Intensity-modulated radiation therapy in advanced head and neck patients treated with intensive chemoradiotherapy: Preliminary experience and future directions

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Abstract. We review our recent experience with intensity-modulated radiation therapy (IMRT) and conventional three-dimensional radiation therapy (C3DRT) in advanced head and neck cancer. Sixty-nine patients with Stage IV head and neck cancer (and stage III base of tongue and hypopharynx) enrolled in a Phase II study of definitive chemoradiation; 20 received all or part of their radiation with IMRT. Image-guided set-up, using video subtraction techniques, was used in all patients. Six weekly doses of induction carboplatin (AUC=2) and paclitaxel (135 mg/m^2) were followed by alternating weekly chemoradiation to 75 Gy with 1.5 Gy BID fractions, concurrent with paclitaxel (100 mg/m^2/week), 5-fluorouracil (600 mg/m^2/d) and hydroxyurea (500 mg PO BID). Two consecutive cohorts enrolled, differing in radiation scheme: 75 Gy to gross disease in both, 60 or 54 Gy to first echelon lymphatics and 45 or 39 Gy to second echelon lymphatics. With a median follow-up of 47 months, 3-year overall survival is 68.5% and 3-year locoregional control is 94.0%, with no significant differences between those treated with C3DRT versus IMRT, nor between the two radiation dosing schemes. Actuarial overall survival without tracheostomy or laryngectomy, or without a gastrostomy tube was also similar. Acute mucositis, dermatitis and pain were similar with C3DRT and IMRT. Preliminary data suggests IMRT is well tolerated, and does not compromise locoregional control, indicating that IMRT adequately covers the clinical volume at risk. Building on the present clinical experience, future directions include more directed efforts at reducing toxicity, with better planning software and planning techniques.

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Introduction

Intensity-modulated radiation therapy (IMRT) is a means of delivering radiation dose in a more conformal manner than conventional three-dimensional radiation therapy (C3DRT). The physician delineates targets to treat and targets to avoid. More conformal dose delivery is accomplished by varying the radiation beams spatially and/or temporally (1). C3DRT is forward planned, with the field shapes and beam intensities determined prior to running the plan. In contrast, IMRT utilizes inverse planning, with the field modulation optimized by the planning software. IMRT is particularly well-suited for head and neck neoplasms for several reasons: there are critical structures in the head and neck (i.e. spinal cord, parotid glands and oral cavity) which might be spared from radiation toxicity by conforming delivery of dose (2-4); the head and neck can be relatively immobilized, and reproducibly positioned, ensuring quality control (5); and, because of normal tissue sparing and reproducible patient positioning, higher radiation doses can be administered. In a recent survey of members from the American Society for Therapeutic Radiation Oncology, of those using IMRT in their clinics, 87% treat head and neck cancer with IMRT (6).

We have participated in previously published multi-institutional studies treating advanced head and neck cancer with induction cisplatin, 5-fluorouracil, leucovorin and α-interferon followed by concurrent 5-fluorouracil and hydroxyurea with daily (1.8-2.0 Gy) C3DRT to a dose of 65-75 Gy (7-11). Treatment was administered for five days, followed by a nine-day rest period. Surgery of the primary tumor was

generally reserved for residual disease, and neck dissection was recommended after chemoradiation for ≥N2 disease (12). Five-year locoregional control (LRC) was 70-78%, distant control (DC) >90%, progression-free survival (PFS) 64-78% and overall survival (OS) 47-62%. With nasopharyngeal cancer, 5-year LRC was 93%, PFS 86% and OS 77% (11).

In a subsequent study, cisplatin, 5-fluorouracil and hydroxyurea were administered concurrently with twice-daily radiation (1.5 Gy BID) to a dose of 70-75 Gy; while in later studies, concurrent paclitaxel, 5-fluorouracil and hydroxyurea (THF) were used (13-15). These regimens yielded OS and PFS similar to the preceding studies, with a higher LRC of 80-92%. Induction chemotherapy was not utilized in these studies, as it was hypothesized that controlling local disease would result in better DC. However, distant metastasis developed in roughly 20%, more than twice that seen in preceding trials. As more intensive chemotherapy may be necessary to control distant spread, induction chemotherapy was reintroduced in ensuing trials.

Induction carboplatin and paclitaxel, followed by TFH chemoradiation has yielded a 3-year PFS of 80% and OS of 70%, and a 2-year LRC of 94-97% and DC of 93% (16,17). In May 1999, less than one year into this multi-institutional trial, the University of Chicago instituted IMRT treatment planning and delivery. We hypothesized that conformal radiation with IMRT would deliver an adequate dose to volumes at risk of failure with no compromise in locoregional control, and result in reduced acute and late toxicity by better sparing of normal tissue. This study reviews this experience with IMRT, and compares outcome and toxicity between C3DRT and IMRT.

