Published in final edited form as:

Am J Clin Oncol. 2015 December ; 38(6): 588–594. doi:10.1097/COC.0000000000000001.

WHOLE-FIELD SEQUENTIAL INTENSITY-MODULATED RADIOTHERAPY FOR LOCAL-REGIONAL ADVANCED HEAD- AND-NECK SQUAMOUS CELL CARCINOMA

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Abstract

Purpose—There is little published data on the technique and results of whole-field (WF) sequential-intensity-modulated radiotherapy (S-IMRT) for patients with head and neck squamous-cell carcinoma (HNSCC). We report the treatment outcomes, adverse events (AEs), and dosimetric parameters in local–regional advanced (LRA) HNSCC patients treated with the WF S-IMRT technique.

Methods—The IRB approved this retrospective study. Patients received WF S-IMRT with or without concomitant chemotherapy. Three separate IMRT plans corresponding to three planning target volumes were generated. This study reports patient and tumor characteristics; treatment-induced acute AEs based on CTCAE version 3.0; chronic AEs according to RTOG scale and treatment outcomes; local–regional control (LRC); distant metastases (DM); relapse-free survival (RFS); and overall survival (OS).

Results—Between January 2003 and December 2010, 103 patients with LRA HNSCC were treated either definitively or postoperatively with WF S-IMRT, with (99 patients) or without (4 patients) concurrent chemotherapy. The median age was 55 years (range 30–89). The median cumulative target dose was 70 Gy (range 60–75 Gy). At a median follow-up of 40 months (range 4–95 months), the 2- and 5-year rates of OS were 94% and 77%; RFS were 90% and 84%; LRC were 97% and 93%; and DM were 9% and 11%, respectively. Grade 3 acute AEs included mucositis (68%); dysphagia (35%); weight loss (19.6%); and xerostomia (7.8%). Chronic worst

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Disclosure Statement: There is no actual or potential conflict of interest with the production and publication of this work. No author has a direct or indirect commercial financial incentive associated with the publication of this article.

grade 3 AEs included xerostomia (21.9%); weight loss (12.8%); and dysphagia (12.5%). Chronic grade 3 AEs at last follow-up included weight loss (6.25%); dysphagia (6.2%); and xerostomia (6.2%). No patient had an acute or chronic grade 4 AE, brachial plexopathy, or spinal cord injury.

Conclusion—WF S-IMRT results in excellent tumor control and an acceptable toxicity profile in LRA HNSCC patients treated with this technique.

Keywords

Whole-field; Sequential-IMRT; Head-and-Neck Cancer

INTRODUCTION

Concurrent chemoradiotherapy (CRT) is commonly used for local–regional advanced (LRA) head and neck squamous cell carcinoma (HNSCC) (1). Although CRT improves treatment outcomes, it results in higher treatment–induced acute and chronic adverse events (AEs) (2–3).

Intensity–modulated radiation therapy (IMRT) has been increasingly adopted as an effective radiation technique that provides excellent local–regional control (LRC), fewer treatment–induced AEs, and improved quality of life (QOL) (4–9).

IMRT techniques vary according to institutional preference, with most institutions using either simultaneous integrated boost (SIB) or sequential-IMRT (S-IMRT). SIB-IMRT uses multiple radiation beams to simultaneously irradiate the tumor target and adjacent areas to different doses during a single treatment session, resulting in higher dose per fraction for gross target volume (GTV), and lower doses per fraction for areas at low and intermediate risk of harboring microscopic disease. S-IMRT uses sequentially shrinking fields with the same fraction size throughout the entire course of treatment. Whole-field (WF) IMRT entails treating the entire HNSCC target volume (TV) without a junction between upper and lower neck fields.

