

Intensity Modulated Radiation Therapy (IMRT) in the Treatment of Squamous Carcinoma of the Oropharynx: An Overview

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Abstract

Background: Intensity Modulated Radiotherapy (IMRT) is being used increasingly for the radical treatment of oropharyngeal cancers. We have reviewed the evidence and summarised the data to enable readers to decide whether the dosimetric advantages of IMRT have been translated into clinical benefit in oropharyngeal cancer treatment.

Methods: We searched Medline and the Cochrane library for published studies investigating the role of IMRT in reducing rates of xerostomia, osteoradionecrosis and difficulties with swallowing.

Results: Despite heterogeneity in the assessment of xerostomia following radiotherapy, 20 out of the 22 studies reported lower xerostomia rates following parotid-sparing IMRT. There is only limited information on the consequences of sparing dose to the submandibular gland and emerging clinical information on the benefits of reducing dose to the pharyngeal constrictor muscles. Rates of osteoradionecrosis are lower with IMRT.

Conclusion: Rates of xerostomia are lower with IMRT than with conventional radiotherapy techniques. Prospective evaluation of IMRT techniques to assess whether lower doses to the submandibular glands and constrictor muscles are associated with clinical benefit is essential. Although there appear to be lower rates of osteonecrosis with IMRT, pre treatment evaluation of dental status and maintenance of dental hygiene remain important.

Keywords: Oropharynx; IMRT; Clinical Benefits

Introduction

Intensity modulated radiotherapy (IMRT) is a technique which offers the possibility of delivering a relatively high dose of radiotherapy to a Planning Target Volume (PTV) whilst sparing the dose to Organs At Risk (OAR) [1,2]. This technique is particularly applicable to tumours, such as those of the oropharynx, which are often of advanced clinical stage by the time they are diagnosed [3]. IMRT may improve the therapeutic index for such tumours by causing less morbidity for any given probability of tumour control. Xerostomia, dysphagia and aspiration are important late effects of radiation therapy to the oropharynx that have significant functional, quality of life and resource implications after treatment. IMRT, by excluding the muscles of mastication and the pharyngeal constrictors from the high-dose volume, might lower both the incidence and severity of radiation-induced damage to the swallowing mechanism [4].

Osteoradionecrosis is a potentially catastrophic complication of radical radiotherapy to the head and neck [5]. The use of IMRT should, potentially at least, enable the radiation dose to the mandible to be decreased and thereby lower the incidence of osteoradionecrosis.

The aim of this review of the published literature was to estimate if the dosimetric advantages of IMRT over conventional radiotherapy techniques have been translated into clinical benefit. We have assessed the benefits that have been achieved by IMRT and suggest how we might use data collected prospectively on patients treated with IMRT to improve outcomes for patients with cancer of the oropharynx.

Materials and Methods

In August 2011, we searched for published articles in peer reviewed journals using two search engines: Pubmed - (Medline - The

National Library of Medicine) and the Cochrane library. The specified search criteria included: "Oropharynx and IMRT", "Oropharyngeal carcinoma and IMRT" and "IMRT and Head and Neck". Online electronic databases were searched to identify papers published in English from January

2001 to August 2011. Papers were selected for inclusion in this review based on original studies on patients treated with IMRT for oropharyngeal cancer with data reported for the following endpoints:

- Xerostomia
- Parotid-sparing IMRT
- Submandibular gland sparing IMRT
- Dysphagia, and other swallowing disorders
- Osteoradionecrosis

The available evidence for each morbidity was reviewed separately. We used the system for grading the quality of evidence that was used in the Scottish Intercollegiate Guidelines Network (SIGN) guidelines [6], "Diagnosis and Management of Head and Neck cancer". In summary, a

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meta-analysis, Randomised Controlled Trials (RCT) or systemic review of RCTs were assigned an evidence level of 1, case control or cohort studies and their systematic review was assigned evidence level of 2 whilst case series, case reports or expert opinions were considered as level 3 evidence. In some of the reviewed evidence only questionnaires were used to evaluate xerostomia post RT, these studies were included as level 4 evidence.