Patients and methods

Patients with Stage IV (M0) squamous cell carcinoma, poorly differentiated carcinoma or lymphoepithelioma of the head and neck enrolled into a multi-institutional advanced head and neck protocol (16,17). Patients with Stage III base of tongue and hypopharynx were also eligible based on poor prognosis. The protocol was approved by the institutional review boards of all participating institutions. All patients signed a written informed consent prior to treatment. Patients analyzed here were enrolled at the University of Chicago. A major goal of this trial was organ preservation. Surgery prior to chemoradiation was allowed for oral cavity and tonsillar primaries amenable to resection, without anticipated loss of function. Neck dissection was also allowed prior to chemoradiation.

Induction chemotherapy comprised 6-8 weeks of weekly carboplatin (intravenously over 30 min, calculated AUC=2) and paclitaxel (intravenously over 3 h, 135 mg/m^2). Radiation was then delivered on an alternating weekly schedule, with concurrent 5-fluorouracil (600 mg/m^2/d continuous infusion for 5 days), paclitaxel (100 mg/m^2 intravenously over 1 h every week) and hydroxyurea (500 mg orally twice daily), with each week of treatment comprising one cycle. Radiation was administered five days a week, twice-daily at 1.5 Gy per fraction, with fractions separated by >6 h. A 2 Gy daily fraction was allowed if the patient could only be treated once on a given day. Simultaneous integrated boosting was not employed (i.e. patients received the same dose with each treatment fraction, with subsequent cone-down boosts as described below).

The radiation dose was prescribed to a planning target volume (PTV), which was generated on the treatment-planning CT using AcQSim VoxelQ software (Philips Medical Systems, Cleveland OH). The PTV encompassed the clinical target volume (CTV), representing gross tumor volume (GTV) plus microscopic disease. The GTV, which included gross primary and gross nodal disease, was determined from radiological studies and clinical examination, including tumor mapping under anesthesia. Microscopic disease included areas at risk for microscopic extension of the tumor as well as cervical lymphatics at risk for disease spread. The GTV and CTV were contoured directly onto each CT slice.

The initial CTV encompassed the GTV (volume expanded with ~7-10 mm margins) and first and second echelon uninvolved lymph nodes. The initial target volume (PTV_1) was generated via a 3-mm volume expansion of the CTV. The PTV expansion of the CTV accounts for patient set-up uncertainty and organ motion (5). The subsequent boost target volume (PTV_2) encompassed the expanded GTV and first echelon uninvolved lymph nodes, again with a 3-mm volume expansion of the CTV. The final cone-down boost target volume (PTV_3) included the GTV with a volume expansion of ~1 cm.

After the volume expansion generated a PTV, the PTV was modified on each CT slice to avoid extension beyond skin and to avoid overlap with the spinal cord. For the latter, the PTV was adjusted such that the contour encompassed a narrow rim (several mm) around the vertebral body. Volumes were entered by one radiation oncologist (DJH) in the same manner for IMRT and C3DRT plans.

In an initial cohort, prescribed doses were 45, 60 and 75 Gy to PTV_1, PTV_2, and PTV_3 respectively (16). In a subsequent cohort, accruing after January 2000, doses were changed to 39, 54 and 75 Gy respectively (17). The rationale for this change was based on the discovery that, in the first cohort, there were no failures in grossly uninvolved areas (16), and also based on the desire to reduce acute toxicity (17). The prescribed dose to microscopic, resected disease was ~60 Gy in both cohorts. Thus, patients who had no measurable disease (see below) received only 4 cycles of treatment.

A litecast, used for immobilization, was marked at the time of simulation to enable accurate alignment. Treatment-planning CT scans (PQ5000 CT Simulator, Marconi Medical Systems, Cleveland, OH) with intravenous contrast were obtained prior to and after induction chemotherapy. Using the AcQSim VoxelQ software package (Philips Medical Systems), image correlation was used to fuse the pre-induction scan with the post-induction scan. Thus, the pre-induction scan was used to help define the GTV on the post-induction CT scan. With complete or near complete response to induction and/or substantial weight loss during induction, the two scans would be substantially different. In these instances, efforts were made to recreate the original tumor as accurately as possible, with appropriate adjustments.

Prior to starting treatment, patients underwent set-up verification, at which time orthogonal images were obtained and compared to digitally reconstructed simulation films.

Additionally, a video image was captured with the patient precisely aligned in the treatment position. On each subsequent treatment, real-time images of the patient were acquired and video subtraction techniques were used to enable an interactive image-guided patient set-up (5). Weekly lateral and anterior-posterior port films were also used to verify the isocenter. Patients were treated with a Varian 21EX linear accelator (Varian Associated, Palo Alto, CA). In most patients, a mid-treatment CT simulation scan was performed, with a new litecast, to correct for changes resulting from weight loss and/or tumor reduction. The resimulated CT scan was correlated to the initial treatment CT scan to assist in target delineation.

The first 15 patients enrolled were treated with C3DRT, after which IMRT was implemented. Patients were selected for IMRT-planning if time and resources were available, and if an adequate treatment plan (see below) could be obtained. Two patients planning to receive IMRT had difficulty remaining motionless in the litecast; because of the longer treatment times and the sharper dose fall-off with IMRT, these patients were instead treated with C3DRT in order to minimize the possibilty of underdosing the tumor (neither has failed). The last 9 patients enrolled were treated with C3DRT, during a CORVUS software upgrade. The relatively slow planning with IMRT prohibited the use of IMRT in all patients.

C3DRT plans were generated using PlanUNC. With C3DRT, the PTV was treated with opposed lateral 6 MV photon fields, with a matched AP supraclavicular field as described previously (13,14). Segmented fields were used to increase dose homogeneity. The spinal cord dose was kept below 39 Gy. High-energy electron fields were matched to anterior neck photon fields to boost the posterior neck.

With IMRT, 6 MV photons were exclusively used. The entire PTV was treated with IMRT (as opposed to matching a supraclavicular AP field to the IMRT fields), thus eliminating high-dose regions that occur at field match lines (where dose heterogeneity can be >150%). IMRT plans were generated using commercial inverse planning software (CORVUS, version 3.0, NOMOS Corp.), which produces optimal intensity-modulated profiles using a simulated annealing algorithm. Dynamic multileaf collimators were used to shape fields. Multiple (7-9)-field coplanar plans were used, with fields evenly separated around a 360˚ arc. If an adequate plan (see below) could not be achieved with a 9-field arrangement, a 7-field arrangement was attempted (and was used in 5/20 patients). The dose-volume constraints of the target and normal tissues were defined. The spinal cord was strictly kept below 39 Gy. Radiation dose to the parotid glands (one or both) and oral cavity were minimized as much as possible without compromising target coverage.

The goal for mean parotid dose was dependent on the extent of nodal involvement, (i.e. how close clinically involved nodes approached the parotids). Unfortunately, precise calculations of the parotid mean doses and dose thresholds are not readily attainable for several compounding reasons: i) CORVUS ignores the region of overlap between expanded PTV and normal structures, requiring the dose matrix to be imported into other software to accurately calculate normal structure DVHs; ii) patients underwent 2 or more planning CT scans during treatment to correct for weight loss and tumor volume reduction; iii) nearly all patients received only a portion of their treatment with IMRT (see below); and iv) patients were treated with 3 different consecutive PTVs. Generally, the accepted mean parotid dose was <35% of the prescribed dose to PTV_1 and PTV_2. With a portion of the treatment delivered by C3DRT (see below), this equates to the parotids in most patients receiving ~50% of the total prescribed dose.

Most patients received their first week of treatment via C3DRT, which allowed time for IMRT-planning. The planning time with earlier versions of CORVUS was relatively slow, prohibiting upfront IMRT delivery in most patients, given the relatively short window (~1 week) between the post-induction CT simulation and the start of radiotherapy, and the need to run multiple plans on each patient in order to optimize planning. Many patients received their boost dose via C3DRT; generally the final boost was delivered via C3DRT if the IMRT plan would have resulted in a cumulative spinal cord maximum >39 Gy. Since patients underwent two or more CT simulations, the cumulative spinal cord maxima were simply added, an admittedly stringent criteria since the worst case scenario of overlapping hot-spots was assumed. IMRT was delivered between 34-100% (mean 71%, median 64%) of the treatment. Table I outlines the IMRT treatment for each patient.

The IMRT plans were normalized to the 85% isodose line (i.e. 15% of the volume was planned to receive less than the prescription dose). The IMRT treatment plan was considered adequate if: a) no more than 2% of the prescribed volume received >115% of the prescribed dose and b) there was no volume within the GTV or CTV receiving <95% of the prescribed dose. For the latter, each CT scan slice was carefully examined to assure that there were no low dose regions within the GTV or CTV (i.e. the low dose regions were only at the periphery of the PTV). Multiple plans were run for each patient. If an adequate plan could not be achieved, C3DRT was used.

The Performance Status Scale for Head and Neck Cancer (PSS-HN) (18,19) and Head and Neck Radiotherapy Questionnaire (20) were administered to assess late toxicity and quality of life.

All patients have been followed until recurrence or death. No patient was lost to follow-up. Survival and disease control parameters were calculated using Kaplan-Meier actuarial analyses, with survival and failure times defined from the first day of treatment until an event or date of last follow-up. PFS events included locoregional failure (LRF), distant failure (DF) and treatment-related death. Survival without a permament gastrostomy tube and survival without a permanent tracheostomy or laryngectomy were scored as failures if a patient required permanent intervention (G tube, tracheo-sotomy or laryngectomy) and/or died. Patients dying without evidence of disease recurrence were censored at the time of death in the analyses of PFS, time to LRF, and time to DF.

Results

Sixty-nine patients from the University of Chicago enrolled between November 1998 and January 2001, and were analyzed until February 2005. The mean and median follow-ups were

Table I. Treatment parameters and outcome for 20 IMRT patients.