SIB-IMRT requires one treatment plan and is more conformal, (10) while S-IMRT requires multiple plans but delivers the same fraction size used historically, as reported in published studies with longer follow-up. Because of its larger fraction size, the SIB technique results in a higher biological dose to normal tissues embedded in primary TV, and has the potential for increased AEs (11). However, the SIB-IMRT delivers smaller fraction size (1.65–1.8 Gy/fraction) to low and intermediate risk microscopic disease in the neck potentially reducing normal tissue toxicity embedded in these targets. This advantage is offset due to higher total dose delivered to these targets in SIB-IMRT technique, in order to achieve comparable Biological Equivalent Dose (BED) delivered with S-IMRT using conventional fractionation.

There is a paucity of published data on the technique and treatment outcome of WF S-IMRT (9). In our study, we report treatment outcomes, acute and chronic AEs, and dosimetric parameters in the largest series of LRA HNSCC patients treated with WF S-IMRT technique.

METHODS AND MATERIALS

Patient selection and staging

Our Institutional Review Board approved this study, which includes patients with LRA HNSCC (oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, and unknown primary). These patients presented to our department between January 2003 to December 2010 and were treated consecutively, either postoperatively or definitively, using WF S-IMRT with or without chemotherapy.

All patients had a complete physical examination, blood work-up, and imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), as indicated. Feeding was assured and, when necessary, a feeding tube was used. Patients received a thorough dental evaluation and pretreatment swallowing study before they began treatment.

Treatment planning

All patients were immobilized with an aquaplast mask. All patients underwent a planning CT scan with the majority receiving IV contrast. CT imaging included the region between the vertex superiorly and the carina inferiorly, with a slice thickness of 3 mm.

Target volumes

1. Definitive WF S-IMRT—The GTV included clinically and/or radiologically visible disease. Clinical target volume 1 (CTV₁) included GTV and high- and low-risk elective nodal regions in the neck, with a 1–2 cm margin. Clinical target volume 2 (CTV₂) included GTV and high-risk elective nodal region with 0.75–1.5 cm margin. Clinical target volume 3 (CTV₃) included GTV expanded by 0.5–1 cm to cover any microscopic soft-tissue extension.

Three planning target volumes (PTV_{1–3}) were created that encompassed corresponding CTV with a margin of 3–5 mm to account for set-up and patient movement errors. Later on, for the sake of simplicity, we only outlined GTV and three PTVs, described above. We used the axial images from the planning CT to identify nodal levels in the neck, as described by Som *et al.* (12). We used the historical data primarily for neck metastases, summarized by Chao *et al.* (13) to stratify nodal disease as high-risk and low-risk for elective neck irradiation.

2. Post-operative WF S-IMRT—The surgical bed was defined as the area of preoperative GTV and the operated area that included the resected tumor, the lymph nodes involved, and postsurgical changes. CTV₁ included the surgical bed and regional high- and low-risk elective nodal chain with a 1–2 cm margin. CTV₂ included the surgical bed and high-risk elective nodal chain with a 1–2 cm margin. In patients with high-risk features such as extra-capsular extension (ECE), the surrounding soft tissue was included with a generous margin. Each CTV was expanded by 3–5 mm to create PTV₁ and PTV₂; later on, for simplicity's sake, the surgical bed and 2–3 PTVs were created. In both definitive and postoperative S-IMRT, TVs were drawn 2–3 mm deeper to the skin surface to spare dermal structures unless the gross tumor or ECE was very close to the skin.

Dose specifications

Radiation doses were sequentially prescribed using conventional fractionation of 180–200 cGy or 150 cGy BID according to institutional protocol. Typically, low-risk target volumes (PTV₁) received 45–50 Gy; intermediate to high-risk targets (PTV₂) received 56–66 Gy; and the gross tumor with expansion (PTV₃) was treated to 70–72 Gy. Three separate IMRT plans corresponding to each PTV were generated and whole-neck IMRT was used (Fig. 1). Every attempt was made to ascertain that the prescribed dose covered 95% of the TV, with the hot spot not exceeding 10% of the prescribed dose.

