AHRQ Comparative Effectiveness Review

Surveillance Program

CER # 20:
Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer

Original release date:
May 27, 2010

Surveillance Report 1st Assessment/ cycle 1:
October, 2011

Surveillance Report 2nd Assessment/cycle 2:
August, 2012

Key Findings (1st assessment/cycle1):
- 1 of 3 conclusions for KQ1 possibly out of date
- 1 of 2 conclusions for KQ2 possibly out of date
- 1 of 1 conclusions for KQ3 possibly out of date
- KQ4 up to date
- Expert opinion: conclusions for KQ1-4 still valid
- There are no new significant safety concerns

Key Findings (cumulative: 1st and 2nd assessments/cycles 1-2):
- 1 of 3 conclusions for KQ1 is possibly out of date
- 2 of 2 conclusions for KQ2 are possibly out of date
- 1 of 1 conclusions for KQ3 is possibly out of date
- KQ4 is up to date
- Expert opinion: conclusions for KQ1-4 are still valid
- There are no new significant safety concerns

Summary Decision
This CER's priority for updating is **Medium** (unchanged from the 1st assessment)

Authors:

Investigators: Nadera Ahmadzai, Alexander Tsertsvadze, Becky Skidmore
Technical support: Raymond Daniel
Advisory panel: David Moher, Mohammed T. Ansari
Oversight/supervision: David Moher, Chantelle Garritty

Contents

Tables

Appendices
Appendix A: Search Methodology
Appendix B: Updating signals
Appendix C: Evidence Table
Appendix D: Questionnaire Matrix

1. Introduction

The purpose of this mini-report is to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether the CER No. 20 (Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer), is in need of updating.[1] This CER was originally released in May, 2010. When the Surveillance program began in the summer of 2011, this CER was selected to be in the first wave of reports to go through the assessment. The first surveillance assessment report of this CER was submitted to AHRQ in November, 2011.[2] This second assessment was completed in August 2012.

This CER included 108 unique studies identified by using searches through the September 28, 2009 and addressed four key questions to compare alternative radiotherapy modalities in the treatment of head and neck cancer. The following four treatment modalities were compared: intensity-modulated radiotherapy (IMRT), 3-dimentional conformal radiotherapy (3DCRT), 2-dimentional radiotherapy (2DRT), and proton beam. The key questions of the original CER were as follows:

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?

The conclusion(s) for each key question are found in the executive summary of the CER report.[1]

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might need to be updated. The Food and Drug Administration (FDA) surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. All of this evidence was taken into consideration leading to a, consensus-based decision on whether any conclusion warrants updating. Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere. [3-5]

2.1 Literature Searches

Cycle 2 (2nd assessment)

Cycle 2 (2nd assessment)

The same search strategy was used as in the 1st assessment (cycle 1) but using different search dates for MEDLINE (August 22, 2011 to May 10, 2012), EMBASE (2011 Week 33 to 2012 Week 18), and Cochrane Central Register of Controlled Trials (August 22 2011 – May 10, 2012) as per the original search strategies appearing in the CER's Appendix A.[1]

Cycle 1 (1st assessment)

The original CER search strategies were reconstructed in MEDLINE (March 29, 2009-August 22, 2011), EMBASE (2009 to 2011 Week 33), and Cochrane Central Register of Controlled Trials (CCRCT; search date: August 22, 2011). The original CER search strategies for update search purposes were derived from the PubMed strategy appearing in the Appendix A.[1] The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were adjusted according to the three databases indicated in the appendix and in the search strategy section of the report. Journal titles were entered according to the style used by each of the selected OVID databases. The electronic searches in MEDLINE and EMBASE were limited to five general medical journals (Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine) and several specialty journals (Journal of Surgical Oncology, Cancer Radiotherapy, Breast Cancer Research, British Journal of Cancer, Cancer, International Journal of Radiation Oncology Biology Physics, Journal of Clinical Oncology, Radiotherapy & Oncology, and Head & Neck). Restricting by journal title was not possible in the Cochrane search and pertinent citations were instead selected from the results. Study design filters were not applied to any of the searches although the Cochrane Central Register only contains randomized

or controlled clinical trials. Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using the same inclusion/exclusion criteria as described in the original CER.

2.3 Expert Opinion

<u>Cycle 2 (2nd assessment)</u>

We contacted the three experts (one CER-specific and two local) that had responded to the first assessment.