Stage	Subsite	Initial C3DRT dose	IMRT dose	Final C3DRT dose	Total dose	% IMRT	Permanent G-tube placed	Permanent tracheostomy placed	Outcome
T1N2b	Hypopharynx	15.0	24.5	33.5	73.0	34			NED: alive
T4N0	Oral cavity	15.0	29.0	17.5	61.5	47			NED: dead (AML)
T3N2c	Hypopharynx	15.0	39.0	21.0	75.0	52			NED: alive
T4N0	Hypopharynx	15.0	39.0	21.0	75.0	52	7 M	7 M	NED: dead (choking on food)
T4N2b	Hypopharynx	15.0	39.0	19.5	73.5	53	During induction		NED: alive
T4N0	Hypopharynx	15.0	39.5	18.5	73.0	54			NED: alive
T4N0	Larynx	15.0	42.0	15.0	72.0	58			NED: alive
T4N1	Larynx	15.0	43.5	15.0	73.5	59			NED: alive
T2N2b	Oropharynx	15.0	45.0	14.0	74.0	61			NED: alive
T4N2c	Larynx	15.0	45.0	12.5	72.5	62	During radiation	Before induction	NED: dead (multiple medical problems)
T2N2b	Oral cavity	15.0	39.0	6.0	59.0	66	1 M		NED: alive
T1N2a	Oropharynx	15.0	46.0	0	61.0	75			NED: alive
TxN3	Unknown primary	15.0	58.0	0	73.0	79	7 M		DF 4 M
T2N2a	Oropharynx	15.0	59.0	0	74.0	80			NED: alive
T3N2a	Hypopharynx	15.0	59.0	0	74.0	80			NED: alive
T4N0	Oropharynx	15.0	60.0	0	75.0	80		Before induction	NED: alive
T4N0	Suprglottic larynx	15.0	60.0	0	75.0	80			Treatment-related death at 9 M
T4N2b	Oropharynx	15.0	60.0	0	75.0	80			NED: dead (seizure disorder)
T4N3	Oropharynx	14.0	58.0	0	72.0	81		38 M	NED: alive
T1N2a	Oropharynx	0	74.0	0	74.0	100			NED: alive

The initial C3DRT dose was given in the first week of treatment, prior to IMRT delivery. The final C3DRT dose was given after IMRT delivery. The listed doses do not correspond to doses administered to PTV1-3. For example, 19 patients received 39-45 Gy to PTV1, in which 14-15 Gy was given by C3DRT. % IMRT, percent of total dose delivered via IMRT. M, months post-chemoradiotherapy. NED, no evidence of disease. Doses in Gy.

42.6 and 47.0 months respectively. C3DRT was used in 49 patients (median follow-up of 45.5 months) and IMRT in 20 (median follow-up 51.4 months). All living patients were followed for at least 2 years.

The patient characteristics are outlined in Table II. All patients had an ECOG performance status of 0-1. The two groups are comparable, except there are significantly more patients with hypopharyngeal cancer (a subsite which tends to have a poorer outcome) in the IMRT group (30% versus 4.3%, p=0.006). Table III outlines the surgical procedures performed. The goal of this trial was organ preservation; only 13% were treated with no measurable disease. Neck dissections were performed after chemoradiation in 29 patients with N2-3 disease. None of these patients had pathological residual disease. This contrasts with our earlier experience, in which ~35% of N2-3 patients (mostly ≥N2b) had pathologic residual disease after post-chemoradiation neck dissection (12,15).

Acute toxicity. Table IV lists the acute chemoradiation toxicities. There are no significant differences in acute

Table II. Patient characteristics.

	All patients	C3DRT	IMRT
No. of patients	69	49	20
Age range (years)	36.4-76.82	36.4-76.8	38.0-67.7
Median	57.9	58.6	57.4
Mean	56.8	57.6	55.0
Follow-up (months)	4.5-74.5	4.5-74.5	7.4-69.3
Median	47.0	45.5	51.4
Mean	42.6	42.9	42.1
Mean (living)	55.4	57.1	55.0
Radiation dose scheme[b]			
Scheme 1	35	25	10
Scheme 2	34	24	10
Gender			
Male	51	36	15
Female	18	13	5
Site			
Nasopharynx	2	2 (4.3)	0
Hypopharynx	8	2 (4.3)	6 (30.0)
Larynx	14	10 (20.4)	4 (20.0)
Oropharynx	33	26 (53.1)	7 (35.0)
Oral Cavity	7	5 (10.2)	2 (10.0)
Unknown primary	5	4 (8.2)	1 (5.0)
T Stage[a]			
X	5	4 (8.5)	1 (5.0)
1-2	16	10 (21.3)	6 (30.0)
3-4	46	33 (70.2)	13 (65.0)
N Stage[a]			
0-1	20	13 (27.7)	7 (35.0)
2	38	27 (57.4)	11 (55.0)
3	9	7 (14.9)	2 (10.0)
1997 AJCC Stage Group			
III	3	3	0
IV	66	46	20

Numbers in parenthesis represent percentage of patients. [a]Excludes the two nasopharynx patients in C3DRT group: T1N3a and T2aN3a. [b]See text for doses to PTVs.

Table III. Surgical therapy.

	All patients	C3DRT	IMRT
Number of patients	69	49	20
Neck dissection or excisional biopsy			
None	30	20	10
% which were N2-3	37%	35%	40%
Before treatment			
LND:	7	4	3
Excisional biopsy	2	1	1
After treatment			
Unilateral LND	22	17	5
Bilateral LND	8	7	1
Neck biopsy only	1	1	0
Pre-treatment surgery of the primary			
Tonsillectomy	6	5	1
Other[a]	3	1	2
No measurable disease before chemoradiation			
After primary surgery + LND	6	3	3
After LND (unknown primary)	3	3	0
Total	9	6 (12.2)	3 (15.0)

Numbers in parenthesis represent percentage of patients. [a]Includes a wide local excision of a T2 buccal mucosal lesion and a mandibulectomy for a T4 floor of mouth cancer in the IMRT group, and a partial glossectomy for a T2 tongue cancer in the C3DRT group. These 3 patients, and 3 of 6 patients who had a tonsillectomy, also had a neck dissection prior to treatment.

dermatitis, mucositis or pain between IMRT and C3DRT. There is significantly less grade 3-4 dermatitis (p=0.046) in the cohort treated with less radiation to first and second echelon lymph nodes.

Clinical outcome. There were 6 deaths in the IMRT group: 1 from cancer, 1 from treatment toxicity and 4 intercurrent. The cancer death occurred at 23.6 months in a TxN3 patient who developed DF at 7.6 months. The toxic death occurred at 12.6 months in a patient with T4N0 tonsil cancer, who developed radiation necrosis and carotid blow-out. A patient with T4N0 pyriform sinus cancer died while choking on food (though the patient had no medical clearance for oral intake after being unable to swallow during an oropharyngeal motility test). One developed acute myleogenous leukemia at 20 months and died 6 months later. Two others died at 7.4 and 17.3 months from comorbid illnesses. There were no LRF. Table I outlines the outcome of the IMRT patients.

There were 16 deaths in the C3DRT group: 6 from cancer, 1 from sepsis 1 week after completing treatment, 4 from second primary cancers (2 lung, esophagus and pancreas) and 5 intercurrent (sepsis at 33 months, car accident and 3 from comorbid illnesses). There were 6 failures, all of whom died from disease: 2 DF only, 2 LRF alone (at sites of original gross disease in a T4N0 oropharynx and T3N2B tonsillar cancer with simultaneous primary and nodal failures) and 2 LRF which later developed DF (positive post-treatment biopsies at the primary sites in a T4N2c oropharynx cancer and T4N2c supraglottic cancer).

Table IV. Acute toxicity.

	All patients	C3DRT[a]	IMRT	Scheme 1	Scheme 2
No. of patients	68	48	20	34	34
Mucositis					
Grade 2	(19.1)	(20.8)	(15.0)	(14.7)	(23.5)
Grade 3	(79.4)	(79.2)	(80.0)	(85.3)	(73.5)
Grade 4	(1.5)	(0)	(5.0)	(0)	(2.9)
Dermatitis					
Grade 0-1	(17.6)	(18.8)	(15.0)	(5.9)	(29.4)
Grade 2	(42.6)	(45.8)	(35.0)	(41.2)	(44.1)
Grade 3	(25.0)	(25.0)	(25.0)	(35.3)	(14.7)
Grade 4	(14.7)	(10.4)	(25.0)	(17.6)	(11.8)
Pain					
Grade 0-1	(10.3)	(10.4)	(10.0)	(11.8)	(26.5)
Grade 2	(17.6)	(12.5)	(30.0)	(38.3)	(44.1)
Grade 3	(47.1)	(50.0)	(40.0)	(41.2)	(26.5)
Grade 4	(25.0)	(27.1)	(20.0)	(8.8)	(2.9)

Numbers in parenthesis represent percentage of patients. [a]Excludes one C3DRT patient treated with radiation alone.

Table V. Clinical outcome.

	All patients	C3DRT	IMRT	p-value[a]
Number	69	49	20	
Overall survival (OS) (%)				
1 year	97.1	98.0	95.0	
3 year	68.5	68.1	69.6	>0.5
Progression-free survival (%)				
1 year	92.5	91.7	94.7	
3 year	88.0	87.3	89.5	>0.5
Locoregional control (%)				
1 year	95.5	93.8	100	
3 year	94.0	91.6	100	0.20
Distant control (%)				
1 year	94.0	93.8	94.7	
3 year	92.4	91.5	94.7	>0.5
OS without a tracheostomy or laryngectomy (%)				
1 year	84.1	85.7	80.0	
3 year	64.1	64.0	64.6	>0.5
OS without a gastrostomy tube (%)				
1 year	79.7	83.7	70.0	
3 year	64.5	66.3	60.0	>0.5

[a]Calculated using log-rank test.

Table V summarizes the 1-year and 3-year OS, LRC and DC. There are no differences between the two radiation schemes (data not shown). Comparing IMRT versus C3DRT, there is a nonsignificant trend toward improved LRC (p=0.20) with IMRT. Certainly, IMRT delivered an adequate dose to the clinical volume at risk, with no compromise in locoregional control.

