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REVIEW ARTICLE

Clinical evaluation of intensity-modulated radiotherapy for head and neck cancers

[1]S A BHIDE, PhD, FRCR, [1]K L NEWBOLD, MRCP, FRCR, [2]K J HARRINGTON, PhD, FRCR and [2]C M NUTTING, MD, FRCR

[1]*Head and Neck Unit, Royal Marsden Hospital, Downs Road, Sutton, Surrey, UK, and* [2]*Head and Neck Unit, Royal Marsden Hospital, Fulham Road, London, UK*

ABSTRACT. Radiotherapy and surgery are the principal curative modalities in treatment of head and neck cancer. Conventional two-dimensional and three-dimensional conformal radiotherapy result in significant side effects and altered quality of life. Intensity-modulated radiotherapy (IMRT) can spare the normal tissues, while delivering a curative dose to the tumour-bearing tissues. This article reviews the current role of IMRT in head and neck cancer from the point of view of normal tissue sparing, and also reviews the current published literature by individual head and neck cancer subsites. In addition, we briefly discuss the role of image guidance in head and neck IMRT, and future directions in this area.

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Radiotherapy (RT) is an extremely effective treatment for head and neck cancer, both as a primary modality and as an adjuvant treatment following surgery. RT causes significant acute (during and up to 3 months post radiation) and late toxicities when used at doses required to sterilise the locoregional disease (radical doses). The acute toxicities of RT include mucositis, dysphagia, xerostomia, dermatitis and pain. Radiation-induced mucositis of the upper aerodigestive tract results in significant morbidity and altered quality of life (QOL) during RT [1]. The late radiation-induced toxicities include xerostomia [2] (60–90% incidence), grade 3 dysphagia [2, 3] (15–30%), osteoradionecrosis (ORN) of the jaws [4] (5–15%), sensorineural hearing loss [5] (40–60%), skin fibrosis and laryngeal cartilage necrosis. The late radiation toxicity is permanent and results in reduced QOL for the patient (particularly xerostomia and dysphagia) [6].

Intensity-modulated radiotherapy (IMRT) is an advanced approach to three-dimensional (3D) treatment planning and conformal therapy. It optimises the delivery of irradiation to irregularly shaped volumes and has the ability to produce concavities in radiation treatment volumes. For head and neck cancer, the clinical target volume 1 (CTV1), which includes the primary tumour and the involved nodes, typically receives a higher radiation dose than CTV2. The different doses to CTV1 and 2 can be delivered simultaneously, while sparing the parotid salivary glands and the spinal cord. In the head and neck region, IMRT has a number of potential advantages: (i) it allows for greater sparing of normal structures such as salivary glands, oesophagus, optic nerves, brain stem and spinal cord [7, 8]; (ii) it allows treatment to be delivered in a single treatment phase without the requirement for matching additional fields to provide tumour boosts, and eliminates the need for electron fields to the posterior (levels II and V) neck nodes; and (iii) it offers the possibility of simultaneously delivering higher radiation doses to regions of gross disease and lower doses to areas of microscopic disease—the so-called simultaneous integrated boost (SIB) IMRT [9].

IMRT can be delivered using linear accelerators with static multileaf collimators (MLCs; step and shoot IMRT) or dynamic leaf MLCs, tomotherapy machines or volumetric modulated arc therapy (VMAT). Tomotherapy enables the simultaneous use of image guidance and treatment delivery [10]. However, adaptive RT based on image guidance is yet to be clinically optimised in head and neck cancer. VMAT is a newer technique of delivering IMRT. VMAT delivers IMRT-like distributions in a single rotation of the gantry, varying the gantry speed and dose rate during delivery, in contrast to standard IMRT, which uses fixed gantry beams. Planning studies using RT demonstrate shorter planning and treatment time, fewer monitor units for treatment delivery and better dose homogeneity and normal tissue sparing [11, 12]. There is a lack of data as regards clinical implementation of this technique.

