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ORIGINAL RESEARCH

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Organ preservation following radiation therapy and concurrent intra-arterial low dose cisplatin infusion for advanced T2 and T3 laryngeal cancer: Long-term clinical results from a pilot study

Takeharu Ono MD[1] | Norimitsu Tanaka MD[2] | Syuichi Tanoue MD[2] | Yusaku Miyata MD[2] | Koichiro Muraki MD[2] | Chiyoko Tsuji MD[2] | Etsuyo Ogo MD[2] | Takeichiro Aso MD[1] | Shun-ichi Chitose MD[1] | Buichiro Shin MD[1] | Tatsuyuki Kakuma PhD[3] | Hidehiro Etoh MD[2] | Chikayuki Hattori MD[2] | Toshi Abe MD[2] | Hirohito Umeno MD[1]

[1]Department of Otolaryngology–Head and Neck Surgery, Kurume University School of Medicine, Kurume, Japan

[2]Department of Radiology, Kurume University School of Medicine, Kurume, Japan

[3]Biostatistics Center, Kurume University School of Medicine, Kurume, Japan

Correspondence
Takeharu Ono, Department of Otolaryngology–Head and Neck Surgery, School of Medicine, Kurume University, Asahimachi 67, Kurume 830-0011, Japan.
Email: ono123@med.kurume-u.ac.jp

Abstract

Background: This pilot study evaluated the long-term outcomes of patients with advanced T2 or T3 squamous cell carcinoma of the larynx (SCC-L) who were treated with selective intra-arterial cisplatin and concomitant radiotherapy (RADPLAT).

Methods: We retrospectively investigated the data of 49 patients with advanced T2 or T3 SCC-L who received a RADPLAT regimen with low-dose cisplatin.

Results: The 5-year locoregional control, disease-specific survival, and overall survival rates were 83.3%, 88.1%, and 82.6%, respectively, while the 5-year freedom from laryngectomy, laryngectomy-free survival, and laryngo-esophageal dysfunction-free survival rates were 89.6%, 79.4%, and 77.1%, respectively. The incidences of grade 3-4 hematologic and nonhematologic toxicities were 18% and 6%, respectively. Although two patients (4%) developed late toxicities within 5 years following RADPLAT, no other events were noted beyond 5 years.

Conclusion: This pilot study demonstrated that RADPLAT is feasible and safe and yielded favorable survival outcomes and functional laryngeal preservation in patients with advanced T2 or T3 SCC-L.

Level of evidence: 3

KEYWORDS

concurrent intra-arterial low dose cisplatin infusion, laryngeal preservation, late toxicity, radiation therapy, squamous cell carcinoma

1 | INTRODUCTION

Laryngeal cancer is among the most common malignant tumors arising in the head and neck region. Although the overall incidence of squamous cell carcinoma of the larynx (SCC-L) has decreased over time, the associated survival rates have also decreased in past decades.[1] This change may be due to a shift from radical surgery to treatments such as radiotherapy (RT), chemoradiotherapy (CRT), and biotherapy, which aim to preserve the larynx and its functions.[2-4] Although total laryngectomy followed by radiotherapy is usually recommended for the treatment of locally advanced laryngeal cancer, this procedure often causes difficulties with breathing, speaking, and smelling, which reduce the quality of life. For these reasons, many institutions opt for intensive treatments, such as CRT, to improve organ and functional preservation, despite the lower survival rates of patients who receive with nonsurgical treatments.[5] The adverse effects of chemoradiation therapy, including laryngeal edema, mucosal fibrosis, and decreased laryngeal sensation, can lead to reduced respiratory and deglutitory functions. Generally, patients with T4 laryngeal cancer are treated via total laryngectomy according to the National Comprehensive Cancer Network (NCCN) guidelines.[6] However, the management of advanced T2 or T3 laryngeal cancer has not been elucidated.

The selective radiotherapy and concomitant intra-arterial cisplatin (RADPLAT) regimen was first reported by Robbins et al in 1992 and has since been used to improve organ and functional preservation.[7] In Japan, reports have demonstrated favorable survival and organ preservation rates among patients with head and neck cancer who were treated with RADPLAT at several institutions.[8-11] A Dutch randomized phase 3 trial that compared RADPLAT with intravenous (IV) cisplatin-based CRT did not identify any additional benefits of RADPLAT in terms of locoregional control (LRC) and survival.[12] However, that trial did not include patients with laryngeal cancer.

Although few studies have evaluated the use of RADPLAT in patients with SCC-L,[13,14] very little is known about the long-term effects of this regimen on survival or the structural and functional preservation of the larynx. Accordingly, this retrospective study aimed to investigate survival outcomes, organ and functional preservation of the larynx, and toxicities in patients with advanced T2 or T3 SCC-L who underwent RADPLAT at a single institution.

2 | MATERIALS AND METHODS

2.1 | Patients

Untreated patients with histologically confirmed, locally advanced-stage (advanced T2 or T3) SCC-L were eligible for the study. Advanced T2 was defined as an impaired vocal fold or transglottic tumor spanning from the supraglottic to the subglottic site. Patients with level IV metastatic neck lymph nodes, distant metastases, bilaterally fixed vocal folds, a history of tracheostomy before treatment or cerebral infarction, and an Eastern Cooperative Oncology Group (ECOG) performance status >2 were excluded from the study. TNM staging was determined according to the 7th Edition of the Union for International Cancer Control (UICC) staging system and was based on enhanced computed tomography (CT), magnetic resonance imaging (MRI), ultrasound examination, and positron emission tomography findings. All patients were assessed by a multidisciplinary team that included radiation oncologists, diagnostic radiologists, and head and neck surgeons.

The present study (Reference number: 18191) was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Kurume University Hospital. Informed consent was obtained from each patient.

