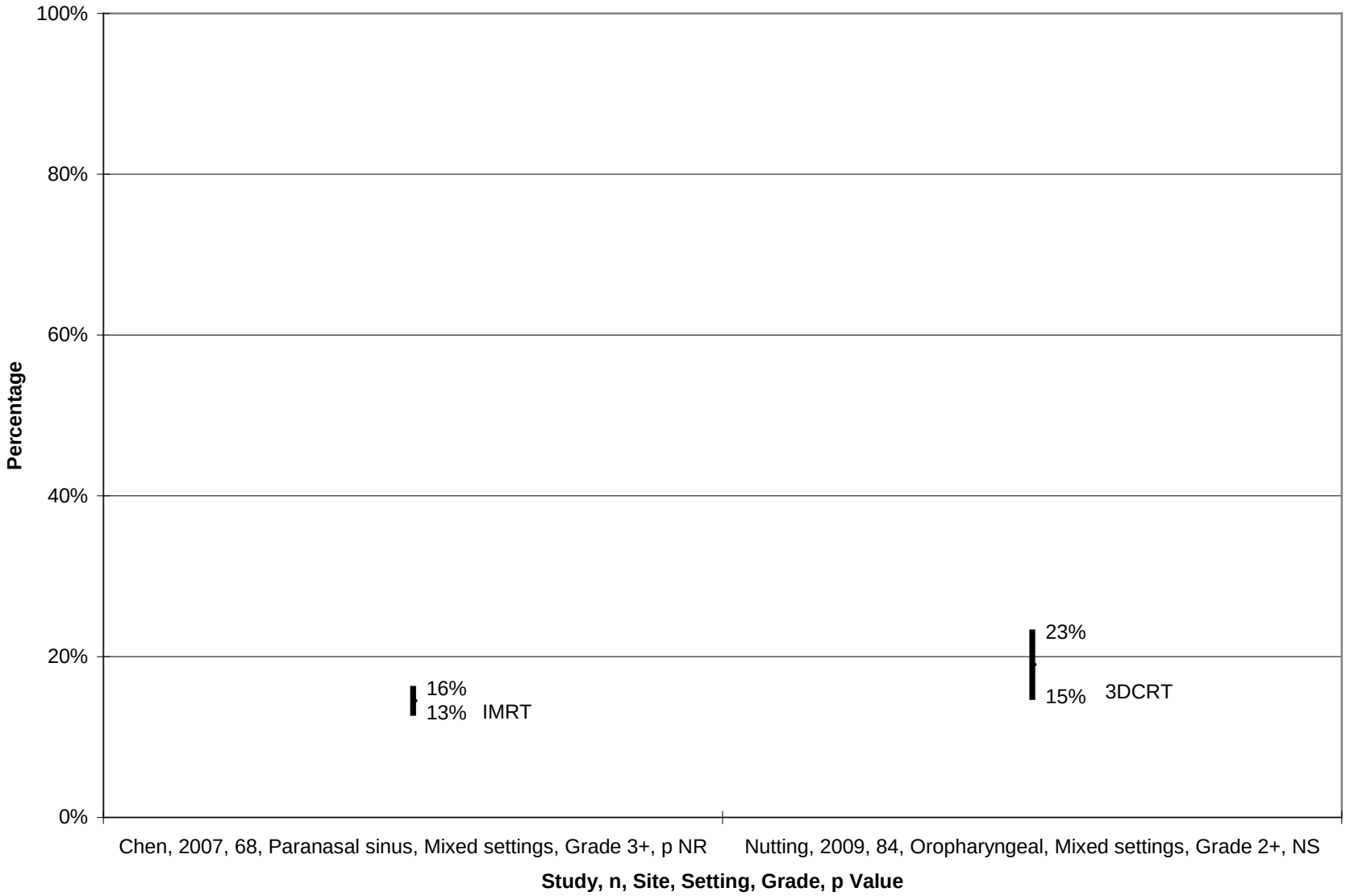


Figure C5. Acute dysphagia, IMRT vs. 3DCRT

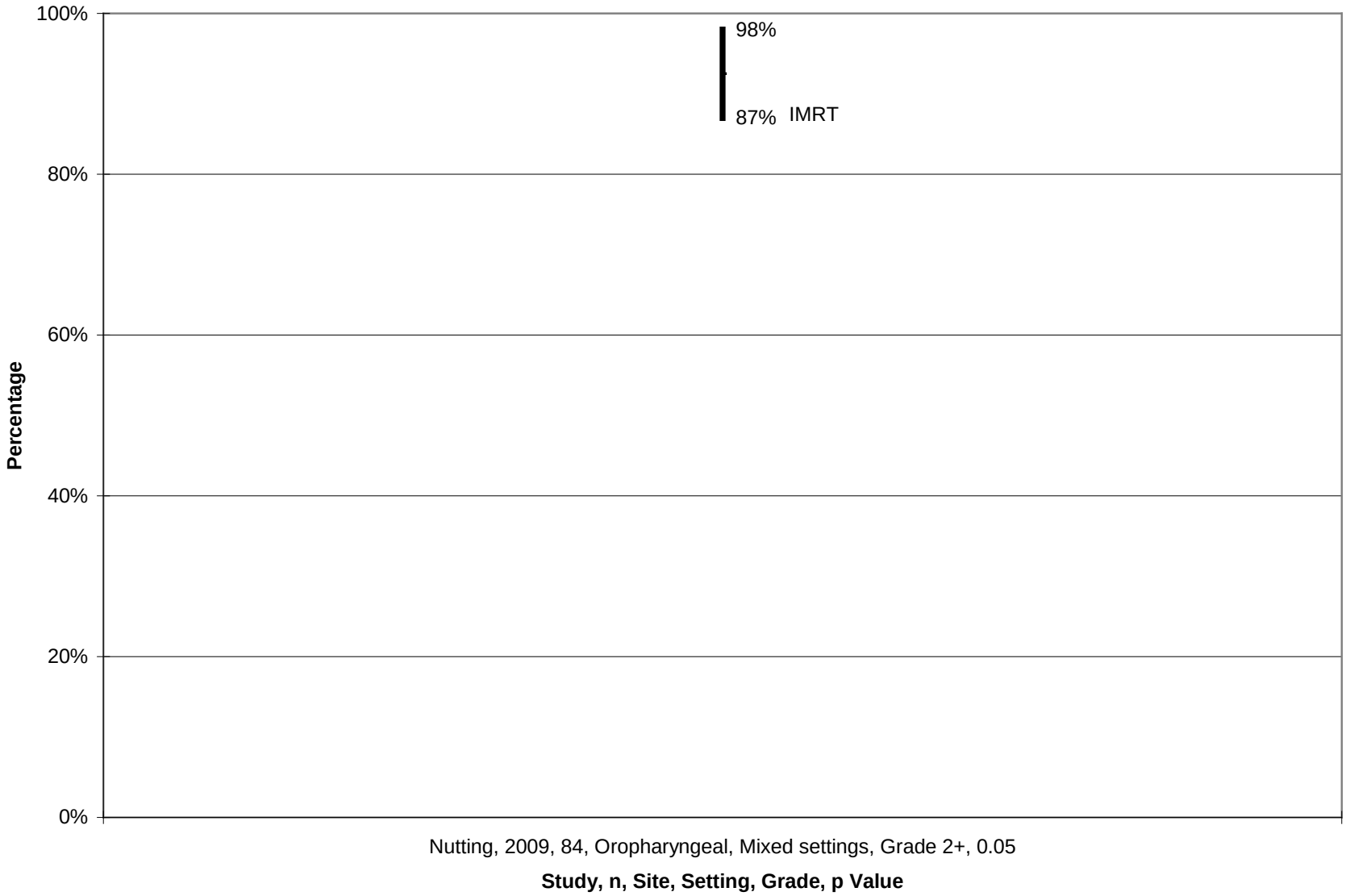


Figure C6. Late dysphagia, IMRT vs. 3DCRT

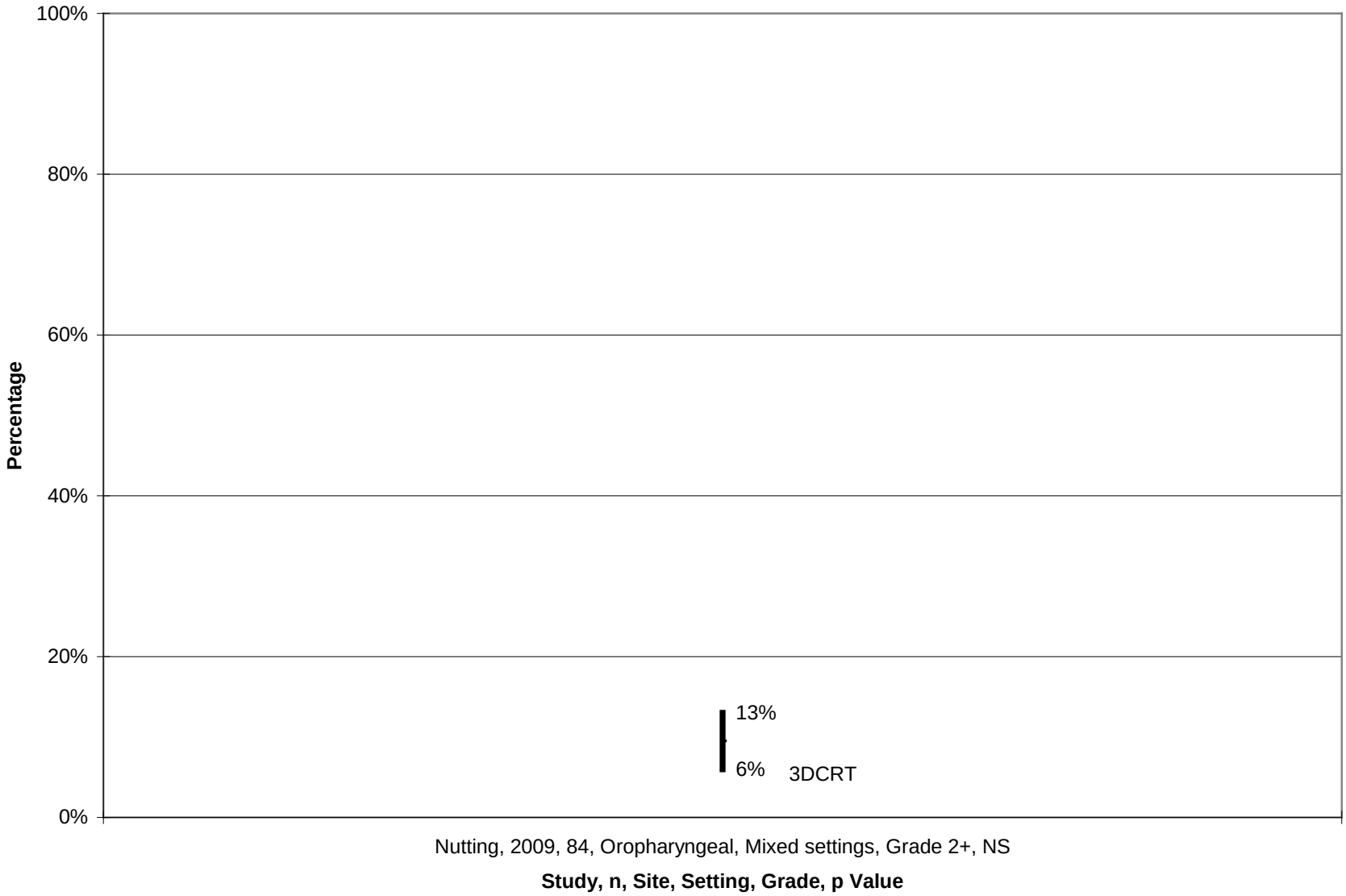


Figure C7. Acute skin toxicity, IMRT vs. 3DCRT

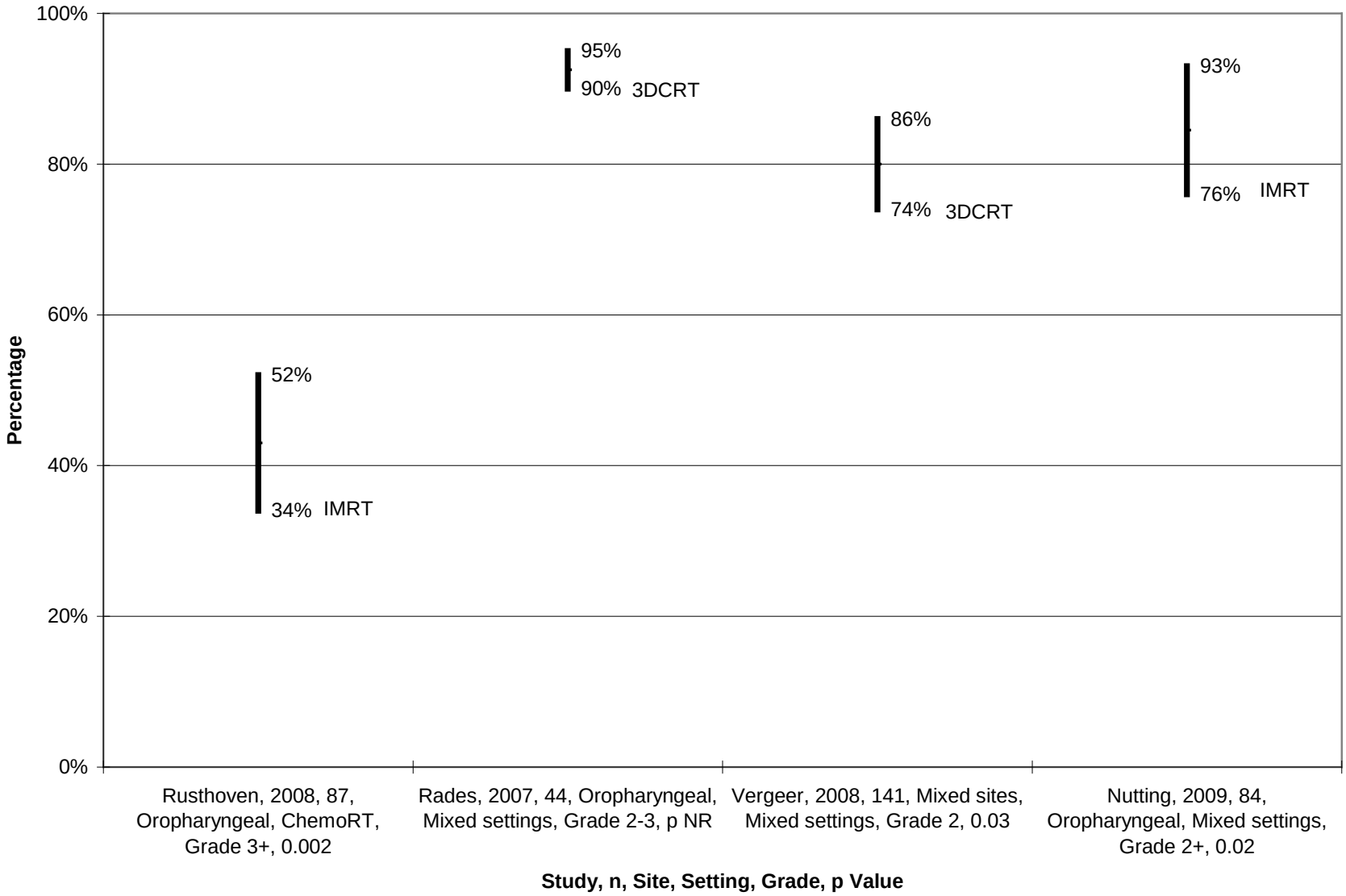


Figure C8. Late skin toxicity, IMRT vs. 3DCRT

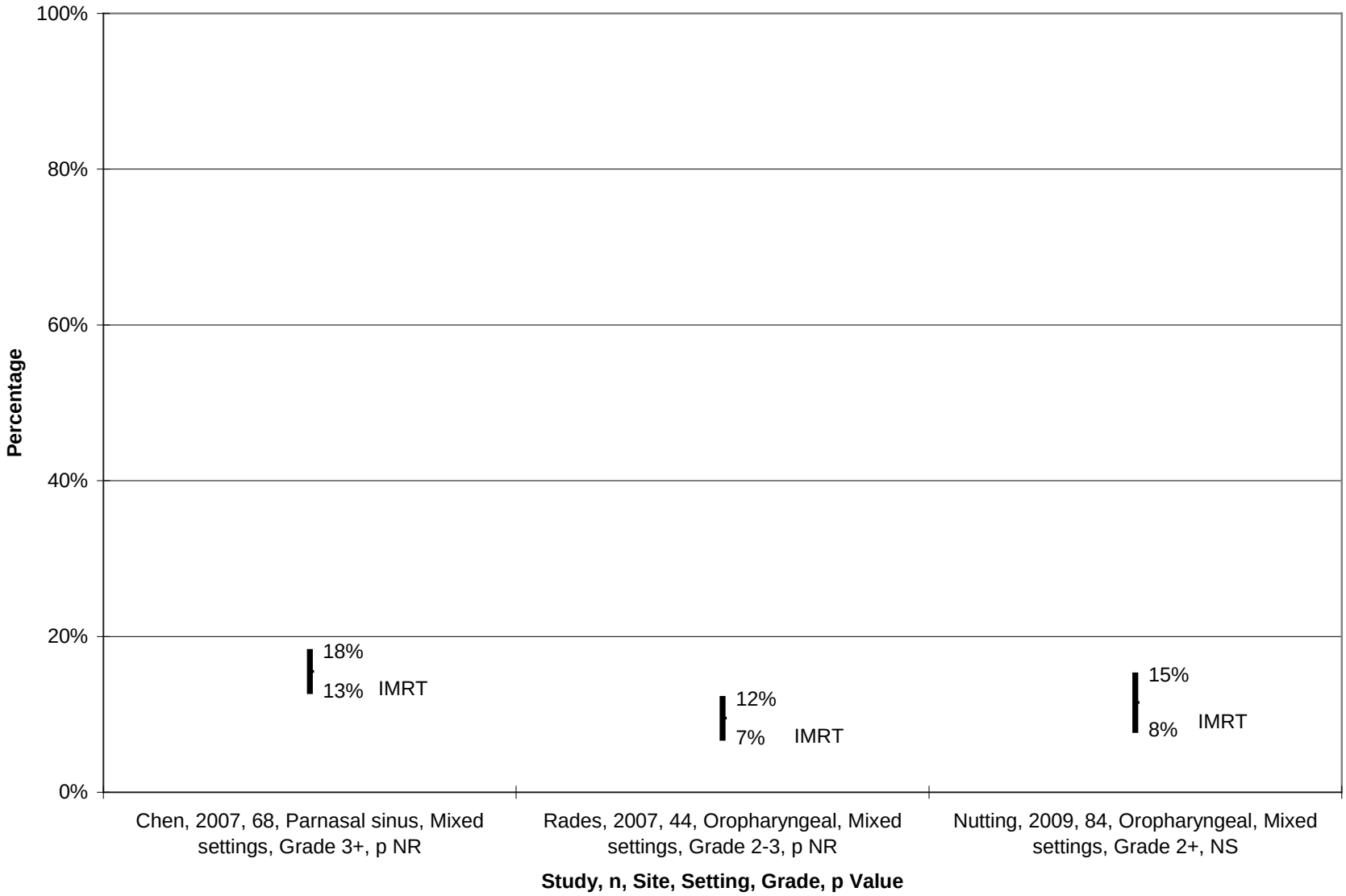


Figure C9. Late osteoradionecrosis/bone toxicity, IMRT vs. 3DCRT

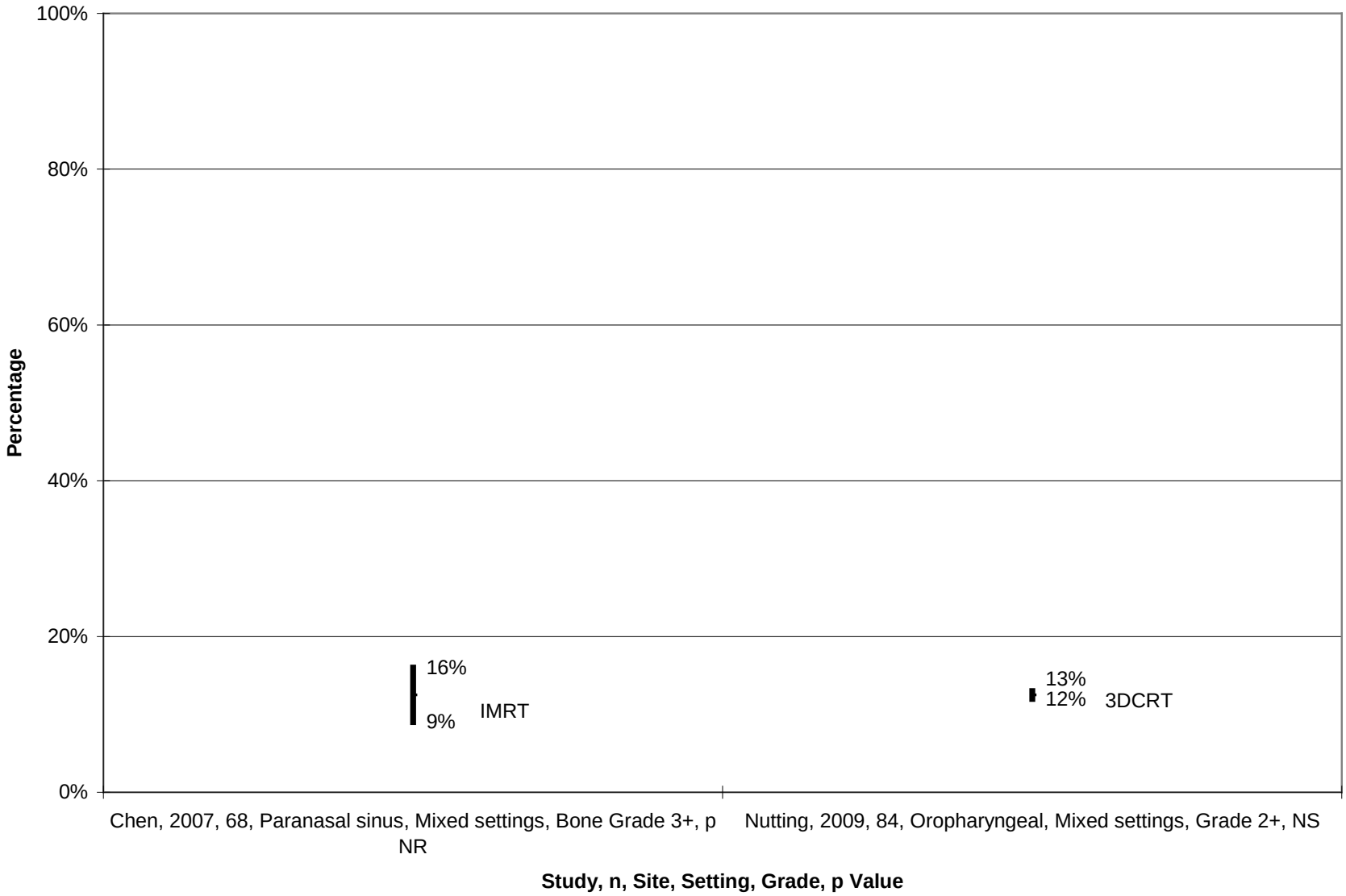


Figure C10. Late xerostomia, 3DCRT vs. 2DRT

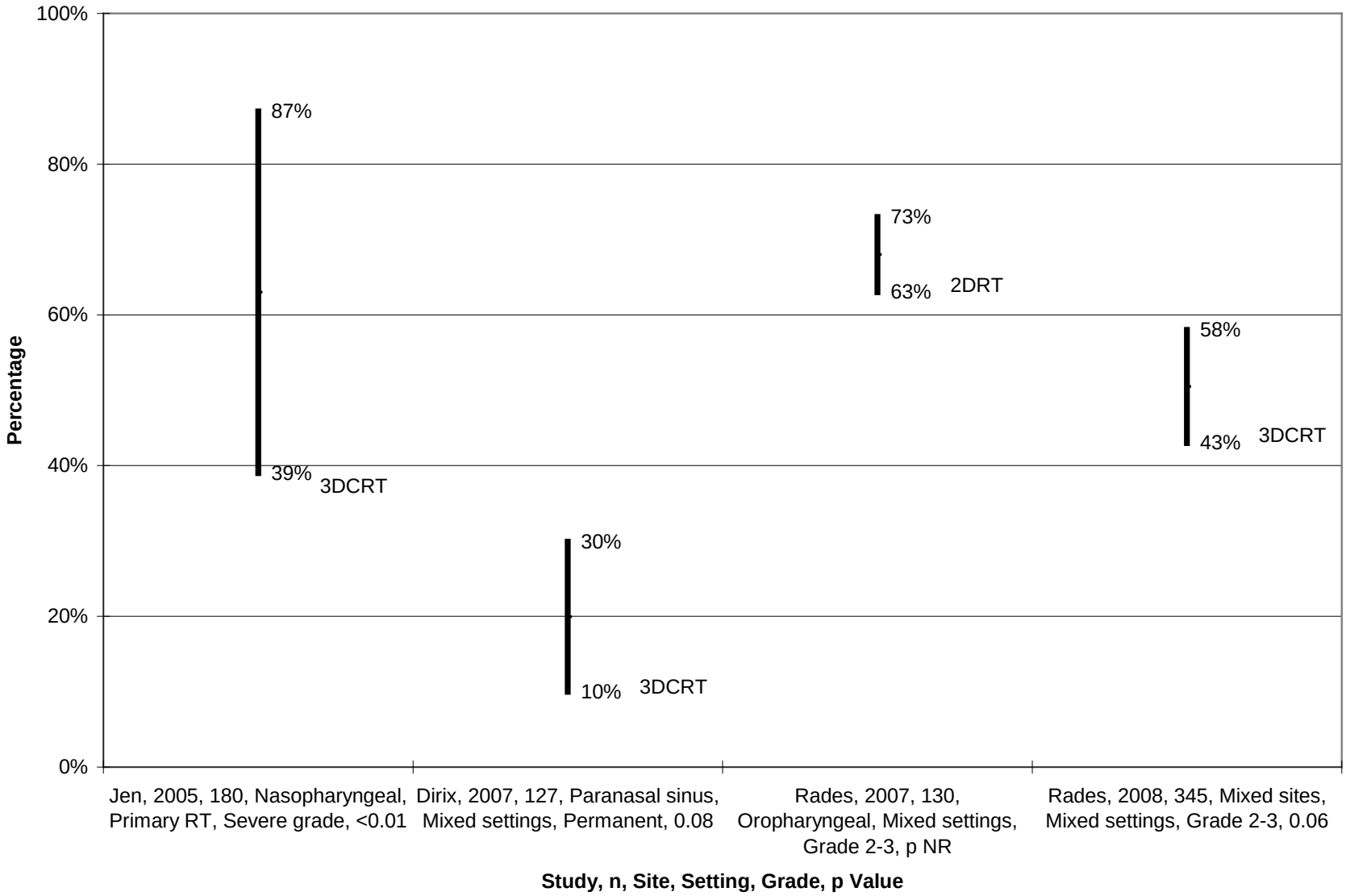


Figure C11. Acute mucositis, 3DCRT vs. 2DRT

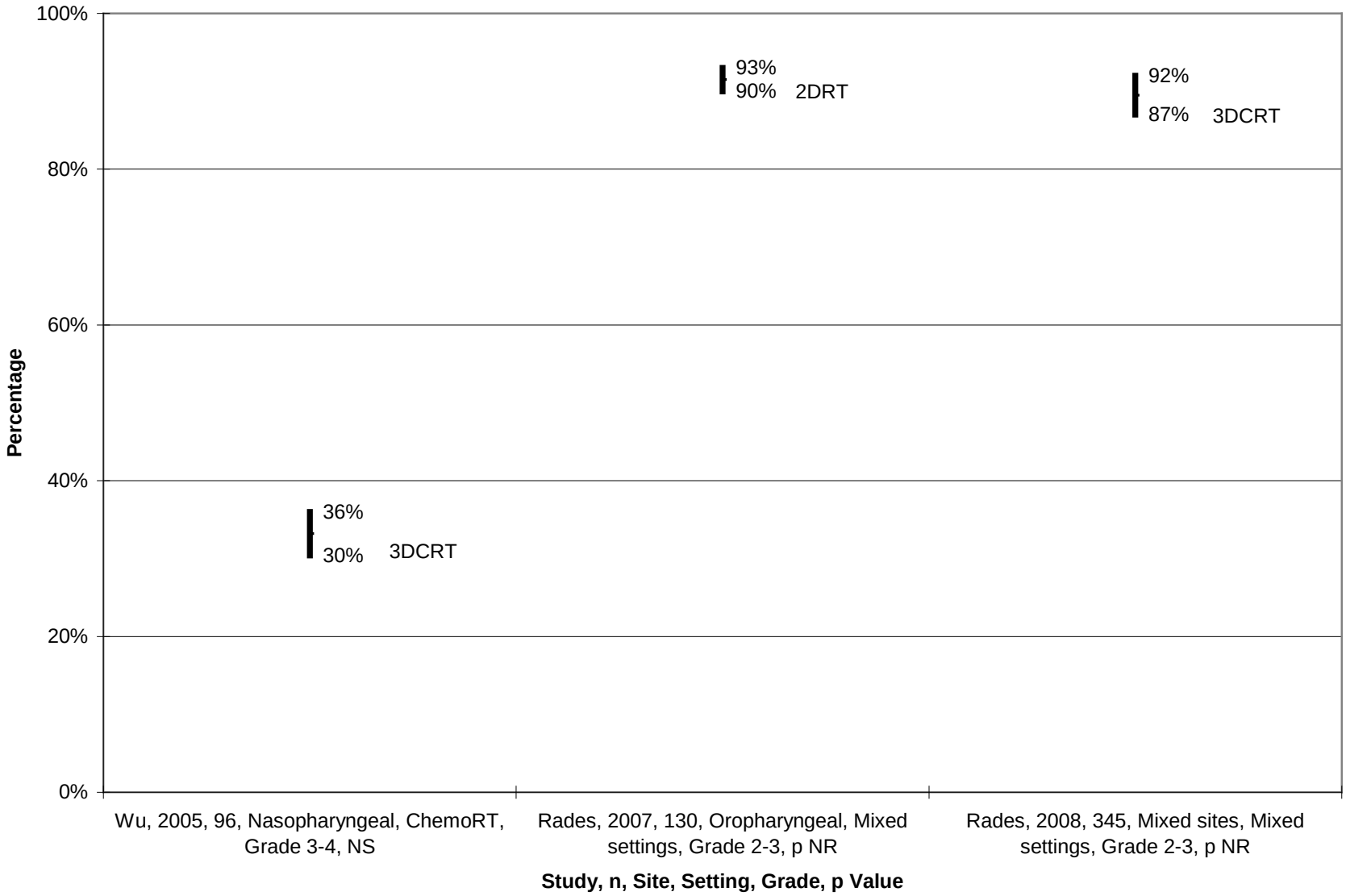


Figure C12. Late mucositis, 3DCRT vs. 2DRT

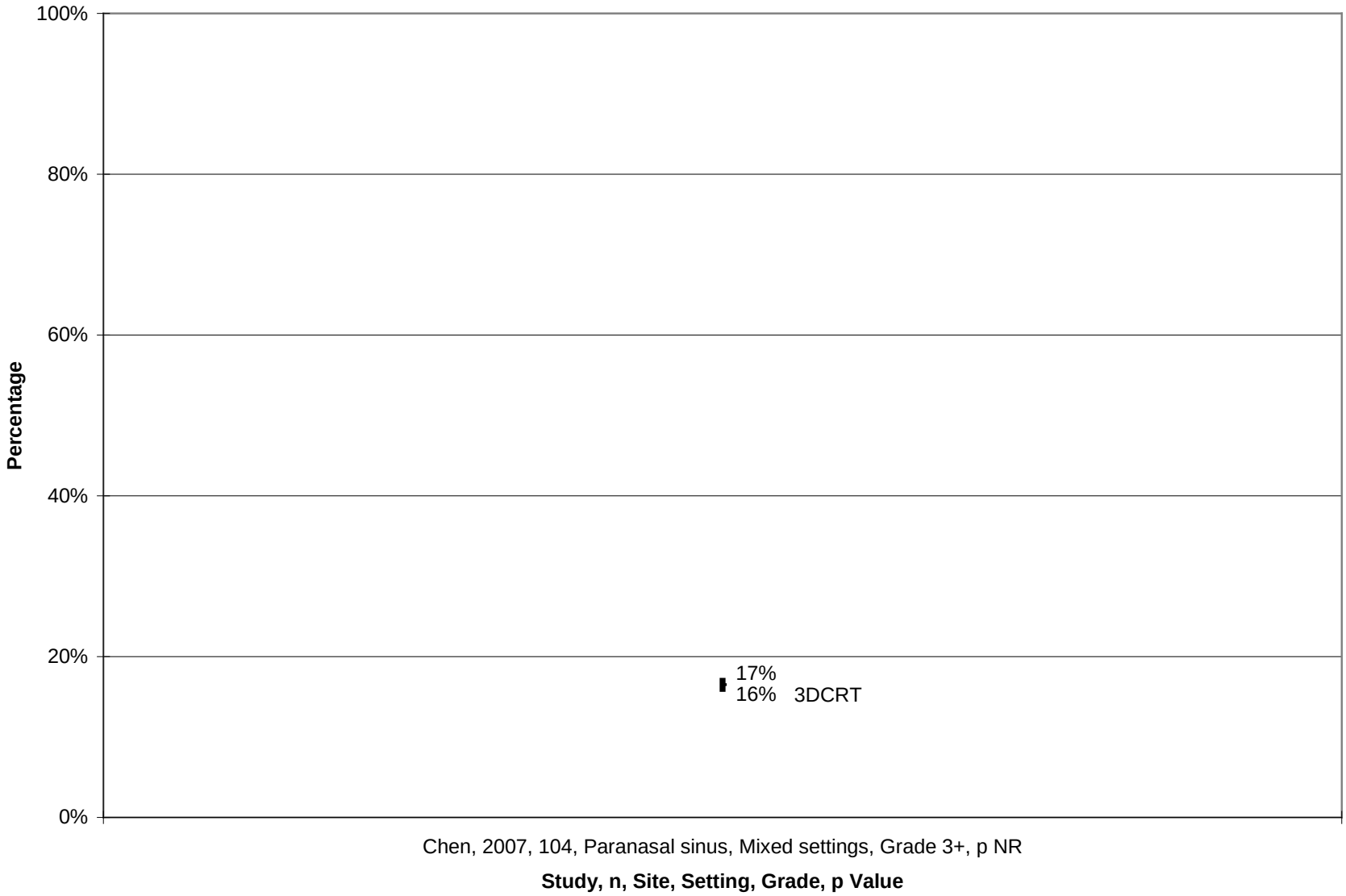


Figure C13. Acute skin toxicity, 3DCRT vs. 2DRT

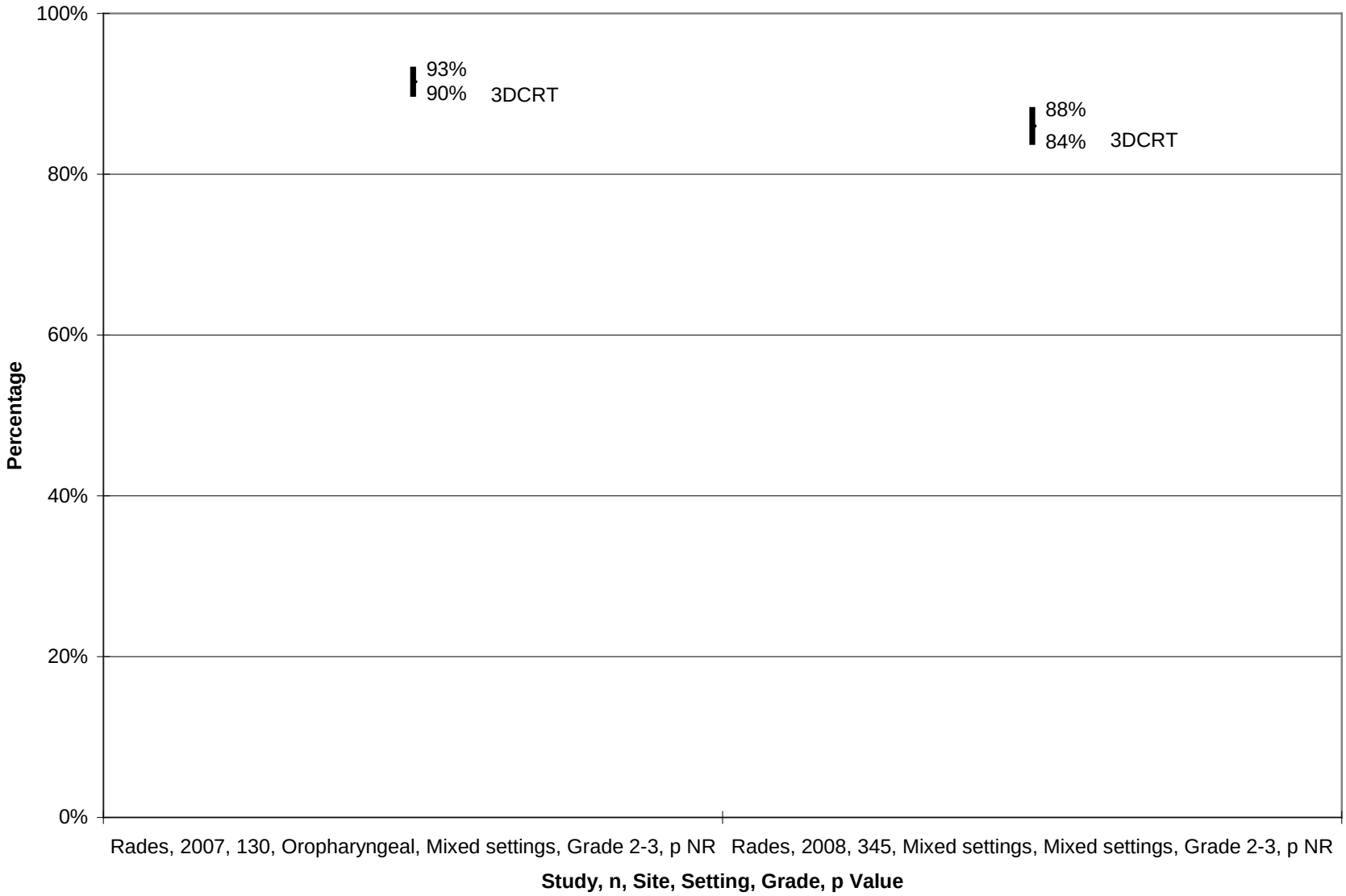


Figure C14. Late skin toxicity, 3DCRT vs. 2DRT

