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ORIGINAL ARTICLE

Radiotherapy-related quality of life in patients with head and neck cancers: a meta-analysis

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Abstract

Objectives To compare effects of intensity-modulated radiotherapy (IMRT) with those of conventional radiotherapy on quality of life (QoL) and severity of xerostomia in patients with head and neck cancer.

Material and methods PubMed, Cochrane, and Embase databases were searched to July 1, 2019, to identify relevant studies, using the following terms: radiotherapy, head and neck cancer, quality of life, cognition, xerostomia, two-/three-dimensional conformal radiation therapy, IMRT, conformal proton beam radiation therapy, stereotactic radiosurgery, and volumetric modulated arc therapy. The outcomes of interest were QoL measured by global health status; emotional, social, and cognitive function; and severity of xerostomia.

Results Seven studies with a total of 761 patients ($n = 369$ with IMRT; $n = 392$ with conventional RT) were included in this study. Median patient age was 18–65 years. IMRT group patients had better global health status (pooled standardized mean difference [SMD] = 0.80, 95% CI 0.26 to 1.35, $P = 0.004$) and cognitive function (pooled SMD = 0.30, 95% CI 0.06 to 0.54, $P = 0.013$) than the conventional RT group. Patients receiving IMRT also had significantly lower scores for xerostomia than those receiving conventional RT (pooled SMD = − 0.60, 95% CI − 0.97 to − 0.24, $P = 0.001$). No differences were found in emotional function ($P = 0.531$) and social function ($P = 0.348$) between the two groups.

Conclusion IMRT significantly improves QoL and reduces the severity of xerostomia in patients with head and neck cancer. Results of this study provide clinicians with guidelines for decisions on the use of IMRT versus conventional RT.

Keywords Intensity-modulated radiotherapy · Conventional radiation therapy · Quality of life · Head and neck cancer · Dry mouth

Abbreviations

CCB	Concomitant boost technique
EORTC	European Organization for Research and Treatment of Cancer
EORTC H&H35	European Organization for Research and Treatment of Cancer head and neck cancer questionnaire

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EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Module for Head and Neck Cancer
FACT	Functional Assessment of Cancer Treatment questionnaire
FACT	Functional Assessment of Cancer
H&H	Treatment head and neck questionnaire
GTV	Gross tumor volume
HR	Hazard ratio
HNQOL	Head and Neck Quality of Life instrument
IMRT	Intensity-modulated radiotherapy
OARs	Organs at risk
OR	Odds ratio
PGTVnx	Primary gross tumor volume of nasopharynx
PGTVnd	Primary gross tumor volume of neck dissection
PCTV	Primary control tumor volume
PCTVnd	Primary control tumor volume of neck dissection
PTV	Planning target volume
QoL	Quality of life
RT	Radiation therapy
SF-36	Medical Outcomes Study Short-Form (36-item) Health Survey
UWQOL	University of Washington Quality of Life Questionnaire
VMAT	Volumetric modulated arc therapy
XQ	Xerostomia questionnaire
2D-RT	Two-dimensional radiation therapy
3D-CRT	Three-dimensional conformal radiation therapy

Introduction

The optimal management of patients with head and neck squamous cell carcinoma requires a multidisciplinary approach. Cure for tumors is possible, even for locally advanced tumors, by surgery or radiation therapy (RT) alone, or combined treatments, including surgery, RT, and chemotherapy [1–3]. High survival rates can be achieved for local tumors using RT, with 5-year survival rates at > 80% for stages 1 and 2 and 60–70% for stages 3 and 4 tumors [4]. However, the occurrence of significant long-term treatment sequelae of RT may impact patients' quality of life (QoL) [5, 6]. In particular, radiation-induced xerostomia (dry mouth), a common side effect of RT, may affect speech, swallowing, and overall oral problems [7].

Currently, the radiation methods used to treat head and neck squamous cell carcinoma include conventional RT and intensity-modulated radiation therapy (IMRT) [2]. IMRT is an advanced type of radiation therapy that uses computed tomography-based planning to deliver precise radiation doses to a malignant tumor or specific areas within the tumor. IMRT has superior advantages compared to conventional RT treatments. It allows the radiation dose to conform more precisely to the three-dimensional (3D) shape of the tumor by computer controlling the intensity of the radiation beam in multiple small volumes, which minimizes the radiation doses to organs at risk (OARs) [8]. This function is important particularly for OARs in the head and neck region, including the spinal cord, brain stem, optic pathway, parotid glands, and inner ear [8]. In addition, the high radiation beam dose conformed to the shape of the tumor and spared the dose to surrounding normal tissue, which allowed escalating the radiation dose for tumors and the possible reduction of side effects [9]. Small randomized controlled studies (RCTs) and a meta-analysis had previously provided evidence to support the potential benefits of IMRT over conventional radiation therapy [2, 9].

Among long-term outcomes, it is especially important to maximize and preserve QoL in patients with head and neck cancer. The instruments used to evaluate QoL vary between studies and may include tumor size, side effects of RT, global health status, emotional status, social function, cognitive function, and severity of xerostomia. Some studies have reported associations between QoL and survival before, during, and after treatment [8]. IMRT allows the sparing of OARs and other non-tumor tissues and has the potential to induce a less negative impact on QoL compared with conventional RT. Several previous RCTs reported significant reduction in moderate to severe xerostomia with IMRT compared with either two-dimensional RT (2D-RT) or 3D conformal radiation therapy (3D-CRT); however, the impact upon tumor and survival has been inconsistent due to small sample size and the associated low statistical power of individual studies.