TABLE 1 Patient characteristics (n = 49)

Variables	No. of patients (%)
Age	
Median	66
Range	37-81
Sex	
Male	46 (94)
Female	3 (6)
Subsite	
Supraglottis	19 (39)
Glottis	27 (55)
Subglottis	3 (6)
T classification	
Advanced T2	10 (20)
T3	39 (80)
N classification	
N0	41 (84)
N1	1 (2)
N2b	4 (8)
N2c	3 (6)
Clinical stage	
II	8 (16)
III	34 (70)
IVA	7 (14)
Total cisplatin dose (mg)	
Median	300
Range	150-450
Total irradiation (Gy)	
Median	66
Range	60-71
Vocal fold movement	
Impaired	5 (10)
Fixed	13 (27)
No	31 (63)
Follow-up (mo.)	
Median	64
Range	25.4-145.2

2.2 | Treatments

2.2.1 | Selective intra-arterial cisplatin infusion

An intra-arterial cisplatin infusion was administered by the diagnostic radiologist and radiation oncologist using the Seldinger technique, which involves a transcutaneous femoral insert. A microcatheter was inserted intra-arterially and advanced selectively to the arteries that supplied nutrients to the tumors, including the superior thyroid artery and/or lingual artery. These nutrient-supplying arteries were identified using cone-beam CT and imaged using angiography (3D-CTA). Before the infusion of cisplatin, a 5-HTT3 receptor antagonist was administered intravenously to prevent nausea and vomiting. Cisplatin (75 mg body^{-1} wk^{-1}) was administered intra-arterially at a flow rate of 0.1 mg s^{-1}. Simultaneously, sodium thiosulfate (20-25 g) was administered intravenously to neutralize the acidity of cisplatin and reduce the incidence of systemic toxicities such as renal dysfunction or vessel damage. The catheters were removed after drug administration, and saline was administered for 24 hours to protect renal function. Cisplatin was administered four times (total 300 mg), although an additional one or two cycles (75-150 mg) were given in cases with a suspected residual tumor.

2.3 | Radiotherapy

External radiotherapy was administered to all patients five times per week (1.8 Gy fraction^{-1} d^{-1}) using a three-dimensional (3D) method and 4-MV X-ray beam linear accelerator. In the primary region, the gross tumor volume (GTV) was evaluated using CT and/or MRI, and the clinical target volume (CTV) was defined as the GTV plus a safety margin of 5 mm. The planning target volume was calculated as the CTV

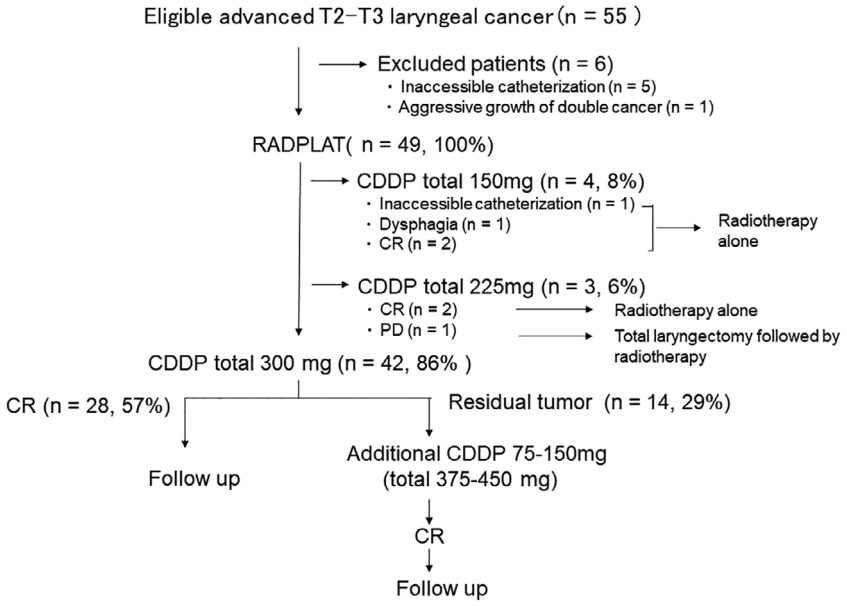

FIGURE 1 Schema of eligibility and response data to selective radiotherapy and concomitant intra-arterial cisplatin (RADPLAT). CDDP, cisplatin; CR, complete response; PD, progressive disease

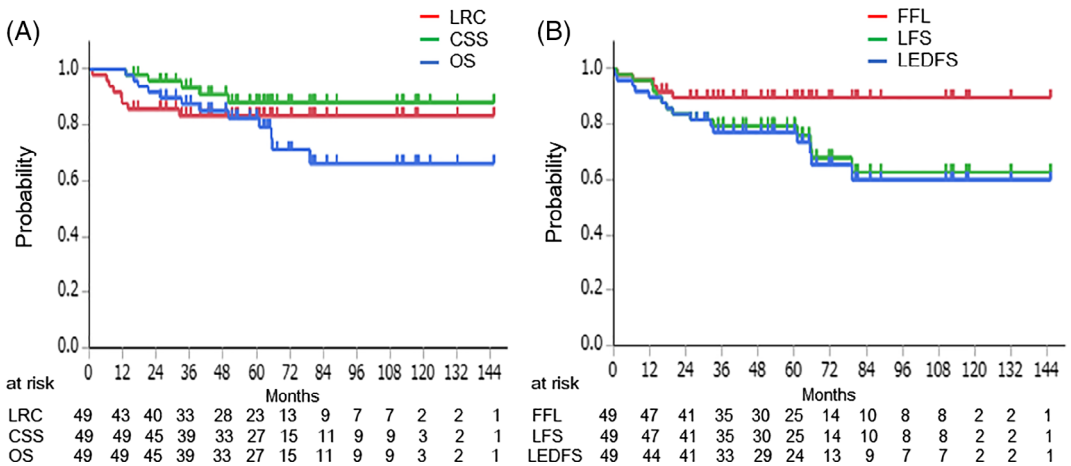

FIGURE 2 Clinical outcomes after RADPLAT. Kaplan-Meier curves of LRC, DSS, OS, FFL, LFS, and LEDFS in patients with all SCC-L. DSS, disease-specific survival; FFL, freedom from laryngectomy; LEDFS, laryngo-esophageal dysfunction-free survival; LFS, laryngectomy-free survival; LRC, locoregional control; OS, overall survival; SCC-L, squamous cell carcinoma of the larynx

plus 5 to 10 mm. The neck irradiation fields in patients with glottic or supraglottic cancer with metastatic neck lymph nodes or T3 cancers included bilateral neck levels II, III, IVa, IVb + Vc; in patients with subglottic cancer or tracheal invasion, the fields included bilateral neck levels II, III, IVa, IVb + Vc, and VIb. In patients with T2 cancer without lymph node metastasis, the neck irradiation fields for supraglottic cancer included bilateral neck levels II, III, and IVa, while those for subglottic cancer included bilateral neck levels II, III, IVa, and VIb. Prophylactic neck irradiation was not administered to patients with T2 glottic cancer without metastatic neck lymph nodes.