<u>Cycle 1 (1st assessment)</u>

In total, 3CER-specific (e.g., lead author, clinical content experts, and technical expert panel members) and 8 additional (local) clinical content experts were requested to provide their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only, as was the case for this CER. For any CER that contains meta-analysis (es) we first assess for, the qualitative signal(s), and if no qualitative signal(s) are found, we then assess for quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might need updating. The definition and categories of updating signals are presented in Appendix B.

2.5 Compilation of Findings and Conclusions

All of the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and FDA surveillance alerts) was collated, summarized and presented in a table. We determined whether the conclusions of the CER warranted updating using a four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating

- Original conclusion is **possibly out of date** and this portion of CER may need updating

- Original conclusion is **probably out of date** and this portion of CER may need updating

- Original conclusion is **out of date** and this portion of CER is in need of updating

We used the following factors when making our assessments to categorize the CER conclusions:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.

- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.

- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

Determining the priority groups (i.e., Low, Medium, and High) for updating any given CER is based on the following two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?

- How out of date are conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

Cycle 2 (2nd assessment)

A total of 303 bibliographic records were identified (MEDLINE=132, EMBASE=169, and Central =2). After de-duping, 301 records remained (MEDLINE=132, EMBASE=169, and Central=0), from which 21 potentially eligible records were selected for full text screening. Of these, five met the eligibility criteria and were included in this update. [6-10]

Cycle 1 (1st assessment)

A total of 7 studies (one pivotal randomized controlled trial and six observational cohorts) were included in the first assessment. [11-17]

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

The study population demographics, treatment characteristics, and results for the five included studies are presented in Appendix C (Evidence Table).[6-10] In brief, all five studies were observational comparative studies. The sample size of the studies ranged from 33[6] to 1613. [9] The included studies compared conventional radiotherapy (2DRT) to intensity-modulated radiotherapy (IMRT) alone, [6,7,9,10] and to conformal radiotherapy (3 DCRT)[8] assessing the overall survival, [8-10] cause-specific survival, [9,10] local/regional control, [7,8,10] and adverse events such as dysphagia, xerostomia, dermatitis, and mucositis. [6,7] Of the five included studies two were conference abstracts. [6,8]

3.2.2 Qualitative signals

Key question #1

Xerostomia: Consistent to the original CER finding, IMRT was associated with fewer cases of xerostomia at 6, 12, 24, and 36 months compared to 2DRT. [7] **No signal**

Other Adverse Events: The incidence of other adverse events i.e. dermatitis [7] and dysphagia [6] favored IMRT treatment groups compared to 2DCRT groups. The original CER reported inconsistent results for other adverse events. **No signal**

Survival: Of the four studies reported survival, one [7] favored IMRT over 2DRT demonstrating a statistically significant difference:

- Overall survival: HR =2.64; 95% CI= 1.15, 6.04; p=0.026
- Disease –free survival: HR= 2.11; 95% CI= 1.06, 4.17; p=0.033

1 Signal

However, two studies [9,10] demonstrated non-significant findings and their results are inconclusive due to lack of reporting 95% CI and point estimates (they only reported proportions of patients in each treatment group with the outcome and a p-value), and small sample size. **No Signal**

Only one study [8] reported that they did not find any differences in survival for the 3DCRT versus 2DRT (data was not shown). **No Signal**

Tumor control: Of the three studies [7,8,10] reporting tumor control, one [7] demonstrated a statistically significant finding for locoregional control after receiving IMRT versus 2DR: HR= 3.54; 95% CI= 1.04; p= 0.043. **1 Signal**

The other study [10] reported a non-significant difference. Another study [8] did not find any difference after receiving 3DCRT versus 2DRT (data not shown). **No Signal**

Key question #3:

No study was identified. **No Signal**

Key question #4:

No study was identified. **No Signal**

3.2.3 Quantitative signals

Since the CER did not include a meta-analysis, only the presence/absence of qualitative signals was examined.

3.3 FDA surveillance alerts [cycle 2]

None of the FDA surveillance alerts were relevant to radiotherapy treatments for head and neck cancer.

3.4 Expert opinion [cycle 2]

Two (one CER-specific and one local) of the 3 contacted clinical experts provided their responses/feedback in the matrix table (Appendix D). The responses from both experts were in agreement that all four conclusions (outlined in the executive summary of the original CER) were still valid and the experts were not aware of any new evidence that would invalidate these conclusions. One expert suggested one publication [13]; however, this article was already included in the first assessment report of this CER 6 months earlier.

Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from newly identified studies, FDA surveillance alerts, and expert opinion) are provided in Table 1 (summary table). Based on the two assessments (cycles 1-2), this CER is categorized in **Medium** (unchanged from the 1st assessment) priority group for updating.

Key Question # 1

Signals from update search (Cycle 2): No qualitative signal was identified. **No Signal**

Experts (Cycle 2): Both stated the conclusions for key question #1 are still valid.

FDA surveillance alerts (Cycle 2): No relevant safety alerts.

1st Assessment Conclusion: **1 of 3 conclusions for Key Question # 1 is possibly out of date.**

Total (cumulative) Assessments Conclusion: **1 of 3 conclusions for Key Question # 1 is possibly out of date.**

Key Question # 2

Signals from update search (Cycle 2): Two qualitative signals were identified. **Two signal (Other).**

Experts (Cycle 2): Both stated the conclusions for key question #2 are still valid.

FDA surveillance alerts (Cycle 2): No relevant safety alerts.

1st Assessment Conclusion: **1 of 2 conclusions for Key Question # 2 is possibly out of date**.

Total (cumulative) Assessments Conclusion: **2 of 2 conclusions are possibly out of date.**

Key Question # 3

Signals from update search(Cycle 2): No new study identified.

Experts (Cycle 2): Both stated the conclusions for key question #3 are still valid.

FDA surveillance alerts (Cycle 2): No relevant safety alerts.

1st Assessment Conclusion: **The only conclusion for Key Question # 3 is possibly out of date.**

Total (cumulative) Assessment Conclusion: **The only conclusion for Key Question # 3 is possibly out of date.**

Key Question # 4

Signals from update search (Cycle 2): No new study identified. **No signal**

Experts (Cycle 2): Both stated the conclusions for key question #4 are still valid.

FDA surveillance alerts (Cycle 2): No relevant safety alerts.

1st Assessment Conclusion: **Up to date.**

Total (cumulative) Assessment Conclusion: **Up to date.**

Table 1. Summary Table

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		FDA surveillance alerts	Expert opinion (CER + local)	Validity of CER conclusions	
		Qualitative	Quantitative			Cycle 1 assessment	Cycles 1-2 (total cumulative assessment)
Key Question 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy 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 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. 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.	**Cycle 2 (August 2012)**					**Possibly out of date**	**Possibly out of date**
	No evidence	**None**	**None**	**None**	Both experts stated that the conclusion is still valid. One expert suggested one publication (Nutting et al, Lancet Oncol 2011); however, this article was already included in the first cycle assessment report 6 months earlier.		
	Cycle 1 (November 2011)						
	1 RCT[13] and 4 cohort studies [12,14,16,17]	**No signal** Findings in studies identified from update search were in agreement with those from the original CER in indicating reduced late xerostomia rates in IMRT vs. 3DCRT or 2DRT	NA (no meta-analysis in CER)	None	All 3 experts stated that this conclusion (for key question #1) is still valid; one expert noted the publication of full text of an RCT[13] – pivotal trial		

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.	3 cohort studies [14,16,17]	**No signal** 2 studies showed significantly reduced rates of adverse events in IMRT compared to 3DCRT, but in another study the rate of mucositis was higher in IMRT compared to 2DRT. Similarly inconsistent results for adverse events were found in the original CER					
	2 cohort studies [12,13]	**1 signal (A1)** The pivotal trial and one cohort study showed no significant difference in QOL between IMRT and 3DCRT. This is opposing to the finding of the original CER, where IMRT was better than 3DCRT in improving QOL					
		Cycle 2 (August 2012)					
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	**1 Retrospective [7]**	**No Signal** IMRT vs. CRT (2DRT) Grade 2 Xerostomia at 12 and 24 months: In IMRT< In CRT (2DRT)	None	None	Both experts stated that the conclusion is still valid.		

