YBJOM-5235; No. of Pages 5
ARTICLE IN PRESS
Available online at www.sciencedirect.com
ScienceDirect
British Journal of Oral and Maxillofacial Surgery xxx (2017) xxx–xxx
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Review

Intensity-modulated radiotherapy in head and neck cancer — an update for oral and maxillofacial surgeons

P.A. Brennan [a,*], K.L. Bradley [b], M. Brands [a]

[a] Department of Oral and Maxillofacial Surgery, Queen Alexandra Hospital, Portsmouth, PO6 3LY, UK
[b] Department of Oncology, Queen Alexandra Hospital, Portsmouth, PO6 3LY, UK

Accepted 31 July 2017

Abstract

Intensity-modulated radiation therapy (IMRT), a relatively new method of delivering radiotherapy, can precisely target a point within a specific tumour and reduce the dose to nearby anatomical structures. This is particularly important in the head and neck where radiotherapy can easily and irreparably damage the salivary glands, spinal cord, and eyes, and where, with increasingly better outcomes and survival, late complications of conventional radiotherapy (including osteoradionecrosis of the cervical spine) can be difficult to manage. IMRT has the potential advantage of reducing side effects including xerostomia and myelopathy of the cervical spinal cord. Several clinical trials have recently been published, and in this update we give an overview of IMRT for oral and maxillofacial surgeons, and discuss what the future may hold for radiotherapy.

Keywords: Review; intensity-modulated radiotherapy; head and neck cancer; oral cancer; complications; xerostomia

Introduction

Intensity-modulated radiation therapy (IMRT), which has been available for the last 15 years, is a highly-targeted, computer-planned treatment that is delivered by a linear accelerator to a solid tumour.[1] Unlike conventional 3-dimensional conformal radiotherapy, the dose can be matched precisely to a complex 3-dimensional treatment volume that incorporates concavities (Figs. 1–3). Typically, the summation of seven beams, each with "intensity modulation" (variation of the strength of the beam in different parts of it)[1] gives a mathematical solution to the 3-dimensional problem of how to deliver different doses to different parts of a tumour.

In volumetric modulated arc therapy (VMAT), a variant of IMRT, a beam rotates in an arc around the patient while its shape and intensity are varied. IMRT delivers a therapeutic dose to the tumour and protects nearby dose-limiting structures such as the parotid glands,[2] eyes and orbital regions,[3] and cervical spinal cord.[4] Since these normal structures are relatively spared, it has been reported to be associated with fewer side effects such as xerostomia and cervical myelopathy, and it now appears in several head and neck cancer guidelines (including the UK National Guidelines and those of the National Comprehensive Cancer Network) because of the possibility of reducing the toxicity of treatment.

Sparing of these dose-limiting structures however, comes at the cost of a low "dose bath" of radiation to other normal tissues. For example, the anterior mouth has little or no exposure to radiation with conventional radiotherapy, whereas doses of around 25 Gy may be seen with IMRT.

Better matching of the therapeutic dose to a target volume risks the under-treatment of areas that might contain microscopic tumour spread. It is therefore vital to delineate the target volume accurately, and this relies on close cooperation between the radiation oncologist, radiologist, and

* Corresponding author. Tel.: +44 2392 286736; fax: +44 2392 286089.
E-mail address: Peter.brennan@porthosp.nhs.uk (P.A. Brennan).

http://dx.doi.org/10.1016/j.bjoms.2017.07.019
0266-4356/

Please cite this article in press as: Brennan PA, et al. Intensity-modulated radiotherapy in head and neck cancer — an update for oral and maxillofacial surgeons. *Br J Oral Maxillofac Surg* (2017), http://dx.doi.org/10.1016/j.bjoms.2017.07.019