Dose Optimization

For all target PTV's, maximum dose was used to restrict dose to less than 110% of the prescribed dose, while maximum DVH was used to restrict the 105% dose volume inside PTV and minimum DVH used to ascertain that at least 95% of the PTV is covered by 100% of the prescribed dose.

For normal structures, a combination of max dose, max DVH and max Equivalent Uniform Dose (EUD) were used as optimization criteria. To achieve a clinically acceptable plan, the objective values and weights were iteratively adjusted with the following order of priority: (1) minimize the maximum dose to the serial organs like the spinal cord and brainstem (2) minimize the mean dose to the swallowing organs at risk like the pharyngeal constrictors, larynx, and post-cricoid esophagus, and (3) minimize the mean dose to parotids and oral cavity.

Organs at risk

For each patient, 27 organs at risk (OARs) were outlined and dose–volume histograms (DVH) were generated. OARs included: brain stem; pituitary gland; spinal cord (SC); cochlea; optic nerve; optic chiasm; eyes; parotid glands; submandibular glands; oral cavity; oropharynx; base of the tongue (BOT); entire larynx; supraglottic larynx; glottis larynx; hyoid bone; postcricoid-esophagus; cervico-thoracic esophagus; lips; mandible; superior, middle, inferior, and combined pharyngeal constrictors; carotid vessels; thyroid gland; and the brachial plexus (BP). The doses to each TV and OAR were reported and analyzed. Pinnacle inverse planning system versions 6.2b, 7.6c, 8.0m, and 9.0 using computerized optimization (Philips Radiation Oncology Systems, Fitchburg, WI) were used to generate three separate plans for PTV₁, PTV₂, and PTV₃, as well as cumulative DVHs.

Treatment-plan statistics for relevant OARs were exported from the Pinnacle 3 treatment planning system file of each patient, using a customized script that deposited the data into text files. The statistics were taken from composite trials that contained beam data from all PTVs used in a given patient's treatment. For all OARs, volume and maximum, minimum, and mean doses were exported. For ease of use, data were then transferred to Excel files using a MATLAB program, although this program performed no mathematical manipulation.

The median, mean, minimum, maximum, and standard deviation of the maximum and mean doses in cGy, as well as median and mean volumes in cc for all OARs, were collected and reported.

Follow-up

Patients were seen for follow-up 1 month after radiation was completed, then approximately every 3 months during the first year, every 4 months during the second year, and every 6 months for the subsequent 5 years, with yearly follow-up thereafter. Physical examination included fiberoptic laryngoscopy at each follow-up visit. The first imaging study (CT images and/or FDG-PET) was obtained 1–3 months after treatment to assess response and thereafter as indicated; for all patients, an imaging study was usually performed once a year.

Toxicities were categorized into acute toxicity according to the Common Terminology Criteria (CTC) for AEs, version 3.0 (<90 days post-treatment); and chronic toxicity according to the RTOG scale. To assess the incidence of severity of complications and their resolution during follow-up, the worst chronic toxicity and toxicity at the most recent follow-up were reported. Toxicities were registered at each treatment check and at each follow-up visit. Toxicities were coded for skin, mucosa, dysphagia, salivary gland, mandible, thyroid function, larynx, pain, and weight loss. Other variables included G-tube placement, cervical/esophageal stricture formation, or any other significant toxicity a patient experienced.

Statistical analyses

Descriptive statistics were shown in the form of frequencies, and percentages for categorical variables, and medians, means, standard deviations, minimums and maximums for continuous variables. Univariate logistic regression was used to relate the occurrence of death, local-regional recurrence, or aspiration according to patient or radiation-dose parameters. Relapse-free survival (RFS) is defined as the time from first radiation treatment to any local, regional, or distant tumor progression, whichever occurred first. LRC is defined as the time from first radiation treatment to any local or regional tumor progression, whichever occurred first. Distant metastases-free survival (DMFS) is defined as the time from first radiation treatment to any distant tumor progression. Overall survival (OS) was measured from the first radiation treatment to death as a result of any cause. OS curves were estimated using the Kaplan-Meier method and compared across site and stage using the log rank test. RFS, LRC and DMFS were estimated using the method of cumulative incidence (14) and differences were assessed by Gray's test (15).