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.		Dermatitis (RTOG Grade 3–4) 44 (45) vs. 92 (65); p=0.02 Mucositis (RTOG Grade 3–4) 73 (75%) vs. 111 (77%); p= 0.33 Death during and up to 30 days after CTRT 1 (1%) vs. 2 (1%); p=1			
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.	**1 Retrospective** [6]	**No Signal:** IMRT vs. CRT (2DRT) Grade 3 dysphagia 57% vs. 58% Time of onset of grade 3 dysphagia 6.4 vs. 4.8 weeks; p = 0.05 Duration grade 3 dysphagia toxicity 4.9 vs. 7.5 weeks; p = 0.03			
	Cycle 1 (November 2011)				
	No evidence	**None**	**None**	**None**	**See above (cycle 1)**

13

Key question 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy 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 single randomized, controlled trial had too small of a sample size and too short of a follow up 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	**Cycle 2 (August 2012)**					**Possibly out of date**	**Possibly out of date**
			None	**None**	Both experts stated that the conclusion is still valid.		
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.	**1 Retrospective** [9]	**No Signal** IMRT vs. CRT (2DRT) Overall Survival (3 yr) 50.0% vs. 49.6% (p=0.47) Cancer-specific Survival (3 yr) 60.0% vs. 58.8% (p=0.45)					
The IMRT group appeared to have better overall survival than the 2DRT group, but the results were statistically significant in one study66 (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.(Taken from Results section of	**1 Retrospective** [7]	**2 Signals** IMRT vs. CRT (2DRT) Overall Survival HR= 2.64; 95% CI= 1.15, 6.04; p= 0.026 Disease-Free Survival HR= 2.11; 95%CI= 1.06, 4.17; p= 0.033					

14

the CER)		Locoregional control HR= 3.54; 95% CI= 1.04, 12.02; p= 0.043			
	1 Non RCT [10]	**No Signal** Overall Survival (2 yr) 72.0% vs. 63% (p=0.08) Cause-specific Survival (2 yr) 74.0% vs. 69% (p=0.26) local control 74.0% vs. 78.0% (p = 0.50)			
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.	**1 Non RCT** [8]	**No Signal** 3DCRT vs. 2DRT Overall Survival No difference (data not shown) Local control No difference (data not shown)			
Cycle 1 (November 2011)					
	1 RCT[13]	**No signal**	NA	None	All 3 experts stated

15

	and 5 cohort studies [11,14-17]	The evidence from update search and the original CER showed no significant differences in the 2-5-year overall survival between IMRT and 3DCRT (or 2DRT) and was inconclusive due to very small sample sizes and/or failure to report 95% CIs **1 Signal** Although results of studies from update search and those in the original CER were consistent in showing no significant difference in 2-3 year tumor control between IMRT and 3DCRT, one large cohort study with a longer follow-up reported that IMRT compared to 2DRT improved 5-year local tumor control	(no meta-analysis in CER)		that this conclusion (for key question #2) is still valid

Key question 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?						
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	**Cycle 2 (August 2012)**					**Possibly out of date**	**Possibly out of date**
	No new evidence	**No Signal**	**NA**	**None**	Both experts stated that the conclusion is still valid.	
	Cycle 1 (November 2011)					

as no comparative studies addressed these key questions	1 cohort study [11]	**1 signal (A7)** The original CER did not include studies answering this key question. One large cohort study from the update search showed significantly improved 5-year survival for IMRT vs. 2DRT in T1 stage patients	NA (no meta-analysis in CER)	None	All 3 experts stated that this conclusion (for key question #3) is still valid		

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?

No conclusions can be reached on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	Cycle 2 (August 2012)					**Up-to-date**	**Up-to-date**
	No new evidence	**No Signal**	**NA**	**None**	Both experts stated that the conclusion is still valid.		
	Cycle 1 (November 2011)						
	No new evidence	**No Signal**	**NA (no meta-analysis in CER)**	**None**	All 3 experts stated that this conclusion (for key question # 4) is still valid		

CER=comparative effectiveness review; IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy; FDA=food and drug administration; NA=not applicable; QOL=quality of life; CI=confidence interval

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Appendix A: Search Methodology

Journal limits were incorporated into the OVID searches, and the equivalent limit was imposed manually by the search expert on the Central search results. All searches were limited to the following journals:

General biomedical - Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and New England Journal of Medicine

Specialty journals - Journal of Surgical Oncology; Cancer Radiotherapy; Breast Cancer Research; British Journal of Cancer; Cancer; International Journal of Radiation Oncology Biology Physics; Journal of Clinical Oncology; Radiotherapy & Oncology; Head & Neck.

 Database: Ovid MEDLINE(R)
Time period covered by the search: August 22, 2011 to May 10, 2012.