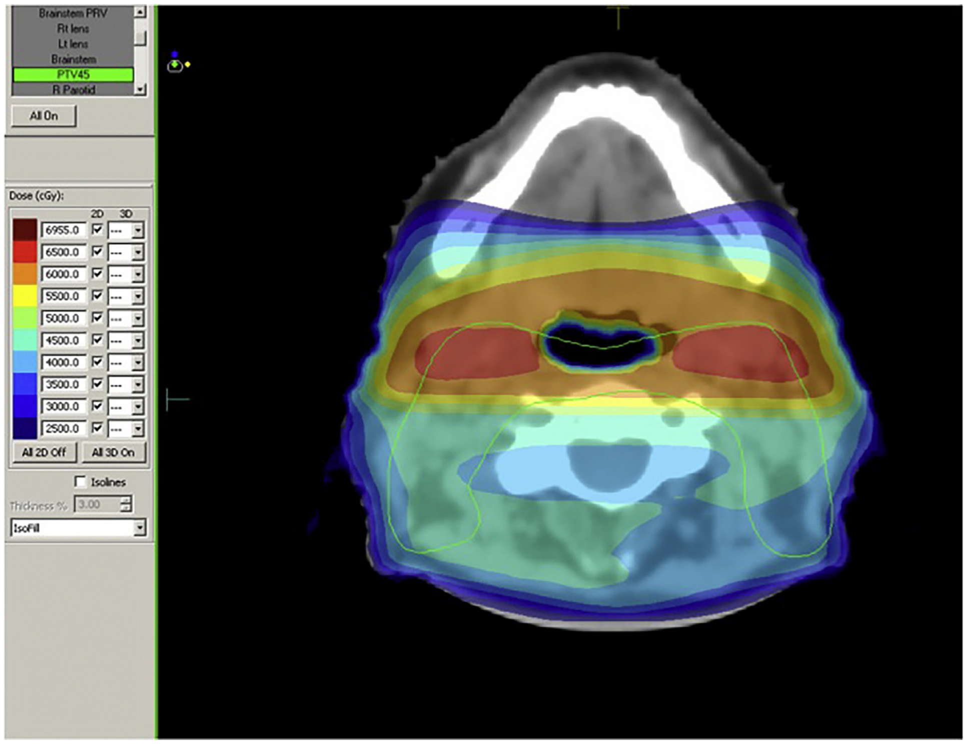

Fig. 1. Conventional radiotherapy for an unknown primary oropharyngeal carcinoma showing sparing of the anterior mouth.

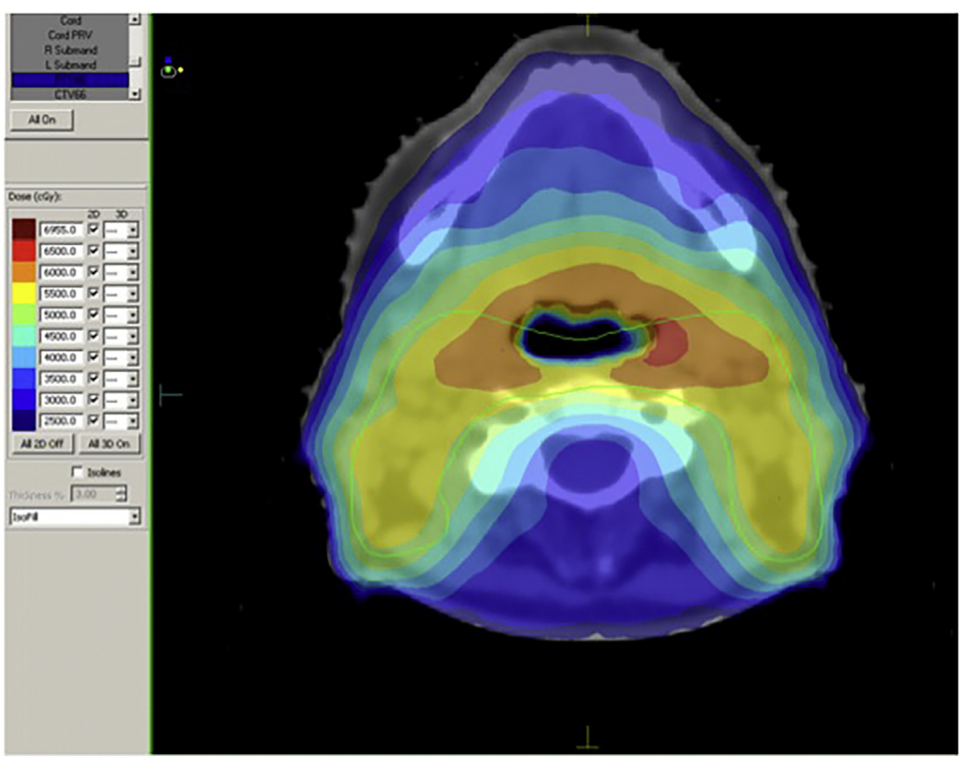

Fig. 2. IMRT in the same patient showing the low “dose bath” affecting the anterior mouth, but much better shaping of the dose to the target volume (outlined with a faint green line) while sparing the spinal cord.