Results

Effect of IMRT on xerostomia

Effect of IMRT on salivary morbidity: Parotid Gland Sparing IMRT: We identified 22 studies [7-29] which reported the clinical effects of parotid-sparing techniques using IMRT for oropharyngeal cancer (Table 1). These studies had reported one or more measures

Study	Treatment Period (year from- to)	Dose/ delivery of IMRT	IMRT/ non IMRT: No of Patients		Primary in oropharynx IMRT/non IMRT		Type of Study	Parotid functional Imaging done?	Salivary output measurements?	Questionnaire based or rated xerostomia evaluation?	Salivary function benefit with parotid sparing?
Nutting et al. [7]	2003-2007	60-65 Gy in 30 fr, Linac	47	47	40	40	Randomized control trial	No	No	Yes	Yes
van Rij et al. [8]	1999-2003	≥ 60 Gy/ Linear Accelerator (Linac) based	75	87	37	45	Retrospective case-control	No	No	Yes	Yes
Rudat et al. [9]	2000-2005	≥ 50 Gy/ Linac based	31	69	26	13	Prospective Cohort study	Yes	No	Yes	Yes
Dijkema et al. [10]	1996-2007	≥ 66 Gy Linac based	64	157	48	28	Prospective Cohort study	No	Yes (cup)	No	No
Ortholan et al. [11]	2001-2004	> 50 Gy Linac based	24	20	*	35*	Prospective Cohort study	No	Yes (parafilm chewing)	No	Yes
Chao et al. [12]	1970-1999	55.1-72 Gy Segmental Tomotherapy	26	404	26	404	Prospective cohort for patients after 1996 ^u	No	No	Yes	Yes
Daly et al. [13]	2000-2005	60-66 Gy Linac	29 [†]	75	**	**	Retrospective case control	No	No	Yes	Yes
Saarihahti et al. [14]	2000-2002	56-72 Gy Linac	17	0	11	0	Prospective Cohort study	No	Yes (paraffin wax chewing)	Yes	Yes
Parliamen et al. [15]	2000-2002	60-70 Gy Linac	23	0	3	0	Prospective Cohort study	No	Yes (spitting)	Yes	Yes
Marzi et al. [16]	2003*	60-70 Gy	59	0	9	0	Prospective Cohort study	No	Yes (spitting)	Yes	Yes
Eisbruch et al. [17]	1994- 2000	56-70 Gy Linac	132±	0	56	0	Prospective Cohort study	No	Yes (cup)	Yes	Yes
Hodge et al. [18]	1995-2005	65.1- 70.4 Gy Linac	52	143	52	143	Retrospective case control	No	No	Yes	No
Lee et al. [19]	1998-2004	70-72 Gy Linac	41	71	41	71	Retrospective case control	No	No	Yes	Yes
Rusthoven et al. [20]	1998-2007	66-70 Gy Linac	32	55	32	55	Retrospective case control	No	No	Yes	Yes
Vergeer et al. [21]	1999- 2004	56-70 Gy	91	150	34	46	Prospective Cohort study	No	No	Yes	Yes
Huang et al. [22]	2000- 2004	70 Gy Linac	71	0	71	0	Audit	No	No	Yes	Yes
Anand et al. [23]	2003-2004	66-70 Gy Linac	19	0	7	0	Prospective Cohort study	Yes	No	Yes	Yes
Lee et al. [24]	2003- 2004	60- 64.8 Gy Linac	34	0	5	0	Prospective Cohort study	No	Yes (spitting)	Yes	Yes
Pacholke et al. [25]	1996-2002	> 50 Gy Linac	27	183	24	78	Retrospective case control	No	No	Yes	Yes
Setton et al. [26]	1998-2009	66-70 Gy by conventional fr, linac	442	0	442	0	Prospective Cohort study	No	No	Yes	Yes
Dirix et al. [27]	2006-2008	72 Gy by Linac	42	0	12	0	Prospective Cohort study	No	No	No	Yes
Stock et al. [28]	2007-2009	66-70 Gy by conventional fr, linac	46	0	46	0	Prospective Cohort study	No	Yes	No	Yes

* break down of IMRT and non IMRT for oropharynx, not available.

