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Xerostomia and Clinical Outcomes in Definitive Intensity Modulated Radiotherapy (IMRT) *Versus* Three-dimensional Conformal Radiotherapy (3D-CRT) for Head and Neck Squamous Cell Carcinoma: A Meta-analysis

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Abstract. *Background/Aim: Intensity modulated radiotherapy (IMRT) has been compared with three-dimensional conformal radiotherapy (3D-CRT) in randomized clinical trials for head and neck squamous cell carcinoma (HNSCC). The aim of this meta-analysis was to evaluate the efficacy and toxicity of IMRT and 3D-CRT and identify differences in grade ≥2 xerostomia incidence and clinical outcomes. Materials and Methods: The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was applied. Random-effects models were used. Primary endpoint was xerostomia of grade 2 or worse. Secondary endpoints were overall survival (OS) and loco-regional control (LRC). Results: Three randomized clinical trials representing 213 patients were identified. Global, grade ≥2 acute xerostomia and late xerostomia at 1 and 2 years after treatment were reduced with the IMRT technique (RR=0.71, 95%CI=0.59-0.86, RR=0.45, 95%CI=0.31-0.65 and RR=0.26, 95%CI=0.15-0.46, respectively). IMRT was not associated with significant OS and LRC improvement compared with 3D-CRT, with OR of 0.70 (95%CI=0.39-1.24; p=0.22) and 1.50 (95%CI=0.75-2.98; p=0.25). Conclusion: This meta-analysis explored the value of IMRT compared to 3D-CRT and confirmed the superiority of IMRT over 3D-CRT in terms of grade ≥2 xerostomia rates, but not on clinical outcomes. Its positive impact on tumor control and survival remains to be proven.*

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Radiation therapy (RT) with or without chemotherapy plays a central role in the treatment of head and neck squamous cell carcinoma (HNSCC), in both definitive and adjuvant setting (1). Intensity modulated RT (IMRT) technique is currently considered standard in RT treatment plans, mainly because of its ability to better limit the dose to adjacent organs at risk over three-dimensional conformal RT (3D-CRT). However, due to the anatomical complexity of the head and neck region, the risk of RT-induced toxicities remains significant and xerostomia still represents a frequent RT-related complication in HNSCC patients (2). However, different studies have demonstrated that IMRT reduces moderate to severe xerostomia onset compared to 3D- CRT treatment (3-9). Whereas its real benefit on clinical outcomes, including overall survival (OS) and loco-regional control (LRC) rates, is still unclear, mostly because these studies were too small to allow any definite conclusion (3-9). Therefore, a pooled analysis of their results is necessary to power IMRT efficacy on clinical outcomes in HNSCC.

The aim of this meta-analysis was to perform a systematic review of the literature, to compare RT-induced xerostomia and clinical outcomes in HNSCC patients treated with IMRT or 3D-CRT and to provide valuable evidence for future research.

Materials and Methods

Data extraction and trials selection. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was followed to perform search strategy and selection processes (10). The meta-analysis included trials without any restrictions on publication date. The last search was carried out on May 2019. Systematic literature electronic search was conducted in Pubmed, Embase and Cochrane central register of controlled trials databases, using the following research criteria: "Head and Neck Neoplasms/radiotherapy"(Mesh) AND ("xerostomia" (MeSH Terms) OR "xerostomia"(All Fields)). The

search strategy was linked with the Cochrane highly sensitive search strategy for identifying randomized trials in Pubmed (11). To be eligible, trials needed to compare IMRT and 3D-CRT in definitive HNSCC treatment. Randomized clinical trials, written in English, were included and reference lists of previously published reviews and meta-analysis were explored. Narrative or systematic review articles, retrospective studies, case series, case reports, commentaries, letters to editors and studies involving animals or *in vitro* models were not included. Meeting abstracts were not considered because of the insufficient data provided by the authors.

Two independent reviewers (NP and PP) selected the identified studies based on the title and abstract. If the topic of the study could not be ascertained from its title or abstract, the full-text version was retrieved for evaluation. Disagreement was resolved by a third party (FDF).

Trials were eligible if participants were newly diagnosed, with histologically proven squamous cell carcinoma at study entry. In closer evaluation of potentially eligible articles, when two articles appeared to report results with overlapping data, only the data representing the most recent publication were included in the meta-analysis. Extracted data were recorded into standardized database according to the following parameters: first author's surname, year of publication, sample size of IMRT group and 3D-CRT group, tumor and treatment details, duration of follow-up, xerostomia rates and clinical outcomes.

Focus question. This study attempted to address the following question: does the use of IMRT compared to 3D-CRT reduce the risk of acute and late xerostomia and improve LRC and OS in HNSCC patients?

Outcomes. The intent of the analysis was to evaluate the proportion of patients with grade ≥2 acute and late xerostomia. Late xerostomia was assessed at 12 months and 24 months after treatment. We also planned to analyze OS and LRC. Xerostomia was graded using the radiation therapy oncology group and the European organization for research and treatment of cancer (RTOG/EORTC) +/– the late effects of normal tissues subjective-objective management analytic (LENT SOMA) (12). The definition of both OS and LRC was similar across trials. OS and LRC were defined as time from the date of randomization to the defined event using Kaplan–Meier method. The number of events (side effect, death and recurrence), when available, were derived from each study. At least one of these three outcomes should have been assessed and reported in the trial to be included in the present analysis.

Statistical analysis. The grading of recommendations assessment, development and evaluation (GRADE) system was used to rate quality of evidence and grade the strength of recommendations for all included studies (13). Statistical analysis was performed using Review Manager 5.0 (14). The pooled odds ratio (OR) and risk ratio (RR) were calculated using a fixed- or random-effects model. Forest plots were used for graphical representation of each study and pooled analysis. The size of each box represents the weight that the corresponding study exerts in the meta-analysis; confidence intervals (CIs) for each study are displayed as a horizontal line through the box. The pooled OR and RR are symbolized by a solid diamond at the bottom of the forest plot, and the width of the square represents the 95%CI of the OR and RR. OR, RR and 95%CI, for each study were extracted or calculated, based on the published studies, according to the methods described by Tierney *et al*. in 2007 (15). A significant two-way *p*-value for comparison was defined as $p<0.05$. Statistical heterogeneity among studies was examined using both the Cochrane Q statistic (significant at $p<0.1$) and the I^2 value (significant heterogeneity if >50%) (16).

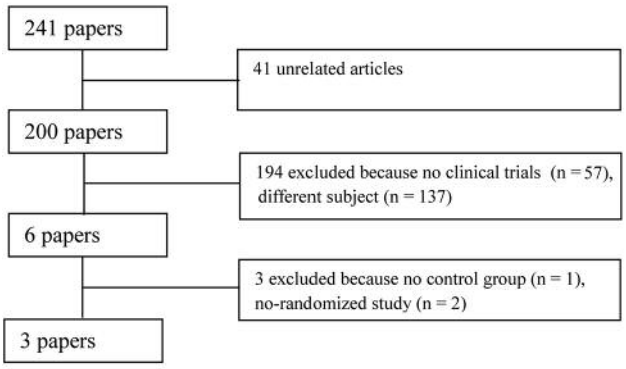

Figure 1. *Flow chart*.

Results

Studies' characteristics. Flowchart of the retrieved studies and their main characteristics are presented in Figure 1 and Table I. Overall, 3 randomized clinical trials, representing 213 patients were included in the final analysis (5, 8-9). Studies included only patients with oral cavity (n=3), oropharynx (n=137), hypopharynx (n=0) and larynx (n=23) cancer, except T1N0 glottic larynx. Patients were randomly assigned to 3D-CRT (n=104) *versus* IMRT (n=109). Except for 23 adjuvant treatments [in Nutting *et al*. trial (5)], all patients received definitive chemoradiotherapy.

Xerostomia. Grade ≥2 toxicity analysis mainly demonstrated a benefit in favor of IMRT. The risk of acute (RR=0.71, 95%CI=0.59-0.86), 1-year (RR=0.45, 95%CI=0.31-0.65) and 2-year (RR=0.26, 95%CI=0.15-0.46) xerostomia was consistently and significantly reduced with the IMRT technique. Details are presented in Figure 2. Quality of evidence and strength of recommendation is summarized in Table II.

Survival outcomes. Compared to 3D-CRT, IMRT was not associated with a significant reduction in the risk of death (OR=0.70, 95%CI=0.39-1.24; $p=0.22$). There was no significant difference in LRC between IMRT and 3D-RT (OR=1.50, 95%CI=0.75-2.98; $p=0.25$). The χ^2 tests for heterogeneity of both comparisons showed no significant heterogeneity. Details are shown in Figure 3. The quality of evidence and strength of recommendations for survival outcomes are presented in Table II.