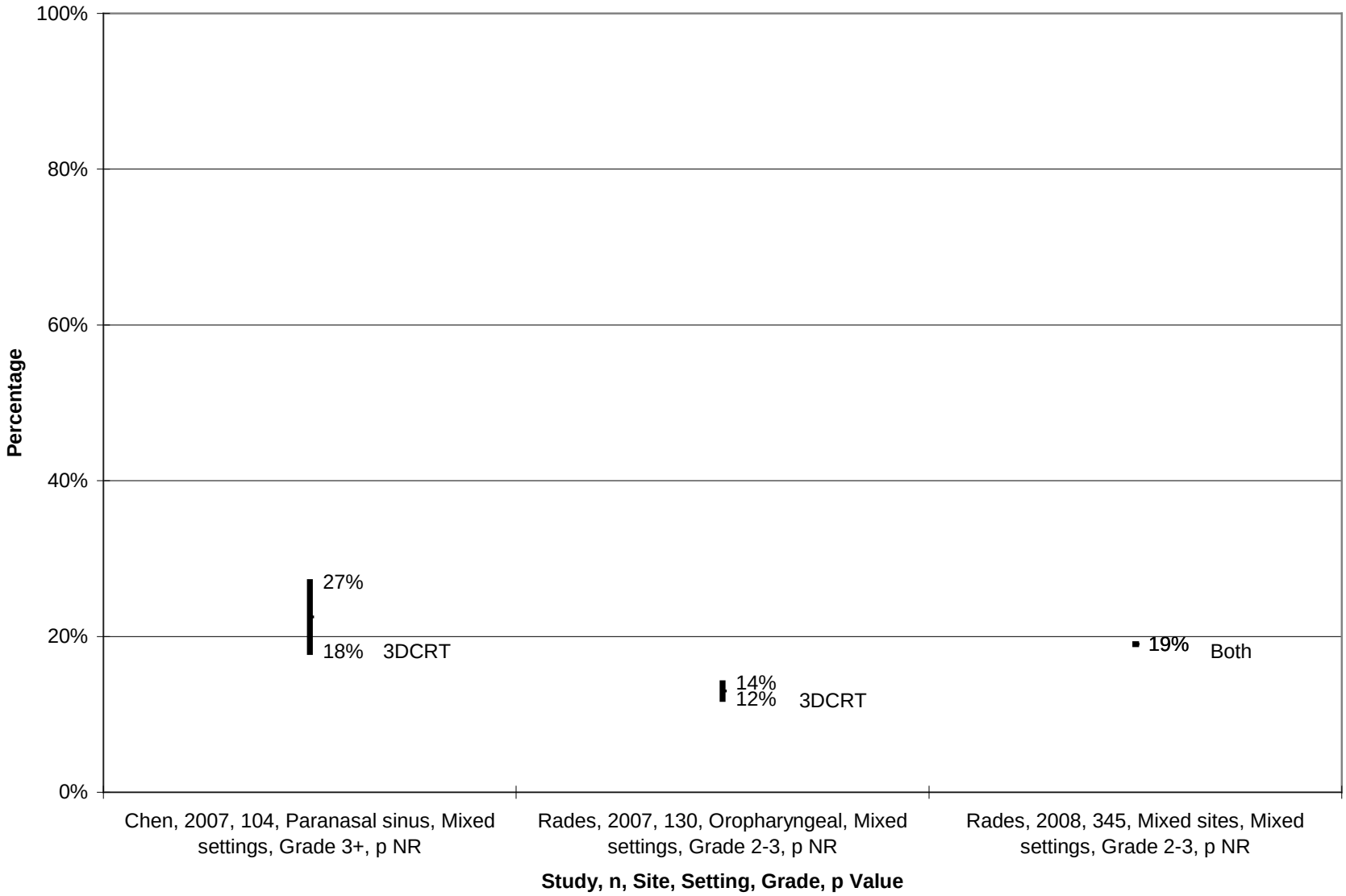


Figure C15. Late osteoradionecrosis/bone toxicity, 3DCRT vs. 2DRT

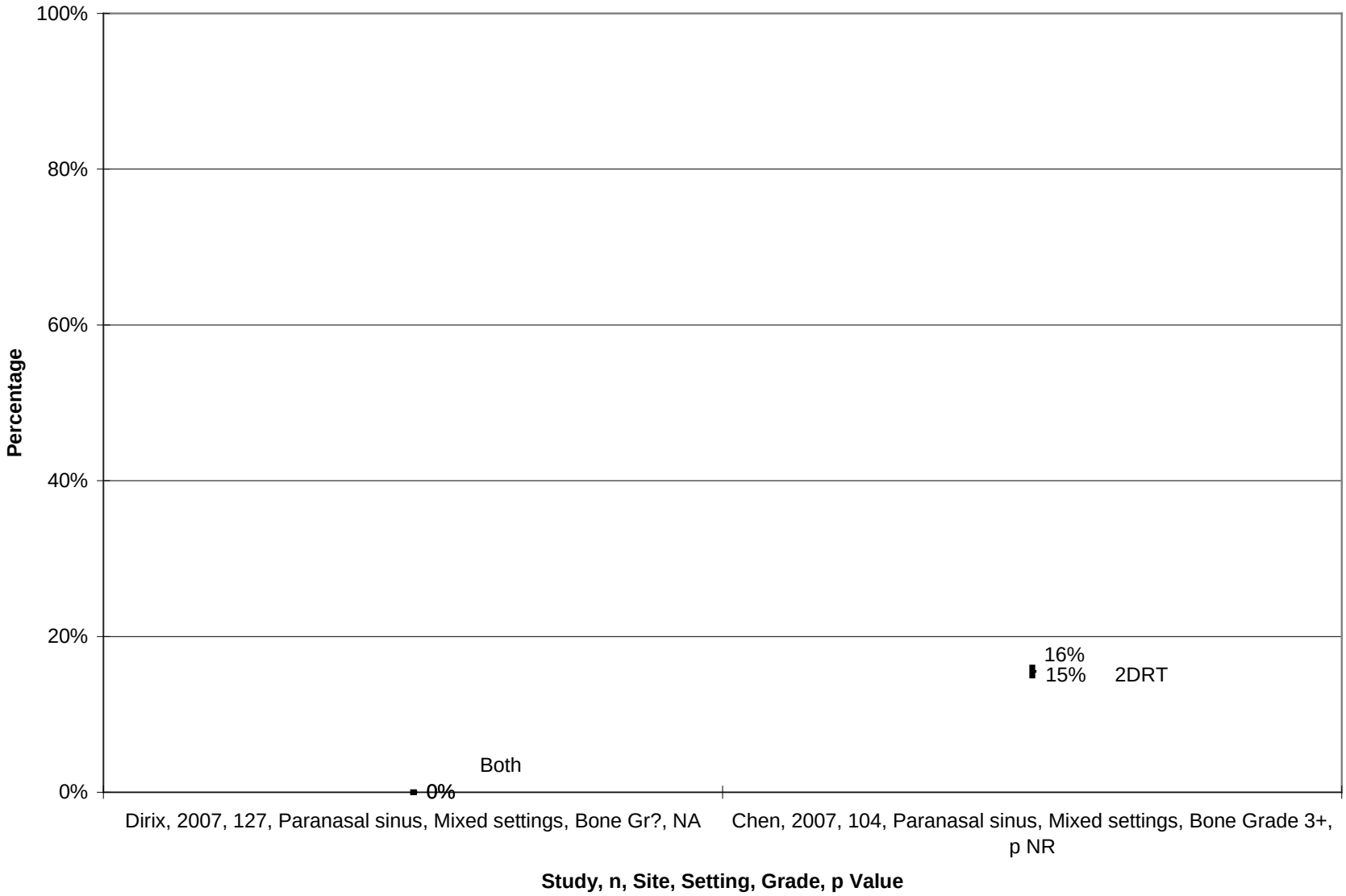


Figure C16. Acute xerostomia, IMRT vs. 2DRT

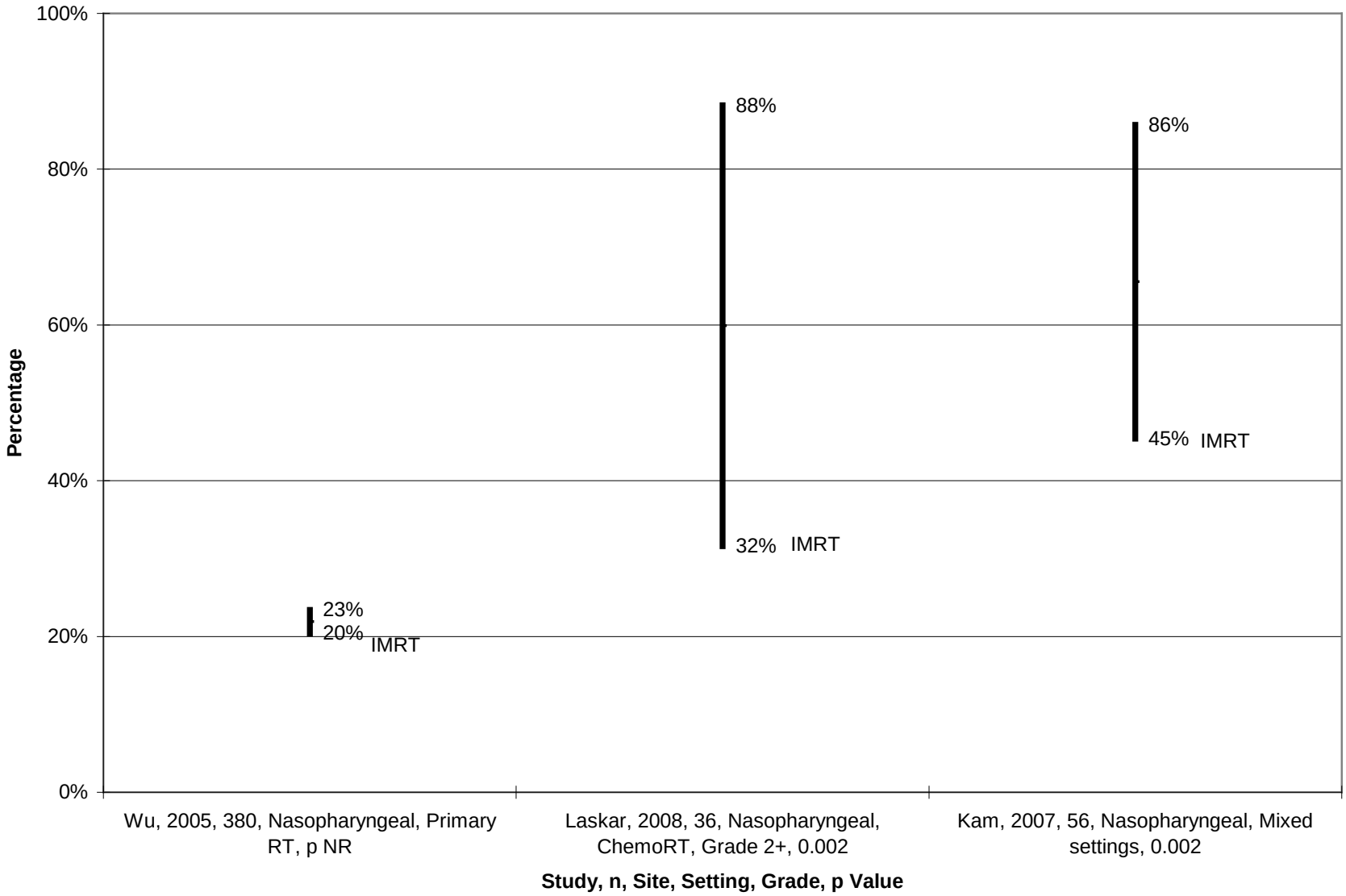


Figure C17. Late xerostomia, IMRT vs. 2DRT

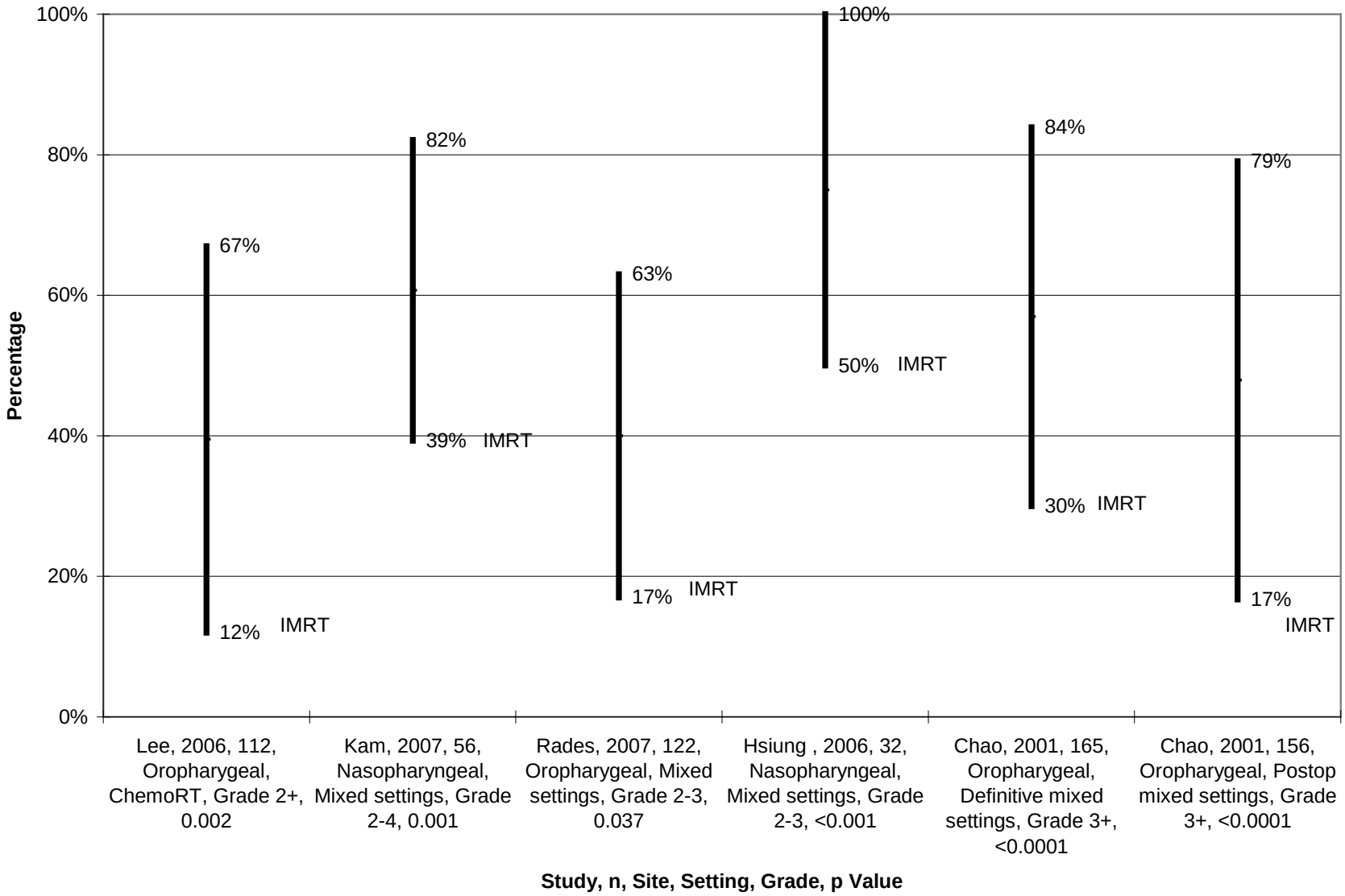


Figure C18. Acute mucositis, IMRT vs. 2DRT

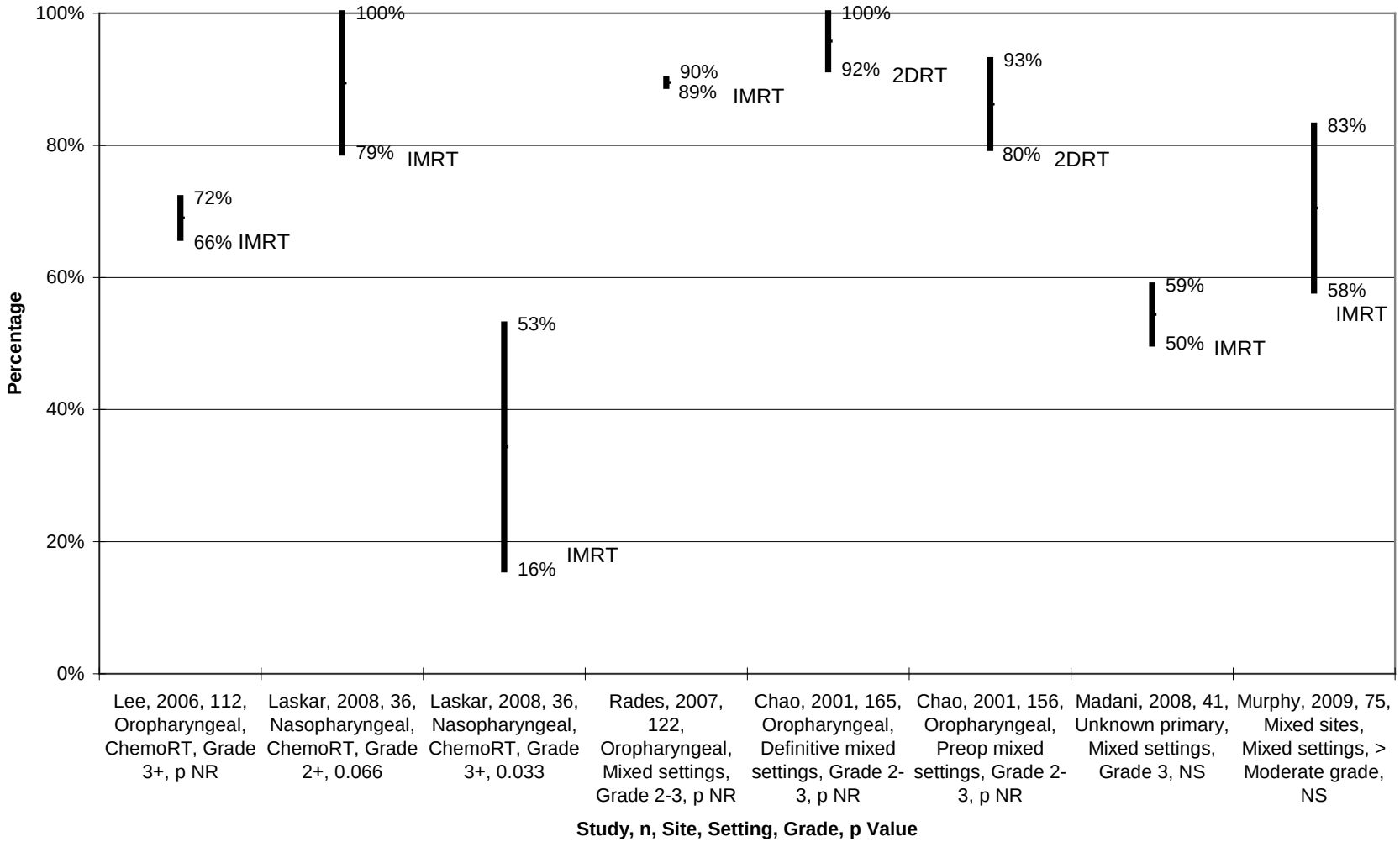


Figure C19. Late mucositis, IMRT vs. 3DRT

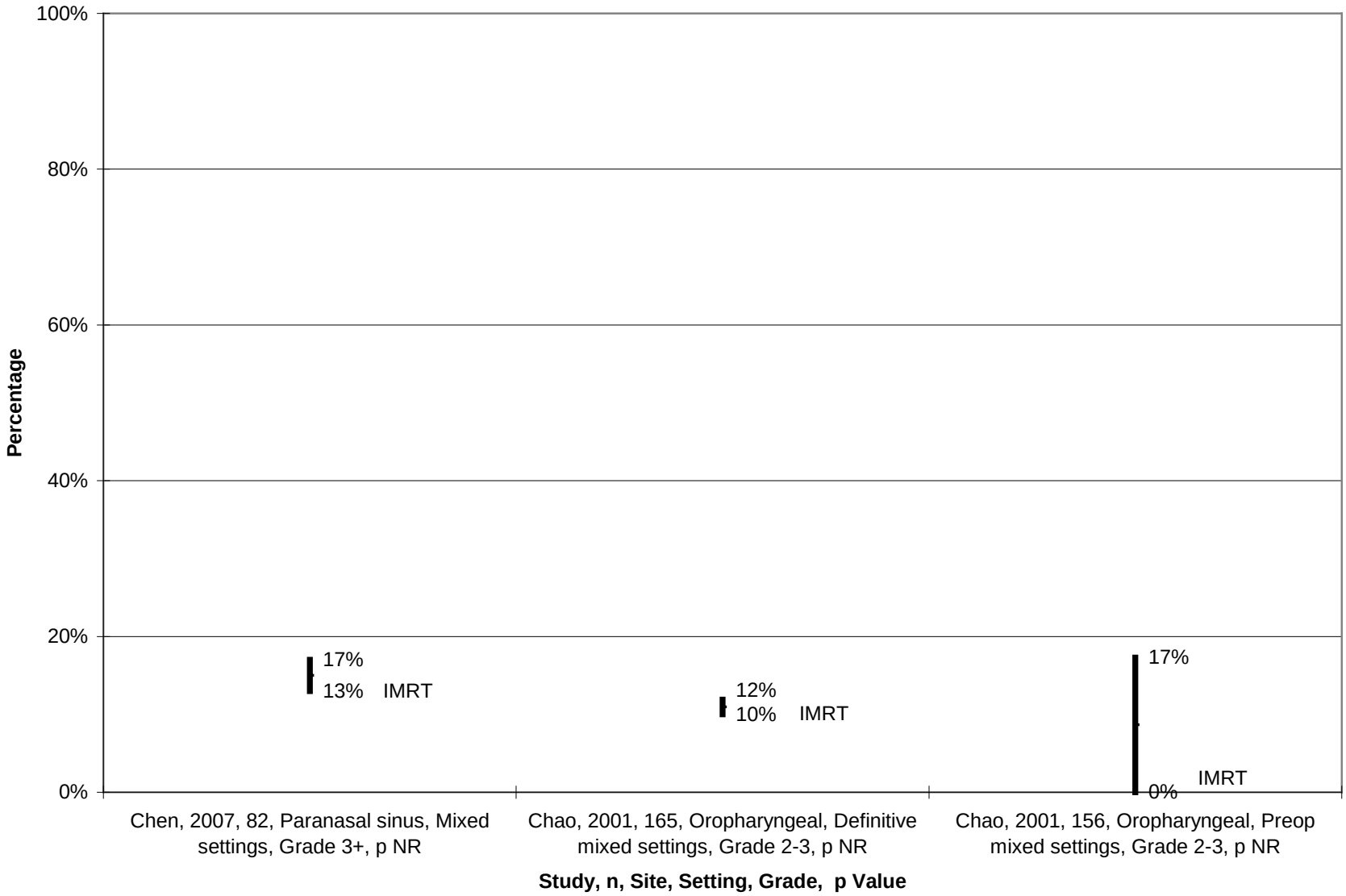


Figure C20. Acute dysphagia, IMRT vs. 2DRT

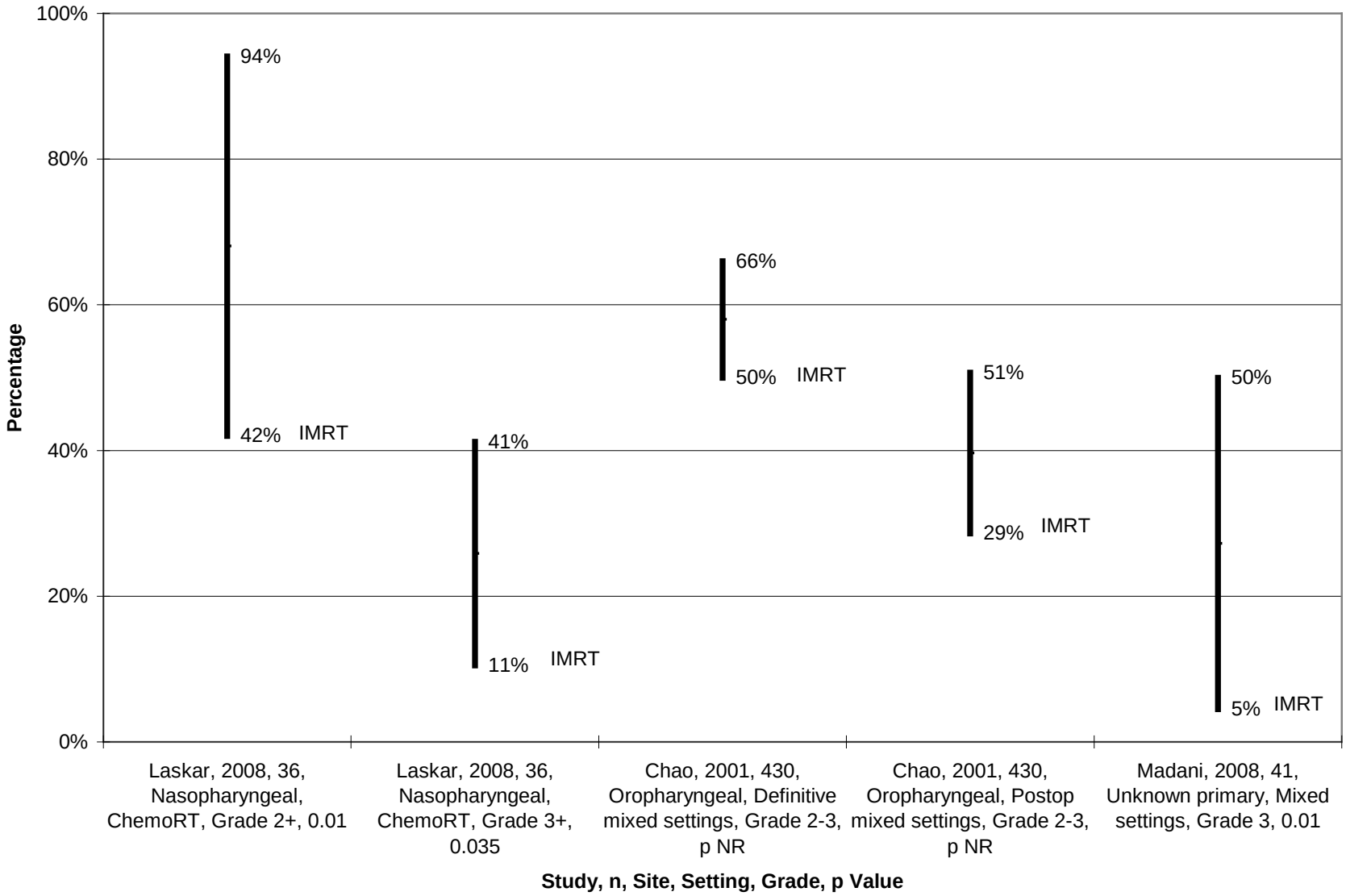


Figure C21. Late dysphagia, IMRT vs. 2DRT

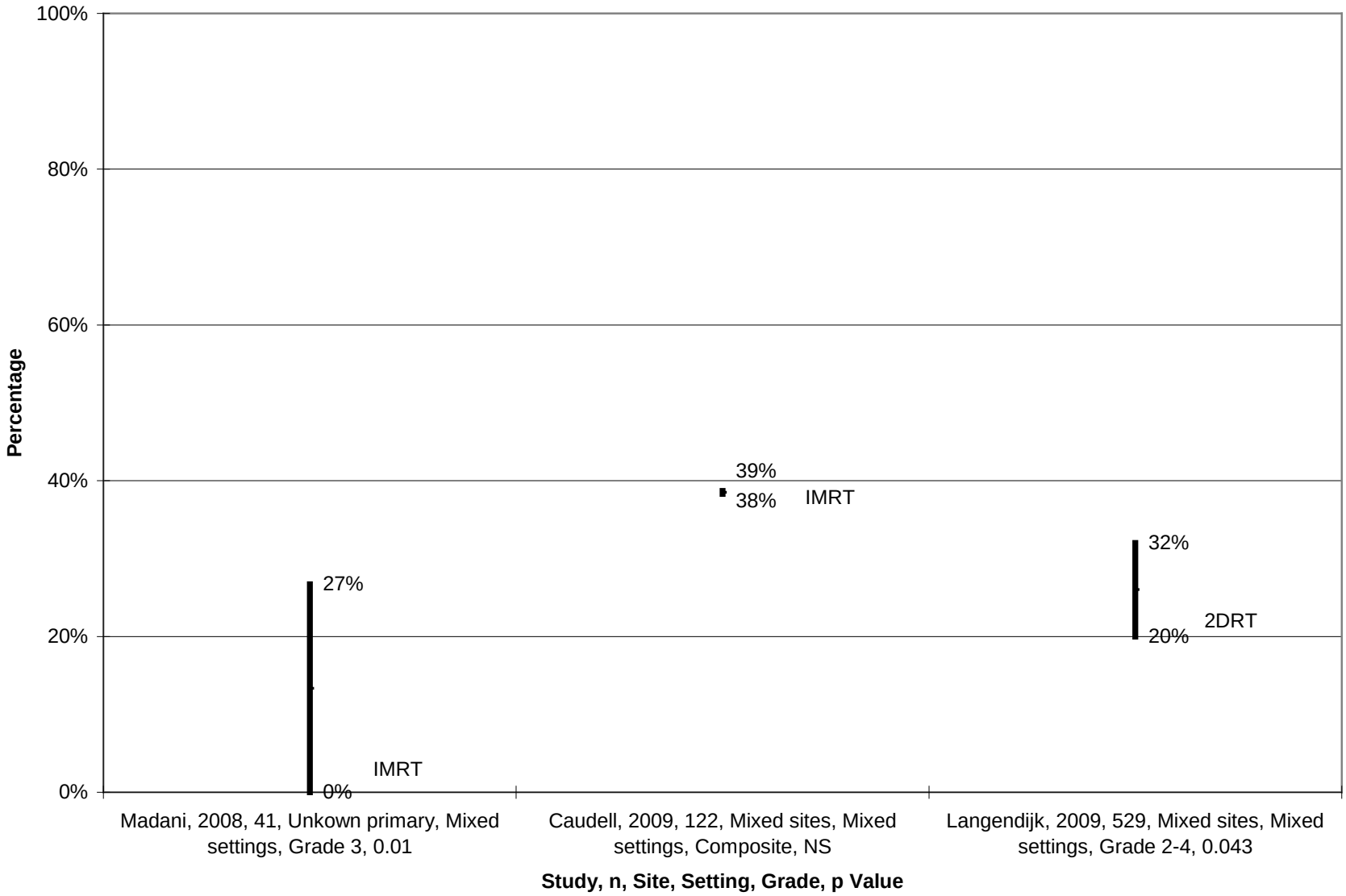


Figure C22. Acute skin toxicity, IMRT vs. 2DRT

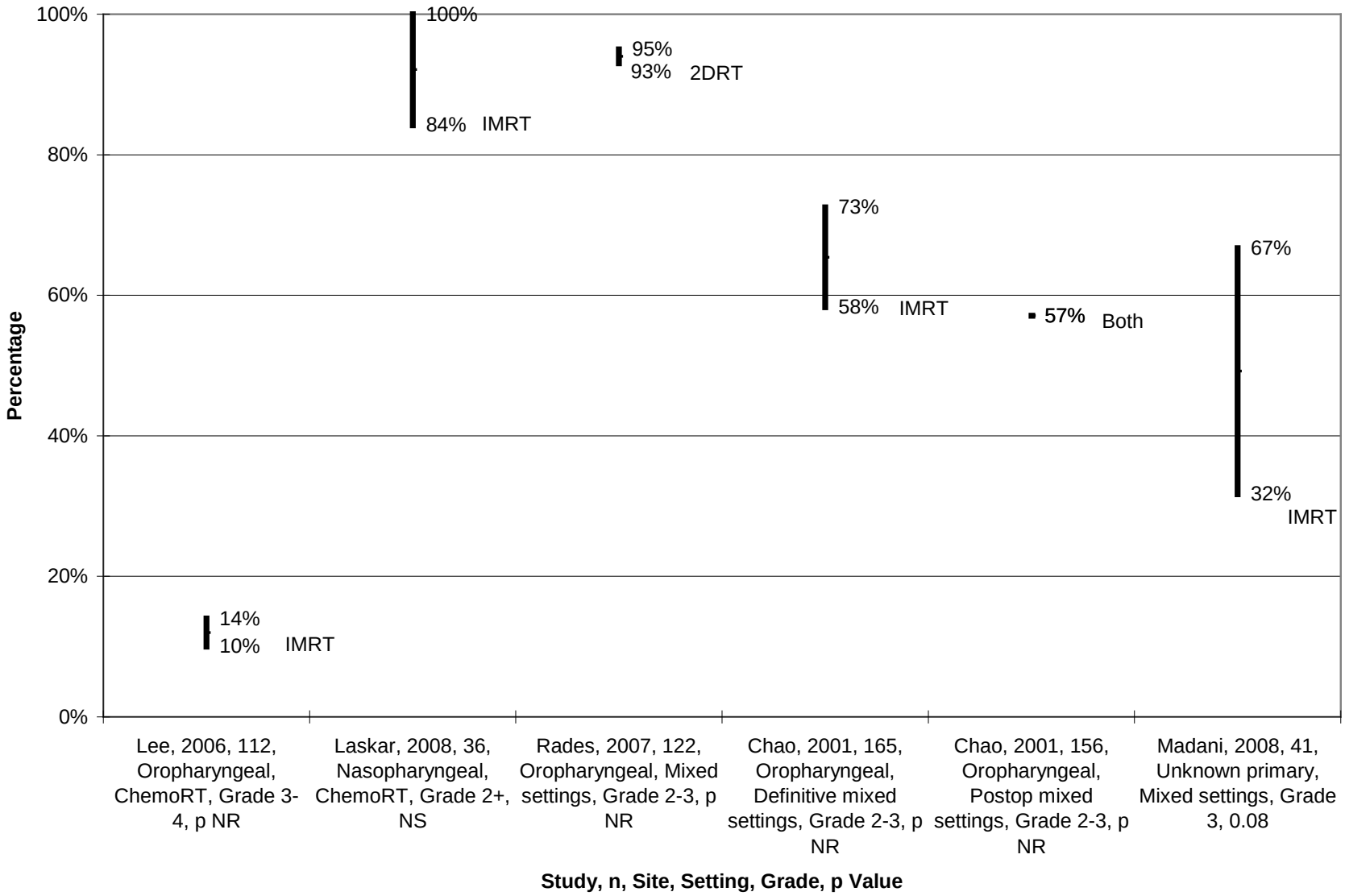


Figure C23. Late skin toxicity, IMRT vs. 2DRT

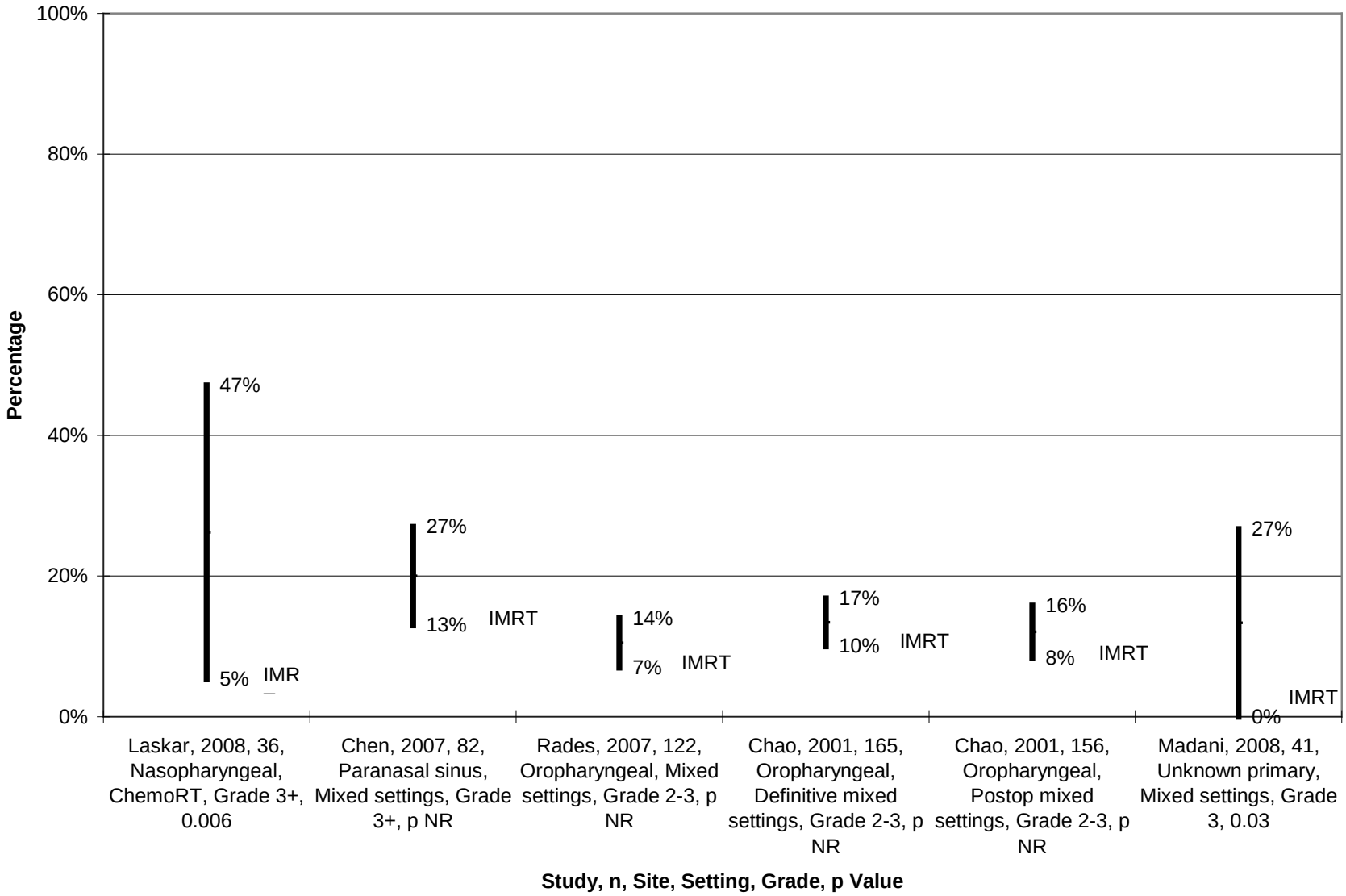
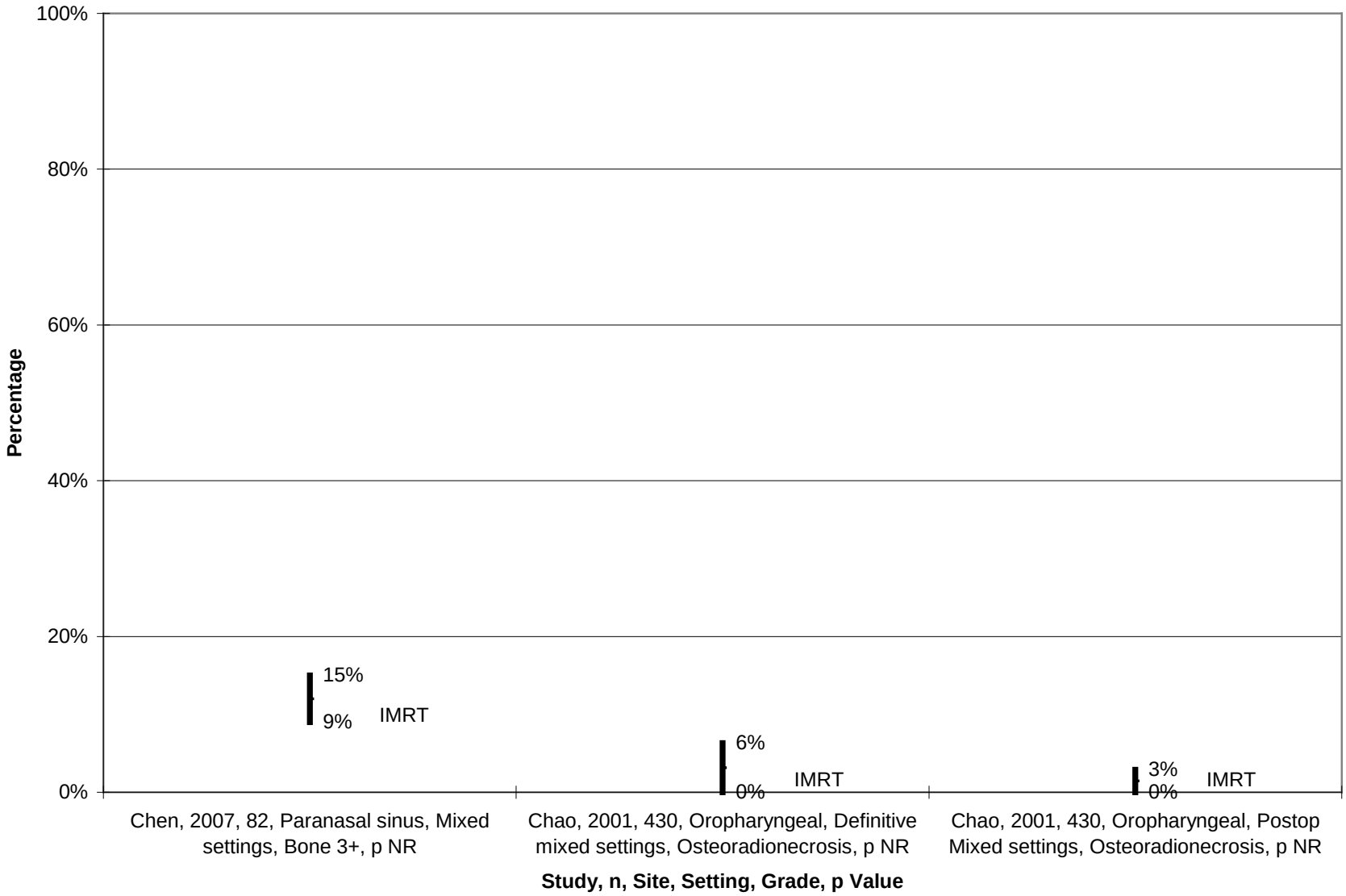


