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Outcomes after Radiation Therapy for T2N0/Stage II Glottic Squamous Cell Carcinoma

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Abstract

BACKGROUND—We report outcomes for patients with T2N0M0 glottic squamous cell carcinoma (SCC) treated with radiation therapy (RT).

METHODS—Patients who received definitive RT for T2 glottic SCC from 2000 through 2013 were retrospectively reviewed.

RESULTS—113 patients were analyzed (median follow-up time 91 months; 85 patients received 3D-CRT and 28 received IMRT). Fractionation was conventional (58%) or altered (42%); 20 patients (18%) received concurrent chemotherapy. 5-year LC was 83% for the 3D-CRT vs. 81% for the IMRT group (P=0.76). The ultimate locoregional control at 5 years was 100% for IMRT vs. 91% for 3D-CRT (P=0.1). The 5-year OS was 78% for 3D-CRT vs. 81% for IMRT (P=0.83). On multivariate analysis, younger age was the only independent predictor of improved OS (P=0.0002).

CONCLUSIONS—Oncologic and survival outcomes were excellent for patients with T2N0 glottic cancer. Patients treated with IMRT and 3D-CRT had no statistically significant differences in all investigated endpoints.

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Keywords

T2; larynx; outcomes; radiotherapy; survival

INTRODUCTION

Radiation therapy (RT) is the treatment of choice for early-stage glottic cancer at many institutions [1–7]. Alternatives to external beam RT in the treatment of early-stage glottic cancer include transoral laser excision and open partial laryngectomy, with similar oncological outcomes to external beam RT, although there may be differences in cost and voice outcomes [8–10]. T2 glottic cancer is relatively uncommon and should be reported as a separate disease entity as it has different prognosis and treatment outcomes compared with T1 disease. However, the majorty of early-stage glottic cancer studies report the RT outcomes of both T1 and T2 disease combined together without stratification [7,11,12]. It is also important to study the outcomes of T2 glottic cancer in the current treatment era, with the advent of more complex radiation therapy techniques.

The three main controversies in treatment of T2 glottic cancer are as follows: First, intensity-modulated radiation therapy (IMRT) is not currently considered the standard of care for early-stage disease, despite its proven dosimetic benefits in normal tissue sparing. In particular for glottic cancer, the use of IMRT has been driven mainly by a desire to reduce the dose to the carotid arteries, which is hoped to reduce the risk of subsequent stroke [13–16]. At our institution, IMRT is used to treat T1 glottic cancer for carotid artery dose sparing and has led to excellent oncologic outcomes [17]. Although IMRT may be beneficial for T1 disease, it may not be ideal for all patients with T2 disease, especially those with bulky disease, with the corresponding increases in uncertainties in target delineation and risk of missing subclinical disease at the primary site or adjacent lymph nodes [18].

The second controversial topic in stage II glottic cancer are the uses of chemotherapy or altered RT fractionation, especially for patients with impaired vocal cord mobility. Limited series have shown that the addition of concurrent chemotherapy could be beneficial for stage II glottic cancer [19–21], whereas other studies have shown no real benefit [22,23]. Similarly, altered RT fractionation may be of benefit, but the the only prospective randomized trial conducted to date showed only a trend to an improvement in local control [24].

The third controversy is whether elective nodal irradiation is required. The risk of nodal disease in T2 glottic cancer is small but higher than that in T1 disease, which has direct bearing on the safety of using IMRT and limited volumes to achieve carotid artery radiation dose sparing for T2 cancers.

The aim of this study was to report oncologic and functional outcomes for patients with stage II (i.e., T2N0M0) squamous cell carcinoma (SCC) of the glottis treated with RT. We investigated the potential correlations of patient- and treatment-related factors with oncologic and survival endpoints. We also focused on outcomes comparison for IMRT versus conventional RT techniques, and for treatment intensification with chemotherapy or altered fractionation versus standard treatment.

PATIENTS AND METHODS

This single-institution retrospective chart review was conducted after approval by the appropriate institutional review board. Patients were identified through an instituitional registry as having T2N0M0 SCC of the glottic larynx and treated with definitive RT from 2000 through 2013. Disease stage was reviewed according to the 8th (2018) edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Information on demographics (age at diagnosis, sex, ethnicity), smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, clinical factors (tumor grade, disease stage, and pathologic characteristics), imaging findings on contrast-enhanced computed tomography (CT) scans, and treatment modalities (chemotherapy and its sequence with RT, RT total dose, fractionation, and delivery technique) was extracted from the electronic medical records. Biologically effective dose (BED) was calculated by using the simple BED equation [25], and adjusted for overall treatment time with the following formula:

$$\text{Overall treatment time-adjusted BED} = \text{BED} - (\text{Ln}(2)/0.3) \times ((\text{Overall treatment time} - 22)/3)$$

Outcomes were categorized as local recurrence (at the site of primary tumor), locoregional recurrence (at the site of primary tumor and regional lymph nodes), or distant metastasis. Because of the difficulty in distinguishing distant metastasis from a second primary tumor in this retrospective review, all such cases were considered distant metastasis. Death was classified as cancer-related or non-cancer-related depending on the presence of active cancer at the time of death. Functional outcomes including the need for a feeding tube, dysphagia, and hoarseness at last follow-up visit were also recorded. All cerebrovascular events were also recorded. These findings were coded and entered into a database for analysis.