Database: EMBASE
Time period covered by the search: 2011 Week 33 to 2012 Week 18.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2012 Week 18> Search Strategy:

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1   exp "Head and Neck Neoplasms"/ (414059)
2   (larynx or laryngeal or supraglottic or glottic or subglottic or pharynx or pharyngeal or hypopharynx or hypopharyngeal or hypo-pharynx or hypo-pharyngeal or oropharynx or oropharyngeal or oro-pharynx or oro-pharyngeal or nasopharynx or nasopharyngeal or naso-pharynx or naso-pharyngeal or lip or lips or oral or paranasal or para-nasal or nasal or sinus or salivary or parotid).ti,ab. (1428510)
3   (neoplasm or neoplasms or tumor or tumors or tumour or tumours or cancer or cancers or adenocarcinoma or carcinoma).ti,ab. (3920775)
4   ("occult primary" or "unknown primary").ti,ab. (5776)
5   2 and (3 or 4) (239504)
6   1 or 5 (536466)
7   exp Radiotherapy, Conformal/ (14822)
8   (IMRT or 3dcrt or "3D-CRT" or "3-D CRT" or "3D CRT").ti,ab. (11745)
9   (intensity and modulated).ti,ab. (15226)
10   (conformal or proton or protons).ti,ab. (160411)
11   protons/ (46397)
12   or/7-11 (197574)
13   6 and 12 (6517)
14   limit 13 to human (5776)
15   (in process or publisher or pubmednotmedline).st. (223002)
16   13 and 15 (32)
17   14 or 16 (5808)
18   jama.jn. (62217)
19   "annals of internal medicine".jn. (56486)
20   bmj.jn. (78760)
21   "new england journal of medicine".jn. (102403)
22   (lancet or lancet oncology).jn. (244193)
23   journal of surgical oncology.jn. (13535)
24   cancer radiotherapie.jn. (2648)
25   breast cancer research.jn. (2980)

26   british journal of cancer.jn. (38637)
27   cancer.jn. (69288)
28   international journal of radiation oncology biology physics.jn. (40283)
29   journal of clinical oncology.jn. (50473)
30   radiotherapy & oncology.jn. (5106)
31   head & neck.jn. (3361)
32   or/18-31 (770370)
33   17 and 32 (1562)
34   ("20110215" or "20110216" or "20110217" or "20110218" or "20110221" or "20110222" or
"20110223" or "20110224" or "20110225" or "20110228" or 201103* or 201104* or 201105* or
201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012*).ed. (1179857)
35   33 and 34 (137)
36   35 use prmz (137)
37   exp "head and neck tumor"/ (194924)
38   (larynx or laryngeal or supraglottic or glottic or subglottic or pharynx or pharyngeal or hypopharynx
or hypopharyngeal or hypo-pharynx or hypo-pharyngeal or oropharynx or oropharyngeal or oro-pharynx
or oro-pharyngeal or nasopharynx or nasopharyngeal or naso-pharynx or naso-pharyngeal or lip or lips or
oral or paranasal or para-nasal or nasal or sinus or salivary or parotid).ti,ab. (1428510)
39   (neoplasm or neoplasms or tumor or tumors or tumour or tumours or cancer or cancers or
adenocarcinoma or carcinoma).ti,ab. (3920775)
40   ("occult primary" or "unknown primary").ti,ab. (5776)
41   38 and (39 or 40) (239504)
42   37 or 41 (377692)
43   exp computer assisted radiotherapy/ (23075)
44   (IMRT or 3dcrt or "3D-CRT" or "3-D CRT" or "3D CRT").ti,ab. (11745)
45   (intensity and modulated).ti,ab. (15226)
46   (conformal or proton or protons).ti,ab. (160411)
47   exp proton/ (46397)
48   or/43-47 (204447)
49   42 and 48 (5342)
50   limit 49 to human (4612)
51   ("jama journal of the american medical association" or "jama the journal of the american medical
association").jn. (42133)
52   "annals of internal medicine".jn. (56486)
53   (bmj or bmj clinical research ed).jn. (107476)
54   "new england journal of medicine".jn. (102403)
55   (lancet or lancet oncology).jn. (244193)
56   ("journal of surgical oncology" or "journal of surgical oncology supplement").jn. (13723)
57   cancer radiotherapie.jn. (2648)
58   breast cancer research.jn. (2980)
59   "british journal of cancer".jn. (38637)
60   cancer.jn. (69288)
61   international journal of radiation oncology biology physics.jn. (40283)
62   ("journal of clinical oncology" or "journal of clinical oncology official journal of the american
society of clinical oncology").jn. (57949)
63   "radiotherapy and oncology".jn. (14027)
64   head neck.jn. (156)
65   or/51-64 (792382)
66   50 and 65 (1442)
67   (2011* or 2012*).em. (2750814)
68   66 and 67 (334)

69   68 use emez (250)
70   36 or 69 (387)
71   remove duplicates from 70 (301)
72   71 use prmz (131)
73   71 use emez (170)

****

Database: Cochrane Central Register of Clinical Trials (Wiley Interface).