Figure C24. Late osteoradionecrosis/bone toxicity, IMRT vs. 2DRT



Appendix D: Comparative Studies: Full Evidence/Data Abstraction Tables

Table D1a. Nasopharyngeal cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
1° RT															
3DCRT vs 2DRT															
Jen, 2005	5240	180	1° RT		X										
IMRT vs 2DRT															
Pow, 2006 (RCT)	2340	45	1° RT	X		X									
Wu, 2005	4520	380	1° RT		X	X									
1° RT + split CTx															
3DCRT vs 2DRT															
Wu, 2005 (RCT)	4360	96	1° RT + split CTx					X			X				X
IMRT vs 2DRT															
Laskar, 2008	39050	36	1° RT + split CTx		X		X	X	X			X	X		X
Mixed Settings															
IMRT vs 3DCRT															
Fang, 2007	2250	85	1° RT ± CTx (timing?)	X	X										
Fang, 2008	39090	203	1° RT ± CCTx	X								X			X
3DCRT vs 2DRT															
Fang, 2007	2250	94	1° RT ± CTx (timing?)	X	X										
IMRT vs 2DRT															
Kam, 2007 (RCT)	530	56	1° RT ± ICBRT		X	X									
Fang, 2007	2250	113	1° RT ± CTx (timing?)	X	X										
Hsiung, 2006	3070	32	1° RT± CCTx		X										
Comparisons	11			5	8	3	1	2	1	0	1	2	1	0	3
Studies	9			3	6	3	1	2	1	0	1	2	1	0	3
Total n	1174														

Table D1b. Nasopharyngeal cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Completed RT (%)
1^{o} RT										
3DCRT vs 2DRT										
Jen, 2005	5240	180	1^{o} RT	3DCRT 2DR	15 18	43 (19-80) 44 (18-84)	59.7 58.3	70 (all)	26	100 (all)
IMRT vs 2DRT										
Pow, 2006 (RCT)	2340	45	1^{o} RT	IMRT 2DR	25 19	46 (26-69) 50 (37-75)	0 (all)	68 68-72	NR	NR
Wu, 2005	4520	380	1^{o} RT	IMRT 2DR	32 (all)	38 (15-64) (all)	85.8 (all)	75 70	NR	NR
1^{o} RT + split CTx										
3DCRT vs 2DRT										
Wu, 2005 (RCT)	4360	96	1^{o} RT + split CTx	3DCRT 2DR	35 34	45 (16-68) 44 (18-67)	100 (all)	66-86 (all)	NR	NR
IMRT vs 2DRT										
Laskar, 2008	39050	36	1^{o} RT + split CTx	IMRT 2DR	26 18	14 (5-18) (all)	84.2 94.1	70 (all)	27 (4-42)	100 88
Mixed Settings										
IMRT vs 3DCRT										
Fang, 2007	2250	85	1^{o} RT ± CTx (timing?)	IMRT 3DCRT	33 24	49 51	48.1 48.5	65-76 (all)	NR	NR
Fang, 2008	39090	203	1^{o} RT ± CCTx	IMRT 3DCRT	22 17	NR	52.8 55.9	65-76 (all)	40 (5-57) 46 (10-59)	NR
3DCRT vs 2DRT										
Fang, 2007	2250	94	1^{o} RT ± CTx (timing?)	3DCRT 2DR	24 28	51 51	48.1 50.8	65-76 (all)	46 (10-59)	NR
IMRT vs 2DRT										
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT	IMRT 2DR	25 32	46 50	0 (all)	66 + 18 Gy ICB 66 + 12 Gy ICB	NR	100 (all)
Fang, 2007	2250	113	1^{o} RT ± CTx (timing?)	IMRT 2DR	29 28	49 51	48.5 50.8	60-70 (all)	NR	NR
Hsiung , 2006	3070	32	1^{o} RT± CCTx	IMRT 2DR	31 25	NR	50 37.5	67-70 68-76	24 (14-34)	NR

Table D1c. Nasopharyngeal cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT																				
3DCRT vs 2DRT																				
Jen, 2005	5240	180	R	N	N	?	N	Y	?	E	NA	NA	NA	NA	Y	N	Y	md 26	Y/?	Poor
IMRT vs 2DRT																				
Pow, 2006 (RCT)	2340	45	P	Y	Y	Y	Y	Y	Y	?	NA	Y	Y	Y	Y	Y	Y	?	N	Poor
Wu, 2005	4520	380	R	Y	Y	?	N	?	?	?	NA	NA	NA	NA	Y	N	Y	?	N	Poor
1° RT + split CTx																				
3DCRT vs 2DRT																				
Wu, 2005 (RCT)	4360	96	P	Y	Y	?	Y	Y	Y	?	Y	?	Y	Y	Y	N	Y	?	N	Poor
IMRT vs 2DRT																				
Laskar, 2008	39050	36	P	Y	Y	Y	N	Y	Y	A/P	Y	?	Y	Y	Y	?	Y	md 27	Y/?	Poor
Mixed Settings																				
IMRT vs 3DCRT																				
Fang, 2007	2250	85	R	Y	N	Y	N	Y	N	E	?	NA	NA	NA	Y	N	Y	?	N	Poor
Fang, 2008	39090	203	P	Y	Y	Y	N	Y	Y	A/P	Y	?	Y	Y	Y	?	Y	md 40,46	Y/?	Poor
3DCRT vs 2DRT																				
Fang, 2007	2250	94	R	Y	N	Y	N	Y	N	E	?	NA	NA	NA	Y	N	Y	?	N	Poor
IMRT vs 2DRT																				
Kam, 2007 (RCT)	530	56	P	Y	Y	Y	Y	Y	Y	Y	N	?	Y	Y	Y	?	Y	?	Y	Fair
Fang, 2007	2250	113	R	Y	N	Y	N	Y	N	E	?	NA	NA	NA	Y	N	Y	?	N	Poor
Hsiung , 2006	3070	32	R	Y	?	N	N	Y	N	E	N	NA	NA	NA	Y	N	Y	md 24	N	Poor

Table D1d. Nasopharyngeal cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
1° RT															
3DCRT vs 2DRT															
Jen, 2005	5240	N	N	Y	Y	NA	Y	?	md 26	Y	N	?	?	?	N
1° RT + split CTx															
IMRT vs 2DRT															
Laskar, 2008	39050	Y	N	N	Y	NA	Y	Y	md 27	N	?	?	?	?	N
Mixed Settings															
IMRT vs 3DCRT															
Fang, 2008	39090	Y	N	Y	Y	NA	N	Y	md 40, 46	N	?	?	?	?	N

Table D1e. Nasopharyngeal cancer, quality of life

EORTC QLQ-C30

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Global health	54.9 63.2 63.9	52.8 61.9 63.5	2 6 12 all		41 44 58 61	46 56 63 64	0 3 12 24	<0.05	49	61	64	24-36	NS
Global health-revised	53.8 61.5 62.2	53.6 60.3 62.3	2 6 12 all										NS
Physical function	84.4 86.9 91.1	83.8 88.3 90.5	2 6 12 all		84 79 86 87	87 86 90 91	0 3 12 24		80	87	91	24-36	NS
Role function	94.4 96.5 97.2	94.4 97.6 96.0	2 6 12 all		86 84 90 90	86 88 92 92	0 3 12 24		82	90	92	24-36	NS
Role function-revised	81.9 92.4 100.0	84.9 96.8 95.2	2 6 12 all	<0.05									NS
Emotional function	87.8 91.3 91.7	83.7 89.7 88.9	2 6 12 all						76	84	85	24-36	NS
Cognitive function	86.1 86.8 89.6	85.7 86.5 84.1	2 6 12 all						77	85	85	24-36	NS
Social function	81.3 91.0 93.1	83.3 91.3 92.9	2 6 12 all		72 71 82 82	71 77 81 83	0 3 12 24		75	82	83	24-36	NS

EORTC QLQ-C30 (continued)

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Fatigue	20.4 16.7 13.0	20.1 14.8 13.8	2 6 12 all		36 39 25 24	34 29 24 25	0 3 12 24	<0.05	35	24	25	24-36	NS
Nausea/ vomiting	7.6 0.0 0.7	3.2 0.0 2.4	2 6 12 all		26 15 8 4	22 11 8 4	0 3 12 24		9	4	4	24-36	NS
Pain	7.6 6.3 2.8	7.9 7.1 9.5	2 6 12 all		35 26 10 11	28 18 14 12	0 3 12 24		25	11	12	24-36	NS
Dyspnea	13.9 8.3 4.2	12.7 9.5 3.2	2 6 12 all		11 16 6 6	13 11 7 6	0 3 12 24		17	6	6	24-36	NS
Insomnia	15.3 6.9 6.9	14.3 12.7 11.1	2 6 12 all		27 30 22 19	23 25 22 21	0 3 12 24		27	19	21	24-36	NS
Appetite loss	23.6 8.3 8.3	15.9 7.9 7.9	2 6 12 all		43 32 10 9	41 21 11 8	0 3 12 24		19	9	8	24-36	NS
Constipation	11.1 6.9 5.6	15.9 7.9 11.1	2 6 12 all		16 20 17 15	17 11 13 13	0 3 12 24		17	15	13	24-36	NS
Diarrhea	0.0 4.2 1.4	11.1 7.9 4.8	2 6 12 all	<0.05 0.009	19 16 10 10	14 11 10 11	0 3 12 24		12	10	11	24-36	NS
Financial difficulties	15.3 11.1 5.6	11.1 14.3 11.1	2 6 12 all		25 30 20 22	23 22 22 23	0 3 12 24		26	22	23	24-36	NS

SF-36

	Pow, 2006, Rec# 2340			
Domain	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**
Physical function	89.4 92.5 94.4	88.3 92.6 93.8	2 6 12 all	
Role-physical	33.3 60.4 86.5	27.4 48.8 58.3	2 6 12 all	<0.05
Bodily pain	78.0 85.4 89.8	76.2 82.5 75.6	2 6 12 all	<0.05
General health	51.8 55.8 65.7	47.9 52.9 58.7	2 6 12 all	
Vitality	58.1 65.2 70.6	57.6 61.2 63.1	2 6 12 all	
Social functioning	71.4 92.2 91.7	70.2 86.9 92.3	2 6 12 all	
Role-emotional	50.0 77.8 86.1	47.6 55.6 73.0	2 6 12 all	
Mental health	76.5 80.8 84.5	74.5 76.8 80.8	2 6 12 all	

EORTC QLQ-H&N35

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Pain	15.6 9.4 7.3	16.7 15.1 12.7	2 6 12 all		37 27 15 13	34 20 11 10	0 3* 12 24		18	13	10	24-36	NS
Swallowing	9.0 8.7 6.6	13.5 10.7 10.7	2 6 12 all	<0.05 0.022	38 26 23 22	35 21 17 16	0 3* 12 24		30	22	16	24-36	NS
Taste/smell	42.4 27.1 20.1	28.6 17.5 18.3	2 6 12 all	<0.05	36 35 23 22	40 22 21 19	0 3 12 24	<0.05	29	22	19	24-36	NS
Speech	12.5 7.4 3.2	13.2 15.9 10.1	2 6 12 All	<0.05 <0.05 0.053	18 26 14 12	19 17 14 12	0 3 12 24		25	12	12	24-36	NS
Social eating	22.2 11.1 7.3	22.5 13.6 11.5	2 6 12 all		35 27 17 16	37 22 14 13	0 3 12 24		30	16	13	24-36	NS
Social contact	6.4 3.3 0.8	7.6 2.5 2.2	2 6 12 all		15 18 9 9	20 15 10 8	0 3 12 24		18	9	8	24-36	NS
Sexuality	31.1 24.2 22.0	35.6 26.7 25.6	2 6 12 all		27 33 24 24	30 25 19 19	0 3 12 24		27	24	19	24-36	NS
Teeth	8.3 5.6 6.9	5.0 5.0 5.0	2 6 12 all		23 24 23 21	21 20 22 21	0 3 12 24		40	21	21	24-36	NS
Opening mouth	8.3 15.3 12.5	14.3 23.8 19.0	2 6 12 all		24 21 16 15	21 15 15 14	0 3* 12 24		33	15	14	24-36	NS

EORTC QLQ-H&N35 (continued)

	Pow, 2006; Rec # 2340				Fang, 2008; Rec # 39090				Fang, 2007; Rec # 2250				
Item	**Mean IMRT n=24**	**Mean 2DRT n=21**	**Mo F/U**	**p Value**	**Mean IMRT n≥79**	**Mean 3DCRT n≥66**	**Mo F/U**	**p Value**	**Mean IMRT n=52**	**Mean 3DCRT n=33**	**Mean 2DRT n=61**	**Mo F/U**	**IMRT vs 3DCRT p value**
Dry mouth	72.2 59.7 47.2	81.0 69.8 60.3	2 6 12 all	 0.021	54 59 45 44	50 49 41 41	0 3 12 24	 <0.05 	53	44	41	24-36	NS
Sticky saliva	62.5 44.4 40.3	87.3 79.3 66.7	2 6 12 all	<0.05 <0.05 <0.05 <0.001	46 45 34 35	46 44 34 34	0 3 12 24	 	47	35	34	24-36	NS
Coughing	12.5 6.9 4.2	11.1 19.0 12.7	2 6 12 all	 <0.05 	31 30 20 19	27 25 20 20	0 3 12 24	 	27	19	20	24-36	NS
Feeling ill	4.2 4.2 4.2	6.3 9.5 6.3	2 6 12 all	 	38 36 24 23	34 25 20 20	0 3 12 24	 <0.05 	34	23	20	24-36	NS
Pain killers	4.2 4.2 12.5	14.3 4.8 9.5	2 6 12 all	 									
Nutrition supplement	33.3 20.8 20.8	9.5 23.8 28.6	2 6 12 all	 									
Feeding tube	4.2 0.0 0.0	0.0 0.0 0.0	2 6 12 all	 									
Weight loss	25.0 8.3 4.2	9.5 19.0 0.0	2 6 12 all	 									
Weight gain	16.7 25.0 37.5	47.6 23.8 28.6	2 6 12 all	<0.05 									

Table D1f. Nasopharyngeal cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1^{o} RT												
3DCRT vs 2DRT												
Jen, 2005	5240	180	1^{o} RT	3DCRT 2DRT	59.7 58.3	RTOG	2-3			OR: 0.55	0.0053	MVA: GEE method
IMRT vs 2DRT												
Wu, 2005	4520	380	1^{o} RT	IMRT 2DRT	85.8 (all)	?	?	20.4 23.4	NR			
1^{o} RT + split CTx												
IMRT vs 2DRT												
Laskar, 2008	39050	36	1^{o} RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	$\geq$ 2	31.6 88.2	0.002			
Mixed Settings												
IMRT vs 2DRT												
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT	IMRT 2DRT	0 0	RTOG EORTC 6 wk, 6 mo, 1 yr	2-4	45.4 85.7	0.002	75 92.9 39.3 82.1	0.001	
Hsiung , 2006	3070	32	1^{o} RT± CCTx	IMRT 2DRT	50 37.5	RTOG	2-3			50 100	<0.001	

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Scale	Item	Mean	F/U	p value	Comments
Mixed Settings											
IMRT vs 3DCRT											
Fang, 2007	2250	85	1^{o} RT ± CTx (timing?)	IMRT 3DCRT	48.1 48.5	QLQ-H&N35 item	Dry mouth	41 44	2-3 yr	NR	MVA combined IMRT+3DCRT
3DCRT vs 2DRT											
Fang, 2007	2250	94	1^{o} RT ± CTx (timing?)	3DCRT 2DRT	48.5 50.8	QLQ-H&N35 item	Dry mouth	44 53	2-3 yr	<0.05	MVA combined IMRT+3DCRT
IMRT vs 2DRT											
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT	IMRT 2DRT	0 0	6-item XST scale	Total (follow-up minus baseline)	-38.4 -37.2 -30.7 -31.8 -24.3 -33.1	6 wk 6 mo 1 yr 	0.99 0.86 0.32 	
Fang, 2007	2250	113	1^{o} RT ± CTx (timing?)	IMRT 2DRT	48.1 50.8	QLQ-H&N35 item	Dry mouth	41 53	2-3 yr	<0.05	MVA combined IMRT+3DCRT

Table D1g. Nasopharyngeal cancer, salivary flow

Study	Rec#	No. Pts	Setting	Group	% Stage 0/I/II	% Stage III/IV	Mos Post-RT	Stimulated Flow Ratio % of Baseline	Unstimulated Flow Ratio % of Baseline	Comments
1° RT										
IMRT vs 2DRT										
Pow, 2006 (RCT)	2340	45	1° RT	 IMRT 2DRT IMRT 2DRT IMRT 2DRT IMRT 2DRT IMRT 2DRT IMRT 2DRT	 100 100	 0 0	SWS 2 2 6 6 12 12 SPS 2 2 6 6 12 12	(calculated) 0.14 0.08 0.19 0.04 0.26 0.06 0.28 0 0.57 0 1.28 0	NR	Saliva stimulated by chewing on sterile rubber tubing. SWS collected 5 min in cup; SPS collected 15 min w/ Lashley cup & suction over parotid duct on one side. SWS: 2DRT vs IMRT, $p < 0.003$ at 2, 6, 12 mos (ANOVA) SPS: 2DRT vs IMRT, $p < 0.002$ at 2, 6, 12 mos (ANOVA) SEE IF INFO ON DOSE-SLOW FOR THIS AND PREVIOUS ARTICLE
Wu, 2005	4520	380	1° RT	 2DRT IMRT	14.2 (all)	85.8 (all)			% w/ ↓ in parotid 82 70	For static secretion function (rated as a decrease if flow < 0.3 mL/min, i.e., no baseline measure), $p < 0.05$ CF, LCAF vs IMRT for percentage pts decreased post-RT. Measured 3 hrs after last food or mouthwash, then removed from parotid gland w/ catheter for 15 min.

Table D1g. Nasopharyngeal cancer, salivary flow (continued)

Study	Rec#	No. Pts	Setting	Group	% Stage 0/I/II	% Stage III/IV	Mos Post-RT	Stimulated Flow Ratio % of Baseline	Unstimulated Flow Ratio % of Baseline	Comments
Mixed Settings										
IMRT vs 2DRT										
Kam, 2007 (RCT)	530	56	1^{o} RT ± ICBRT					Fractional SWSFR	NR	Measured amount spit out for 5 minutes after stimulated using gum for 1 min: 2DRT vs IMRT $p < 0.01$ at 12 mos (paired t-test).
				IMRT	100	0	1.5	0.32		
				2DRT	100	0	1.5	0.28		
				IMRT			6	0.30		
				2DRT			6	0.20		
				IMRT			12	0.41		
				2DRT			12	0.20		
								Fractional SPFR		Measured amt collected with suction cup from orifice of each parotid duct for 15 min after stimulated w/ lemon candy w/ fixed citric acid content: 2DRT vs IMRT $p < 0.001$ at 1.5, 6, 12 mos (paired t-test)
				IMRT			1.5	0.39		
				2DRT			1.5	0.09		
				IMRT			6	0.70		
				2DRT			6	0.04		
				IMRT			12	0.90		
				2DRT			12	0.05		

Table D1h. Nasopharyngeal cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + split CTx												
IMRT vs 2DRT												
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	≥ 2 ≥ 3	42.0 94.1 10.5 41.2	0.01 0.035			

Table D1i. Nasopharyngeal cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + split CTx												
3DCRT vs 2DRT												
Wu, 2005 (RCT)	4360	96	1° RT + split CTx	3DCRT 2DRT	100 100	?	1-2 3-4	69.6 64.0 30.4 36.0	0.563			
IMRT vs 2DRT												
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	≥ 2 ≥ 3	78.9 100 15.8 52.9	0.066 0.033			

Table D1j. Nasopharyngeal cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + split CTx												
IMRT vs 2DRT												
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	RTOG	≥ 2 ≥ 3	84.2 100 5.3 47.1	0.136 0.006			

Table D1k. Nasopharyngeal cancer, oteoradionecrosis/bone

No studies.

Table D1l. Nasopharyngeal cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1° RT + split CTx													
3DCRT vs 2DRT													
Wu, 2005 (RCT)	4360	96	1° RT + split CTx	3DCRT 2DRT	100 100	LC	97.8 78.0					0.003	
IMRT vs 2DRT													
Laskar, 2008	39050	36	1° RT + split CTx	IMRT 2DRT	84.2 94.1	LRC		84.2 68.3				0.201	RT tech not entered in MVA
						DFS		67.5 55.8				0.477	RT tech not entered in MVA
Mixed Settings													
IMRT vs 3DCRT													
Fang, 2008	39090	203	1° RT ± CCTx	IMRT 3DCRT	52.8 55.9	LRC	~95 ~98	84.2 ~90	84.2 84.8	84.2 ~83		0.85 (3 yr)	RT tech NS in MVA

Table D1m. Nasopharyngeal cancer, patient survival

Overall Survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1^{o} RT + split CTx													
3DCRT vs 2DRT													
Wu, 2005 (RCT)	4360	96	1^{o} RT + split CTx	3DCRT 2DRT	100 100	OS	100 96					0.17	
IMRT vs 2DRT													
Laskar, 2008	39050	36	1^{o} RT + split CTx	IMRT 2DRT	84.2 94.1	OS		80.8 66.7				0.641	RT tech not entered in MVA
Mixed Settings													
IMRT vs 3DCRT													
Fang, 2008	39090	203	1^{o} RT ± CCTx	IMRT 3DCRT	52.8 55.9	OS	~96 ~98	~90 ~92	85.4 81.7	~79 ~78		0.58 (3 yr)	RT tech NS in MVA

Table D2a. Oropharyngeal cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	All LC	LRC	DFS	DSS	OS
1° RT + CCTx															
IMRT vs 3DCRT															
Rusthoven, 2008	13200	87	1° RT + CCTx		X			X	X			X	X		X
IMRT vs 2DRT															
Lee, 2006	2350	112	1° RT + CCTx		X			X	X		X		X		X
Mixed Settings															
IMRT vs 3DCRT															
Hodge, 2007	570	195	1° RT ± CCTx		X			X				X		X	X
Rades, 2007	2710	44	postop RT ± CCTx		X			X	X		X				X
Nutting, 2009 (RCT)	41220	84	1° RT/postop ± pre RT CTx		X		X	X	X	X		X			X
3DCRT vs 2DRT															
Rades, 2007	2710	130	postop RT ± CCTx		X			X	X		X				X
IMRT vs 2DRT															
Yao, 2007	1120	53	1° RT ± CTx (timing?)	X											
Rades, 2007	2710	122	postop RT ± CCTx		X			X	X		X				X
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx		X		X	X	X	X		X	X		X
Comparisons	9			1	8	0	2	8	7	2	4	4	3	1	8
Studies	7			1	6	0	2	6	5	2	2	4	3	1	6
Total n	1109														

Table D2b. Oropharyngeal cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
1^o RT + CCTx										
IMRT vs 3DCRT										
Rusthoven, 2008	13200	87	1^o RT + CCTx	IMRT 3DCRT	12 9	NR	100 (all)	70-72 66-70	24 (3-103)	100 97
IMRT vs 2DRT										
Lee, 2006	2350	112	1^o RT + CCTx	IMRT 2DR	12 17	55 (28-78) 56 (33-80)	100 98.6	66-70 70-72	46 (3-93)	100 99
Mixed Settings										
IMRT vs 3DCRT										
Hodge, 2007	570	195	1^o RT ± CCTx	IMRT 3DCRT 3DCRTpre	27 5 29	NR	86 100 78	65-70 60-78	31 (3-166) (all)	NR
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	NR	NR	≥ 50 ≥ 65 balance?	60-70 (all)	NR	NR
Nutting, 2009	41220	84	1^o RT/postop ± preRT CTx	IMRT 3DCRT	28% (all)	58.4 (mn all)	77 (all)	65, 61 64, 61 (1^o, postop)	31.9 (23.5-38.8, all)	NR
3DCRT vs 2DRT										
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DR	NR	NR	≥65 ≥54	60-70 (all)	NR	NR
IMRT vs 2DRT										
Yao, 2007	1120	53	1^o RT ± CTx (timing?)	IMRT 2DR	19.2 18.5	58 53	96.2 85.2	70 (all)	NR	NR
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DR	NR	NR	≥50 ≥54	60-70 (all)	NR	NR
Chao, 2001	9940	430	1^o/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	8 25 14 26 27	56 (50-71) 61 (43-86) 49 (42-76) 60 (30-81) 58 (33-83)	91.7 63.7 85.7 86.7 71.6	70.3 (70.2-72) 70 (60-76) 63.6 (55.1-66.5) 64.8 (50-72) 30 (28-70)	47 (12-276)	NR

Table D2c. Oropharyngeal cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initial Grps Comp	Bal by Design (Mtch)	BL Chars Clear Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Outcomes Val, Rel, =	Assessors Blind	Txs Clear	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT + CCTx																				
IMRT vs 3DCRT																				
Rusthoven, 2008	13200	87	R	Y	Y	N	N	N	?	?	N	NA	NA	NA	Y	N	Y	md 24	Y/?	Poor
IMRT vs 2DRT																				
Lee, 2006	2350	112	R	Y	Y	?	N	Y	?	?	Y	NA	NA	NA	Y	N	Y	md 46	N	Poor
Mixed Settings																				
IMRT vs 3DCRT																				
Hodge, 2007	570	195	R	Y	Y	Y	N	Y	Y+N	Y/E	Y	NA	NA	NA	Y	N	Y	md 31	Y/?	Poor
Rades, 2007	2710	44	R	Y	Y	Y	N	Y	?	WL	Y	NA	NA	NA	Y	N	Y	?	Y/?	Poor
Nutting, 2009 (RCT)	41220	84	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	md 32	Y	Good
3DCRT vs 2DRT																				
Rades, 2007	2710	130	R	Y	Y	Y	N	Y	?	WL	Y	NA	NA	NA	Y	N	Y	?	Y/?	Poor
IMRT vs 2DRT																				
Yao, 2007	1120	53	P	Y	Y	N	N	N	N	E	N	NA	Y	Y	Y	?	Y	?	N	Poor
Rades, 2007	2710	122	R	Y	Y	Y	N	Y	?	WL	Y	NA	NA	NA	Y	N	Y	?	Y/?	Poor
Chao, 2001	9940	430	R	Y	Y	N	N	Y	N	E	N	NA	NA	NA	Y	N	Y	?	Y/?	Poor

?: unclear; Adj for Conf: adjustment for confounders; Alloc: allocation; Attr: attrition; B: both concurrent and nonconcurrent control groups; Bal: balanced; BL chars: baseline characteristics; comp: comparable; CR: consecutive retrospective; E: era; F/U: followup; Grps: groups; M: mostly; md: median; Maint: maintenance; Mtch: matched design; N: no; NA: not applicable; Non-diffl: nondifferential; NR: not reported; P/pro: prospective; R/retro: retrospective; Rep: representative; Select: selection; Txs: treatments; W: waiting list; Y: yes; Y/?: multivariate analysis performed of uncertain quality

Table D2d. Oropharyngeal cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Large, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Sufficiently long F/U	Clear cand var select	Clear, appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Validation
1° RT + CCTx															
IMRT vs 3DCRT															
Rusthoven, 2008	13200	N	N	N	Y	NA	Y	NA	md 24	Y	?	?	?	Y	N
Mixed Settings															
IMRT vs 3DCRT															
Hodge, 2007	570	N	N	Y	Y	NA	N	NA	md 31	N	?	?	?	?	N
Rades, 2007	2710	N	N	Y	Y	NA	N	NA	?	Y	N	?	N	?	N
3DCRT vs 2DRT															
Rades, 2007	2710	N	N	Y	Y	NA	N	NA	?	Y	N	?	N	?	N
IMRT vs 2DRT															
Rades, 2007	2710	N	N	Y	Y	NA	N	NA	?	Y	N	?	N	?	N
Chao, 2001	9940	N	N	Y	Y	NA	N	NA	?	N	?	?	?	?	N

Assmpt test: model assumptions tested; Blinded assess pred factor: blinded assessment of predictive factor; Clear, appr model bldg GLs: clear, appropriate model-buliding guidelines followed; Clear cand var select: clear candidate variable selection for multivariate analysis; Cont vars well hndld: continuous variable well-handled; Homog txs, rand/unbiased alloc: homogeneous treatments, randomized or otherwise unbiased allocation to treatment group; Prespec hypoths: prespecified hypotheses relating predicting factor to outcome; well-defd, rep study pop: well-defined, representative study population; pred factor study meths well-descrd: predictive factor study methods well-described; Stand prong vars incld: standard prognostic variables included

Table D2e. Oropharyngeal cancer, quality of life

Head and Neck Cancer Inventory (HNCI)

Mixed Settings *IMRT vs 2DRT*	**Yao, 2007, Rec # 1120**					
Domain	**Mean IMRT n=26**	**Mean 2DRT n=27**	**Mo F/U**	**p Value**	**Difference**	**Magnitude of Clinically Important Difference**
Eating	34.5 42.1 55.4	34.9 31.7 39.0	3 6 12	 0.007	0.4 10.2 16.4	 Small Medium
Speech	83.2	74.3		0.059	8.9	Small
Aesthetics	90.4	79.3		0.069	11.1	Small
Social Disruption	86.1	78.8		0.115	7.3	Small

Table D2f. Oropharyngeal cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1^{o} RT + CCTx												
IMRT vs 3DCRT												
Rusthoven, 2008	13200	87	1^{o} RT + CCTx	IMRT 3DCRT	100 100	RTOG	$\geq$ 2			62 100 15 94 6 93	<0.001 <0.001 <0.001	6 mo 12 mo 18 mo
IMRT vs 2DRT												
Lee, 2006	2350	112	1^{o} RT + CCTx	IMRT 2DRT	100 98.6	RTOG/ EORTC	$\geq$ 2			12 67	0.002	
Mixed Settings												
IMRT vs 3DCRT												
Hodge, 2007	570	195	1^{o} RT ± CCTx	IMRT 3DCRT 3DCRT pre	86 100 78	RTOG	mod			56 63 67	0.3	
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	$\geq$50 $\geq$65	RTOG	2-3			17 73	0.037	
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	LENT SOM	$\geq$ 2	71 91	0.02	62 83 60 86 39 74 29 71	0.04 0.01 0.004 0.003	late = 3 mo 6 mo 12 mo 18 mo
				IMRT 3DCRT		RTOG	$\geq$ 2			56 78 47 83 41 64 20 81	0.03 0.001 0.05 0.001	late = 3 mo 6 mo 12 mo 18 mo

Table D2f. Oropharyngeal cancer, xerostomia (continued)

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
3DCRT vs 2DRT												
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	RTOG	2-3			73 63		
IMRT vs 2DRT												
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	RTOG	2-3			17 63	0.037	
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	> 2	75 69.3 64.3 63.4 18.3	NR	30 83.9 16.7 79.1 31.7	<0.0001	

Table D2g. Oropharyngeal cancer, salivary flow

No studies.

Table D2h. Oropharyngeal cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	CTCAE v3 (acute) LENT SOM (late)	$\geq$ 2	87 98	0.05	13 6	0.44	
IMRT vs 2DRT												
Chao, 2001	9940	430	1^{o}/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3	50 66 28.6 50.7 32.1	NR			

Table D2i. Oropharyngeal cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1° RT + CCTx												
IMRT vs 3DCRT												
Rusthoven, 2008	13200	87	1° RT + CCTx	IMRT 3DCRT	100 100	CTC	≥ 3	81 78	NR			
IMRT vs 2DRT												
Lee, 2006	2350	112	1° RT + CCTx	IMRT 2DRT	100 98.6	RTOG/ EORTC	3-4	66 72	NR			
Mixed Settings												
IMRT vs 3DCRT												
Hodge, 2007	570	195	1° RT ± CCTx	IMRT 3DCRT 3DCRTpre	86 100 78	RTOG	3	58 75 65	0.2 1.0			pre=preIMRT era
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	≥50 ≥65	CTC	2-3	~89 ~93	NR			
Nutting, 2009	41220	84	1° RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	CTCAE v3 (acute) LENT SOM (late)	≥ 2	91 98	0.18	23 15	0.55	
3DCRT vs 2DRT												
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	CTC	2-3	~93 ~90	NR			
IMRT vs 2DRT												
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	CTC	2-3	~89 ~90	NR			
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3	100 91.5 92.9 79.6 36.8	NR	10 11.90 17.32	NR	

Table D2j. Oropharyngeal cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
1^{o} RT + CCTx												
IMRT vs 3DCRT												
Rusthoven, 2008	13200	87	1^{o} RT + CCTx	IMRT 3DCRT	100 100	CTC	$\geq$ 3	34 52	0.002			
IMRT vs 2DRT												
Lee, 2006	2350	112	1^{o} RT + CCTx	IMRT 2DRT	100 98.6	RTOG/ EORTC	3-4	10 14	NR			
Mixed Settings												
IMRT vs 3DCRT												
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	$\geq$50 $\geq$65	Acute-CTC; Late-RTOG	2-3	~95 ~90	NR	~7 ~12	NR	
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	CTCAE v3 (acute) LENT SOM (late)	$\geq$ 2	76 93	0.02	8 15	0.46	
3DCRT vs 2DRT												
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	$\geq$65 $\geq$54	Acute-CTC; Late-RTOG	2-3	~90 ~93	NR	~12 ~14	NR	
IMRT vs 2DRT												
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	$\geq$50 $\geq$54	Acute-CTC; Late-RTOG	2-3	~95 ~93	NR	~7 ~14	NR	
Chao, 2001	9940	430	1^{o}/preop/ postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3	58.3 72.5 57.1 57.7 27.5	NR	10 16.8 8.3 15.8 5.0	NR	

Table D2k. Oropharyngeal cancer, oteoradionecrosis/bone

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Nutting, 2009	41220	84	1^{o} RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	LENT SOM	$\geq$ 2			13 12	1.00	
IMRT vs 2DRT												
Chao, 2001	9940	430	1^{o}/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	RTOG	2-3			0 6.3 0 2.9 5.9	NR	

Table D2l. Oropharyngeal cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1° RT + CCTx													
IMRT vs 3DCRT													
Rusthoven, 2008	13200	87	1° RT + CCTx	IMRT 3DCRT	100 100	LRC	~100 ~87	96 81	96 81	96 81		0.21	MVA IMRT vs 3DCRT+AFxCB HR 5.20 p=0.075
				IMRT 3DCRT		DFS	~90 ~63	79 56	~68 56	~68 ~50		0.18	RT tech NS in MVA
IMRT vs 2DRT													
Lee, 2006	2350	112	1° RT + CCTx	IMRT 2DRT	100 98.6	LC	~100 ~90	95 ~90	95 85	95 85	95 85	0.17	
				IMRT 2DRT		LRC	~100 ~90	~95 ~92	92 82	92 82	92 ~75	0.18	
				IMRT 2DRT		DFS	~92 ~86	~86 ~86	82 76	82 76	82 ~70	0.57	
Mixed Settings													
IMRT vs 3DCRT													
Hodge, 2007	570	195	1° RT ± CCTx	IMRT 3DCRT 3DCRTpre	86 100 78	LRC	96.1 ~87 ~84	96.1 78.1 82.3	96.1 78.1 81.1	96.1 78.1 78.5	78.5		pre=preIMRT era
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	≥ 50 ≥ 65	LC		89 79				0.34	RT tech NS in MVA
Nutting, 2009	41220	84	1° RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	LRC	87.3 88.0					NS	IMRT:3DCRT HR=1.59 (0.67, 3.80)

Table D2l. Oropharyngeal cancer, tumor control (continued)

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
3DCRT vs 2DRT													
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	LC		79 78				0.34	RT tech NS in MVA
IMRT vs 2DRT													
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	LC		89 78				0.34	RT tech NS in MVA
Chao, 2001	9940	430	1°/preop/postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	LRC		88 68 100 76 78				NS NS	
				defIMRT def2DRT postopIMRT postop2DRT preop2DRT		DFS		80 58 92 74 68				0.002 0.008	

Table D2m. Oropharyngeal cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1° RT + CCTx													
IMRT vs 3DCRT													
Rusthoven, 2008	13200	87	1° RT + CCTx	IMRT 3DCRT	100 100	OS	~90 ~80	86 73	~72 ~70	~72 ~55		0.48	RT tech NS in MVA
IMRT vs 2DRT													
Lee, 2006	2350	112	1° RT + CCTx	IMRT 2DRT	100 98.6	OS	~100 ~88	~96 ~88	91 81	91 ~70	91 ~70	0.10	
Mixed Settings													
IMRT vs 3DCRT													
Hodge, 2007	570	195	1° RT ± CCTx	IMRT 3DCRT 3DCRTpre	86 100 78	DSS	~99 ~98 ~93	97.7 83.5 87.7	97.7 83.5 79.7	97.7 83.5 ~76	 73.5	NR	
				IMRT 3DCRT 3DCRTpre		OS	~98 ~95 ~90	94.5 81.1 87.7	88.2 81.1 79.7	88.2 81.1 ~56	 54.6	0.02	pre=preIMRT era RT tech NS in MVA (w/ T stage)
Rades, 2007	2710	44	postop RT ± CCTx	IMRT 3DCRT	≥50 ≥65	OS		86 80				0.30	RT tech NS in MVA
Nutting, 2009	41220	84	1° RT/postop ± preRT CTx	IMRT 3DCRT	77 (all)	OS	93.6 90.8					NS	IMRT:3DCRT HR=1.05 (0.38, 2.90)
3DCRT vs 2DRT													
Rades, 2007	2710	130	postop RT ± CCTx	3DCRT 2DRT	≥65 ≥54	OS		80 74				0.30	RT tech NS in MVA
IMRT vs 2DRT													
Rades, 2007	2710	122	postop RT ± CCTx	IMRT 2DRT	≥50 ≥54	OS		86 74				0.30	RT tech NS in MVA
Chao, 2001	9940	430	1°/preop/ postop RT ± CCTx	defIMRT def2DRT postopIMRT postop2DRT preop2DRT	91.7 63.7 85.7 86.7 71.6	OS		100 57 100 71 67				0.001 0.003	

Table D3a. Nasal cavity and paranasal sinus cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
Mixed Settings															
IMRT vs 3DCRT															
Chen, 2007	1560	68	1°/preop/postop RT± postRT CTx/CCTx					X	X	X	X		X		X
3DCRT vs 2DRT															
Dirix, 2007	1360	127	1°/preop/postop RT		X			X		X	X		X	X	X
Chen, 2007	1560	104	1°/preop/postop RT± postRT CTx/CCTx					X	X	X	X		X		X
IMRT vs 2DRT															
Chen, 2007	1560	82	1°/preop/postop RT± postRT CTx/CCTx					X	X	X	X		X		X
Comparisons	4			0	1	0	0	4	3	4	4	0	4	1	4
Studies	2			0	1	0	0	2	1	2	2	0	2	1	2
Total n	254														

Table D3b. Nasal cavity and paranasal sinus cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
Mixed Settings										
IMRT vs 3DCRT										
Chen, 2007	1560	68	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	40 (all)	61 (27-92) (all)	≥87.4 (all)	66-72 50-73	49 (3-151)	NR
3DCRT vs 2DRT										
Dirix, 2007	1360	127	1^{o}/preop/postop RT	3DCRT 2DR	16 (all)	58 (27-85) (all)	≥93.7 (all)	50-80 (all)	67 (3-307)	100 (all)
Chen, 2007	1560	104	1^{o}/preop/postop RT± postRT CTx/CCTx	3DCRT 2DR	40 (all)	61 (27-92) (all)	≥87.4 (all)	50-73 50-74	49 (3-151)	NR
IMRT vs 2DRT										
Chen, 2007	1560	82	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 2DR	40 (all)	61 (27-92) (all)	≥ 87.4 (all)	66-72 50-74	49 (3-151)	NR

Table D3c. Nasal cavity and paranasal sinus cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
Mixed Settings																				
IMRT vs 3DCRT																				
Chen, 2007	1560	68	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 49	N	Poor
3DCRT vs 2DRT																				
Dirix, 2007	1360	127	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 67	Y/N	Poor
Chen, 2007	1560	104	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 49	N	Poor
IMRT vs 2DRT																				
Chen, 2007	1560	82	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 49	N	Poor

Table D3d. Nasal cavity and paranasal sinus cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
Mixed Settings															
3DCRT vs 2DRT															
Dirix, 2007	1360	N	N	Y	Y	NA	N	?	md 67	Y	N	?	N	?	N

Table D3e: Nasal cavity and paranasal sinus cancer, quality of life

No studies.

