Laryngo-esophageal Dysfunction-free Survival in a Preservation Protocol for T3 Laryngeal Squamous-cell Carcinoma

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Abstract. *Background:* We reviewed the outcomes of patients with T3 laryngeal neoplasms with a fixed hemilarynx, a large gross tumor volume or a subglottic extension (SGE), treated with a laryngeal-preservation protocol with induction chemotherapy. *Patients and Methods:* The study end-points were laryngo-esophageal dysfunction-free survival (LEDFS), laryngectomy-free survival (LFS), overall survival (OS), and disease-free survival (DFS). *Results:* A total of 104 patients were included. The 2-year and 5-year OS rates were 70.4% and 54.5%, respectively. OS and DFS were independent of the treatment modality in the whole cohort ($p=0.6546$ and $p=0.3006$, respectively) and in patients with SGE ($p=0.529$ and $p=0.255$, respectively). The 2-year and 5-year LEDFS rates were 44.3% and 28.2%, respectively. LEDFS was not associated with initial hemilaryngeal fixation or SGE ($p=0.5772$ and $p=0.0623$, respectively). *Conclusion:* Chemoselection is feasible without compromised oncological or functional outcomes in patients with an initially fixed hemilarynx or subglottic extension.

In 1991, the Veterans Department phase III trial demonstrated the feasibility of laryngeal preservation in patients with advanced-stage laryngeal squamous-cell carcinoma (SCC) who achieved a good response to induction chemotherapy followed by radiotherapy (1). In 2003 the Radiation Therapy Oncology Group (RTOG) trial 91-11 demonstrated the benefit of primary concurrent chemoradiotherapy in laryngeal preservation without a difference in survival (2, 3). Both

studies led to a major paradigm shift from surgery to chemoradiotherapy for the treatment of advanced-stage pharyngo-laryngeal SCC (4, 5). However, the treatment must take into account laryngeal function preservation and quality of life (6, 7). In 2009, the Larynx Preservation Consensus Panel recommended using laryngo-esophageal dysfunction-free survival (LEDFS) as a composite primary endpoint in preservation studies (8). To date, the results obtained using this end-point have never been published specifically for laryngeal cancer. We report on the outcomes of patients with resectable locally advanced American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) T3 laryngeal SCC unamenable to partial laryngectomy with a large gross tumor size, a fixed hemilarynx or subglottic spread, treated with a laryngeal-preservation protocol.

Patients and Methods

Patients. This study received Institutional Review Board approval. We retrospectively reviewed patients treated at our cancer center between 2001 and 2013 for a laryngeal SCC. At our center, laryngeal-preservation protocols with induction chemotherapy for AJCC/UICC T3 tumors of the larynx is offered to patients with a resectable tumor unamenable to partial laryngectomy with a fixed hemilarynx or with compromised functions because of a large tumor volume or subglottic extension (SGE) not requiring a tracheotomy before treatment. Patients with small T3 tumors and a functional larynx were treated with concurrent chemoradiotherapy. Patients with a resectable T3 tumor and a non-functional larynx that required an initial tracheotomy or definitive enteral nutrition were treated with upfront total laryngectomy.

Treatments. Induction chemotherapy comprised three courses of a combination of cisplatin and fluorouracil (PF), or more recently docetaxel, cisplatin and fluorouracil (TPF) administered every 3 weeks. Response was insufficient when tumor volume shrinkage was less than 50% clinically or radiologically, 2 weeks after the second cycle, or if the hemilarynx remained fixed. Radiotherapy was delivered at a dose of 70 Gy to good responders to induction chemotherapy. Patients with an insufficient response underwent a total laryngectomy with adjuvant radiotherapy according to

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Key Words: Laryngeal neoplasm, fixed larynx, subglottic extension, laryngeal preservation, induction chemotherapy, radiotherapy, laryngectomy.

Table I. Characteristics of 104 successive patients with American Joint Committee on Cancer/Union for International Cancer Control T3 intermediate gross laryngeal squamous-cell carcinoma treated with laryngeal preservation protocol with selection by induction chemotherapy.

Characteristic	
Gender, n (%)	
Male	93 (89.4%)
Female	11 (10.6%)
Median age (range), years	58 (38-77)
Initial disease site, n (%)	
Glottic	35 (33.7%)
Supraglottic, epilaryngeal	53 (51%)
Supraglottic, other	16 (15.3%)
Laryngeal fixation, n (%)	
Yes	42 (40.4%)
No	62 (59.6%)
Initial disease assessment, n (%)	
Subglottic extension	23 (22.1%)
cN0	55 (52.9%)
cN1	16 (15.3%)
cN2a	8 (7.7%)
cN2b	6 (5.8%)
cN2c	10 (9.6%)
cN3	9 (8.7%)

pathological features and the patient's clinical status. When indicated, radiosensitizing agents (e.g. platinum-based chemotherapy or targeted therapy) were used.