RESULTS

Patient and tumor characteristics

From January 2003 to December 2010, 103 LRA HNSCC patients (stages III, IVA, and IVB) were treated with WF S-IMRT with (99 patients) or without (4 patients) concurrent chemotherapy. The median follow-up for all patients was 40 months (range 4–95 months, mean 42.3 months). Table 1 lists patient demographics, including sex, age, race, smoking

history, performance status, tumor characteristics including site and stage distribution, and treatment modalities.

Radiation therapy

The median cumulative radiation dose was 70 Gy (range 60–75 Gy, mean 69.35 Gy, SD 4.01Gy) and the median treatment duration was 50 days (range 41–91 days, SD 7.6 days). Every patient had WF S-IMRT with the same fraction size throughout the treatment course. All patients who had BID IMRT had 1.5 Gy per fraction, according to institutional protocol. Patients with once-a-day IMRT had 1.8–2 Gy/fraction, with the majority of patients receiving 2 Gy/fraction. The maximum and mean doses in cGy and mean and median volumes for all OARs are shown in Table 2.

Treatment outcomes

Of the 103 patients, 3 patients (2.9 %) had local–regional failure only; 9 patients (8.7%) had DM only; and 3 patients (2.9 %) had both local–regional failure and DM. The median 2-year and 5-year OS, RFS, LRC, and DMFS are stratified and detailed in Table 3 and Fig. 2. Log-rank and Gray's tests showed no statistical significance for stratification by stage or tumor site. Smokers had a significantly higher incidence of death (odds ratio=2.26, $p=0.003$) and local-regional recurrence (odds ratio=2.6, $p=0.037$).

Adverse events

All patients in our study were followed regularly to monitor acute and chronic AEs. Table 4 shows acute and chronic AEs (worst and at last follow-up visit) based on CTCAE version 3.0 and RTOG scale, respectively. None of the patients had SC injury or brachial plexopathy. Two patients (1.9%) had mandibular osteoradionecrosis; one was treated by hyperbaric oxygen and the other had mandibular resection and a fibula flap. Four patients had aspiration (3.88%), with smoking significantly associated with aspiration (odds ratio=1.87, $p=0.021$). Feeding tubes (FTs) were used in 35 patients (34%) during or soon after their treatment course; only 3 patients (2.9%) were maintained on FTs during their most recent follow-up visit.

Logistic regression was used to find a statistically significant association between aspiration and maximum radiation dose delivered to superior, middle, inferior, and combined pharyngeal constrictors; BOT; supraglottic and whole larynx ($P=0.011$, 0.01, 0.01, 0.013, 0.011, 0.012, and 0.013, respectively); and mean doses to middle and inferior pharyngeal constrictors and supraglottic larynx and whole larynx ($P=0.033$, 0.05, 0.025, and 0.02, respectively). Also, there was a statistically significant association between grade 3 chronic dysphagia and maximum RT dose delivered to postcricoid esophagus ($P=0.05$) and mean RT dose delivered to the cervicothoracic esophagus ($P=0.005$). There was a statistically significant association between mean dose delivered to combined parotid glands and xerostomia ($P=0.039$), but no significant association between maximum or mean doses and combined submandibular glands.