Table D3f: Nasal cavity and paranasal sinus cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
3DCRT vs 2DRT												
Dirix, 2007	1360	127	1^{o}/preop/ postop RT	3DCRT 2DRT	≥93.7 (all)	?	Perm-anent			10.0 29.9	0.08	

Table D3g. Nasal cavity and paranasal sinus cancer, salivary flow

No studies.

Table D3h. Nasal cavity and paranasal sinus cancer, dysphagia

No studies.

Table D3i. Nasal cavity and paranasal sinus cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Chen, 2007	1560	68	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 16	NR	
3DCRT vs 2DRT												
Dirix, 2007	1360	127	1^{o}/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	?	?				NS	
Chen, 2007	1560	104	1^{o}/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			16 17	NR	
IMRT vs 2DRT												
Chen, 2007	1560	82	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 17	NR	

Table D3j. Nasal cavity and paranasal sinus cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Chen, 2007	1560	68	1°/preop/ postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 18	NR	
3DCRT vs 2DRT												
Chen, 2007	1560	104	1°/preop/ postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			18 27	NR	
IMRT vs 2DRT												
Chen, 2007	1560	82	1°/preop/ postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			13 27	NR	

Table D3k. Nasal cavity and paranasal sinus cancer, osteoradionecrosis/bone

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Chen, 2007	1560	68	1°/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			9 16	NR	
3DCRT vs 2DRT												
Dirix, 2007	1360	127	1°/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	?	?			0 0		≥ 2 yr
Chen, 2007	1560	104	1°/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			16 15	NR	
IMRT vs 2DRT												
Chen, 2007	1560	82	1°/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	RTOG/ EORTC	≥ 3			9 15	NR	

Table D3l. Nasal cavity and paranasal sinus cancer, tumor control

Local Control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Chen, 2007	1560	68	1°/preop/postop RT ± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	LC	~85 ~79	~77 ~72	~71 ~66	~65 ~66	65 62	>0.05	
						DFS						0.89	
3DCRT vs 2DRT													
Dirix, 2007	1360	127	1°/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	LC						NS	
Chen, 2007	1560	104	1°/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	LC	~79 ~83	~72 ~62	~66 59	~66 59	62 59	>0.05	
						DFS						0.89	
IMRT vs 2DRT													
Chen, 2007	1560	82	1°/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	LC	~85 ~83	~77 ~62	~71 59	~65 59	65 59	>0.05	
						DFS						0.89	

Table D3m. Nasal cavity and paranasal sinus cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Chen, 2007	1560	68	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 3DCRT	≥87.4 (all)	OS					47 57	0.60	
3DCRT vs 2DRT													
Dirix, 2007	1360	127	1^{o}/preop/postop RT	3DCRT 2DRT	≥93.7 (all)	OS						NS	
						DSS						NS	
Chen, 2007	1560	104	1^{o}/preop/postop RT± postRT CTx/CCTx	3DCRT 2DRT	≥87.4 (all)	OS					57 51	0.60	
IMRT vs 2DRT													
Chen, 2007	1560	82	1^{o}/preop/postop RT± postRT CTx/CCTx	IMRT 2DRT	≥87.4 (all)	OS					47 51	0.60	

Table D4a. Unknown primary cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
Mixed Settings															
3DCRT vs 2DRT															
Beldi, 2007	990	87	1°/postop RT± preRT CTx/CCTx										X		X
IMRT vs 2DRT															
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)				X	X	X						X
Comparisons	2			0	0	0	1	1	1	0	0	0	1	0	2
Studies	2			0	0	0	1	1	1	0	0	0	1	0	2
Total n	128														

Table D4b. Unknown primary cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
Mixed Settings										
3DCRT vs 2DRT										
Beldi, 2007	990	87	1°/postop RT± preRT CTx/CCTx	3DCRT 2DR	18 (all)	59 (23-88) (all)	100 (all)	45-70 (all)	32	NR
IMRT vs 2DRT										
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DR	26 22	61 (47-85) 58 (38-75)	100 (all)	56-69 66	17 (2-39)	87 100

Table D4c. Unknown primary cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
Mixed Settings																				
3DCRT vs 2DRT																				
Beldi, 2007 2007	990	87	R	Y	Y	?	N	?	N	E	?	NA	NA	NA	Y	N	Y	md 32	Y/N	Poor
IMRT vs 2DRT																				
Madani, 2008	37700	41	R	N	?	N	N	Y	N	E	?	NA	NA	NA	Y	N	Y	md 17	N	Poor

Table D4d. Unknown primary cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
Mixed Settings															
3DCRT vs 2DRT															
Beldi, 2007 2007	990	N	N	Y	Y	NA	N	Y	md 32	Y	N	?	N	?	N

Table D4e. Unknown primary cancer, quality of life

No studies.

Table D4f. Unknown primary cancer, xerostomia

No studies.

Table D4g. Unknown primary cancer, salivary flow

No studies

Table D4h. Unknown primary cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 2DRT												
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	Acute-RTOG Late-LENT/ SOMA	≤ 2 3	95.5 50 4.5 50	0.003	100 72.3 0 26.7	0.01	

Table D4i. Unknown primary cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 2DRT												
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	RTOG	≤ 2 3	50 41.2 50 58.8	0.82			

Table D4j. Unknown primary cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 2DRT												
Madani, 2008	37700	41	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	Acute-RTOG Late-LENT/ SOMA	≤ 2 3	68.2 33.3 31.7 66.7	0.08	100 73.3 0 26.7	0.03	

Table D4k, Unknown primary cancer, osteoradionecrosis/bone

No studies.

Table D4l. Unknown primary cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
3DCRT vs 2DRT													
Beldi, 2007 2007	990	87	1°/postop RT± preRT CTx/CCTx	3DCRT 2DRT	100 100	DFS					48.3 15.2	<0.01	RT tech NS in MVA

Table D4m. Unknown primary cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
3DCRT vs 2DRT													
Beldi, 2007 2007	990	87	1^{o}/postop RT± preRT CTx/CCTx	3DCRT 2DRT SCC only	100 100	OS					69.1 26.3 69.1 30.8	<0.01 <0.05	RT tech NS in MVA
IMRT vs 2DRT													
Madani, 2008	37700	41	1^{o}/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	OS	74.8 61.1					0.97	

Table D5a. Laryngeal cancer, outcomes by study

				QOL/Adverse Events							Tumor Control			Patient Survival	
Study	Rec#	No. Pts	Setting	QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
1° RT															
3DCRT vs 2DRT															
Zouhair, 2004	7400	122	1° RT								X				
Comparisons	1			0	0	0	0	0	0	0	1	0	0	0	0
Studies	1			0	0	0	0	0	0	0	1	0	0	0	0
Total n	122														

Table D5b. Laryngeal cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
1° RT										
3DCRT vs 2DRT										
Zouhair, 2004	7400	122	1° RT	3DCRT 2DR	13 (all)	62 (35-92) (all)	0 (all)	60-74 (all)	85 (12-178)	NR

Table D5c: Laryngeal cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT																				
3DCRT vs 2DRT																				
Zouhair, 2004	7400	122	R	Y	Y	N	N	?	N	E	Y	NA	NA	NA	Y	N	Y	md 85	Y/?	Poor

Table D5d. Laryngeal cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
1° RT															
3DCRT vs 2DRT															
Zouhair, 2004	7400	N	N	Y	Y	NA	Y	NA	md 85	N	?	?	?	?	N

Table D5e. Laryngeal cancer, quality of life

No studies.

Table D5f. Laryngeal cancer, xerostomia

No studies.

Table D5g. Laryngeal cancer, salivary flow

No studies.

Table D5h. Laryngeal cancer, dysphagia

No studies.

Table D5i: Laryngeal cancer, mucositis

No studies.

Table D5j: Laryngeal cancer, skin

No studies.

Table D5k: Laryngeal cancer, osteoradionecrosis/bone

No studies.

Table D5l. Laryngeal cancer, tumor control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
1^{o} RT													
3DCRT vs 2DRT													
Zouhair, 2004	7400	122	1 setting: 1^{o} RT	3DCRT 2DRT	0 (all)	LC					86 81	0.55	RT tech NS in MVA

Table D5m. Laryngeal cancer, patient survival

No studies.

Table D6a. Mixed head and neck cancer, outcomes by study

Study	Rec#	No. Pts	Setting	QOL/Adverse Events							Tumor Control			Patient Survival	
				QOL	XST	SF	DYS	MUC	SKN	ORN or BON	LC	LRC	DFS	DSS	OS
1° RT															
IMRT vs 3DCRT															
Golen, 2007	14200	40	1° RT		X										
Mixed Settings															
IMRT vs 3DCRT															
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx		X								X		X
Chao, 2001	10470	41	1°/postop RT ± postRT CTx/CCTx			X									
Gomez, 2008	13390	32	1°/postop RT± CTx (timing?)										X		X
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/CCTx + preRT CTx		X		X	X	X						
Langendijk, 2009	39950	529	1°/postop RT± CTx (timing?)				X								
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	X	X			X	X						
3DCRT vs 2DRT															
Kuhnt , 2005	4840	33	1°/postop RT			X									
Rades, 2008	13180	345	1°/postop RT± CCTx		X			X	X			X			X
Gomez, 2008	13390	42	1°/postop RT± CTx (timing?)										X		X
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/CCTx + preRT CTx		X		X	X	X						
IMRT vs 2DRT															
Sanguineti, 2007	1740	66	1° RT ± CTx (timing?)												
Daly, 2007	2470	69	1°/postop RT ± CCTx/CTx (timing?)		X										
Jabbari, 2005	4480	106	1°/postop RT ± CTx (timing?)	X	X										
Pacholke, 2005	4830	210	1°/postop RT ± CTx (timing?)		X										
Kent, 2008	13300	40	1°/postop RT ± CTx (timing?)												
Gomez, 2008	13390	44	1°/postop RT± CTx (timing?)										X		X
Palazzi, 2008	13850	45	1°/postop RT ± CCTx/CCTx + preRT CTx		X		X	X	X						
van Rij, 2008	38520	162	1°/postop RT ± CCTx		X										
Caudell, 2009	39420	122	1° RT ± preRT CTX and/or CCTx				X								
Murphy, 2009	40430	75	1°/postop RT± CTx (timing?)					X							
Comparisons	**21**			**2**	**11**	**2**	**5**	**6**	**5**	**0**	**0**	**1**	**4**	**0**	**5**
Studies	**17**			**2**	**9**	**2**	**3**	**4**	**3**	**0**	**0**	**1**	**2**	**0**	**3**
Total n	**2274**														

Table D6b. Mixed head and neck cancer, participants and treatments

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
1° RT										
IMRT vs 3DCRT										
Golen, 2007	14200	40	1 setting: 1° RT	IMRT 3DCRT	28 (all)	NR	40 (all)	62-72 (all)	NR	NR
Mixed Settings										
IMRT vs 3DCRT										
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT			≥19.5 ≥21.7			
Chao, 2001	10470	41	1°/postop RT ± postRT CTx/CCTx	IMRT 3DCRT	29 (all)	58 (36-75) (all)	82.9 (all)	50-70 (all)	NR	100 (all)
Gomez, 2008	13390	32	1°/postop RT± CTx (timing?)	IMRT 3DCRT	59 (all)	52 (15-85) (all)	≥47.4 (all)	52-70 (all)	71 (6-180)	100 (all)
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	22 (all)	57 (27-94) (all)	87 (all)	60-70 (all)	NR	NR
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	IMRT 3DCRT	44 31	NR	77 62	54-70 46-70	NR	NR
Langendijk, 2009	39950	529	1°/postop RT± CTx (timing?)	IMRT 3DCRT	25 (all)	60 (all)		70 (all)	≥ 6 mo	NR
3DCRT vs 2DRT										
Kuhnt , 2005	4840	33	1°/postop RT	3DCRT 2DR	23 20	56 (44-68) 60 (41-74)	NR	?	?	?
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DR	25 29	NR	100 (All)	60-72 60-70	NR	NR
Gomez, 2008	13390	42	1°/postop RT± CTx (timing?)	3DCRT 2DR	59 (all)	52 (15-85) (all)	≥47.4 (all)	52-70 (all)	71 (6-180)	100 (all)
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DR	22 (all)	57 (27-94) (all)	87 (all)	60-70 (all)	NR	NR

Study	Rec#	No. Pts	Setting	Tx Group	% Female	Median Age (rng, yrs)	% Stage III/IV	Prescribed RT Dose to Primary Tumor (Gy)	Median Follow-up (rng, mos)	Com-pleted RT (%)
IMRT vs 2DRT										
Sanguineti, 2007	1740	66	1^{o} RT ± CTx (timing?)	IMRT 2DR	18 (all)	54 (35-85) (all)	≥75.8 (all)	60-78 60-72	17 (0.4-50)	NR
Daly, 2007	2470	69	1^{o}/postop RT ± CCTx/CTx (timing?)	IMRT 2DR	10 13	58 (39-73) 58 (35-80)	96.6 96	66 NR	25 (10-60)	NR
Jabbari, 2005	4480	106	1^{o}/postop RT ± CTx (timing?)	IMRT 2DR	23 30	53 (29-85) 53 (28-81)	100 (all)	60-78 63-77	NR	NR
Pacholke, 2005	4830	210	1^{o}/postop RT ± CTx (timing?)	IMRT 2DR	NR	NR	NR	> 50 (all)	NR	NR
Kent, 2008	13300	40	1^{o}/postop RT ± CTx (timing?)	IMRT 2DR	NR	NR	NR	NR	NR	100 (all)
Gomez, 2008	13390	44	1^{o}/postop RT± CTx (timing?)	IMRT 2DR	59 (all)	52 (15-85) (all)	≥47.4 (all)	52-70 (all)	71 (6-180)	100 (all)
Palazzi, 2008	13850	45	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DR	22 (all)	57 (27-94) (all)	87 (all)	60-70 (all)	NR	NR
van Rij, 2008	38520	162	1^{o}/postop RT ± CCTx	IMRT 2DR	28 36	59 (all)	100 (all)	≥ 60 (all)	NR	NR
Caudell, 2009	39420	122	1^{o} RT ± preRT CTX and/or CCTx	IMRT 2DR	24 (all)	55 (18-83) (all)	100 (all)	65-79 (all)	32 (12-73)	NR
Murphy, 2009	40430	75	1^{o}/postop RT± CTx (timing?)	IMRT 2DR	19 (all)	mn 59 (40-86) (all)	84 (all)	NR	1.4	

Table D6c. Mixed head and neck cancer, comparative study quality items

Study	Rec#	No. Pts	Select Pro/ Retro	Incl/ Excl Clear	Rep Select	Initl Grps Comp	Bal by Design (Mtch)	BL Chars Clr Comp	Txs Same Time Per	Unbiased Alloc	Other Txs Equal	Maint Comp Grps	Overall Attr <20%	Non-diffl Attr <15%	Out-comes Val, Rel, =	Assessors Blind	Txs Clr	Adequate F/U	Analysis: Adj for Confs	USPSTF
1° RT																				
IMRT vs 3DCRT																				
Golen, 2007	14200	40	R	N	?	?	N	?	Y	R	Y	NA	NA	NA	Y	N	Y	?	N	Poor
Mixed Settings																				
IMRT vs 3DCRT																				
Marchal, 2004	5580	87	P	N	?	?	N	?	Y	?	?	?	?	?	Y	?	N	?	N	Poor
Chao, 2001	10470	41	P	N	?	?	N	?	Y	?	?	Y	Y	Y	Y	?	Y	?	Y/?	Poor
Gomez, 2008	13390	32	R	Y	Y	?	N	?	N	?	?	NA	NA	NA	Y	N	Y	md 71	Y/?	Poor
Palazzi, 2008	13850	116	P	Y	?	?	N	?	N	E	?	?	?	?	Y	?	Y	?	Y/?	Poor
Vergeer, 2008	38540	141	P	Y	Y	N	N	N	N	E	N	NA	?	?	Y	?	Y	?	Y/?	Poor
Langendijk, 2009	39950	529	P	Y	N	?	N	?	?	?	?	?	?	?	Y	?	Y	6	Y/N	Poor
3DCRT vs 2DRT																				
Kuhnt , 2005	4840	33	P	Y	Y	?	N	?	Y	?	?	?	Y	Y	Y	?	Y	?	N	Poor
Rades, 2008	13180	345	R	Y	Y	Y	N	Y	Y	?	Y	NA	NA	NA	Y	N	Y	?	Y/N	Poor
Gomez, 2008	13390	42	R	Y	Y	?	N	?	N	?	?	NA	NA	NA	Y	N	Y	md 71	Y/?	Poor
Palazzi, 2008	13850	137	P	Y	?	?	N	?	N	E	?	?	?	?	Y	?	Y	?	Y/?	Poor
IMRT vs 2DRT																				
Sanguineti, 2007	1740	66	R	Y	N	?	N	?	?	?	?	NA	NA	NA	Y	N	Y	md 17	Y/N	Poor
Daly, 2007	2470	69	R	N	?	Y	N	Y	?	?	Y	NA	NA	NA	Y	N	Y	md 25	N	Poor
Jabbari, 2005	4480	106	P	N	?	?	Y	Y	Y	Risk	Y	N	N	?	Y	?	N	?	N	Poor
Pacholke, 2005	4830	210	R	Y	Y	?	N	?	?	?	?	NA	NA	NA	Y	N	N	?	Y/?	Poor
Kent, 2008	13300	40	R	Y	N	?	N	?	?	?	?	NA	NA	NA	Y	N	N	?	N	Poor
Gomez, 2008	13390	44	R	Y	Y	?	N	?	N	?	?	NA	NA	NA	Y	N	Y	md 71	Y/?	Poor
Palazzi, 2008	13850	45	P	Y	?	?	N	?	N	E	?	?	?	?	Y	?	Y	?	Y/?	Poor
van Rij, 2008	38520	162	R	Y	Y	?	N	N	N	?	N	NA	NA	NA	Y	N	N	md 31	Y/?	Poor
Caudell, 2009	39420	122	R	Y	Y	?	N	?	?	?	?	NA	NA	NA	Y	N	Y	md 32	Y/N	Poor
Murphy, 2009	40430	75	P	Y	Y	?	N	?	Y	?	?	?	?	?	Y	?	N	1.4	N	Poor

Table D6d. Mixed head and neck cancer, multivariate adjustment for confounders quality items

Study	Rec#	Pro design	Prespec hypoths	Lrg, well-defd, rep study pop	Pred factor meths well-descrd	Blinded assess pred factor	Homog txs, rand/unbiased alloc	Low rate of missing data (<15%)	Suffici-ently long F/U	Clear cand var select	Clear appr model bldg GLs	Asmpt tested	Stand progn vars incld	Cont vars well hndld	Valid-ation
Mixed Settings															
IMRT vs 3DCRT															
Gomez, 2008	13390	N	N	Y	Y	NA	N	NA	md 71	Y	?	?	?	?	N
Palazzi, 2008	13850	Y	N	Y	Y	NA	N	N	?	N	?	?	?	?	N
Vergeer, 2008	38540	Y	N	Y	Y	NA	N	?	?	N	?	?	?	?	N
3DCRT vs 2DRT															
Rades, 2008	13180	N	N	Y	Y	NA	N	NA	?	N	N	?	N	?	N
Gomez, 2008	13390	N	N	N	Y	NA	N	NA	md 71	Y	?	?	?	?	N
Palazzi, 2008	13850	Y	N	Y	Y	NA	N	N	?	N	?	?	?	?	N
IMRT vs 2DRT															
Sanguineti, 2007	1740	N	N	N	Y	NA	N	NA	md 17	N	N	?	N	?	N
Pacholke, 2005	4830	N	N	N	Y	NA	?	NA	?	N	?	?	?	?	N
Gomez, 2008	13390	N	N	N	Y	NA	N	NA	md 71	Y	?	?	?	?	N
Palazzi, 2008	13850	Y	N	Y	Y	NA	N	N	?	N	?	?	?	?	N
van Rij, 2008	38520	N	N	Y	Y	NA	N	NA	?	N	?	?	?	?	N
Caudell, 2009	39420	N	N	Y	Y	NA	N	NA	md 32	N	N	?	N	?	N

Table D6e. Mixed head and neck cancer, quality of life: head and neck cancer-related quality of life (HNQOL)

EORTC QLQ-C30

	Vergeer, 2008, Rec # 38540			
Item	**Mean IMRT n=91**	**Mean 3DCRT n=150**	**Mo F/U**	**p Value Linear-l Quadratic-q**
Global health	76.0 79.2	64.9 65.6	1.5 6 all	 <0.004-l
Physical function	77.4 80.7	73.3 74.4	1.5 6 all	
Role function	81.5 82.1	65.6 70.8	1.5 6 all	 0.042-l
Emotional function	78.2 85.3	73.5 73.2	1.5 6 all	
Cognitive function	87.8 93.6	83.9 84.6	1.5 6 all	 0.033-l
Social function	82.7 92.0	76.1 76.5	1.5 6 all	 <0.001-l
Fatigue	30.9 24.2	40.5 40.4	1.5 6 all	 0.026-l
Nausea/ vomiting	12.8 6.4	13.6 8.4	1.5 6 all	
Pain	14.1 19.2	25.2 23.3	1.5 6 all	 0.042-q
Dyspnea	11.9 10.7	19.1 22.4	1.5 6 all	
Insomnia	27.4 16.7	26.3 30.1	1.5 6 all	 0.021-l
Appetite loss	19.8 12.3	32.5 24.2	1.5 6 all	 0.018-l
Constipation	10.7 10.7	17.1 12.1	1.5 6 all	
Diarrhea	11.5 2.6	7.8 8.5	1.5 6 all	
Financial difficulties	16.7 15.4	12.6 14.8	1.5 6 all	

EORTC QLQ-H&N35

	Vergeer, 2008, Rec # 38540			
Item	**Mean IMRT n=91**	**Mean 3DCRT n=150**	**Mo F/U**	**p Value Linear-l Quadratic-q**
Pain	19.9 18.9	33.0 28.3	1.5 6 all	 0.030-l 0.046-q
Swallowing	35.5 21.1	36.1 33.7	1.5 6 all	 0.042-l
Taste/smell	32.7 16.7	34.0 26.8	1.5 6 all	
Speech	23.0 19.8	31.2 29.9	1.5 6 all	
Social eating	23.0 15.9	35.7 30.9	1.5 6 all	 0.011-l
Sexuality	30.7 13.3	45.5 38.1	1.5 6 all	 0.003-l
Teeth	4.3 7.2	19.6 24.3	1.5 6 all	 0.015-l
Opening mouth	8.6 17.3	27.1 30.2	1.5 6 all	 0.026-q
Dry mouth	43.2 48.1	62.2 68.6	1.5 6 all	 <0.001-l
Sticky saliva	41.3 32.0	61.3 56.9	1.5 6 all	 0.001-l
Coughing	35.8 27.2	33.3 35.4	1.5 6 all	
Feeling ill	21.0 6.2	1.1 19.1	1.5 6 all	 0.011-l

	Jabbari, 2005, Rec # 4480						
Domain	**Median IMRT n=30**	**IMRT Trend for Improvement p Value**	**Median 2DRT n=10**	**2DRT Trend for Improvement p Value**	**F/U**	**Difference Adjusted for Baseline**	**p Value**
Total	~31 ~31 ~20 17 ~13 ~7	 0.04	~31 ~32 ~58 68 ~4 ~47	 0.97	1 3 6 12 18 24 all	 19.2	 NS
Communication		0.11		0.56	all		
Eating		0.07		0.78	all		
Emotion		0.04		0.11	all		
Pain		0.05		0.38	all		

Table D6f. Mixed head and neck cancer, xerostomia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT	≥21.7 ≥19.5	RTOG	≥ 2 ≥ 3	23 24		42 50 7 18	0.06	
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	IMRT 3DCRT	77 62	RTOG ? mn QLQ-H&N35 XST item RTOG	2 12 wk 6 mo mod-sev ≥ 2 6 mo	~25 ~42	0.014	 41 67 32 56	 <0.001 <0.01 0.002	p<0.02 at 3, 4, 5 wk; NS at 0, 1, 2, 6, 7, 8 wk; 6 mo MV ORa (95% CI): 0.27 (0.13, 0.54); IMRT<3DCRT at end RT, 6 wk, 6mo, 12 mo MV ORa (95% CI): 0.24 (0.12, 0.51)
3DCRT vs 2DRT												
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DRT	100 100	RTOG	2-3			43 58	0.06	
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1°/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Scale	Item	Mean	F/U	p value	Comments
1° RT											
IMRT vs 3DCRT											
Golen, 2007	14200	40	1 setting: 1° RT	IMRT 3DCRT	40 (all)	CTC SOMA-LENT	Mean grade by group	~2.75 ~2.4 ~2.4 ~2.6 ~2.25 ~2.5 ~2.25 ~2.25 ~2.25 ~2.2 ~2.5 ~2.0 ~5.0 ~5.4 ~4.3 ~5.2 ~4.3 ~5.0 ~3.9 ~4.8 ~3.6 ~3.8 ~2.5 ~4.1	3 mo 6 mo 12 mo 18 mo 24 mo 30 mo 3 mo 6 mo 12 mo 18 mo 24 mo 30 mo	NR NR	
Mixed Settings											
IMRT vs 2DRT											

Daly, 2007	2470	69	1°/postop RT ± CCTx/CTx (timing?)	IMRT 2DRT	96.6 96.0	XQ	Talking difficult Chewing difficult Swallow difficult Sleeping problems Dry w/ eating Dry w/o eating Freq sipping w/ eat Freq sipping w/o eat Total	3.0 4.8 3.9 5.3 5.2 6.0 3.0 2.8 4.7 6.0 3.8 5.0 5.5 7.8 3.8 5.9 33.0 43.7	> 6 mo	0.003 0.03 0.16 0.76 0.02 0.03 0.002 0.0006 0.006	
Jabbari, 2005	4480	106	1°/postop RT ± CTx (timing?)	IMRT 2DRT	100 100	XQ	Total	~3 ~7 ~39 ~58 ~53 ~68 ~43 ~58 32 67 ~35 ~23 ~28 ~88	Pre 1 mo 3 mo 6 mo 12 mo 18 mo 24 mo	0.7	at 12 mo, adjusting for baseline, IMRT-2DRT difference NS (p=0.2)
Pacholke, 2005	4830	210	1°/postop RT ± CTx (timing?)	IMRT IMRT>26Gy IMRT≤26Gy 2DRTbilat-tot 2DRTbilat-par		XQ	Total above or below median	36 50 34 64 53	> 1 yr		RT tech p<0.001 on MVA

van Rij, 2008	38520	162	1°/postop RT ± CCTx	IMRT 2DRT	100 100	Blend of EORTC H&N35 & XQ XST in rest XST during meals	Mean in rest	7.6 10.3	med 2.6 yrs	UVA	MVA p value
							↓/much ↓ saliva	78 85		0.07	0.008
							↓/much ↓ Δ saliva	22 27		1.0	0.7
							F/A dry not eating	36 61		0.004	0.001
							F/A probs gumbs	13 13		0.3	0.2
							F/A probs speaking	29 57		<0.0001	<0.0001
							F/A drink H_2O day	55 79		0.001	0.001
							F/A trouble sleeping	20 25		0.5	0.2
							F/A drink H_2O night	28 47		0.05	0.03
							Mean during meals	7.2 11.5			
							F/A probs solid food	29 62		<0.001	<0.001
							F/A probs grnd food	14 34		<0.001	0.001
							F/A swallow solid	30 61		<0.001	<0.001
							F/A swallow grnd	19 36		0.007	0.02
							F/A dry meals	25 55		<0.001	<0.001
							F/A H_2O to swallow	38 71		<0.001	<0.001
							F/A eat w/ others	19 34		0.006	0.02
							Grnd/liquid diet	9 22		0.03	0.3
							Swallow more freq	34 21		0.2	0.2

Table D6g. Mixed head and neck cancer, salivary flow

Study	Rec#	No. Pts	Setting	Group	% Stage 0/I/II	% Stage III/IV	Mos Post-RT	Stimulated Flow Ratio % of Baseline	Unstimulated Flow Ratio % of Baseline	Comments
Mixed Settings										
IMRT vs 3DCRT										
Chao, 2001	10470	41	1°/postop RT ± postRT CTx/CCTx	IMRT post op IMRT definitive 3DCRT post op 3DCRT definitive	14.6 (all)	82.9 (all)	6	0.70±.35 0.61±.30 0.38±.28 0.67±.25	0.50±.40 0.39±.21 0.22±.20 0.38±.10	UWS: After swallowing let saliva drip into cup for 5 min. SWS: Chewed on paraffin strip for 2 min, then collected saliva for 5 min in cup while still chewing. RT technique did not independently influence stimulated whole salivary flow.
3DCRT vs 2DRT										
Kuhnt , 2005	4840	33	1°/postop RT	3DCRT 2DRT 3DCRT 2DRT 3DCRT 2DRT 3DCRT 2DRT 3DCRT 2DRT			0.7 1.4 2.3 6 12	~0.69 ~0.55 ~0.42 ~0.19 ~0.43 ~0.19 ~0.64 ~0.21 ~0.50 ~0.25		P<0.1 for difference between treatment groups in salivary flow rate at 10 wks.

Table D6h. Mixed head and neck cancer, dysphagia

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Palazzi, 2008	13850	116	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Langendijk, 2009	39950	529	1^{o}/postop RT± CTx (timing?)	IMRT 3DCRT		RTOG	2-4			31.5 19.5	0.043	
3DCRT vs 2DRT												
Palazzi, 2008	13850	137	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Caudell, 2009	39420	122	1^{o} RT ± preRT CTX and/or CCTx	IMRT 2DRT	100 100	Long-term PEG dependence/ aspiration pneumonia/ pharyngeal-esophogeal stricture/ stenosis	any (com-posite)			38.3 38.7	0.97	RT tech NS in MVA (p=0.68)

Table D6i. Mixed head and neck cancer, mucositis

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Palazzi, 2008	13850	116	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Vergeer, 2008	38540	141	1^{o}/postop RT ± CCTx	IMRT 3DCRT	77 62	RTOG	$\geq$ 3 12 wk	~0 ~4	NS			p<0.05 at 3, 4, 5, 6, 7 wk; NS at 0, 1, 2, 8 wk
3DCRT vs 2DRT												
Rades, 2008	13180	345	1^{o}/postop RT± CCTx	3DCRT 2DRT	100 100	CTC	2-3	~87 ~92	NR			
Palazzi, 2008	13850	137	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1^{o}/postop RT ± CCTx/CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Murphy, 2009	40430	75	1^{o}/postop RT± CTx (timing?)	IMRT 2DRT	84 (all)	MTS	> mod	58 83	0.175			

Table D6j. Mixed head and neck cancer, skin

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Rating System	Grade	Acute %	p value	Late %	p value	Comments
Mixed Settings												
IMRT vs 3DCRT												
Palazzi, 2008	13850	116	1°/postop RT ± CCTx/ CCTx + preRT CTx	IMRT 3DCRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
Vergeer, 2008	38540	141	1°/postop RT ± CCTx	IMRT 3DCRT	77 62	RTOG	2 7 wk	86 74	0.03			
3DCRT vs 2DRT												
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DRT	100 100	Acute-CTC; Late-RTOG	2-3	~84 ~88	NR	~19 ~19	NR	
Palazzi, 2008	13850	137	1°/postop RT ± CCTx/ CCTx + preRT CTx	3DCRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute
IMRT vs 2DRT												
Palazzi, 2008	13850	45	1°/postop RT ± CCTx/ CCTx + preRT CTx	IMRT 2DRT	87 (all)	CTC	> 2					RT tech NS in MVA, acute

Table D6k. Mixed head and neck cancer, oteoradionecrosis/bone

No studies.

