

HEAD AND NECK

Salvage total laryngectomy after conservation laryngeal surgery for recurrent laryngeal squamous cell carcinoma

Laringectomia totale di salvataggio nel trattamento delle recidive di carcinoma squamocellulare laringeo dopo terapia chirurgica conservativa

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SUMMARY

The aim of the present study was to evaluate the oncological efficacy of salvage total laryngectomy in patients who had previously undergone supracricoid partial laryngectomy or transoral laser microsurgery for treatment of laryngeal squamous cell carcinoma. We retrospectively reviewed the medical, surgical and pathological records of 35 patients who underwent salvage total laryngectomy after recurrence of laryngeal cancer (following supracricoid partial laryngectomy or transoral laser microsurgery). Kaplan-Meier survival curves as well as univariate and multivariate analyses of prognostic factors were performed. No statistically significant differences were seen comparing the supracricoid partial laryngectomy group with the transoral laser microsurgery group for overall survival and disease-specific survival at 3 years (OS = 38% vs. 52%, $p = 0.16$; DSS = 40% vs. 61%, $p = 0.057$) or locoregional control at 2 years (LRC = 40% vs. 54%, $p = 0.056$). A trend indicating worse survival and locoregional control for supracricoid partial laryngectomy patients emerged. Preservation of the osteocartilaginous frame in transoral laser microsurgery could hypothetically result in better salvageability of anterior recurrences with extralaryngeal spread.

KEY WORDS: Carcinoma • Larynx • Salvage total laryngectomy • Supracricoid laryngectomy • Transoral laser microsurgery

RIASSUNTO

Lo scopo del presente studio è stato quello di valutare l'efficacia oncologica della laringectomia totale di salvataggio in pazienti precedentemente sottoposti a laringectomia subtotale open o microchirurgia laser transorale affetti da carcinoma squamocellulare laringeo. Abbiamo analizzato retrospettivamente le informazioni cliniche, chirurgiche e patologiche di 35 pazienti sottoposti a laringectomia totale di salvataggio dopo recidiva di carcinoma laringeo (laringectomia subtotale open o transorale). Le informazioni sono state analizzate tramite l'utilizzo delle curve di Kaplan-Meier nonché tramite l'analisi univariata e multivariata dei fattori prognostici. Non sono emerse differenze statisticamente significative nel confronto tra il gruppo di pazienti precedentemente sottoposti a laringectomia subtotale ed il gruppo sottoposto a microchirurgia laser transorale sia in termini di overall survival (OS) e disease specific survival (DSS) a 3 anni (OS = 38% vs 52%, $p = 0,16$; DSS = 40% vs 61%, $p = 0,057$) che di controllo locoregionale (LRC) a 2 anni (LRC = 40% vs 54%, $p = 0,056$). È stata tuttavia messa in evidenza una tendenza che indica una sopravvivenza e controllo locoregionale peggiore nei pazienti sottoposti a laringectomia subtotale. La conservazione dello scheletro osteocartilagineo della microchirurgia laser transorale si traduce ipoteticamente in una maggiore probabilità di salvataggio delle recidive anteriori con diffusione extralaringea.

PAROLE CHIAVE: Carcinoma • Laringe • Laringectomia totale di salvataggio • Laringectomia sopracricoidea • Microchirurgia laser transorale

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Introduction

Supracricoid partial laryngectomy (SPL) and transoral laser microsurgery (TLM) are conservative surgical techniques performed for treatment of laryngeal squamous

cell carcinoma (LSCC) allowing for effective preservation of laryngeal function with excellent oncological results^{1,2}.

SPL is an 'open' technique that involves the opening of the laryngeal box, removal of the thyroid cartilage, false

cords, true vocal cords, epiglottis (or part of it) and, when necessary, one arytenoid. At the end of the procedure, a pexy between the cricoid cartilage and the hyoid bone is performed^{1,3}. TLM is an endoscopic technique through which the LSSC is removed, generally without violating cartilage structures. The procedure does not involve the creation of communications between the laryngeal box and laterocervical spaces^{2,4}. SPL and TLM pose important decisional problems in cases of suspected local recurrence with anterior extralaryngeal extension.

In general, the anterior extralaryngeal spread of a relapsing LSCC can occur in supraglottic primary (mainly through the thyrohyoid membrane) and glottic primary cases (through the thyrohyoid and cricothyroid membranes or directly through the thyroid cartilage)^{5,6}. The latter rarely occurs. However, the potential for tumour extralaryngeal spread increases in anterior relapsing lesions previously treated with conservative surgical techniques, such as supracricoid partial laryngectomy (SPL) or transoral laser microsurgery (TLM). In these cases, the complete absence of the thyroid cartilage (in the case of SPL) or of the internal perichondrium (in the case of TLM) may facilitate anterior extralaryngeal spread⁷. In the majority of cases it is possible to classify LSSC anterior relapse into 3 categories:

1. local recurrent tumour inside the neolarynx;
2. extra-laryngeal only pattern: no tumour inside the neolarynx, fully extra-laryngeal recurrence;
3. undetermined recurrence pattern.

The treatment of recurrent LSCC with suspected anterior extralaryngeal extension in the absence of direct invasion of vital structures is surgical. In most cases, an extended total laryngectomy is required that includes not only the removal of the larynx in its entirety, but also prelaryngeal muscles, thyroid gland, and when necessary, a portion of the overlying skin⁸. The aim of the present study was to evaluate the oncological efficacy of salvage total laryngectomy (STL) in recurrent LSCC with anterior extralaryngeal invasion in patients who had previously undergone to SPL or TLM.