IMRT was first described in 1999; in the last decade numerous retrospective case series (single and multi-institution) and a few randomised trials have been published studying the clinical implementation of this technique. Here we review the current clinical evidence for the use of IMRT in head and neck cancer.

Address correspondence to: Dr Chris Nutting, Department of Radiotherapy, Royal Marsden Hospital, 203 Fulham Road, London SW3 6JJ, UK. E-mail: chris.nutting@rmh.nhs.uk

The role of intensity-modulated radiotherapy in head and neck cancer

Parotid sparing

IMRT was first used to spare salivary gland tissue in head and neck cancer patients in Phase I/II studies performed at the University of Michigan [8, 13]. IMRT reduced the radiation dose to the contralateral parotid gland to 32% compared with 93% for the standard plans. Follow-up of these patients showed that spared parotid glands received a mean dose of 19.9 Gy and recovered 63% of their pre-treatment stimulated salivary flow rates at 1 year. This compared with only a 3% recovery for treated parotid glands, which received 57.5 Gy. A mean dose threshold for reduction in salivary output to less than 25% of the baseline was found for both stimulated (26 Gy) and unstimulated (24 Gy) saliva flow rates. Subsequent studies from other institutions have established similar threshold doses [7, 14, 15]. Local control and disease-specific survival were equivalent to patients treated with conventional treatment [16–21].

The multicentre study (PARSPORT) that compared parotid sparing IMRT with standard RT in patients with oropharyngeal and hypopharyngeal cancer showed a significant reduction (40 *vs* 74%) in the rate of grade 2 xerostomia (LENT-SOMA scale) in the IMRT arm at 1 year post-radiotherapy without affecting treatment outcomes [22]. Two Phase III randomised controlled trials, investigating parotid gland sparing using IMRT for patients with nasopharyngeal cancer, showed similar results [23, 24].

Initial studies have focused on the prevention of xerostomia and included patients with a mixture of head and neck cancer subsites [7, 25]. Single-centre experiences with various head and neck subsites have been reported and have demonstrated non-inferior disease-related outcomes with a reduced incidence of xerostomia.

Prevention of late dysphagia

Late radiation damage to the structures involved in swallowing leads to dysphagia and dependence on assisted feeding. Several studies using chemoradiation or altered radiation fractionation strategies have reported rates of 12–50% significant late dysphagia (*i.e.* feeding tube dependency at 1 year that significantly affects the patient's QOL) [26–31]. Studies have reported that late dysphagia following treatment for head and neck cancer is dependent on the dose to the pharyngeal constrictors (PCs), particularly the superior constrictor [32–35]. IMRT has the potential to prevent radiation-induced dysphagia by limiting the dose to the constrictors. Feng et al [33] recently reported on a prospective study of the constrictor-sparing approach using IMRT in patients with oropharyngeal cancer. The authors minimised the dose to the PCs by not treating the medial retropharyngeal nodes. Patients with posterior pharyngeal wall and retropharyngeal node involvement were excluded. At a median follow-up of 36 months, the treatment outcomes were equivalent to historical controls. The patient reported that QOL parameters improved post treatment. However, the late feeding-tube rates in patients were similar to historical controls and there was no improvement in objective videofluoroscopy measures at 24 months.

The constrictors lie in close proximity to the parapharyngeal spaces and cervical lymph node areas. Therefore, constrictor sparing could result in a geographical miss. In addition, a study has demonstrated that the swallowing-related QOL at 1 year post-treatment (slightly accelerated RT with concomitant cisplatin) does not correlate to the dose to the PCs [36]. Long-term data on locoregional recurrence are required before the constrictor-sparing approach can be used in standard practice.