In the last decade, several RCTs and meta-analyses have directly compared IMRT with either 2D-RT or 3D-RT in head and neck cancer. While nearly all studies reported the data of severe xerostomia, tumor and survival with IMRT and conventional RT, the impact upon different QoL domains were not included or meta-analysis was not performed. Therefore, we have performed the first meta-analysis including the most recently published data. Our hypothesis was that patients receiving IMRT may have better QoL than those receiving conventional RT in head and neck cancers. The present study aimed to compare the effects of IMRT with those of conventional radiotherapy, including 2D-RT and 3D-CRT, on QoL and specific QoL domains, including cognition, emotional function, and the severity of xerostomia in patients with head and neck cancer.

Methods

Search strategy

This study was performed in accordance with the PRISMA guidelines. PubMed, Cochrane, and EMBASE databases were searched to July 1, 2019, using the following search terms: (head and neck cancer) AND (radiotherapy OR radiation therapy OR 2D-CRT OR 3D-CRT OR IMRT OR Conformal proton beam radiation therapy OR stereotactic radiosurgery OR volumetric modulated arc therapy OR VMAT) AND (neuropsychological OR cognition OR quality of life) AND (nasopharyngeal carcinoma OR oral cancer OR buccal caner OR head and neck cancer) AND (squamous cell carcinoma) AND (radiotherapy OR radiation therapy OR radiosurgery) AND (neuropsychological OR cognition OR xerostomia). PubMed search filters: Abstract available, English, Clinical Trial; Embase search filters: Abstract, English, Human, Full text, Clinical Article.

RCTs, two-arm prospective and retrospective studies were included. Included studies were required to have evaluated patient-reported QoL and xerostomia between patients with head and neck cancer who received IMRT and patients with head and neck cancer who received any other type of radiotherapy. Studies were also required to have reported quantitative outcomes of interest. One-arm studies, cohort studies, review articles, letters, comments, editorials, case reports, proceedings, and personal communications were also excluded.

Study selection and data extraction

Studies identified by the search strategy were screened using a two-step process. First, the title and abstract of each article were examined and citations not meeting the inclusion criteria were discarded. Second, full-text review of the remaining studies was performed by two independent reviewers. If any uncertainties existed regarding eligibility, a third reviewer was consulted. The reference lists of the relevant studies were also hand searched to identify other studies that met the inclusion criteria. Data from the included studies were extracted by two independent reviewers and a third consulted when necessary to resolve any disagreements. The following data were extracted: name of first author, study design, interventions, patient number, age, gender, and site and stage of cancer. In addition, information regarding radiation and chemotherapy, and the percentage of patients with neck dissection or surgery was extracted.

Quality assessment

The quality of the included studies was performed using the Quality In Prognosis Studies (QUIPS) tool [10]. The QUIPS tool evaluates six sources of bias, including study participation, study attrition, prognostic factor measurement, confounding and account measurement, outcome measurement, and analysis. The quality of included studies was independently appraised by two reviewers, and any disagreements were resolved by a third reviewer.

Outcomes

The primary outcomes were QoL measured by global health status, emotional function, social function, and cognitive function. The secondary outcome was the severity of xerostomia.

Data analysis

Standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs: lower and upper limits) was calculated for each individual study and for all studies combined, because measurements were determined by various instruments. A χ^2-based test of homogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. If the I^2 statistic was > 50%, a random-effects model (DerSimonian and Laird) was used. Otherwise, a fixed-effects model (inverse-variance method) was employed. Pooled effects were calculated and a 2-sided P value < 0.05 indicated statistical significance. Sensitivity analysis was carried out using the leave-one-out approach. In addition, publication bias was only assessed if there were > 10 studies, because > 10 studies are necessary to detect funnel plot asymmetry [11]. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Search results

A total of 2017 studies were identified in the initial research (Fig. 1). Of those, 1939 were excluded for not being relevant by reviewing titles and abstracts. In total, 78 studies underwent full-text review for eligibility and 71 were excluded for not reporting QoL, that is, being single-arm studies, duplicates, review articles, not comparing IMRT with another type of radiation, or not evaluating head and neck cancer and the data cannot be pooled. Finally, 7 studies were included for analysis in this study [3, 12–17].

Study characteristics

The main characteristics of these 7 included studies are summarized in Table 1, with a total of 761 patients, including 369 patients who received IMRT and 392 patients treated with conventional RT [3, 12–17]. Three studies were RCTs

