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Intensity Modulated Radiotherapy (IMRT) In Head And Neck Cancers – An Overview

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Abstract

Radiotherapy (RT) is effective in head and neck cancers. Following RT, dryness and dysphagia are the 2 major sequelae which alter the quality of life (QOL) significantly in these patients. There is randomized evidence that Intensity Modulated Radiotherapy (IMRT) effectively spares the parotid glands. IMRT has been attempted in all head and neck sub-sites with encouraging results (discussed below). Role of IMRT in swallowing structure (constrictor muscles) sparing is less clear. Further improvement in results may be possible by using functional imaging at the time of RT planning and by image guidance/verification at the time of treatment delivery. The following text discusses these issues in detail.

Keywords

Head and neck cancer, IMRT

Introduction

Radiotherapy is an extremely effective treatment for head and neck cancers, both as a primary modality and as an adjuvant treatment following surgery. RT causes significant acute (during and up to three months post-radiation) and late toxicities when used at doses required to sterilize the loco-regional disease (radical doses). The acute toxicities of RT include mucositis, dysphagia, xerostomia, dermatitis and pain. Radiation-induced mucositis of the upper aero-digestive tract results in significant morbidity and reduced QOL during radiotherapy. The late radiation induced toxicities include xerostomia (60-90% incidence), grade 3 dysphagia (15-30%\(^{(1)}\)), osteoradionecrosis (ORN) of the jaws (5-15%)\(^{(2)}\), sensori-neural hearing loss (40-60%)\(^{(3)}\), skin fibrosis and laryngeal cartilage necrosis. The late radiation toxicity is permanent and results in reduced QOL for the patient; xerostomia and dysphagia in particular\(^{(1)}\).

IMRT is an advanced approach to 3-D treatment planning and conformal therapy. It optimizes the delivery of irradiation to irregularly-shaped volumes and has the ability to produce concavities in radiation treatment volumes. Typically for head and neck cancer the Clinical target volume 1 (CTV1), which includes the primary tumour and the involved nodes receives a higher radiation dose as compared to the clinical target volume 2 (CTV2). CTV2 includes nodal regions likely to be involved. 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 \(^{(4)}\); (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 (level II, V) neck nodes; (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 \(^{(5)}\).

IMRT can be delivered using linear accelerators with static multi-leaf collimators (MLC, step and shoot IMRT) or dynamic leaf MLCs, tomotherapy machines or volumetric arc modulated therapy (VMAT). Tomotherapy technique enables the simultaneous use of image guidance and treatment delivery. However,
adaptive RT based on image guidance is yet to be clinically optimized in head and neck cancer. VMAT is a newer technique of delivering IMRT. It 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 VMAT/RapidArc™ (RA) demonstrate shorter planning and treatment time, lesser monitor units for treatment delivery, better dose homogeneity and normal tissue sparing(6). There is a lack of data as regards to clinical implementation of this technique.

IMRT was first described in 1997. In the last decade, numerous retrospective case series (single and multi-institution) and 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.

The role of IMRT 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 (UM)(4). Unstimulated and stimulated salivary flow was measured from each parotid gland before and after radiotherapy and then at three, six, and twelve months. IMRT reduced the radiation dose to the contra-lateral parotid gland to 32% compared to 93% for the standard plans. Follow up of these patients showed that spared parotid glands received a mean dose of 19.9Gy and recovered 63% of their pre-treatment stimulated salivary flow rates at one year. This compared to only a 3% recovery for treated parotid glands, which received 57.5Gy. A mean dose threshold for reduction in salivary output to less than 25% of the baseline was found for both stimulated (26Gy), and unstimulated (24Gy) saliva flow rates. Subsequent studies from other institutions have established similar threshold doses(7). Local control and disease specific survival were equivalent to patients treated with conventional treatment (8,9).

The multi-centre study (PARSPORT) that compared parotid sparing IMRT with standard radiotherapy in patients with oropharyngeal and hypopharyngeal cancer showed a significant reduction (40% vs. 74%) in rate of grade 2 xerostomia (LENT-SOMA) in the IMRT arm at one year post-radiotherapy (10). Two phase III randomised controlled trials, investigating parotid gland sparing using IMRT for patients with nasopharyngeal cancer showed similar results(11,12).

The initial studies focused on the prevention of xerostomia and included patients with a mixture of head and neck cancer sub-sites (4). Single centre experiences with various head and neck sub-sites have been reported and have demonstrated non-inferior disease related outcomes with reduced incidence of xerostomia(13).