[†] Total 69 patients with IMRT given questionnaire, 29 responded.

** Breakdown by site not available.

± Patients had parotid sparing IMRT or conformal parotid sparing techniques.

^u Data was collected retrospectively for patients treated before 1996. IMRT patients recruited only after 1996.

* Date of last recruited patient not given.

Table 1: Studies reporting on parotid salivary gland sparing.

of xerostomia as a clinical endpoint. These measures included: functional imaging of gland activity; measurements of salivary output; observer-assessed toxicity grading; patient-reported evaluation using questionnaires. If a series was reported more than once we used the data from the most recently published account. Most of these studies described patients with primary tumours arising from various sites within the head and neck. Twenty of the twenty two level 2 studies found a clinical benefit from IMRT in reducing the rates of xerostomia and preserving salivary function. The studies reported had significant difference in patient numbers, age, sex, radiation dose prescribed to PTV, duration of follow up and in the assessment criteria for xerostomia. The only Randomised control trial, the PARSPORT trial [7] published in 2011 showed a significant reduction of radiation induced xerostomia for patients treated with IMRT compared with conventional radiotherapy by use of both LENT SOMA and RTOG scales. Furthermore, it was shown recovery of saliva flow by quantitative measurements and improvements in QoL were associated with IMRT treatment. To our knowledge this trial is the first to show that parotid-sparing IMRT reduces xerostomia in oropharyngeal HNSCC. As compared to others Dirix et al. [27], treated 42 patients with Stage IV head-and-neck squamous cell carcinoma with a unique hybrid fractionation schedule between 2006 and 2008 in two phases comprising of 20 fractions of 2 Gy (once daily), followed by 20 fractions of 1.6 Gy (twice daily), to a total dose of 72 Gy.

Clinical benefits of submandibular gland (SMG) sparing IMRT:

We identified two studies (Table 2) reporting clinical outcomes in patients treated with SMG sparing IMRT [29,30]. Both studies reported xerostomia score benefits with submandibular sparing techniques. In the study by Murdoch-Kinch et al. [30] saliva flow rates were assessed in 124 patients’ pre-radiotherapy but at 2 years follow up data was available for only 46 patients.

Effect on swallowing of sparing dose to muscles involved in swallowing and mastication

Eight studies [27,31-37], summarised in Table 3, have assessed swallowing after IMRT for patients with tumours of the oropharynx. The studies used questionnaires with or without video-fluoroscopy to assess the swallowing dysfunction. Seven of the eight reported studies showed improvement in dysphagia scores with IMRT treatment. In the study by Levendag et al. [34] 43 patients received brachytherapy boost (20-22 Gy) after external beam radiotherapy treatment to 46 Gy (IMRT or conformal). Patients receiving brachytherapy boost had a smaller physical dose of radiation to a smaller volume of superior and middle constrictor muscles.

Osteoradionecrosis (ORN)

Osteoradionecrosis of the jaw remains one of the most problematic consequences of radiotherapy in head and neck cancer where the treatment is often complicated and multimodal. New theories

Study	Treatment Period (Year from-to)	Total number of patients	No. of patients with Oropharyngeal Primary	Benefit with xerostomia scores?	SIGN Evidence Level
Saarilahti et al. [29]	2000-2004	18	14	Yes	3
Murdoch-Kinch et al. [30]	1995-2005	148*	Not specified	Yes	2

* Only 124 patients had pre RT saliva flow rate measurement, 46 had measurements at 2 years follow up.