2.4 | Statistical analysis

LRC, disease-specific survival (DSS), and overall survival (OS) were calculated from the date of diagnosis using the Kaplan-Meier method. Total laryngectomy, tracheostomy, and/or feeding tube placement/retention after 2 years of treatment were defined as events associated with laryngeal preservation (LP) and function.[15] Freedom from laryngectomy (FFL) was defined according to the date of salvage laryngectomy for an event, while laryngectomy-free survival (LFS) was defined according to the date of salvage laryngectomy and/or any death related to an events. The functional and mortality endpoints were evaluated using the laryngo-esophageal dysfunction-free survival (LEDFS), which included death, local recurrence, salvage total laryngectomy, tracheotomy, and/or feeding tube placement/retention recorded after 2 years of treatment. The survival rates were compared using a log-rank test. Clinical variables associated with a P value <.2 in the univariate analysis were subjected to a multivariate analysis using the Cox proportional hazard model. Probabilities <.05 were considered statistically significant. All statistical analyses were conducted using JMP Pro 13 statistical software (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Patient characteristics

Between July 2006 and October 2016, 342 patients with laryngeal SCC were referred to the Kurume University Hospital. Of the 55 patients with advanced T2 or T3 deemed eligible for RADPLAT, six were excluded because of (a) catheter obstruction (n = 4), (b) severe cough due to stimulation of the inserted catheter (n = 1), and (c) aggressive growth of a double cancer (n = 1). Forty-nine patients were eligible for the final evaluation, of whom 18 (37%) had an impaired or fixed vocal fold. The median age of the patients was 66 years (range: 37-81), and the median follow-up period was

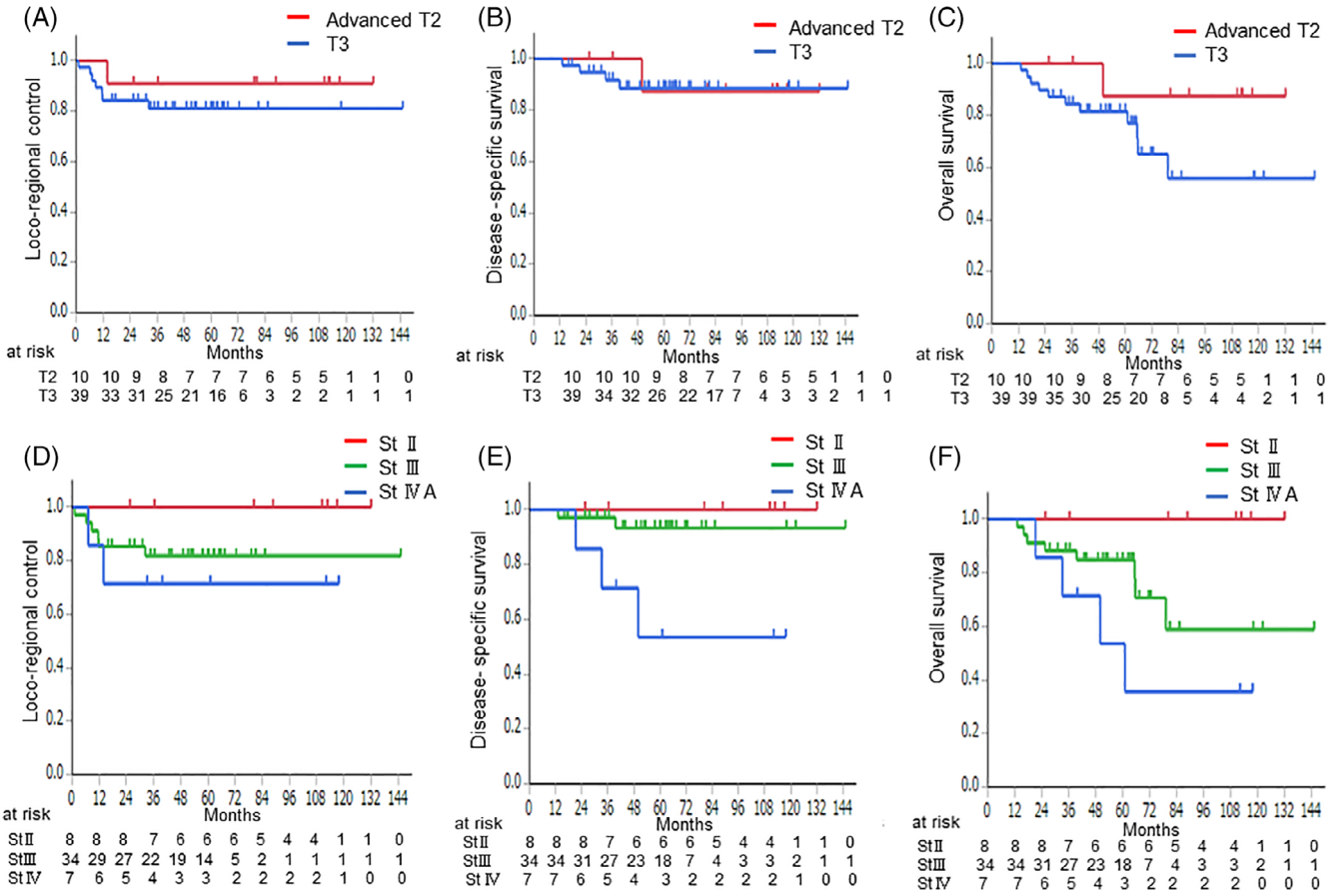

FIGURE 3 Kaplan-Meier curves of LRC, DSS, OS in patients with SCC-L according to, A-C, T stage and, D-F, clinical stage. DSS, disease-specific survival; LRC, locoregional control; OS, overall survival; SCC-L, squamous cell carcinoma of the larynx

64 months (range: 25.4-145.2 months). The clinical features of the patients are shown in Table 1.

3.2 | Treatment outcomes

The total cisplatin dose range administered in this study was 150 to 450 mg, and the total irradiation dosage range was 60 to 71 Gy. At a total administered cisplatin dose of 150 mg and irradiation dose of 18 to 27 Gy, two of four patients had an early complete response (CR) to treatment at the local site as determined endoscopically, one had grade 3 dysphagia, and the fourth patient had a severe cough stimulated by inserting the catheter into the tumor feeding artery. In these patients, further cisplatin administration was stopped and radiotherapy alone was administered, although one patient also temporarily stopped receiving radiotherapy. At a total administered cisplatin dose of 225 mg and irradiation dose of 36 to 45 Gy, two of three patients achieved an early CR, and the third developed progressive disease. Further cisplatin administration was stopped in the first two patients, who were given sequential radiotherapy, while the third patient underwent total laryngectomy followed by postoperative irradiation at a dose of 36 Gy. Twenty-eight patients achieved a clinical CR at a total administered cisplatin dose of 300 mg, although 14 had locally residual tumors. These latter patients received an additional cisplatin infusion (additional dose: 75-150 mg, total dose: 375-450 mg). The treatment regimens are summarized in Figure 1. The median cisplatin and irradiation doses were 300 mg (range: 150-450 mg) and 66 Gy (range: 60-71 Gy), respectively. Among all patients, eight presented with metastatic neck lymph nodes before treatment, and one underwent neck dissection for persistent metastatic lymph nodes after treatment. Local recurrences were observed in four patients, of whom three and one underwent total and partial laryngectomies, respectively. Deaths due to nonlaryngeal cancers were recorded for seven patients (ureteral cancer, n = 1; lung cancer, n = 2; colon cancer, n = 2; oral cancer, n = 1; esophageal cancer, n = 1), while deaths due to locoregional recurrences and distant metastases occurred in two and three patients, respectively.