Statistical Analyses

Descriptive statistics were used to analyze distribution of the sample by sex, ethnicity, age, clinical data, treatment modality, fractionation schemes, and functional outcomes. The Kaplan-Meier product limit method was used to calculate survival endpoints, and log-rank tests were used to compare the survival distributions of two samples. All survival endpoints were calculated from the date of diagnosis until the date of the event. Local control (LC) was defined as time without local recurrence, with any local recurrence coded as an event (and all others censored); locoregional control (LRC) as time without locoregional disease, with any local recurrence or neck recurrence coded as an event (and all others censored); ultimate locoregional control (uLRC) as time without a second locoregional disease after salvage surgery; freedom from distant metastasis (FDM) as time without disease outside the therapy fields, with disease outside the treated fields coded as an event (and all others censored); disease-specific survival (DSS) as death from disease as an event (and all others censored); and overall survival (OS) as death from any cause as an event (and all others censored). Both univariate and multivariate Cox proportional hazards analyses were used to investigate potential correlations between patient- and treatment-related factors (age at diagnosis, sex, smoking status, ethnicity, pathologic grade, vocal cord mobility, RT technique, time-adjusted BED, and chemotherapy use) and outcomes (disease control and survival endpoints). Univariate Cox proportional hazards analysis was also used to stratify LC, LRC, uLRC, and

OS by RT modality and assess the impact of IMRT as compared with conventional three-dimensional conformal radiotherapy (3D-CRT) or opposed laterals, as well as treatment intensification versus standard treatment. JMP 14 Pro statistical software (SAS Institute, Cary, NC) was used for data analysis, and statistical significance was determined by using a prespecified α of 0.05.

RESULTS

Patients

The study group consisted of 113 consecutive patients (85% men and 15% women). Mean age at the time of histologic diagnosis was 63 years (range 18–88). Most patients (90%) were fully active and able to carry on all pre-disease activities (ECOG PS score 0). Forty-seven patients (42%) had impaired VC mobility. Patient and disease characteristics are listed in Table 1.

Treatment

All patients were treated with curative intent; 69 (62%) were treated with 4–6 MV x-rays, and 44 (39%) were treated with Cobalt-60. Most patients (85 [75%]) received 3D-CRT with lateral opposed/oblique fields, with both fields treated at each session; the other 28 patients (25%) received IMRT for carotid sparing. Treatment characteristics are summarized in Table 2.

The 3D-CRT treatments were planned with two- or three-field techniques. No elective nodal irradiation was used, though with parallel opposed fields, the majority of level III was in-field. The IMRT treatment included the entire glottis, with no elective nodal irradiation. Various fractionation patterns and different chemotherapeutic radiosensitizers were used during the study period; 66 patients (58%) received standard fractionation, and 47 received altered fractionation, which included twice-daily treatment (29 patients), concomitant boost (15 patients), and 6 weekly fractions (2 patients [26]). The total RT dose ranged from 58 Gy to 79.2 Gy (median 70 Gy, mean total dose 70.8 ± 5.1 Gy). Most patients (93 [82%]) received RT without chemotherapy, and 20 (18%) received concurrent chemoradiation. The most commonly used chemotherapy regimen was concurrent cisplatin. 48 patients (42%) received some form of treatment intensification, 20 with chemotherapy and 32 with overall treatment time-adjusted BED ≥70 Gy (4 patients received both). Of the 47 patients with impaired vocal cord mobility, 23 (49%) received treatment intensification, 12 with chemotherapy and 14 with overall treatment time-adjusted BED ≥70 Gy (3 patients received both). Salvage surgery (total laryngectomy) was used for 26 patients who had residual tumor or developed recurrence.

Oncologic Endpoints

Median follow-up time was 91.2 months (interquartile range [IQR] 50.1−134.4) for all patients and 102.5 months (IQR 66.3–142.5) for patients alive at the time of analysis. By treatment modality, median follow-up time for patients treated with 3D-CRT was 130.5 months (IQR 78.0−159.0 months) and that for patients treated with IMRT was 66.3 months (IQR 53.3−103.2).