Table 2: Studies reporting on submandibular salivary gland sparing IMRT.

Study	Treatment Period (Year from- to)	IMRT/ non IMRT: No of Patients		Primary in oro pharynx IMRT/ non IMRT patients		Constrictors outlined as OAR?	Decreased dose to constrictors with IMRT vs. CRT?	% with RTOG Grade 2 or above dysphagia	Video-fluoroscopy to assess dysphagia	Questionnaire based or rated dysphagia evaluation?	Swallowing function benefit with constrictors sparing?	SIGN Evidence Level
		IMRT	non IMRT	IMRT	non IMRT							
Dirix et al. [27]	2006-2008	42	55	12	34	Yes	Yes	<5%	No	No	No	2
Anand et al. [31]	2002-2004	62	0	10	0	Yes (only 4 patients for comparison)	Yes*	12.7% at 6 months	No	Yes	Yes	3
Bhide et al. [32]	2006-2007	37	0	7	0	Yes	N/A	6.67% at 1 year	No	Yes	No	2
Feng et al. [33]	2003-2008	73	0	73	0	Yes	N/A	<6% at 1 year	Yes	Yes	Yes	2
Levendag et al. [34]	2000-2005	35	46	35	46	Yes	N/A **	23% at 3 years ***	No	Yes	Yes	2
Schwartz et al. [35]	2008-2009	31	0	31	0	Yes	Yes	Yes	No	Yes	2
Caudell et al. [36]	2001-2006	83	0	44	0	Yes	Yes	14.2% at 2 Years	Yes	Yes	Yes	2
Peponi et al. [37]	2002-2005	82	0	55	0	Yes	Yes	18% at 20 months	No	Yes	Yes	2

* Comparison done between IMRT plans with representative conformal radiotherapy plans (4 patients). More than 50% of the volume of “dysphagia related structures” received a lower mean radiation dose in the IMRT plans.

** Patients receiving brachytherapy boost received lower dose to the constrictors and a smaller volume of their constrictors was irradiated.

*** Patients were treated with IMRT or 3 dimensional conformal radiotherapy (3dCRT) up to 46 Gy followed by brachytherapy boost. If ineligible for brachytherapy, patients had surgery and post operative IMRT or 3dCRT.

Table 3: Studies reporting on dysphagia scores with IMRT.

on its pathophysiology have promoted more frequent use of new treatment modalities including the use of IMRT. We identified nine studies [3,22,38-45] which had included patients with oropharyngeal carcinoma treated with IMRT and which had reported the incidence of osteoradionecrosis. Table 4 shows a summary of the results. All the reported studies have shown a lower rate of osteoradionecrosis with IMRT.

Discussion

Radical radiotherapy, particularly when combined with synchronous chemotherapy (chemoradiation) offers acceptable local control rates for oropharyngeal carcinoma with tolerable long-term toxicity [46,47] and is a reasonable alternative to radical surgery for many patients. Nevertheless, radiotherapy does cause damage to important structures and can lead to problems with dry mouth, swallowing and aspiration, and mandibular damage. IMRT, by reducing the dose to the critical normal tissues, whilst maintaining a high dose to the tumour, offers the potential for improving the therapeutic ratio in the radiation therapy of oropharyngeal carcinoma - maintained (or even improved) control of tumour and, at the same time, a decrease in the probability and severity of radiation-induced toxicity [48].

We have systematically reviewed the available evidence to assess whether or not the theoretical promise of IMRT for this group of tumours is borne out by the clinical reality.

Only the reported studies had published data in sufficient detail for inclusion in this analysis. This amounts to less than 10% of all centres worldwide using IMRT to treat cancers of the oropharynx. This implies that reporting may be selective, and raises the question of publication bias.

Does IMRT improve xerostomia?