Time period covered by the search: August 22 2011 – May 10, 2012

ID	Search	Hits
#1	MeSH descriptor Head and Neck Neoplasms explode all trees	3287
#2	(larynx or laryngeal or supraglottic or glottic or subglottic or pharynx or pharyngeal or hypopharynx or hypopharyngeal or hypo-pharynx or hypo-pharyngeal or oropharynx or oropharyngeal or oro-pharynx or oro-pharyngeal or nasopharynx or nasopharyngeal or naso-pharynx or naso-pharyngeal or lip or lips or oral or paranasal or para-nasal or nasal or sinus or salivary or parotid):ti,ab,kw	80650
#3	(neoplasm or neoplasms or tumor or tumors or tumour or tumours or cancer or cancers or adenocarcinoma or carcinoma):ti,ab,kw	68444
#4	("occult primary" or "unknown primary"):ti,ab,kw	71
#5	(#2 AND (#3 OR #4))	6435
#6	(#1 OR #5)	8441
#7	MeSH descriptor Radiotherapy, Conformal explode all trees	236
#8	(IMRT or 3dcrt or "3D-CRT" or "3-D CRT" or "3D CRT"):ti,ab,kw	144
#9	(intensity and modulated):ti,ab,kw	301
#10	(conformal or proton or protons):ti,ab,kw	2217
#11	MeSH descriptor Protons explode all trees	121
#12	(#7 OR #8 OR #9 OR #10 OR #11)	2479
#13	(#6 AND #12)	91
#14	(#13), from 2011 to 2012	8

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) denotes findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of "opposing findings" – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details
**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B - continued

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the 'borderline' changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old <=0.5 or RRR new / RRR old >=1.5. Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old <=0.5 or RD new / RD old >=1.5).

* Please, see Shojania et al. 2007 for further definitions and details

Appendix C: Evidence Table

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
Key Question # 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?						
Cycle 2 (August 2012)						
Kumar, 2011 [6]	Retrospective	33 pts with oropharyngeal cancer; mean age: NR; female: NR	IMRT (n=19; dose: NR) vs. CRT (n=14; dose: NR)	2008- 2010 Or Minimum (12 months)	Grade 3 dysphagia	**IMRT vs. Conventional RT(2DRT)** Grade 3 dysphagia 57% vs. 58% Time of onset of grade 3 dysphagia 6.4 vs. 4.8 weeks; p = 0.05 Duration grade 3 dysphagia toxicity 4.9 vs. 7.5 weeks; p = 0.03
Clavel, 2012 [7]	Non RCT	249 pts with locally advanced oropharyngeal cancer; mean age: 56.5 yrs; female: 22%	IMRT (n=100; 70 Gy in 33 fractions) vs. CRT(n=149; 70 Gy in 35 fractions)	Median (42 months)	Toxicity	**IMRT vs. Conventional RT(2DRT)** Grade 2 xerostomia at 12 and 24 months In IMRT arm < In CRT arm; (p<0.001) Dermatitis (RTOG Grade 3–4) 44 (45) vs. 92 (65); p=0.02 Mucositis (RTOG Grade 3–4) 73 (75%) vs. 111 (77%); p= 0.33 Death during and up to 30 days after CTRT 1 (1%) vs. 2 (1%); p=1
Huang, 2011 [8]	Non RCT	104 pts with Nasopharyngeal	Conventional RT (n= 44; 73.9 Gy) vs.	January 2000 - July 2007	toxicity	**Conformal RT (3 DCRT) vs. Conventional RT(2DRT)**