Table D6l. Mixed head and neck cancer, tumor control

Local Control

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Marchal, 2004	5580	87	1^{o}/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT	≥21.7 ≥19.5	DFS	88 85					NS	
Gomez, 2008	13390	32	1^{o}/postop RT± CTx (timing?)	IMRT 3DCRT	≥47.4 (all)	DFS						NS	RT tech not entered in MVA
3DCRT vs 2DRT													
Rades, 2008	13180	345	1^{o}/postop RT± CCTx	3DCRT 2DRT	100 100	LRC	76 82	71 72	68 65			0.71	
Gomez, 2008	13390	42	1^{o}/postop RT± CTx (timing?)	3DCRT 2DRT	≥47.4 (all)	DFS						NS	RT tech not entered in MVA
IMRT vs 2DRT													
Gomez, 2008	13390	44	1^{o}/postop RT± CTx (timing?)	IMRT 2DRT	≥47.4 (all)	DFS						NS	RT tech not entered in MVA

Table D6m.: Mixed head and neck cancer, patient survival

Study	Rec#	No. Pts	Setting	Group	% Stage III/IV	Out-come	1 yr	2 yr	3 yr	4 yr	5 yr	p value	Comments
Mixed Settings													
IMRT vs 3DCRT													
Marchal, 2004	5580	87	1°/postop/repeat RT ± pre/post RT CTx/CCTx	IMRT 3DCRT	≥21.7 ≥19.5	OS	90 87					NS	
Gomez, 2008	13390	42	1°/postop RT± CTx (timing?)	IMRT 3DCRT	≥47.4 (all)	OS						NS	RT tech not entered in MVA
3DCRT vs 2DRT													
Rades, 2008	13180	345	1°/postop RT± CCTx	3DCRT 2DRT	100 100	OS	75 84	62 66	57 62			0.15	
Gomez, 2008	13390	32	1°/postop RT± CTx (timing?)	3DCRT 2DRT	≥47.4 (all)	OS						NS	RT tech not entered in MVA
IMRT vs 2DRT													
Gomez, 2008	13390	44	1°/postop RT± CTx (timing?)	IMRT 2DRT	≥47.4 (all)	OS						NS	RT tech not entered in MVA

Appendix E: Single-Arm Studies

Questions 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-A. Design, participant selection and enrollment

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
560, Biagioli et al., 2007	Retrospective	Histologically proven locoregionally recurrent or second primary HNC with no distant metastases (01/2001-11/2006)	Definitive or salvage IMRT plus CTx Cisplatin or carboplatin with or w/out docetaxel or 5-FU, induction or concurrent	62	41 Ctx 54 21 excluded (n = 4 treated 2x daily; n = 2 no records available; n = 15 treated w/non-IMRT method)	1 Died during tx 7 did not complete prescribed RT course
580, Dirix et al., 2007	Prospective	Histologically proven AJCC stage T2-T4 primary sinonasal malignancy (01/2003-03/2007)	Adjuvant IMRT	43	25 18 excluded for recurrence (n = 3); melanoma or sarcoma (n = 7); too short F/U (n = 8)	0
1010, Urbano et al., 2007	Prospective dose-escalation	Histologically proven locally advanced stage T2-4, N1-3, M0 laryngeal or hypopharyngeal SCC (02/2002)	Definitive IMRT plus CTx Neoadjuvant cisplatin and 5-FU plus concurrent cisplatin during IMRT	30 (15 per dose cohort)	30 Neoadjuvant CTx 15 DL1 13 DL2 Concurrent CTx 15 DL1 14 DL2	0
1420, Feng et al, 2007	Prospective	Stage III/IV oropharyngeal or nasopharyngeal cancer	Definitive IMRT plus CTx Concurrent carboplatin and taxane (oropharynx) or cisplatin (nasopharynx)	36	36 CTx 36	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
1430, Scrimger et al., 2007	Prospective	Histologically proven AJCC stage I-IV SCC at various head and sites (07/2000-12/2004)	Definitive or adjuvant IMRT with or w/out concurrent CTx Usually platinum-based CTx	64	47 CTx 12	17 incomplete salivary flow data or lost to F/U
1500, Lee et al., 2007	Retrospective	Histologically proven AJCC stage III-IV laryngeal and hypopharyngeal SCC (01/2002-06/2005)	Definitive IMRT plus CTx Concurrent cisplatin alone, carboplatin plus 5-FU, or carboplatin plus paclitaxel	37	31 CTx 37	6 2 had early-stage disease 3 had postoperative IMRT 1 refused CTx
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	Retrospective	Histologically proven AJCC stage T0-4, N2-3 SCC at various head and neck sites (12/1999-07/2005)	Definitive IMRT alone or plus CTx Concurrent or induction cisplatin Neck dissection in 13 pts	100	90 CTx 74	10 4 with NPH carcinoma 5 with pre-RT neck dissection, 1 lost to F/U
1780, Lee et al., 2007	Retrospective	Histologically proven recurrent cancer of the head and neck (07/1996-09/2005)	Definitive or adjuvant IMRT with or w/out CTx Induction, concurrent, or adjuvant mostly platinum-based regimens	155	105 CTx 45	5 did not complete prescribed RT 6 lost to F/U

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
1900, Ben-David et al., 2007	Retrospective	Histologically proven AJCC stage I-IVB or recurrent head and neck cancer at various sites (03/1996-03/2005)	Definitive or adjuvant IMRT, with or w/out CTx Concurrent cisplatin, carboplatin or carboplatin plus paclitaxel	188	176 CTx 108	12 5 lost to F/U at < 6 mos 2 died of pneumonia or trauma 2 died of lung metastases 3 did not complete RT course
1990, Yao et al., 2007	Retrospective	Histologically proven AJCC stage I-IV SCC of the oral cavity (05/2001-07/2005)	Definitive or adjuvant IMRT, with or w/out CTx Concurrent, adjuvant, or neoadjuvant cisplatin	55 CTx 6	55	0
2180, Daly et al., 2007	Retrospective	Histologically proven AJCC stage Tis-T4 malignancies of the nasal cavity and paranasal sinuses (04/1998-12/2004)	Definitive or adjuvant IMRT, with or w/out CTx CTx not described	45 CTx 8	36	9 3 excluded received boost IMRT after CRT 3 treated for recurrent disease 3 had inadequate F/U
2290, Yao et al., 2006	Retrospective	Histologically proven AJCC stage I-IV oropharyngeal SCC (01/2000-07/2004)	Definitive or adjuvant IMRT, with or w/out CTx Cisplatin alone or with 5-FU	69	66 Ctx 46	3 2 presented with metastatic disease 1 lost to F/U after 6 mos. of tx

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
2370, Garden et al., 2007	Retrospective	Histologically proven AJCC stage T1-x primary SCC of the oropharynx (10/2000-06/2002)	Definitive or adjuvant IMRT, with or w/out CTx CTx not described	54	51 CTx 5	3 1 received IMRT to boost field only 1 received boost with CRT 1 switched from IMRT to CRT
2430, Vosmik et al., 2006	Prospective	Histologically proven stage I-IV (staging system not identified) carcinoma of the head and neck region with regional nodal involvement (12/2003-09/2005)	Definitive or adjuvant IMRT, with or w/out concurrent CTx Cisplatin	41	38 CTx 5	3 RT terminated early due to toxicity and inability to continue
2770, Cheng et al., 2006	Prospective	Histologically proven AJCC stage T1-4, N0-3b, M0 primary NPC with regional nodal involvement (04/1990-12/2002)	Definitive 3DCRT with or w/out CTx Concurrent cisplatin plus 5-FU	719 CTX 586	630	89 48 presented with metastatic disease 9 did not receive full RT dose 32 had no MRI data for F/U analysis
3080, Meirovitz 2006	Prospective cross-sectional	Pts with H & N cancer txd with IMRT at a single institution (11/2001-10/2003)	IMRT Adjuvant or definitive Concurrent CTx	38 Definitive 20 (15 also rec'd concurrent CT) Post op RT 18 (1 rec'd concurrent CT)	38	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
3220, Portaluri et al., 2006	Prospective	Histologically proven locally advanced AJCC staged, previously untreated SCC of the head and neck (2001-2003)	Definitive or adjuvant 3DCRT with or w/out CTx Cisplatin alone or plus 5-FU	49	49 CTx 13	0
3340, Studer 2006	CS with historical controls (3DCRT)	Consecutive patients with HYP cancer (01/2002-07/2005)	SIB IMRT Adjuvant or definitive Concurrent CTx	29 definitive 25 adjuvant 4 CTx cisplatin-based 25	29	0
3400, Studer 2006	CS with historic controls (IMRT v 3DCRT)	OPH or oral cancer	IMRT with simultaneously integrated boost (SIB) Adjuvant or definitive Concurrent CTx	123 21 adjuvant 52 definitive CTx cisplatin-based 56	73 73 considered “at risk” for ORN (defined as receiving >60Gy for primary OPH or oral cancer) OPH (n=55) Oral cancer (n=18)	0
3570, Saarilahti 2006	Cohort	Cohort with stage 2 or higher primary squamous ca H & N and at least one parotid gland spared from PTV. (07/2000-04/2004)	IMRT Adjuvant or definitive Concurrent CTx	36 Definitive 16 Adjuvant 20 CTx 16	36 (evaluated as whether or not the contralateral submandibular gland was spared [n=18] or not [n=18]).	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
3790, Ozsahin et al., 2006	Retrospective	Histologically proven IUAC locally advanced cancer of the head and neck with regional nodal involvement (11/2000-01/2003)	Definitive or adjuvant 3DCRT with or w/out CTx Concurrent cisplatin plus 5-FU	33	33 CTx 26	0
3820, McMillan 2006	Prospective, longitudinal	Histologically confirmed NPC Stage 1 and 2	IMRT with parotid sparing	32	32	0
4290, Lau et al., 2006	Retrospective	Histologically proven AJCC stage I-IV primary, non-nasopharyngeal SCC of the head and neck (09/2000-12/2002)	Definitive or adjuvant 3DCRT with or w/out CTx Concurrent cisplatin	57	56 CTX 57	1 Died with MI 1 wk after CRT
4430, Kwong 2006	CS	Histologically proven NPC, locally advanced (skull base involvement or intracranial extension by CT scan). No evidence distant mets. (09/2000-06/2004)	IMRT with dose escalation. Concurrent, adjuvant or induction CTx	50 CTx cisplatin plus 5-FU 34	50	0
4630, Yao	CS	H & N squamous ca txd at one institution (U of Iowa) (10/1999-04/2004).	IMRT Concurrent or induction CTx	151 Definitive n=99 Post op n=51 Concurrent or induction cisplatin-based CTx 68	150	1 (lost to f/u p 2 mos.)

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
5020, Nishimura et al., 2005	Retrospective cohort study assessing Xerostomia incidence after IMRT w/ boost	33 patients with pharyngeal cancer (32 SCC, 1 Non-Hodgkin lymphoma) treated w/ whole neck IMRT Stage II, III, IV	Definitive , Postoperative RT Definitive RT, Postop RT 45, 55 Concurrent Chemotherapy: Cisplatin, Docetaxel, None 30, 39, 30	33	33	0
5120, Wolden et al., 2006	Retrospective 2-arm 3DCRT vs. IMRT	Histologically proven stage I-IV NPC (AJCC) T1-T4/N0-N3, without prior treatment or distant metastasis (07/1998-11/2004)	Definitive RT	109	109 (3DCRT: 35, IMRT: 74)	6 1 refusal T3N0 5 not receiving chemotherapy due to stage I
5210, Duthoy et al., 2005	Prospective cohort comparing postoperative IMRT to historic 3DCRT control	Patients treated w/ postoperative IMRT for adenocarcinoma or SCC of the paranasal sinuses or nasal cavity. T2, T3, T4a, T4b	Postoperative RT	39	39	2
5310, Zheng et al., 2005	Prospective	Histologically proven locally recurrent AJCC T1-4, N0-2 NPC (07/1997-03/2003)	Salvage 3DCRT with or w/out CTx	86	86 CTx 46	0
5330, Lu et al., 2005	Prospective	Histologically proven AJCC stage II nasopharyngeal squamous cell carcinoma (SCC) (08/2001-02/2003)	Definitive 3DCRT	25	24	1 Declined to participate due to inconvenience
5420, Pan et al., 2005	Prospective	Histologically proven stage I-IV head and neck cancer at various sites	Definitive or adjuvant 3DCRT with or w/out CTx Concurrent cisplatin	40	35 CTx 4	5 Did not participate in hearing tests

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
5740, Thorstad et al., 2004	Prospective	Histologically proven AJCC staged, previously untreated SCC of the head and neck	Adjuvant IMRT	27	25	2 Discontinued treatment
6430, Kwong et al, 2004	Prospective cohort of	Newly diagnosed NPC treated w/ IMRT T1, N0-N1, M0	Definitive RT	30	30	0
7090, Chao et al., 2004	Retrospective cohort	TIV, TII, TII, TI SCC of oropharynx were treated w/ IMRT	Definitive and postoperative RT	74	74	0
7110, Sze et al., 2004	Retrospective	Histologically proven AJCC T1-T4 NPC (11/1998-06/2001)	Definitive 3DCRT with or w/out CTx Concurrent cisplatin Induction cisplatin plus 5-FU	308	308 CTx 128	1 Discontinued treatment
7370, Lu et al., 2004	Prospective	Histologically or clinically diagnosed 1992 Fuzhou, China staging system I-IV locoregional recurrent NPC (01/2001-02/2002)	Definitive IMRT with or w/out adjuvant CTx Cisplatin plus 5-FU	49	49 CTx 3	0
7570, Levendag et al., 2004	Prospective	Histologically proven AJCC node-positive or node-negative primary squamous cell carcinoma (SCC) of the head and neck (12/1998-03/2001)	Definitive or adjuvant 3DCRT	57	46	11 Received brachytherapy boost to primary tumor and ipsilateral neck dissection

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
7750, Liu et al., 2003	Prospective	Histologically proven AJCC I-IV nasopharyngeal carcinoma (NPC) (06/1999-04/2003)	Definitive IMRT with or w/out concurrent CTx Cisplatin alone or plus 5-FU	103	83 CTx 63	20 6 distant metastasis 7 local recurrence with previous RT 7 did not complete RT
8250, Munter et al., 2003	Prospective	Histologically proven AJCC staged carcinoma of the head and neck (10/1999-04/2002)	Definitive or adjuvant IMRT with or w/out CTx	48	48 CTx 9	1 Did not complete RT
8270, Braaksma 2003	CS, prospective	Consecutive pts with LN negative histologically proven squamous ca of the LAR, for whom elective LN irradiation was indicated (07/1998-01/2000)	3DCRT	26	26	0
8370, Padovani 2003	Prospective	Consecutive patients with PNS CA (01/1995-07/2001)	3DCRT CTx Resection	25 CTx 7 Resection 22	25	0
8400, Amosson 2003	CS	Histologically confirmed H & N cancer (01/1996-06/2000) No evidence of mets	SMART boost technique with IMRT	30	30	0
9290, Teh 2002	CS	28 pts with primary H & N cancer	IMRT with SMART boost with parotid preservation. No chemotx	28	28	0
9330, Kovacs 2002	CS	Histologically proven primary squamous cell ca of the OC or OPH	Adjuvant 3DCRT Concurrent CTx	73 Concurrent CTx	50 CTx 42	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
9510, Jian 2002	Prospective phase 2	T3 or T4 histologically proven NPH Ca with apparent base of skull and intracranial disease. ECOG PS 0-1 Adeq renal and BM fxn (01/1992112/1998)	3DCRT and concomitant and adjuvant CT	48	48	0
10740, Pommier et al, 2000	Retrospective review 3D CRT	Primary tumor including the paranasal sinuses and undergoing CRT	Definitive(10) or Postoperative (30) RT	40	40	3
11650, Kuppersmith et al., 1999	Retrospective	Histologically proven AJCC staged primary or recurrent cancer of the head and neck (03/1994-04/1997)	Definitive or palliative IMRT	28	28	0
13270, Lawson 2008	CS Retrospective	Pts who underwent definitive RT for BOT SCC using SMART and CT (01/2003-08/2005)	Definitive IMRT (SMART) and platinum-based CT	34	34	0
13340, Ikushima et al, 2008	Retrospective cohort study SIC and CRT	Stage III and IV SCC of the oral cavity treated with CRT and Superselective intra-arterial infusion chemotherapy (SIC)	Preoperative RT	40	40	0
16840, Wu et al, 2006	Retrospective cohort study IMRT	Histologically confirmed nasopharyngeal carcinoma patients treated with modulated accelerated radiation therapy boost technique.	Definitive RT	75	75	0
26140 , Scorsetti 2001	CS	Relapsed H & N cancer (04/1993-06/2000)	3DCRT	58	58	0
24330, Pfreunder et al., 2003	Prospective Cohort paclitaxel/cisplatin induction chemotherapy (ICHT) and RT	Patients eligible for total laryngectomy (TL) and TL plus partial pharyngectomy (TLPP) were enrolled in an ICHT RT study	Postoperative RT	50	50	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
37660, Wendt et al, 2006	Prospective cohort study examining tissue sparing of 3D-c-IMRT w/ compensators	SCC of HnN using 3D conformal IMRT	Definitive, Postoperative, concomitant RT	39	38	1
38290, Anand et al., 2008	Prospective	Histologically proven AJCC staged locoregionally advanced cancer of the head and neck (12/2002-12/2004)	Definitive or adjuvant IMRT with or w/out CTx Concurrent cisplatin alone, or cisplatin ifosphamide, and 5-FU	67	62 CTx 29	5 Did not complete RT 13 had interruption of RT
38530, Studer et al., 2008	Retrospective	Histologically proven stage pT1-pT4, N0-N2c recurrent SCC of the head and neck (04/2003-09/2008)	Definitive or adjuvant salvage IMRT with or w/out CTx Concurrent cisplatin or cetuximab	44	44 CTx 32	0
38640, Studer et al., 2008	Prospective	Histologically proven AJCC staged Tx-T4, N0-N3 primary or recurrent head and neck cancer at various sites (01/2002-12/2007)	Definitive or adjuvant IMRT with or w/out CTx Concurrent cisplatin or cetuximab	409	409 CTx 343	0
38840, Seung 2008	CS Retrospective	Histologically proven cancer of NPH or OPH (04/2003-04/2007)	All with curative intent. Concurrent CTx	69 definitive 60 adjuvant 9 CTx 45	69	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
38850, Caglar 2008	CS Retrospective	Consecutive pts with newly dxd HNSCC between Excluded if had distant mets, previous RT, sal gl tumor or did not have pharynx in the field. (09/2004-08/2006)	IMRT Concurrent or induction CTx	96 definitive 82 adjuvant 14 Induction CTx 28 Concurrent CTx 59	96	0
39000, Sanguineti 2008	CS	Pathologically proven OPH SCC, no surgery x pretx tonsillectomy (05/2002-02/2006)	Definitive IMRT	50	50	0
39020, Rosenthal 2008	CS Retrospective	Consecutive pts for OPH cancer (09/2002-11/2006)	IMRT definitive or IMRT with concurrent CTx	160 IMRT alone 93 Concurrent cisplatin 40 Other concurrent CTx 27	160	0

Study	Design	Participant Selection (Treatment Period)	Therapeutic Setting	n, Enrolled	n, Evaluated	n, Withdrawn (Lost to F/U)
39300, Hoppe et al., 2008	Retrospective	Histologically proven AJCC staged recurrent or primary T1-T4, N0-N2 head and neck cancer at various sites (11/1999-06/2006)	Adjuvant IMRT with or w/out CTx Concurrent or adjuvant platinum containing regimens	151	37 CTx 6	114 39 received RT at different center 29 received definitive RT or CRT only for stage 4B disease 7 treated with 3DCRT 7 treated with IMRT boost 5 had prior RT for paranasal sinus cancer 27 had melanoma 1 did not complete RT (received 40 Gy)
39390, Worden et al., 2008	Prospective	Histologically confirmed, previously untreated stage III-IV SCC of the oropharynx (01/2000-11/2002)	Definitive IMRT with CTx Neoadjuvant cisplatin or carboplatin plus 5-FU, concurrent cisplatin or carboplatin	66	53 CTx 53 concurrent	13 11 did not respond to induction CTx prior to RT 1 died due to CTx toxicity 1 died from disease prior to RT

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-B. Participant characteristics

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
560, Biagioli et al., 2007	med 63 rng 19-82		10	Recurrent	SCC 85 Malignant neoplasm 4 Adenoid cystic carcinoma 2 Adenocarcinoma 2 Mucoepidermoid 2 Small cell carcinoma 2 Larynx 29 Oropharynx 29 Parotid 15 Oral cavity 12 Paranasal sinuses 5 Unspecified 5 Nasopharynx 2 Hypopharynx 2		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
580, Dirix et al., 2007	med 65 rng 39-82		20	T2 16 T3 32 T4 52 None had evidence of LN or DM at diagnosis	Adenocarcinoma 68 Neuroendocrine 16 Esthesioneuroblastoma 8 SCC 8 Ethmoid sinus 72 Nasal cavity 16 Maxillary sinus 12		
1010, Urbano et al., 2007	63 Gy cohort med 59 rng 37-77 67.2 Gy cohort med 66 rng 60-85		30	T1 3.3 T2 20 T3 53.3 T4 23.3 N0 40 N1 20 N2a 3.3 N2b 16.7 N2c 16.7 N3 3.3	SCC Laryngeal 47 Hypopharyngeal 53		
1420, Feng et al, 2007	56 ± 9		17	T1 6 T2 31 T3 25 T4 39 N0 8 N1 11 N2 72 N3 8	Oropharyngeal 31 Nasopharyngeal 5 Tongue base 53 Tonsil 33 Nasopharynx 14		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
1430, Scrimger et al., 2007	≤ 50 n = 16 > 50 n = 31		21	T0 4 T1 15 T2 43 T3 26 T4 13 N0 32 N1 26 N2 40 N3 1 AJCC I 4 II 23 III 23 IV 49	SCC 100 Oral cavity 42 Nasopharynx 21 Oropharynx 19 Larynx/hypopharynx 13 Unknown primary 4	Current 28 Past 49 Never 17 Unknown 6	
1500, Lee et al., 2007	med 57 rng 36-78		32	T1-2 26 T3 42 T4a 29 T4b 3 N0 23 N1 23 N2 54 AJCC III 29 IVA 68 IVB 3	SCC 100 Larynx 65 Hypopharynx 35		KPS 90 65 70-80 35
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	med 57 rng 36-85		19	T0 2 Tx 7 T1 11 T2 34 T3 20 T4 26 N2a 12 N2b 43 N2c 31 N3 13	SCC 100 Oropharynx 71 Larynx 13 Hypopharynx 3 Oral cavity 3 Sinus/nasal 2 Unk primary 7		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
1780, Lee et al., 2007	med 58 (rng 31-84)		34	Recurrent	SCC 86 Adenoid cystic 5 Mucoepidermoid 5 Adenocarcinoma 4 Nasopharynx 20 Neck 20 Paranasal sinus 17 Oropharynx 15 Larynx 10 Oral cavity 8 Parotid 6 Hypopharynx 4		Neck dissection pre-RT 10
1900, Ben-David et al., 2007	med 55 rng 29-86	white 98 Black 1 Asian 1	48	AJCC I 1 II 4 III 23 IVA 65 IVB 7 Rec 1	Oropharynx 68 Oral cavity 18 Hypopharynx 7 Larynx 4 Other 2		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
1990, Yao et al., 2007	med 62 rng 26-90		40	T0 4 T1 14 T2 25 T3 11 T4 45 N0 31 N1 33 N2A 4 N2B 27 N2C 5	SCC 100 Tongue 36 Mouth floor 27 Buccal mucosa 11 Retromolar trigone 11 Alveolar ridge 11 Lip 4		
2180, Daly et al., 2007	≤ 60 n = 19 > 60 n = 17		53	Tis 3 T1 3 T2 3 T3 22 T4 69	SCC 33 Esthesio 19 Adeno 14 Adenoid cystic ca 14 Sinonasal undiff ca 14 Mucoepidermoid 3 Neuroendocrine ca 3		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
2290, Yao et al., 2006	med 53 rng 36-84		12	T1 20 T2 39 T3 12 T4 29 N0 12 N1 6 N2A 11 N2B 38 N2C 20 N3 14 AJCC I 2 II 6 III 4 IV 88	Tonsil 47 Tongue base 39 Oropharynx 9 Oropharyngeal wall 3 Soft palate 1		
2370, Garden et al., 2007	med 54 rng 30-75		14	T1 37 T2 35 Tx 27 N0 16 N1 14 N2A 20 N2B 27 N2C 2 N3 4 Nx 18	Tonsil 65 Tongue base 31 Pharyngeal wall 4		> 10 drinks/wk 20 1-10 drinks/wk 43 Rare/never drink 37

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
2430, Vosmik et al., 2006	med 55 rng 25-83		16	I 3 II 18 III 29 IV 50	SCC 92 Other 8 Oropharynx 34 Larynx 21 Hypopharynx 16 Nasopharynx 13 Maxillary sinus 10 Nasal cavity 5		
2770, Cheng et al., 2006	≤ 40 223 > 40 407		30	T1 25 T2a 7 T2b 19 T3 22 T4 27 N0 11 N1 23 N2 55 N3a 4 N3b 6	WHO 1 3 WHO 2 21 WHO 3 76		Parapharyngeal space extension 60 Cranial nerve involvement 12 LDH ≥ 410 13 LDH < 410 87
3080 Meirovitz 2006			n=8 (21%)	Stage I n=2 II n=4 III n=6 IVA n=24 IVB n=2	OPH n=26 OC n=9 LAR n=1 HYP n=1 UNP n=1		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
3320, Portaluri et al., 2006	med 61 rng 37-81		25	AJCC II 12 III 31 IVA 33 IVB 4	SCC 100 Larynx 36 Oropharynx 24 Oral cavity 24 Nasopharynx 12 Other 4		
3340 Studer 2006	Mean 60.8 (34-87 years)		F:M ratio 1:5 (6:23)	T1N2a n=1 T1N3 n=1 T2N0 n=3 T2N2a n=1 T2N2b n=8 T2N2c n=2 T3N0 n=1 T3 N1 n=1 T3N2a n=1 T 3N2b n=2 T3N2c n=1 T4N0 n=1 T4N1 n=2 T4N2b n=2 T4N2c n=2 Stage 1 n= (%) Stage 2 n= (%) Stage 3 n= (%) Stage 4 n= (%)	HYP cancer (100%)		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
3400 Studer, 2006	Mean 60.2 (41-85)		14(19.2%)	Locally advanced stage ¾ n=37 T1/2N2c n=5 Recurrent dz n=6 T1-2 N0-2b N=25	OPH (75%) Oral cavity (25%)		
3570 Saarilahti 2006	Submandibular gland spared Mean 55.4 (29-78) Not spared 52.0 (36-68)		21/36 (58%)	Tumor stage Submand gl spared: T0: n=1 (6) T1-2: n=12 (67) T3-4: n=5 (28) Submand gl not spared: T0: n=0 (0) T1-2: n=10 (56) T3-4: n=8 (44) Nodal stage NPH Submand gl spared: N0: 1 N1: 1 N2: 1 Submand gl not spared: N0: 2 N1: 2 N2: 1 OPH Submand gl spared: N0: 1 N1: 3 N2a: 3 N2b: 0 N2c: 0 N3: 0	NPH 8/36 (22.2%) OPH 28/36 (77.8%)		WHO PS Subgl spared 0 n=10 1 n=8 Subgl not spared 0 n=9 1 n=9

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
				Submand gl not spared: N0: 2 N1: 2 N2a: 0 N2b: 5 N2c: 3 N3: 2			
3790, Ozsahin et al., 2006	med 54 rng 39-76		18	T1-2 30 T3-4 70 N0-1 45 N2-3 55	Oropharynx 34 Oral cavity 27 Nasopharynx 15 Hypopharynx 12 Larynx 12		
3820 McMillan 2006	Mean 45.9 (28-63)	Southern Chinese	n=13 (40.6%)	AJCC Tumor stage 1: n=15(47%) 2: n=17 (53%)	NPH (100%)		
4290, Lau et al., 2006	med 58 (rng 38-77)		25	Tx 12 T1 14 T2 27 T3 25 T4 21 N0 18 N1 20 N2 59 N3 3 AJCC X 12 II 7 III 20 IV 61	SCC Oropharynx 48 Hypopharynx 18 Larynx 16 Unknown primary 12 Oral cavity 5		KPS 90-100 75 70-80 21 ≤ 60 4

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
4430 Kwong 2006	Median 48 (24-74 years)		n=11 (28%)	T3 (n=16) T4 (n=34) Stage III (n=14) Stage IVA-B (n=36) No evidence distant mets.	NPC either poorly or undifferentiated (100%)		
4630 Yao	56 (20-90)		n=32 (21%)	AJCC Stage I n=1 II n=10 III n=25 IV n=103 Unk n=11	NPH n=5 OPH n=56 LAR n=33 OCL n=29 HYP n=8 PNS n=8 UNP n=11		
5020, Nishimura et al., 2005	57 (35 – 81)		21	UICC II, III, IV 27, 15, 58	Nasopharynx, Oropharynx, Hypopharynx: 39, 30, 30		Performance Status: 0, 1, PS2 67, 30, 3
5120, Wolden et al., 2006	Med (rng) 48 (13-79)	Caucasian, Asian, Black, Hispanic, Other 3DCRT 43, 29, 11, 6, 11 IMRT 35, 32, 19, 8, 5	3DCRT 26 IMRT 28	AJCC I, IIB, III, IV A/B 3DCRT 0, 20, 31, 49 IMRT 7, 16, 30, 47 T1,2,3,4 3DCRT 11, 23, 29, 37 IMRT 20, 28, 20, 31 999N0, 1, 2, 3 3DCRT 9, 40, 13, 5 IMRT 22, 31, 23, 24	NPC		LCC at 3-yr negatively influenced by increasing T stage p=.001

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
5210, Duthoy et al., 2005	IMRT Group: 62 (30-78)			IMRT: T1=0, T2=13, T3=4, T4=11 Historic 3DCRT Cohort: T1=2, T2=8, T3=9, T4=11	IMRT: Adenocarinoma: 31 SCC: 8 Ethmoid Sinus: 30 Maxillary Sinus: 6 Nasal Cavity: 3		IMRT Group: 2 patients treated for recurrent tumor 24 patients w/ history of occupational wood exposure 3 patients w/ neurological symptoms 5 patients w/ cheek swelling 14 patients w/ epitaxis 26 patients w/ nasal obstruction
5310, Zheng et al., 2005	med 47 (rng 25-71)		30	T1 18 T2 31 T3 28 T4 23 N0 91 N1-2 9	WHO II 13 WHO III 87		Complications at dx Grade0/1 61 Grade 2 31 Grade 3 8
5330, Lu et al., 2005	med 44 ≥ 60 5 (20) < 60 20 (80)		36	T1 52 T2 48 N0 16 N1 84	WHO I 4 WHO II 8 WHO III 88		KPS ≥ 70 100
5420, Pan et al., 2005	mn 58 (SD 16)		49	Nonmalignant 9 I/II 20 III 23 IV 49	Oral cavity 31 Paranasal 26 Salivary gland 23 Nasopharynx 11 Skin 9 Oropharynx 3		Hypertension 31 Diabetes mellitus 15

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
5740, Thorstad et al., 2004	> 18				SCC Oropharynx Hypopharynx Larynx Paranasal sinus		KPS > 70 100
6430, Kwong et al, 2004	43 (29-74)		51.5	T1, T2, T3 94, 3, 3% N0, N1 81.8, 18.2%	NPC 100%		Two patients found not to be T1 stage after MRI (1 T2, 1 T3)
6530 Zheng 2004	≤45 n=26 >45 n=28		N=15 (28%)	AJCC Stage 1 n=5 (9.3) Stage 2 n=16 (29.6) Stage 3 n=18 (33.3) Stage 4 n=15 (27.8) rT1 n=15 rT2 n=25 rT3 n=14 T1 n=7 T2 n=16 T3 n=18 T4 n=13 N0 n=15 N1 n=17 N2 n=17 N3 n=5	NPC (100%) WHO type 2 n= 6 (11%) type 3 n=48 (89%)		
7090, Chao et al., 2004	55 (35-76)		17.6	T1, T2, T3, T4: 22, 35, 19, 26 N0, N1, N2, N3: 17, 22, 58, 6	Tonsil, base of tongue, soft palate: 70, 25, 5		
7110, Sze et al., 2004	med 48 rng 17-83		29	T1 9 T2 41 T3 35 T4 21	WHO II-III 99 Nasopharynx		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
7370, Lu et al., 2004	med 45 rng 28-70		24	T1 8 T2 18 T3 22 T4 51 N0 94 N1 4 N2 0 N3 2 AJCC I 8 II 18 III 20 IV 51	Carcinoma 100		
7570, Levendag et al., 2004	mn 61 rng 41-82		21	N0 72 N+ 28 AJCC stage III/IV reported in 75% of all cases	SCC 100 Larynx 48 Oropharynx 39 Hypopharynx 11 Oral cavity 2		
7750, Liu et al., 2003	med 48 rng 25-85		16	T1 23 T2 42 T3 7 T4 28 N0 23 N1 33 N2 30 N3 14 AJCC I 7 II 30 III 24 IV 39	WHO I 2 WHO II 56 WHO III 42		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
8250, Munter et al., 2003	med 55 rng 21-78		33	AJCC I-IVB T1-T4 N0-N1 M0-M1 (not clearly compiled)	SCC 54 Adenoid cystic carcinoma 38 Adenocarcinoma 8 Salivary glands 38 Maxillary sinus 19 Oropharynx 19 Nasopharynx 17 Larynx/hypophar 4 Unknown primary 4		
8270 Braaksma 2003	Median 62 (42-81)		n=6 (23.1%)	T1 n=6 (23.1) T2 n=10 (38.5) T3 n=9 (34.6) T4 n=1 (3.8)	Squamous ca (100) Well diff n=3 (11.5) Mod diff n=15 (57.7) Poor diff n=4 (15.4) Unk n=4 (15.4)		
8370 Padovani 2003	67 (34-86)			T4 n=17 T3 n=4 T2 n=4 (disease was recurrent in 4 pts)	25 PNS CA (18 ETH and 7MAX) 13 adenoca and 12 sq ca		Major adverse px fx was initial involvement of CNS (n=3) or base of skull or dura mater (n=8) and mets to LNs.

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
8400 Amosson 2003	Mean 60.5 Median 63.0 Range 43-73		20%	Stage 1 n=3 (10.0%) Stage 2 n=7 (23.3%) Stage 3 n=9 (30.0%) Stage 4 n=9 (30.0%) Recurrent n=1 (3.3%)	OPH n=16 (53.3) NPH n=4 (13.3) OC n=2 (6.7%) LAR n=4 (13.3) HYP n=1 (3.3) PNS n=2 (6.7) UNP n=1 (3.3) Included squamous cell ca, adenoca and adenoid cystic ca (numbers not provided)		
9290 Teh 2002					NPH n=7 (25%) OPH n=12 (43%) HYP n=3 (11%) LAR n=4 (14%) OC n=2 (7%)		
9330 Kovacs 2002	Ave 59.6		27% *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not	Stage 1 n=12 (16.4%) Stage 2 n=19 (26.1%) Stage 3 n=10 (13.7%) Stage 4 n=32 (43.8%) *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not	OPH n=10 (14%) OC n=63 (86%) *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not		ECOG status 0: 84% I: 15% II: 1% *note= these numbers include all 73 pts and are not broken out for the pts who rec'd RT vs. those that did not
9510 Jian 2002	n (%) ≤40 n=14 (29.2) 41-50 n=16 (33.3) 51-60 n=7 (14.6) >60 n=11 (22.9)		8 (16.7)	T3 n=11 (23) T4 n=37 (77)	NPC (100) WHO type 2 n=17 (35.4) WHO type 3 n=31 (64.6)		
10740, Pommier et al, 2000	67 (28 – 86)		35%		Paranasal Sinuses: 70% Nasal cavities: 10% Hard Palate: 20%		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
13270 Lawson 2008	Mean 61 (34-76)		11 (32)	AJCC Stage 1 0(0) Stage 2 2 (6) Stage 3 3 (9) Stage 4 29 (85) T1N0-3 n=10 T2N0-3 n=10 T3N0-3 n=4 T4N0-3 n=10	BOT SCC 100%	24 (71)	
11650, Kuppersmith et al., 1999	med 55 rng 10-92		14	T1-T4 N0-N2C M0	SCC 64 Other 36 Nasopharynx 25 Maxillary sinus 14 Base of tongue 14 Other 47		
13340 Ikushima et al, 2008	63.1 (27-81)		35	III,IV 33, 77	Tongue, gingiva, bucca mucosa, oral floor, soft palate 35, 47.5, 10, 5, 4		SIC chemotherapy
16840, Wu et al, 2006	52 (24-82)		28	I, II, III, IV 5.3, 38.6, 38.6, 17.3 WHO type 1,2,3 2.6, 88, 9.3			
26140 Scorsetti 2001	46 (20-71)		20 (34.5)		Undiff NPC n=16 (27.6%) Squamous cell ca n=10 (17.2) Adenoid cystic ca n=9 (15.5) Adenocarcinoma n=8 (13.8) Various n=15 (25.9)		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
24330, Pfreunder et al., 2003	58 (42-77)		16	T2N0, T3N0, T3N1, T3N2a, T3N2c, T4n), T4N1, T4N2b, T4N2c, T4N3 2, 28, 8, 2, 2, 6, 18, 10, 6, 14, 4%	Resectable carcinomas of the glottic (T3-T4) and supraglottic larynx/hypopharynx (T2-T4, N0-N3, M0)		
38840 Seung 2008	Median 56 yrs (35-89)		14 (20)	AJCC stage I n=2 (3) II n=11 (16) III n=16 (23) IV n=40 (58)	NPH n=11 (16) BOT n=18 (26) Tonsil n=40 (58) n=66 (95.7) SCC n=2 (2.9) LELCarc n=1 (1.4) undiff carc		
38850 Caglar 2008	Median 55 (20-87)	White n=70 (73) Nonwhite n=9 (9) Unk n=17 (18)	17 (18%)	Stage I n=1 (1) II n=3 (3) III n=23 (24) IV n=69 (72)	OPH n=43 (45%) NPH 11(11) OC 13(14) HYP 17(18) MAX 2(2) UNP 10(10)	Yes n=48 (50%) No 48 (50)	
39000 Sanguineti 2008				Stage 1 n=1 (2%) 2 n=5 (10%) 3 n=15 (30%) 4 n=29 (58%)	Tonsil n= 34 (68%) BOT n=8 (16) Pharyngeal wall 2 (4) Soft palate 6 (12)		
39020 Rosenthal 2008	Median 58 (34-81)		21 (13.1)	T1N0-3 n=48 T2N0-3 n=72 T3N0-3 n=21 T4N0-3 n=19	BOT n=78 (48.8) Tonsil n=80 (50) OPH n=2 (1.2)		
37660, Wendt et al, 2006	57 (37-76)		10%		Nasopharynx, oropharynx, oral cavity/tongue, hypopharynx/supraglottic larynx, CUP-syndrome 10, 51, 23, 13, 3%		Radical RT alone: 26% Postoperative RT: 74% RT without simultaneous chemotherapy: 51 RT with simultaneous cDDP: 49

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
38290, Anand et al., 2008	med 56 rng 27-85		23	AJCC I 6 II 16 III 27 IVA 39 IVB 11	SCC 89 Adenoid cystic carcinoma 6 Mucoepidermoid carcinoma 3 Adenocarcinoma 2 Nasopharynx 24 Larynx 21 Oropharynx 16 Tongue 14 Hypopharynx 13 Alveolus 6 Paranasal sinus 5		
38530, Studer et al., 2008	mn 64 rng 35-87		36	pT1 32 pT2 52 pT3 2 pT4 7 T unk 7 N0 59 N1 11 N2a/b 20 N2c 5 N unk 5	SCC 100 Oral cavity 66 Glottic 18 Oropharynx 9 Sinonasal 5 Skin 2		Grade 1 5 Grade 2 34 Grade 3 27 unk 25

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
38640, Studer et al., 2008	mn 60 rng 21-87		22	Tx 1 T1 11 T2 31 T3 17 T4 28 N0 17 N1 12 N2a/b 32 N2c 27 N3 5 Recurrent 17	SCC 95 Lymphoepithelial carcinoma 5 Oropharynx 40 Oral cavity 19 Hypopharynx 15 Larynx 12 Nasopharynx 10 Sinonasal 2 Unknown 1		

Study	Age (yrs)	Race (%)	Female (%)	Disease Stage/Category (%)	Disease Histology/Site (%)	History of Tobacco Use (%)	Comorbidities or Other Prognostic Factors (%)
39300, Hoppe et al., 2008	med 55 rng 15-88	White 73 Asian 11 Black 11 Other 5	49	T1 0 T2 17 T3 17 T4 55 N0 90 N1 10 Kadish A 0 B 66 C 33	SCC 46 Sarcoma 14 Adenoid cystic 11 Undifferentiated 8 Adenocarcinoma 8 Esthesioneuroblastoma 8 Myoepithelial 5 Maxillary sinus 54 Nasal cavity 27 Ethmoid sinus 11 Lacrimal gland 3 Sphenoid sinus 3 Frontal sinus 3		KPS med 90 (rng 70-100)
39390, Worden et al., 2008	Male med 55 rng 37-77 Female med 61 rng 50-74		23	T1 8 T2 26 T3 35 T4 32 N0 18 N1 23 N2 50 N3 9	SCC 100 Base of tongue 61 Tonsil 39	Never 24 Past 42 Current 33	HPV titer pos 41 neg 23 unk 36 KPS 80 9 90 20 100 71

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-C. Treatment characteristics