Prevention of late dysphagia

Late radiation damage to the structures involved in swallowing leads to dysphagia and dependence on assisted feeding. Several studies using chemo-radiation (CRT) or altered radiation fractionation strategies have reported rates of 12-50% significant late dysphagia i.e. feeding tube dependency at 1 year which significantly affects the patient’s quality of life (QOL) (14,15). Studies have reported that late dysphagia following treatment for head and neck cancer is dependent on the dose to the pharyngeal constrictors (PC), particularly the superior constrictor(16-18). IMRT has the potential to prevent radiation-induced dysphagia by limiting the dose to the constrictors(19, 20). Feng et al recently reported on a prospective study of constrictor sparing approach using IMRT in patients with oropharyngeal cancer. The authors minimised the dose to the constrictors by not treating the medial retropharyngeal nodes. Patients with posterior pharyngeal wall and retropharyngeal node involvement were excluded. At median follow-up of 36 months, the treatment outcomes were equivalent to historical controls. The patient reported 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 video fluoroscopy measures at 24 months (17).

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 one year post-treatment (slightly accelerated RT with concomitant cisplatin) does not correlate to the dose to the constrictors (21). Long term data on loco-regional recurrence is required before 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 60Gy cause damage to the mandible and result in osteoradionecrosis (2). The incidence of severe osteoradionecrosis after treatment to oropharyngeal cancer is 5-15% depending on the dose to the mandible and other factors such as dental hygiene (2). Studies have demonstrated that the dose to the mandible can be minimised without affecting the dose to the target volumes (22). Table 1 summarises the published reports of IMRT in oropharyngeal cancer. These studies demonstrate excellent loco-regional 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) (23-27). In the study by Sanguineti et al the 4% failures outside the high dose region was due to involved lymph nodes not being identified on the pre-treatment diagnostic imaging and hence were included in the low dose volume (23).

**Laryngeal and hypopharyngeal cancer**

Concurrent chemo-radiation 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 (28). The overall survival at 5 years for stage III and IV laryngeal cancers using the most aggressive chemo-radiation 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 (SCC) of the larynx/hypopharynx

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Stage</th>
<th>CRT</th>
<th>LRC</th>
<th>OS</th>
<th>Incidence &gt; Grade 2 xerostomia</th>
<th>Incidence ORN</th>
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<td>50</td>
<td>I-IV</td>
<td>86%</td>
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<td>0%</td>
<td>All HD</td>
</tr>
<tr>
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<td>41</td>
<td>III-IV</td>
<td>100%</td>
<td>92% (2 yrs)</td>
<td>91% (2 yrs)</td>
<td>12%</td>
<td>0%</td>
<td>All HD</td>
</tr>
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<td>9%</td>
<td>93% (2 yrs)</td>
<td>93% (2 yrs)</td>
<td>NR</td>
<td>2%</td>
<td>All HD</td>
</tr>
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<td>69</td>
<td>I-III</td>
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<td>91% (2 yrs)</td>
<td>95.5% (2 yrs)</td>
<td>16%</td>
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<td>All HD</td>
</tr>
<tr>
<td>Sanguineti et al (23)</td>
<td>50</td>
<td>III-IV</td>
<td>0</td>
<td>94% (3 yrs)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mendenhall et al (26)</td>
<td>130</td>
<td>III-IV 90%</td>
<td>61%</td>
<td>84% (5yr)</td>
<td>76% (5yrs)</td>
<td>-</td>
<td>3%</td>
<td>88% HD</td>
</tr>
</tbody>
</table>

Table 1: Single institution reports of outcomes and toxicity using IMRT in oropharyngeal cancers.

Legend: N. – number of patients, yrs - years, CRT- concomitant chemotherapy, LRC – loco-regional control, OS - overall survival, ORN - osteoradionecrosis of the mandible, POF- pattern of failure, NR- not reported, HD- high dose region.
have recently been reported\(^{(29)}\). The patients were initially treated with a standard dose equivalent of 63Gy in 28 fractions (2.25Gy/fraction). Subsequently the dose was escalated to 67.2Gy in 28 fractions (2.4Gy/fraction). Acute radiation toxicity was comparable to standard radiotherapy and recovered over time. After two years of follow-up only 5\% of the patients had grade 2 xerostomia. The 2-year disease specific survival (DSS) was 73\% and 84\% for the standard and escalated dose patients, respectively. There was no other significant late toxicity of note. Although the patient numbers are small and the follow-up short, the results are encouraging and justify further investigation\(^{(30)}\).

There are 4 retrospective single centre experiences using IMRT for laryngeal and hypopharyngeal cancer as reported in the literature. These are summarised in Table 2.