Oropharyngeal carcinoma

The critical structures when treating oropharyngeal cancers are the parotid salivary glands and the mandible. The role of IMRT in sparing the parotid glands has been described above. Radiation doses in excess of 60 Gy cause damage to the mandible and result in osteoradionecrosis [37]. The incidence of severe osteoradionecrosis after treatment to oropharyngeal cancer is 5–15%, depending on the dose to the mandible and factors such as dental hygiene [4, 38]. Studies have demonstrated that the dose to the mandible can be minimised without affecting the dose to the target volumes [38, 39]. Table 1 summarises the published reports of IMRT in oropharyngeal cancer. These studies demonstrate excellent locoregional control and overall survival rates. The rates of xerostomia and osteoradionecrosis of the mandible are lower than the historical controls. The normal tissue sparing, however, has not resulted in marginal failure (geographical miss). In the study by Sanguineti et al [40], the 4% failure outside the high-dose region was due to involved lymph nodes not being identified on the pre-treatment diagnostic imaging and hence being included in the low-dose volume.

Laryngeal and hypopharyngeal cancer

Concurrent chemoradiation is now the standard of care as an organ-sparing approach in the treatment of Stage III and IV squamous cell carcinomas of the larynx and the hypopharynx [41–43]. The overall survival at 5 years for Stage III and IV laryngeal cancers using the most aggressive chemoradiation approaches is only 50–60%. Escalation of radiation dose may improve outcomes in this group of patients, taking advantage of the steep dose–response relationships for squamous cell carcinomas. The initial results from a Phase I dose-escalation study using IMRT in patients with squamous cell carcinoma of the larynx/hypopharynx have recently been reported [44]. The patients were initially treated with a standard dose equivalent of 63 Gy in 28 fractions (2.25 Gy fraction^{-1}). Subsequently the dose was escalated to 67.2 Gy in 28 fractions (2.4 Gy fraction^{-1}). Acute radiation toxicity was comparable to standard RT and recovered over time. After 2 years of follow-up, only 5% of the patients had Grade 2 xerostomia and 5% had Grade 3 dysphagia (feeding tube dependency). The 2-year disease-specific survival was 64% and 78% for the standard and escalated dose patients, respectively. There was no other significant late toxicity of note.

Table 1. The various published single-institution reports of outcomes and toxicity using intensity-modulated radiotherapy for radiation delivery in oropharyngeal cancers

Author	Patients, *n*	Stage	CRT	LRC	OS	Incidence >Grade 2 xerostomia	Incidence ORN	POF
Huang et al [80]	71	III–IV	100%	94% (3 years)	83% (3 years)	33%	1%	All HD
De Arruda et al [81]	50	I–IV	86%	98% (2 years)	98% (2 years)	33%	0%	All HD
Lee et al [18]	41	III–IV	100%	92% (2 years)	91% (2 years)	12%	0%	All HD
Chao et al [82]	74	I–IV	22%	87% (4 years)	87% (4 years)	12%	0%	All HD
Garden et al [83]	51	I–IV	9%	93% (2 years)	93% (2 years)	NR	2%	All HD
Eisbruch et al [84]	69	I–III	0%	91% (2 years)	96% (2 years)	16%	6%	All HD
Sanguineti et al [40]	50	III–IV	0%	94% (3 years)	NR	NR	NR	96% in HD

CRT, concomitant radiotherapy; HD, high-dose region; LRC, locoregional control; NR, not reported; ORN, osteoradionecrosis of the mandible; OS, overall survival; POF, pattern of failure.

Although the patient numbers are small and the follow-up short, the results are encouraging and justify further investigation [45].

There are three retrospective single-centre experiences using IMRT for laryngeal and hypopharyngeal cancer reported in the literature, and these are summarised in Table 2.