Permanent xerostomia is one of the commonest late side effects of head and neck radiotherapy [48]. Over the last two decades, radiotherapy treatment techniques have been investigated to explore the possibility of reducing xerostomia. The bulk of the evidence seen in this study suggests improved preservation of salivary function preservation with IMRT. The evidence for this until recently was at best Grade B but, with full publication of the results of the PARSPORT trial [7] the evidence for reducing xerostomia with IMRT can now be regarded as Grade A.

Twenty of the 22 studies (Table 1) found a clinical benefit from IMRT in reducing the rates of xerostomia and preserving salivary function. The studies reported had significant difference in patient numbers, age, sex, and dose prescribed to PTV, duration of follow up and in the assessment criteria for xerostomia. The majority of the studies used questionnaires to assess the patients' clinical condition. Only 2 studies [9,23] used parotid functional imaging, but failed to show any strong correlation between imaging scores and salivary flow rates. Although 8 studies included salivary flow rate measurement as a means to show preservation of salivary function, there were differences between the methods used to measure the saliva flow. The lack of standardised measurement techniques means that it is not possible to make meaningful comparisons between these studies.

Two studies have reported no benefit in xerostomia with the use of IMRT. In the study by Dijkema et al. [10] there was a significant difference in the primary tumour "site" being treated, between patients groups receiving Conformal Radiotherapy (CRT) versus IMRT. The IMRT group had more patients with oropharyngeal primary (18% vs 75% respectively). The proximity of the high dose PTV to the parotid glands, in oropharyngeal cancers could be one of the reasons why the IMRT group had higher mean dose delivered to the parotids compared to the CRT group. The second negative study is a comparison [18] of treatment outcomes in patients treated in the "pre IMRT" era versus "IMRT era". The "IMRT era" patients could have had IMRT or CRT. The reasons for the lack of benefit on parotid gland function from IMRT are not discussed. PARSPORT trial, the only Randomised control trial looking at parotid sparing IMRT in oropharyngeal cancers, [7] showed a significant reduction of radiation induced xerostomia for patients treated with IMRT compared with conventional radiotherapy by use of both LENT SOMA and RTOG scales. Furthermore, it was shown recovery of saliva flow by quantitative measurements, and QoL measures were associated with the use of IMRT. To our knowledge this trial is the first Level 1 evidence confirming the reduction in xerostomia following IMRT in oropharyngeal HNSCC.

The totality of the evidence suggests improved preservation of salivary function preservation with IMRT. The evidence for this does reach Grade A. Submandibular gland sparing techniques using either surgery or IMRT [29,30,49-51] have emerged over the last few years, but prospective randomised controlled studies are needed to explore the benefits of submandibular gland sparing IMRT. Moreover submandibular gland sparing techniques may be more specialised than parotid sparing, requiring either transposition of submandibular

Arruda et al. [3]	1998- 2004	70 Gy	50	50	18	0	0	Yes	3
Huang et al. [22]	2000-2004	70 Gy	71	71	33	1**	1.4%	Yes	3
Ben-david et al. [38]	1996-2005	56-65 Gy	176	120	26	0*	0	Yes	3
Studer et al. [39,40]	2002- 2007	65-72 Gy	204	146	20.1	1	<1%	Yes	3
Eisbruch et al. [41]	2001- 2005	66 Gy	67	67	32	3	6%	Yes	2
Garden et al. [42]	2000- 2002	63-66 Gy	51	51	45	1	1.96%	Yes	3
Gomez et al. [43]	2000-2007	70 Gy	168	41	37.4	2	1.1%	Yes	2
Sher et al. [44]	2004-2009	70 Gy	42	42	25	1	2.3%	Yes	2
Montejo et al. [45]	2003-2008	67.5 Gy	43	43	36.7	1	2.3%	Yes	2

*Common Terminology Criteria for Adverse Events, version 3.0.

**RTOG criteria.

***2.2 Gy per fraction.

¶ 2 of 3 ORN patients had 69 Gy and 70 Gy at the point of ORN, mean mandibular dose was <45 Gy.

