Intensity-modulated Radiation Therapy for Head and Neck Cancer

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Opinion statement

Intensity-modulated radiation therapy (IMRT) involves the delivery of optimized nonuniform beam intensities to the patient. In the head and neck region, there are many critical structures in close proximity to the target, with little influence from internal organ motion. Because IMRT produces tightly conformal doses and steep-dose gradients next to normal tissues, it provides the potential for organ sparing and improved tumor control. The dosimetric superiority of head and neck IMRT over conventional techniques has been demonstrated. The initial results of clinical IMRT studies showed reduction in xerostomia with no compromise in locoregional control if caution and appropriate knowledge are exercised in target determination and delineation.

Introduction

Intensity-modulated radiation therapy (IMRT) is a major advance in radiation oncology. IMRT delivers optimized nonuniform beam intensities to the tumor. The peacock system was the first commercially available system for IMRT. Initially used for IMRT treatment in March 1994 at The Methodist Hospital (Houston, TX), this system received US Food and Drug Administration clearance for its hardware in 1995 and its totally integrated system in 1996. Since 1996, many commercially available IMRT systems have been developed and installed at many institutions worldwide, with thousands of patients being treated with IMRT.

Head and neck cancers are often in close proximity to the spinal cord, brain stem, parotid glands, and optic pathway structures. Therefore, although conventional therapies are frequently inadequate in tumor target coverage and normal tissue sparing, IMRT has demonstrated better target coverage with steep-dose gradient once it reaches surrounding normal tissues [1–3,4•,5•,6].

Intensity-modulated radiation therapy offers improved tumor control by avoiding the restrictions of tumor boost doses, frequently imposed by spinal cord and brain stem dose limits, and eliminating the need for posterior neck electron fields, commonly used in traditional radiotherapy [7••,8,9••]. IMRT in this region is more feasible compared to other anatomic sites because organ motion is virtually absent in many tumor subsites in the head and neck area.

However, the drawbacks of IMRT should be recognized. Head and neck IMRT is a labor-intensive procedure and it is prone to a high risk of error secondary to the complexity of planning and delivery. There are difficulties in quality assurance, radiation safety, and portal imaging verification [10••]. Although a multitude of reports pertaining to the planning, delivery, and quality assurance of IMRT have been published, there are few clinical outcomes regarding IMRT [10••]. Furthermore, crucial issues for IMRT, such as target determination and delineation, and dose prescription strategies require refinement based on information derived from previous experiences with conventional radiation techniques [11••]. Another clinical concern is the unknown mutagenic potential of the tissues receiving low to moderate scattered radiation dose exerted by IMRT compared to standard techniques [12]. Long-term follow-up of patients receiving IMRT is necessary to clarify this issue.