Please cite this article in press as: Brennan PA, et al. Intensity-modulated radiotherapy in head and neck cancer — an update for oral and maxillofacial surgeons. *Br J Oral Maxillofac Surg* (2017), http://dx.doi.org/10.1016/j.bjoms.2017.07.019

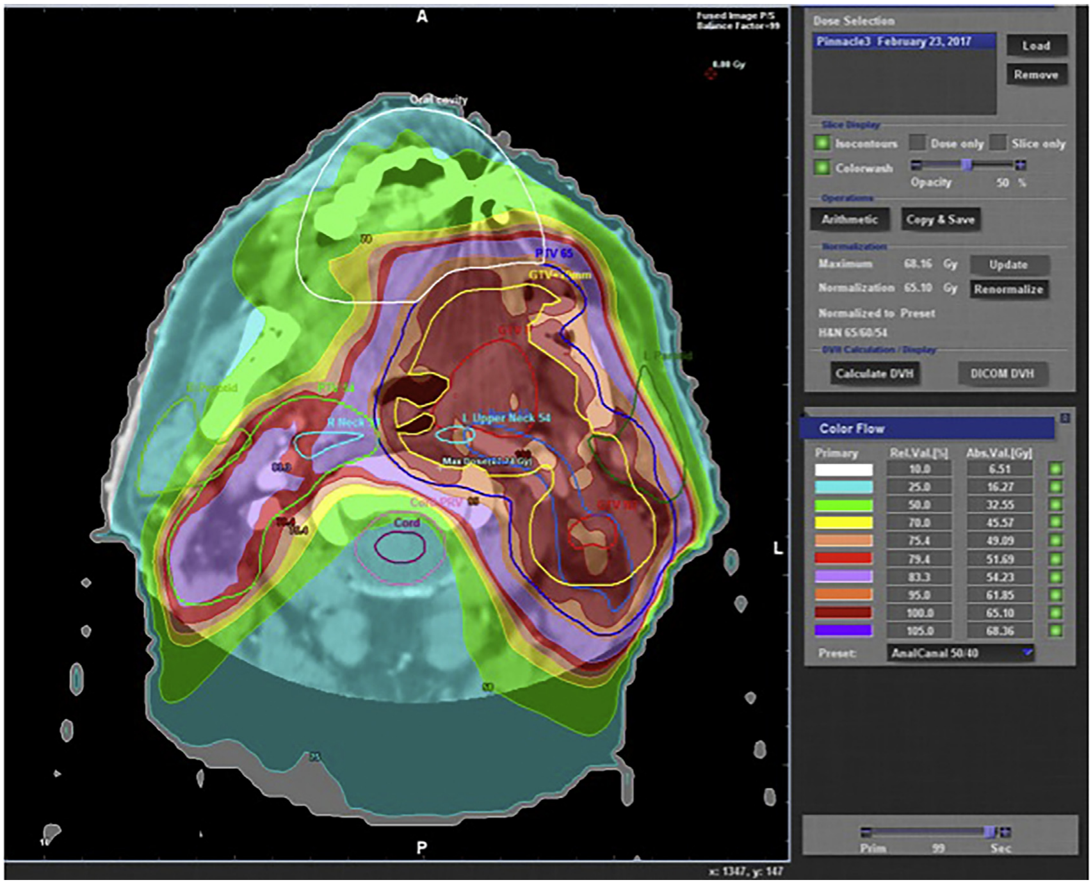

Fig. 3. A therapeutic dose of 65 Gy delivered to the left oropharyngeal primary tumour and involved ipsilateral neck, with a lower dose of 54 Gy (sufficient to eradicate microscopic disease) given to the uninvolved right neck. The dose is shaped away from the spinal cord and parotids to minimise the chance of complications.

surgeon; where the tumour is not easily seen on imaging, its definition depends on clinical description.[1] Overall and locoregional survival are similar for both IMRT and conventional radiotherapy.[5]

Knowledge about IMRT for oral and maxillofacial surgeons (OMFS) is important for two main reasons: to understand the increased need for precise diagnostic information, and to know about the potential impact or complications, particularly in the mouth (typically osteoradionecrosis). The aim of this review is to provide an overview of the most recent developments.