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
		Carcinoma; mean age: NR; female: NR	Conformal RT (n= 60; 73.9 Gy)			Greater toxicities (Grade 3) OR= 0.25, 95% CI= 0.10 - 0.61
Cycle 1 (November 2011)						
Chen 2010[15]	Non-RCT	130 pts with nonmetastatic squamous-cell carcinoma of the oral cavity, oropharynx, larynx/hypopharynx (T1-T4, N0-N3); concurrent chemotherapy: 63%; median age: 61 yrs; female: 41%	IMRT (n=52; 60-66 Gy) vs. 2DRT (n=78; 60-66 Gy)	NR	Survival, tumor control	Survival (3 yr) 72% vs. 69%, p=0.49 (IMRT = 2DRT) Tumor control (3 yr) 73% vs. 70%, p=0.33 (local) (IMRT = 2DRT)
Chen 2011[14]	Non-RCT	51 pts with squamous-cell carcinoma of the head and neck involving the cervical lymph nodes (N1-N3); median age: 60 yrs; female: 31%	IMRT (n=27; 70 Gy) vs. 2DRT (n=24; 60-66 Gy)	NR	Late xerostomia, harms, Survival, tumor control	Survival (2 yr) 87% vs. 86%, p=0.43 (IMRT=2DRT) Tumor control (2 yr) 92% vs. 87%, p=0.44 (local) (IMRT=2DRT)
Lai 2011[11]	Non-RCT	1276 pts with nonmetastatic nasopharyngeal carcinoma (T3-T4, N2-N3); median age: 45 yrs; female: 24%	IMRT (n=512; 54-64 Gy) vs. 2DRT (n=764; 68-76 Gy)	NR	Survival, tumor control	Survival (5 yr) 75.9% vs. 71.4%, p=0.088 (IMRT=2DRT) Tumor control (5 yr) 92.7% vs. 86.8%, p=0.007 (local) (IMRT > 2DRT)
Key question # 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?						
Cycle 2 (August 2012)						
Yu, 2011[9]	Non RCT	1613 pts with head and neck cancer; age: 66 - ≥ 86 yrs; female: 34%	Standard RT (n=1069; NR) vs. IMRT (n=544; NR)	2000- 2005	survival	**IMRT vs. Conventional RT(2DRT)** Overall Survival (3 yr)

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
						50.0% vs. 49.6% (p=0.47) Cancer-specific Survival (3 yr) 60.0% vs. 58.8% (p=0.45)
Fried, 2011 [10]	Non RCT	192 pts with head and neck squamous cell carcinomas; age: NR; female: NR	IMRT (n= 96; dose: NR) vs. CRT (n=96; dose: NR)	2000-2010 Or Median (34.4 months)	Survival, local control	**IMRT vs. Conventional RT(2DRT)** Overall Survival (2 yr) 72.0% vs. 63% (p=0.08) Cause-specific Survival (2 yr) 74.0% vs. 69% (p=0.26) local control 74.0% vs. 78.0% (p = 0.50)
Huang, 2011 [8]	Non RCT	104 pts with Nasopharyngeal Carcinoma; mean age: NR; female:NR	Conventional RT (n= 44; median dose 73.9 Gy) vs. Conformal RT (n= 60; 73.9 Gy)	January 2000 - July 2007	local control, overall survival, toxicity	**Conformal RT (3 DCRT) vs. Conventional RT(2DRT)** Overall Survival No difference (data not shown) Local control No difference (data not shown)
Clavel, 2012 [7]	Non RCT	249 pts with locally advanced oropharyngeal cancer; mean age: 56.5 yrs; female: 22%	IMRT (n=100; 70 Gy in 33 fractions) vs. CRT(n=149; 70 Gy in 35 fractions)	Median (42 months)	Survivial, locoregional control	**IMRT vs. Conventional RT(2DRT)** Locoregional control HR= 3.54; 95% CI= 1.04, 12.02; p= 0.043 Disease-Free Survival HR= 2.11; 95%CI= 1.06, 4.17; p= 0.033 Overall Survival HR= 2.64; 95% CI= 1.15, 6.04; p= 0.026

