

Intensity-Modulated Radiotherapy for Head and Neck Cancer

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Abstract: Intensity-modulated radiation therapy (IMRT) is a new radiation delivery technique that allows more precise delivery of radiation and optimization of the dose intensity to specific volumes while sparing the dose to critical normal structures. Using IMRT in head and neck cancers is attractive because of close proximity of the tumor targets to critical normal structures such as the spine, eyes, and parotid glands. IMRT has been shown in a number of clinical sites to improve local control and decrease side effects. Specifically, IMRT has shown the ability to preserve salivary function through sparing of the parotid glands. At the same time, there remain some uncertainties in terms of target delineation, secondary cancers, and side effects to swallowing function that may be increased with IMRT. Multi-institutional studies of IMRT are under way, and these studies, combined with refinements of the technique, should lead to continued improvement in the radiotherapeutic management of head and neck cancer.

Head and neck cancers account for 3% of all cancers in the United States.¹ Radiotherapy (RT) has long been a critical therapeutic modality in head and neck squamous cell carcinoma (HNSCC), along with surgery and chemotherapy. RT in the head and neck is challenging because of the complex and delicate anatomy in that region. Functional organs for breathing, eating, speech, and facial expression, which are critical to patients' quality of life, often lie in direct proximity to the disease. In order to improve the radiotherapeutic management of HNSCC, intensity-modulated radiotherapy (IMRT) was developed. IMRT has the ability to deliver high doses of radiation to the tumor with very high precision while minimizing the dose received to the surrounding normal tissue.²⁻⁴

IMRT utilizes the latest in computer-optimized treatment planning and a computer-controlled treatment delivery system. The actual therapeutic particles of IMRT are the identical photons that have been used for decades in conventional radiotherapy. There are, however, two technological developments that distinguish IMRT: the introduction of computer-controlled multileaf collimators (MLCs; Figure 1) and the development of computerized optimization, or inverse planning, which determines the intensity of the beams required to satisfy a specified set

Keywords

IMRT, head and neck, radiation therapy



Figure 1. Multileaf collimators. Each of the 5 mm “leaves” has its own small motor and they continually move to create the dose distribution.

of dose constraints. The advantage of MLCs is that they allow a careful shaping of the beam of radiation down to the millimeter (Figure 2). Inverse planning allows radiation oncologists to use the technology of dynamic MLCs to create the dose distributions they want using a computer-controlled algorithm to target the tumor and avoid normal tissue. The computer then determines what sequences of beams and intensities are required to optimally achieve these goals^{5,6} (Figure 3). The result is dose distributions, which were inconceivable with standard radiotherapy planning.

Clinical Data

IMRT has been used in two clinical arenas with HNSCC. First, it has shown promise for targets close to critical normal tissues such as nasopharyngeal cancers near the base of the skull, maxillary sinus malignancies near the optic apparatus, and in reirradiation to spare the spinal cord. The second arena has been to attempt to reduce late toxicity by sparing the salivary structures.

Most of the data investigating the use of IMRT come from single-institution phase II studies that have been segregated by disease site. There are also a select number of studies examining multiple disease sites.

Chao and colleagues reported on 126 patients treated with IMRT at Washington University.⁷ Forty percent of the patients were treated with definitive intent; a small number of this group received concurrent chemotherapy. Ninety percent of the patients were stage III–IV. The 2-year ultimate locoregional control after surgical salvage was 89%. Lee and associates studied 150 patients with head and neck cancer who underwent IMRT at the University of California—San Francisco (UCSF).⁸ With a

median follow-up of 25 months, the 3-year local freedom-from-progression rate was 95% in those who underwent definitive IMRT.