DISCUSSION

The majority of published data on the use of IMRT for the treatment of HNSCC are based on the SIB technique (5–8). With the introduction of IMRT, to prevent unintended consequences of new technology, we used S-IMRT to deliver historically proven cumulative dose of 7000 cGy to areas of gross disease, and 4600 and 6000 cGy to areas of low risk and high risk microscopic disease respectively, with fraction size of 180 – 200 cGy throughout the treatment course. In 22% of the patients reported in this study, 150 cGy BID fractionation was used as per an institutional protocol. We also used WF S-IMRT to prevent dosimetric and set-up uncertainties at the junction between the upper and lower neck fields. At the start, our radiation fields were generous. However, gradually, we started to reduce dose to salivary glands, oral cavity, and OAR involved in swallowing. In patients with positive level II neck nodes, we did not attempt to spare ipsilateral parotid and submandibular glands that might explain the relatively higher mean doses delivered to the salivary glands in our cohort.

In our study, the 2-year LRC, DMFS, RFS, and OS were 97%, 91%, 90%, and 94%, respectively; and the 5-year LRC, DMFS, RFS, and OS were 93%, 89%, 84%, and 77%, respectively. Recently, Garden *et al.* (5) reported a retrospective analysis of 776 oropharyngeal cancer patients (OPC) treated with IMRT during the period between 2000 and 2007; 5-year LRC, overall recurrence-free survival, and OS were 90%, 82%, and 84%, respectively. The majority of those patients (89%) were treated with SIB IMRT with split beam to treat the lower neck. Similar to our study, smoking was associated with poorer survival ($P<0.001$). Chao *et al.* (6) reported the 2-year LRC of 79% and 90% in 126 HNSCC patients who were treated with split-field IMRT using the SIB technique for definitive and postoperative treatments, respectively.

Feng *et al.* (7) reported a prospective study that included 73 patients with stages III to IV OPC treated with chemo-IMRT using the WF SIB technique. At a median follow-up of 36 months, 3-year disease-free survival and LRC were 88% and 96%, respectively. Our results are comparable to the 3-year actuarial LRC, DMFS, PFS, and OS rates of 92%, 86%, 82%, and 91%, respectively, for 41 LRA HNSCC patients treated with IMRT; and most (32 patients) were treated with the SIB technique, as reported by Lee *et al.* (8). Yao *et al.* (9) reported comparable 2-year LRC (92%), DMFS (87%), and OS (85%) for 150 HNSCC patients who were treated using different IMRT techniques; most patients had LRA disease (85.4%). In this report, patients with OPC had significantly better ($P=0.005$) 2-year LRC (98%) than patients with oral-cavity (78%) and laryngeal cancer (85%), although our study showed no significant differences among patients in whom different tumor sites ($p=0.42$) were treated.

The WF S-IMRT-induced AEs in our study were relatively tolerable and acceptable. None of the patients had spinal cord or brachial plexus damage or any grade 4 acute or chronic AEs. Our data regarding the need of FTs during the acute phase of treatment and on follow-up (34%) compares to the 47% reported by Garden *et al.* (5) and the 29% reported by Feng *et al.* (7). In our study, at the last follow-up visit, only 3 patients (3.1%) required FTs and 6 patients (6.2%) had grade 3 xerostomia. Our study showed an incidence of mandibular

osteoradionecrosis (1.9%) comparable to that reported by Garden *et al.* (3.9%) (5). Our study also showed the association between the maximum and mean RT doses delivered to pharyngeal constrictors and the larynx (specifically supraglottic larynx), and the likelihood of treatment-induced aspiration.

Our study and several other reports have shown that IMRT provides excellent LRC and acceptable AEs, and improves QOL (5–9). Dosimetry studies based on 5 HNSCC patients and 1 schematic HNSCC example have shown that, in terms of equal PTV coverage, SIB is more conformal than S-IMRT (10–11). However, Lamers-Kuijper *et al.* (16) evaluated 50 patients and concluded that S-IMRT results in a better treatment plan for most patients compared with SIB-IMRT if the boost PTV is more than 1 cm away from at least one parotid gland. In certain cases, more conformity and steep dose gradients may result in marginal misses (17–19). From the beginning of our study we did not try to spare ipsilateral parotid glands in our patients with positive level II lymph nodes, therefore none of our patients had ipsilateral marginal failure in the parotid region.