Late toxicity. The 3-year survival without a laryngectomy or permanent tracheostomy (in place at last follow-up) was 64.6% in the IMRT group and 64.0% in the C3DRT group (p>0.5). Table VI details the tracheostomy placement in all patients. Of the IMRT patients, 2 long-term survivors were left with a permanent tracheostomy: one with T4N0 oropharynx cancer, in whom the tracheostomy was placed before treatment, and another with T4N3 oropharynx cancer who had a tracheostomy at 3.5 years for obstructive sleep apnea. Of the C3DRT patients, 3 long-term survivors were left with a permanent tracheostomy: one with a T3N2b larynx cancer, in whom the tracheostomy was placed 7 months after treatment; another with a T4N1 larynx cancer, in whom the tracheostomy was placed before treatment; and a patient who had a tracheostomy placed >4 years after treatment following extensive surgery for osteoradionecrosis. One patient underwent a total laryngectomy 4.5 years after treatment after developing a radiation-induced sarcoma. Additionally, a patient with T4N2c larynx cancer underwent a laryngectomy after LF and later died. There are no significant differences between the two radiation schemes in terms of survival without a laryngectomy or tracheostomy survival without a G tube (data not shown).

The 3-year survival without a permanent gastrosotomy (G) tube (in place at last follow-up) was 60.0% in the IMRT group and 66.3% in the C3DRT group (p>0.5). Table VII details the G-tube placement in all patients. Of the IMRT

Table VI. Tracheostomy and laryngectomy.

	All patients	C3DRT	IMRT	p-value[a]
No. of patients	69	49	20	
Tracheostomy before treatment	9	4	5	
Subsequently removed	7	3	4	
Persistent until death (<2-year survival)	0	0	0	
Persistent until death (>2-year survival)	0	0	0	
Present in long-term survivor	2	1	1	
Early tracheostomy (during and ≤6 months after treatment)	8	6	2	
Subsequently removed	3	2	1	
Persistent until death (<2-year survival)	4	3	1	
Persistent until death (>2-year survival)	0	0	0	
Present in long-term survivor	1	1	0	
Late tracheostomy (>6 months after treatment)	5	3	2[b]	
Subsequently removed	1	1	0	
Persistent until death (<2-year survival)	2	1	1	
Persistent until death (>2-year survival)	0	0	0	
Present in long-term survivor	2	1	1	
Laryngectomy	2	2[c]	0	
Tracheostomy or laryngectomy at >24 months	6/54 (11.1)	4/39 (10.3)	2/15 (13.3)	>0.5

Numbers in parenthesis represents percentage of patients. [a]Calculated using Fisher's exact test. [b]This was the second tracheostomy for one of these patients; the first tracheostomy was previously removed. [c]One patient is a long term survivor, while the other was an early death.

Table VII. Gastrostomy (G)-tube placement.

	All patients	C3DRT	IMRT	p-value[a]
Number of patients	69	49	20	
G tube placed before treatment	9	7	2	
Subsequently removed	6	6	0	
Persistent until death (<2-year survival)	2	1	1	
Persistent until death (>2-year survival)	1	0	1	
Present in long-term survivor	0	0	0	
G tube placed early (during and ≤6 months after treatment)	33	22	11	
Subsequently removed	22	16	6	
Persistent until death (<2-year survival)	6	3	3	
Persistent until death (>2-year survival)	3	3	0	
Present in long-term survivor	2	0	2	
G tube placed late (>6 months after treatment)	4	2[b]	2	
Subsequently removed	1	0	1	
Persistent until death (<2-year survival)	1	0	1	
Persistent until death (>2-year survival)	0	0	0	
Present in long-term survivor	2	2	0	
Refused G tube against medical advice	1	1	0	
G tube at >24 months	8/54 (14.8)	5/39 (12.8)	3/15 (20.0)	>0.5

Numbers in parenthesis represents percentage of patients. [a]Calculated using Fisher's exact test. [b]This was the second G tube in both patients; the first G tube was previously removed in both.

patients, 2 long-term survivors were left with a permanent G tube: one patient with a T4N2b hypopharynx cancer who had severe swallowing dysfunction and aspiration prior to treatment, and another with T2N2b oral cavity cancer who developed esophageal strictures post-treatment. Of the C3DRT patients, 2 long-term survivors were left with a permanent G tube: one with T3N2c oropharynx cancer who developed swallowing impairment after treatment; and another who had a G tube placed afer developing a radiation-induced sarcoma (see above). Another patient with T3N2c oropharyngeal cancer refused a G tube 1.5 years after completing therapy, despite an oropharyngeal motility study demonstrating severe swallowing impairment.

Two C3DRT patients who developed soft tissue necrosis, including one who had a tracheostomy for laryngeal necrosis and another who had a poorly healing neck wound, were managed medically. Two C3DRT patients developed osteonecrosis: one underwent extensive mandibular reconstruction and another underwent hyperbaric oxygen treatment. Two IMRT patients developed soft tissue necrosis, including one who developed wound dehiscence after a post-operative neck dissection. Another developed fatal necrosis as described above.