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
			Cycle 1 (November 2011)			
Nutting 2011 PARSPORT[13]	RCT	94 pts with pharyngeal squamous-cell carcinoma (T1-T4, N0-N3, M0); mean age: 58 yrs; female: 28%	IMRT (n=47; 60-65 Gy) vs. 3DCRT (n=47; 65 Gy)	4 wks	Late xerostomia, QOL, survival	Survival (2 yr) HR=0.68 (0.34, 1.37) RD=2% (-20.0, 16.0) (IMRT=3DCRT)
Dirix 2010a[17]	Non-RCT	81 post-operative pts with sinonasal or nasal cavity cancer; mean age: 62 yrs; female: 16%	IMRT (n=40; 60-66 Gy) vs. 3DCRT (n=41; 60-66 Gy)	2 yrs	Tumor control, survival, harms	Survival (2 yr) 89% vs. 73%, p=0.07 (IMRT=3DCRT) Tumor control 76% vs. 67%, p=0.06 (local) 89% vs. 89%, p=0.68 (distant) (IMRT=3DCRT)
Dirix 2010b[16]	Non-RCT	97 pts with primary tumor of the oral cavity, oropharynx, larynx, or hypopharynx with majority in stage 4, treated with chemotherapy (cisplatinum 100 mg/m^2) at wk 1 and 4; mean age: 56 yrs; female: 17.5%	IMRT (n=42; 72 Gy) vs. 3DCRT (n=55; 72 Gy)	6 wks	Tumor control, survival, harms	Survival (2 yr) 56% vs. 73%, p=0.29 (IMRT=3DCRT) Tumor control 81% vs. 66%, p=0.38 (local) 61% vs. 73%, p=0.13 (distant) (IMRT=3DCRT)
Chen 2010[15]	Non-RCT	130 pts with nonmetastatic squamous-cell carcinoma of the oral cavity, oropharynx, larynx/hypopharynx (T1-T4, N0-N3); concurrent chemotherapy: 63%; median age: 61 yrs; female: 41%	IMRT (n=52; 60-66 Gy) vs. 2DRT (n=78; 60-66 Gy)	NR	Survival, tumor control	Survival (3 yr) 72% vs. 69%, p=0.49 (IMRT = 2DRT) Tumor control (3 yr) 73% vs. 70%, p=0.33 (local) (IMRT = 2DRT)

28

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
Chen 2011[14]	Non-RCT	51 pts with squamous-cell carcinoma of the head and neck involving the cervical lymph nodes (N1-N3); median age: 60 yrs; female: 31%	IMRT (n=27; 70 Gy) vs. 2DRT (n=24; 60-66 Gy)	NR	Late xerostomia, harms, Survival, tumor control	Survival (2 yr) 87% vs. 86%, p=0.43 (IMRT=2DRT) Tumor control (2 yr) 92% vs. 87%, p=0.44 (local) (IMRT=2DRT)
Lai 2011[11]	Non-RCT	1276 pts with nonmetastatic nasopharyngeal carcinoma (T3-T4, N2-N3); median age: 45 yrs; female: 24%	IMRT (n=512; 54-64 Gy) vs. 2DRT (n=764; 68-76 Gy)	NR	Survival, tumor control	Survival (5 yr) 75.9% vs. 71.4%, p=0.088 (IMRT=2DRT) Tumor control (5 yr) 92.7% vs. 86.8%, p=0.007 (local) (IMRT > 2DRT)
Key question # 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?						
Cycle 2 (August 2012)						
No studies	NA	NA	NA	NA	NA	NA
Cycle 1 (November 2011)						
Lai 2011[11]	Non-RCT	1276 pts with nonmetastatic nasopharyngeal carcinoma (T3-T4, N2-N3); median age: 45 yrs; female: 24%	IMRT (n=512; 54-64 Gy) vs. 2DRT (n=764; 68-76 Gy)	NR	Survival, tumor control	Survival (5 yr) In T1 stage patients 100% vs. 94.4%, p=0.016 (IMRT > 2DRT)
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?						
Cycle 2 (August 2012)						
No studies	NA	NA	NA	NA	NA	NA
No studies	NA	NA	NA	NA	NA	NA
IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy; RCT=randomized controlled trial; QOL=quality of life; T=tumor; M=metastasis; N=node; wk(s)=week(s); HR=hazard ratio; RD=risk difference; pts=patients; yr(s)=years; NR=not reported; CTRT= concurrent chemotherapy and radiotherapy						

Appendix D: Questionnaire Matrix

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

AHRQ Publication No. 10-EHC014-EF May 2010

Access to full report:

http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=447

Access to previous mini-report of this CER:
http://www.effectivehealthcare.ahrq.gov/ehc/products/19/447/Radiotherapy_SurveillanceAssessment_20120419.pdf

Clinical expert name:

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question # 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy 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 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. 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. 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			
Key question # 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy 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 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			
Key question # 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?			
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			

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?			
No conclusions can be reached on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions			
CER=comparative effectiveness review; IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy			