Multimodal Treatment for T1-2 Supraglottic Cancer: The Impact of Tumor Location

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Abstract. *Aim: To examine the outcome and prognostic factors after multimodal treatment of T1-2 supraglottic cancer. Patients and Methods: We analyzed 49 patients with T1-2 supraglottic cancer who received multimodal treatment between 1990 and 2011. Their age range was 43-86 years (median=66 years). Fifteen patients had a T1 tumor and 34 had a T2 tumor (40 N0, 3 N1, 4 N2, and 2 N3). Debulking using transoral laser excision was employed in 25 patients. Neck dissection was performed in four patients. Chemotherapy was administered to 29 patients: intra-arterial infusion in four and systemic infusion in 25. Radiotherapy was administered at a median dose of 64.8 Gy (range=30-70 Gy) with once- or twice-daily fractionation. Median follow-up time was 60 months (range=12-153 months). Results: Two patients interrupted radiotherapy because of a poor response at 30 Gy (T2N2) and 49.9 Gy (T2N0). They underwent total laryngectomy and were still alive without any evidence of cancer 48 and 28 months after treatment, respectively. The other 47 patients (96%) had a complete local response to treatment. Locoregional failure was observed in six tumor sites, and one patient had simultaneous locoregional recurrence. The 5-year local control, disease-free, overall survival, and laryngeal preservation rates were 82%, 74%, 82%, and 90%, respectively. The location of a primary tumor within the supraglottis (epilarynx or elsewhere) was identified as the only factor predictive of progression-free survival by univariate and multivariate analyses (p=0.04). Acute adverse reactions of grade 3 or more were: one grade 3 laryngeal edema, one grade 3 dyspnea, and one grade 5 hematological toxicity (disseminated intravascular coagulation). Among late adverse events, one grade 1, one grade 2 hoarseness, and grade 3 laryngeal necrosis were observed. Conclusion: Multimodal radiotherapy produced a good outcome. Localization of the tumor in the epilarynx was associated with a better progression-free survival rate than that in the other parts of the supraglottis.*

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Management of supraglottic laryngeal carcinoma has changed in recent decades, although the change has not always resulted in a significant improvement in outcomes (1-6). There have been changes in surgical approaches, with increasing use of laser resection and decreasing use of open surgical procedures. Radiotherapy approaches have also changed, with altered fractionation methods and increased use of concurrent chemotherapy (6-9). Laryngeal function has emerged as an important end-point, especially voice quality; thus, preservation of anatomical structure of the larynx with a high risk of aspiration is no longer regarded as a worthwhile goal (10).

Although the treatment outcome of supraglottic carcinoma is relatively good, the decision regarding treatment options remains controversial. In contrast to tumors confined to the glottis, supraglottic squamous cell carcinoma has a substantially different prognosis because of its higher tendency to spread locally and to develop a higher proportion of local lymph node metastases (1-6). Surgical resection and radiotherapy-alone, or in combination, are the mainstay of laryngeal cancer treatment, but the choice of treatment often depends on the experience of the physician and on hospital policies (3, 9). Our Institute has adopted a multidisciplinary approach that includes transoral laser excision (tumor debulking), chemotherapy (systemic or intra-arterial infusion), and

radiotherapy (daily or twice daily). This study was conducted to review our clinical data on patients with T1-2 supraglottic carcinoma treated with radiotherapy. We assessed prognostic factors and treatment results. To limit the influence of tumor type on treatment results, only patients with T1-2 tumors were included in the analysis. Prognostic factors that could be useful for making optimal therapeutic decisions were the focus of the study.

Patients and Methods

Forty-nine patients with T1-2 supraglottic cancer received definitive multimodal radiotherapy at the Kurume University Hospital between 1990 and 2011. The patients' characteristics are summarized in Table I. Tumors were staged according to the sixth edition of the Union for International Cancer Control staging (11). Transoral laser excision was performed in 25 patients for debulking since the tumor had an exophytic appearance. Twenty-nine patients received chemoradiotherapy, which consisted of four rounds of intra-arterial infusion chemotherapy and 25 rounds of concurrent systemic chemotherapy: 12 rounds of FP therapy [daily 5-fluorouracil (5-FU) at 250 mg/m^2 and cisplatin at 5 mg/m^2 for the initial three weeks), three rounds of FAR therapy (5-FU at 250 mg *i.v.* and vitamin A, 50,000 units i.m. daily), and 10 daily rounds of cisplatin infusion at 6 mg/m^2. Intra-arterial infusion chemotherapy (cisplatin at 75 mg/week, 4-5 times) was performed in cases of a tumor at T2N1 or higher. One patient (cT1N3) had a complete response to induction chemotherapy (TPF: Docetaxel, cisplatin, and 5-FU). He then received concurrent chemoradiotherapy (FP and 61 Gy of radiotherapy). Four patients with advanced neck cancer were scheduled to undergo neck dissection before radiotherapy (2 T1N2, 1 T1N3, and 1 T2N2 cases). External-beam radiotherapy was administered 5-10 times a week in once-daily (1.8-2.0 Gy/day) or twice-daily fractions (1.6 Gy plus 0.8 Gy) using a 4- to 6-MV photon beam (median=64.8 Gy; range=30-70 Gy). Radiotherapy was initially administered at 40-46 Gy, with opposed lateral fields for primary and upper neck areas matched to anterior fields for lower neck and supraclavicular regions if necessary. The primary lesion and the affected neck nodes received a further boost of 60-70 Gy (even in postoperative cases), with oblique parallel opposed fields or an electron boost to spare the spinal cord. Gross tumor volume was defined as the total volume of the primary lesion and the affected lymph nodes and was determined using laryngoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scans. A positive lymph node was defined as a node with a size of more than 10 mm along the short axis on CT/MRI or positive by ^{18}F-FDG PET findings. Prophylactic areas were designed to include the lymph nodes at levels II-V and retropharyngeal and subclavicular lymph nodes if necessary.