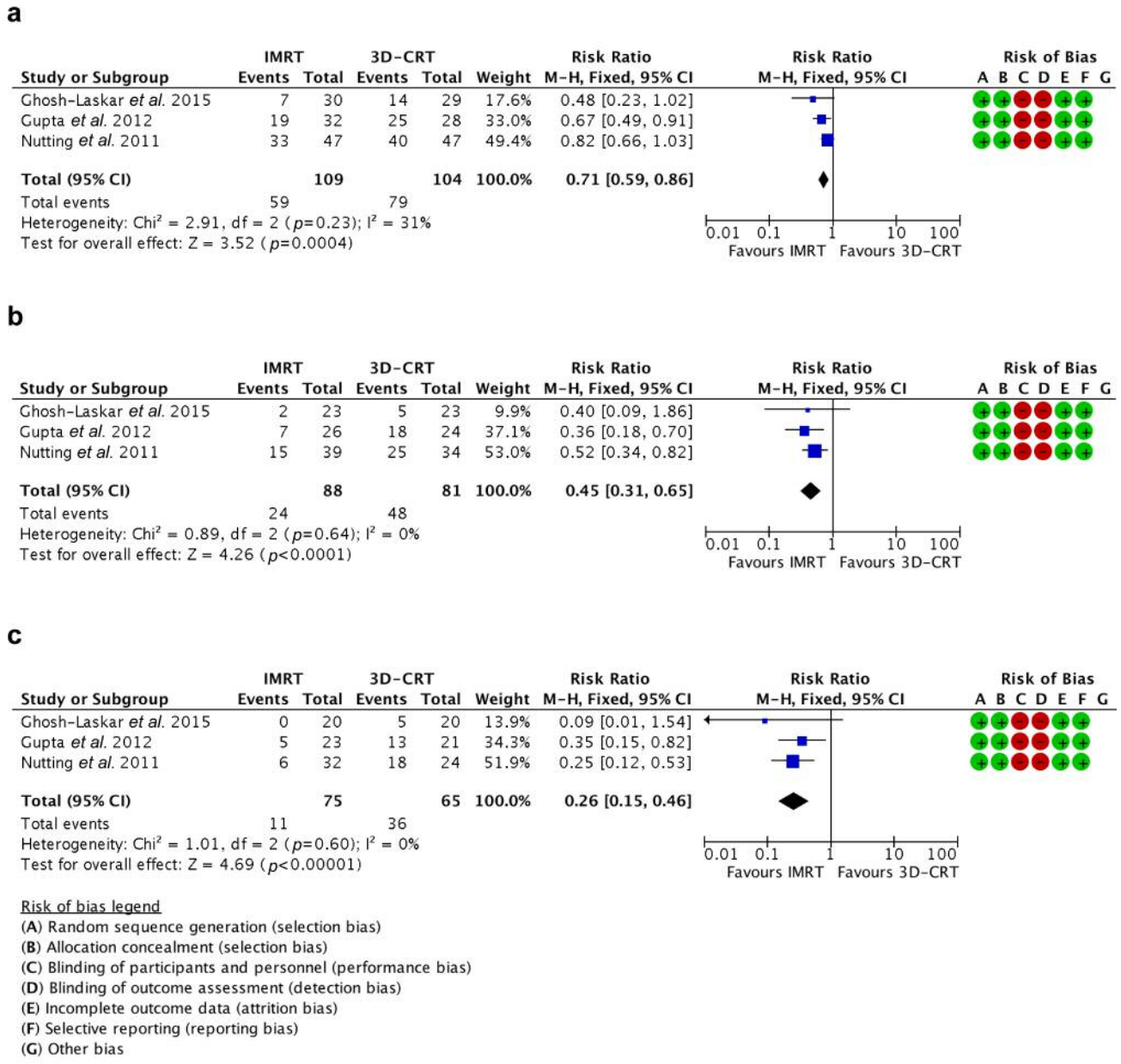

Figure 2. *Forest plot of acute (a), 1-year (b) and 2-year (c) xerostomia profile.*

Discussion

Our results indicated that for HNSCC patients IMRT was superior to 3D-CRT in the xerostomia-related toxicity profile, while showed no benefit on OS and LRC rates. Data were statistically homogeneous and results were robust. IMRT was associated with decreased grade ≥2 acute xerostomia and there was a significant difference in late xerostomia between 3D-CRT and IMRT at 1-year and 2-years after treatment. Although the direct comparison between IMRT and 3D-CRT did not show the superiority of IMRT regarding clinical outcomes, there was a slight increase in local recurrence events in the IMRT group. This higher proportion of events was small but it may have important implications for RT treatment planning. In fact, despite significant progress in the RT technique, the risk of loco-regional failure remains a challenge, mainly related to radio-resistant tumor areas and/or geographic miss (17). In order to improve accuracy in target definition to guarantee good outcomes in terms both of cure and toxicity, fusion of