Nasopharyngeal cancer

CTVs for tumours of the nasopharynx lie in close proximity to the optic nerves, optic chiasm, orbit, pituitary gland and brain stem. In addition, the parotid glands and the cochlea receive a significant radiation dose. Radical treatment of nasopharyngeal cancers frequently requires treatment of multiple cervical lymph node areas, which entails radiation delivery using large field portals, treatment field matching and use of electrons to keep the spinal cord dose below 48 Gy. Radiation delivery using the SIB-IMRT technique enables delivery of a single-phase treatment while sparing the organs at risk (OARs). Two Phase III randomised controlled trials investigating parotid gland sparing using IMRT for patients with nasopharyngeal cancer have been reported in the literature [23, 24]. Kam et al [23] randomised 60 patients between IMRT and conventional RT. The primary end point of observer-assessed xerostomia score was significantly better for the IMRT group, as were the secondary end points of parotid and whole salivary flow rates. However, there was no statistically significant difference in the patient-reported xerostomia score [23]. Pow et al [24] randomised 51 patients to receive either IMRT or conventional RT. 83% of patients in the IMRT group had recovered parotid salivary flow *vs* 9.5% in the conventional group at 1 year. The global QOL was significantly better in the IMRT group *vs* the conventional group [24]. These findings of improved QOL were confirmed in a longitudinal non-randomised study comparing IMRT with conventional RT [46]. Reports of single-institution retrospective studies reporting on outcomes and xerostomia rates have been summarised in Table 3.

Paranasal sinus tumours

Tumours of the nasal cavity and the paranasal sinuses lie in close proximity to vital structures like the optic nerves, the orbit, optic chiasm, pituitary gland and brain stem. IMRT enables delivery of adequate doses to these tumours while minimising the dose to these OARs [47]. Combs et al [48] and Daly et al [49] have reported on the outcomes and toxicity with IMRT as the primary treatment for this site. There were no incidences of Grade 3 late radiation toxicities affecting the OARs in either of the studies. The local control rates were 62% at 2 years in the study by Daly et al [48] and 81% at 3 years in the study by Combs et al [49]. The overall survival rates were 45% (5 years) and 80% (3 years), respectively. Two studies have been reported using IMRT for post-operative radiotherapy for the tumours of paranasal sinuses [50, 51]. There were no reported Grade 3 late radiation toxicities with satisfactory tumour control rates.

Parotid tumours

Radiation to the post-operative (after parotidectomy for malignant parotid tumours) parotid bed results in damage to the cochlea as it lies within the high-dose volume. This results in sensorineural hearing loss, especially at higher frequencies. The literature review suggests a significant effect of RT on auditory apparatus, especially hearing (incidence 40–60%) [5, 52]. The sensorineural hearing loss that results after RT is permanent. Sensorineural hearing loss has been shown to result in significant cognitive impairment, depression and reduction in functional status [53]. Planning studies indicate that the dose to the cochlea can be reduced with the use

Table 2. The various published single-institution reports of outcomes and toxicity using intensity-modulated radiotherapy for radiation delivery in laryngeal/hypopharyngeal cancers

Author	Patients, *n*	Stage	CRT	LRC (2 years)	OS (2 years)	Grade 3 dysphagia
Studer et al [85]	29	III–IV	86%	90%	90%	20 % (1 year)
Lee et al [86]	31	III–IV	100%	84%	63%	46 % (2 year)
Studer et al [87]	123	I–IV	86%	77%	83%	6% (1 year)

CRT, concomitant radiotherapy; LRC, locoregional control (excluding laryngectomy); OS, overall survival.

Table 3. The various published single institution reports of outcomes and toxicity using intensity-modulated radiotherapy for radiation delivery in nasopharyngeal cancers

Author	Patients, *n*	Stage	CRT	LRC	OS	Incidence >grade 2 xerostomia (late)
Sultanem et al [19]	35	I–IV	91%	100% (4 years)	94% (4 years)	0%
Lee et al [88]	67	I–IV	74%	98% (4 years)	88% (4 years)	0.3%
Kam et al [89]	63	I–IV	30%	92% (3 years)	90% (3 years)	23%
Wolden et al [90]	74	I–IV	93%	91% (3 years)	83% (3 years)	32%
Lai et al [91]	512	I–IV	82%	93% (5 years)	76% (5 years)	NR
Han et al [92]	305	I–IV	85%	98% (3 years)	89% (3 years)	7%
Lin S [93]	323	II–IV	90%	98% (3 years)	90% (3 years)	8%

CRT, concomitant radiotherapy; LRC, locoregional control; NR, not reported; OS, overall survival.

of IMRT [54]. This might reduce the incidence of sensorineural hearing loss. IMRT needs to be evaluated in the setting of a randomised controlled trial comparing it against standard 3D-conformal RT with sensorineural deafness as the primary end point. A Phase III study of cochlear-sparing IMRT is now open and recruiting (COchlear Sparing Therapy And conventional Radiation; COSTAR).