Dabaja *et al.* (20) and Mendenhall *et al.* (18) reported the advantage of WF-IMRT if there was uncertainty at the match line, compared with the traditional half-beam split-field IMRT where the tumor and upper neck are being treated with IMRT and the lower neck is treated with a matching anterior beam. WF S-IMRT eliminates possible junction uncertainties associated with the split-field SIB technique, particularly in patients with large-neck disease and a low-lying primary tumor site. Daly *et al.* (21) have reported a failure at the junction between upper- and lower-neck fields. However, WF IMRT can result in an increased radiation dose to midline structures in the lower neck-field (22).

We believe that SIB and WF S-IMRT are not competing but complementary techniques, and that many factors should be considered when selecting the technique that best suits each clinical scenario in order to achieve an individualized treatment plan. These factors include the expertise of the radiation oncologist; the experience of the institution; the availability of resources and personnel (WF S-IMRT requires the development of 2–3 IMRT plans per patient vs. a single IMRT plan in SIB); patient preference (SIB might entail a slightly shorter treatment duration); and the tumor location, including critical OARs in primary TV, with the SIB technique resulting in a higher, biologically equivalent, normalized total dose to these OARs (11).

CONCLUSION

Our study reports that WF S-IMRT results in excellent tumor control and an acceptable toxicity profile in this largest series of LRA HNSCC patients. A controlled comparison of SIB vs. S-IMRT would be of interest.

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Figure 1.

A patient with stage IVA (T₂ N_{2b} M₀) tonsillar SCC: Gross Target Volume (red); Planning Target Volume₁ (PTV₁) (green); PTV₂ (yellow); and PTV₃ (blue).

Figure 2. Local-regional control; distant metastases-free survival; relapse-free survival; and overall survival.

Table 1

Patient demographics, tumor characteristics, and treatment modalities

Age			
	Median	55	
	Range	30–89	
		N	%
Sex			
	Male	86	83.5
	Female	17	16.5
Smoking			
	Smoker		
	<20 p/y	26	25.49
	20–40 p/y	25	24.51
	>40 p/y	15	14.71
	Unknown	1	0.9
	Non-smoker	36	35.29
ECOG Performance status			
	0	68	66.02
	1	35	33.98
Race			
	White	84	81.55
	Black	11	10.68
	Other	8	7.77
Tumor Site			
	Oral Cavity	4	3.88
	Oropharynx	60	58.25
	Hypopharynx	3	2.91
	Nasopharynx	9	8.74
	Larynx	14	13.59
	Unknown Primary	13	12.62
T Stage of Primary tumor			
	T ₀	13	12.62
	T ₁	21	20.39
	T ₂	42	40.78
	T ₃	16	15.53
	T ₄	11	10.68
Nodal Stage			
	N ₀	11	10.68
	N ₁	14	13.59

	N ₂	74	71.84
	N ₃	4	3.88
Stage			
	III	19	18.45
	IVA	79	76.7
	IVB	5	4.85
Feeding Tube			
	Yes	35	33.98
	No	68	66.02
Treatment Modality			
	Definitive Chemoradiation	78	75.73
	Radiation Therapy	1	0.97
	Surgery and Postoperative Radiation	3	2.91
	Surgery and Postoperative Chemoradiation	21	20.39
Dose per Fraction			
	1.5 Gy BID	23	22.33
	1.8–2 Gy QD	80	77.67