Early and late effects of IMRT

Dysphagia and xerostomia

IMRT has been found to reduce xerostomia when compared with conventional radiotherapy because it can reduce the radiation dose to the salivary glands.[6] The PARSPORT study (parotid-sparing intensity-modulated versus conventional radiotherapy in head and neck cancer) found that IMRT with parotid sparing significantly reduced the incidence of xerostomia when compared with conventional radiotherapy, and improved quality of life.[6] A study that spared level IB nodes in patients having chemoradiotherapy for node-positive oropharyngeal cancer found no difference in locoregional control between the group that spared level IB and the group that did not ($p = 0.021$). However, a considerable difference in quality of life was reported.[7] The addition of chemotherapy to IMRT does not have an impact on the incidence of acute or late xerostomia in patients with locally advanced cancer of the head and neck when compared with IMRT alone.[8]

Dysphagia after radiotherapy is caused by several factors including the effect of xerostomia on dysfunction of the swallowing muscles. Another less common cause is hypoglossal nerve palsy, which may occur many years after radiotherapy, and is reported in up to 5% of patients treated with IMRT.[9] Several studies have focused on improved functional outcomes after reduced doses of radiation to the swallowing muscles.[10] Currently, in the hope of improving long-term swallowing outcomes, the DARS trial is investigating a

Please cite this article in press as: Brennan PA, et al. Intensity-modulated radiotherapy in head and neck cancer — an update for oral and maxillofacial surgeons. *Br J Oral Maxillofac Surg* (2017), http://dx.doi.org/10.1016/j.bjoms.2017.07.019

reduced dose to the pharyngeal constrictor muscles in patients with oropharyngeal cancer.[11]

Osteoradionecrosis (ORN)

The incidence of ORN has decreased over the past 20 years because of greater awareness of dental health before treatment and the development of more targeted radiotherapy techniques including IMRT.[12] The risk of ORN after IMRT for cancer of the head and neck is reported to range from 0%–6.3%,[13] but the reason for the reduced incidence with IMRT compared with conventional radiotherapy remains unclear.[14,15] One study found that a high radiation dose, poor periodontal status, and intake of alcohol were related to a greater risk of its development.[16] It developed in 96% of 44 patients who had had doses of over 60 Gy to parts of the mandible, which confirmed that such a dose, irrespective of how it is delivered, is a threshold for the development of ORN.[16]

Quality of life

In their comprehensive review published in 2010, Scott-Brown et al concluded that the association between improved quality of life and the use of IMRT has not yet been proved. This was based on patients treated with radiotherapy having a relatively good quality of life after treatment in any event, and on the fact that quality-of-life scores do not directly reflect all functional problems.[17] A more recent study found that IMRT led to clinically meaningful and significant improvements in quality of life ($p < 0.01$) on general domain scores and on those specific to head and neck cancer when compared with conventional 3-dimensional conformal radiotherapy.[18]

IMRT in HPV-related cancers

With increasing numbers of patients with HPV-related oropharyngeal squamous cell carcinoma (SCC), the role of IMRT should be considered. Outcomes after treatment with IMRT in this group seem to be better than after treatment with conventional radiotherapy, and often there are fewer side effects (including xerostomia and dysphagia). One study of 186 patients with oropharyngeal SCC, which analysed toxicity and survival after treatment with IMRT (with or without chemotherapy), found good overall disease-free and disease-specific survival, particularly in patients with HPV, and a feeding tube retention rate of 6% at two years.[19] It is well known that outcomes in patients with HPV-positive cancers are better than those with HPV-negative disease. A recent clinical trial evaluated xerostomia and survival outcomes depending on HPV status. It included 120 patients at risk of bilateral neck metastases who were treated by induction chemotherapy and chemo-IMRT (with parotid sparing) for midline tumours. There was a median (range) follow up of 50 months (range 7 months – 6 years). Subjective xerostomia at 12 months was lower in the HPV-positive group (17% compared with 21% in the HPV-negative group). Survival at two years differed considerably between HPV-positive and HPV-negative tumours (92% (55 patients) compared to 53% (32 patients) respectively).[20]