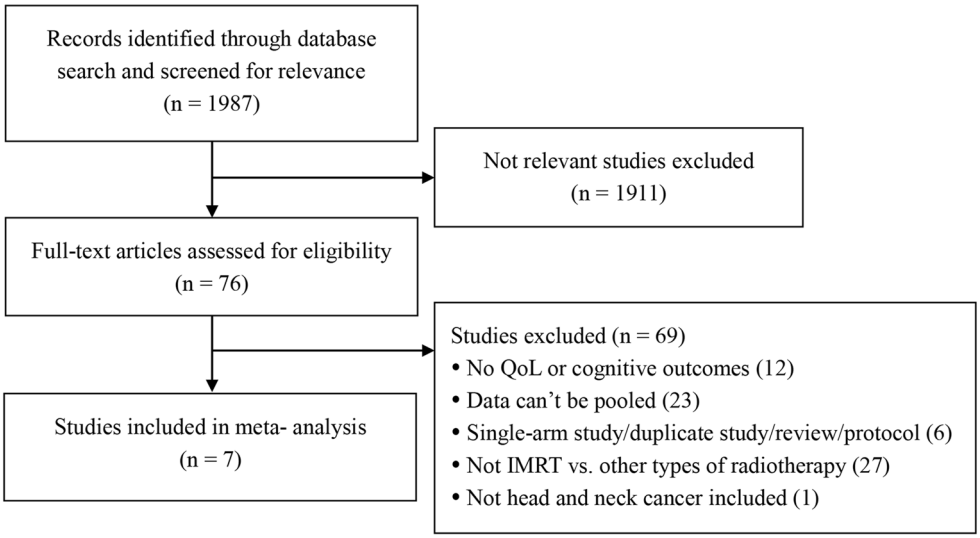


Fig. 1 Flow diagram of study selection

(Nutting [2011], Kam [2007], Pow [2006]), and the others were prospective or retrospective studies. The median age among the studies ranged from 18 to 65 years. The majority of participants were male, ranging from 59 to 81%. The site and stage of cancer varied across the studies.

Treatment protocols and QoL assessment

Table 2 summarizes the treatment protocols of the included 7 studies. Diverse radiotherapy protocols were used in patients with head and neck squamous cell carcinoma. The number of patients receiving either IMRT or RT was equally distributed. Chemotherapy was also administered to 35 to 63% of patients as a combination treatment with RT. Where reported, 9 to 62% of patients had received either neck dissection or neck surgery. The instruments used to evaluate QoL varied across studies (Supplemental Table S1). The studies included in our analysis used European Organization for Research and Treatment of Cancer Quality of Life questionnaire C30 (EORTC QLQ-C30), EORTC QLQ Module for Head and Neck Cancer (EORTC QLQ H&N35), Head and Neck Quality of Life instrument (HNQOL), University of Washington Quality of Life Questionnaire (UWQOL), Medical Outcomes Study Short-Form (36-item) Health Survey (SF36), and xerostomia questionnaire (XQ).

Meta-analysis

Global health status was firstly performed analyses to assess QoL. A total of five studies (Chen [2012], Nutting [2011], Vergeer [2009], Pow [2006], and Jabbari [2005]) provided information on global health status before and after treatment. Since a statistically significant heterogeneity was found when data from the 5 studies were pooled (Q statistic = 32.673, I^2 = 87.76%, $P < 0.01$), a random effects model of analysis was used (Fig. 2a). The analysis revealed that patients who received IMRT had significantly better global health status compared with those who received conventional RT (pooled SMD = 0.80, 95% CI 0.26 to 1.35, $P = 0.004$).

We examined the emotional function of QoL and included three studies (Chen [2015], Vergeer [2009], and Pow [2006]). As shown in Fig. 2b, a fixed-effect model of analysis (Q statistic = 2.528, $I^2 = 20.90\%$, $P = 0.282$) revealed no significant differences between pooled effects in the emotional function between patients treated with IMRT and those who received conventional RT (pooled SMD = 0.06, 95% CI − 0.13 to 0.26, $P = 0.53$).

Three studies (Chen [2015], Vergeer [2009], and Pow [2006]) provided complete data for changes in social function with treatment (Fig. 2c). A significant observed heterogeneity was found in emotional function among these studies (Q statistic = 22.231, $I^2 = 91.00\%$, $P < 0.001$). However, this result in pooled effects indicated that social function was comparable between the two treatment groups using a random effects model (pooled SMD = 0.35, 95% CI − 0.38 to 1.08, P = 0.348).

We then examined the effects of treatment on cognitive function (Fig. 2d), and only two studies [Vergeer (2009), Pow (2006)] were included. No significant observed heterogeneity was found between the two treatment groups (Q statistic = 1.114, $I^2 = 10.24\%$, $P = 0.291$) so a fixed-effect model was then used. The overall analysis revealed that patients in the IMRT group had significantly better cognitive function compared with those in the conventional RT group (pooled SMD = 0.30, 95% CI 0.06 to 0.54, $P = 0.013$).

Six studies (Chen [2015], Nutting [2011], Vergeer [2009], Kam [2007], Pow [2006], and Jabbari [2005]) were used to evaluate the severity of patient-reported xerostomia (dry month) following treatments (Fig. 2e). A significant observed heterogeneity was found among the studies (Q statistic =

Table 1 Summary of basic characteristics of selected studies

First author (year)	Study design	Interventions	Number of patients	Median age (years)	Male (%)	Cancer, *n* (%)	
						Site	Staging (AJCC)
Chen (2015)	Prospective	IMRT	65	40–60: 49%	78.5%	Nasopharyngeal carcinoma, 100%	NA
		Conventional RT	65	40–60: 49%	73.9%		
Chen (2012)	Retrospective	IMRT	84	56	59.0%	Oropharynx, 38%; oral cavity, 27%; larynx/hypopharynx, 13%; unknown primary, 12%; nasopharynx, 10%	NA
		3D-CRT	71			Oropharynx, 41%; oral cavity, 28%; larynx/hypopharynx, 12%; unknown primary, 10%; nasopharynx, 7%	
Nutting (2011)	RCT	IMRT	47		70.0%	Oropharynx, 85%; hypopharynx, 15%	I and II, 32%; III and IV, 68%
		Conventional RT	47		74.0%	Oropharynx, 85%; hypopharynx, 15%	I and II, 17%; III and IV, 83%
Vergeer (2009)	Prospective	IMRT	91	18–65 years: 75%	56.0%	Oral cavity, 14%; oropharynx, 37%; nasopharynx, 3%; hypopharynx, 19%; larynx, 23%	UICCI, 1%; II, 22%; III, 20%; IV, 57%
		3D-CRT	150	18–65 years: 63%	69.0%	Oral cavity, 11%; oropharynx, 31%; nasopharynx, 3%; hypopharynx, 8%; larynx, 46%	I, 5%; II, 33%; III, 14%; IV, 47%
Kam (2007)	RCT	2D-CRT	28	50.5	68%	Nasopharyngeal carcinoma, 100%	WHO type II/III
		IMRT	28	45.5	75%	Nasopharyngeal carcinoma, 100%	WHO type II/III
Pow (2006)	RCT	IMRT	24	46	75.0%	Nasopharyngeal carcinoma, 100%	II, 100%
		CRT	21	50	81.0%		
Jabbari (2005)	Prospective case control	IMRT	30	53	76.7%	Oral tongue, 13%; base of tongue, 27%; retromolartrigone and alveolar ridge, 13%; tonsil, 17%; pyriform sinus, 10%; supraglottic larynx, 20%	III, 43%; IV, 57%
		Standard RT	10	53	70.0%	Oral tongue, 10%; base of tongue, 30%; retromolartrigone and alveolar ridge, 10%; tonsil, 10%; pyriform sinus, 10%; supraglottic larynx, 30%	III, 50%; IV, 50%