Thyroid cancer

For patients with thyroid cancer considered at high risk of locoregional recurrence after thyroidectomy, external beam RT is used, sometimes in addition to radio-iodine. With current RT techniques, 32% do not obtain a complete response (CR), and of those obtaining a CR 39% relapse within the radiation portals, especially in the thyroid bed. Techniques that enable safe dose escalation to the thyroid bed and/or nodal areas may be able to improve local control. Planning studies have shown that the maximal spinal cord dose can be reduced, so that the dose to the thyroid bed can be escalated above the standard dose of 60 Gy, and possibly to doses of 65–68 Gy. Moreover, the coverage of the thyroid and node target volume is also significantly improved with IMRT [55]. Preliminary results on acute toxicity from a study using IMRT for dose escalation in patients with thyroid cancer requiring external beam therapy have recently been reported [56]. The results on late toxicity and disease outcomes from this study are awaited. Schwartz et al [57] performed a retrospective review of 131 patients treated with external beam RT for thyroid cancer, of whom 57 had IMRT. The use of IMRT reduced the late treatment-related morbidity but not outcomes [57].

Squamous cell carcinoma with unknown primary

Typically, patients with squamous cell carcinoma with unknown primary (SCCUP) are treated with ipsilateral modified radical neck dissection and post-operative RT or chemoradiotherapy. There is a lack of consensus on the RT target volumes that should be treated after neck dissection. The most common RT techniques are either unilateral cervical lymph node irradiation to achieve local control in the ipsilateral neck, or total mucosal irradiation (TMI) of the head and neck region with the aim of eradicating the primary and the microscopic neck disease. Treatment of the ipsilateral hemi-neck alone is of low toxicity and may achieve local control in the cervical nodes. Some groups recommend bilateral neck and TMI in this setting, claiming improved local control [58, 59]. With conventional RT technique, this is at the price of significant acute toxicity and chronic morbidity (mainly xerostomia with its associated complications [6, 60, 61] and effects on QOL [13, 62]).

In a planning study, Bhide et al [63] showed that, using SIB-IMRT technique for TMI, 60 Gy in 30 Gy fractions or equivalent to the post-operative bed and 50 Gy in 25 Gy fractions or equivalent (*i.e.* 54 Gy in 30 Gy fractions) to the contralateral neck and the mucosal axis could be delivered in a single phase. The dose to the contralateral parotid gland was less than 26 Gy and the dose to other OARs was within tolerance [63]. Three centres have reported their experience of using IMRT to deliver TMI for SCCUP [64–66]. The 2-year locoregional control and overall survival were 85–88% and 74–85%, respectively. The TMI was well tolerated. The results are summarised in Table 4.

Intensity-modulated radiotherapy and image guidance

Target volume delineation

The sharp dose gradients required for optimum target sparing during IMRT necessitate accurate delineation of targets. CT scans are the standard imaging modality used in radiation treatment planning as they provide a

Table 4. The various published single-institution reports of outcomes and toxicity using intensity-modulated radiotherapy for total mucosal irradiation in squamous cell carcinoma with unknown primary

Author	Patients, *n*	RT alone	Surgery and RT	Chemoradiation therapy	LRC (2 years)	OS (2 years)	Acute Grade 3 mucositis
Klem [64]	21	5	16	14	85%	85%	14%
Madani [66]	23	4	19	3	NR	75%	50%
Lu [65]	18	6	12	6	88%	74%	NR

LRC, locoregional control rate; NR, not reported; OS, overall survival; RT, radiotherapy.