However, to reduce recurrence, target volumes for HPV-positive cancers must be planned carefully when IMRT is used. In a recent study of 83 recurrences in 50 patients with HPV-positive oropharyngeal SCC, Chen et al found that of 35 recurrences, 41% were the result of incomplete coverage of the tumour, and 18% were true misses (IMRT did not encompass the primary tumour).[21] They highlighted the importance of meticulous planning, particularly in relation to continuing efforts to reduce the overall dose of radiation in this group of patients.[21]

The role of reduced doses in IMRT is also being investigated in the context of transoral robotic surgery (TORS). The ECOG 3011 trial is evaluating postoperative treatment for patients with stage III-IVb oropharyngeal cancer by comparing TORS-only, TORS with low-dose IMRT, TORS with standard-dose IMRT, and TORS with standard-dose IMRT plus chemotherapy.[22] The results are expected from 2020.

As patients with HPV-positive cancer are often younger, the risk of radiation-induced second primary tumours should be considered.[1] IMRT exposes more tissues in the body to low doses of radiation than conventional radiotherapy so the risk of radiation-induced malignancies might therefore be considered higher, but this is controversial in the head and neck.[1] IMRT has not been used widely for long enough to draw any firm conclusions about such malignancies.

Cost-effectiveness

Planning takes considerably longer for IMRT than for conventional radiotherapy, and questions have been raised about its cost-effectiveness. Some suggest that the relatively small benefit to quality of life such as reduced xerostomia and dysphagia is not cost-effective in the short term after treatment has been completed, but may become more so over many years if the patient survives.[23,24]

The future

In addition to IMRT, intensity-modulated proton therapy (IMPT) is being tested in some units for the treatment of oropharyngeal carcinoma.[25] It uses heavily charged protons of variable intensity and energy that can be targeted precisely to spare surrounding tissue. However, it is largely experimental at this stage. There are few large randomised trials and the long-term biological effects of this method of proton delivery are incompletely understood.[25] It is also considerably more expensive than IMRT, which itself is far more costly than conventional radiotherapy.[25]

Please cite this article in press as: Brennan PA, et al. Intensity-modulated radiotherapy in head and neck cancer — an update for oral and maxillofacial surgeons. *Br J Oral Maxillofac Surg* (2017), http://dx.doi.org/10.1016/j.bjoms.2017.07.019

In conclusion, IMRT has become the standard of care for delivering radiotherapy in patients with cancer of the head and neck. Locoregional recurrence and overall survival are comparable to conventional radiotherapy and rates of xerostomia are considerably improved. In the future we expect IMRT to have a role in the de-escalation of dose in selected patients, and the further tailoring of target volumes will help to improve quality of life.

Conflict of interest

We have no conflicts of interest.

Financial support

None.

Ethics approval and patients' consent/permission

Not required.