Treatment

Target determination and delineation

- Target determination and delineation is a crucial step for IMRT. Protecting critical normal tissue without compromising tumor target coverage requires an extensive knowledge of the patterns of tumor extension and spread and an ability to accurately delineate the target volume and normal structures.
- Division of lymph node by levels serves as the basis for describing the cervical lymphatic network. The Committee for Head and Neck Surgery and Oncology of the American Academy for Otolaryngology-Head and Neck Surgery revised the Robbins' classification, which divides the neck into six levels or eight nodal groups for the lymph nodes routinely removed during neck dissection [13••]. This system describes the boundaries of the nodal regions based on anatomic structures, such as major blood vessels, muscles, nerves, bones, and cartilage. Lymph nodes that are not routinely dissected, such as retropharyngeal nodes, are not included in this classification. Recent papers have defined the radiologic boundaries of these levels with computed tomography (CT) slices. They have discussed the lymphatic regions at risk that should be included in radiation field and demonstrated how to delineate various lymph node levels with planning CT or magnetic resonance imaging slices [11••,14•,15•,16••].
- Thorough understanding of the natural course of tumor spread in head and neck area ensures the delineation of clinical target volume (CTV) that represents the regions potentially containing microscopic disease as defined in the International Commission on Radiation Units and Measurement reports 50 and 62 [17,18]. Based on definitions by the International Commission on Radiation Units and Measurement, we previously defined two CTVs: CTV1 for the high-risk region and CTV2 for the low-risk region or prophylactically treated neck [11••]. The CTVs used were elected to be generous to avoid marginal failure. We reported the patterns of failure among 126 patients receiving head and neck IMRT [9••]. Most of the failures occurred in CTV1, which was the high-risk region, and received the full prescribed dose. Based on this observation and clinical outcome analysis, we adopted a revised strategy for target volume specification [19].
- Clinical target volume 1 for patients receiving definitive IMRT is defined as gross tumor volume or nodal gross tumor volume with 5- to 20-mm margins based on clinical and radiologic justification. CTV1 for postoperative patients receiving IMRT encompasses the preoperative gross tumor volume plus a 1- to 2-cm margin, including the resection bed with soft-tissue invasion by the tumor or extra capsular extension by metastatic neck nodes. Preoperative CT imaging, surgical defects, or postsurgical changes seen on postoperative CT scan determines the surgical bed. CTV2 for patients receiving definitive IMRT encompasses the CTV1 and the region adjacent to CTV1, but it does not directly involve the tumor based on clinical and CT or magnetic resonance imaging findings truncating air and bone. CTV2 for postoperative patients primarily includes the clinically and radiologically or pathologically uninvolved cervical lymph nodes, deemed as elective nodal regions, or prophylactically treated neck. CTV3 for patients receiving definitive IMRT include the clinically and radiologically or pathologically uninvolved cervical lymph nodes, deemed as elective nodal regions, or prophylactically treated neck. Based on these definitions, all margins of these CTVs can be demarcated on axial CT sections (Fig. 1).
- Intensity-modulated radiation therapy is generally applied to the upper neck for salivary sparing. The lower neck is treated with a conventional anterior-posterior lower neck port if indicated [9••,20]. Standard superior