The 2- and 5-year actuarial LC rates 85% and 83%, respectively (Fig. 1). Isolated regional recurrences were encountered only in three patients (two from the 3D-CRT arm and one from the IMRT arm). LRC rates were 82% at 2 years and 80% at 5 years, with no differences by RT modality used (80% vs. 79% at 5 years for 3D-CRT vs. IMRT, respectively, P=0.9) or treatment intensification group (73% vs. 86% at 5 years for treatment intensification vs. none, respectively, P=0.07). The uLRC the rates were 93% at both 2 and 5 years, with all 7 failures after salvage treatment occurring in patients treated with non-IMRT techniques while all patients in the IMRT arm were salvaged successfully with total laryngectomy (91% vs. 100%, P=0.1). The FDM rates were 99% at 2 years and 98% at 5 years (Fig. 1), with no patients having isolated distant failure. The DSS rates for all patients were 93% at 2 years and 91% at 5 years (Fig. 2) and did not differ by vocal cord mobility (normal 94% at 2 and 5 years vs. impaired 93% at 2 years and 88% at 5 years; log rank p =0.33), nor by the use of treatment intensification (87% vs. 73% at 5 years for treatment instensification vs. none, respectively, P=0.5). The OS rates for all patients were 87% at 2 years and 79% at 5 years (Fig. 2) and did not differ by vocal cord mobility (normal 89% at 2 years and 80% at 5 years vs. impaired 85% and 78%; log rank P=0.99) nor by RT modality (3D-CRT 87% at 2 years and 78% at 5 years vs. IMRT group 89% and 81%; log rank P=0.83) nor by the use of treatment intensification. (80% vs. 79% at 5 years for treatment instensification vs. none, respectively, P=0.6).

Correlates with Survival and Other Endpoints

None of the examined clinical and treatment variables were associated with better LRC. Younger age (P=0.0068) was the sole factor associated with better DSS on univariate analysis, and remained significant on multivariate analysis (P=0.0049). Younger age (P<0.0001) and being a non-smoker (HR=0.34, P=0.0334) were associated with improved OS in univariate analysis, but ethnicity, pathologic grade, overall treatment time-adjusted BED, use of chemotherapy and RT modality were not. On multivariate analysis, younger age at diagnosis remained the only independent predictor of improved OS (P=0.0002).

Adverse Events and Functional Outcomes

Eighty-two patients (75%) developed laryngeal mucositis, which in most cases was a patchy pseudomembranous reaction. Grade 1 radiation dermatitis developed in 46 patients (41%), grade 2 in 48 patients (42%), and grade 3 radiation dermatitis in only 4 patients (4%). As for functional outcomes, 48 patients (43%) reported no subjective hoarseness at last follow-up, 83 patients (73%) reported no aspiration, and most patients (98 patients [88%]) did not require a feeding tube (6 patients needed a tube at 6 months, 5 patients at 12 months, and 11 at last follow-up). In patients who received treatment intensification, there was significantly more reported hoarseness (58% versus 33%, P=0.02). There were no significant differences in any of these adverse events and functional outcomes based on RT modality. Two patients had a carotid event at 7 and 8 years respectively after definitive RT (one was treated with 2D/3D-CRT, and one was treated with IMRT but had re-irradiation 3 years after his/her first course of RT).

DISCUSSION

In this series, definitive RT led to excellent oncologic outcomes for patients with T2 glottic cancer, with 5-year rates of LC (83%) and uLRC (93%) similar to those in the literature (Table 3). Notably, both LC and LRC rates for patients treated with IMRT were as good as, and certainly not inferior to, those for patients treated with 3D-CRT, and have the additional advantage of sparing the carotid artery. In this series, the lack of any elective nodal irradiation in the IMRT cohort did not increase rates of regional relapse, and patients with impairment in vocal cord mobility fared as well as those with intact mobility.

Several reports emphasize the dosimetric advantage of IMRT for carotid artery sparing, as carotid irradiation is well known to increase the relative risk of stroke and may limit the use of re-irradiation if needed [13,15,38]. For example, a Surveillance, Epidemiology, and End Results (SEER)-Medicare study showed that the 10-year risk of cerebrovascular events for patients with head and neck cancer was 34% after conventionally delivered definitive RT versus 26% after surgery alone ($P<0.01$) [39]. A recent series from our group on T1 glottic cancer showed no cerebrovascular events among patients treated with carotid-sparing IMRT versus 3% among patients treated with conventional RT [17]. In the current T2 series, only 2 patients developed a carotid event several years after RT.

The impact of IMRT on outcomes in T2 larynx remains controversial (9,16). Similar to our findings, a recent single-institution retrospective study of 139 patients who received moderately accelerated IMRT with daily laryngeal soft tissue matching reported a high 3-year LC rate of 89% [40]. On the other hand, a population-based analysis of 1,929 patients with early stage T1-T2N0 laryngeal cancer from the National Cancer Data Base revealed a statistically significant decline in OS from the use of IMRT relative to 3D-CRT, which was attributed to possible marginal miss or less dose to subclinically involved neck lymph nodes [41]. In the current series, no association was found between radiation therapy modality (3D-CRT/opposed laterals versus IMRT) and outcomes, a finding we attribute to the stringent IMRT quality assurance process used for patients with head and neck cancer [42] as well as our routine use of image-guided RT.

Patients given IMRT in this study were treated only to the primary site: the carotid arteries were spared, and so were the adjacent level III lymph nodes. In contrast, patients treated with opposed lateral fields receive level III nodal irradiation. Our isolated regional nodal recurrence rate, 2.7%, was no different than in conventionally treated patients and was comparable to published regional failure rates of about 5% [43]. The benefit of elective nodal irradiation in T2 glottic cancer is minimal at best, and its likely overshadowed by long-term carotid artery and other morbidity.

Patients with impaired vocal cord mobility are generally thought to do worse than those with intact vocal cord mobility [7,11,24,29,44–46]. A meta-analysis of 21 retrospective studies of patients with T2 glottic cancer showed impaired vocal cord mobility to be associated with a statistically significant decrease in LC [45]. In the prospective randomized RTOG 9512 study, LC, LRC, DFS, and OS were significantly worse among patients with impaired vocal cord mobility [24]. Contrarily, impaired vocal cord mobility was not associated with worse

outcomes in our study. We attribute this finding to selection bias, as approximately half of such patients received intensified treatment, with either altered RT dose fractionation or concurrent chemotherapy. Another potential explanation is inadequacies in the current American Joint Committee on Cancer staging system, as patients with T2 glottic cancer and impaired vocal cord mobility seem to have outcomes similar to patients with stage T3 cancer. The 5-year LC rate for patients with stage III and IV glottic cancer treated with concurrent chemoradiation in RTOG 9111 was 71.1% [47], comparable to the 5-year LC rate for patients with T2 glottic cancer with impaired vocal cord mobility in RTOG 9512, which was 70% [24]. The older (2nd edition) staging system was useful for making this distinction, classifying tumors with intact vocal cord mobility as T2a, and tumors with impaired vocal cord mobility as T2b.

Treatment intensification for T2 glottic cancer via use of concurrent chemotherapy or altered RT fractionation did not improve outcomes in this study, but the introduction of chemotherapy was relatively recent and was given to only 18% of patients. The addition of chemotherapy for T2 glottic cancer has been shown to be beneficial in several retrospective studies [19,20]. In contrast, a recent SEER cohort analysis reported increased disease-specific mortality in patients with T1–2N0M0 glottic cancer treated with chemoradiation relative to patients treated with RT alone, presumably from the acute and late toxicity of concurrent chemotherapy [23]. In view of this limited evidence on the concurrent addition of chemotherapy to RT for patients with T2 laryngeal cancer, further studies should focus on selecting appropriate patients for concurrent therapy versus altered fractionation according to criteria such as tumor volume and impaired vocal cord mobility.

Altered RT fractionation also did not affect outcomes in this series. This is in contrast to results from other series, for which hypofractionation and hyperfractionation were found to be superior (or at least trending to superiority) to standard fractionation [32,48,49]. Moreover, in the prospective RTOG 9512 trial, while hyperfractionated RT was associated with modestly but not significantly better LC rates relative to standard fractionation, it did have higher rates of acute toxicity [24].

We believe that selection is the reason that treatment intensification with either chemotherapy or altered fractionation did not improve outcomes in this study. Patients were triaged to these modalities when once-daily RT alone was thought to be insufficient based on tumor volume, unfavorable growth pattern, or impaired vocal cord mobility; in other words, had these patients not received intensified treatment, they might have fared worse than those who received once-daily RT alone. We currently tend to favor concurrent chemotherapy for patients with impaired vocal cord mobility, and altered fractionation for bulky but unimpaired vocal cord mobility.

We acknowledge that this study had inherent limitations related to its retrospective nature and the small numbers of patients with (a) impaired vocal cord mobility, (b) IMRT, and (c) chemotherapy. Also, the follow-up duration for patients treated with non-IMRT was significiantly longer than that for patients treated with IMRT. Longer follow-up is likely to be required to detect potential cerebrovascular events, but carotid events might have been underreported if they occurred in an outside hospital, or in more remotely treated patients

potentially lost to follow-up. So far, no events have been reported in our IMRT cohort. Another limitation of our study is the lack of formal voice quality assessment, which should be included in future prospective trials. Future studies should also incorporate human papillomavirus (HPV) testing, HPV has been implicated in laryngeal cancer oncogenesis, although its influence on prognosis remains unclear [50–52]. Despite these limitations, this study represents one of the largest series reporting outcomes for patients with T2 glottic cancer in the modern era.

CONCLUSION

Excellent 5-year oncologic and functional outcomes were achieved in this series of 113 patients with T2 glottic cancer. The use of altered fractionation, concurrent chemotherapy, or IMRT (vs. 3D-CRT) was not associated with differences in outcomes. Additional experience with larger groups of patients and longer follow-up will be necessary to determine outcomes associated with carotid artery irradiation to better explore cerebrovascular events, and studies with formal assessment of voice quality and swallowing are also needed to understand functional outcomes in patients with T2 glottic cancer. IMRT without elective nodal irradiation is now our standard approach, with treatment intensification for patients with bulky cancers and/or those with impaired vocal cord mobility.