Table 2

Radiation doses to organs at risk reported in cGy; volumes reported in cc

Area of Interest	Maximum Dose (cGy)			Mean dose (cGy)			Volume (cc)	
	Median	Mean	SD	Median	Mean	SD	Median	Mean
Brain Stem	4974.58	4632.49	1113.8	2153.38	2237.77	961.36	27.35	28.05
Spinal Cord	4740.98	4767.63	766.39	3081.18	3166.39	764.76	21.41	21.52
Lt Cochlea	4358.3	4010.69	1850.8	3714.04	3293.93	1674.28	0.72	0.86
Rt Cochlea	4206.66	4026.96	1770.9	3232.12	3236.66	1611.77	0.76	0.89
Lt Optic Nerve	361.38	526.84	752.12	323.27	423.74	536.26	0.7	3.36
Rt Optic Nerve	365.6	535.98	771.31	319.32	430.88	618.61	0.75	0.85
Lt Eye	371.31	617.37	795.76	250.33	305.6	314.47	8.93	8.64
Rt Eye	377.61	823.77	1379.3	249.78	433.09	894.23	8.91	9.5
Chiasm	389.13	659.23	1109.7	347.45	571.23	995.91	1.37	1.6
Pituitary Gland	535.26	986.72	1401.2	453.58	791.97	1158.09	0.57	0.65
Lt Parotid	7022.74	6717.87	1157.2	4677.04	4717.9	1866.18	26.86	27.62
Rt Parotid	7216.67	6832.62	983.11	4836.7	4602.48	1786.79	27.56	28.08
Cb Parotid	7509.4	7376.47	631.29	4611.08	4638.36	1121.77	55.56	55.77
Rt Submandibular Gland	7424.31	7234.4	689.6	7163.49	6844.55	841.54	8.96	9.34
Lt Submandibular Gland	7457.66	7163.48	916.47	7174.58	6787.66	1040.42	8.84	9.35
Cb Submandibular Gland	7548.35	7394.99	695.29	6907.23	6741.55	974.65	17.78	18.12
Oral Cavity	7514.51	7363.95	665.91	6276.85	6049.23	1182.79	73.31	73.21
Lips	4773.32	4712.26	1446.5	3082.37	3096.79	1164.1	7.53	8.71
Oropharynx	7568.19	7451.38	592.27	7185.86	6762.44	1033.83	76.81	78.63
Base of Tongue	7546.42	7403.74	592.92	7221.39	6938.61	804.47	24.06	25.52
Supraglottic Larynx	7513	7427.27	502.59	6796.23	6669.28	690.53	22.43	23.57
Glottic Larynx	7371.15	7109.86	755.07	6225.59	6125.37	958.13	13.69	13.66
Larynx (entire)	7517.58	7444.33	498.38	6555.48	6449.25	756.77	41.5	41.16
Superior Pharyngeal Constrictors	7544.95	7428.23	586.85	6978.75	6460.4	1358.77	17.87	18.66
Middle Pharyngeal Constrictors	7463.08	7358.62	579.96	7032.5	6892.6	723.01	3.11	3.17
Inferior Pharyngeal Constrictors	7401.13	7300.91	541.53	6384.57	6274.3	834.97	4.98	5.36

Area of Interest	Maximum Dose (cGy)			Mean dose (cGy)			Volume (cc)	
	Median	Mean	SD	Median	Mean	SD	Median	Mean
Cb Pharyngeal Constrictors	7565.67	7484.57	517.19	6769.89	6527.91	885.66	25.3	32.91
Mandible	7517.23	7351.36	655.04	5763.62	5585.78	1135.2	74.76	75.72
Hyoid Bone	7492.83	7396.56	569.03	7162.04	6975.64	650.8	4.07	4.21
Thyroid Gland	7303.53	6951.71	823.33	5783.9	5685.8	1072.28	15.68	24.7
Rt Brachial Plexus	7115.03	6930.28	766.03	4961.42	4946.71	740.97	11.59	11.71
Lt Brachial Plexus	7156.32	6880.33	943.63	4927.94	4935.56	865.84	11.33	12.13
Cb Brachial Plexus	7456.38	7328.29	578.76	4935.77	4919.06	759.19	22.89	23
Lt Carotid	7491.75	7148.01	754.43	6149.68	6069.4	891.05	8.77	9.82
Rt Carotid	7433.79	7093.38	995.7	6281.38	6131.94	909.95	8.86	10.04
Post-Cricoid Esophagus	6473.25	6366.83	998.29	5815.16	5692.06	1168.71	1.38	1.64
Cervico- Thoracic Esophagus	6069.83	6018.72	1036.5	3261.2	3404.34	1245.02	12.16	12.48