IMRT intensity-modulated radiotherapy, *RT* radiation therapy, *2D-CRT* two-dimensional conformal radiation therapy, *3D-CRT* three-dimensional conformal radiation therapy, *NA* not available

Table 2 Summary of treatment protocols of selected studies

First author (year)	Interventions	Number of patients	Protocol of radiotherapy	Chemotherapy (%)	Protocol of chemotherapy	Operation (%)
Chen (2015)	IMRT	65	PGTVnx = 68.2 Gy/31f; PGTVnd = 66.6 Gy/31f; PCTV at high risk = 62.0 Gy/31f; PCTV2 at low risk = 52.7 Gy/31f; PCTVnd = 52.7 Gy/31f.	66%	Single-agent chemotherapy with 100 mg/m^2 cis-platinum within 3 days.	NA
	Conventional RT	65	The median dose on the ICRU point of PGTV of nasopharynx was 72 Gy/36f; the dose in tumor target volume at high risk was 60–64 Gy/ 30–32f; the dose in tumor target volume at low risk was 50–54 Gy/25–27f and 2 Gy/f; conventional fractionated irradiation, 1f/d, 5f/w.	63%		
Chen (2012)	IMRT	84	The median radiation dose to the primary site was 66 Gy (range,60–74 Gy). The median doses for those treated postoperatively and definitively were 60 Gy (range, 54–66 Gy) and 70 Gy (range,66–74 Gy), respectively.	44%	NA	Neck dissection, 58%
	3D CRT	71		51%		Neck dissection, 62%
Nutting (2011)	IMRT	47	65 Gy in 30 daily fractions given Monday to Friday. 60 Gy in 30 fractions was delivered to postoperative patients unless there was macroscopic residual disease in which case 65 Gy in 30 fractions was given. Nodal groups at risk of harboring occult metastatic disease received a biologically equivalent dose of either 50 Gy in 25 daily fractions (conventional radiotherapy) or 54 Gy in 30 fractions (IMRT).	43%	Neoadjuvant	NA
	Conventional RT	47		40%)		
Vergeer (2009)	IMRT	91	In cases of primary radiotherapy with or without chemotherapy, the PTV1 was treated with 35 fractions of 1.55 Gy up to a total dose of 54.25 Gy. The total dose of 54.25 Gy was chosen to compensate for the lower dose per fraction and the longer overall treatment time; this is radiobiological equivalent to 46 Gy in 2-Gy fractions. The PTV2 was treated with 35 fractions of 2 Gy up to a total dose of 70Gy. In the postoperative setting, the dose per fraction to the PTV1 was 1.64 Gy up to a total dose of 54.12 Gy when the total dose to thePTV2 was 66 Gy. When the PTV2 was irradiated to a total dose of 56 Gy, PTV1 received 1.8 Gy fractions to a total dose of 50.4 Gy.	43%	Concomitant chemoradiation (three cycles of cisplatin 100 mg/m^2 given on days 1, 22, and 43).	Surgery of the neck, 25%
	3D-CRT	150	In the primary irradiated patients, the PTV1 was treated with 46 Gy in 2-Gy fractions. PTV2 (boost) was treated with 2 Gy per fraction up to a total dose of 70 Gy. In case of primary radiotherapy, an accelerated fractionation schedule was used using a CCB. The CCB accelerated fractionation schedule included the primary field (23 fractions of 2 Gy, five times per week) plus an extra fraction on Fridays including the boost with an interval of at least 6 h. Patients treated in the postoperative setting also received 46 Gy to PTV1 in 2-Gy daily fractions. At the primary site and nodal metastases, the total dose to the PTV2 was 56 Gy or 66 Gy, depending on surgical margin status and the presence of pathological lymph nodes with or without extranidal spread, respectively.	35%		Surgery of the neck, 9%

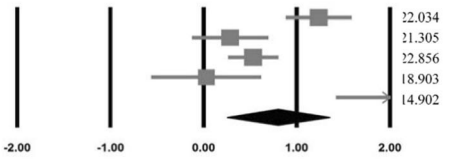
Table 2 (continued)