Table 4: Studies reporting on osteoradionecrosis following IMRT.

glands or selecting patients where the contralateral submandibular gland can be spared [29,49]. The evidence that sparing submandibular dose with IMRT might improve salivary function is Grade D.

Does IMRT improve swallow wing muscle function and reduce risk of trismus?

After Eisbruch et al. [4] described the “dysphagia and aspiration related- DARS” structures in 2004, Feng and Lavendag et al. [33,34] have prospectively evaluated the long term benefits of limiting the dose to these - putatively critical – structures and shown benefit with this technique. These two studies have opened up a new concept in improving swallowing function with IMRT. However, the retrospective evaluation by Bhide et al. [32] from the Royal Marsden Hospital in London failed to demonstrate any relationship between radiation dose to the constrictors and swallowing function. These differing findings could be a result of small patient numbers, the retrospective nature of these studies, and the use of differing outcome measures across the studies. It is also possible that the absolute amount of sparing of dose to these structures with IMRT is insufficient to translate into detectable improvements in function.

If this controversy is to be resolved, further prospective studies with large sample sizes and robust multidimensional outcome measures will need to be performed. The outcome measures must be analysed with respect to detailed dose volume histograms and dose distribution maps for the structures involved in swallowing. We need to know more than simply the mean dose to some arbitrary point within the constrictor complex. The evidence to support the contention that swallowing difficulties after IMRT will be less than those after conventional XRT for oropharyngeal cancer is Grade C.

Does IMRT reduce the risk of osteoradionecrosis (ORN)?

Radiotherapy for oropharyngeal cancers is associated with high doses to the retromolar trigone area, the mandibular ramus and the molar region [52]. Irradiated bone becomes hypocellular, hypoxic and therefore more prone to ORN [53]. It is well recognised that dental examination before treatment together with close multi-disciplinary team working with the local restorative dentist and dental hygienist will significantly reduce the risk of ORN [31]. The studies [3,22,39-45] that have evaluated the reduction of ORN with IMRT in oropharyngeal cancer treatment have reported an extremely low rate of ORN with IMRT. However, the RTOG -0022 [35] study has reported a 6% ORN rate. This appears to be higher than the other IMRT studies. The reasons cited include lack of standardised dental evaluation and the use of (relatively) hypofractionated regimes (2.2 Gy per fraction). The argument that 2.2 Gy per fraction may be the contributor to such an increase in the ORN rate may be less robust given that other studies [3,22,43] have used more than 2 Gy per fraction and have reported less ORN with IMRT. In summary, there are multiple reports from single centres flow rates of ORN with IMRT.

The evidence that rates of ORN are lower with IMRT than they are with conventional XRT is Grade C.

Conclusions

This review of the literature on the treatment of cancer of the oropharynx with radiotherapy suggests that the use of IMRT, as opposed to conventional radiotherapy planning techniques, is associated with decreases in the rates of xerostomia, of problems with swallowing and aspiration, and of osteoradionecrosis. Apart from xerostomia,

the published evidence on these questions is of disappointingly low quality, there is a pressing need for well-designed prospective studies which might permit accurate assessment of the clinical, as opposed to the dosimetric, benefits arising from the use of IMRT. Moreover heterogeneity of assessment methods used for assessing the benefits of IMRT have made it difficult to assess consistency of the possible benefits across the reported patient population.

Despite the widespread adoption of IMRT for treating cancers of the head and neck, there is remarkably little evidence available on the key functional outcomes that have a significant impact on the quality of life. This reflects a recurring problem for technologically driven specialties such as radiotherapy. IMRT is resource intensive [54] and newer technology using rotational arc therapy [55] has claimed to have further dosimetric advantages compared to linear accelerator based IMRT. This reflects a recurring problem for technologically driven specialties such as radiotherapy. This is the assumption that, because something ought to be beneficial, it must be beneficial, and the consequent perception that there is no real need to go out to seek evidence that the theoretical advantages are detectable clinically.

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