3D view of the tumours and normal anatomy, along with the electron density data which enables dose calculations. However, CT scans are inferior to MRI scans in providing detailed definition of soft tissues (microscopic tumour extension) and tissue planes, and can be affected by artefact-like dental amalgam and hip arthroses. CT–MRI fusion should be considered for RT planning wherever possible, especially when delineating gross tumour volume (GTV), particularly in central nervous system and skull base tumours. Initial studies using 18-F fludeoxyglucose-positron emission tomography (FDG-PET), which highlights the proliferating areas of the tumour, have been reported [67] and have shown that FDG-PET can aid delineation of the GTV [68–73]. Detailed clinical and radiological assessment of the tumours should be undertaken to ensure that the entire microscopic disease is encompassed in the high-dose CTV1. The selection and delineation of lymph node areas in N+ and N0 neck should be based on the international consensus guidelines [16, 74]. The choice of the dose delivered to nodal areas should be based on the primary site and evidence from patterns of recurrences after surgical treatment and pathological assessment of neck dissection specimens.

Image guidance for treatment verification

Verification is a vital cog in the radiation treatment delivery cycle, especially with IMRT where the sharp dose gradients increase the likelihood of a geographical miss. Verification is undertaken both before treatment starts and regularly during treatment, and ensures that underdosing to the tumour and overdosing to the OARs is avoided by minimising the systematic and random errors. In addition to the conventional two-dimensional verification using portal imaging, modern devices also enable 3D volumetric verification (using kilovoltage cone beam CT) and *in vivo* dosimetry.

Future directions

IMRT has become the standard of care for delivery of RT for head and neck cancer. The role of IMRT in salivary gland sparing is well established. IMRT can be optimised further, making use of advances in the imaging techniques (*i.e.* image-guided RT). Radiation dose escalation (taking advantage of the slope of the dose–response curves) could improve the outcomes in advanced head and neck cancers. Clinical trials that attempted to further intensify RT using hyperfractionation and/or acceleration have had to close prematurely or have the radiation schedule modified owing to excessive acute toxicity [75, 76]. Selective dose escalation based on the biological activity of tumours might improve the outcomes without increasing the normal tissue toxicity. PET enables biological imaging of tumours. Initial studies using FDG-PET, which highlights the proliferating areas of the tumour, have been reported [67]. These have shown that FDG-PET guided dose escalation using IMRT is feasible. Hypoxic regions of tumours are radioresistant and increasing the radiation dose might help overcome the radioresistance. PET scanning using two radioactive tracers—namely F-18-labelled fluoromisonidazole and copper (II)-diacetyl-bis[N(4)-methylthiosemicarbazone]—have been shown to highlight the hypoxic areas of tumours. Preliminary studies escalating the radiation dose to the hypoxic areas have demonstrated the feasibility of this approach in terms of acute toxicity [77, 78]. The PET images could be fused with the planning CT scans, and these could be used for biological dose optimisation (as opposed to the currently used dose–volume histogram-based optimisation) during inverse planning IMRT. However, follow-up data for outcomes and toxicity from larger studies using PET-guided dose escalation are required before this approach can be used in standard clinical practice.

Conclusions

The role of IMRT in salivary gland sparing is well established. The role of IMRT for constrictor sparing is less well established. The future of head and neck RT lies in optimally using IMRT for biologically based individualised patient treatment in order to maximise the therapeutic ratio. However, IMRT uses two to three times more monitor units, which results in increased total body dose due to increased radiation leakage. Optimal organ sparing using IMRT necessitates the use of more treatment fields, which results in larger volume of normal tissue exposed to a lower radiation dose. These factors increase the risk of radiation-induced malignancies twofold compared with 3D concomitant radiotherapy [79]. Therefore, IMRT is not recommended in situations where it fails to offer significant advantages while delivering radical RT. This includes target volumes that can be covered using a wedge pair technique (ipsilateral oropharynx, oral cavity) or treating small target volumes, such as for T_1 tumours of the larynx.

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