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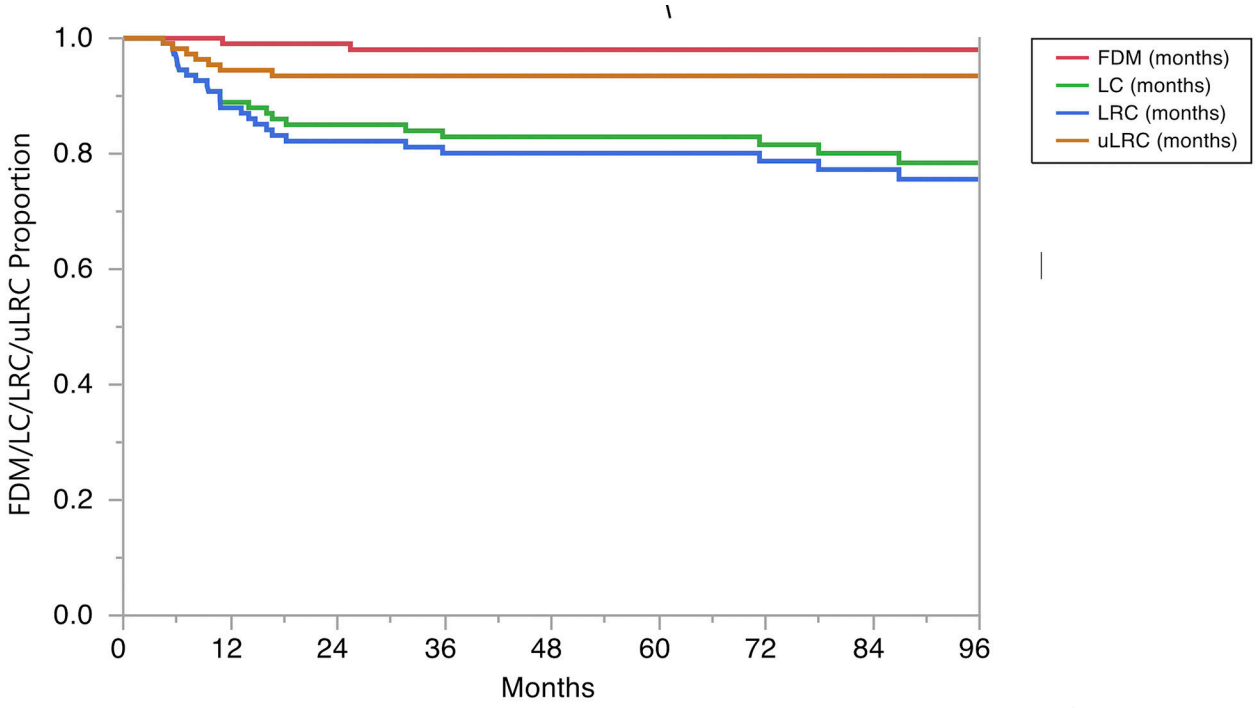
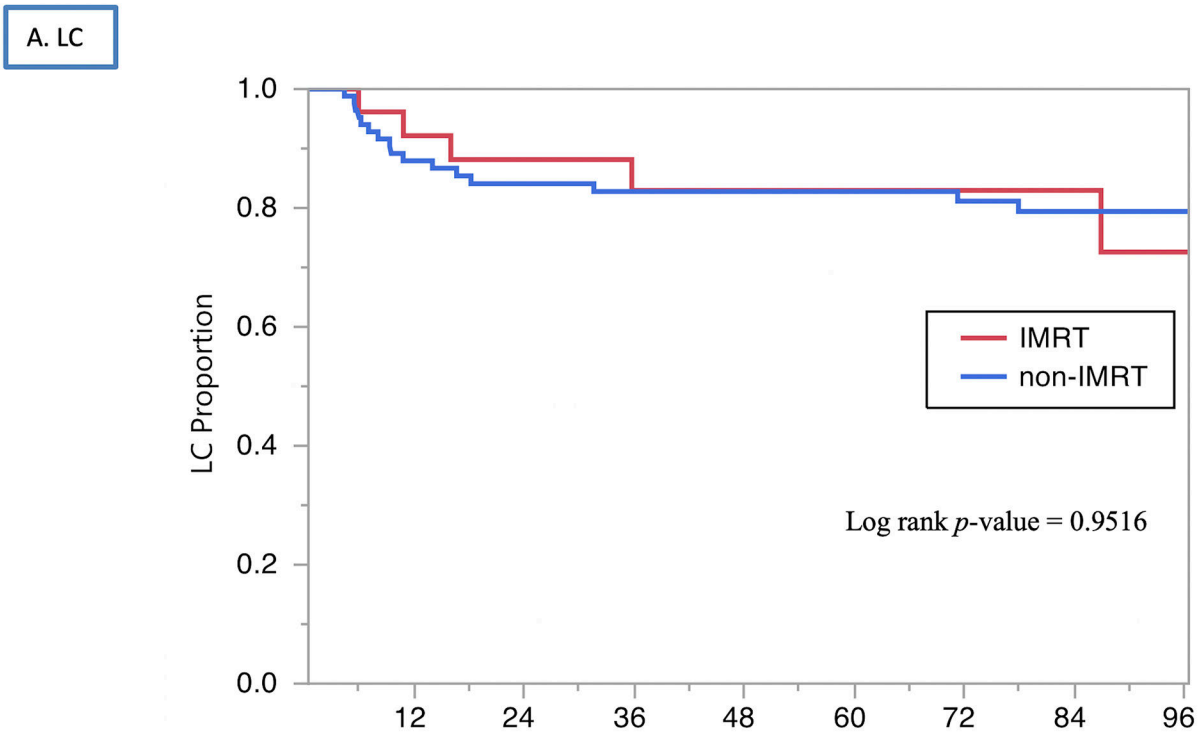
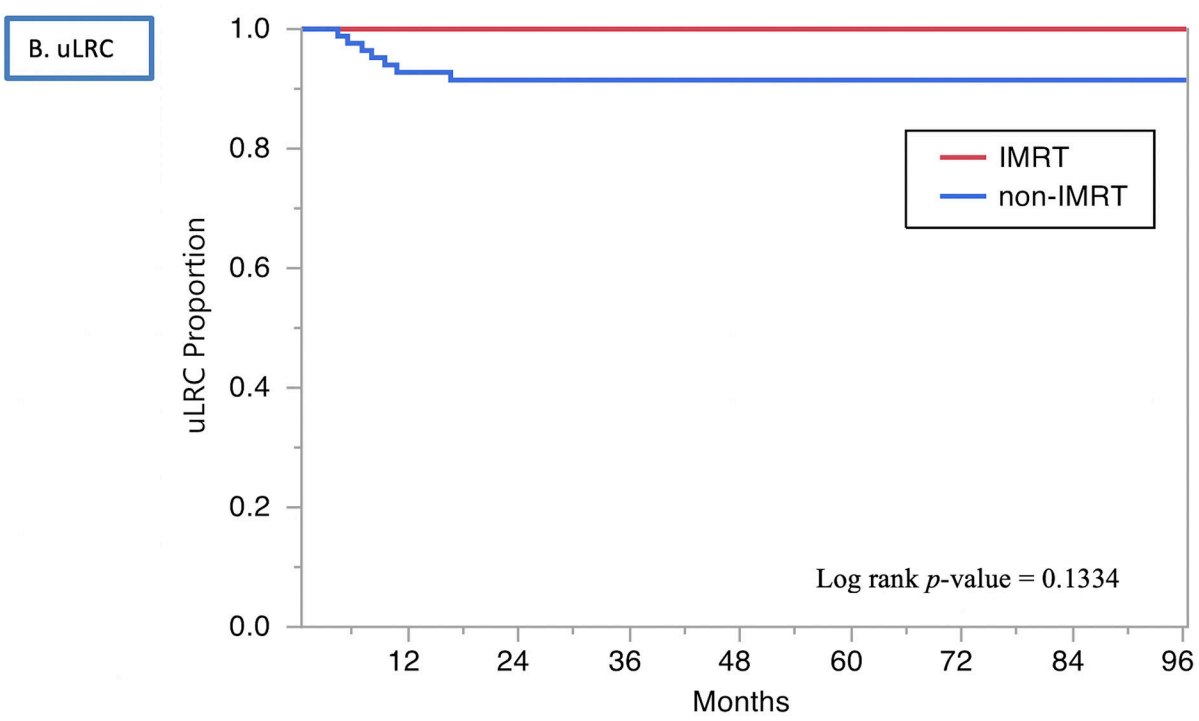