All patients were enrolled in this study after providing written informed consent. Patients were followed-up every month during the first six months and every 3-6 months thereafter. The median follow-up time for surviving patient was 60 months (range=12-153 months). Acute and late adverse events were scored according to the Common Terminology Criteria of Adverse Events, version 3.0 (12). To analyze prognostic factors, we divided tumor locations into the superior epilaryngeal portion (suprahyoid epiglottis, arytenoid, and aryepiglottic fold) and the inferior parts (infrahyoid epiglottis and false vocal cord).

Table I. *Patients' characteristics*.

Variable	Sub-class	n	%
Gender	Male	46	(94%)
	Female	3	(6%)
Age, years	Median (range)	66 (43-86)	
Site	Marginal	21	(43%)
	Suprahyoid epiglottis	5	
	Arytenoid	9	
	Aryepiglottic fold	7	
	Non-marginal	28	(57%)
	Infrahyoid epiglottis	12	
	False vocal cord	16	
T category	T1	15	(31%)
	T2	34	(69%)
N	N0	41	(84%)
	N1	3	(6%)
	N2	4	(8%)
	N3	1	(2%)
Stage	I	12	(20%)
	II	29	(49%)
	III	3	(5%)
	IV	5	(8%)

Statistical analysis. All statistical analyses were performed using Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). Frequencies were analyzed using the χ^2 test. Survival data and cumulative incidences were estimated by the Kaplan–Meier method and examined for significance using the log-rank test. Cox's proportional hazard model was used for the multivariate analysis. Cutoff values were set at the average or the median value of each variable unless otherwise stated. All analyses used the conventional $p<0.05$ level of significance.

Results

Two patients discontinued radiotherapy at 49.9 Gy (a T2N0 case) and 30 Gy (a T2N2 case) because of a poor response (partial response). They underwent total laryngectomy and were still alive without any evidence of cancer 48 and 28 months after treatment, respectively. The other 47 patients showed a complete response to treatment in the primary site, including one patient with a T1N3 tumor who had a complete response to neoadjuvant chemotherapy (TPF) and concurrent FP chemoradiotherapy. Before radiotherapy, four patients underwent planned neck dissection because of the affected lymph nodes. Local failure was observed in six patients, and locoregional simultaneous recurrence was observed in one. Those patients underwent a salvage surgical

Table II. *Analysis for prognostic factors (at 5 years)*.

Variable	Sub-class	n	PFS	*p*-Value	OS	LC
Age	70 or more	17	65%		76%	87%
	<70	32	74%	0.65	86%	80%
T category	1	15	72%	0.87	86%	84%
	2	34	70%		81%	82%
N category	0	40	72%	0.29	84%	84%
	1-3	9	61%		71%	76%
Stage	I	12	67%	0.64	83%	76%
	II	29	75%		85%	85%
	III	3	67%		67%	100%
	IV	5	47%		67%	53%
Hemoglobin level	≥14 g/dl	28	67%	0.32	76%	80%
	<14 g/dl	21	76%		90%	85%
Tumor subsite	Epilarynx	21	*84%	*0.04	89%	90%
	Other	28	61%		78%	77%
Chemotherapy	Yes	29	71%	0.98	81%	81%
	No	20	70%		85%	84%
Debulking	Yes	25	76%	0.32	88%	80%
	No	24	64%		77%	86%

PFS: Progression-free survival; OS: overall survival; LC: local control rate; *statistically significant.

Table III. *Adverse reactions*.