3.3 | LRC and survival

Kaplan-Meier analyses of the LRC, DSS, and OS rates for all patients and subsets according to T stage and clinical stage are shown in Figures 2A and 3, respectively. The 5-year LRC, DSS, and OS rates for all patients were 83.3%, 88.1%, and 82.6%, respectively. The 5-year LRC rates for patients with advanced T2 or T3 disease were 90% and

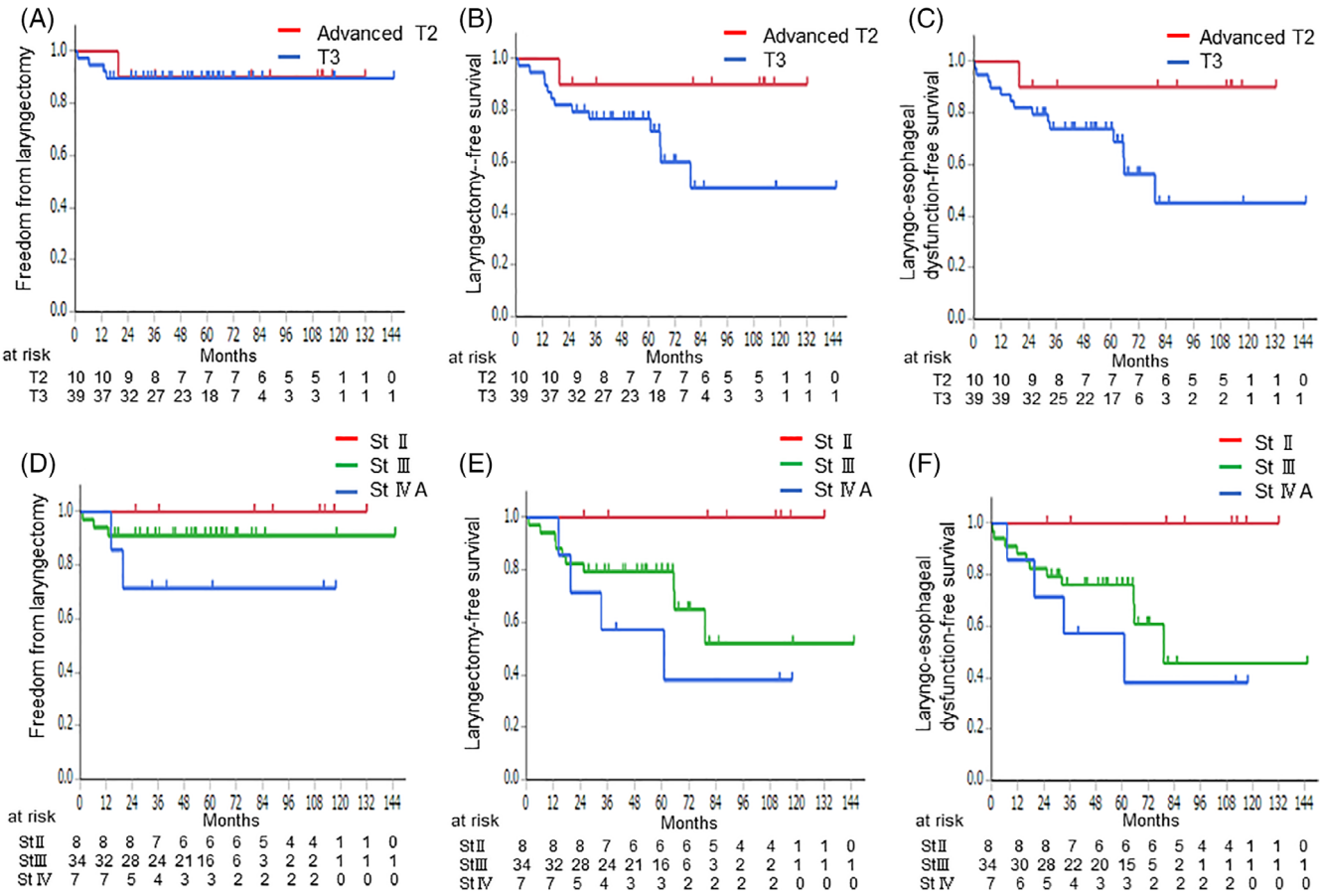

FIGURE 4 Kaplan-Meier curves of FFL, LFS, and LEDFS in patients with SCC-L according to, A-C, T stage and, D-F, clinical stage. FFL, freedom from laryngectomy; LEDFS, laryngo-esophageal dysfunction-free survival; LFS, laryngectomy-free survival; SCC-L, squamous cell carcinoma of the larynx

81.6%, respectively. The 5-year DSS and OS rates for patients with advanced T2 disease were both 87.5%, while the rates for patients with T3 disease were 88.6% and 81.5%, respectively. The 5-year LRC rates for patients with stage II, III, or IVA disease were 100%, 81.7%, and 71.4%, respectively. The 5-year DSS rates for patients with stage II, III, or IVA disease were 100%, 93.3%, and 53.6% respectively, while the corresponding 5-year OS rates were 100%, 84.8%, and 53.6%, respectively (Figure 3).

3.4 | Organ and functional preservation

Kaplan-Meier analyses of the FFL, LFS, and LEDFS rates for all patients and subsets according to T stage and clinical stage are shown in Figures 2B and 4, respectively. The 5-year FFL, LFS, and LEDFS rates for all patients were 89.6%, 79.4%, and 77.1%, respectively. For patients with advanced T2 and T3 disease, the 5-year FFL rates were 90% and 89.7%, respectively, the LFS rates were 90% and 76.8%, respectively, and the LEDFS rates were 90% and 73.8%, respectively. The 5-year FFL rates for patients with stage II, III, or IVA disease were 100%, 91.2%, and 71.4%, respectively, while the corresponding LFS and LEDFS rates were 100%, 79.4%, and 57.1%, respectively, and 100%, 76.1%, and 57.1%, respectively (Figure 4).