Nasopharynx

The nasopharynx is the site where the most clinical data exist for the benefit of IMRT. The target in nasopharyngeal cancer is adjacent to many critical normal structures, such as cranial nerves, cavernous sinus, as well as auditory and optic structures. In addition, when treating nasopharyngeal cancer, the target volume often includes the clivus, base of the skull, pterygoid fossa, parapharyngeal space, or the paranasal sinuses, which can themselves involve the intracranial contents. Tumor control for carcinoma of the nasopharynx is highly correlated with the dose delivered to the tumor.⁹ IMRT provides the ideal vehicle to deliver adequate doses to this organ while sparing the surrounding normal tissue. Clinicians at UCSF were among the pioneers in this area. Xia and coauthors compared IMRT treatment plans with conventional plans for a patient with locally advanced nasopharyngeal carcinoma and reported that IMRT provided improved target coverage with significantly greater sparing of sensitive normal tissue structures (ipsilateral parotid gland, optic nerve, optic chiasm, brainstem).¹⁰ Clinicians at Memorial Sloan-Kettering Cancer Center substantiated the claim of improved target coverage with IMRT.^{11,12} Hunt and coworkers reported that there is better coverage of the retropharynx, base of the skull, and medial aspects of the nodal volumes with IMRT plans.¹² Kam and coauthors performed a dosimetric analysis comparing IMRT with two- and three-dimensional treatment planning techniques for three different stages of nasopharyngeal carcinoma.¹³ In all stages, IMRT was found to have significant dosimetric advantages. In early stages, it provided better parotid gland and temporomandibular joint-sparing, whereas in locally advanced stages, it provided better target volume coverage with better brainstem and temporal lobe coverage.¹³ Initial reports from a phase III randomized study showed the advantage of IMRT in terms of xerostomia compared with conventional RT.¹⁴

The dosimetric advantages seen with IMRT for nasopharyngeal cancer have also translated into excellent clinical outcomes. The most mature data on local control using IMRT for locally advanced nasopharyngeal cancer come from UCSF. Lee and colleagues reported on 67 patients who underwent IMRT for nasopharyngeal cancer.¹⁵ Fifty of the patients received chemotherapy, according to the design of the Intergroup 0099 trial. With a median follow-up of 31 months, 4-year local progression-free survival was 97%. Bucci and associates updated these results: with a total of 118 patients and median 30-month follow-up, the 4-year local progres-