	Grade 2	Grade 3	Grade 4	Grade 5
Acute reaction				
Laryngeal edema		1		
Dyspnea		1		
Hematopoietic toxicity (disseminated intravascular coagulation)				1
Late reaction		1		
Laryngeal necrosis		1		
Hoarseness	1			

procedure. Later, only one patient (who had initial T2N0 cancer) experienced a recurrence, which resulted in death 36 months after radiotherapy. At the last follow-up, 39 (80%) patients were alive without any evidence of cancer and 10 (20%) had died, including one death from supraglottic cancer and one from a complication. The 5-year local control, disease-free and overall survival, and laryngeal preservation rates were 82%, 74%, 82%, and 90% respectively. Local control (and laryngeal preservation) rates for T1 and T2 tumors were 84% (92%) and 82% (90%), respectively. In multivariate analysis, the location of the primary tumor (epilarynx *vs*. elsewhere) was identified as the only significant predictive factor of progression-free survival (p=0.04; hazard ratio=3.65; 95% confidence interval=1.01-13.25; Table II, Figure 1). The 5-year progression-free survival rate was 84% for patients with an epilaryngeal tumor, whereas that for patients with tumors at other locations was 61%.

Three acute adverse events (6% of cases) interrupted radiotherapy: (one grade 3 laryngeal edema, one grade 3 dyspnea, and one grade 5 hematological toxicity (Table III). A 75-year-old male patient with T1N0 cancer underwent

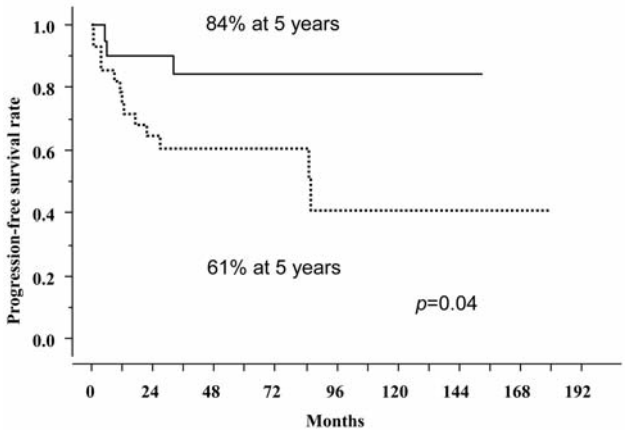

Figure 1. *Influence of tumor location on survival. Progression-free survival rates according to location of tumor. At five years, 84% of patients with epilaryngeal tumor (solid line) showed progression-free compared with 61% of those with tumors located elsewhere (dotted line) (p=0.04).*

systemic chemoradiotherapy (FAR treatment) and developed disseminated intravascular coagulation, which resulted in death for months later. Among late adverse events, one grade 1 and one grade 2 hoarseness and one grade 3 laryngeal necrosis were observed. Grade 3 necrosis was incidentally identified by fiberscope during regular follow-up examination and was asymptomatic.

Discussion

In the literature, 5-year local control rates vary from 63% to 100% for T1 and from 50% to 85% for T2 supraglottic lesions (13). We used a multidisciplinary approach to maximize preservation of organ function. The observed local control rates (and laryngeal preservation rates) for T1 and T2 tumors were 84% (92%) and 82% (90%), respectively. These findings are in line with those of previous studies. We believe that debulking using transoral laser excision may have contributed to the similarity of outcomes for T1 and T2 tumors because tumor volumes were reduced to the smallest extent possible. The observed survival rates (a 5-year overall survival rate of 67% for stage III and stage IV supraglottic cancer, with local control rates of 100% and 53%, respectively) are promising and comparable to previously published data (*i.e.* 40-53% for stage III and 31-53% for stage IV supraglottic cancer) (5, 6). Use of intensive chemotherapy including intra-arterial infusion must also have contributed to tumor control (14). These data suggest that multimodal intensive treatment is an effective approach and should be more widely adopted in clinical practice.

It is noteworthy that localization of the tumor in the epilarynx was associated with a better outcome than that in the other parts of the supraglottis. Tumors located at the suprahyoid epiglottis, arytenoid, aryepiglottic fold (superior location) show growth by exophyting extension, whereas those of hypohyoid epiglottis and false cord (inferior location) show growth by infiltrating (13). These tumor characteristics may have contributed to the difference in outcomes observed in this study. On the other hand, several authors reported that there is no difference in outcomes among patients with different sublocations of supraglottic cancer (5, 6). Therefore, further research is needed to resolve this discrepancy.

There are several limitations to our study. The high-intensity treatment caused a severe adverse event, although it was a singular case. We observed one grade 5 acute reaction (disseminated intravascular coagulation) during chemoradiotherapy in a male patient with a T1 lesion; the adverse event resulted in death, although the patient had a complete response to treatment in the local tumor. This type of toxicity is unacceptable for the treatment of early laryngeal cancer. Although the decision tree in the treatment of early supraglottic carcinoma remains controversial and we took all necessary precautions, in retrospect, we should have sought a safer scheme for the high-risk patient with an early lesion. In this case, the patient was 75 years old and exhibited anemia (hemoglobin, 11.5 g/dl). In the future, we will avoid treating fragile elderly patients with systemic chemotherapy. In addition, the local control rate for T1 tumors did not reach a satisfactory level, and there is room for improvement. One possible strategy is to increase the total radiotherapy dose, with or without hyperfractionation.

In summary, multimodal treatment appears to be effective in supraglottic cancer, and localization of the tumor in the epilarynx is associated with a better progression-free survival rate.

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