3.5 | Prognostic factors

The results of the univariate analyses of LRC, DSS, and OS are shown in Table 2. No significant differences were observed in terms of the LRC. In contrast, statistically significant associations were observed between the DSS and the N classification (P = .021), clinical stage (P = .017), and total cisplatin dosage (P = .010). The clinical stage and total cisplatin dosage were not included in the multivariate analysis because they also exhibited significant correlations with the N

TABLE 2 Univariate and multivariate analyses of clinical factors associated with locoregional control, disease-specific survival, and overall survival

		LRC		DSS		OS	
Factor		Univariate *P* value[a] HR (95% CI)	Multivariate *P* value[a] HR (95% CI)	Univariate *P* value[a] HR (95% CI)	Multivariate *P* value[a] HR (95% CI)	Univariate *P* value[a] HR (95% CI)	Multivariate *P* value[a] HR (95% CI)
Age (y)							
<66	24	.487		.114	.283	.420	
≥66	25	0.60 (0.12-2.47)		4.78 (0.70-93.60)	0.33 (0.02-2.33)	1.60 (0.51-5.41)	
Subsite							
Supraglottis	19	.151	.243	.356		.276	
Sub or glottis	30	2.79 (0.69-13.62)	2.4 (0.55-12.64)	2.30 (0.38-17.44)		1.88 (0.60-6.39)	
T classification							
T3	39	.496		.805		.096	.062
Advanced T2	10	1.95 (0.35-36.57)		1.31 (0.19-25.60)		4.26 (0.80-78.67)	4.94 (0.93-91.24)
N classification							
N+	8	.507		.021*	.042*	.020*	.014*
N–	41	1.77 (0.26-7.68)		8.66 (1.43-65.97)	6.64 (1.07-51.69)	4.36 (1.28-13.75)	4.88 (1.42-15.49)
Clinical stage							
IVA	7	.408		.017*		.076	
II-III	42	2.06 (0.30-8.92)		9.21 (1.52-70.0)		3.26 (0.87-10.4)	
Total CDDP dose							
<375 mg	35	.553		.010*		.037*	
≥375 mg	14	0.64 (0.16-3.13)		0.08 (0.004-0.56)		0.28 (0.09-0.93)	
Irradiation dose							
<66 Gy	24	.086	.105	.114	.293	.702	
≥66 Gy	25	3.65 (0.84-24.92)	3.48 (0.78-24.21)	4.78 (0.71-93.58)	2.99 (0.42-59.67)	0.80 (0.25-2.59)	
Vocal fold impaired or fixed							
Yes	18	.104	.394	.446		.512	
No	31	0.23 (0.02-1.30)	0.41 (0.02-2.38)	0.45 (0.02-3.06)		0.65 (0.14-2.20)	

Abbreviations: CDDP, cisplatin; CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; LRC, locoregional control; OS, overall survival.
[a]Cox proportional hazards model.
*P < .05.

TABLE 3 Toxicity (n = 49)

	No. of patients (%)			
Acute toxicities	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic toxicity	19 (39)	18 (37)	8 (16)	1 (2)
Leukopenia	9 (18)	17 (35)	6 (12)	0
Neutropenia	10 (20)	9 (18)	6 (12)	1 (2)
Anemia	24 (49)	9 (18)	2 (4)	0
Thrombocytopenia	14 (29)	1 (2)	2 (4)	0
Renal failure	0	0	0	0
Nonhematologic toxicity	15 (31)	31 (63)	3 (6)	0
Nausea/vomiting	4 (8)	1 (2)	0	0
Dysphagia	15 (31)	15 (31)	2 (4)	0
Mucositis	18 (37)	28 (57)	2 (4)	0
Fever	2 (4)	1 (2)	0	0
Radiation dermatitis	27 (55)	21 (43)	0	0
Lung infection	1 (2)	0	0	0

classification (Table S1). The multivariate analyses identified the N classification as an independent and significant factor affecting DSS (hazard ratio [HR] = 6.64; 95% confidence interval [CI] = 1.07-51.69, P = .042). The univariate analysis also indicated significant associations of the OS with the N classification (P = .020) and total cisplatin dosage (P = .037), while the multivariate analysis identified positive nodal disease as an independent and significant risk factor for OS (HR = 4.88; 95% CI = 1.42-15.49, P = .014).

3.6 | Toxicities

Grade 3 and 4 hematologic and nonhematologic toxicities were observed in nine (18%) and three (6%) patients, respectively (Table 3). The following grade >3 toxicity events were observed: leukopenia in six (12%) patients, neutropenia in seven (8%), anemia in two (4%), thrombocytopenia in two (4%), dysphagia in one (2%), and pharyngeal mucositis in two (4%) patients. Although one patient temporarily stopped receiving sequential irradiation because of grade 3 dysphagia, the patient eventually completed the planned irradiation dosage (total dose: 61 Gy). Late toxicities were observed in two patients. One patient developed chondronecrosis of the cricoid cartilage and underwent debridement of the affected lesion, which preserved the larynx. The other patient developed severe dysphasia 2 years after completing RADPLAT and underwent a laryngectomy.

4 | DISCUSSION

Most previous studies reported that organ-preserving therapies, including radiation therapy, chemoradiation therapy, and transoral laser microsurgery, are generally administered to patients with local early-stage laryngeal cancers.[16-18] In contrast, many patients with locally advanced tumors require radical surgery, including total or partial laryngectomy.[19-21] In this study, the 5-year LRC rates of patients with advanced T2 and T3 cancers were 90% and 81.6%, respectively, whereas the corresponding 5-year DSS rates and OS rates were 87.5% and 88.6%, respectively, and 87.5% and 81.5%, respectively. Furthermore, for clinical stage II, III, and IVA disease, the 5-year LRC rates were 100%, 81.7%, and 71.4%, respectively, the 5-year DSS rates were 100%, 93.3%, and 53.6%, respectively, and the OS rates were 100%, 84.8%, and 53.6%, respectively. Table 4 summarizes a literature review of the different therapeutic options. In several studies of surgical treatments, including total laryngectomy, the 5-year OS rates ranged from 41% to 85.5%.[20,22-25] Although it is difficult to compare these earlier results directly with our findings, the survival rates in our study tended to be favorable. Specifically, the nonsurgical treatments, including definitive RT and systemic CRT, yielded 5-year local control (LC) or LRC rates of 62% to 65% and OS rates of 40 to 67% in patients with clinically advanced-stage disease.[16,26-30] Al-Mamgani et al reported a 5-year LRC rate of 64% in patients with advanced T2 (T2b) disease treated with definitive RT.[16] Additionally, Bhateja et al reported the 3-year LRC rates of 73.2% and 91.5% in patients with (a) T2bN0 treated with RT or (b) T2b-3N0-2 treated with IV-CRT, respectively, thereby demonstrating that CRT is a more favorable treatment for patients with T2b relative to RT alone.[30] In a recent study of LP, Timme et al calculated a 2-year LEDFS rate of 40% in patients with T3 disease treated with IV-CRT.[24] Fuller et al reported 5-year LFS rates of 38% and 62% in patients with T3 disease treated with definitive RT or systemic CRT, respectively, and 5-year LEDFS rates of 37% and 59% in patients with T3 disease treated with definitive RT or systemic CRT, respectively.[25] Therefore, our findings appear to demonstrate more favorable outcomes of disease control, survival, and LP, compared to previous studies.