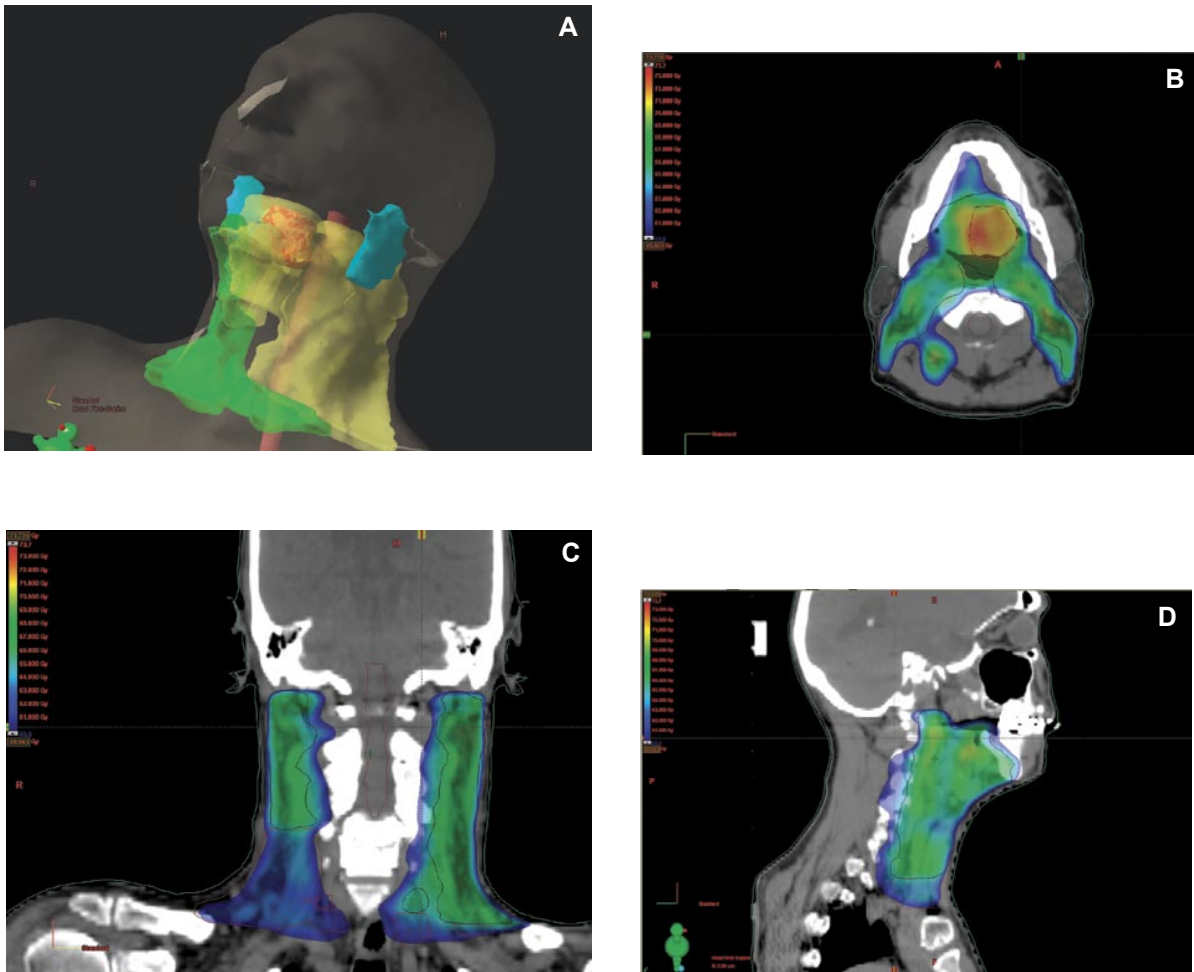


Figure 2. Treatment planning for oropharyngeal tumor. A) Three-dimensional reconstruction of target volumes and normal tissue. IMRT dose distribution B) axial, C) coronal, D) sagittal view.

sion-free survival was 96%.¹⁶ Kwong and coworkers reported 100% local control with IMRT for early-stage nasopharyngeal carcinoma, with a median follow-up of 2 years.¹⁷ In another study, Kam and coauthors reported the results of 63 newly diagnosed nasopharyngeal patients treated with IMRT with or without chemotherapy.¹⁸ With a median follow-up of 29 months, 3-year local relapse-free survival was 92%. Recently, researchers at Memorial Sloan-Kettering Cancer Center reported results for 74 nasopharyngeal cancer patients treated with IMRT; 80% of the patients were stage III–IV. Three-year actuarial local control was 91%, with a median follow-up of 35 months.¹⁹ With these excellent results, it has been suggested that IMRT for nasopharyngeal cancer should become the standard of care (Table 1). Overall, the use of IMRT for nasopharyngeal cancer has become widely accepted.

A phase II Radiation Therapy Oncology Group (RTOG) trial exploring IMRT with or without chemotherapy for all localized nasopharyngeal cancer was recently closed to patient accrual and the results are anticipated. This protocol is important because it is one of the first protocols testing IMRT in a multi-institutional setting.

Oropharynx

Multiple trials have made organ preservation therapy using chemoradiation the key management strategy for oropharyngeal tumors.^{20–22} However conventional RT frequently impairs salivary gland function, causing permanent xerostomia. After conventional RT for oropharyngeal tumors, 60–75% of patients are expected to have grade 2 or higher xerostomia.²³ The permanent loss of saliva can have a negative effect on nutrition, dentition, communication, and

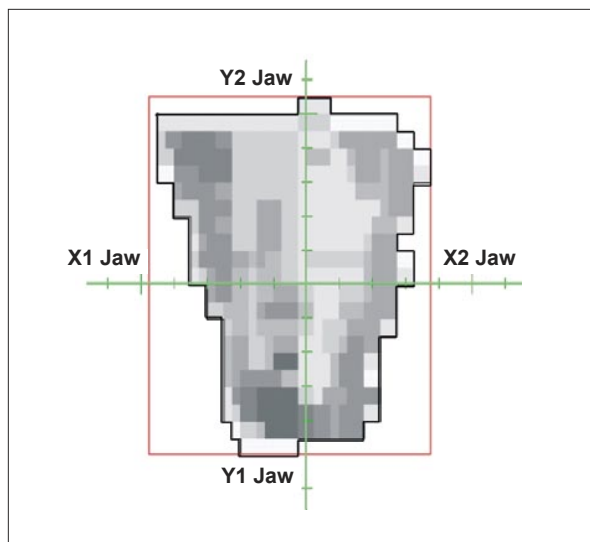


Figure 3. The intensity can be varied across a field to help sculpt the dose distribution.

quality of life, and can lead to infections of the oral cavity.²⁴⁻³¹ Patients with oropharyngeal carcinoma are ideally suited for IMRT because this technique can conform to tumors, optimize the target coverage, and spare adjacent critical structures, especially salivary glands.