References

1. Gutiontov SI, Shin EJ, Lok B, et al. Intensity-modulated radiotherapy for head and neck surgeons. *Head Neck* 2016;**38**:E2368–73.
2. Lee SW, Kang KW, Wu HG. Prospective investigation and literature review of tolerance dose on salivary glands using quantitative salivary gland scintigraphy in the intensity-modulated radiotherapy era. *Head Neck* 2016;**38**:E1746–55.
3. Thariat J, Racadot S, Pointreau Y, et al. Intensity-modulated radiotherapy of head and neck cancers: dose effects on the ocular, orbital and eyelid structures. *Cancer Radiother* 2016;**20**:467–74 [In French].
4. Boisselier P, Racadot S, Thariat J, et al. Intensity-modulated radiotherapy of head and neck cancers. Dose constraint for spinal cord and brachial plexus. *Cancer Radiother* 2016;**20**:459–66 [In French].
5. Marta GN, Silva V, de Andrade Carvalho H, et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. *Radiother Oncol* 2014;**110**:9–15.
6. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;**12**:127–36.
7. Tam M, Riaz N, Kannarunimit D, et al. Sparing bilateral neck level IB in oropharyngeal carcinoma and xerostomia outcomes. *Am J Clin Oncol* 2015;**38**:343–7.
8. Miah AB, Gulliford SL, Bhide SA, et al. The effect of concomitant chemotherapy on parotid gland function following head and neck IMRT. *Radiother Oncol* 2013;**106**:346–51.
9. Hutcheson KA, Yuk M, Hubbard R, et al. Delayed lower cranial neuropathy after oropharyngeal intensity-modulated radiotherapy: a cohort analysis and literature review. *Head Neck* 2017;**39**:1516–23.
10. Hegde JV, Chen AM, Chin RK. Advances in radiation oncology: what to consider. *Otolaryngol Clin North Am* 2017 [Epub ahead of print].
11. Petkar I, Rooney K, Roe JW, et al. DARS: a phase III randomised multicentre study of dysphagia-optimised intensity-modulated radiotherapy (Do-IMRT) versus standard intensity- modulated radiotherapy (S-IMRT) in head and neck cancer. *BMC Cancer* 2016;**16**:770.
12. Wahl MJ. Osteoradionecrosis prevention myths. *Int J Radiat Oncol Biol Phys* 2006;**64**:661–9.
13. De Felice F, Musio D, Tombolini V. Osteoradionecrosis and intensity modulated radiation therapy: an overview. *Crit Rev Oncol Hematol* 2016;**107**:39–43.
14. Maesschalck T, Dulguerov N, Caparrotti F, et al. Comparison of the incidence of osteoradionecrosis with conventional radiotherapy and intensity-modulated radiotherapy. *Head Neck* 2016;**38**:1695–702.
15. Tsai CJ, Hofstede TM, Sturgis EM, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys* 2013;**85**:415–20.
16. Owosho AA, Tsai CJ, Lee RS, et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): the Memorial Sloan Kettering Cancer Center experience. *Oral Oncol* 2017;**64**:44–51.
17. Scott-Brown M, Miah A, Harrington K, et al. Evidence-based review: quality of life following head and neck intensity-modulated radiotherapy. *Radiother Oncol* 2010;**97**:249–57.
18. Rathod S, Gupta T, Ghosh-Laskar S, et al. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. *Oral Oncol* 2013;**49**:634–42.
19. Bird T, De Felice F, Michaelidou A, et al. Outcomes of intensity-modulated radiotherapy as primary treatment for oropharyngeal squamous cell carcinoma – a European single institution analysis. *Clin Otolaryngol* 2017;**42**:115–22.
20. Miah AB, Schick U, Bhide SA, et al. A phase II trial of induction chemotherapy and chemo-IMRT for head and neck squamous cell cancers at risk of bilateral nodal spread: the application of a bilateral superficial lobe parotid-sparing IMRT technique and treatment outcomes. *Br J Cancer* 2015;**112**:32–8.
21. Chen AM, Chin R, Beron P, et al. Inadequate target volume delineation and local-regional recurrence after intensity-modulated radiotherapy for human papillomavirus-positive oropharynx cancer. *Radiother Oncol* 2017;**123**:412–8.
22. Eastern Cooperative Oncology Group. *Transoral surgery followed by low-dose or standard-dose radiation therapy with or without chemotherapy in treating patients with HPV positive stage III-IVA oropharyngeal cancer (NCT01898494)*. Available from URL: https://clinicaltrials.gov/ct2/show/NCT01898494. (Last accessed 24 July 2017).
23. Sheets NC, Wheeler SB, Kohler RE, et al. Costs of care in a matched pair comparison of intensity-modulated radiation therapy (IMRT) versus conventional radiation therapy (CRT) for the treatment of head and neck cancer. *Am J Clin Oncol* 2014;**37**:539–44.
24. Kohler RE, Sheets NC, Wheeler SB, et al. Two-year and lifetime cost-effectiveness of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2013;**87**:683–9.
25. Blanchard P, Garden AS, Gunn GB, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer – a case matched analysis. *Radiother Oncol* 2016;**120**:48–55.

Please cite this article in press as: Brennan PA, et al. Intensity-modulated radiotherapy in head and neck cancer — an update for oral and maxillofacial surgeons. *Br J Oral Maxillofac Surg* (2017), http://dx.doi.org/10.1016/j.bjoms.2017.07.019