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
560, Biagioli et al., 2007	CT	Yes (Nomos.)	Photons (6-MV)	60 Gy, 2 Gy/frac, 5 frac/wk Lifetime dose to spinal cord ≤ 60 Gy			GTV = gross tumor volume PTV = GTV and areas at risk of microscopic disease expanded by 5-20-mm margin	
580, Dirix et al., 2007	CT, MRI	Yes (Helios, Cadplan, Eclipse)	Photons (6-MV)	60 Gy 2 Gy/frac, 5 frac/wk IMRT boost 6 Gy, 2 Gy/frac in 10 pts In regions where PTV and OAR overlapped (optic structures) underdosage of the PTV was tolerated No elective irradiation of cervical LNs	Non-coplanar 6-field arrangement consisting of 5 fields of 6-MV photons and 1 filed of 10 or 18 MV photons from LA	3-point fixation thermoplastic mask	CTV included GTV plus margin (not defined) to account for microscopic disease at margin, encompassing resection cavity plus all paranasal sinuses that were invaded PTV included CTV plus 5-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1010, Urbano et al., 2007	CT	Yes (Helios, Cadplan, Eclipse or Helax-TMS and Pinnacle)	Photons (6-MV)	Dose level (DL) 1: Primary tumor site 63 Gy, 2.25 Gy/frac Elective nodal areas 51.8 Gy, 1.85 Gy/frac With IMRT SIB DL 2: Primary tumor site 67.2 Gy, 2.4 Gy/frac Elective nodal areas 56 Gy, 2 Gy/frac Mn Tx time: DL1 = 39±3 days DL2 = 38±1 days Maximum mean dose to parotids 24 Gy where possible	5- and 7-beam arrangements	Custom-made cabulite head and neck mask	CTV1 = entire larynx and hypopharynx complex, including thyroid cartilage, from 1 cm above the tip of the epiglottis to below the cricoid cartilage; adjacent sites invaded by tumor as well as all involved nodal areas and retropharyngeal nodes were included; CTV2 = elective nodal volume, including uninvolved levels 2-5 and supraclavicular fossa nodes bilaterally; PTV1/PTV2 = CTV1/CTV2 plus 3-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1420 Feng et al, 2007	CT	Yes (in-house system)		70 Gy, 2.0 Gy/frac to gross disease 59-63 Gy, 1.7-1.8 Gy/frac to low- and high-risk subclinical targets Maximal mandibular dose < 72 Gy Mean parotid gland dose ≤ 26 Gy Mean noninvolved oral cavity dose ≤ 30 Gy	Inverse-planned beamlet (not further described)		CTV = primary tumor and include lateral retropharyngeal (RP) nodes PTV = CTV plus a 3-mm margin Targets in low neck were included I IMRT plans, but anterior low neck fields abutting upper neck plans were not used	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1430, Scrimger et al., 2007		Yes (Helax v.6.02)	Photons	2 Gy/frac, 5 frac/wk initially, then 1.8-2.2 Gy/frac in SIB protocol Planning goal to keep RT dose to spared portion of parotids as low as possible (mean dose to spared portion of parotid 18.4 Gy Mean dose to all parotid tissue 27.1 Gy	7 gantry angles, 128-leaf MLC		In most patients, the CTV was immediately adjacent to the deep lobe of the parotid; entire target volume, including low neck, treated as 1 volume with no separate supraclavicular field PTV = CTV plus 5-mm margin PTV66 = areas of gross disease PTV60 = high-risk operative bed PTV54 = low-risk operative bed or undissected nodal regions	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1500, Lee et al., 2007	CT with contrast	Yes (MSKCC tx planning system)	Photons (6-MV)	70-72 Gy, 1.64-2.12 Gy/frac, once daily with concomitant boost (n = 4) or SIB (n = 27) When possible, a mean parotid dose of ≤ 26 Gy was achieved; efforts were made to prevent unwarranted hot spots within the glottic larynx	7-field	Thermoplastic head, neck, and shoulder mask	GTV = any visible tumor on imaging studies and/or physical examination CTV = GTV plus 5-10-mm margin, including levels II-IV nodal regions in the neck, retropharyngeal region in pts with clinically involved neck nodes, levels I-II in pts with node-positive disease at level II, and pts who had a primary hypopharyngeal tumor PTV = GTV or high-risk CTV plus a 3-mm margin In some cases a low-risk CTV and corresponding low-risk PTV involved the clinically uninvolved contralateral neck and base of skull	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	CT, MRI	Yes (Corvus v.3.0, Nomos.)	Photons	50-74 Gy, 1.2-1.25 Gy/frac, once daily (n = 83), twice-daily (n = 5), 2 with accelerated fractionation with noncomitant boost	Multivane, intensity-modulating collimator	Thermoplastic facemask	CTV1 = primary tumor and involved lymph nodes with margins CTV2 = high-risk areas harboring microscopic disease, including soft tissue surrounding CTV1 and lymphatic areas with high risk of metastasis CTV3 = areas with intermediate risk of microscopic disease	
1780, Lee et al., 2007	CT with or w/out contrast	Yes (MSKKC in-house)	Photons (6-MV)	30-70 Gy med 59 Gy Dose constraints: Spinal cord 50 Gy	Beams chosen to ensure at least 95% of dose encompassed the target volume	Thermoplastic mask	GTV = any visible evidence of disease CTV = at minimum the preoperative GTV and postop tumor bed PTV = GTV and CTV plus 10-20-mm margins	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1900, Ben-David et al., 2007	CT	Yes	Photons	70 Gy, 2 Gy/frac to gross tumor, 56-64 Gy, 1.6-1.8 Gy/frac to low- and high-risk targets Maximal mandibular dose < 72 Gy Mean parotid gland dose ≤ 26 Gy Mean noninvolved oral cavity dose ≤ 30 Gy	Static multisegmental or inverse-planned beamlet (not further described)		CTV = not described PTV = CTV plus 5-mm margin	Radiation guards used in all pts with metallic dental restorations to reduce electron backscatter to adjacent soft tissue

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
1990, Yao et al., 2007	CT	Yes	Photons	50-70 Gy, 2 Gy/frac Definitive IMRT pts received additional SIB of 10 Gy, 2 Gy/frac High-risk postoperative sites (extracapsular extension, positive or close margins, tumor involvement of soft tissue or bone) received additional SIB of 4-6 Gy, 2 Gy/frac No SIB given for intermediate-risk sites (w/out extracapsular extension, no positive or close margins, no soft tissue or bone involvement)			CTV1 = tumor bed, including preoperative primary tumor volumes and involved LNs CTV2 = high-risk areas harboring microscopic disease, including normal structures immediately surrounding CTV1 with high risk of local tumor invasion (primary tumor CTV2) and high-risk lymphatic regions (lymphatic CTV2) CTV3 = intermediate-risk lymphatic areas PTV = CTV plus 5-8-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
2180, Daly et al., 2007	CT	Yes (Nomos.)	Photons	60-70 Gy, 1.8-2.12 Gy/frac, once daily Dose constraints: 1% of brainstem and optic nerves volume 54 Gy < 1% temporal lobes volume 60 Gy Half the contralateral parotid gland 25 Gy Upper neck or high-risk subclinical region 60 Gy Low neck and supraclavicular region 50-54 Gy	Continuous course RT delivered using an auto-sequence MLC	Perforated, thermoplastic head mask	GTV = gross extent of tumor CTV = GTV plus margin of 10-20 mm for microscopic disease PTV = CTV plus 3-5-mm margin to account for patient setup error Elective neck radiation administered at the discretion of the treating physician (n = 10) Two methods used to treat neck: Primary tumor and upper neck above vocal cords treated with IMRT, anterior field for lower neck and supraclavicular fossae Extended field IMRT for primary tumor plus all regional LNs including supraclavicular	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
2290, Yao et al., 2006	CT	Yes (Nomos.)	Photons	Definitive IMRT: 70-74 Gy to PTV1, 60 Gy tp PTV2, 50-54 Gy to PTV3 Adjuvant IMRT: 60-66 Gy to PTV1, 60 Gy to PTV2, 50-54 Gy to PTV3	Multivane intensity modulating collimator		CTV1 = primary tumor and involved cervical LNs CTV2 = high-risk areas harboring microscopic disease CTV3 = intermediate-risk lymphatic areas PTV 1-2 = CTV 1-3 plus 5-mm margin	
2370, Garden et al., 2007	CT	Yes (CORVUS v.4.0, Nomos.)	Photons (6-MV)	66-70 Gy, 1.8-2.2 Gy/frac to CTV1 57-64 Gy, 1.9-2.1 Gy/frac to CTV2 54 Gy, 1,8 Gy/frac to CTV3 Concomitant boost 15-18 Gy in10 frac in 4 pts Dose constraints: Parotid glands 26 Gy Larynx 30-40 Gy	MLC		CTV1 = gross disease with minimum 5-mm margin CTV2 = CTV1 with additional margin CTV3 = subclinical sites in both sides of upper neck Lower neck treated with anterior field matched to inferior borders of IMRt delivery	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
2430, Vosmik et al., 2006	CT (with or w/out contrast), MRI in some cases	Yes (CadPlan, Helios)	Photons	54-66 Gy, 1.8-2.2 Gy/frac, 6 wks 66 Gy to PTV66 60 Gy to PTV60 54 Gy to PTV54 With IMRT simultaneous integrated boost (SIB) Dose constraints: Spinal cord maximum dose < 44 Gy Brain stem maximum dose < 54 Gy mean dose < 28 Gy Larynx (if not part of PTV) 67% volume < 50 Gy	Dynamic MLC, 2x26 leafs	Thermoplastic mask	CTV, GTV, PTV defined according to ICRU Report 50 GTV = all macroscopic disease CTV = gross disease plus 0.5-20-mm margin for microscopic disease PTV = CTV plus 0.5-20-mm margin for setup errors	
2770, Cheng et al., 2006	CT	Yes	Photons (6-MV and 18-MV)	70 Gy, 2 Gy/frac, 5 frac/wk 74.4 Gy, 1.2 Gy/frac, 2 frac daily, 10 frac/wk Dose constraints: Spinal cord 43-44 Gy	Opposed fields with or w/out anterior field		Bilateral, off-cord or posterior cord boost, separate anterior field for low neck and supraclavicular fossa	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
3080 Meirovitz 2006				Tumor dose NR Mean dose to contra and ipsilateral parotid ave 22 Gy (SD 5 Gy) and 53 Gy (SD 7 Gy) Mean dose to contra and ipsilat submandibular gland 57 Gy (SD 8) and 65 Gy (SD 7)			Bilateral neck in all 38	
3320, Portaluri et al., 2006	CT with or w/out contrast	Yes (Eclipse)	Photons (6-MV)	44-64 Gy to PTV1, 2 Gy/frac, 5 frac/wk Boost to CTV2 Dose constraints: Median Dmax (overall population) Spinal cord 44 Gy Ipsilateral parotid 48 Gy Contralateral parotid 42 Gy	Multileaf collimator with 80 leaves, 11 fields (minimum 10, maximum 14)	Head-and-shoulder mask	CTV1 = tumor bed and bilateral LN levels depending on tumor site and stage CTV2 = tumor bed and involved LNs PTV1 and PTV2 = CTV1 and CTV 2 plus 4-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
3340 Studer 2006	CT, MRI and PET	Varian treatment-planning system (Eclipse®, Version 7.3.10, Varian Medical Systems, Hansen Way, Palo Alto CA, USA)	6 MV photon beams	Simultaneous integrated boost (SIB) doses between 60 and 71 Gy (five fractions/week) with 2.0 (n = 8), 2.11 (n = 17), and 2.2 Gy (n = 4)/fraction to the boost volume (planning target volume, PTV1) were applied. Organs at risk: Sp cd max <45 Gy, parotids mean <26 Gy, OC mean <35 Gy, nuchal tissue mean <45 Gy. Mean total treatment time was 45.4 days (32–58 days).	5-field equiangular.	Commercially available thermoplastic mask	GTV with a margin of 10–15 mm was included in the SIB volume. Elective lymph node regions (PTV2, 50–57 Gy) level 2–5 were included bilaterally.	
3400 Studer 2006		IMRT: Varian Treatment planning system (Eclipse®, version 7.3.10, Varian medical system, Hansen Way, Palo Alto, CA, USA)	IMRT: 6-MeV photon beams	In all patients, SIB-IMRT technique was performed using the following schedules: • 30 × 2.2/1.8 Gy to 66 Gy (PTV1)/54 Gy (PTV2; n = 28); • 33 × 2.11/1.64 Gy to 69.6 Gy/54	Most were 5-field arrangements (n=61) 6-fields (n=5) 7-fields (n=7) Sliding window MLC			Doses delivered to partial volumes of mandibular bone using IMRT with doses between 60-75Gy (mean 67) on

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				Gy (n = 25); • 30 × 2.11/1.8 Gy to 63.3/54 Gy (n = 3); • 30–35 × 2.0 Gy to 60–70 Gy (n = 16 postoperative patients). In one case with large necrotic nodes, a higher SIB dose of 2.35 Gy per fraction to 75.2 Gy to the nodal GTV was chosen. Dose to spinal cord, parotids, TMJ, brain, OC outside of PTV, nuchal tissue: Max <45 Gy, mean ≤26, <50, <40, mean <35, mean <45				average 7.8, 4.8, 0.9 and 0.3 cm^3 were exposed to doses >60, 65, 70 and 75 Gy respectively. [mean mandibular bone volume 58.4 cm^3 (33-88cm^3)

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
3570 Saarilahti 2006		IMRT: Helios inverse treatment planning software with Cadplan® system version 6.27(Varian Medical Systems, Helsinki, Finland)	IMRT: 6 MV photon beam	IMRT: Parotids excluded from PTV: Max 25 Gy 1st 5 patients and 16-20 Gy in rest of patients. Dose constraints for spared submandibular glands varied 20-25 Gy. Mean total dose to parotids and submand gl not treated as OAR was 49 Gy(45-54)		Conventional thermoplastic mask for immobilization in 1st 10 patients (Posicast®, Sinmed BV, EM Reenwijk, the Netherlands). Remaining pts stereotactic H & N immobilization device (BrainLab, Heinstetten, Germany).		Both parotids spared in 7 (19%) patients, one contralateral parotid in 29 (81%). Contralateral submandibular spared in 18 (50%) of patients.
3790, Ozsahin et al., 2006	CT, MRI		Photons (6-MV) and electrons	Definitive tx: 70 Gy, 2 Gy/frac, 6 wks Adjuvant RT: 66 Gy, 2 Gy/frac, 5 wks, 3 days RT delivered as concomitant-boost accelerated schedule in single daily fracs M-Th, 2 frac on F Parotids received ≥ 50 Gy in all pts		Thermoplastic mask	Surgical margins, extracapsular nodal infiltration, regional nodes	Amifostine 500 mg sc prior to each RT frac except Friday pm session

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
3820 McMillan 2006	CT	Corvus system (version 3.0)		IMRT: To PTV 66-68 Gy (included deep lobe of parotid and posterior ½ of submandibular) To GTV 68-72 Gy 34 fractions over 7 weeks		Cast	IMRT: CTV= GTV + 1 cm PTV added 2 mm margin and included level 2 and 4 Cx LNs.	
4290, Lau et al., 2006	CT w/contrast	Yes (Pinnacle3)	Photons (6-MV) and electrons	70 Gy, 2 Gy/frac, 7 wks 50 Gy to areas of microscopic spread Dose constraints: Spinal cord 36-40 Gy	Shaped lateral opposed fields, matching anterior low-neck field 0.5-cm multileaf collimator (MLC)	Hard plastic immobilization shell	GTV = primary tumor and involved LNs Upper and lower neck	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
4430 Kwong 2006	CT	Inverse planning Corvus System version 3.0 (NOMOS. Corp, Sewickley, PA)		Prescribed dose: GTV: 76 Gy. Nodal GTV: 72 PTV:70 35 fractions over 7 weeks. Fractional dose PTV: 2 Gy daily GTV: 2.17 Gy daily (SMART boost technique) Dose to lower neck 60 Gy if N0, 66 Gy if node-positive in 2 Gy daily fractions.	9 coplanar equally spaced beam angles	Tailor-made thermoplastic cast from head to shoulders with neck support and mouth bite.	IMRT: GTV includes whole NP, tumor extending out of NP, any skull-base erosion and intracranial disease. GTV_n: enlarged neck nodes CTV: in some cases, just GTV (if close to critical structures), some were GTV + 5mm-1.5 cm. If palpable residual neck node present after IMRT completion, boost dose of up to 10 Gy may have been given.	
4630 Yao	CT, MRI, FDG-PET	Corvus treatment planning system, NOMOS Version 3.0		<u>Definitive IMRT</u> Prescribed dose PTV1 70-74 Gy PTV2 60 PTV3 50-54 <u>Postop high risk</u> Prescribed dose PTV1 64-66 PTV2 60 PTV3 50-54 <u>Postop intermediate risk</u> PTV1 60 PTV2 60 PTV3 50-54 Total (daily) dose SEB=sequential boost <u>Definitive IMRT:</u>		Thermoplastic face mask	CTV_1: GTV with 5-10 mm margins CTV_2: high-risk areas harboring microscopic disease (incl normal structures immediately surrounding CTV with high risk of local tumor invasion and high risk lymphatic regions. CTV_3: Intermediate-risk lymphatic areas.	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				SIB: CTV1/CTV2: 60 (2) CTV3: 54 (1.8) SEB: CTV1:10-14 (2) <u>High risk post op</u> SIB: CTV1/CTV2: 60 (2) CTV3: 54 (1.8) SEB: CTV 1: 4-6 (2) <u>Intermed risk postop</u> SIB: CTV 1/CTV 2: 60 (2) CTV 3: 54 (1.8) SEB: CTV1: no Max to normal tissues: Sp cd 45 Gy Br stm 54 Optic n/chiasm 54 Retina 50 Temp lobes 60 Glottic larynx 2/3 < 50 Mandible 70 Parotid mean <30 or 50% of either <30.				

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
5020, Nishimura et al., 2005	CT	IMRT treatment planning done by Cadplan Helios, Varian associates, Palo Alto, CA; Eclipse, Varian Medical Systems International Inc, Baden, Switzerland) Treatment delivery by: Clinac-600C accelerator (Varian Associates)	4MV X-Ray	Whole neck irradiation with 46 to 50 Gy in 23-25 frac IMRT boost to PTV to a total dose of 56 to70Gy in 28-35 frac (med, 68 Gy) Dose constraints to spinal cord, brain, ipsilateral parotid gland, contralateral parotid glad: 40, 50, 25-30, 20-25 Gy	5 or 7 co-planar beams: angles of 60-75, 105-115, 135-150, 180, 210-225, 245-255m 285-300	Type-S theromoplastic based system (med-tec, Orance City, IA)	Bilateral and submandibular (Ib) and jugular chain (level II-IV) nodes were included in CTV. The planning organ at risk volume a 3mm margin was added for the spide with no margin to parotid	.
5120, Wolden et al., 2006	CT, MRI	3DCRT (not specified) IMRT (not specified)		IMRT 70 Gy total dose; accelerated fractionation/ 59 patients treated with hyperfractionated concomitant boost/ 15 patients dose painting (PTVm 1.8 Gy/frac 54 Gy total and PTVg 2.34 Gy/frac 70.2 Gy)	IMRT Multiple beams tailored to patient anatomy and NPC distribution using dynamic multileaf collimators	Aquaplast masks for IMRT	IMRT PTVg included GTV w/ 1-cm margin increase with the exception of posterior dimension to the primary tumor where a 5-mm margin was added. PTVm consisted of PTVg plus the area encompassing the nasopharynx and all cervical lymph nodes w/ a 5-mm margin.	Limitation of parotid gland mean dose limited to 26 Gy when possible; cochlea dose reduced as much as possible

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
5210, Duthoy et al., 2005	CT/MRI			IMRT: End dose of 60 Gy in 4 patients, 66 Gy in 6 patients and 70 Gy in 29 patients all in 35 frac. Prescribed dose not reached in 2 patients (1 death after 21 frac and 1 was stopped due to liver mets) 3DCRT: 19 patients had 65Gy (61-70Gy) 1.8Gy/ frac 11 patients had noncoplanar beam w/ median dose of 66 Gy (54-66Gy) 2Gy/frac	3DCRT: 19 patients had coplanar beams 10 had non-coplanar	‘	No elective radiation of cervical lymph nodes (ELNI) 3mm margin used for expansion from CTV to PTV	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
5310, Zheng et al., 2005	CT, MRI		Photons (6-MV)	66-72 Gy, 2 Gy/frac, once daily 5 days/wk, 6-7 wks Dose constraints: Mean Dmax Gy (rng) Brainstem 32 (19-45) Spinal cord 24 (13-42) Temporal lobe I 42 (17-68) Temporal lobe C 23 (7-47) Optic nerve I 36 (7-67) Optic nerve C 31 (6-56) Optic chiasm 31 (6-56) Eyeball I 21 (2-39) Eyeball C 15 (1-22)	5-7 static coplanar or noncoplanar beams with 3-7-mm block aperture margin from the PTV boundary, with wedges to improve dose conformity and homogeneity as needed		GTV = primary tumor CTV = GTV plus extent of subclinical microscopic disease, usually 5-10-mm margin For high risk subclinical sites (eg, skull base, parapharyngeal space, oropharynx) 8-10 mm of CTV margin was delineated PTV = CTV plus 2.5-mm margin PRV (planning risk volume) = 2.5-mm margin around organs at risk	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
5330, Lu et al., 2005	CT	Yes		Total to CTV 72 Gy, 1.7 Gy/frac, 6 wks Initial dose to GTV 54 Gy, 1.8 Gy/frac, 5 frac/wk, 6 wks Accelerated boost added 1.5 Gy/frac as second daily frac for 12 days Dose constraints: Spinal cord 39.6 Gy			GTV = primary tumor plus draining anterior neck LNs Clinically involved and uninvolved posterior neck Boost target volume included primary tumor plus involved LNs plus 2-cm margin Supraclavicular fossae	
5420, Pan et al., 2005	CT	Yes (UMPlan in-house)		40-70 Gy med 64 Gy			Primary tumor Unilateral neck	
5740, Thorstad et al., 2004	CT	Yes (Nomos.)	Photons (6-MV)			Aquaplast face mask	CTV1 = preop gross tumor volume plus 10-2—cm margin, including resection bed with invasion, or extracapsular extension by metastatic neck LNs CTV2 = uninvolved cervical LNs	Amifostine 500 mg sc prior to each RT frac

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
6430, Kwong et al, 2004	CT	IMRT delivered with Mimic (NOMOS. Corporation) Inverse planning by Corvus v3.0 (NOMOS. Corporation)	4 or 6 MV	GTV: 68-70Gy to at least 95% and 70 Gy to macroscopically enlarged nodes in 2-2.06Gy/ 34 frac PTV:66-68Gy to 95% 1.9-2.0Gy/frac 60-66Gy 2Gy daily frac from neck caudal to the chin or caudal to the most distal enlarged lymph node. Organ at risk Gy are listed in rightmost column. Dose constraints to organs at risk: Spinal cord, [Eye, optic nerve, optic chiasm, temporal lobes, brain], brainstem, parotid glands, pituitary glands, [inner ears, middle ears, tempromandibular joints] – 40, 50, 50, 20, 25, 50 Gy	9 co-planar beam angels equally spaced. 0, 40, 80, 120, 160, 200, 240, 280, 320, 360 degrees	Custom thermoplastic cast from head to shoulders	Potential sites of local infiltration 1mm from GTV were included in CTV. CTV included: sphenoid sinus caudal to the base of pituitary fossa, cavernous sinuses on both sides, base of skull, including petrous temporal bones and excluding internal auditory canals and cochleae, inferior orbital fissures, foramen ovale and foramen spinosum, anterior half of the clivus and posterior third nasal cavity and antrum, medial pterygoid muscles and parapharyngeal space up to the styloid process and anterior one-half of the arch of the cervical vertebrae (C1) and prevertebral muscles inferior to C1. Enlarged cervical lymph nodes were localized as separate GTV	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
6530 Zheng 2004	CT/MRI	3D planning (AcQPlan 3D RTP, Marconi Medical Systems)		Salvage dose ranged from 16-38 Gy (median 24) with 2 Gy/fraction, one fraction daily, 5d/wk. (Initial external beam RT doses: median to NPH 70 Gy, to negative neck 50, and to positive neck 68, fraction 2.0/d).			PTV= persistent disease + 5mm margin	
7090, Chao et al., 2004	CT	i		70 + or – 1.1 Gy to CTV1 definitive, 66.3 + or – 3.6Gy, CTV for definitive patients was 64+ or -4.2 Gy, and 66.3 + or – 3.6 Gy. 1.9 to 2.0 Gy /frac 5 frac/wk			CTV1 encompassed GTV and region adjacent to GTV, the surgical bed w/ soft-tissue invasion, and regions with extracapsular extension by metastatic neck nodes, CTV2 was primarily prophylactically treated nodal stations. Dose to each target volume was normalized to 80-90% of maximal isodose reference point.	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
7110, Sze et al., 2004	CT w/out contrast	Yes (Helax TMS)		70 Gy, 2 Gy/frac, 5 or 6 frac/wk, 7 wks 70 Gy to grossly enlarged LNs 50-60 Gy to supraclavicular fossae med 46 days (rng 36-55 days	5-7 beams	Rigid immobilzation device	GTV-P = gross tumor volume plus adjoining involved retro-pharyngeal LNs PTV = GTV-P and whole nasopharynx, plus 7-12-mm margin Parapharyngeal spaces, posterior nasal fossae and maxillary sinuses, sphenoid and posterior ethmoid sinuses, base of skull and cavernous sinuses	
7370, Lu et al., 2004	CT, MRI	Yes (Nomos.)		66-70 Gy, 1.8-2.8 Gy/frac, 5 frac/wk 60 Gy to positive LNs in neck Dose constraints: According to ICRU 50 guidelines Brainstem mn dose 28 Gy Optic chiasm mn dose 22 Gy Optic nerves mn dose 19 Gy Lens mn dose 4 Gy	Dynamic multivane intensity modulating collimator (MIMiC) using segmental tomotherapy techniques		GTV = gross extent of tumor shown on imaging studies CTV = GTV plus 5-10- and 10-15-cm margins	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				Temporal lobes mn dose 22 Gy Temporomandib 28 Gy Mandible mn dose 20 Gy Pituitary mn dose 33 Gy				
7570, Levendag et al., 2004	CT	Yes (3D Cadplan)	Photons (6-MV)	70 Gy to gross primary tumor and involved neck LNs 46 Gy to uninvolved neck LNs	Dynamic multileaf collimator, abutted AP portal with midline shield for lower neck	PVC head cast	CTV = primary tumor plus neck PTV = CTV plus 5-mm margin Unilateral and bilateral neck	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
7750, Liu et al., 2003	CT, MRI	Yes (Pinnacle3)	Photons (6- or 15-MV)	60-77 Gy, 1.8 Gy/Frac, 5 frac/wk 70-77 Gy to primary tumor and positive neck LNs 60-65 Gy to CTV 50 Gy to clinically negative neck Limit dose to 1% of volume of critical structures as follows: Brainstem and optic nerves 50 Gy Spinal cord and optic chasm 45 Gy Temporal lobes 60 Gy 50% of contralateral parotid 25 gy	Static multisegmental multileaf collimator Split-beam technique for anterior lower neck field		GTV = gross extent of tumor, including nasopharyngeal primary and retropharyngeal lymphadenopathy CTV = GTV plus margin of potential microscopic spread	
8250, Munter et al., 2003	CT, MRI	Yes (KonRad, VIRTUOS)	Photons (6- or 15-MV)	55-72 Gy to primary PTV, GTV, positive LNs, 1.6-2.0 Gy/frac or 1.6-2.0 Gy/ frac IMRT boost or	Integrated multileaf collimator, 5-9 beams (med 7)	Scotch-Cast mask	GTV = visible tumor in imaging studies CTV = GTV plus 5-mm margin; in postop cases GTV included surgical bed and margins according to	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				integrated boost also used 50-65 Gy to secondary PTV Dose constraints: Cervical spinal cord 50 Gy Brainstem 60 Gy Optic nerve and chiasm 54 Gy Protected parotid < 26 Gy			assessed risk Primary PTV = CTV plus 3-mm margin to compensate internal organ motion and setup variability Secondary PTV = LNs or surgical neck levels at risk of subclinical disease, including LN level II-V (depending on tumor site), retropharyngeal LNs, and in some cases level I All pts with ipsilateral LN involvement also had contralateral neck RT Tumor suspicious LNs and LN levels with radiographic evidence were defined as a target volume	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
8270 Braaksma 2003	CT	Non commercial inverse planning module "Optimize" Computer planning purposes: Cadplan versions 2.7.9 and 3.1.2, Varian-Dosetek, Finland.	10 MV	3DC 46 Gy to primary tumor and LN levels of neck (PTV1); then boosted to cumulative dose of 70 Gy primary tumor (PTV2). Mean dose to R and L parotids was 29.2 and 28.7, respectively.			PTV= CTV + 5mm margin	
8370 Padovani 2003		Focus logical, CMS, St Louis, MO	6-18 MV	3DC RT delivered in doses of 2 Gy/fraction at 5 fractions weekly. Median dose PTV was 63 Gy (range 30-70). Ipsilateral neck 60 Gy Max dose to chiasma and CNS limited to 54 and 60 Gy, respec, ipsi optic n and retina 60 Gy.	Noncoplanar	Thermoplastic face mask	CTV = pretx GTV and microscopic extension PTV= CTV plus additional uniform 5 mm expansion Ipsi Cx LN in 5 pts; contra Cx LN in 1 pt.	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
8400 Amosson 2003	CT	NOMOS. Peacock	10 MV	Ipsilat and contralat parotids had threshhold limits of 35 Gy and 25 Gy, respectively. (ave mean doses to ipsilat and contralat parotids were 24.2 and 19.1 Gy, respectively) No attempt made to avoid submandibular glands. Sp cd 40 Mandible 58		n=13 with "Talon" fixation device n=17 Reinforced Aquaplast mask.		
9290 Teh 2002				Daily fractions of 2.4 and 2 Gy to primary and secondary targets to a total dose of 60 and 50 Gy, respectively. Overall tx course was five weeks (daily tx). Dose to parotids limited- for midline tumors to 25 Gy, for unilateral tumors the ipsilat parotid was limited to 30-35 and contralat 25 Gy.				

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
9330 Kovacs 2002		HELAX TMS	6 MeV	Prescription dose 51.3 Gy with 1.9 Gy/d		Mask fixation	Planning included pretherapeutic tumor extension and cx LN bilaterally	
9510 Jian 2002	CT	FOCUS (computerized medical systems, Inc., St Louis, MO)	6MV, 18MV and 9MeV	40.8-43.2 Gy @ 1.2/frac, 2 frac/day, 6 hr interval betw doses with 6 MV. After 1 wk brk, off-cord 16.8-19.2, 1.2/frac, 2 frac/d with 18MV. Finally, an additional 14.4 Gy in 12 fracs off brnstm. Boost to upper neck by electron beam if necessary. Total dose to primary tumor 74.4 Gy, to involved neck nodes 68-74.4 and to uninvolved neck nodes 50-60 Gy. Dose constraints: Brstm 60-65 Gy Sp cd 50 Gy			NPH and upper neck	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
10740, Pommier et al, 2000	CT	Elektra linear accelerator w/ multileaf collimator	Mixed X-ray 6 to 18 MV	63.5 Gy (56-68) 2 Gy frac/ 5 frac wk	6 to 15 (median 11)portals w/ multileaf collimation field shaping	Thermoplastic face mask	PTV including CTV plus 5 mm expansion Ipsilateral lymph nodes treated In 7 patients	Palatine prosthesis to protect floor of mouth Dose limited to 12 Gy for contralateral eye, 56 Gy to optic chiasm and contralateral optic nerve, 60 Gy to frontal CNS
11650, Kuppersmith et al., 1999	CT with contrast	Yes		14-71 Gy, 1.5-4.0 Gy/frac, 1 frac/day Dose constraints: Parotid glands 30 Gy	Dynamic multivane collimator, 40 beams	Screws in skull vertex attached top docking device		

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
13270 Lawson 2008	CT and PET	Eclipse (Varian Medical Systems)	6 MV	Mean (median, range) total dose to gross dz: 70.14 Gy (70.29, 69.3-70.4). Per fraction to gross dz: 2.13 (2.13, 2.1-2.2). To remainder of clinically involved neck: 61.05 (63.03, 54.4-63.03). Per fraction to clinically invol neck: 1.85 (1.91, 1.7-1.95). Clinically uninvolved neck: 58.34 (57.75, 54.4-63.03). Per fraction to clinically uninvolved neck: 1.77 (1.75, 1.7-1.91). 5 daily fractions per week, to median (range) of 33 fractions (31-35).			CTV= PTV + 1-1.5 cm margins.	
13340 Ikushima et al, 2008	CT MRI	Clinac 2100C, Arian Alpatro	4 and 10 MV	30 Gy, 2.0 Gy daily frac	Three to five ports with a 1.5 cm margin to CTV			

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
16840, Wu et al, 2006	CT, MRI		Electron beam	Simultaneous modulated accelerated RT-GTV, CTV 70/2.5 Gy frac, 56/ 2.0 Gy frac With 28 frac within 6 weeks	IMRT using split-beam technique w/ middle and lower neck fields treated with single anterior field joined by CRT Coplanar means positioned every 40 degrees from the posterior and lateral directions	BrainLAB noninvasive thermoplast mask and localizer frame	CTV plus areas of potential microscopic spread including: nasopharynx, retropharyngeal nodes, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, posterior third of the nasal cavity and maxillary sinuses. Included ipsilateral and contralateral neck nodes of level 1,2,3, 5	Brainstem, spinal cord, parotid glands, and lens specified at risk for inverse planning with different weights.
24330, Pfreunder et al., 2003	CT		5 MV linear accelerator	HnN compartments and lymphatic drainages were irradiated with 50.4 Gy/1.8 frac 5 frac/ wk GTV received 2nd 1.4 Gy frac after wk 4 of RT resulting in total 69.9 Gy in 5.5 weeks to GTV and 50.4 total to lymphatic drainage	Static wedge fields	Individualized masks for patient fixation		

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
26140 Scorsetti 2001			6MV	1-18 fractions (med 8) at median dose of 30 Gy (range 6-54). Second boost of 10-30 Gy to reduced target volume if good responders.			PTV= GTV + 2-10 mm margin.	
37660, Wendt et al, 2006	CT	Mevatron KD2, Siemens Medical Solutions, Germany Inverse planning software: Helax TMS, Nucletron, Europe w/ KonRad, Siemens		5 frac/wk Median parotid gland dose 30 Gy or less in 37 or 39 patients and less than 26 in 29 patients rng 21-52.8 Gy.	Bilateral 3D-C-IMRT using standard 7-portal arrangement. Each portal modified by # D metallic compensator Lower neck and supraclavicular fossae (region II, IV, IV B) used single anterior field		Tumors of the nasopharynx, oropharynx, oral cavity, floor of mouth, gross primary tumor bed and lymph node down to the level of hyoid bone were irradiated	Median dose to one parotid gland at aimed at 26Gy or less
38290, Anand et al., 2008	CT, MRI	Yes (Plato ITPc or Primus)	Photons (6-MV)	Definitive IMRT 66 Gy, 1.9-2.0 Gy/frac, 33-35 frac to CTV1 and 70 Gy, 2.0-2.1 Gy/frac , to GTV for pts receiving CTx 70 Gy, 1.9-2.0 Gy/frac, 35-37 frac for pts	Multileaf collimator or compensators, 7-9 fields Separate low anterior field with midline laryngeal block	Thermoplastic mask for head and neck	GTV = primary tumor volume and metastatic LNs CTV1 = GTV plus 10-12-mm margin CTV2 = ipsilateral high risk but clinically negative LNs CTV3 = contralateral	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
				receiving IMRT alone Adjuvant IMRT 56-62 Gy toCTV1, 50-54 Gy to CTV2 and CTV3 50-52 Gy to supraclavicular region Dose constraints: Median Dmax Gy (rng) Spinal cord 45 (37-48) Brainstem 51 (33-58) Optic nerve 24 (1-61) Optic chiasm 26 (2-62) Cochlea 42 (0.5-53) Mandible 72 (28-77)			uninvolved LNs CTV1 for adjuvant IMRT included preop GTV and 15-20-mm margin to encompass surgical bed with soft tissue or bone invasion, or metastatic neck node regions with extracapsular extension PTV = CTV1 plus 5-mm margin	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
38530, Studer et al., 2008	CT			Definitive IMRT 69-72 Gy, 2.0-2.2 Gy/frac, 5 frac/wk Postop IMRT 66 Gy, 2 Gy/frac, 5 frac/wk All schedules based on SIB delivery				
38640, Studer et al., 2008	CT			Definitive IMRT 70-73 Gy, 2.1-2.2 Gy/frac, 33-35 frac to boost PTV 73 Gy, 2,2 Gy/frac, 33 frac to large GTVs 70 Gy, 2 Gy/frac, 35 frac in pts with CNS structures in the PTV Adjuvant IMRT 60-66 Gy, 2 Gy/frac, 30-33 frac to boost PTV Elective dose 54 Gy in most pts, 60-66 Gy prescribed for higher risk pts All schedules based on SIB delivery			GTV = primary or total gross tumor volume	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
38840 Seung 2008	CT	ADAC Pinnacle version 7.4; Phillips/ADAC	6 MV	SIB Median prescribed dose 69.96 Gy (66-70) to PTV70/66; 59.4 Gy (59.4-60) to PTV59.4; and 54 (54-54.12) to PTV 54. Median dose per frac: 2.12 (2.12-2.2) to PTV70/66; 1.8 (1.8-2.0) to PTV59.4 and 1.64 (1.64-1.8) to PTV54. Normal tissue dose limitation max ≤45 to sp cd, and ≤54 brstm. Mean to parotids ≤26.	7-9 equally placed coplanar beams	Aquaplast mask	Primary tumor and upper neck above VCs GTV:gross extent of tumor and LNd > 1cm diameter. CTV70:GTV plus margin for potential microscopic spread. CTV59.4 (highrisk CTV):CTV70 + retropharyngeal nodes and levels IB-V on LN positive side. PTV: CTV + margin 0.3-1 cm	
38850 Caglar 2008		ECLIPSE (Varian Medical Systems)		IMRT 70 Gy at 2Gy/fraction to GTV, 64 to high-risk CTV, and 60 to low-risk CTV. Post op cases 64 Gy. Parotid glands mean dose 26 Gy. Sp cd dose 46 Gy.		thermoplastic	GTV: for definitive cases = tumor and involved LNs High-risk CTV for definitive = GTV plus margin for subclinical dz and neck nodal regions at greatest risk of subclinical involvemt. Low risk CTV included uninvolved Cx LNs. PTV: CTV + 5 mm margin.	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
39000 Sanguineti 2008	CT	Pinnacle[3]	6 MV	Early stage lesions (stage 1-2) hypofractionated schedule. Adv stage dz acc/hyperfrac 78 Gy to PTV1 at 1.3 Gy twice daily. Others rec'd conventional frac at 2 Gy/frac to PTV1.		Thermoplastic	CTV1=CTV + GTV CTV2=included tissue at high risk of containing microscopic dz. CTV3=included tissue at low risk of microsc dz. PTV1, PTV2 and PTV3 expanded the corresponding CTV by 5mm.	
39020 Rosenthal 2008		ADAC Pinnacle		To primary site: 60-63/30 fx n=5 66/30 fx n=79 66-68/33 fx n=5 70/33 fx n=56 72/40 fx (concomitant boost) n=15				

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
39300, Hoppe et al., 2008	CT, MRI	Yes (MSKKC system)	Photons (6-MV)	70 Gy, 2.1 Gy/frac to PTV1 60 Gy, 2 Gy/frac to PTV2 54 Gy, 1.8 Gy/frac to PTV3 54 Gy to involved neck All treated once daily, 5 days/wk Dose constraints: Brainstem < 50 Gy Spinal cord < 45 Gy Cochlea < 50 Gy Retina/eye < 45 Gy Optic nerve < 54 Gy Optic chiasm < 54 Gy	Dynamic multileaf collimator with dynamic leaf sequencing	Custom Aquaplast mask that also immobilizes shoulders when neck is treated	CTV1 = clinical tumor volume included gross disease with 3-5-mm margin CTV2 = surgical bed and areas at high risk of microscopic disease CTV3 = LN regions at risk PTV1, 2, 3 = CTV 1, 2, 3 plus 5-10-mm margin, expanded 1-mm in areas adjacent to critical normal structures Bilateral or ipsilateral neck irradiation for involved LNs	

Study	Localization or Staging Methods	Computerized Treatment Planning (system/vendor)	Radiation Delivery Source (energy level)	Duration of Treatment, Dose, Fractionation, Boost	Beam Characteristics (number, shaping)	Immobilization/ Repositioning Procedures	Scope of treatment (bilateral, lymph nodes in neck)	Measures to reduce toxicity, e.g., moving salivary gland
39390, Worden et al., 2008	CT, PET			70 Gy, 2 Gy/frac daily, 5 frac/wk to gross disease and 10-20-cm margins 59-63 Gy, 1.7-1.8 Gy/frac to tissue volumes at risk of harboring subclinical disease			Gross tumor volume plus 10-20-cm margins Bilateral neck	

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT
Single-Arm Studies

Table E-D. Outcome assessment

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
560, Biagioli et al., 2007	Tumor response, DFS, PFS, OS, LRRFS	Acute and late toxicities	CR = NED after tx PR = ≥ 50% reduction of tumor SD = < 50% reduction to 25% enlargement of tumor PD = > 25% tumor enlargement		med 14 mos. (rng 1-53 mos.)
580, Dirix et al., 2007	2-yr LC, OS, DFS Acute and late toxicities, in particular ocular				Baseline, every 2 mos. in first 2 yrs, every 3 mos. in third yr, every 4 mos. in fourth yr, every 6 mos. in fifth yr, annually thereafter med 24 mos. (rng 7-47 mos.)
1010, Urbano et al., 2007	Acute and late toxicities, in particular laryngeal	Tumor control	CR: No evidence of disease (clinical, radiographic, or pathologic		Acute toxicity: 2.5 mos. after commencement of CRTx (1.5 mos. of Tx plus 1 mo after) and at wk 14 (2mos. post Tx) Late toxicity: 3, 6, 12, 18, 24 mos, yearly thereafter Tumor response: 1-1.5 mos. post-Tx
1420 Feng et al, 2007	Dysphagia measures	Patient-reported QoL Acute and late observer-assessed toxicity			Baseline, weekly during therapy, 1 (acute) and 3 (late) mos. after therapy
1430, Scrimger et al., 2007	Salivary function, QoL	QoL, late salivary gland and other toxicities			
1500, Lee et al., 2007	2-yr LPFS, LRPFS, RPFS, DMFS, OS, laryngectomy-free survival	Tracheostomy tube placement, acute and late toxicities			Weekly during treatment, every 1-2 mos. for first 2 yrs, every 4-6 mos. thereafter
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	LRFS, RRFS, DMFS, OS				1 mo after treatment, every 1.5-2 mos. for first yr, every 2-3 mos. in second yr med 29 mos. (rng 0.2-74 mos.)