LT=Left; RT=Right; CB=Combined

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Table 3

Treatment outcomes

Treatment Outcomes		Median in months	2-years (%)	5-years (%)	Log-rank P value
Overall Survival (OS)		85.91	94	77	
OS According to Primary Tumor Site					
	Oral Cavity	NA	100	75	0.85
	Oropharynx	NA	97	84	
	Nasopharynx	70.14	88	88	
	Hypopharynx	NA	100	50	
	Larynx	63.87	81	61	
	Unknown Primary	NA	100	86	
OS According to Tumor Stage					
	III	70.14	87	77	0.29
	IVA	85.91	96	73	
	IVB	NA	100	100	
Relapse-Free Survival (RFS) ANY EVENT Local, Regional, or Distant					
RFS According to Tumor Site					
	Oral Cavity	NA	100	75	0.72
	Oropharynx	NA	89	84	
	Nasopharynx	67.94	87	87	
	Hypopharynx	NA	100	100	
	Larynx	NA	84	72	
	Unknown Primary	NA	92	92	
RFS according to stage					
	III	67.94	94	86	0.41
	IVA	NA	88	83	
	IVB	NA	100	100	
Local-regional Control (LRC)					
LRC According to Tumor Site					
	Oral Cavity	NA	100	75	0.42

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Treatment Outcomes		Median in months	2-years (%)	5-years (%)	Log-rank P value
	Oropharynx	NA	98	95	
	Nasopharynx	NA	87	87	
	Hypopharynx	NA	100	100	
	Larynx	NA	91	91	
	Unknown Primary	NA	100	100	
LRC According to Stage					0.14
	III	NA	94	86	
	IV A	NA	97	95	
	IV B	NA	100	100	
Distant Metastases-Free Survival (DMFS)					
DMFS According to Tumor Site				89	
	Oral Cavity	NA	100	100	0.56
	Oropharynx	NA	89	89	
	Nasopharynx	NA	100	100	
	Hypopharynx	NA	100	100	
	Larynx	NA	84	72	
	Unknown Primary	NA	92	92	
DMFS According to Stage					0.55
	III	NA	94	94	
	IV A	NA	89	87	
	IV B	NA	100	100	

NA=median was not attained because of too few events

Table 4

Treatment–induced adverse events (AE)

	Acute CTC AE Grade						Worst Chronic RTOG AE Grade						Last Follow-up RTOG AE Grade					
	0-1		2		3		0-1		2		3		0-1		2		3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Skin	4	3.88	52	50.49	47	45.63	57	59.38	30	31.25	9	9.38	59	60.82	31	31.96	7	7.22
Dysphagia	27	26.21	40	38.83	36	34.95	64	66.67	20	20.83	12	12.5	82	84.54	9	9.28	6*	6.19*
Xerostomia	10	9.71	85	82.52	8	7.77	25	26.04	50	52.08	21	21.88	61	62.89	30	30.93	6	6.19
Pain	45	43.69	58	56.31	0	0	94	97.92	2	2.08	0	0	96	100	0	0	0	0
Weight loss	30	29.41	52	50.98	20	19.61	57	60.64	25	26.6	12	12.77	80	83.33	10	10.42	6	6.25
Larynx	87	90.63	9	9.38	0	0	91	96.81	3	3.19	0	0	91	96.81	3	3.19	0	0
Mucositis	5	4.85	28	27.18	70	67.96												

CTC AE=Common Toxicity Criteria for Adverse Events

RTOG= Radiation Therapy Oncology Group

None of the patients had Grade 4 acute, or chronic worst, or at last follow-up AE.

* Three patients were maintained on feeding tubes and three patients had esophageal dilatation.