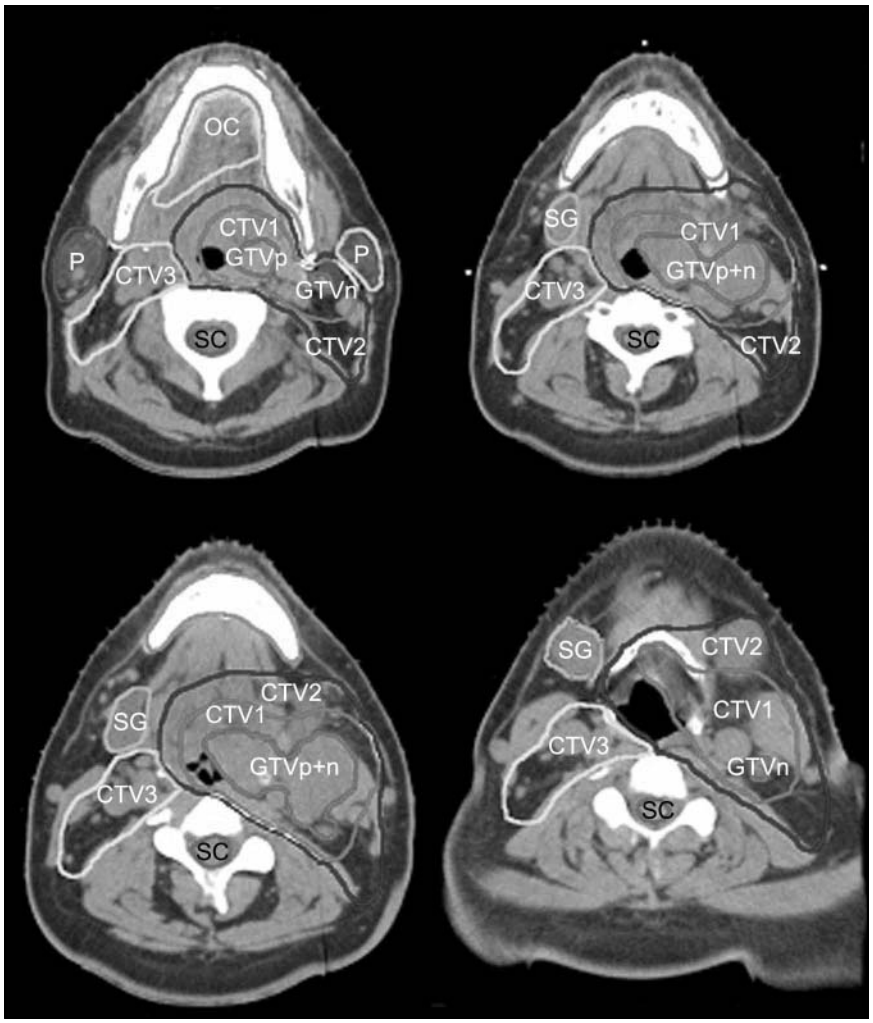

Figure 1. Delineation of CTV1 and CTV2 in a patient with T2N2bM0 base of tongue carcinoma treated with definitive intensity-modulated radiation therapy. CTV—clinical target volume; GTVn—nodal gross tumor volume; GTVp—primary gross tumor volume; OC—oral cavity; P—parotid gland; SC—spinal cord, SG—submandibular gland.

border for the lower neck field is at the level of the thyroid notch. In patients with tumor or metastatic lymph node extending below this level, the junction line is adjusted to avoid bisecting gross disease.

- Margins for organ motion or patient set-up error need to be determined by individual institutions implementing a head and neck IMRT program. Using reinforced thermoplastic mask for immobilization, our experience indicated that a 3-mm margin was needed for the IMRT plan computation to count for patient set-up uncertainty [21].

Dose prescription for head and neck intensity-modulated radiation therapy

- Intensity-modulated radiation therapy can deliver different doses per fraction to multiple target volumes using a single plan. This ability allows flexibility and represents a departure from the dose prescription strategy of conventional radiotherapy. Two different dose prescription philosophies have emerged and been described in the literature. There are various examples in implementing IMRT dose prescription within these two categories (Table 1). The first prescription strategy sets the daily fraction size to the low-dose target volume at 1.8 to 2 Gy and increases the daily fraction size to the high-dose region. This approach can be considered an accelerated fractionation schedule. In keeping with classic principles of altered fractionation schemes, the total dose to the high-dose target is typically reduced. There are two examples with this approach.

Table 1. Head and neck intensity-modulated radiation therapy target-dose specification strategies

Study	Concurrent chemotherapy	Sites	Fractions	CTV1 (70/2 Gy)*	CTV2 (60/2 Gy)*	CTV3 (50/2 Gy)*
Butler *et al.* [25]	No	All sites	25	60/2.4 Gy	—	50/2 Gy
RTOG H-0022†	No	Oropharynx (early stage)	30	66/2.2 Gy	60/2 Gy	54/1.8 Gy
Lee *et al.* [7••]	Yes	Nasopharynx	33	70/2.12 Gy	59.4/1.8 Gy	—
Chao *et al.* [9••]	Yes	All sites	35	70/2 Gy	63/1.8 Gy	56/1.6 Gy

*Conventional prescription.
†http://www.rtog.org/members/protocols/h0022/main.html.

- Butler *et al.* [22] use an inverse-planning IMRT-based accelerated-fractionation schedule for the treatment of head and neck cancer called simultaneous modulated accelerated radiation therapy (SMART). SMART used higher daily doses (2.4 Gy) to CTV1 to shorten the overall treatment time to 5 weeks without requiring multiple daily doses. They have tried to limit the high-dose volume and reduce the risk of late complications associated with larger fraction size. However, critical normal tissues, such as muscle, mucosa, blood vessels, and nerves are embedded within the target volumes. Furthermore, IMRT prescription is commonly normalized to 80% to 90% of the isodose line to provide adequate target volume coverage, thus resulting in a 10% to 20% hot spot (daily fraction size reaching 2.64 to 2.88 Gy) within the target volume. Therefore, this treatment delivers a significantly higher daily dose per fraction and raises a genuine concern for potential worsening of late effects. The long-term quality of life data using this approach are not available.
- An ongoing Radiation Therapy Oncology Group study (H-0022) adopted a strategy to accommodate the fraction size differences and deliver a dose higher than conventional dose per fraction to the gross tumor containing CTV of early-stage oropharyngeal cancer (T1–2 and N1) with no chemotherapy. In this study, the high-dose CTV received a total of 66 Gy in 30 fractions at 2.2 Gy per fraction. High-risk CTVs received 60 Gy and low-risk CTVs received 54 Gy at 2 Gy and 1.8 Gy per fraction, respectively. This approach may be suitable for patients with early-stage head and neck cancer who receive high doses of therapy to small target volumes without concurrent chemotherapy.
- The second IMRT prescription strategy has been proposed by Chao *et al.* [9••]. This particular strategy maintains the daily fraction size to the high-dose region within conventional limits (1.9–2.0 Gy) and increases the total dose to the low-dose region to compensate for a lower daily fraction size (1.7–1.6 Gy).
- Our approach to limit the daily fraction size to high-dose target to 2 Gy has met skepticism because of concerns that lower fraction size to the prophylactically treated areas may lead to higher local failure rates. As detailed in our previous reports, our experience has not revealed an increase in tumor recurrence rates and serves to validate our dose prescription strategy [23]. We also favor limiting the fraction size to the high-dose target because of the potential for increased toxicity among the patients treated with concurrent chemotherapy. Taking into account typical IMRT prescription normalization at the 80% to 90% isodose line, our approach is able to limit the