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
1780, Lee et al., 2007	2-yr LRPFS				Baseline, every 1-2 mos. post-RT for first 2 yrs, then every 4-6 mos med 35 mos (rng 2-80 mos.)
1900, Ben-David et al., 2007	Mandibular osteoradionecrosis (ORN)				Every 1.5-2 mos. during first 2 yrs after therapy, every 3-4 mos. thereafter
1990, Yao et al., 2007	OS, DSS, LRFS, LRRFS, DMFS				1 mo post-RT, every 1.5-2 mos. in first yr, every 2-3 mos. in second yr med 17 mos. (rng 0.3-59 mos.)
2180, Daly et al., 2007	OS. LPFS, DFS	Acute and late toxicities			Every 1-2 mos. for first 6 mos. post RT, every 3 mos. for next 6-12 mos, every 4-6 mos. from 18-36 mos, annually thereafter med 39 mos. (rng 6-82 mos.)
2290, Yao et al., 2006	OS, LPFS, LRC, DMFS, DFS	Acute and late toxicities			1 mo post RT, every 1.5-2 mos. in the first yr, every 2-3 mos. in the second yr
2370, Garden et al., 2007	OS, LRC, RFS	Acute and late toxicities			med 45 mos. (rng 15-63 mos.)
2430, Vosmik et al., 2006	Acute toxicities				
2770, Cheng et al., 2006	5-yr LRC, DMFS, OS				med 58 mos
3080 Meirovitz 2006	XST SLF				At 6-24 months (median 12 mos.) after completion of therapy same
3320, Portaluri et al., 2006	Xerostomia				med 18 mos. (rng 16-19 mos.)
3340 Studer 2006	LC Distant control Nodal control Overall DFS	SKN MUC DYS LX SPN QOL (weight loss)			Mean 16 months (4-44 months) During treatment, pts clinically assessed at weekly intervals, and at 2 weeks and 2 months after completion of treatment.
3400 Studer, 2006	ORN	LRC			

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
3570 Saarilahti 2006	XST and SLF	MUC LRC			XST: 2-3 month intervals after IMRT SLF: measured before therapy (baseline), and 6 and 12 months after last date of RT. LRC: median F/U 31 months (14-62 mos.)
3790, Ozsahin et al., 2006	Acute and late toxicities	OS, LRC,			med 36 mos. (rng 8-37 mos.)
3820 McMillan 2006	QoL SLF XST				SLF assessed baseline, then 2,6, and 12 months after IMRT.
4290, Lau et al., 2006	OS, DSS, LRRFS	Acute toxicities	CR according to physical examination with or w/out imaging		Every mo during first yr, every 2 mos. in second yr, every 3-4 mos. in third yr med 16 mos
4430 Kwong 2006	LRC MFS PFS OS	MUC SKN			Median follow-up 25 months (3-55.5 months) Assessed weekly during treatment. At 6 and 8 weeks after completion of IMRT, biopsied to assess dz remission. After IMRT completion, f/u q month during 1st yr, q 2 mos. during 2nd yr, then q 3-6 mos. afterwards.
4630 Yao	LC LRC MFS OS				Median time from tx completion to LR recurrence was 4.7 mos. (1.8-15.6 mos.)
5020, Nishimura et al., 2005	Xerostomia and parotid dose volume				
5120, Wolden et al., 2006	3-yr LC, LRC, MFS, PFS, OS	Other acute and late toxicities			Median follow up 35 mos. (3-74)
5210, Duthoy et al., 2005	OS, DFS, DSS, LC	Toxicity			
5310, Zheng et al., 2005	OS, LFFS	Major late toxicities			med 35 mos. (rng 9-71 mos.)
5330, Lu et al., 2005	LC, LRC, DFS, OS	Acute and late toxicities	PCR defined as no evidence of malignant cells in tumor bed biopsy 4 mos. after completion of RT		Every 2-3 mos. for first 3 yrs post RT, every 4-6 mos. for next 2 yrs, annually thereafter med 24 mos. (rng 15-31 mos.)

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
5420, Pan et al., 2005	Hearing loss				Baseline, 1, 6, 12, 24, 36 mos
5740, Thorstad et al., 2004	Salivary function	Acute nonhematologic toxicities			Baseline, 6 mos, 12 mos
6430, Kwong et al, 2004	Salivary Function	Dose Volume			Weekly during RT, 6-8 wks after RT completion. Every month of 1st year, every 2 months 2nd year, 3-6 mo thereafter
6530 Zheng 2004	LFFS (local failure free survival) DSS OS	Radiation induced toxicities			After salvage tx completion, q 2-3 months for first 2 yrs, then q 4-6 mos. thereafter. Median f/u58 mos. (12-95)
7090, Chao et al., 2004	DMFS, LRC, DFS, Gross tumor volume	Toxicity			
7110, Sze et al., 2004	LFFS, PFS, OS				med 23 mos. (rng 1-47 mos.)
7370, Lu et al., 2004	LRC	Acute toxicities			med 9 mos. (rng 3-13 mos.)
7570, Levendag et al., 2004	3-yr RRFS, LRRFS, OS, DFS				med 29 mos
7750, Liu et al., 2003	OS, DFS, DSS	Acute and late toxicities			Every 1-2 mos. post-RT for first yr, every 3 mos. for second yr, every 6 mos. thereafter med 17 mos. (rng 3-42 mos.)
8250, Munter et al., 2003	2-yr OS, LC	Acute and late toxicities			1.5 mos. post-RT, every 3 mos. for first yr, every 6 mos. thereafter med 14 mos. (rng 3-34 mos.)
8270 Braaksma 2003	SLF XST	LRC DFS OS			Median f/u 18 mos. (2.4-39.6)
8370 Padovani 2003	PFS OS	Acute and late toxicities			Med f/u 25 mos. (4-51 mos.) **Note: ?? should we abstract the number of local relapses??**
8400 Amosson 2003	XST				

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
9290 Teh 2002	QOL TAE XST				Median f/u 11.5 months
9330 Kovacs 2002	Toxicities and survival				
9510 Jian 2002	LRC DFS OS	acute toxicity (MUC and QOL incl weight loss)			q 2 mos. 1st 2 yrs q 3-6 mos. yrs 3-5 and 1 yr intervals thereafter
10740, Pommier et al, 2000	OS, LPFS, LPFR,	Toxicity			
11650, Kuppersmith et al., 1999	Acute toxicity				
13270 Lawson 2008	LC LRC MFS OS	Acute and late toxicities (MUC, ESO, LAR, sal gl, SKN, SUB, blood cnt)			Mean (median, range) 22.2 mos. (20.1, 3.6-42.8) F/U 1 month p tx, then q 1-3 mos.
13340 Ikushima et al, 2008	SR, cause of death	Toxicity			
16840, Wu et al, 2006	Local regional FS, OS	Toxicity			
24330, Pfreunder et al., 2003	OS, LTC, larynx preservation	Toxicity			
26140 Scorsetti 2001	OS TAE				
37660, Wendt et al, 2006	RTOG toxicity				Median FU 21 mo
38290, Anand et al., 2008	2-yr LRC, OS	Acute and late toxicities			Baseline, 3 mos, 6 mos med 19 mos. (rng 6-36 mos.)
38530, Studer et al., 2008	LC, DSS, DFS				med 21 mos. (rng 3-67 mos.)
38640, Studer et al., 2008	3-yr LC, LRC, DFS, OS, DMFS				med 20 mos. (rng 3-72 mos.)
38840 Seung 2008	LC OS Cause specific survival (CSS)	Acute and late toxicities			p RT, q 2-3 mos. for first 2 yrs, then q 3-6 mos. thereafter.

Study	Primary Outcomes	Secondary Outcomes	Tumor Response Criteria	Independent Response Assessor	F/U Frequency/Duration
38850 Caglar 2008	DYS	Aspiration (*I did not abstract this intermediate outcome)			Median 10 mos
39000 Sanguineti 2008	Local and regional failure LC LRC				Q 2-3 mos. dur 1st 2 yrs, then q 3-4 mos. dur yrs 3-5.
39020 Rosenthal 2008	Acute toxicities				
39300, Hoppe et al., 2008	2-yr LPFS, OS	Acute and late toxicities			1-2 mos. post-RT, every 3 mos. for the next 3 yrs, annually thereafter med 28 mos. (rng 11-57 mos.)
39390, Worden et al., 2008	Tumor response, DSS, OS	Acute and late toxicities	Biopsy-proven residual disease		2 mos. post-RT for initial assessment med 64 mos

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-E. Time to event outcomes

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
560, Biagioli et al., 2007	OS		41	18	77	49	~ 40	~ 34					
	OS w/CR		24	33									
	OS w/PR		7	12									
	OS w/SD		4	12									
	OS w/PD		6	7									
	OS w/resect		17	31	~ 77	~ 66	~ 66	~ 66		M-C	0.14		
	OS w/out resect		24	23	~ 69	~ 36	~ 28	~ 18					
	OS + cisplatin		15	32	~ 70	~ 63	~ 48	~ 48		M-C	0.17		
	OS + carboplatin		26	13	~ 44	~ 39	~ 39	~ 29					
	OS w/induction CTx		13	13	~ 60	~ 37	~ 37			M-C	0.4		
	OS w/out induction Ctx		28	19	~ 70	~ 44	~ 34						
	DFS (CR only)		24	27	~ 60	48	~ 48	~ 48					
	PFS (CR only)		24	11	~ 42	38	~ 38	~ 38					
580, Dirix et al., 2007	LC		25	nr	~ 88	81	~ 80						
	DFS		25	nr	~ 85	77	~ 78						
	OS		25	nr	~ 93	88	~ 88						
	DMFS		25	nr		88							
1010, Urbano et al., 2007	OS	DL1	15	17 (12-37)									
		DL2	15	8 (1-14)									
	TTR	DL1/DL2	30	9 (6-13)									

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
1420 Feng et al, 2007													
1430, Scrimger et al., 2007													
1500, Lee et al., 2007	LPFS		31		~88	86	86	86	86				
	LRPFS				84	84	84	84					
	RPFS						94						
	DMFS						92						
	OS						63						
	OS	larynx pts	20		~84	69	69						
		hypopharynx	11		~82	53	53	53					
	laryngectomy-FS				~92	89	89	89					
1770, Yao et al., 2007 (see 4630, Yao et al., 2005)	LRFS		90		~98	96	96	~96	~96				
	RRFS				~95	95	95	~95	~95				
	DMFS				~88	82	80	~80	~80				
	OS				~88	80	68	~68	~68				
1780, Lee et al., 2007	2-yr LRPFS	IMRT		28		52				L-R	< 0.001		Not comparative study but gave separate data for IMRT and non-IMRT
		non-IMRT		~4		20							
1900, Ben-David et al., 2007													

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
1990, Yao et al., 2007													
	OS		55		~70	68	68	68	68				
	DSS				~75	74	74	74	74				
	LRFS				~85	85	85	85	85				
	LRRFS				~84	82	82	82	82				
	DMFS				~94	89	89	89	89				
2180, Daly et al., 2007													
	OS		36	~48	~100	69	~69	~45	45				
	LPFS				~84	62	~62	~58	58				
	DFS				~84	62	~60	~60	55				
2290, Yao et al., 2006													
	OS		66		~96	91	78	~80	~80				
	LPFS				~98	98	92	~92	~92				
	LRC				~98	98	92	~92	~92				
	DMFS				~87	88	80	~80	~80				
	DFS				~92	84	64	~64	~64				
2370, Garden et al., 2007													
	OS		51		100	93	87	87	~80				
	LRC				~95	93	93	93	93				
	RFS				~93	87	84	~82	~82				
2430, Vosmik et al., 2006													

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
2770, Cheng et al., 2006	LRC	overall	630						89				
		T1 dis	155		~98	96	~96	~95	95	L-R	0.001		
		T2 dis	163		~98	97	~96	~96	91				
		T3 dis	140		~98	92	~91	~90	87				
		T4 dis	172		~96	91	~92	~85	81				
		< 40 yrs	223		~98	97	~96	~95	93	L-R	0.018		
		> 40 yrs	407		~95	93	~90	~88	87				
		WHO I, II	148		~92	89	~85	~82	81	L-R	1E-04		
		WHO III	482		~98	96	~94	~92	91				
		LDH < 410	548		~98	95	~93	~92	91	L-R	3E-04		
		LDH > 410	82		~95	89	~85	~81	75				
		AG2 < 2 sites	373		~98	96	~95	~94	93	L-R	< 0.0001		
		AG2 > 2 sites	257		~95	91	~89	~83	81				
		RS0 (low)	96		~100	100	~100	~100	100	L-R	< 0.0001		
		RS1 (int-low)	266		~98	96	~95	~95	93				
		RS2 (int-high)	184		~98	94	~91	~87	83				
		RS>3 (high)	84		~90	81	~78	~73	71				
	MFS	RS0 (low)	96		~98	97	~97	~95	95	L-R	0.002		
		RS1 (int-low)	266		~95	88	~86	~86	85				
		RS2 (int-high)	184		~95	85	~81	~80	78				
		RS>3 (high)	84		~88	81	~78	~76	73				
	OS	RS0 (low)	96		~100	100	~98	~96	94	L-R	< 0.0001		
		RS1 (int-low)	266		~98	93	~89	~88	87				
		RS2 (int-high)	184		~96	93	~86	~83	76				
		RS>3 (high)	84		~90	83	~70	~63	63				

Study	Outcome	Grp	N	Med (mos.)	1 yr	2 yr	3 yr	4 yr	5 yr	Test	p	HR (95%CI)	Comments
3320, Portaluri et al., 2006													
3340, Studer, 2006	Local DFS				~90	90	~90						
	Regional DFS				~93	93	~93						
	Distant DFS				~93	93	~93						
5120, Wolden et al., 2006	LC	IMRT 3DCRT	74 35	35	~95 ~95	~93 ~82	91 79	~91 ~74	~84 ~74		.11 .11		P=.11
	LRC	IMRT											
	MFS	IMRT					78						
	PFS	IMRT					67						
	OS	IMRT			~97	~87	83	~79	~73				

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-F. Time to event outcome regression modeling

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
4290, Lau et al., 2006	OS	age, initial Hb, KPS, % CTX (< 50%, > 50%), T, N, overall stage, tumor site	age, initial Hb, < 50% CTx, T, N stage (< 0.07, 2-tailed)	age, initial Hb, KPS, % CTx, T, N, overall stage		CTX, N stage (<0.07, 2-tailed)		
	LRRFS	same	age, KPS, CTX, T, N stage (< 0.07. 2-tailed)					

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
5020, Nishimura et al., 2005	Dose to parotid correlated w/ incidence of Xerostomia grade Mean and median parotid dose decreased significantly from CT1-CT2	Initial Volume of parotid glands CT-1 43.1+ or – 15.2 ml CT-2 (3-4 wks of IMRT) 32 + or – 11.4ml	0.04 P<0.0001 (regression rate of parotid glands not significantly correlated w/ grade of xerostomia p=.186)					

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
5310, Zheng et al., 2005	OS LFFS	age, sex, histo, mn dose primary RT, vol irrad primary RT, T stage, GTV local recurrence, int initial RT to dx recur, late tox from prev RT, CTx, simultan RR	T stage, GTV (< 0.01)	same		T stage (< 0.01)		
6430, Kwong et al, 2004								

Study	Design/ Outcome /Model	Candidate predictors/Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Proportional Hazards Assumption Assessed?/ Interactions Considered	Multivariate Model Results, Variable (p value)	Discrimination/Validation Methods/Results	Calibration/Goodness of Fit
7090, Chao et al., 2004	Univariate analysis of 4 yr estimate DFS, LRC, DMFS	Gender	.7, .5, .9	Definitive IMRT Group DFS, LRC, DMFS	Gross tumor volume, nodal gross tumor volume	DFS:		
						GTV .03		Standard Error
		Subsite	.5, .6, .6			nGTV .05		0.01
								0.03
		IMRT(Postop/Definitive)	.02, .07, .2			LRC		
						GTV .03		
		Chemotherapy				nGTV .01		0.07
			.6, .7, .8					0.01
		T stage				DMFS		
						GTV .03		
		Nodal status	.14, .4, .2					0.009
		AJCC stage	.56, .4, .9					
		Fraction size	.2, .3, .4					
			.14, .5, .2					

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-G. Tumor response

Study	Group	N	CR	PR	SD	PD	NE	Test	p	Comments
560, Biagioli et al., 2007		41	24(58)	7(17)	4(10)	6(15)				
1010, Urbano et al., 2007	DL1 DL2	15 15	80 87							
4290, Lau et al., 2006		56	82							
4430 Kwong 2006										2 pts had persistent NP disease after IMRT. (both received salvage stereotactic radiosurgery – 1 remained well, 1 died of progressive local dz) 3 pts relapsed 14-37 mos. after dx and all died of progressive dz.
4630 Yao										11 LR failures 7 local failures 3 regional failures 1 failure at both the primary and reg LN 16 patients failed distantly
5330, Lu et al., 2005		25	96							
7370, Lu et al., 2004		49	100(at 3 mo f/u)							
8370 Padovani 2003	3DRT					N=2 during RT				
9290 Teh 2002			n=25 (89%)	n=3 (11%)						
38840 Seung 2008	All	69								Of 69, 1 had persistent local dz after tx.
39390, Worden et al., 2008	CRT	53	92			8				

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-H. Quality of life

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
1420 Feng et al, 2007	UWQOL	1 swallowing question w/ 5 answers	Pre-RT, 3mos	Overall		36	Med10 (rng 10-30), 20 (10-50)	P<0.001
	HNQOL	2 questions related to dysphagia with 5 answers each		Liquids			Med 0(rng 0-3), 1 (0-3)	P<0.001
				Solids			Med 0 (rng 0-3), 2 (0-4)	P<0.001
1430, Scrimger et al., 2007	UWQOL	9 health-related questions, total score reported	Pre-RT, 3, 6, 12 mos	NPH OPH OC LAR UKP All pts		10 9 20 6 2 47	92.5, 77.5, 82.0, 78.5 71.0, 73.0, 71.0. 78.0 73.0, 76.0, 76.5, 79.0 83.5, 85.0, 86.5, 85.5 80.5, 79.5, 83.0, 82.5 ~79, ~76, ~78, 80	
	Xerostomia QOL	9 questions related to oral moisture, total score reported	Pre-RT, 3, 6, 12 mos	All pts		47	~.6, ~ 1.4, ~1.4, ~1.2	
	RTOG late xerostomia score	0-5 scale total score	Pre-RT, 3, 6, 12 mos	All pts		47	0, ~1.2, ~1.0, ~1.0	
3340 Studer 2006	SOMA-LENT and RTOG/EORTC radiation morbidity score used to assess toxicity.							Feeding tube inserted in 9 patients (30%). Mean body weight loss at 1 yr after tx was 3.3% (+11% to -11%)
3820 McMillan 2006	Medical outcomes short form (SF-36) Scale of 0-100 (higher score better health status)				BL, 2, 6, 12	32	Mean (SD) BL, 2 mo, 6 mo, 12 mo/p value all 4 visits, BL vs. 2 mo, BL vs. 6 mo, BL vs. 12 mo Physical function 94.4 (9.0) 89.4 (6.3) 92.3 (6.2) 92.7 (8.6) <.001 .001 .028 .190 Role—physical 64.8 (35.3) 32.0 (38.2) 55.5 (41.5) 72.7 (40.3) <.001 .001 .291 .330 Bodily pain 88.2 (20.3) 75.6 (26.9) 84.6	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
	EORTC QLC-30 questionnaire Scale of 0-100 (higher score higher/healthier level of functioning)						(20.0) 81.1 (28.3) .387 .023 .498 .166 General health 57.2 (21.1) 48.3 (19.4) 52.7 (22.5) 62.0 (23.3) .014 .049 .163 .172 Vitality 72.7 (16.8) 55.9 (20.2) 64.4 (18.9) 67.7 (19.6) .006 .001 .012 .138 Social functioning 82.4 (24.4) 71.5 (26.8) 89.1 (19.8) 89.5 (19.9) .001 .049 .123 .085 Role—emotional 61.5 (38.0) 52.1 (47.1) 71.9 (40.7) 78.1 (37.5) .009 .462 .207 .073 Mental health 71.0 (17.7) 75.1 (19.1) 77.25 (16.8) 80.3 (19.0) .089 .121 .073 .036 Mean (SD) BL, 2 mo, 6 mo, 12 mo/p value all 4 visits, BL vs. 2 mo, BL vs. 6 mo, BL vs. 12 mo <u>Global health status/QOL</u> Global health status 55.5 (19.6) 54.7 (15.4) 65.9 (19.6) 67.2 (20.3) .001 .989 .004 .004 Global health status(revised) 57.6 (18.9) 54.9 (13.4) 65.6 (18.2) 66.7 (19.6) .011 .474 .013 .006 <u>Functional scales</u> Physical functioning (revised) 92.7 (9.5) 83.3 (7.2) 88.5 (9.6) 89.6 (10.7) <.001 <.001 .027 .082 Role functioning 97.9 (7.0) 92.7 (10.3) 94.3 (10.0) 96.4 (8.2) .004 .002 .020 .180 Role functioning (revised) 85.9 (15.3) 81.3 (16.8) 90.1 (14.0) 92.2 (13.4) .008 .112 .290 .089 Emotional function 80.5 (15.5) 86.5 (12.3) 87.8 (15.0) 88.8 (15.2) .097 .036 .034 .014 Cognitive function 86.5 (15.5) 83.9 (19.2) 83.3 (13.4) 85.9 (16.5) .729 .533 .530 1.000 Social function 82.8 (21.8) 77.1 (21.5) 91.1 (13.4) 90.6 (16.9) <.001 .118 .016 .095 <u>Symptom scales</u> Fatigue 14.2 (15.5) 25.7 (17.3) 16.0 (13.5) 14.9 (16.6) <.001 .002 .479 .743 Nausea/vomiting 3.1 (6.6) 7.8 (15.3) 1.0 (4.1) 1.0 (4.1) .032 .101 .157 .157 Pain 7.8 (12.7) 8.3 (14.0) 8.3 (12.0) 7.3 (16.4) .685 .715 .793 .593	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
	EORTC QLQ-H&N35 Score of 1-100 (higher score higher/healthier level of functioning)						Symptom items Dyspnea 10.4 (17.8) 10.4 (19.7) 9.4 (15.2) 8.3 (14.7) .949 1.000 .763 .593 Insomnia 24.0 (31.9) 15.6 (23.9) 13.5 (23.7) 13.5 (20.5) .141 .118 .049 .062 Appetite loss 15.6 (20.7) 24.0 (22.8) 6.3 (13.2) 5.2 (12.3) <.001 .103 .013 .008 Constipation 5.2 (12.3) 8.3 (14.7) 6.3 (13.2) 9.4 (19.4) .447 .180 .655 .157 Diarrhea 5.2 (12.3) 2.1 (8.2) 9.4 (17.4) 7.3 (14.0) .120 .180 .248 .527 Financial difficulties 17.7 (25.4) 12.5 (20.3) 7.3 (14.0) 6.3 (15.7) .012 .218 .019 .005 Mean (SD) BL, 2 mo, 6 mo, 12 mo/p value all 4 visits, BL vs. 2 mo, BL vs. 6 mo, BL vs. 12 mo Pain 8.3 (9.0) 18.5 (14.3) 14.8 (11.9) 9.1 (12.2) .001 <.001 .016 .797 Swallowing 1.6 (3.3) 11.5 (9.6) 9.6 (7.7) 9.6 (9.3) <.001 <.001 <.001 <.001 Senses problem 6.7 (15.2) 42.2 (22.4) 25.0 (18.5) 17.7 (19.8) <.001 <.001 .002 .048 Speech problem 6.3 (10.2) 12.8 (15.5) 11.1 (10.6) 8.7 (12.5) .006 .010 .008 .129 Trouble social eating 2.3 (6.1) 20.1 (16.0) 12.5 (12.5) 9.4 (11.3) <.001 <.001 <.001 .006 Trouble social contact 1.5 (5.3) 8.3 (11.0) 5.0 (7.4) 3.1 (7.8) <.001 .001 .003 .044 Less sexuality 16.1 (19.7) 35.1 (36.1) 23.0 (26.9) 25.0 (30.6) .017 .001 .194 .087 Teeth 5.2 (12.3) 9.7 (17.6) 8.3 (14.7) 9.4 (15.2) .712 .285 .366 .102 Open mouth 0.0 (0.0) 9.4 (15.2) 17.7 (18.9) 10.4 (15.7) <.001 .003 <.001 .002 Dry mouth 13.5 (20.5) 82.3 (20.7) 64.6 (26.7) 47.9 (29.3) <.001 <.001 <.001 <.001 Sticky saliva 4.2 (11.2) 63.9 (38.0) 40.7 (31.1) 34.6 (25.3) <.001 <.001 <.001 <.001 Coughing 19.8 (20.5) 14.6 (20.6) 11.5 (21.8) 10.4 (15.7) .742 .766 .315 .479 Felt ill 6.3 (13.2) 8.3 (14.7) 5.2 (12.3) 6.3	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
							(13.2) .767 .068 .436 .238 Pain killers 9.4 (29.6) 0.0 (0.0) 12.5 (33.6) 3.1 (17.7) .141 .083 .655 .317 Nutrition supplement 18.8 (39.7) 28.1 (45.7) 25.0 (44.0) 25.0 (44.0) .809 .317 .564 .564 Feeding tube 0.0 (0.0) 0.0 (0.0) 0.0 (0.0) 0.0 (0.0) - - - - Weight loss 31.2 (47.1) 40.6 (49.0) 12.2 (33.6) 9.4 (29.6) .005 .467 .083 .020 Weight gain 15.6 (36.9) 15.6 (36.9) 21.9 (42.0) 40.6 (49.9) .050 1.000 .480 .033	
9290 Teh 2002	RTOG							23 of 28 pts (82%) lost 10% or less of pre-tx weight. 13 of 28 (46%) required IV fluids and/or tube-feeding.

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
9510 Jian 2002	NCI toxicity criteria 1-4	Weight loss	Concomitant phase	CDDP		31	Grade 1 32.3% Grade 2 22.6% Grade 3 0 Grade 4 0	
				CDDP/5-FU		17	Grade 1 17.6 Grade 2 47.1 Grade 3 0 Grade 4 0	
		Vomiting	Concomitant phase	CDDP		31	Grade 1 25.8 Grade 2 35.5 Grade 3 6.5 Grade 4 3.2	
				CDDP/5-FU		17	Grade 1 23.5 2 52.9 3 11.8 4 0	
		Vomiting	Adjuvant phase	CDDP		28	1 25.0 2 25.0 3 7.1 4 7.1	
				CDDP/5-FU		16	1 37.5 2 25.0 3 0 4 0	
		Leukopenia/Hb/Plt	Concomitant phase	CDDP		31	1 35.5/48.4/16.1 2 22.6/9.7/0 3 0/3.2/0 4 0/0/0	
				CDDP/5-FU		17	1 35.3/47.1/0 2 5.9/11.8/0 3 0/0/0 4 0/0/0 1 10.7/50.0/21.4	

Study	Scale	Domain	F/U	Group	Mos.	n	mn±sd	Comments
		Leukopenia/Hb/Plt	Adjuvant phase	CDDP		28	2 42.9/25.0/0 3 7.1/0/0 4 0/0/0	
				CDDP/5-FU		16	1 31.3/50.0/18.8 2 31.3/6.3/0 3 0/0/0 4 0/0/0	
		Tube feeding rate		CDDP		31	64.5%	
			Concomitant phase	CDDP/5-FU		17	35.3%	
			Concomitant phase					

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-I. Response/adverse event regression modeling

Study	Design/ Outcome/ Model	Candidate Predictors/ Method for Identifying Candidates	Univariate Results, Variable (p value)	Selected Predictors/ Methods for Selecting Predictors for Multivariate Model	Interactions Considered?	Multivariate Model Results, Variable (p value)	Discrimination/ Validation Methods/ Results	Calibration/ Goodness of Fit
5310, Zheng et al., 2005	Major late tox	age, sex, histo, mn dose primary RT, vol irrad primary RT, T stage, GTV local recurrence, int initial RT to dx recur, late tox from prev RT, CTx, simultan RR	T stage, GTV (< 0.01)	same		GTV (< 0.04)		

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-J. Xerostomia incidence

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
580, Dirix et al., 2007	NCI CTC (v3.0) RTOG/EORTC	0, 1, 2 0, 1, 2, 3, 4	acute 6 mos			20, 4, 1, 9, 9	40, 56, 4 80, 16, 4, 0, 0		
1010, Urbano et al., 2007	NCI CTC (v2.0)	2, 3	12 mos 6 mos	DL1 DL2	10, 14, 1	15 15	60/0 73/7		
1500, Lee et al., 2007	NCI CTC (v 2.0)	0-1 2	12 mos			25 1	81 3		
1780, Lee et al., 2007	NCI CTC						100 pre-RT		
2430, Vosmik et al., 2006	RTOG	0,1,2,3,4				0, 15, 23, 0, 0	0, 39, 60, 0		
3080 Meirovitz 2006	RTOG/EORTC XST questionnaire (0-100 with higher number representing greater levels of XST)	0-3			6-24 (med 12) 6-24 (med 12)	38 38	100 100	Mean score of 3 observers 0.34 (SD 0.48) Range 0-2 Mean 37.3 (SD 24.4) Median 35 Range 0-86	
3320, Portaluri et al., 2006	RTOG/EORTC	0,1,2,3		38pts		12, 9, 14, 3	32, 24, 37, 8		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
3570 Saarilahti 2006	XST: LENT-SOMA scale (reported both by patient [subjective] and by radiotherapist [objective].				12	36	100	<u>Subj XST Subman gl spared</u> Y N Grade 0/1 14 (78) 7 (39) Grade 2/3 4 (22) 11(61) p=0.018 <u>Obj XST Subman gl spared</u> Y N Grade 0/1 14 (78) 9 (50) Grade 2/3 4 (22) 9 (50) P=0.083 <u>Managemt of XST Subman gl spared</u> Grade 0/1 13 (72) 7 (39) (none needed) Grade 2/3 5 (28) 11 (61) (occ/freq) P=0.044	
3790, Ozsahin et al., 2006	RTOG/EORTC	0, 1, 2, 3, 4				33	13, 36, 36, 15, 0		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
5020, Nishimura et al., 2005	RTOG	G0,1,2,3	3-4mo after start IMRT			33		3, 55, 36, 6%	
5120, Wolden et al., 2006	NCI	0 1 2 3		IMRT	12 mo	59	80	25 42 32 0	
5310, Zheng et al., 2005	RTOG	1, 2, 3	acute			45, 41	52, 48		
5330, Lu et al., 2005	RTOG	1, 2, 3, 4	<90 days >90 days			1, 3, 1, 0 5, 9, 0, 0	4, 12, 4, 0 20, 36, 0 ,0		
7090, Chao et al., 2004		Grade 1,2		IMRT		32,9		43, 12%	
7370, Lu et al., 2004	RTOG	0, 1, 2, 3	9 mos			0, 26, 23, 0	0, 53, 47, 0		
7750, Liu et al., 2003	RTOG	1, 2, 3, 4	> 90 days			0, 3,0, 0	0, 4, 0, 0		
8250, Munter et al., 2003	RTOG	0, 1, 2, 3	acute			23, 9, 10, 6	48, 19, 21, 12		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
8270 Braaksma 2003	VAS score (10-point scale) 0=no complaints 10=severe complaints				BL End of RT 1 3 6 12 24	21 17 15		Mean [25th to 75th percentile] 0 6.1 [~3.7-~8.8] ~4.5 [~2.4-~6.8] 7.0 [~1.0-~7.8] ~6.8 [~2.0-~7.6] 3.2 [~1.8-~6.4] 5.2 [~1.7-~8.2]	
8400 Amosson 2003/ 8600 Amosson 2002	Subjective questionnaire RTOG/EORTC Visual analog scale (VAS)	1-4		IMRT with SMART boost	Median time from completion of IMRT 38.5 months (mean 39.9- range 16.6-71.4 months)	30	100	A questionnaire was used to assess long-term xerostomia. Thirty patients responded to the 10 question questionnaire for subjective assessment of mouth dryness. Questions with significant correlation to dosimetric parameters 1. "What is the overall comfort of your mouth?" n=9 (30%) felt that their mouth was very comfortable. n=11 (36.7%) had slight dryness (RTOG	Should we report p values from table 8??

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
								Grade 1) n=6 (20%) had moderate dryness (RTOG Grade 2) n=4 (13.3%) developed severe dryness (RTOG Grade 3). 2: “Does your mouth feel dry when eating?” n=9 (30%) no n=12 (40%) mild n=5 (16.7%) moderate n=4 (13.3) severe 3: “do you have difficulty swallowing any foods?” n=19 (63.3) yes n=11 (36.7%) no 4: “ do you need to sip liquids to swallow dry food?” n=23 (76.7%) yes n=7 (23.3%) no 6. “do you feel like the amount of saliva in your mouth is… n=14 (46.7%) too little n=16 (53.3%) adequate	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
								n=0 (0%) too much 9. “has your taste changed due to salivary gland function?” n=13 (43.4%) yes n=17 (56.7%) no <u>Questions without significant correlation to dosimetric parameters</u> 5. “do you feel thirsty all the time?” n=6 (20%) n=24 (80%) 7. “do you have problems with speech b/c of dry mouth?” n=10 (33.3) yes n=20 (66.7%) no 8. “does dry mouth interfere with your ability to sleep all the time?” n=17 (56.7%) no n=10 (33.3%) occasionally n=3 (10%) frequently 10. “do you need to carry a water bottle	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
								daily?" n=15 (50%) no n=4 (13.3%) occasionally n=4 (13.3%) frequently n=7 (23.3%) all the time	
9290 Teh 2002	Subjective (none, mild, moderate and severe or complete) RTOG	0 1 2				2 13 13	7 46 46		
9330 Kovacs 2002	CTC v. 2.0	0 1 1-2 2 2-3 3 3-4 4				4 7 0 32 0 6 0 0	8 14 65 12		n=49 I'm not clear which population this is- in the text they report that 42 pts who rec'd RT got concomitant CT, but the table (4) adds up to 49.
11650, Kuppersmith et al., 1999	RTOG					2	7	Not defined	
13340 Ikushima et al, 2008	RTOG	0, 1, 2, 3, 4	75	IMRT	36mo			20, 49.3, 18.7, 12%	
24330, Pfreunder et al., 2003	RTOG	1,2,3,4	50	ICHT				22, 65, 12, 0%	
37660, Wendt et al, 2006	RTOG	0,1,2,3,4	38	IMRT	21mo	38		~18, ~41, ~28, ~13, 0%	
38290, Anand et al., 2008	NCI CTC v3.0	0, 1, 2	3 mos 6 mos			31, 24, 4 35, 18, 4	52, 41, 7 61, 32, 7		

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Incidence (%)	Comment
38840 Seung 2008	RTOG	0 1 2 3 4 0 1 2 3 4	Acute Late (f/u at least 1 yr)			0 0 29 40 0 0 27 17 0 0	0 0 42 58 0		
39300, Hoppe et al., 2008	RTOG	0, 1, 2, 3, 4	<3 mos > 3 mos			7, 23, 7, 0, 0 30, 3, 3, 0, 0	19, 62, 19, 0, 0 83, 8, 8, 0, 0		

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-K. Salivary flow

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Salivary Flow	Comment
3080 Meirovitz 2006	Stimulated (ml/min)			IMRT	6-24 (med 12)	38	100	Mean 0.55 (SD 0.27) Median 0.57 (0.01-2.42)	
	Unstimulated (ml/min)				Same	38	100	Mean 0.10 (SD 0.16) Median 0.13 (0-0.96)	
	% stimulated (relative to pretx)				Same	38	100	Mean 40 (SD 32) Median 30 (0-140)	
	% unstimulated (relative to pretx)				same	38	100	Mean 32 (SD 27) Median 18 (0-243)	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Salivary Flow	Comment
3570 Saarilahti 2006	SLF: LENT-SOMA score (percent of pretreatment value)				12 months after last RT			Basal SLF Subman gl spared Y N Grade 0 or 1 (76-100% of pretx value) 10 (56) 3 (17) Grade 2,3 or 4 (0-75% of pretx value) 8 (44) 15 (83) p=0.015 Stimulated SLF Subman gl spared Y N Grade 0 or 1 10 (56) 7 (39) Grade 2,3 or 4 8 (44) 11 (61) P=0.32 Six months following RT, mean unstimulated SLF was 57% of the BL value among the patients who had one submandibular gland spared and 27% among those who did not. Values 12 months after RT were 60 and 25%, respectively (p=0.006). One patient (6%) with contralateral submandibular gland sparing had severe (grade 4) reduction in the unstimulated SLF (to 0–25% of the pre-treatment value) 12 months after completion of IMRT as compared to 7 (39%) of the rest of the patients (p=0.016).	