First author (year)	Interventions	Number of patients	Protocol of radiotherapy	Chemotherapy (%)	Protocol of chemotherapy	Operation (%)
Kam (2007)	2D-CRT	28	During first phase, the primary tumor and upper cervical lymphatics were covered by a pair of laterally opposed faciocervical photon fields, while the lower neck was covered by an anterior cervical field with a midline shield. In the second phase, a three-field setup (anterior plus right and left lateral fields) was used for the primary tumor, and an anterior cervical field for the neck. 40 Gy/20 fractions/4 weeks were prescribed in phase I, and 26 Gy/13 fractions/2.6 weeks were prescribed in phase II. Tissue heterogeneity correction was not performed because 2DRT was not computer planned.	NA	NA	NA
	IMRT	28	The tumor targets in the nasopharynx and upper neck were treatedby IMRT using seven coplanar beams, while the lower neck was treated by aseparate anterior photon field. 66 Gy/33 fractions/6.6 weeks were prescribed to the PTVg, and 60 Gy/33 fractions/6.6 weeks were prescribed to the PTVc. The anterior cervical field delivered 66 Gy/33 fractions to the node-positive region, and 54 to 60 Gy to the node-negative region. Attempts were made to spare the parotid glands, but not the other salivary glands.	NA	NA	NA
Pow (2006)	IMRT	24	The prescribed dose to GTV and GTVn was 68–72 Gy in 34 fractions over 7 weeks. The prescribed dose to the PTVwas 66–68 Gy.	NA	NA	NA
	CRT	21	Total dose to nasopharynx was 68 Gy and 66 Gy to neck. An additional parapharyngeal boost dose (10 Gy) was given with a posterior oblique field if there was initial parapharyngeal extension of disease at diagnosis.			
Jabbari (2005)	IMRT	30	NA	40%	NA	NA
	Standard RT	10		30%		

CCB concomitant boost technique, *GTV* gross tumor volume, *GTVn* gross tumor volume of metastases lymph nodes, *NA* not available, *PGTVnx* primary gross tumor volume of nasopharynx, *PGTVnd* primary gross tumor volume of neck dissection, *PCTV* primary control tumor volume, *PCTVnd* primary control tumor volume of neck dissection, *PTV* planning target volume, *PTVg* planning gross tumor volume, *PTVc* planning target volume of primary tumor, *ICRU* international standards for radiation units, *2DRT* two-dimensional radiation therapy

a Meta-analysis for global health status

Study name	SMD	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Chen (2012)	1.24	0.89	1.58	7.03	<0.001	22.034
Nutting (2011)	0.29	-0.12	0.69	1.38	0.168	21.305
Vergeer (2009)	0.53	0.27	0.80	3.95	0.000	22.856
Pow (2006)	0.03	-0.56	0.62	0.10	0.919	18.903
Jabbari (2005)	2.30	1.43	3.18	5.15	<0.001	14.902
Pooled effects	**0.80**	**0.26**	**1.35**	**2.88**	**0.004**	

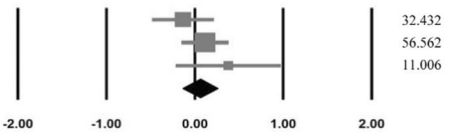


Heterogeneity test:
Q-value = 32.673, df = 4, P < 0.001, I-square = 87.76%

Favors Conventional RT Group | Favors IMRT Group

b Meta-analysis for emotion

Study name	SMD	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Chen (2015)	-0.14	-0.48	0.21	-0.77	0.440	32.432
Vergeer (2009)	0.11	-0.15	0.38	0.86	0.388	56.562
Pow (2006)	0.38	-0.21	0.97	1.26	0.209	11.006
Pooled effects	**0.06**	**-0.13**	**0.26**	**0.63**	**0.531**	

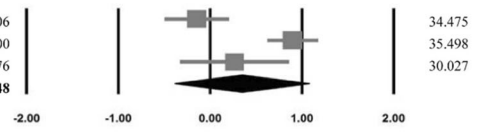


Heterogeneity test:
Q-value = 2.528, df = 2, P = 0.282, I-square =20.90%

Favors Conventional RT Group | Favors IMRT Group

c Meta-analysis for social function

Study name	SMD	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Chen (2015)	-0.15	-0.49	0.20	-0.83	0.406	34.475
Vergeer (2009)	0.90	0.63	1.17	6.46	0.000	35.498
Pow (2006)	0.27	-0.32	0.85	0.89	0.376	30.027
Pooled effects	**0.35**	**-0.38**	**1.08**	**0.94**	**0.348**	

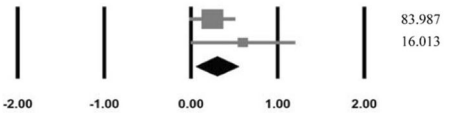


Heterogeneity test:
Q-value = 22.231, df = 2, P < 0.001, I-square = 91.00%

Favors Conventional RT Group | Favors IMRT Group

d Meta-analysis for cognitive function

Study name	SMD	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Vergeer (2009)	0.25	-0.01	0.51	1.85	0.064	83.987
Pow (2006)	0.60	0.00	1.20	1.96	0.050	16.013
Pooled effects	**0.30**	**0.06**	**0.54**	**2.48**	**0.013**	

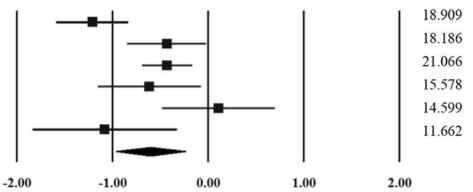


Heterogeneity test:
Q-value = 1.114, df = 1, P = 0.291, I-square = 10.24%

Favors Conventional RT Group | Favors IMRT Group

e Meta-analysis for dry mouth

Study name	SMD	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Chen (2015)	-1.21	-1.59	-0.84	-6.35	<0.001	18.909
Nutting (2011)	-0.43	-0.84	-0.02	-2.08	0.038	18.186
Vergeer (2009)	-0.43	-0.69	-0.17	-3.19	0.001	21.066
Kam (2007)	-0.62	-1.15	-0.08	-2.25	0.024	15.578
Pow (2006)	0.11	-0.48	0.70	0.36	0.716	14.599
Jabbari (2005)	-1.08	-1.84	-0.33	-2.81	0.005	11.662
Pooled effects	**-0.60**	**-0.97**	**-0.24**	**-3.28**	**0.001**	