Statistical design and analysis. Our main objective was to describe the results according to laryngeal fixation and SGE. Laryngeal fixation was defined as fixation of both the vocal cord and arytenoid cartilage (9). SGE was defined as tumor invasion 5 mm below the free margin of the vocal cords. Survival endpoints were defined as the time between the date of initial consultation in multidisciplinary staff for treatment proposal and the date of first event. The primary endpoint was LEDFS. The secondary endpoints were overall survival (OS), disease-free survival (DFS), laryngectomy-free survival (LFS) and laryngeal preservation.

The results are expressed as percentages or medians (with range), and data were analyzed using chi-squared tests. Analyses of LEDFS, OS and DFS were performed using the Kaplan-Meier method. The events for LEDFS were death, local relapse, total or partial laryngectomy, tracheotomy, and chronic enteral nutrition. The events for LFS were total laryngectomy or death. Death from any cause was the event for OS and the events for DFS were death or disease recurrence. Survival curves were compared using the log-rank test for univariate analyses. Variables associated with a *p*-value of less than 0.1 in the univariate analyses and confounding variables correlated with initial laryngeal mobility were included in the multivariate analyses using a Cox model. Statistical analyses were performed using software Prism® 6.04 (GraphPad Software, La Jolla, CA, USA) and STATA® 13.0 software (StataCorp LP, College Station, TX, USA) for Windows. All reported *p*-values are two-sided, and *p*-values lower than 0.05 were considered significant.

Table II. Details of evaluation outcomes and treatment given after induction chemotherapy in 104 sequential patients with American Joint Committee on Cancer/Union for International Cancer Control T3 intermediate gross laryngeal squamous-cell carcinoma. Good responders were treated with radiotherapy, insufficient responders were treated with total laryngectomy.

	No. of patients Fixed larynx	
Treatments and outcomes	No	Yes
Induction chemotherapy regimen		
PF	27	19
TPF	35	23
Evaluation of volume response		
Complete response	12	8
Partial response	34	21
Insufficient response	16	13
Recovery of laryngeal mobility		29
Treatment after induction chemotherapy		
Definitive radiotherapy	19	12
Concomitant chemoradiotherapy	27	17
Surgery alone	1	4
Surgery and radiotherapy	6	8
Surgery and chemoradiotherapy	9	1

PF: Cisplatin-fluorouracil; TPF: taxotere-cisplatin-fluorouracil.

Results

Patients. Between 2001 and 2013, 411 patients were treated at our Institution for a T3 SCC of the larynx. Study criteria requirements were fulfilled by 104 patients (Table I). Hemilaryngeal fixation was present in 42 patients and was more common in lesions originating from the glottis than from the supraglottis (*p*=0.0194).

Induction chemotherapy and response. Fifteen patients (14.4%) received only 2 cycles of chemotherapy: 10 achieved a complete response and were treated with radiotherapy, five failed to respond to induction chemotherapy and underwent a total laryngectomy. Details of tumor response and treatment received are given in Table II. The PF and TPF regimens were well balanced between groups. Disease in seven out of 29 patients operated on was upstaged from cT3 to pT4a (24.1%) due to invasion through the thyroid cartilage in two cases and lysis of the cricoid cartilage, cricothyroid membrane invasion and prelaryngeal invasion in five.

Outcomes and survival. Recurrences occurred in nine patients submitted to a total laryngectomy (31%), three of which were local (median time to onset, 3 months). After radiotherapy, eight patients (four with a fixed hemilarynx) required a definitive tracheotomy and eight patients (three

Table III. Multivariate analyses of prognostic factors for laryngo-esophageal dysfunction-free survival (LEDFS), overall survival (OS), disease-free survival (DFS) and laryngectomy-free survival (LFS) in 104 patients treated with laryngeal-preservation protocol with induction chemotherapy for American Joint Committee on Cancer/Union for International Cancer Control T3 intermediate gross squamous-cell carcinoma of the larynx. Good responders were treated with radiotherapy, insufficient responders were treated with total laryngectomy.

Variable	Multivariate analyses							
	LEDFS		OS		DFS		LFS	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Laryngeal fixation	1.32 (0.6-2.93)	0.495	1.26 (0.46-3.47)	0.651	1.06 (0.42-2.67)	0.897	1.33 (0.61-2.94)	0.474
Glottic initial disease	1.88 (0.81-4.34)	0.14	2.85 (1.05-7.77)	0.04	1.83 (0.71-4.77)	0.214	2.01 (0.86-4.69)	0.107
Subglottic extension	0.54 (0.21-1.41)	0.209	0.14 (0.04-0.51)	0.003	0.3 (0.1-0.89)	0.03	0.52 (0.2-1.36)	0.183
Radiological nodal invasion	1.27 (0.68-2.38)	0.448	1.67 (0.79-3.53)	0.181	1.27 (0.65-2.47)	0.48	1.19 (0.63-2.22)	0.594
PF chemotherapy	1.28 (0.78-2.11)	0.327	1.25 (0.69-2.28)	0.462	1.04 (0.6-1.82)	0.881	1.22 (0.73-2.03)	0.449
Insufficient response	-	-	1.39 (0.68-2.82)	0.364	1.02 (0.5-2.08)	0.96	-	-

PF: Cisplatin-fluorouracil; HR:hazard ratio; CI: confidence interval.

with a fixed hemilarynx) required definitive enteral nutrition without a tracheotomy. One patient underwent a functional laryngectomy 22 months after the end of radiotherapy. Recurrences occurred in 24 patients treated with radiotherapy (32%), 15 of which were local (20%, eight with initial hemilaryngeal fixation). Fourteen patients underwent salvage total laryngectomy, in 11 cases performed within two years after the end of radiotherapy. In the total cohort, the 2- and 5-year laryngeal-preservation rates were 60.4% and 53.4%, respectively, and the corresponding LFS rates were 46.1% and 30%, respectively. The median LFS in the whole cohort was 21 months (Figure 1). SGE was associated with decreased LFS in the univariate analyses ($p=0.0215$). The results of the multivariate analyses are reported in Table III.

Median LEDFS was 15 months (Figure 1). The 2- and 5-year LEDFS rates were 44.3% and 28.2%, respectively (Figure 1). LEDFS was not associated with initial hemilaryngeal fixation or SGE in the univariate analyses of the entire cohort ($p=0.5772$ and $p=0.0623$, respectively), nor in the subgroup of patients treated with radiotherapy ($p=0.9963$ and $p=0.6950$, respectively). The median OS and DFS for the whole cohort were 70 months and 44 months, respectively, (Figure 1). The 2- and 5-year OS rates were 70.4% and 54.5%, respectively, and the corresponding DFS rates were 56% and 47.8%, respectively. Decreased OS and DFS were associated with SGE in the univariate analyses ($p=0.0109$ and $p=0.0456$, respectively) and multivariate analyses (Table III) but not with hemilaryngeal fixation ($p=0.7490$ and $p=0.8841$, respectively). OS and DFS were not associated with a sufficient response or not (and therefore radiotherapy or surgery) ($p=0.6546$ and $p=0.3006$, respectively) in the whole cohort, nor in patients with hemilarynx fixation ($p=0.846$ and $p=0.598$) or with SGE ($p=0.529$ and $p=0.255$, respectively).

Figure 1. Kaplan-Meier curves of overall survival (OS), disease-free survival (DFS), laryngo-esophageal dysfunction-free survival (LEDFS) and laryngectomy-free survival (LFS) in 104 patients treated in laryngeal-preservation protocol with induction chemotherapy for American Joint Committee on Cancer/Union for International Cancer Control T3 intermediate gross squamous-cell carcinoma of the larynx.

Discussion

As expected, in our study, patients with T3 laryngeal cancer who achieved a good response to induction chemotherapy were able to benefit from treatment with radiotherapy without a decrease in survival compared to treatment with total laryngectomy with postoperative radiotherapy. Our major findings were the feasibility of chemoselection without compromised oncological or functional outcomes in patients with an initially fixed hemilarynx or SGE. The 2-year OS and 2-year laryngeal preservation rates in our cohort were

Table IV. Available data of criteria of inclusion, evaluation and response with results of 2-year survival and laryngeal preservation in the four landmark randomized trials of laryngeal-preservation protocols with induction chemotherapy for selection of radiotherapy or total laryngectomy according to the response.