**Nasopharyngeal Cancer:**

Clinical target volumes for tumours of the nasopharynx lie in close proximity to the optic nerves, optic chiasm, orbit, pituitary gland, and the 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 48Gy. Radiation delivery using the SIB-IMRT technique enables delivery of a single-phase treatment while sparing the organs at risk. Two phase III randomised controlled trials, investigating parotid gland sparing using IMRT for patients with nasopharyngeal cancer have been reported in the literature\(^{(11, 12)}\). Kam et al randomised sixty patients between IMRT and conventional radiotherapy. The primary endpoint of observer assessed xerostomia score was significantly better for the IMRT group as were the secondary endpoints of parotid and whole salivary flow rates. However, there was no statistically significant difference in the patient reported xerostomia score\(^{(11)}\). Pow et al randomised fifty-one patients to receive either IMRT or conventional radiotherapy. Eighty three percent of patients in the IMRT group had recovered parotid salivary flow versus 9.5\% in the conventional group at one year. The global QOL was significantly better in the IMRT group versus the conventional group\(^{(12)}\). These findings of improved QOL were confirmed in a longitudinal non-randomised study comparing IMRT and conventional radiotherapy\(^{(30)}\).

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. Daly et al have reported on the outcomes and toxicity with IMRT as the primary treatment for this site\(^{(39)}\). There were no incidences of grade 3 late radiation toxicities affecting the OARs in either

![](image.png)

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Stage</th>
<th>CRT</th>
<th>LRC (2 yrs)</th>
<th>OS (2 yrs)</th>
<th>Grade 3 dysphagia</th>
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<tr>
<td>Studer et al (^{(31)})</td>
<td>29</td>
<td>III-IV</td>
<td>86%</td>
<td>90%</td>
<td>90%</td>
<td>20 % (1 yr)</td>
</tr>
<tr>
<td>Lee et al (^{(32)})</td>
<td>31</td>
<td>III-IV</td>
<td>100%</td>
<td>84%</td>
<td>63%</td>
<td>46 % (2 yr)</td>
</tr>
<tr>
<td>Studer et al (^{(33)})</td>
<td>123</td>
<td>I-IV</td>
<td>86%</td>
<td>77%</td>
<td>83%</td>
<td>6% (1 yr)</td>
</tr>
</tbody>
</table>

Table-2: Single institution reports of outcomes and toxicity using IMRT in laryngeal-hypopharyngeal cancers

Legend: N – number of patients, yrs - years, CRT - concomitant chemotherapy, LRC – loco-regional control (excluding laryngectomy), OS - overall survival,
of the studies. The local control rates were 62% at 2 years in the study by Daly et al and 81% at three years in the study by Combs et al. The overall survival rates were 45% (5 years) and 80% (3 years) respectively. Several studies have been reported using IMRT for post-operative radiotherapy for the tumours of paranasal sinuses\(^{(40-42)}\). 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 sensori-neural hearing loss, especially at higher frequencies. The literature review suggests a significant effect of radiotherapy on auditory apparatus, especially hearing (incidence 40-60%) \(^{(3)}\). The sensori-neural hearing loss that results after radiotherapy is permanent. Sensori-neural hearing loss has been shown to result in significant cognitive impairment, depression and reduction in functional status.

Planning studies indicate that the dose to the cochlea can be reduced with the use of IMRT\(^{(43)}\). This might reduce the incidence of sensori-neural hearing loss. IMRT needs to be evaluated in the setting of a randomised controlled trial comparing it against standard 3D-conformal radiotherapy with sensori-neural deafness as the primary end point. A phase III study of cochlear sparing IMRT is now open and recruiting (Co-Star trial) in these tumors.

**Thyroid cancer**

For patients with thyroid cancer considered at high risk of loco regional recurrence after thyroidectomy, external beam radiotherapy is used, sometimes in addition to radio-iodine. With present radiotherapy techniques 32% do not obtain a complete response (CR), and of those obtaining 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 60Gy, and possibly to doses of 65-68Gy. Moreover the coverage of the thyroid and node target volume is also significantly improved with IMRT \(^{(44)}\). 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. The results on late toxicity and disease outcomes from this study are awaited \(^{(45)}\).

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Stage</th>
<th>CRT</th>
<th>LRC</th>
<th>OS</th>
<th>Incidence &gt;Grade 2 xerostomia (late)</th>
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<tr>
<td>Sultanem et al</td>
<td>35</td>
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</tr>
<tr>
<td>Lee et al</td>
<td>67</td>
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<td>74%</td>
<td>98% (4 yrs)</td>
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<td>0.3%</td>
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<tr>
<td>Kam et al</td>
<td>63</td>
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<td>30%</td>
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<td>90% (3 yrs)</td>
<td>23%</td>
</tr>
<tr>
<td>Wolden et al</td>
<td>74</td>
<td>I-IV</td>
<td>93%</td>
<td>91% (3 yrs)</td>
<td>83% (3 yrs)</td>
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</tr>
<tr>
<td>Lai et al</td>
<td>512</td>
<td>I-IV</td>
<td>82%</td>
<td>93% (5 yrs)</td>
<td>76% (5 yrs)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Table 3: Single institution reports of outcomes and toxicity using IMRT in nasopharyngeal cancers.