At 1-year follow-up, quality of life and performance data were available on 14/19 IMRT and 37/48 C3DRT patients. There was no significant difference between groups with respect to the types of foods patients could eat (Normalcy of Diet scale on PSS-HN), with roughly 40% in both groups reporting dietary restrictions (i.e. soft diet, puree foods, liquids or tube feeding). Moderate to severe swallowing difficulty was reported in 29% of IMRT patients versus 20% of C3DRT patients (p=0.53), with similar percentages reporting chewing difficulty. Moderate to severe dry mouth was reported in 40% of patients in both groups. Moderate to severe sticky saliva was reported in 55% of C3DRT patients versus 38% of IMRT patients (p=0.32). Significantly more IMRT patients reported moderate to severe hoarseness (36% versus 10%, p=0.04). Virtually all patients (96% in IMRT group and 94% in C3DRT group) had completely understandable speech.

Of the 4 C3DRT patients treated below 62 Gy, there were no permanent G tubes or tracheostomies. Two of these patients developed xerostomia. One IMRT patient treated to 59 Gy has a permanent G tube, while 2 others treated below 62 Gy have no late toxicities. Of the 9 IMRT patients who received at least 75% of their dose from IMRT, no patients are G-tube dependent, and only 1 is G-tube assisted.

Discussion

The present study compares LRC of IMRT to C3DRT in patients with advanced head and neck cancer treated definitively with induction chemotherapy and hyperfractionated chemoradiotherapy. The rationale for induction chemotherapy in advanced head and neck cancer stems from organ preservation trials for laryngeal (21,22) and oropharyngeal cancer (23), as well as our multi-institutional experience of poor DC in patients treated with chemoradiation without induction. Concurrent chemoradiotherapy has been shown to improve LRC, PFS and OS over radiation alone in multiple randomized trials (24-34). Several of these studies used twice daily radiation (24,26,27,30). Twice daily radiation (81.6 Gy in 1.2 Gy BID fractions) afforded improved LRC compared to daily radiotherapy (70 Gy in 2 Gy fractions) in an RTOG study, in which chemotherapy was not used (35). The use of a week-on/week-off chemoradiation for advanced head and neck cancer was pioneered by our institution, and has yielded promising LRC and OS (7-15,36,37). An RTOG study has corroborated these results (38). After 1993, hyperfractionated (1.5 Gy BID) week on/week off chemoradiation was implemented (13-15). With induction carboplatin and paclitaxel, followed by THF chemoradiotherapy, we have maintained excellent 2-year LRC (94%-97%) and DC (93%) (16,17).

With our intensive chemoradiotherapy regimen, acute toxicity was not significantly different between IMRT and C3DRT (Table IV). The oral cavity (or portion of oral cavity not in the PTV) was entered as an avoidance structure, but did not seem to impact rates of acute mucositis. Most (~80%) patients developed grade 3 mucositis. Perhaps with our chemoradiotherapy regimen, the threshold dose of mucositis is well below that which is delivered. Interestingly, skin toxicity was reduced in the second cohort treated with lower doses to uninvolved regional lymphatics. Though we did not assign skin as an avoidance structure, we did not find worse skin toxicity with IMRT. Lee and coworkers have shown a reduction in skin toxicity by defining the skin of the neck as a sensitive structure (39).

LRC with IMRT is dependent upon adequate PTV coverage, which relies upon knowledge of the tumor as well as areas at risk of spread (40-42). A unique aspect of IMRT raises concerns about its efficacy: volumes of tissue that receive a substantial fraction of the prescribed dose with C3DRT are selectively not treated with IMRT. However, the efficacy of IMRT is supported by the absence of LRF in the 20 patients in this study. IMRT-planning adequately delivered doses to areas at risk of locoregional failure.

Washington University published extensive treatment guidelines and outcomes for definitive (52 patients) and post-operative (74 patients) IMRT treatment planning (41,43,44). Ten percent of patients had stage I-II cancer. Concurrent cisplatin based chemotherapy was given to 67% of the definitively treated patients. With definitive IMRT, 2-year LRC was 79% (after salvage, 84%). With post-operative IMRT, 2-year LRC was 90% (after salvage, 93%).

In another study, LRC with IMRT was compared to C3DRT in patients with early and advanced oropharyngeal cancer (45). Concurrent cisplatin based chemotherapy was given to 75% of the 12 definitively-treated IMRT patients versus 5% of the 153 definitively-treated C3DRT patients. No differences in acute toxicity were seen. Aside from improved late xerostomia in the IMRT group, late complications were similar in both groups. For IMRT and C3DRT, the 2-year LRC was 88% versus 68% (NS), and 2-year PFS was 80% versus 58% (p=0.002). The 2-year LRC for post-operatively-treated patients was 100% versus 76% (NS), and 2-year PFS was 92% versus 74% (p=0.008).

The University of Michigan reported 2-year LRC in 79% of 58 patients with advanced head and neck cancer treated with IMRT (4). Seventy-one percent of patients were treated post-operatively; 27% received induction chemotherapy and 26% received platinum-based chemoradiation. Of the 12

patients who developed LRF, none failed in the high jugular lymph nodes (deep to the parotid glands), which were partially spared from radiation dose.

