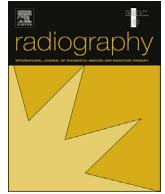




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Review article

Reduction of xerostomia in head and neck cancer patients. A critical review of the literature

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ABSTRACT

Background: Radical radiotherapy given with or without concurrent chemotherapy is the main treatment modality in non-surgical patients for the management of squamous cell carcinoma in the head and neck. Xerostomia, which results from reduced salivary production is a debilitating side-effect of radiation therapy to these patients. Xerostomia may greatly impact on quality of life for head and neck cancer patients for up to 24 months post-radiation therapy. Such effects include difficulties in fundamental daily activities such as speech, mastication and swallowing. It is believed that modulated techniques provide better sparing to surrounding salivary glands. The aim of this critical review of the literature is to investigate what advantage intensity modulated radiotherapy (IMRT) can provide over 3 dimensional conformal radiation therapy (3DCRT) in reducing xerostomia in this subset of patients.

Search methodology: An extensive literature search was undertaken to compare the incidence of grade 2 or worse xerostomia in HNSCC patients treated with IMRT or 3DCRT (\pm chemotherapy).

Results: Studies reported a lower incidence of grade 2 or worse xerostomia with IMRT over patients treated with 3DCRT. The highest incidence of xerostomia was reported at 6 months following the completion of radiotherapy treatment. The incidence of xerostomia in patients declined with time, in both patients treated with IMRT and those of the 3DCRT cohort. The incidence of xerostomia was greater in the acute setting than in the late.

Conclusion: An IMRT technique can consistently reduce grade 2 or worse xerostomia in head and neck cancer patients over conformal techniques. This will not compromise dose homogeneity or dose coverage. IMRT should remain the standard of care for head and neck patients.

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Introduction

Xerostomia is a debilitating side-effect of head and neck radiation therapy treatment. It is recognised by a reduction to <25% of initial pre-treatment volume of saliva.^{1,2} Weakened salivary flow rate causes functional impairment and patient discomfort requiring the patient to modify their daily activities. These can include the inability to articulate correctly, due to a dry mouth as well as an inability to chew and swallow food. These, coupled with oral hygiene and halitosis issues also caused by a dry mouth, may also impact on the patient's social functioning. The reduction in saliva predisposes the patient to infection,³ composition change in oral flora,⁴ periodontal disease³ or caries⁵ and osteoradionecrosis.⁶ It highly disturbs the patient's ability to speak and swallow as the

patient is deprived of saliva, an oral mucosal lubricant. Xerostomia may cause psychosocial distress^{7,8} to the patient, inhibiting social eating and speaking.

Literature review

A number of studies have measured the incidence of xerostomia caused by conventional and more recently, by modulated radiotherapy techniques.^{1,2} This review will determine the evidence based optimum technique to reduce xerostomia in both the acute and late settings in patients presenting with head and neck squamous cell carcinoma (HNSCC).

In these studies, IMRT has been shown to offer potential dosimetric improvement in sparing organs at risk while delivering high doses to the target volume. This technique enables a more conformal treatment delivery providing a further tailored treatment delivery to the target volume. In HNSCC patients, many critical structures are in close proximity to the gross disease, making

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IMRT and its improved sparing to surrounding organs more appealing. Chemo-radiotherapy is a common treatment modality for HNSCC patients. The ability to spare normal tissue through optimal techniques may compensate for some of the added toxicity of the chemotherapy regimen.⁹

Materials and methods

Search strategy for identification of studies

An electronic search was carried out on the following databases; Science Direct, Embase, Google Scholar, Pubmed and the Cochrane library. Search terms used were a combination of: head and neck squamous cell carcinoma, intensity modulated radiotherapy, xerostomia, three dimensional conformal radiotherapy, conventional radiotherapy.

Further articles cited in these studies were screened to ensure no relevant article was overlooked. These articles were screened and included if the material was relevant to the topic of the review. From this list of studies, the number of included studies was narrowed down by selecting those that were available in the English language, did not contain exclusion criteria (see 'Types of Participants'), contained the relevant intervention of interest and were accessible.