Study	Definition/ Scale	Grade	F/U	Group	Mos. post Tx	n	%	Salivary Flow	Comment
3820 McMillan 2006	Stimulated whole salivary (SWS) flow rate (ml/min) Stimulated parotid Salivary (SPS) flow rate (ml/min)				BL,2,6,12 BL,2,6,12	32 32	100 100	Mean (SD) .91 (.53), .10 (.08), .18 (0.16), .28 (.27) p<.001 for all 4 visits, BL vs. 2 mo, BL vs. 6 mo and BL vs. 12 mo. .06 (.09), .01 (.02), .02 (.03), .06 (.10) p=.005 for all 4 visits, <.001 for BL vs. 2 mo and BL vs. 6 mo, .217 for BL vs. 12 mo	
6430, Kwong et al, 2004	Mean flow mL/min		0,2,6,12,18,24 mo	IMRT	19 patients @ baseline 17 patients @ 12 mo, 7 patients @ 24 mo.	19, 17, 7		Stimulated Whole Saliva (mL/min) 0,2,6,12,18,24 mo: 4.78, .47, .92, 1.33, 1.42, 2.73 Stimulated parotid saliva (mL/min) 0,2,6,12,18,24 mo: .92, .16, .21, .59, .62, .69	
8270 Braaksma 2003	Stimulated whole saliva flow measurements (WS)- mL/min as a % of BL before RT.				BL, weekly during RT, and at regular intervals after (1-3-6-12-24 mos.) Median BL,1,3,6,12,24 (25^{th} to 75^{th} %)	18	69	Pretx median SLF 1.96 mL/min (range .06-6.25). SLF decreased to 35% of BL (at 6 mos. post RT) and 37% (at 12 mos.). Partial recovery observed with a median of 48% of pretx SLF at 2 yrs post tx in 9 pts. 1.96 mL/min (~1.3-2.75), ~.80 (~.4-~1.25),~.85 (~.3-~.9), ~.80 (~.5-~.9), ~.82 (~.25-~1.1), ~1.2 (~.4-~1.9)	

Question 1-3: Toxicity, Efficacy, and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-L. Dysphagia incidence

Study	Definition/Scale	Grade	F/U	Group	Mos. post Tx	n	%	Comment
580, Dirix et al., 2007	NCI CTC (V 3.0)	0, 1, 2, 3, 4	Acute			17, 7, 1, 0, 0	68, 28, 4, 0, 0	
1010, Urbano et al., 2007	NCI CTC (v 2.0)	2,3	12 mos 6 mos	DL1 DL2		15 15	20, 67 13, 87	
1500, Lee et al., 2007	NCI CTC (v 3.0)	3	12 mos			6	19	
2370, Garden et al., 2007	Chronic	Mild				3	6	
2430, Vosmik et al., 2006	RTOG	0, 1, 2, 3, 4				0, 10, 14, 14, 0	0, 26, 37, 37, 0	
2770, Cheng et al., 2006								
3320, Portaluri et al., 2006								
3340 Studer 2006	SOMA-LENT and RTOG/EORTC radiation morbidity score	0/1 3/4				24/27 n=2		
3790, Ozsahin et al., 2006	NCI CTC v 2.0	0, 1, 2, 3, 4				0, 4, 16, 13, 0	0, 12, 49, 39, 0	
4290, Lau et al., 2006	RTOG	0, 1, 2, 3, 4				1, 13, 22, 20, 0	2, 23, 39, 36, 0	
5210, Duthoy et al., 2005	RTOG	G0,1,2, 3	31	IMRT		39	18, 54, 28, 0%	
16840, Wu et al, 2006	Dysphagia					0	0	
24330, Pfreunder et al., 2003	Dysphagia	1, 2, 3,4				6, 25, 17, 0	12, 51, 35, 0	
338850 Caglar 2008	Swallowing Performance Scale (1-7)	1 2 3 4 5 6 7		IMRT (all)	1-2	~32 ~6 ~22 ~14 ~9 ~4 ~9	33.3 6.25 22.9 14.6 9.4 4.2 9.4	

Study	Definition/Scale	Grade	F/U	Group	Mos. post Tx	n	%	Comment
37660, Wendt et al, 2006	RTOG	0,1,2,3	38	IMRT	21		~14, ~38, ~32, ~17	
38290, Anand et al., 2008	NCI CTC V 3,0	0, 1, 2	3 mos 6 mos			41, 7, 11 44, 6, 7	69, 12, 19 77, 10, 12	
38840 Seung 2008	RTOG	0 1 2 3 4 0 1 2 3 4	Acute Late			0 11 52 6 0 0 40 25 4 0	0 15.9 75.4 8.7 0 58.0 36.2 5.8 0	

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-M. Other toxicities to head and neck, e.g., osteoradionecrosis, radiation-induced caries

Study	Toxicity Type	Definition/Scale	Grade	F/U	Group	Mos. post Tx	n	%	Comment
3400 Studer 2006	ORN		3		IMRT	6	1	1.4	Total dose of 66 Gy for T3N2b BOT cancer.
5020, Nishimura et al., 2005									
6430, Kwong et al, 2004									
6530 Zheng 2004	ORN mandible				3DC		0	0	
7090, Chao et al., 2004	Trismus Jaw discomfort		1 2		IMRT IMRT		3 1		

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT, and 2DRT

Table E-N. Other adverse events

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
TRM	5310, Zheng et al., 2005		39		11	13			
	7750, Liu et al., 2003		7, 10		1,1	1,1			
	8370, Padovani et al., 2003	Acute infectious complication leading to death			2	8			
Skin	560, Biagioli et al., 2007	RTOG Grade 3-4	14		2				
	580, Dirix et al., 2007	NCI CTC (v 3.0) dermatitis 0,1,2,34 RTOG/EORTC 0,1,2,3,4,5	Acute 6		3, 17, 5, 0, 0 21, 3, 1, 0, 0	12, 68, 20, 0, 0 84, 12, 4, 0,0			
	1010, Urbano et al., 2007	NCI CTC (v.2.0) Grade 2-3 RTOG Grade 1 LENT SOM	12/6 12/6 12/6	DL1 DL1 DL1	15 11 11	67/20 18 27	DL2 DL2 DL2	15 10 10	47/20 20 40
	1500, Lee et al., 2007	NCI CTC (v.3.0) Grade 0, 1, 2, 3	12 Acute		1 4, 20, 6, 1	3 13, 64, 19, 3			
	2430, Vosmik et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 24, 12, 2, 0	0, 63, 32, 5, 0			
	3340, Studer et al., 2006	"mild to moderate" (no number provided)							
	4430, Kwong et al., 2006	Grade 3			23	46			
	3790, Ozsahin et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 9, 10, 14, 0	0, 27, 30, 43, 0			
	4290, Lau et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 15, 24, 16, 1	0, 27, 43, 29, 2			
	5210, Duthoy et al., 2005	Radiodermatitis G1,2,3	31			64, 31, 5%			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	5310, Zheng et al., 2005	RTOG Grade 1, 2, 3	Acute		40, 2	47, 2			
	5330, Lu et al., 2005	RTOG Grade 1, 2, 3, 4	<90 days >90 days		4, 12, 6, 0 5, 1, 0, 0	16, 48, 24, 0 20, 4, 0, 0			
	5740, Thorstad et al., 2004	Grade 1/2; 3/4	Acute		22, 5 8, 2	82, 18 29, 7			
	7090, Chao et al., 2004	Acute toxicity G1, G2, G3, G4 Late toxicity G1,2		IMRT IMRT		42,35, 15, 5% 3, 1%			
	7370, Lu et al., 2004	RTOG Grade 0, 1, 2, 3	9 mos		29, 19, 1, 0	59, 39, 2, 0			
	8250, Munter et al., 2003	RTOG 0, 1, 2, 3	Acute		0, 25, 21, 2	0, 52, 44, 4			
	9290, The et al., 2002	18 of 28 (64%) grade 1 10 of 28 (36%) grade 2							
	9330, Kovacs et al., 2002	0 1 1-2 2 2-3 3 3-4 4		n=49 I'm not clear which population this is- in the text they report that 42 pts who rec'd RT got concomitant CT, but the table (4) adds up to 49.	5 9 0 31 0 3 0 1	10 18 63 6 2			
	10740, Pommier et al, 2000								
	11650, Kuppersmith et al., 1999	RTOG (not defined)	Acute		3	11			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	13270, Lawson et al., 2008	Acute 1 2 3 4 Late 1 2 3 4			 16 11 0 0 3 0 0 0				
	13340 Ikushima et al, 2008	Dermatitis G 0, 8, 4	36 mo	CRT	28, 8, 4	70, 20, 10			
	16840, Wu et al, 2006	Grade 0, 1, 2, 3, 4	36 mo	IMRT	35, 31, 6, 3, 0	46.7, 41.3, 8, 4, 0%			
	24330, Pfreunder et al., 2003	RTOG 1, 2, 3 4		ICHT	16, 29, 3, 0	32, 58, 6, 0%			
	37660, Wendt et al, 2006	Dermatitis G 1, 2	21	IMRT		~38, ~62			
	38290, Anand et al., 2008	NCI CTC (v.3.0) Grade 1, 2, 3	3 mos		0, 8, 2	0, 13, 3			
	38840, Seung et al., 2008	0 1 2 3 4		All	0 32 32 5 0	0 46.4 46.4 7.2 0			
	39020, Rosenthal et al., 2008	NCI's common toxicity criteria (v3.0)		IMRT alone		28	IMRT + CT		35
	39300, Hoppe et al., 2008	RTOG Grade 0, 1, 2, 3, 4	<3 mos >3 mos		4, 23, 7, 3, 0 33, 2, 1	11, 62, 19, 8, 0 92, 6, 3			
Subcutaneous Tissue	6530, Zheng et al., 2004	Neck fibrosis			1	1.9			
	7750, Liu et al., 2003	RTOG grade 1, 2, 3, 4	> 90 days		0, 0, 0, 0	0, 0, 0, 0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	13270, Lawson et al., 2008	Late 1 2 3 4			 3 5 0 0				
	16840, Wu et al, 2006	Fibrosis G 1, 2, 3, 4	36	IMRT	14,1,0,0	18.6, 1.3,0,0			
	24330, Pfreunder et al., 2003								
	37660, Wendt et al, 2006								
Mucous Membrane	560, Biagioli et al., 2007	RTOG Grade 3-4	14		2	5%			
	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 RTOG/EORTC 0, 1, 2, 3, 4	Acute 6		7, 12, 6, 0, 0 17, 7, 1, 0, 0	28, 48, 24, 0, 0 68, 28, 4, 0, 0			
	1010, Urbano et al., 2007	NCI CTC (v.2.0) Grade 2/3 RTOG Grade 1 LENT SOM Grade 1	12/6 12/6 12/6	DL1 DL1 DL1	15 11 11	33/67 9 36	DL2 DL2 DL2	15 10 10	47/40 60 30
	1420, Feng et al., 2007	NCI CTC Grade 0-4	1	Highest score	Med 3(rng 2-3), mean 2.6 + or – 0.5				
	1500, Lee et al., 2007	NCI CTC (v.3.0) Grade 0, 1, 2, 3	Acute		3, 13, 8, 7	10, 42, 26, 23			
	2180, Daly et al., 2007	RTOG/EORTC Grade 1, 2, 3	Acute		19, 11, 6	53, 30, 17			
	2430, Vosmik et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 4, 23, 11, 0				
	3340, Studer et al., 2006	Grade 2 (n=13) Grade 3 (n=6)							

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	3570, Saarilathti et al., 2006	Grade 1: 3 Grade 2: 11 Grade 3: 19 Grade 4: 3							
	3790, Ozsahin et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 5, 14, 14, 0	0, 16, 42, 42, 0			
	4290, Lau et al., 2006	RTOG Grade 0, 1, 2, 3, 4	Acute		0, 16, 23, 16, 1	0, 29, 41, 29, 2			
	4430, Kwong et al., 2996	Grade 3			39	78			
	5210, Duthoy et al., 2005	Mucositis G1,2,3	31			54, 28, 18%			
	5310, Zheng et al., 2005	RTOG Grade 1, 2,3	Acute		34, 24, 5	40, 28, 6			
	5330, Lu et al., 2005	RTOG Grade 1, 2, 3, 4	<90 days > 90 days		1, 17, 5, 2 0, 2, 0, 0	4, 68, 20, 8 0, 8, 0, 0			
	5740, Thorstad et al., 2004	Grade 1/2, 3/4	Acute		19, 8	70, 30			
	7090, Chao et al., 2004	Acute mucosal toxicity G1, G2, G3, G4 Late mucositis G1		IMRT IMRT		12, 46, 38, 3% 4%			
	7370, Lu et al., 2004	RTOG Grade 0, 1, 2, 3	9 mos		16, 10, 21, 2	33, 20, 43, 4			
	7750, Liu et al., 2003	RTOG Grade 1, 2, 3,4	<90 days		26, 39, 7, 0	31, 47, 9, 0			
	8250, Munter et al., 2003	RTOG 0, 1,2, 3	Acute		8, 10, 21, 9	16, 21, 44, 19			
	9290, The et al., 2002	1 of 28 (3%) grade 1 5 of 28 (18%) grade 2 22 of 28 (79%) grade 3							

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	9330, Kovacs et al., 2002	0 1 1-2 2 2-3 3 3-4 4		n=49 I'm not clear which population this is- in the text they report that 42 pts who rec'd RT got concomitant CT, but the table (4) adds up to 49.	4 6 2 12 7 16 1 1	8 12 4 24.5 14 33 2 2			
	9510, Jian et al., 2002	 1 2 3 4 1 2 3 4		concomitant CDDP Adjuvant CDDP		0.0 22.6 67.7 9.7 25.0 32.1 21.4 10.7	CDDP/5-FU CDDP/5-FU		0.0 11.8 82.4 5.9 31.3 25.0 18.8 12.5
	10740, Pommier et al, 2000	NCI CTC (v.2.0) Grade 2, 3, 4, 5							
	11650, Kuppersmith et al., 1999	RTOG (not defined)	Acute		7	25			
	13270, Lawson et al., 2008	Acute 1 2 3 4 Late 1 2 3 4			 12 19 3 0 4 0 0 0				

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	13340 Ikushima et al, 2008	Mucositis G I, II, III	36 mo	CRT	14,22, 4	35, 55, 10			
	16840, Wu et al, 2006	Mucositis G 0, 1, 2, 3, 4	35mo	IMRT	7, 31, 30, 7	9.3, 41.4, 40, 9.3			
	24330, Pfreunder et al., 2003	Mucositis G 1, 2, 3, 4		ICHT	10, 23, 16, 0	20, 47, 33, 0			
	26140, Scorsetti et al., 2001	"transient"			NR				
	37660, Wendt et al, 2006	Mucositis G, 1, 2, 3	21mo	IMRT		~28, ~60, ~12			
	38290, Anand et al., 2008	NCI CTC (v.3.0) Grade 0, 1, 2, 3	3 mos		2, 27, 33	3, 44, 53			
	38840, Seung et al., 2008	0 1 2 3 4	Acute	All	0 8 33 28 0	0 11.6 47.8 40.6 0			
	38850, Caglar et al., 2008	0 1 2 3 4		IMRT	3 7 34 50 2	3 7 36 52 2			
	39020, Rosenthal et al., 2008	NCI's common toxicity criteria		IMRT alone		9	IMRT + CT	22	
	39300, Hoppe et al., 2008	RTOG Grade 0, 1, 2, 3, 4	< 3 mos >3 mos		2, 18, 12, 5, 0 36, 0 ,0 ,0, 0	5, 49, 32, 14, 0 100,0, 0, 0, 0			
	39390, Worden et al., 2008		acute		21, 42, 3	32, 64, 4			
Hematologic	560, Biagioli et al., 2007	RTOG Grade 3-4	14		5	12			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	4290, Lau et al., 2006	CTC 0, 1,2, 3, 4 Hb WB Neutrophils Platelets Creatine	Acute		25, 25, 2, 1, 1 36, 9, 8, 1, 0 42, 8, 2, 1, 1 49, 4, 1, 0, 0 49,2, 1, 0, 0	45, 45, 4, 2, 2 64, 16, 14, 2 75, 14, 4, 2, 2 88, 7, 2, 0, 0 88, 4, 2, 0, 0			
	38290, Anand et al., 2008	NCI CTC (v.3.0) Grade 1, 2, 3 Anemia Neutropenia thrombocytopenia	3 mos		 3, 2, 0 5, 4, 4 2, 1, 1	 5, 3, 0 8, 6, 6 3, 2, 2			
	39390, Worden et al., 2008	NCI CTC (v.2.0) Grade 2, 3, 4, 5 Anemia Leukopenia Neutropenia Thrombocytopenia Febrile neutropenia	 Acute Late Acute Late Acute Late Acute Late Acute Late		 5, 0, 0, 0 5, 1, 0, 0 44, 0, 0, 0 6, 0, 1, 0 1, 9, 1, 0 12, 4, 2, 0 6, 1, 0, 0 1, 1, 0, 0 0,0,2, 0 0,0,1,0	 8,0, 0, 0 7, 1, 0, 0 66, 0, 0, 0 9, 0, 1, 0 1, 14, 1, 0 18, 6, 3, 0 9, 1, 0, 0 1, 1, 0, 0 0, 0, 3, 0 0, 0, 1, 0			
Nausea/Vomiting	560, Biagioli et al., 2007	RTOG Grade 3-4	14		3	7			
	5330, Lu et al., 2005	RTOG grade 1, 2, 3, 4	<90 days		0, 1, 3, 0	0, 4, 12, 0			
	5740, Thorstad et al., 2004	Grade ½, ¾	Acute		23, 0 12, 0	85, 0 44, 0			
	39390, Worden et al., 2008	NCI CTC (v 2.0) grade 2, 3, 4, 5	Acute		8, 2, 0, 0 5, 3, 0, 0	12, 3, 0, 0 8, 4, 0, 0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Brain	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 RTOG/EORTC Grade 0,1, 2, 3, 4 (headache, other braine)	Acute 6		10, 11, 4, 0, 0 11, 11, 3, 0, 0	40, 44, 16, 0 ,0 44, 44, 12, 0, 0			
	5210, Duthoy et al., 2005	Brain necrosis	31			5%9			
	5310, Zheng et al., 2005	RTOG Grade 3, 4 Temporal lobe necrosis	39 mos		11, 2	13, 2			
Spinal Cord	5310, Zheng et al., 2005	Tog grade 3 or higher, cranial neuropathy	39 mos		25	29			
	5330, Lu et al., 2005	RTOG 1, 2, 3, 4 L'hermitt's syndrome	>90 days		1, 0,0,0	4,0,0,0			
	8370, Padovani et al., 2003	Acute purulent keratoconjunctivitis Uveitis Retinopathy	 17 mos 23 mos		2 1 1				
	13340 Ikushima et al, 2008	Neurology G 0, II	36	CRT	39, 1	97.5, 2.5			
	16840, Wu et al, 2006	Neuropathy G 1, 2, 3, 4	36mo	IMRT	0,2,1,0	0, 2.6, 1.3, 0 %			
	24330, Pfreunder et al., 2003	Vertigo CTC 1, 2, 3, 4 Headache CTC 1, 2, 3, 4 Sensorial disorder CTC 1,2,3,4 Motoric Disorder CTC 1,2,3,4		ICHT	17, 1, 0, 0 1, 5, 0, 0 10, 1, 0 ,0 23, 0 ,0 ,0	34, 2,0 ,0 % 2,10, 0, 0% 20, 2, 0, 0% 46, 0, 0 ,0%			
	39390, Worden et al., 2008	NCI CTC (v 2.0) Grade 2, 3, 4, 5	Acute Late		8,2, 0, 0 2, 7, 0, 0	12, 3, 0 ,0 3, 14, 0 ,0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Eye	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 : conjunctivitis NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4: tearing RTOG/EORTC Grade 0, 1, 2, 3, 4: tearing	Acute Acute 6		5, 10, 10, 0 7, 11, 7, 0,0 14, 11, 0,0,0	20, 40, 40, 0 28, 44, 28, 0, 0 56, 44, 0, 0, 0			
	2180, Daly et al., 2007	RTOG/EORTC Grade 1,2,3 Xeropthalmia Lacrimal stenosis Gyru rectus necrosis	 Acute Chronic Chronic		 18, 10, 1 1 1	 50, 28, 3 3 3			
	5210, Duthoy et al., 2005	Keratitis G2 Photophobia G2, 3 Blurred Vision G2,3 Tearing G0, 1,2,3 Dry Eye G1,2,3 Conjunctivitis G1,2,3	31			8% 8, 3% 10, 3% 13, 62,23,3% 92, 8,0 % 59, 38, 3%			
	11650, Kuppersmith et al., 1999	RTOG (not defined) Irritation	Acute		1	4			
	39300, Hoppe et al., 2008	RTOG grade 0 ,1 ,2, 3, 4 Ipsilateral contralateral	<3 mos >3 mos <3mos >3mos		27, 3, 2, 0, 0 32, 0 ,0 ,0, 0 36, 1, 0, 0, 0 36, 0, 0, 0, 0	73, 8, 5, 0, 0 100, 0, 0, 0, 0 97, 3, 0, 0, 0 100, 0, 0, 0, 0			
Visual Acuity	2180, Daly et al., 2007		Chronic	30 pts	0	0			
Ear	2180, Daly et al., 2007	Vestibular symptoms	Chronic	30 pts	3	10			
	5330, Lu et al., 2005	RTOG Grade 1,2, 3, 4 Ottis media	<90 days >90 days		1, 2, 0, 0 0, 0, 3, 0	4, 8, 0, 0 0, 0, 12, 0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	6530, Zheng et al., 2004	Hearing loss			3	5.6			
	9510, Jian et al., 2002	1 2 3			12 26 2				
	16840, Wu et al, 2006	Hearing Loss Grade 1, 2, 3	36	IMRT	5, 2, 1	6.6, 2.6, 1.3			
	38290, Anand et al., 2008	Otitis media	3 mos		3	5			
	39300, Hoppe et al., 2008	NCI CTC v 2.0 grade 2, 3, 4, 5 Otitis medius	< 2 wks of RT Post RT		4 3	11 8			
	39390, Worden et al., 2008	tinnitus	Acute		5, 2, 0, 0, 0	8, 3, 0, 0, 0			
Auditory Acuity	5310, Zheng et al., 2005	RTOG Grade 3: hearing loss	Med 39mo						
	5330, Lu et al., 2005	RTOG Grade 1, 2, 3, 4 hearing loss	<90days >90days						
	5420, Pan et al., 2005	hearing loss > or = 10 Db	1 mo 6 mo 12 mo 24 mo 36 mo 1 mo 6 mos 12 mos 24 mos 36 mos	8000 Hz 4000 Hz	19 16 14 10 2 23 20 14 12 3	47 44 46 29 6 14 14 20 34 9			
	7750, Liu et al., 2003	RTOG 1, 2, 3, 4 hearing impairment	< 90days		0, 2, 1, 0	0, 2, 1, 0			
	38290, Anand et al., 2008	hearing impairment	3 mos		1	2			
	39300, Hoppe et al., 2008	hearing impairment	6 mos 4 yrs		1 1	3 3			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Larynx	1010, Urbano et al., 2007	RTOG Grade 1-2 LENT SOM Grade 1-2	12/6 12/6	DL1 DL1	11 11	27 27	DL2 Dl2	10 10	20 20
	1500, Lee et al., 2007	NCI CTC (v.3.0)	12		3	10			
	3340, Studer et al., 2006	Grade 4 laryngeal fibrosis (n=1) "Laryngeal preservation maintained in all 23 locally controlled patients who underwent definitive IMRT , ultimate organ preservation in 96% (26/27).							
	5740, Thorstad et al., 2004	Grade 1/2, ¾	Acute		11, 2	41, 7			
	13270, Lawson et al., 2008	Acute 1 2 3 4 Late 1 2 3 4			 3 1 0 0 6 0 0 0				
	38840, Seung et al., 2008	0 1 2 3 4		all	12 51 6 0 0	17.4 73.9 8.7 0 0			
Lung									
Heart									
Esophagus	560, Biagioli et al., 2007	Late	14		1	2			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	1010, Urbano et al., 2007	RTOG Grade 2-3 LENT SOM	12/6 12/6	DL1 DL1	11 11	9 18	DL2 DL2	10 10	10 10
	1420, Feng et al., 2007	NCI CTC RTOG/EORTC	1 3 (late)	Highest score Highest score	Med2 (rng 2-3) Med 1 (rng 0-3)	Mean 2.3 + or - .5 Mean 1.0 + or – 1.1			
	2290, Yao et al., 2006	Stenosis (not defined)			3	4			
	5740, Thorstad et al., 2004	Grade 1/2, 3/4	Acute		23, 2	85, 7			
	8250, Munter et al., 2003	RTOG Grade 0, 1, 2, 3	Acute Late		6, 8, 26, 8 0, 0, 1, 1	12, 17, 54, 17 0,0 ,0, 2, 2			
	13270, Lawson et al., 2008	Acute Grade 1 Grade 2 Grade 3 Grade 4 Late Grade 1 Grade 2 Grade 3 Grade 4			 13 19 1 0 13 3 6 (*note # different than text) 0				

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	38850, Caglar et al., 2008	Stricture (doses significantly associated with stricture development = 54 Gy to mean inferior constrictor muscle [p=.02]; dose to LAR NS). Minimal dose rec'd by 60% of inf constrictor and % volume receiving ≥50 Gy correlated with stricture development [p=.03 and .02, respectively]. NS for larynx.		IMRT	36	37			
Bone	8250, Munter et al., 2003	RTOG Grade 0, 1, 2, 3	late		1	2			
	39390, Worden et al., 2008	NCI CTC (v.2.0) Mandibular necrosis	Late		3	5			
Joint	5310, Zheng et al., 2005	RTOG Grade 3, 4 trismus	Med 39 mos		12, 4	14, 5			
	5330, Lu et al., 2005	RTOG Grade 1,2, 3, 4 Trismus	>90days		10, 3, 0, 0	40, 12, 0,0			
	7750, Liu et al., 2003	RTOG Grade 1,2, 3, 4 trismus	>90days		0, 1, 0, 0	0, 1, 0, 0			
Teeth	1900, Ben-David et al., 2007	NCI CTC (v.3.0) Grade 1-4 Osteoradionecrosis	Med 35(rng 6-129)		0	0			
	2290, Yao et al., 2006	Mild (not define) Osteoradionecrosis			4	6			
	2370, Garden et al., 2007	Not defined Osteoradionecrosis			1	2			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
Pain	560, Biagioli et al., 2007	RTOG Grade 3 – 4	14		4	10			
	1010, Urbano et al., 2007	NCI CTC (v 2.0) grade 2-3	12/6	DL1	15	47/27	DL2	15	53/40
Other	560, Biagioli et al., 2007	Late: fistula carotid hemorrhage persistent PEG tube	14		 2 1 2	 5 2 5			
	580, Dirix et al., 2007	NCI CTC (v. 3.0) Grade 0, 1, 2 sense of smell taste disturbance NCI CTC (v. 3.0) Grade 0, 1, 2, 3, 4 fatigue	Acute		 10, 5, 10 8, 8, 15 4, 10, 11, 0, 0	 40, 20, 40 32, 32, 60 15, 40, 44, 0, 0			
	1420, Feng et al., 2007	PEG insertion	Pre-RT During Tx		2 11				
	1500, Lee et al., 2007	NCI CTC (v.3.0) Grade 2, 3: pharyngitis PEG dependence	 Acute 12		 27, 4 6, 19	 87, 13			
	2180, Daly et al., 2007	keratitis cellulitis dacryocystitis parotiditis	ACUTE		1 1 1 1	3 3 3 3			
	2290, Yao et al., 2006	PEG dependence Tracheotomy	Chronic		10 3	15 4			
	2370, Garden et al., 2007	RTOG/EORTC Grade 0, 1, 2, 3, 4: PEG insertion Fibrosis	 <1yr Late		 21 7, 23, 2, 0, 0	 40 21, 70, 3, 0,0			
	3790, Ozsahin et al., 2006	PEG insertion nasogastric tube wt loss			18 8 Med 4.5kg (rng 0-13kg)	55 24			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	4290, Lau et al., 2006	PEG insertion NG tube	Overall/chronic		13/7 10/2	23/12 18/4			
	5120, Wolden et al., 2006								No cases of temporal lobe necrosis, osteoradionecrosis or clinical hypopituitarism
	5330, Lu et al., 2005	RTOG Grade 1,2, 3, 4 taste disturbance olfactory disturbance	<90 days >90 days > 90 days		1, 4, 0, 4 1, 3, 1, 0 1, 1, 1, 0	4, 16, 0, 16 4, 12, 4, 0 4, 4, 4, 0			
	5740, Thorstad et al., 2004	Grade 1/2, ¾ asthenia fever hypotension salivary weight loss	Acute		 12, 0 2, 0 0,0 27, 0 15, 0	 44, 0 7, 0 0,0 100, 0 56, 0			
	6530, Zheng et al., 2004	Soft tissue necrosis of NPH Cranial neuropathy Trismus Temporal lobe necrosis Endocrine dysfxn		3DC	1 4 2 1 3	1.9 7.4 3.7 1.9 5.6			
	8250, Munter et al., 2003	PEG insertion	Acute		6	13			
	8370, Padovani et al., 2003	Nasal cartilage necrosis- limited			1				
	9290, The et al., 2002	6 of 28 (21) grade 1 pharyngitis 10 of 28 (36) grade2 pharyngitis 12 of 28 (43%) grade 3 pharyngitis							

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	9510, Jian et al., 2002	1 Pharyngitis 2 3 4		Concomitant CDDP		9.7 35.5 48.4 3.2	Concomitant CDDP/5-FU		23.5 47.1 29.4 0
	9510, Jian et al., 2002	1 neurologic deficits			3	6			
	13270, Lawson et al., 2008	Grade 1 salivary gland toxicity Grade 2 salivary gland toxicity WBC 1 2 3 4 Hct/Hb 1 2 3 4 Upper GI 1 2 3 4			18 10 4 10 6 2 13 6 0 0 3 18 2 0	53 29			
	13340 Ikushima et al, 2008	Hematoxicity Grade 0,I, II, III, IV Renal dysfunction G 0,I, II, III, IV	36 mo	CRT	16,13,10,1	40,32.5,25, 2.5, 0 92.5, 2.5, 5, 0 , 0			
	16840, Wu et al, 2006	Trismus	36	IMRT	0	0			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	24330, Pfreunder et al., 2003	Weight loss RTOG G 1, 2 CTC GRADED: Hypotension G 1, 2 Hypertension G1 Alopecia G 3 Fever G 1, G2, Myalgia, Arthralgia G1, 2 Nausea G1,2 Vomiting, G1, 2 Gastritis G1, Diarrhea G1 Constipation G2 Creatine G 1, 2, 3 Urea nitrogen G, 1, 2, 3 Bilirubin G 2, 3 Trans-aminases G 1, 2, 3 Hemoglobin G1, 2, 3 Leucocytes G1, 2, 3 Thrombocytes G 1, 2, 3	75	ICHT	19, 4 6, 8 3 50 3, 1 13, 1 7, 19 4, 12 8 7 2 17, 6, 1 18, 9, 2 17, 1 14, 6, 1 9, 7, 2 17, 7, 2 4, 2, 2	39, 8 12, 16 6 100 6, 2 26, 2 14, 28 8, 24 16 14 4 34,12, 2 36, 28, 4 34, 2 28, 12, 2 18, 14, 4 34, 14, 4 8, 4, 4			
	38290, Anand et al., 2008	enteral tube feeding iv fluids	3 mos		22 27	35 44			

Toxicity Type	Study	Severity or Grade	F/U (mos.)	Group1	n	%	Group2	N	%
	39020, Rosenthal et al., 2008	NCI's common toxicity criteria Nausea Grade 0 1 2 3 4 (p value for IMRT alone vs. with CT for grades 0-4 <.004) Vomiting Grade 0 1 2 3 4 (p value for IMRT alone vs. with CT for grades 0-4 <.04) Occipital scalp epilation Headache		IMRT alone		 76 24 33 38 5 0 38 63 16 18 3 0 40 10	IMRT + CT	 98 2 22 58 18 0 68 32 18 38 12 0 25 30	
	39390, Worden et al., 2008	elevated creatinine enteral tube feeding	NCI CTC (v.2.0) Grade 2, 3, 4, 5	Acute Acute	3, 0, 0, 0, 0 21	4, 0, 0 ,0, 0 32			

Question 1-3: Toxicity, Efficacy and Differences in Comparative Effects of IMRT, 3DCRT, PBT and 2DRT

Table E-O. Case series/single arm trial study quality ratings

Study	Clearly Defined Question	Well-Described Study Population	Well-Described Intervention	Use of Validated Outcome Measures (Indepen-dently Assessed)	Appropriate Statistical Analysis	Well-Described Results	Discussion/ Conclusions Supported by Data	Funding/ Sponsorship Source Acknow-ledged
580, Dirix et al., 2007	Y	Y	Y	Y/N	Y	Y	Y	N
1010, Urbano et al., 2007	Y	Y	Y	Y/N	Y	Y	Y	N
3080 Meirovitz 2006	Y	N	N	U	Y	Y	Y	Y
3340 Studer 2006	Y	Y	Y	U	Y	Y	Y	Y
3400 Studer 2005	Y	Y	Y	U	Y	Y	Y	N
1420 Feng et al, 2007	Y	Y	N	Y	Y	Y	Y	Y
1430, Scrimger et al., 2007	Y	Y	Y	Y/N	?	Y	?	N
1500, Lee et al., 2007	Y	Y	Y	Y/N	Y	Y	Y	N
3570 Saarilahti 2006	Y	Y	Y	U	Y	Y	Y	N
1770, Yao et al., 2007	Y	Y	N	Y	Y	Y	N	N
1780, Lee et al., 2007	Y	Y	N	Y	Y	N	U	N
3820 McMillan 2006	Y	Y	Y	U	Y	Y	Y	Y
1900, Ben-David et al., 2007	Y	Y	N	Y	U	Y	Y	Y
1990, Yao et al., 2007	Y	Y	N	Y	Y	Y	Y	N

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2180, Daly et al., 2007	Y	Y	Y	Y	Y	Y	Y	N
2290, Yao et al., 2006	N	Y	N	Y	Y	N	Y	N
2370, Garden et al., 2007	Y	Y	N	Y	Y	Y	N	Y
4430 Kwong	Y	Y	Y	Y	Y	Y	Y	Y
2430, Vosmik et al., 2006	Y	Y	Y	Y	U	N	N	N
4630 Yao 2005	Y	Y	Y	U	Y	Y	Y	N
2770, Cheng et al., 2006	Y	Y	N	Y	Y	Y	Y	Y
3320, Portaluri et al., 2006	Y	Y	Y	Y	U	N	U	N
3790, Ozsahin et al., 2006	N	Y	N	Y	Y	N	U	N
4290, Lau et al., 2006	Y	Y	Y	Y	Y	Y	Y	N
6530 Zheng 2004	Y	Y	Y	Y	Y	Y	Y	N
5020, Nishimura et al., 2005	Y	Y	Y	Y	Y	N	Y	Y
5210, Duthoy et al., 2005	Y	Y	Y	Y	Y	Y	Y	Y
5310, Zheng et al., 2005	Y	Y	Y	Y	Y	Y	Y	N
5330, Lu et al., 2005	Y	Y	N	Y	Y	Y	U	N
5420, Pan et al., 2005	Y	Y	N	Y	U	Y	U	N
5740, Thorstad et al., 2004	Y	N	N	U	N	N	U	Y

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8270 Braaksma 2003	Y	Y	Y	U	Y	Y	Y	N
8370 Padovani 2003	Y	N	Y	U	Y	Y	Y	N
8400 Amosson 2003	Y	Y	N	U	Y	Y	Y	N
6430, Kwong et al, 2004	Y	Y	Y	Y	Y	Y	Y	N
7090, Chao et al., 2004	Y	Y	Y	Y	Y	Y	Y	N
7110, Sze et al., 2004	Y	N	Y	Y	Y	N	U	N
9290 Teh 2002	Y	N	Y	U	U	Y	Y	N
9330 Kovacs 2002	Y	Y	Y	U	Y	N	Y	N
7370, Lu et al., 2004	Y	Y	Y	U	U	N	U	N
9510 Jian 2002	Y	Y	Y	U	Y	Y	Y	Y
7570, Levendag et al., 2004	N	N	N	Y	U	N	U	N
7750, Liu et al., 2003	Y	Y	Y	Y	Y	Y	Y	N
8250, Munter et al., 2003	Y	Y	Y	Y	U	N	U	N
10740, Pommier et al, 2000	Y	Y	Y	Y	Y	Y	Y	N

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13270 Lawson 2008	Y	Y	Y	U	Y	Y	Y	Y
11650, Kuppersmith et al., 1999	N	N	N	U	U	N	U	N
13340 Ikushima et al, 2008	N	N	Y	Y	Y	Y	Y	N
16840, Wu et al, 2006	Y	N	Y	Y	Y	Y	Y	N
26140 Scorsetti 2001	Y	N	Y	U	Y	Y	Y	N
24330, Pfreunder et al., 2003	Y	N	Y	Y	Y	Y	Y	N
38840 Seung 2008	Y	Y	Y	U	Y	Y	Y	N
38850 Caglar 2008	Y	Y	Y	U	Y	Y	Y	N
39000 Sanguineti 2008	Y	N	Y	U	U	Y	Y	N
39020 Rosenthal 2008	Y	Y	Y	U	Y	Y	Y	Y
37660, Wendt et al, 2006	Y	N	Y	Y	Y	Y	Y	N
38290, Anand et al., 2008	Y	Y	Y	Y	Y	Y	Y	N
38530, Studer et al., 2008	Y	N	N	U	U	N	U	N
38640, Studer et al., 2008	Y	Y	N	Y	Y	N	U	N
39300, Hoppe et al., 2008	Y	Y	Y	Y	Y	Y	Y	N

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39390, Worden et al., 2008	Y	Y	N	Y	Y	N	U	Y