UCSF reported excellent 4-year LRC (97%) and OS (88%) in 67 patients with Stage I-IV nasopharyngeal cancer treated with IMRT (46,47). In an extensive review of the UCSF IMRT experience with 150 patients, the 2-year LRC was 97% with definitive treatment and 83% with post-operative treatment (48). Baylor University employs simultaneous accelerated boost IMRT (49); they reported 2 LF and 2 DF in 25 patients with Stage III-IV disease who were complete responders to IMRT (50).

The University of Michigan has pioneered the use of segmental IMRT with the goal of sparing major salivary glands and oral cavity (2,51). Significant sparing of parotid function was seen, with a threshold mean parotid dose of 26 Gy. Washington University also modeled parotid sparing, demonstrating a threshold dose of ~32 Gy for improved subjective and objective salivary function (52). However, in that study, neither radiation technique (IMRT vs. non-IMRT) nor the addition of chemotherapy impacted salivary functioning. The data from Michigan and Washington University were not published when patients were first enrolled in our study. In our study, parotid sparing techniques were used, with mean target doses of ~30-35 Gy. Lower fraction size, as delivered in our study, could feasibly increase the threshold mean parotid dose. However, we did not find significant differences between IMRT and C3DRT in subjective late xerostomia.

Unlike Eisbruch and Chao, we did not objectively measure salivary flow, and have not rigorously correlated parotid radiation dose to salivary function. Additionally, most of our patients received only a portion of radiation by IMRT. More IMRT patients reported moderate to severe voice hoarseness (36% versus 10%), reflecting the greater percentage of hypopharyngeal patients in the IMRT group (30% versus 6%). Survival without a permanent G tube or without a permanent tracheostomy is similar in both groups. Most patients dependent on a G tube and/or tracheostomy at last follow-up had terminal disease (cancer-related or intercurrent). Late swallowing and respiratory complications arise not only from treatment, but also from permanent changes caused by the cancer. These factors confound the analysis of late G-tube and tracheostomy dependence.

The present study is novel in that all patients had advanced disease treated with induction chemotherapy and chemoradiation, and all head and neck sites were included. There are inherent weaknesses in our analyses. This is a small series in which patients were not randomized or stratified, and patients treated with IMRT were selected on the basis of availability of resources and achieving an acceptable plan. Hence, selection biases (in favor or against IMRT) are possible. Secondly, this study was not designed to discriminate differences between IMRT and C3DRT. Also, the number of failures in our entire cohort is small, which argues strongly for intensive chemoradiation in advanced head and neck cancer, but limits comparison between IMRT and C3DRT. Perhaps with such intensive therapy, subtle differences in radiation therapy may not contribute to large differences in outcome that would be possible to detect in such a small group of patients.

The patients presented here were among the first to be treated on our multi-institutional protocols with IMRT. With increased experience, and newer planning software the efficiency and adequacy of IMRT planning is improving, allowing us to assess multiple plans for each patient.

Since the PTV expansion of the contoured CTV requires extensive and time-consuming modifications of the expanded PTV near the skin and spinal cord, the PTV is now entered directly onto the CT scan slices. We continue to volume expand the GTV (by roughly 1-1.5 cm), which may entail reducing this expansion off of the skin and spinal cord, and then we enter the PTVs, which always encompass the expanded GTV. This approach necessitates an understanding of how a volume expansion not only affects the expansion on axial slices but also in the caudal and cephalad directions.

We now separate the spinal cord into multiple levels along the cranial-caudal axis, and assign dose constraints accordingly. For example, during the planning of PTV1 and PTV2, more stringent constraints are placed upon the portion of spinal cord that traverses through CT scan slices with PTV_3. As a result, our previous practice of adding spinal cord maxima from two planning CT scans to determine the maximum cord dose (described in Patients and methods) is now less stringent, since maxima are added from the appropriate cord level as opposed to the entire length of spinal cord. Thus, IMRT boost plans that previously would have been rejected in favor of C3DRT (because of concern over spinal cord dose) are now acceptable.

With newer versions of CORVUS, dose homogeneity in the IMRT plans is improving. In nearly all advanced head and neck cancer patients, adequate 9-field IMRT plans are now achieved, and IMRT is delivered throughout the entire radiation course. We are now also able to more accurately calculate parotid dose.

Because of the promising locoregional control in the two initial cohorts of this Phase II study (16,17), the last cohort (not analyzed in the present report) was treated with further dose reductions (36, 51 and 72 Gy to PTV_1, PTV_2, and PTV_3 respectively) in an effort to diminish toxicity (53). Nearly all of these patients were treated with IMRT. Perhaps a benefit of IMRT with intensive chemotherapy will become more apparent with reduced radiation doses. A recently published case study provides detailed input and output dose-volume parameters for a typical IMRT treatment plan using these doses (54).

Future directions include more directed attempts at reducing late xerostomia and swallowing complications by better sparing of the parotids, submandibular glands and oral cavity when feasible. In order to improve post-treatment swallowing function, attempts should also be made to spare the pharyngeal constrictors and the glottic and supraglottic larynx when these structures are not involved with cancer (55). IMRT in advanced head and neck cancer is certainly promising and warrants further study.

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