Heterogeneity test:
Q-value = 19.721, df = 5, P = 0.001, I-square = 74.65%

Favors IMRT Group | Favors Conventional RT Group

Fig. 2 Meta-analysis for global health status, emotional function, social function, cognitive function, and dry mouth

19.721, $I^2 = 74.65\%$; $P = 0.001$); therefore, a random effects model was used. The analysis revealed that patients who received IMRT had significantly lower scores for xerostomia than those who received conventional RT (pooled SMD = − 0.60, 95% CI − 0.97 to − 0.24, $P = 0.001$).

Sensitivity analysis

Sensitivity analysis using the leave-one-out approach was performed for outcomes of global health status, emotional status, social function, and the severity of xerostomia (Table 3). However, this analysis was not performed for cognitive function because of the small number of studies reporting cognitive function ($n = 2$). In general, sensitivity analysis of each outcome revealed that the magnitude of combined estimates did not vary markedly with the removal of the studies, indicating good reliability and that the data were not overly influenced by each study. However, the analysis of social function revealed that removal of the study of Chen et al. [3] resulted in the pooled IMRT/conventional RT becoming significant (pooled SMD = 0.64, 95% CI 0.03 to 1.25, $P = 0.04$), indicating that the pooled estimates might be influenced by this individual study. In addition, sensitivity analysis of the severity of xerostomia using the leave-one-out approach revealed that the magnitude of combined estimates did not vary markedly with the removal of the studies, indicating good reliability and that the data were not overly influenced by each study.

Table 3 Sensitivity analysis

	Statistics with study removed				
Study name	Point	Lower limit	Upper limit	*Z* value	*P* value
Global health status					
Chen (2012)	0.68	0.07	1.28	2.19	0.028
Nutting (2011)	0.95	0.28	1.63	2.78	0.005
Vergeer (2009)	0.91	0.12	1.70	2.25	0.025
Pow (2006)	0.98	0.38	1.59	3.18	0.001
Jabbari (2005)	0.55	0.07	1.03	2.26	0.024
Emotion					
Chen (2015)	0.16	− 0.08	0.40	1.30	0.195
Vergeer (2009)	− 0.01	− 0.30	0.29	− 0.04	0.972
Pow (2006)	0.02	− 0.18	0.23	0.22	0.824
Social function					
Chen (2015)	0.64	0.03	1.25	2.05	0.040
Vergeer (2009)	− 0.01	− 0.39	0.37	− 0.06	0.950
Pow (2006)	0.38	− 0.64	1.40	0.73	0.465
Dry mouth					
Chen (2015)	− 0.45	− 0.71	− 0.18	− 3.30	0.001
Nutting (2011)	− 0.64	− 1.09	− 0.20	− 2.82	0.005
Vergeer (2009)	− 0.65	− 1.12	− 0.18	− 2.71	0.007
Kam (2007)	− 0.60	− 1.03	− 0.17	− 2.76	0.006
Pow (2006)	− 0.72	− 1.07	− 0.37	− 4.00	< 0.001
Jabbari (2005)	− 0.54	− 0.93	− 0.15	− 2.72	0.006

Quality assessment

Quality assessment indicated that higher percentages of biases of all included studies were at low risk for influencing the study population, measurement of prognostic factors, evaluation of outcomes, and analysis (Fig. 3a). Figure 3 b shows risk-of-bias summary, which was the quality assessment result of the individual study. Evident risk of bias for study attrition was found due to Jabbari et al. (2005) and confounding measurement and account due to Kam et al. (2007) and Chen et al. (2015). Overall, the included studies were of moderate to high quality.

Discussion

In patients with head and neck cancer, the use of IMRT or conventional RT is frequent in clinical practice, but differences in their impact on QoL and long-term sequelae may be debatable. The present meta-analysis included the most recently published data to July 1, 2019. Our focus was on the QoL of patients after treatment of head and neck cancer with either IMRT or conventional RT, so that clinicians can be more assertive in their decisions to use IMRT or conventional RT. Our findings revealed that patients in the IMRT group had significantly better global health status and cognitive function compared with patients in the conventional RT group ($P \leq 0.013$). No differences were observed in emotional and social function between the two groups. This study also revealed a significant reduction in severity of patient-reported xerostomia in patients receiving IMRT than in those receiving conventional RT ($P = 0.006$), which may also translate into an improvement in xerostomia-specific QoL in patients with IMRT.

The use of chemoradiotherapy for head and neck cancer may expose patients to potential additional neurotoxicity due to the use of cytotoxic drugs. In addition, this patient population may be at a higher risk of reduction in cognitive function as several of the factors shown to be associated with the development of head and neck cancer are also known to negatively impact cognitive function, such as smoking, excess alcohol consumption, and poor diet [18]. Results of the present study indicated that patients with IMRT had better cognitive function than those receiving conventional RT; however, the findings must be interpreted with caution since only two studies were included in this analysis.