Table 2. Reported outcomes of select published head and neck intensity-modulated radiation therapy series

Study	Patients, *n*	Subsite	LC, %	LRC, %	OS, %
Butler *et al*. [22]	20	Multiple	N/A	85	NA
Dawson *et al*. [27]	58	Multiple	N/A	79 (2 years); 75 (5 years)	NA
Lee *et al*. [7••]	67	NPC	97 (4 years)	98 (4 years)	88 (4 years)
Chao *et al*. [9••] and Lin *et al*. [28]	126	Multiple	85 (2 years)	85 (2 years)	87(2 years)

LC—local control; LRC—locoregional control; NA—not available; NPC—nasopharyngeal carcinoma; OS—overall survival.

maximum daily dose to the high-dose target to 2.2 to 2.44 Gy. Further evidence-based investigation to address optimal fractionation dose and scheme for head and neck IMRT is needed.

Clinical outcomes of head and neck intensity-modulated radiation therapy

- There are few clinical outcomes of head and neck IMRT (Table 2). The first results with this new technology on head and neck tumors were from Baylor College of Medicine (Houston, TX) [24]. Kuppersmith *et al.* [24] demonstrated a decrease in the dose to the parotid glands to less than 30 Gy in 28 patients. The incidence of acute toxicity was reported to be drastically lower compared to conventional RT. Butler *et al.* [25], using serial tomotherapy, implemented the SMART technique, finding that 19 of 20 patients treated had a complete response with acceptable toxicity. Van *et al.* [26] reported the clinical outcomes of 30 postoperative patients receiving head and neck IMRT. With a median follow-up time of 24 months, 96.7% local control, 83.3% disease-free survival, and 93.3% overall survival rates were noted in this study. Review of late effects showed 26.7% skin, 3.3% mucosal, 26.7% salivary, and 10% laryngeal/esophageal toxicity (all grade 1 only).
- Dawson *et al.* [27] reported the patterns of failure analysis of 58 patients treated with three-dimensional conformal radiotherapy and forward-planning IMRT. The actuarial locoregional control rate was 79%, with a median follow-up time of 27 months. Ten of 15 patients experienced locoregional failures in the volume of gross disease and adjacent soft tissue and nodal volumes. Chao *et al.* [9••] reported the patterns of failure in 126 patients with head and neck cancer treated with serial tomotherapy. Seventeen locoregional failures were detected, and nine of those failures were inside CTV1. Predominant in-field failure detected in both studies demonstrates the urgent need to discern radioresistant tumors, such as hypoxic tumors, through functional imaging or molecular markers. The 2-year overall survival rate was 87%, and the 2-year disease-free survival rate was 82%. Grade 3 or 4 late dermatitis and xerostomia was observed in 1.6% and 0.8% of patients, respectively [28]. No serious late toxicity, such as osteoradionecrosis, brain necrosis, and radiation myelitis was reported.
- Intensity-modulated radiation therapy is a favorable technique to treat patients with nasopharyngeal carcinoma. Cheng *et al.* [6] showed that target coverage of primary tumor and neck nodes was improved with IMRT in 17 patients with nasopharyngeal carcinoma compared to conventional beam arrangements. The ability of IMRT to spare the parotid gland was considerably superior. Hunt *et al.* [20] demonstrated similar results in 23 patients with primary nasopharyngeal carcinoma.