In a recent study on RADPLAT for head and neck cancers, Robbins et al demonstrated high rates of LRC, survival, and organ preservation in patients with locally advanced T4 tumors.[31] Yokoyama et al reported a 5-year LP rate of 86% in patients with T3 disease,[32] while Yoshizaki et al reported 3-year LC and OS rates of 80.5% and 82.9%, respectively, in patients with advanced SCC-L.[14] Furusaka et al further reported 5-year LP and OS rates of 92.5% and 96.3%, respectively, in patients with T3 who were treated with an intra-arterial (IA) cisplatin and docetaxel infusion combined with intravenous (IV) 5-fluorouracil (5-FU) infusion, followed by CRT via superselective IA chemotherapy with the same three drugs.[33] Given those results, intra-arterial CRT, including RADPLAT, were favorable and might be a suitable option for LP. However, this study had few patients with nodal disease or advanced clinical stage.

Regarding prognostic factors in laryngeal cancers, Zhou et al reported that high lymph node and stage statuses were predictors of disease-free survival and cancer-specific survival (CSS) in patients with T3 glottic cancer treated via surgery, including total or partial laryngectomy.[20] Likewise, Nguyen-Tan et al reported that a lower N status was a favorable prognostic factor of LRC and OS in patients with advanced T3-T4 laryngeal carcinomas.[34] Furthermore, Rosenthal et al and Timmermans et al reported an association of positive lymph

TABLE 4 Summary of organ and functional preservation and survival of patients with laryngeal cancer

Author	No of patients	Stage	Treatment	Laryngeal preservation	Local control and/or survival rates
Surgical treatments					
Chevalier et al[22]	90	T2 (impaired vocal cord motion)	CHEP		5-y LC: 95.4% 5-y OS: 81.3% 5-y CSS: 96%
	22	T3 (fixed vocal cord motion)	CHEP		5-y LC: 94.4% 5-y OS: 85.5% 5-y CSS: 94.1%
Canis et al[23]	127	pT2b	Trans laser microsurgery ±Neck dissection		5-y LC: 67.5% 5-y RFS: 57.3% 5-y DSS: 83.9% 5-y OS: 64.9%
	122	pT3	Trans laser microsurgery ±Neck dissection		5-y LC: 71.5% 5-y RFS: 57.8% 5-y DSS: 84.1% 5-y OS: 58.6%
Timme et al[24]	19	T3	Total or partial laryngectomy		5-y OS: 41%
Fuller et al[25]	125	T3	Total laryngectomy + RT		5-y OS: 50% 5-y DSS:61%
Zhou et al[20]	307	T3	Total or partial Laryngectomy	-	5-y DFS: 61.6% (St III: 63.1%, IV: 33.3%) 5-y CSS: 71.5% (St III: 73.2%, IV: 40.2%)
Nonsurgical treatments					
Hinerman et al[26]	82	St III (all T3)	RT		5-y LRC: 62% 5-y CSS: 84% 5-y OS: 52%
Al-Mamgani et al[27]	170	T3	RT or IV-CRT	3-y LFS: 76.8% (CRT) 3-y LFS: 53.5% (RT)	5-y LRC: 65% 5-y DFS:60% 5-y OS: 49%
Al-Mamgani et al[16]	122	T2b	RT		5-y LC:64%
Timme et al[24]	25	T3	IV-CRT	2-y LEDFS: 40%	5-y OS: 40%
Timmermans et al[28]	84	T3	RT		5-y OS: 51%
	12	T3	IV-CRT		5-y OS: 61%
Fuller et al[25]	121	T3	LP-RT	5-y: LFS: 38% 5-y LEDFS: 37%	5-y OS: 46% 5-y DSS:64%
	166	T3	LP-IV-CRT	5-y: LFS: 62% 5-y LEDFS: 59%	5-y OS: 67% 5-y DSS: 79%
Gorphe et al[29]	104	T3	IC→RT, IV-CRT, or surgery	5-y LP: 53.4% 5-y LFS: 30% 5-y LEDFS: 28.2%	5-y DFS: 47.8% 5-y OS: 54.5%
Bhateja et al[30]	31	T2bN0	RT		3-y LC: 73.2%
	26	T2b-3 N0-2	IV-CRT		3-y LC: 91.5%
Robbins et al[31]	61 (larynx:11%)	St IV	RADPLAT		4-y OS: 49.2% 4-y LRC: 55.4% 4-y DFS: 34.7%

(Continues)

TABLE 4 (Continued)

Author	No of patients	Stage	Treatment	Laryngeal preservation	Local control and/or survival rates
Yokoyama et al[32]	23	T3	RADPLAT	5-y LP: 86%	
Yoshizaki et al[14]	41	St II-IVA (T2 and T3: 73%)	RADPLAT		3-y LC: 80.5% 3-y PFS: 53.7% 3-y OS: 82.9%
Furusaka et al[33]	29	T3	ICT(IA + IV) →CRT (IA + IV) IA: CDDP+DOC IV: 5-FU	5-y LP: 92.5%	5-y OS: 96.3%
Present study	10	Advanced T2	RADPLAT	5-y FFL: 90% 5-y LFS: 90% 5-y LEDFS: 90%	5-y LRC: 90% 5-y DSS: 87.5% 5-y OS: 87.5%
	39	T3	RADPLAT	5-y FFL: 89.7% 5-y LFS: 76.8% 5-y LEDFS: 73.8%	5-y LRC: 81.6% 5-y DSS: 88.6% 5-y OS: 81.5%

Abbreviations: CDDP, cisplatin; CHEP, cricohyoidoepiglottopexy; CRT, chemoradiation therapy; CSS, cancer-specific survival; DFS, disease-free survival; DOC, docetaxel; DSS, disease-specific survival; FFL, freedom from laryngectomy; ICT, induction chemotherapy; LC, local control; LEDFS, laryngo-esophageal dysfunction-free survival; LFS, laryngectomy-free survival; LP, larynx preservation; LRC, locoregional control; OS, overall survival; PFS, progression-free survival; RADPLAT, radiotherapy and concomitant intra-arterial cisplatin; RFS, relapse-free survival; RT, radiation therapy.

node disease with overall mortality.[15,28] In our study, positive nodal disease was associated with a poor DSS and OS in a multivariate analysis. We therefore considered adjuvant therapy for patients with positive nodal-stage cancer who had completed RADPLAT.