A systematic review by Tribius et al. (2011) [8] assessed whether IMRT was associated with better QoL compared with 2D-RT and 3D-CRT. The review included 14 studies, only one of which was an RCT. Those authors found that IMRT was

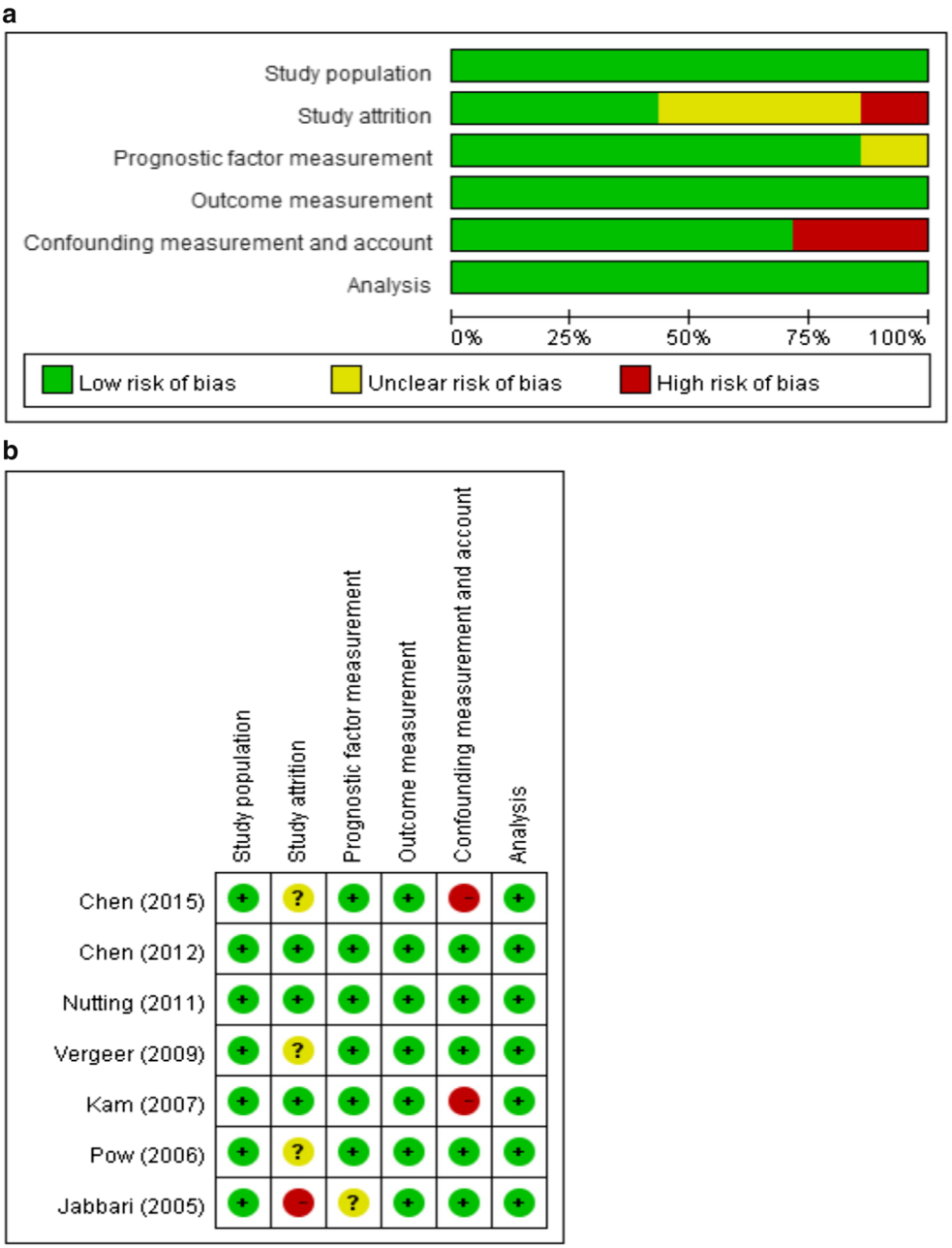


Fig. 3 Quality assessment **a** percentages of biases of all included studies and **b** risk-of-bias summary for individual studies

associated with significant improvements in some QoL domains compared with 2D-RT. This was particularly evident in domains associated with salivary function and domains related to xerostomia, such as speech, swallowing, problems with teeth, and sticky saliva. However, evidence of the benefits of IMRT compared with those of 3D-CRT were less apparent.

Three prior meta-analyses evaluated the efficacy of IMRT compared with conventional RT in treating patients with head and neck cancer [1, 19, 20]. The meta-analysis of Marta et al. (2014) [1] included five phase III RCTs with a total of 871 patients. Consistent with our findings, a significant overall benefit of IMRT was found (hazard ratio [HR], 0.76; $P < 0.0001$) for xerostomia grades 2 to 4, and this benefit was seen up to 5 years following therapy. However, no differences were found between IMRT and conventional RT in loco-regional control ($P = 0.35$) and overall survival ($P = 0.11$). Zhang et al (2015) [19] performed a meta-analysis that compared clinical outcomes and late toxicities of IMRT and conventional RT in nasopharyngeal cancer, including eight studies with 3570 patients. Those authors found that IMRT was associated with better 5-year overall survival (odds ratio [OR], 1.51; $P = 0.0001$) and tumor local control (OR, 1.94; $P < 0.0001$) than conventional RT. In addition, the incidence of late xerostomia was lower in patients who received IMRT than in those who received conventional RT (OR, 0.18; $P = 0.0004$). The frequency of radiation-induced chronic

toxicities of trismus and temporal lobe neuropathy were also significantly lower with IMRT compared with conventional RT (OR, 0.18; $P = 0.03$ for trismus; and OR, 0.44; $P = 0.0003$ for temporal lobe neuropathy). In the review and meta-analysis of Gupta et al. (2019) [20], which focused on xerostomia, the use of IMRT was associated with a 36% relative risk reduction in acute xerostomia and late xerostomia compared to all non-IMRT radiotherapies at all time points. Taken together, the findings of the present study and those of Tribius et al. [8], and the three meta-analyses of Marta et al. [1], Zhang et al. [19], and Gupta et al. [20], suggest that IMRT may have greater benefits than conventional RT with regard to specific QoL domains and xerostomia. However, future studies specifically designed and powered to test the benefits of IMRT over 2D/3D-RT in patients with head and neck cancer in regard to QoL and xerostomia would undoubtedly provide more conclusive evidence.