- In 67 patients, clinical outcome data validated the dosimetric advantage of IMRT as Lee *et al.* [7••] showed that the 4-year local progression-free survival, locoregional progression-free survival, distant metastases recurrence-free survival, and overall survival rates were 100%, 97%, 94%, and 94%, respectively.
- Claus *et al.* [29] observed no dry eye or other visual disturbances in 11 patients with ethmoid sinus cancer, noting that the optic pathway dose can be reduced selectively by IMRT with the potential to save vision. However, no evaluation of retinopathy was performed because the follow-up period was short.
- Regarding a comparison between the clinical outcome of IMRT and conventional radiation techniques, Chao [5•] reported that the dosimetric advantage of IMRT translated into a significant reduction of late salivary toxicity in patients with oropharyngeal carcinoma, with no adverse impact on tumor control and survival. In this study, 430 patients with oropharyngeal carcinoma were treated at the Mallinckrodt Institute of Radiology (St. Louis, MO). Patients were divided into five groups. Group I consisted of 109 patients who received preoperative conventional radiation therapy. Group II consisted of 142 patients who received postoperative conventional radiation therapy. Group III consisted of 153 patients who received definitive conventional radiation therapy. IMRT was used to treat 14 patients postoperatively (group IV) and 12 patients definitively without surgery (group V). With a median follow-up time of 3.9 years, the 2-year locoregional control rates for the five groups were 78%, 76%, 68%, 100%, and 88%, respectively. The 2-year disease-free survival rates for the five groups were 68%, 74%, 58%, 92%, and 80%, respectively. IMRT significantly reduced the incidence of late xerostomia without compromising locoregional control.
- Intensity-modulated radiation therapy is an effective treatment for head and neck carcinomas. The initial results of clinical IMRT studies showed a reduction in xerostomia, with no compromise in locoregional control if caution and appropriate knowledge was exercised in target determination and delineation.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Chao KS, Low DA, Perez CA, *et al.*: **Intensity-modulated radiation therapy in head and neck cancers: the Mallinckrodt experience.** *Int J Cancer* 2000, **90:**92–103.
2. Chao KS, Majhail N, Huang CJ, *et al.*: **Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques.** *Radiother Oncol* 2001, **61:**275–280.
3. Chao KS, Deasy JO, Markman J, *et al.*: **A prospective study of salivary function sparing in patients with head and neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results.** *Int J Radiat Oncol Biol Phys* 2001, **49:**907–916.
4. • Chao CK, Ozyigit G: *Intensity-Modulated Radiation Therapy for Head and Neck Cancer.* Philadelphia: Lippincott Williams & Wilkins; 2002.

The first clinical textbook showing the practical essentials of head and neck IMRT.

5. • Chao KS: **Protection of salivary function by intensity-modulated radiation therapy in patients with head and neck cancer.** *Semin Radiat Oncol* 2002, **12:**20–25.

A review article on the protection of salivary function by IMRT.

6. Cheng JC, Chao KS, Low D: **Comparison of intensity-modulated radiation therapy (IMRT) treatment techniques for nasopharyngeal carcinoma.** *Int J Cancer* 2001, **96:**126–131.

7.•• Lee N, Xia P, Quivey JM, *et al.*: **Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience.** *Int J Radiat Oncol Biol Phys* 2002, **53:**12–22.

This paper provides important clinical data regarding a large number of patients treated with IMRT for nasopharyngeal cancer.

8. Ozyigit G, Chao KS: **Clinical experience of head and neck cancer IMRT with serial tomotherapy.** *Med Dosim* 2002, **27:**91–98.

9.•• Chao KS, Ozyigit G, Tran BN, *et al.*: **Patterns of failure in patients receiving definitive and postoperative IMRT for head and neck cancer.** *Int J Radiat Oncol Biol Phys* 2003, **55:**312–321.

The largest patterns-of-failure study in the current literature involving patients receiving head and neck IMRT.

10.•• Intensity Modulated Radiation Therapy Collaborative Working Group: **Intensity-modulated radiotherapy: current status and issues of interest.** *Int J Radiat Oncol Biol Phys* 2001, **51:**880–914.

An excellent IMRT collaboration group review for the current state of IMRT.

11.•• Chao KS, Wippold FJ, Ozyigit G, *et al.*: **Determination and delineation of nodal target volumes for head and neck cancer based on patterns of failure in patients receiving definitive and postoperative IMRT.** *Int J Radiat Oncol Biol Phys* 2002, **53:**1174–1184.