Fig. 1.

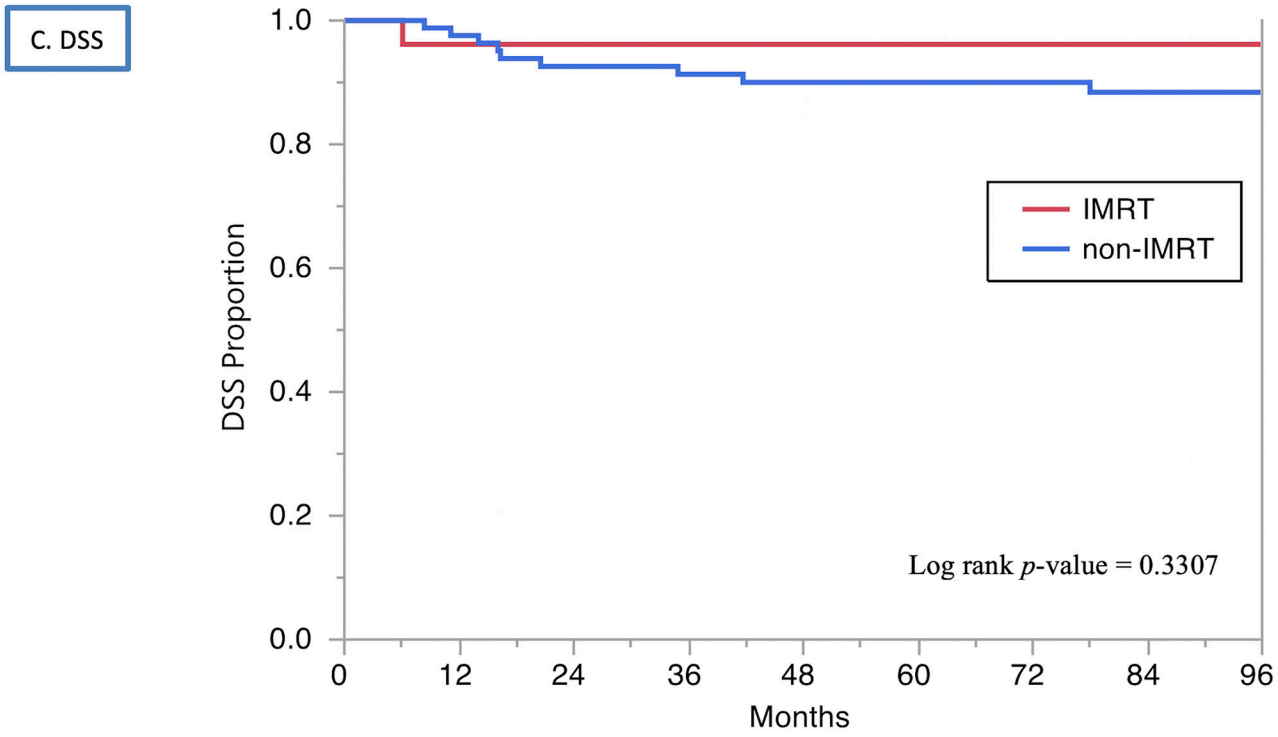
Kaplan Meier curves for freedom from distant metastasis (FDM), local control (LC), locoregional control (LRC), and ultimate locoregional control (uLRC).