Legend: N – number of patients, yrs - years, CRT - concomitant chemotherapy, LRC – loco-regional control, OS - overall survival, NR- not reported.
Squamous cell carcinoma with unknown primary (SCCUP)

Typically patients with SCCUP are treated with ipsilateral modified radical neck dissection (MRND) and post-operative radiotherapy (PORT) or chemo radiotherapy. There is a lack of consensus on the radiotherapy target volumes that should be treated after neck dissection. The most common radiotherapy 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 total mucosal irradiation in this setting claiming improved local control (46). With conventional radiotherapy technique, this is at the price of significant acute toxicity and chronic morbidity, mainly xerostomia with its associated complications and effects on quality of life (QOL) (47).

In a planning study Bhide et al showed that using SIB-IMRT technique for TMI, 60Gy in 30Gy fractions or equivalent to the post-operative bed and 50Gy in 25 fractions or equivalent (i.e. 54Gy in 30 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 26Gy and the dose to the other OARs was within tolerance (16). Three centers have reported their experience of using IMRT to deliver TMI for SCCUP (49-53). The 2-year loco-regional control and overall survival were 85-88% and 74-85%, respectively. The TMI was well tolerated. The results are summarised in Table 4.

IMRT 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 three-dimensional view of the tumours and normal anatomy, along with the electron density data which enables dose calculations. However CT scans are inferior to magnetic resonance imaging (MRI) scans in detailed definition of soft tissues (microscopic tumour extension) and tissue planes and can be affected by artifact like dental amalgam and hip arthroses. CT-MRI fusion should be considered for radiotherapy planning wherever possible especially, when delineating gross tumour volume (GTV) particularly in central

<table>
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<tr>
<th>Author</th>
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<th>Surgery+ RT</th>
<th>CRT</th>
<th>LRC (2-year)</th>
<th>OS (2-year)</th>
<th>Acute Grade 3 mucositis</th>
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<tr>
<td>Madani(50)</td>
<td>23</td>
<td>4</td>
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<td>3</td>
<td>NR</td>
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<td>Lu(49)</td>
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<td>12</td>
<td>6</td>
<td>88%</td>
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<td>8</td>
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<td>Frank (52)</td>
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<td>24</td>
<td>11</td>
<td>22</td>
<td></td>
<td>100%</td>
<td>92%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Table 4: Single institution reports of outcomes and toxicity using IMRT for TMI in SCCUP.

Legend: N- number of patients, RT - radiotherapy, CRT - chemo-radiation, LRC - locoregional control rate, OS - overall survival, NR – not reported
nervous system and skull base tumours. Initial studies using [(18)-F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), which highlights the proliferating areas of the tumour, have been reported (54) and have shown that FDG-PET can aid delineation of the GTV(55). Detailed clinical and radiological assessment of the tumours should be undertaken to ensure that all the microscopic disease is encompassed in the high dose clinical target volume (CTV1). The selection and delineation of lymph node areas in N+ and N0 neck should be based on the international consensus guidelines (56, 57). 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 before treatment starts, and regularly during treatment and ensures that under-dosing to the tumour and over-dosing to the OARs is avoided by minimizing the systematic and random errors (58). In addition to the conventional 2D verification using portal imaging, modern devices also enable 3D volumetric verification (using kVCBCT) and in vivo dosimetry.

**Future directions**

IMRT has become the standard of care for delivery of radiotherapy 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 radiotherapy (IGRT). 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 radiotherapy using hyperfractionation and/or acceleration have had to close prematurely or have the radiation schedule modified due to excessive acute toxicity (59). Selective dose escalation based on the biological activity of tumours might improve the outcomes without increasing the normal tissue toxicity. Positron emission tomography (PET) enables biological imaging of tumours. Initial studies using [(18)-F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), which highlights the proliferating areas of the tumour, have been reported (54). These have shown that FDG-PET guided dose escalation using IMRT is feasible. Hypoxic regions of tumours are radio resistant and increasing the radiation dose might help overcome the radio resistance. PET scanning using two radioactive tracers namely fluorine-18-labeled fluoromisonidazole (F-MISO) and Copper (II)-diacetyl-bis (N (4)-methylthiosemicarbazone) (Cu-ATSM) 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 (60). The PET images could be fused with the planning CT scans and these could be used for biological dose optimization (as opposed to the currently used DVH based optimization) 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 radiotherapy lies in optimally using IMRT for biologically based individualized patient treatment in order to maximize the therapeutic ratio.


IMRT in Head and Neck Cancers, C M Nutting