Initial observations of salivary-sparing by Eisbruch and colleagues from the University of Michigan showed a significant correlation between the mean dose of RT delivered to the parotid glands and the degree of salivary flow following head and neck IMRT.³² This information allowed multiple centers to attempt to improve long-term xerostomia rates with a parotid-sparing approach. Chao and colleagues compared IMRT with conventional techniques for oropharyngeal cancer patients and found the dosimetric advantage of IMRT translated into a significant reduction of late salivary toxicity with no adverse impact on tumor control and disease-free survival.³³

Excellent outcomes for oropharyngeal carcinoma treated with IMRT have been reported from several institutions. Eisbruch and associates reported the University of Michigan experience and showed an actuarial 3-year local recurrence-free survival of 94% for oropharyngeal carcinoma treated with IMRT.³⁴ They showed that parotid sparing is not at the expense of local control. The median follow-up in this study was 32 months. Chao and coauthors reported the Washington University experience, with a slightly longer follow-up; the 4-year estimate of locoregional control was 87% for 74 patients.³³ Huang and coworkers reported 42 oropharyngeal cancer patients treated with IMRT at UCSF and showed 2-year local and locoregional progression-free probabilities of 94% and

89%, respectively.³⁵ De Arruda and colleagues reported 43 patients with stage III and IV oropharyngeal cancer treated with IMRT at Memorial Sloan-Kettering Cancer Center and showed 2-year estimates of local and regional progression-free survival of 97.2% and 85%, respectively, with no grade III xerostomia among the patients with at least 9 months' follow-up.³⁶ Recently, Yao and associates reported results for oropharyngeal cancer patients treated with IMRT. With a median follow-up of 27.3 months, the 3-year estimate of locoregional progression-free survival was 98.8%.³⁷ A summary of these studies is presented in Table 2.

A multi-institutional RTOG study using IMRT for early-stage oropharyngeal cancer has completed patient accrual, and the results are underway. This will be the first publication for IMRT in oropharyngeal carcinoma in a multi-institutional setting.

Paranasal Sinus

Tumors of the paranasal sinus and nasal cavity are commonly associated with a poor prognosis. A majority of the patients present with advanced tumors, often extending into the skull base close to sensitive high-risk structures such as the optic nerves and chiasm, eyes, and brainstem. RT to the paranasal sinuses can therefore result in chronic toxicity to the optic system. The reported rate of RT-induced blindness with conventional RT is approximately 37%.³⁹⁻⁴¹ Attempts to avoid these toxicities often result in underdosage in regions of risk with conventional RT techniques; therefore, the use of IMRT is of clinical interest in this disease site to attempt to overcome these problems. Claus and colleagues reported a prospective study of 11 patients regarding the ability to spare bilateral optic pathways using IMRT for the treatment of ethmoid sinus tumors.⁴² Adams and coworkers compared conventional, 3D conformal, and IMRT treatment plans for maxillary sinus tumors.⁴³ IMRT plans demonstrated increased tumor volume coverage with lower doses to optic pathways and the parotid. Several other studies have shown that IMRT can further decrease the dose delivered to the optic chiasm, brainstem, optic nerves, and the orbits.⁴⁴⁻⁴⁶

Only a few groups have reported their results with IMRT in patients with carcinomas of the paranasal sinus. Duthoy and coauthors published results of 39 patients treated with postoperative IMRT.⁴⁷ With a median follow-up of 31 months, actuarial local control rates were 73% at 2 years and 68% at 4 years. No RT-induced blindness was observed. Recently, Combs and associates reported results of 46 paranasal sinus carcinoma patients treated with IMRT.⁴⁸ With a median follow-up of 16 months, the 3-year local control rate was 49%. The results are superior both in terms of toxicity and outcome to series with conventional RT.

Table 1. Results From Series Treating Nasopharyngeal Carcinoma With Intensity-Modulated Radiation Therapy With or Without Chemotherapy

Study	N	Stage Distribution	Median Follow-up (mo)	Local Control (%)	Regional Control (%)	Distant Metastasis-free Survival (%)	Overall Survival (%)
Lee et al ¹⁵	67	All	31	97, 4 yr	98, 4 yr	66, 4 yr	88, 4 yr
Bucci et al ¹⁶	118	All	30.2	96, 4 yr	98, 4 yr	72, 4 yr	74, 4 yr
Kwong et al ¹⁷	33	Early	24	100, 3 yr	92, 3 yr	100, 3 yr	100, 3 yr
Kam et al ¹⁸	63	All	29	92, 3 yr	98, 3 yr	79, 3 yr	90, 3 yr
Wolden et al ¹⁹	74	All	35	91, 3 yr	93, 3 yr	78, 3 yr	83, 3 yr

Table 2. Results From Series Treating Oropharyngeal Cancer With Intensity-Modulated Radiation Therapy With or Without Chemotherapy

Study	N	Stage Distribution	Median Follow-up (mo)	Local Control (%)	Locoregional Control (%)	Distant Metastasis-free Survival (%)	Overall Survival (%)
Chao et al ³³	74	Mostly III-IV	33	NR	87, 4 yr	90, 4 yr	87, 4 yr
Garden et al ³⁸	80	N+	17	NR	94, 2 yr	NR	NR
Huang et al ³⁵	41	N+	14	94, 2 yr	89, 2 yr	NR	89, 2 yr
De Arruda et al ³⁶	50	Mostly III-IV	18	98, 2 yr	88, 2 yr	84, 2 yr	98, 2 yr
Yao et al ³⁷	66	Mostly IV	27.3	NR	99, 3 yr	80, 3 yr	78, 3 yr

N+=node-positive; NR=not reported.