Table I. *Details of the included studies.*

Author	ID_study	Population	Patients			Median FU	Primary end point	Comments
			Total	IMRT	3D-CRT			
Ghoshlaskar_2015 (8)	NCT652613	T1-3 N0-2b oral cavity, oropharynx, larynx* or hypopharynx	59	29	30	70 months	Xerostomia G≥2	Toxicity was graded using the RTOG scoring system
Gupta_2012 (9)	CTRI/2008/ 091/000045	T1-T3 N0-2b oropharynx, larynx* or hypopharynx	60	28	32	40 months	Xerostomia G≥2	Toxicity was assessed based on the RTOG scoring system
Nutting_2011 (5)	ISRCTN48243537	T1-4 N0-3 oropharynx or hypopharynx	94	47	47	44 months	Xerostomia G≥2	Acute side-effects were graded with NCICT. Late RT side-effects were assessed with LENT SOMA and RTOG scoring systems

*Except T1N0 glottic larynx. ID: Identifier; IMRT: intensity modulated radiotherapy; 3D-CRT: three dimensional conformal radiotherapy; FU: follow-up; NCT: number clinical trial; G: grade; RTOG: Radiation Therapy Oncology Group; CTRI: Clinical Trials Registry-India; ISRCTN: International Standard Randomized Controlled Trial; NCICT: National Cancer Institute Common Toxicity Criteria; LENT SOMA: Late Effects of Normal Tissues Subjective-Objective Management Analytic.

functional imaging examination at the contouring stage should be standardized (18).

To minimize indirectness, we restricted the analysis only to those trials that excluded nasopharynx cancer population. This can be explained clinically by nasopharyngeal cancer specific etiology, histology and natural history. It is not surprising that results on survival were not completely in agreement with the previous meta-analysis (4). Both LRC (HR=0.76, 95%CI=0.57-1.01) and OS (HR=0.70, 95%CI=0.57-0.88) benefits of IMRT compared to non-IMRT techniques were clearly driven by the nasopharyngeal series. Authors performed subgroup analysis stratified by primary tumor site and these results were comparable to our findings. There was no significant difference in LRC (HR=1.06, 95%CI=0.71-1.58) and OS (HR=0.85, 95%CI=0.63-1.15; p=0.29) between IMRT and non-IMRT (4). Also, xerostomia outcomes were not very different compared to our results, reporting a consistent IMRT benefit in salivary function over conventional techniques (4).

Despite the lower incidence, xerostomia remains a major clinical problem in the IMRT era and parotid-sparing is the recommended method to its prevention (5). But, the importance of the other salivary glands, including both mayor – submandibular and sublingual – and minor – upper/lower lip, buccal mucosa, postero-lateral hard palate, Von Ebner and Weber Blandin Nuhn – glands in quantity, quality and consistency of saliva production should be highlighted (19). In contrast to parotid glands, data on anatomic and dosimetric changes of the other salivary glands are scarce. In general, the mucinous component is more radio-resistant than serous cells and thus a higher threshold dose is expected for submandibular and minor salivary glands than parotid glands. Reducing submandibular glands mean dose to 39 Gy resulted in gradually improved flow rates and patient-reported dry mouth symptoms, but it was associated to modest rise in the mean doses to surrounding structures, including parotid glands and swallowing structures (20). Probably, to maximize therapeutic gain, radiation dose should be optimized not only to parotids but to all salivary glands. Both major and minor salivary glands-sparing should be the key to preserve salivary function but this benefit could be achieved at the cost of disease control, resulting in increased risk of marginal failures. The best balance between tumor target coverage and salivary glands-sparing approach requires further clinical investigation before any definitive conclusion can be reached. This meta-analysis did not attempt to evaluate the other potential xerostomia-related complications, such as late radiation-associated dysphagia (RAD) and osteoradionecrosis (ORN). Data were not suitable for a cumulative analysis. Obviously late RAD and ORN are also influenced by the direct irradiation of the swallowing apparatus and segments of mandible, respectively. Due to its ballistic characteristics, IMRT exposed large volume of these normal structures to higher doses than previous less conformal treatment, resulting in the highest risk of their damage (21). To reduce this detrimental RT effect, over the years, specific dose-volume parameters have been proposed in addition to the standard maximum dose constraints (22-23). But, at present, these specific constraints have been definitively