Nodal target determination and delineation guidelines for node-negative, node-positive, and postoperative neck based on patterns of failure in a large number of patients receiving definitive and postoperative IMRT.

12. Hall EJ, Wuu CS: **Radiation-induced second cancers: the impact of 3D-CRT and IMRT.** *Int J Radiat Oncol Biol Phys* 2003, **56:**83–88.

13.•• Robbins KT, Clayman G, Levine PA, *et al.*: **Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery.** *Arch Otolaryngol Head Neck Surg* 2002, **128:**751–758.

The most recent revised Robbins' surgical classification system for cervical lymph nodes.

14.• Som PM, Curtin HD, Mancuso AA: **An imaging-based classification for the cervical nodes designed as an adjunct to recent clinically based nodal classification.** *Arch Otolaryngol Head Neck Surg* 1999, **125:**388–396.

A paper discussing image-based guidelines for cervical lymph nodes.

15.• Nowak PJ, Wijers OB, Lagerwaard FJ, *et al.*: **A three-dimensional CT-based target definition for elective irradiation of the neck.** *Int J Radiat Oncol Biol Phys* 1999, **45:**33–39.

A paper discussing CT-based guidelines for cervical lymph nodes.

16.•• Gregoire V, Coche E, Cosnard G, *et al.*: **Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience.** *Radiother Oncol* 2000, **56:**135–150.

An excellent article on the selection and delineation of lymph node target volumes for conformal therapy.

17. *ICRU: Prescribing, Recording, and Reporting Photon Beam Therapy.* Washington, DC: International Commission on Radiation Units and Measurements; 1993.

18. *ICRU: International Commission on Radiation Units and Measurements Report 62: Prescribing, Recording, and Reporting Photon Beam Therapy (Supplement to ICRU Report 50).* Washington, DC: International Commission on Radiation Units and Measurements; 1999.

19. Ozyigit G, Thorsdat WL, Chao KS: **Outcome of intensity-modulated radiation therapy in organ function preservation for head and neck carcinoma and potential role of amifostine.** *Semin Oncol,* in press.

20. Hunt MA, Zelefsky MJ, Wolden S, *et al.*: **Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer.** *Int J Radiat Oncol Biol Phys* 2001, **49:**623–632.

21. Low DA, Chao KS, Mutic S, *et al.*: **Quality assurance of serial tomotherapy for head and neck patient treatments.** *Int J Radiat Oncol Biol Phys* 1998, **42:**681–692.

22. Butler EB, Teh BS, Grant WH 3rd, *et al.*: **Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity-modulated radiotherapy.** *Int J Radiat Oncol Biol Phys* 1999, **45:**21–32.

23. Chao KS, Ozyigit G: *Intensity-modulated Radiation Therapy for Head and Neck Cancer.* Philadelphia: Lippincott Williams & Wilkins; 2003.

24. Kuppersmith RB, Greco SC, Teh BS, *et al.*: **Intensity-modulated radiotherapy: first results with this new technology on neoplasms of the head and neck.** *Ear Nose Throat J* 1999, **78:**238, 241–246, 248 passim.

25. Butler EB, Teh BS, Grant WH, *et al.*: **SMART (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity-modulated radiotherapy.** *Int J Radiat Oncol Biol Phys* 1999, **45:**21–32.

26. Van TJ, Teh BS, Mai WY: **Postoperative intensity-modulated radiation therapy for head and neck cancer assessment of toxicity and outcome.** *Paper presented at the Annual Meeting of the American Radium Society.* Houston, April 26–30, 2003.

27. Dawson L, Anzai Y, Marsh L, *et al.*: **Patterns of local-regional recurrence following parotid sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer.** *Int J Radiat Oncol Biol Phys* 2000, **46:**1117–1126.

28. Lin M, Ozyigit G, Chao K: **Impact of tumor stage and radiation fraction size on tumor control and treatment toxicity in head and neck cancer patients treated with IMRT.** *Paper presented at the Annual Meeting of the American Society for Therapeutic Radiation and Oncology.* New Orleans, October 7, 2002.

29. Claus F, Boterberg T, Ost P, De Neve W: **Short-term toxicity profile for 32 sinonasal cancer patients treated with IMRT. Can we avoid dry eye syndrome?** *Radiother Oncol* 2002, **64:**205–208.