Reirradiation

Recurrent head and neck cancer poses a challenge to clinicians. Distant metastases are far less frequent than in other solid tumors, and most patients ultimately die of local disease progression. Therefore, reirradiation is frequently employed in recurrent cases. The challenge with reirradiation is sparing of critical structures, most notably the spinal cord.⁴⁹ IMRT allows for conformal reirradiation with spinal-cord sparing. Lu and colleagues have reported the results of 49 recurrent nasopharyngeal carcinoma patients reirradiated with IMRT.⁵⁰ With a median follow-up of 9 months, the locoregional control was 100%, and tumor necrosis was seen in 14 patients. Acute toxicity was acceptable. Chua and associates reported the efficacy of induction chemotherapy and reirradiation in locally advanced recurrent nasopharyngeal carcinoma.⁵¹ With a median follow-up of 14.5 months, 1-year locoregional progression-free survival was 63%. Acute radiation toxicities were mild; 71% of the patients had late radiation toxicities, with 12% grade 3 temporal lobe necrosis.

Pitfalls

Several challenges remain for head and neck programs that utilize IMRT. One concern is that significant variability may exist among clinicians in the delineation of the target structures, which can potentially cause variations in tumor control and adverse events. In particular, the operator-dependency for IMRT may be larger than that for conventional RT. In order to address this problem, consensus guidelines have been issued for the delineation of the target tissues based on CT images.⁵²

A second concern is the radiation dose distributions created by IMRT. On the one hand, the major advantage of IMRT is a more conformal dose distribution with steep dose gradients between the tissues, which results in decreased toxicity and dose escalation as well as improved control. But there are some disadvantages of this treatment modality: an increased risk of a marginal miss, a less homogeneous dose distribution, increased cost, a higher total body dose, and swallowing dysfunction and aspira-

tion. In addition, Hall and Wu have focused specifically on the risk of second malignancy from IMRT.⁵³ They estimated the risk of radiation-induced malignancies increases from 1% to 1.75% in patients who survive at least 10 years after IMRT. Hall and Wu stated that the move from 3D conformal RT to IMRT involves more fields and, as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, because of the greater number of monitor units used, leakage radiation is increased, thus increasing total body exposure to radiation.⁵³

One of the other newer concerns pertains to other side effects that may be increased with IMRT. Specifically, some investigators have reported increasing dysphagia and aspiration with both the use of IMRT and the intensification of systemic therapy. Eisbruch and colleagues reported that the rate of aspiration after therapy increased significantly in 25 patients treated with gemcitabine chemotherapy and IMRT for locally advanced head and neck cancer.⁵⁴ The structures whose damage may cause dysphagia and aspiration for this group of patients are the pharyngeal constrictors and the glottic and supraglottic larynx⁵⁵; data on the radiation doses to those structures associated with dysphagia and aspiration have been presented.⁵⁶ Caglar and coauthors analyzed the factors associated with stricture and aspiration after chemotherapy and IMRT for head and neck cancer.⁵⁷ They found that a history of smoking was a significant factor for stricture. Fua and coworkers assessed the correlation between the dose to the pharyngo-esophageal axis and dysphagia in their nasopharynx patients treated with whole-field IMRT or split anterior-field with central shielding-technique IMRT.⁵⁸ The mean pharyngo-esophageal dose was significantly lower using the modified technique, which led to significantly less day-of tube feeding in that group of patients. Further work is required in this area.

Conclusions

IMRT is a technology that provides improvements in the conformity of the target volume and normal tissue. Clinical studies have confirmed that it is a better treatment technique in terms of reducing xerostomia and avoiding cochlear and optic-nerve toxicity without affecting tumor control. In some cases, especially those involving the nasopharynx and the base of the skull, tumor control may be improved with the use of IMRT. Concerns regarding increased radiation doses to normal tissues and the development of second malignancies require longer follow-up. Phase III trials comparing efficacy and safety of IMRT and chemotherapy with conformal techniques are under way.

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