Type of studies

Prospective and retrospective studies, including randomised controlled trials and meta-analyses were acceptable for this critical review of the literature. Studies examining the cost-effectiveness of reducing xerostomia were excluded as they did not provide dosimetric data. Articles that were inaccessible in full yet abstract was available were considered, where the corresponding author could be contacted for the full paper.

Type of participants

For this review inclusion criteria for participants consisted of patients with histologically proven HNSCC. These patients were of any age. Patients must have been undergoing curative radiotherapy with or without concurrent chemotherapy. Post-operative patients and those receiving radiotherapy for a parotid tumour were excluded as were patients with previous underlying salivary dysfunction. Patients who received previous radiotherapy to the head and neck or those with recurrent disease were excluded.

Type of interventions

A comparison was performed between IMRT and 3DCRT. Studies on 2D-RT versus IMRT and IMRT in single arm studies were also reviewed to extract information on IMRT techniques only. In many instances, 7-field IMRT was used as the beam arrangement in the IMRT technique. Other field arrangements for such a technique included a 9 field arrangement or, less commonly, 5 field. In several studies, the number of fields in the IMRT plan was unspecified. VMAT techniques included both single arc and double arcs. Xerostomia experienced in patients in the IMRT cohort was measured against those in the 3DCRT cohort in these comparative studies. There were insufficient data on volumetric modulated arc therapy in these patients to include in this review.

Type of outcomes

Outcomes measured in the included studies were grade 2 or worse xerostomia at time intervals of between 3 and 24 months or

salivary toxicity. Included studies documented these outcomes at one time interval between 3 and 24 months, at a minimum.

Results

Study description

This electronic search yielded 107 studies, 13 of which were relevant based on inclusion and exclusion criteria. Seven studies compared three dimensional radiotherapy (3DCRT) with IMRT in terms of xerostomia however, one study⁹ used a 2 dimensional radiotherapy (2DRT) technique with a 3D conformal boost. Two of these studies were randomised controlled trials (RCTs).^{10,11} Data on IMRT patients were extracted from 2 studies comparing 2DRT versus IMRT, one of these studies also being a RCT.⁷ The data on 2DRT from these studies were not taken into consideration. Four studies consisted of IMRT patients alone, without comparing it with another radiotherapy technique.

Participants

Out of the included studies, 1396 participants were treated with 3DCRT or IMRT. The data of 55 patients who received 2DRT were excluded.

Risk of bias

As various toxicity scoring systems were used in the cited studies, this may have introduced reporting bias as results were reported in a variety of ways such as xerostomia experienced, parotid gland dose or salivary gland dysfunction.

The search identified a Phase III RCT which included post-operative patients, which was an exclusion criterion. Even though 23 patients were post-operative, this study remained included as it was a Phase III RCT.

Statistical analysis

The sample sizes of all studies were available. Standard deviations and p values were reported in several trials, yet not all. Details on statistical analyses of each study are given in [Table 1](#). Patients lost to follow up were documented in the majority of studies reviewed.

Xerostomia measurement

The measures for scoring xerostomia used in the included studies are given in [Table 1](#). Common Terminology Criteria for Adverse Effects (CTCAE) version 3 was used in 7 of the reported studies.^{3,9,11,13–16} This scoring system recognises adverse effects which may be attributable to treatment.¹² CTCAE reports side-effects in the acute and late setting but primarily in the former. Grade 2 effects are moderate, with possible interventions such as medication required.¹² Grade 3 effects are considered severe, indicating possible treatment disruption.¹²

Another toxicity scoring system used for scoring late effects in 4 studies was the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer system (RTOG/EORTC).^{14,17–19} EORTC QLQ-H&N35 questionnaires assess symptoms of head and neck cancer patients and were reported in 7 studies.^{6,7,14,17,18,20,21}

Together, the EORTC and RTOG devised a scoring system called Late Effects for Normal Tissue, Subjective, Objective, Management and Analytic scales (LENT SOMA) and this was the tool used in 2 studies.^{10,11} The benefit of LENT SOMA, a subjective measurement²²

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