According to a randomized trial (RTOG 91-11) conducted by the Radiation Therapy Oncology Group and the Head and Neck Intergroup, patients treated with cisplatin-based IV-CRT, experienced grade 3-4 hematologic (47%), mucosal (43%), pharyngeal or esophageal (35%), and laryngeal (31%) toxicities. Grade 3-4 nausea or vomiting (20%) and renal or genitourinary effects were also reported.[35] A Dutch randomized trial reported grade >2 hematological (52%), mucosal (50%), and renal (1%) toxicities in patients treated with intra-arterial CRT, although grade >2 renal toxicity was significantly less frequent in patients receiving intra-arterial CRT, compared to intravenous CRT.[12] In our study, we observed no renal toxicity, although grade 3-4 leukopenia, neutropenia, anemia, and thrombocytopenia occurred in 12%, 14%, 4%, and 4% of the cases, respectively. The frequencies of these adverse reactions were much lower than those reported previously in patients who received IV-CRT. Although the intra-arterial approach via the Seldinger method has been reported to cause cerebrovascular accidents in some cases,[12,31] these did not occur in our study. Lin et al reported comparable survival outcomes in patients treated with surgery vs those who received complete CRT but not incomplete CRT.[36] In other words, their study emphasized the importance of completing the full course of CRT.

In our study, only one patient temporarily discontinued treatment because of grade 3 toxicities. Robbins et al reported that 89 out of 213 patients with stage III or IV cancer who were treated with RADPLAT (150 mg m^{-2} wk^{-1} ×4 and 68-72 Gy) developed grade 3-4 toxicities.[36] The Radiation Therapy Oncology Group Trial 9615 reported grade 3-5 hematologic and nonhematologic toxicity rates of 51% and 82%, respectively,[31] whereas the corresponding rates in our study were 18% and 6%, respectively. The toxicity rates in our study were also much lower than those reported from the original RADPLAT studies by Robbins et al.[31,37] The lower toxicity rate in our study may be due to the lower dosage of intra-arterial cisplatin (75 mg $body^{-1}$ wk^{-1} × 2-6 cycles; total median dosage, 300 mg $body^{-1}$) than that used in previous reports.[31,37] Lambert et al reported that 23% of patients treated with IV-CRT developed late toxicities, including percutaneous endoscopic gastrostomy (7%), persistent dysphagia (6%), pharyngoesophageal stenosis (2%), and permanent tracheostomy (8.5%).[38] In our study, late toxicities such as chondronecrosis and severe dysphagia occurred in two patients (3.8%) within 5 years after RADPLAT, while no incident of late dysphagia occurred more than 5 years after RADPLAT. A long-term follow-up study of the RTOG 91-11 trial reported a higher rate of death due to reasons other than laryngeal cancer in the CRT group, suggesting that a higher cisplatin dose affects OS by inducing a high incidence of adverse events in the CRT group.[39] Although Furusaka et al reported higher rates of LP and survival in patients treated with three-agent chemotherapy (IA cisplatin and docetaxel combined with IV 5-fluorouracil), they also reported much higher grade 3-4 leukopenia, neutropenia, and mucositis rates than those in observed in our study. The lower-dose of cisplatin as a single agent and the lower frequencies of adverse events of our study may be due to the attempted long-term preservation during treatment for advanced laryngeal cancer. Therefore, new strategies that would improve organ preservation and function while reducing morbidity are needed.

The present study had several limitations. First, it was a retrospective study with a small cohort. Second, all treatments were performed at a single institution. Third, eligible patients in this study

were selected carefully, and the sample included few patients with nodal disease and an advanced clinical stage. Fourth, the frequency and total dose of cisplatin administration were not consistent. Further large-cohort analyses are required to validate these findings.

In conclusion, our study demonstrates that RADPLAT therapy is safe and feasible in patients with laryngeal cancer while enabling organ and functional preservation. However, the treatment protocol should be standardized. Additionally, the feasibility of RADPLAT therapy in patients with nodal disease and advanced clinical stage should be validated further, as only a few such patients were included in our study.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Takeharu Ono https://orcid.org/0000-0003-2414-7034
Shun-ichi Chitose https://orcid.org/0000-0002-9307-2331