Trial (Ref)	Inclusion criteria				Induction CTx	Evaluation criteria		Response criteria			
	Localization	Stage	T-Stage	Laryngeal mobility		Gross tumor volume evaluation	Laryngeal mobility	Gross tumor response	Laryngeal mobility	OS rate (time point)	Laryngeal preservation rate (time point)
VALCSG (1)	Larynx	III, IV	T2, T3, T4	Information: Vocal cord mobility fixed or not	PF	CT scan: Radiological product of longest and perpendicular dimensions	NA	>50% Volume response	NA	68% (2-year)	NA
EORTC 24891 (10)	Hypopharynx	II, III, IV (except N2c)	T2, T3, T4	NA	PF	Clinical macroscopic evaluation by direct endoscopy performed before each cycle	NA	Complete response after 2nd or 3rd cycle	Complete recovery	Surgical arm 57% vs. radiotherapy arm 43% (3-year)	NA
RTOG 91-11 (2)	Larynx	III, IV	T2, T3, low-volume T4	Stratification: vocal cord fixed or not	PF	Clinical macroscopic evaluation by direct endoscopy and CT scan after 2nd cycle	NA	Complete or partial response	NA	76% (2-year)	75% (2-year)
GORTEC 2000-01 (11)	Larynx and hypopharynx	III, IV	T2, T3, T4 without massive cartilage invasion	Information: Vocal cord mobility normal, impaired or fixed	PF vs. TPF	Clinical examination (indirect laryngoscopy) and CT scan	Clinical examination (indirect laryngoscopy)	Complete response at primary site or partial response >80% and normal laryngeal mobility	Normal	60% (3-year)	57.5% vs. 70.3% (3-year)

VALCSG: Veterans Affairs Laryngeal Cancer Study Group; CTx: chemotherapy; CT: computed tomography; OS: overall survival; RTOG: Radiation Therapy Oncology Group; EORTC: European Organization for Research and Treatment of Cancer; GORTEC: Groupe Oncologie Radiothérapie Tête Et Cou; NA: Not available; PF: cisplatin-fluorouracil; TPF: taxotere-cisplatin-fluorouracil.

70.4% and 60.4%, respectively, similar to the results of the landmark laryngeal preservation trials (Table IV) (1-3, 10-13). The 2-year LEDFS rate in our series was 44.3% and can be used as a benchmark. However, it is difficult to compare articles on laryngeal preservation due to the heterogeneity of inclusion and evaluation criteria (Table IV).

It may seem logical to study laryngeal and hypopharyngeal neoplasms at the same time due to the same issue of deciding between radical surgery and laryngeal preservation. However, the survival results of patients with laryngeal and hypopharyngeal neoplasms and the functional sequelae of treatment are widely different. In fact the AJCC/UICC TNM

staging of the larynx takes into account vocal cord mobility which is staged normal, impaired or fixed whereas staging of the hypopharynx takes into account hemilaryngeal fixation which is defined as fixation of both the vocal cord and arytenoid and is staged as fixed or not. In our experience, impaired laryngeal function is associated with hemilaryngeal fixation more than with vocal cord fixation itself, which can be consistent with normal or subnormal function (14). The heterogeneity of mobility criteria in scientific articles prohibits a comparison of results according to the initial functional assessment.

Moreover the landmark trials included patients with AJCC/UICC stages III/IV with very diverse gross tumors, local

extension and nodal involvement (1, 2, 10, 11). In patients with T2 lesions, the larynx almost always remains functional as in the case of most patients with T3 lesions because of local extension such as minimal invasion of the pre-epiglottic space or paraglottic space. These patients, whose tumors represented 24.1% of the T3 lesions in our study period, were treated with concurrent chemoradiotherapy because in our opinion, the response rate after induction chemotherapy is very high for these low-volume tumors and the laryngeal mobility cannot be used as decision criterion due to the absence of laryngeal fixation. In contrast, treatment with upfront chemoradiotherapy has been reported for T4 tumors but is still controversial because of selection biases and continues to fuel debate because of a low level of evidence (6, 15-21). The standards upheld at our Institution remain in accordance with the National Comprehensive Cancer Network Guidelines which recommend upfront total laryngectomy with postoperative radiotherapy in patients with T4a tumors by seventh edition AJCC criteria (22). Patients who refuse surgery are given concurrent chemoradiotherapy because radiotherapy would ultimately be selected whatever the response to induction chemotherapy.

Our study allowed us to confirm that SGE is an important prognostic factor in laryngeal cancer regardless of treatment. SGE is usually considered to confer a poor prognosis given the high propensity for nodal and distant spread, and the risk of an obstructive lesion with impaired laryngeal function. We previously reported the feasibility of laryngeal preservation in cancer with SGE, with a strategy fine-tuned to the disease stage and local extension (23). We confirm in this study the feasibility of laryngeal preservation in patients with locally advanced T3 intermediate gross laryngeal tumors with SGE or a fixed hemilarynx without compromised outcomes as long as the selection criteria after induction chemotherapy remain rigorously respected.

Conflicts of Interest

None.

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