The present study included the most recently published data and was the first meta-analysis conducted on the QoL of patients following treatment of head and neck cancer with IMRT or conventional RT. The design of our study was very different from the previously published meta-analyses and/or systematic reviews. For example, in 2011, Tribius assessed whether IMRT was associated with QoL benefits versus 2D-RT and 3D-CRT but did not perform meta-analysis [8]. However, both Marta (2014) [1] and Zhang (2015) [19] performed meta-analyses regarding overall survival, locoregional control, and incidence of radiation-induced late toxicities but did not evaluate QoL outcomes. Meanwhile, the present meta-analysis indicated that IMRT conveyed benefits in global health status and cognitive function, and reduced the severity of xerostomia compared with conventional RT. Results for specific QoL domains such as global health status and cognitive function have not been reported previously. Therefore, results of the present study may provide additional useful information for head and neck cancer management.

We examined heterogeneity among our included studies, mainly in terms of QoL and xerostomia outcomes. Heterogeneity in health-related QoL instruments was found between Chen (2012) and Jabbari (2005), who used the UWQOL questionnaire and the HNQOL instrument, respectively; and Nutting (2011), Vergeer (2009), and Pow (2006), who all used the EORTC scale. Tumor sites included in Chen (2012), Vergeer (2009), and Jabbari (2005) were more heterogeneous than Nutting (2011) and Pow (2006). It is well known that cancers at different sites in the head and neck produce different effects on health-related QoL and such site-specific assessment may yield more meaningful and useful QoL outcomes [21, 22]. Moreover, Chen (2012), Vergeer (2009), and Jabbari (2005) were nonrandomized studies. There may be case selection bias. Sensitivity analysis indicated that Chen et al. (2012) may have overly influenced the findings for social function, possibly by using theSF-36 while other studies used the EORTC QLQ-C30. For dry mouth, heterogeneity existed between Chen (2015), who used the SF-36, and Nutting (2011), Vergeer (2009), and Pow (2006), who all used the EORTC QLQ-H&N35 subscale scores. The RCT of Kam et al. (2007) [17] used a self-reported xerostomia questionnaire combined with a 100-mm visual analog scale (VAS) as previously described [23]. The instrument recorded responses to six items: overall mouth and tongue dryness, feeling of mouth/tongue during daytime, difficulty sleeping at night, difficulty speaking without first drinking liquids, difficulty chewing and swallowing food, and difficulty wearing dentures. Jabbari (2005) used a xerostomia questionnaire with eight items, four related to patient-reported dryness while eating or chewing and four related to dryness while not eating or chewing, also described previously [24]. Clearly, if we bring together a body of studies for meta-analysis, we will find variability in the data. However, investigating these differences ultimately gives us greater understanding of the effects of a specific intervention and the influencing factors.

Our study has several limitations that should be considered when interpreting the findings. The number of included studies was small, which prevented the analysis of several other QoL domains. Heterogeneity existed across the studies for type of instrument used to evaluate QoL, type of RT, types of cancer, radiation doses, and the time frame in which endpoints were evaluated. Because of the relatively small sample sizes, we could not perform subgroup analysis of different cancer types or the specific conventional RT used. However, although some heterogeneity was noted across included studies, study design, methodology, analyses, and reporting were quite similar. QoL data were also pooled at later time-points (6–24 months) to ascertain whether the significant benefit of QoL with IMRT persisted over time. The quality of included studies was judged to be from moderately low to having an unclear risk of bias. Nevertheless, no significant publication bias was detected for any of the outcome measures in this analysis. Herein, we have reported a meta-analysis with a smaller sample size, and with so-called small-study effects and reporting bias; however, the findings in smaller studies are more likely to be selected for publication based on statistical significance. It is important to show the observed heterogeneity in effects across multiple independent trials, even some that are much smaller, as heterogeneity occurs normally in clinical practice. While it may be difficult to conclude whether our findings were relevant in terms of evidence-based learning, this study has provided the most up-to-date insight regarding the outcomes of QoL in patients with IMRT or conventional RT in head and neck cancer. Our findings regarding xerostomia were limited because studies that only reported rates of xerostomia were not included in favor of patient-reported xerostomia and its inherent contribution to reduced quality of life, our primary outcome; excluding these studies could represent bias. Also, the severity of xerostomia was self-reported by patients and did not rely upon clinical evaluation. These limitations emphasize the need for prospective, randomized studies that include homogeneous patient populations, xerostomia rates, appropriate QoL

instruments, and relevant clinical end points, as well as to measure the relative impact of different radiation doses on QoL, in order to determine the value of IMRT in head and neck cancer.

In conclusion, IMRT exhibits benefits in global health status and cognitive function, and reduces the severity of xerostomia compared with conventional RT. Results of this study provide clinicians with guidelines for making decisions on the use of IMRT versus conventional RT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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