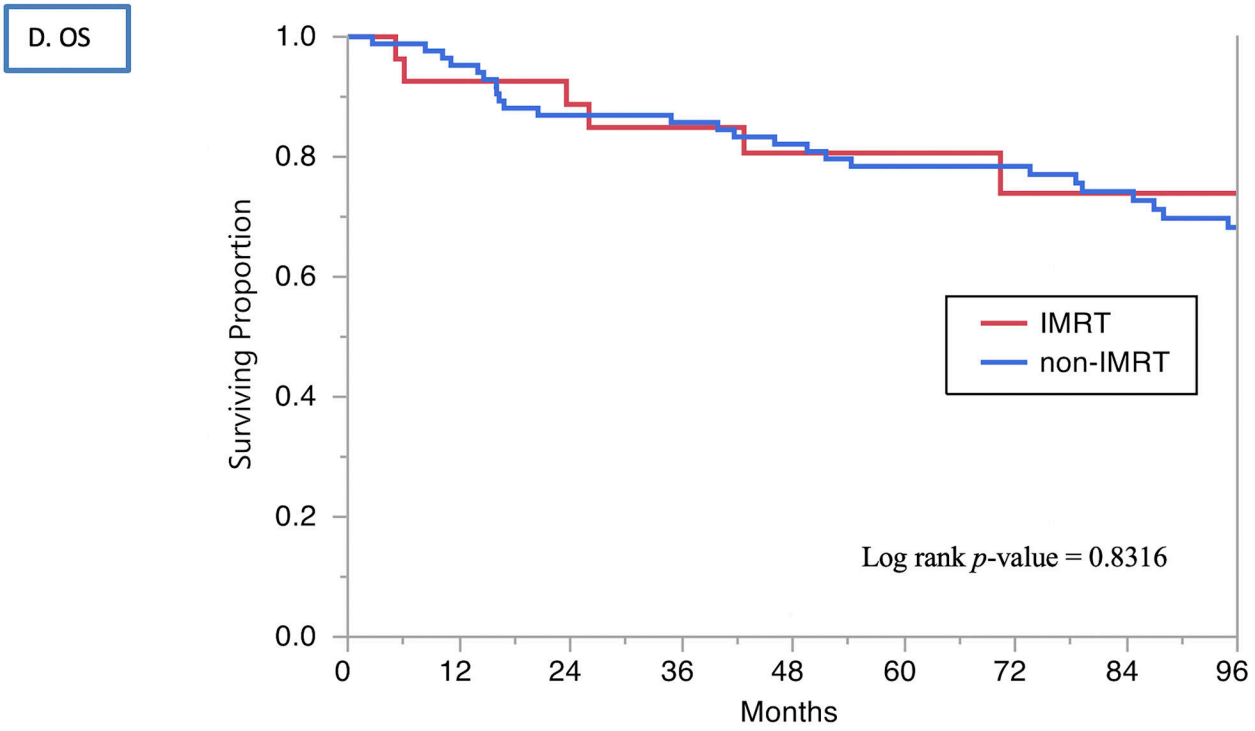
Number at risk									
IMRT	28	24	21	17	16	14	10	9	8
Non-IMRT	85	72	65	64	61	56	50	42	38
Combined	113	95	85	80	76	69	59	50	45



Number at risk									
IMRT	28	26	24	21	20	18	12	11	11
Non-IMRT	85	76	71	71	68	63	58	50	45
Combined	113	101	94	91	87	80	69	60	55



Number at risk									
IMRT	28	26	24	21	20	18	12	11	11
Non-IMRT	85	81	74	73	69	64	59	51	46
Combined	113	106	97	93	88	81	70	62	56



Number at risk									
IMRT	28	26	24	21	20	18	12	11	11
Non-IMRT	85	81	74	73	69	64	59	51	46
Combined	113	106	97	93	88	81	70	61	56

Fig. 2.