REFERENCES

1. Steuer CE, El-Deiry M, Parks JR, Higgins KA, Saba NF. An update on larynx cancer. *CA Cancer J Clin*. 2017;67:31-50.
2. Caudell JJ, Carroll WR, Spencer SA, Bonner JA. Examination of laryngoesophageal dysfunction-free survival as an endpoint in non-surgical treatment of squamous cell carcinomas of the larynx and hypopharynx. *Cancer*. 2011;117:4447-4451.
3. Adelstein DJ, Lavertu P, Saxton JP, et al. Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and IV squamous cell carcinoma of the head and neck. *Cancer*. 2000;88:876-883.
4. Bonner J, Giralt J, Harari P, et al. Cetuximab and radiotherapy in laryngeal preservation for cancers of the larynx and hypopharynx: a secondary analysis of a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2016;142:842-849.
5. Megwalu UC, Sikora AG. Survival outcomes in advanced laryngeal cancer. *JAMA Otolaryngol Head Neck Surg*. 2014;140:855-860.
6. NCCN Clinical Practice Guidelines in Oncology. Head and neck cancers. Version 2, 2018, 07/20/18. National Comprehensive Cancer Network; 2018.
7. Robbins KT, Storniolo AM, Kerber C, Seagren S, Berson A, Howell SB. Rapid superselective high-dose cisplatin infusion for advanced head and neck malignancies. *Head Neck*. 1992;14:364-371.
8. Homma A, Furuta Y, Suzuki F, et al. Rapid superselective high-dose cisplatin infusion with concomitant radiotherapy for advanced head and neck cancer. *Head Neck*. 2005;27:65-71.
9. Homma A, Sakashita T, Yoshida D, et al. Superselective intra-arterial cisplatin infusion and concomitant radiotherapy for maxillary sinus cancer. *Br J Cancer*. 2013;109:2980-2986.
10. Sugimoto H, Ito M, Yoshida S, Hatano M, Yoshizaki T. Concurrent superselective intra-arterial chemotherapy and radiotherapy for late-stage squamous cell carcinoma of the temporal bone. *Ann Otol Rhinol Laryngol*. 2011;120:372-376.
11. Nomura K, Takahara M, Katayama A, et al. Intra-arterial cisplatin with concomitant radiation for advanced hypopharyngeal cancer. *Laryngoscope*. 2013;123:916-922.
12. Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: results of a randomized phase 3 trial. *Cancer*. 2010;116:2159-2165.
13. Wakisaka N, Kondo S, Endo K, Murono S, Yoshizaki T. Adjuvant chemotherapy with an oral fluoropyrimidine, S-1, following reduced RADPLAT in advanced laryngeal cancer. *Ann Otol Rhinol Laryngol*. 2012;121:555-562.
14. Yoshizaki T, Kondo S, Wakisaka N, et al. Concurrent intra-arterial chemotherapy and radiotherapy for advanced laryngeal cancer. *Ann Otol Rhinol Laryngol*. 2009;118:172-178.
15. Rosenthal DI, Mohamed AS, Weber RS, et al. Long-term outcomes after surgical or nonsurgical initial therapy for patients with T4 squamous cell carcinoma of the larynx: a 3-decade survey. *Cancer*. 2015;121:1608-1619.
16. Al-Mamgani A, van Rooij PH, Woutersen DP, et al. Radiotherapy for T1-2N0 glottic cancer: a multivariate analysis of predictive factors for the long-term outcome in 1050 patients and a prospective assessment of quality of life and voice handicap index in a subset of 233 patients. *Clin Otolaryngol*. 2013;38:306-312.
17. Agrawal N, Ha PK. Management of early-stage laryngeal cancer. *Otolaryngol Clin North Am*. 2008;41:757-769.
18. Kimura K, Itoh Y, Okada T, et al. Study protocol: prospective study of concurrent chemoradiotherapy with S-1 and hypofractionated radiotherapy for outpatients with early glottic squamous cell carcinomas. *Asian Pac J Cancer Prev*. 2018;19:1195-1199.
19. Leszczyńska M, Wierzbicka M, Tokarski M, Szyfter W. Attempt to improve functional outcomes in supracricoid laryngectomy in T2b and T3 glottic cancers. *Eur Arch Otorhinolaryngol*. 2015;272:2925-2931.
20. Zhou J, Zhou L, Tao L, et al. Oncologic outcomes of surgical treatment for T3 glottic laryngeal squamous cell carcinoma. *Head Neck*. 2018;40:1734-1742.
21. Ampil FL, Nathan CO, Lian TS, Caldito G, Milligan E. Total laryngectomy and T3-T4 laryngeal cancer without other adverse histopathology. *Otolaryngol Head Neck Surg*. 2007;136:296-300.
22. Chevalier D, Laccourreye O, Brasnu D, Laccourreye H, Piquet JJ. Cricohyoidoepiglottopexy for glottic carcinoma with fixation or impaired motion of the true vocal cord: 5-year oncologic results with 112 patients. *Ann Otol Rhinol Laryngol*. 1997;106:364-369.
23. Canis M, Martin A, Ihler F, et al. Transoral laser microsurgery in treatment of pT2 and pT3 glottic laryngeal squamous cell carcinoma - results of 391 patients. *Head Neck*. 2014;36:859-866.
24. Timme DW, Jonnalagadda S, Patel R, Rao K, Robbins KT. Treatment selection for T3/T4a laryngeal cancer: chemoradiation versus primary surgery. *Ann Otol Rhinol Laryngol*. 2015;124:845-851.
25. Fuller CD, Mohamed AS, Garden AS, et al. Long-term outcomes after multidisciplinary management of T3 laryngeal squamous cell carcinomas: improved functional outcomes and survival with modern therapeutic approaches. *Head Neck*. 2016;38:1739-1751.
26. Hinerman RW, Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB. T3 and T4 true vocal cord squamous carcinomas treated with external beam irradiation: a single institution's 35-year experience. *Am J Clin Oncol*. 2007;30:181-185.
27. Al-Mamgani A, Tans L, van Rooij P, Levendag PC. A single-institutional experience of 15 years of treating T3 laryngeal cancer with primary radiotherapy, with or without chemotherapy. *Int J Radiat Oncol Biol Phys*. 2012;83:1000-1006.
28. Timmermans AJ, de Gooijer CJ, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. T3-T4 laryngeal cancer in The Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/-sacrificing protocol. *Head Neck*. 2015;37:1495-1503.
29. Gorphe P, Matias M, Even C, et al. Laryngo-esophageal dysfunction-free survival in a preservation protocol for T3 laryngeal squamous-cell carcinoma. *Anticancer Res*. 2016;36:6625-6630.

30. Bhateja P, Ward MC, Hunter GH, et al. Impaired vocal cord mobility in T2N0 glottic carcinoma: suboptimal local control with radiation alone. *Head Neck*. 2016;38:1832-1836.
31. Robbins KT, Kumar P, Harris J, et al. Supradose intra-arterial cisplatin and concurrent radiation therapy for the treatment of stage IV head and neck squamous cell carcinoma is feasible and efficacious in a multi-institutional setting: results of Radiation Therapy Oncology Group Trial 9615. *J Clin Oncol*. 2005;23:1447-1454.
32. Yokoyama J, Furukawa M. A novel laryngeal preservation therapy for advanced glottic laryngeal cancer by superselective intra-arterial chemotherapy. *Larynx Japan*. 2006;18:84-88.
33. Furusaka T, Matsuda A, Tanaka A, Matsuda H, Ikeda M. Superselective intra-arterial chemoradiation therapy for functional laryngeal preservation in advanced squamous cell carcinoma of the glottic larynx. *Acta Otolaryngol*. 2013;133:633-640.
34. Nguyen-Tan PF, Le QT, Quivey JM, et al. Treatment results and prognostic factors of advanced T3–4 laryngeal carcinoma: the University of California, San Francisco (UCSF) and Stanford University Hospital (SUH) experience. *Int J Radiat Oncol Biol Phys*. 2001;50:1172-1180.
35. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091-2098.
36. Lin CC, Fedewa SA, Prickett KK, Higgins KA, Chen AY. Comparative effectiveness of surgical and nonsurgical therapy for advanced laryngeal cancer. *Cancer*. 2016;122:2845-2856.
37. Robbins KT, Kumar P, Wong FS, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. *Head Neck*. 2000;22:687-693.
38. Lambert L, Fortin B, Soulières D, et al. Organ preservation with concurrent chemoradiation for advanced laryngeal cancer: are we succeeding? *Int J Radiat Oncol Biol Phys*. 2010;76:398-402.
39. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. 2013;31:845-852.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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