Kaplan Meier curves showing (A) local control (LC), (B) utimate locoregional control (uLRC), (C) disease-specific survival (DSS), and (D) overall survival (OS) by RT technique (IMRT vs. non-IMRT) through 96 months.

Table 1.

Patient and disease characteristics

Characteristic	No. of Patients (%)
Sex	
Male	96 (85)
Female	17 (15)
Ethnicity	
White	79 (70)
Black/ African American	11 (10)
Hispanic/Latino	22 (19)
Other/Unspecified	1 (1)
Smoking history at time of diagnosis	
None	16 (14)
Positive	96 (85)
Unknown or unspecified	1 (1)
Vocal cord mobility at presentation	
Impaired	47 (42)
Not impaired	66 (58)
Eastern Cooperative Oncology Group (ECOG) performance status	
0	102 (90)
1	8 (7)
2	2 (2)
Unknown or unspecified	1 (1)
Pathologic grade	
Well differentiated	19 (17)
Moderately differentiated	56 (50)
Poorly differentiated	4 (4)
Unknown or unspecified	34 (29)

Table 2.

Treatment characteristics

Characteristic	No. of Patients (%)
Radiotherapy technique	
3D-CRT	85 (75)
IMRT	28 (25)
Radiation beam energy	
6 MV	69 (61)
^{60}Co	44 (39)
Mean total radiation dose, Gy ± SD	71.1 ± 4.4
Mean no. of fractions received ± SD	42 ± 13
Fractionation schedule	
Conventional	66 (58)
Altered	
Twice daily (hyperfractionation)	30 (27)
Six weekly fractions (moderate acceleration)	2 (2)
Concomitant boost	15 (13)
Mean overall treatment time, days, ± SD	43.3 ± 5.5
Overall treatment time-adjusted BED, Gy, ± SD	67.1 ± 5.3
Chemotherapy	
Concurrent	20 (18)
None	93 (82)

Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; MV, megavolts; ^{60}Co, cobalt-60; SD, standard deviation; BED, biologically effective dose

Table 3.

Summary of studies reporting outcomes of patients with T2 laryngeal cancer

Author, Year	Follow-up Time	Total No. of Pts.	All stages Included	No. of patients with T2 larynx cancer	Treatment modality	LC rates, %	LC rates with laryngeal preservation, %	uLC rates, %	OS rates, %	Cause-specific survival rates, %
Fletcher et al., 1980 [27]	NR	507	T2	175	RT	74				
Harwood et al., 1981 [28]	NR	244	T2	244	RT	69 (5-y)				
Wang, 1997 [29]	NR	902	T1-T2	T2a 145 T2b 92	RT	77 (5-y) 71 (5-y)				92 (5-y) 84 (5-y)
Le et al., 1997 [30]	Median 9.7 y	398	T1-T2	83	RT	70 (5-y)		uLRC 91 (5-y)	63 (10-y)	91 (10-y)
Warde et al 1998 [31]	Median 6.8 y	735	T1-T2	286	RT	69 (5-y)				
Garden et al., 2003 [32]	Median 6.8 y	230	T2	230	RT	72 (5-y)			73 (5-y)	92 (5-y)
Short et al., 2006 [33]	Median 4.9 y	145	T1-T2	43	RT	80 (5-y LRC)				
Taguchi et al., 2006 [34]	Median 32 mo	20	T2	20	CCRT	95 (3-y)	100 (3-y)		100 (3-y)	
Hafidh et al., 2009 [35]	Mean 37 mo	373	T1-T4	38	RT	63.3 (5-y)				
Chera et al., 2010 [7]	Median 12 y	585	T1-T2	T2a 165 ** T2b 95	RT	T2a: 80 (5-y) T2b: 70 (5-y)		T2a 81 (5-y) T2b 74 (5-y)	T2a 76 (5-y) T2b 78 (5-y)	T2a 94 (5-y) T2b 90 (5-y)
Kim et al., 2012 [12]	Median 7.1 y	157	T1-T2	32	RT	62 (5-y)				
Furusaka et al., 2012 [36]	Median 9.4 y	57	T2	57	RT		60.4 (5-yr) 50.1 (10-yr)		88.5 (5-y) 73.5 (10-y)	
Ermis et al., 2015 [37]	Median 72 mo	132	T1-T2	64	RT	80.9 (5-y)		95.8 (5-y)		

Abbreviations: NR, not reported; y, year(s); mo, month(s); RT, radiation therapy; CCRT, concurrent chemoradiation; LC, local control; LRC: loco-regional control; uLC, ultimate local control; uLRC, ultimate loco-regional control

** T2a and T2b classifications were based on the 2nd edition of the American Joint Committee on Cancer (AJCC) staging system. T2 is not subdivided into T2a and T2b in the 8th edition of the AJCC staging system.