Materials and methods

We retrospectively reviewed the medical, surgical and pathological records of 43 patients who underwent STL between March 1990 and December 2014 at Policlinico Umberto I, 'Sapienza' University of Rome for LSCC with anterior extralaryngeal invasion (rcT4a) at first diagnosis or recurrence after conservative surgical treatment with SPL or TLS. Patient characteristics, including age, gender and KPS at diagnosis, were recorded.

Inclusion and exclusion criteria

We identified 2 patient groups: patients primarily treated with SPL and those primarily treated with TLM. Patients

who were ineligible for treatment with a radical intent and/or with known distant metastases, patients who did not undergo follow-up and those affected by non-squamous histologies were excluded. Patients with an extralaryngeal spreading pattern without clinical evidence of intralaryngeal cancer were excluded as well. Based on inclusion and exclusion criteria, 35 patients were enrolled: 16 patients underwent primary SPL before STL (Group 1) and 19 underwent primary TLM before STL (Group 2). The Institutional Review Board of the Policlinico Umberto I Hospital, Rome, Italy approved the study.

Treatment and indications. In the group of patients who were primarily treated with TLM, the main treatment was endoscopic laser cordectomy (i.e., type II, III, IV, or V) in glottic cases or endoscopic laser horizontal supraglottic laryngectomy associated with mono or bilateral neck dissection in the supraglottic cases (level II-IV + Delphian node in N0 cases; I-VI in N+ cases). In the group of patients who were primarily treated with SPL, the primary treatment was cricohyoidopexy or a cricohyoid-epiglottopexy associated with mono or bilateral neck dissection (level II-IV + Delphian node in N0 cases; I-VI in N+ cases). Cricohyoidopexy was the preferred treatment in cases of anterior commissure involvement. All patients participating in the study underwent STL for anterior LSCC recurrences with suspected extralaryngeal spread.

Salvage total laryngectomy (STL)

When cervical skin removal is planned (according to the clinical status of the tumour), the skin area that is to be removed is outlined. Immediately after the incision of the skin, frozen sections are obtained to determine whether the skin is affected by subcutaneous neoplastic lymphangitis. The incision is continued at full thickness without dissecting the cutaneous, subcutaneous, fascial and muscular planes overlying the laryngeal lodge. When skin removal was not considered, a subplatysmal U-shaped cervical flap was elevated. The upper resection boundaries include the hyoid bone, whereas the lower margins may include, when necessary, the entire thyroid gland and two or more tracheal rings, depending on the subglottic extension of the tumour. Hypopharynx defects are restored as in conventional total laryngectomy, whereas the anterior defect involving skin, fascia and muscle is restored using a pectoralis major myo-cutaneous flap. The lower margin of the myocutaneous flap is sutured to the upper rim of the first remaining tracheal ring. A wide stoma is then created.

Neck dissection and adjuvant treatment

The cN0 patients underwent elective selective neck dissection unless they had already been dissected in a previous surgery, with removal of levels II to IV, according to the main international guidelines. A comprehensive neck dissection was performed for clinically-positive nodal disease. Adjuvant radiotherapy was performed in pN0-N1

cases. Adjuvant chemoradiation was performed (considering the patient's performance status) in high risk patients: extracapsular spread, positive margins, intravascular invasion, perineural invasion, pN2-N3 patients.

Outcome analysis. The follow-up was calculated from the date of the STL. The endpoints included overall survival (OS), disease-specific survival (DSS) and loco-regional control (LRC). Statistical analysis was performed using SPSS for Windows version 15.0. Survival curves were plotted using the Kaplan–Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model. A survival comparison was performed using a log-rank test, and *p* values < 0.05 were considered to be statistically significant.

Results

Age distribution was not significantly different between the two groups. Demographics and stage distribution are reported in Table I. When comparing staging (T and N for primary and recurrent LSCC) and subsites for primary LSCC, no significant differences were found between the groups. The median follow-up in our population was 31 months; therefore, 3-year survival rates are given. The median age of the entire group was 63 years (range 36–74 years). Among recurrences, the median time from primary treatment to first recurrence was 9 months for the SPL group and 13 months for the TLM group, with a mean of 11.5 and 14 months, respectively (*p* = 0.12).

A submucosal recurrent pattern was observed in 29 patients (83%, 12 SPL group, 17 TLM group), while an undetermined spreading pattern was observed in 6 patients (17%, 4 SPL group and 2 TLM group, Table I). Median time from primary treatment to first recurrence was 8 months in the submucosal recurrent pattern (29 patients) and 14 months for the undetermined recurrence pattern (6 patients), with a mean of 7.83 and 14 months, respectively (*p* < 0.001).

A nasogastric feeding tube was placed before the STL in all cases. Early and late sequelae and functional results, as well as the requirement for further adjuvant treatment, are summarised in Table II. We were unable to administer the recommended adjuvant treatment for comorbidities or low compliance in the post-operative period for 2 patients who underwent STL after SPL and 3 patients who underwent STL after TLM.

Pathologic stage. Pre-operative (STL) clinical staging was confirmed by histologic analysis in the majority of cases. In 3 cases, which were clinically classified as T4a, the pathologic staging changed to T3 (3 TLM groups). In 4 cases, which were clinically classified as N+, the pathologic staging changed to N0 (2 SPL groups, 2 TLM groups). The margins on the definitive specimen were positive in 3 cases (2 SPL groups, 1 TLM group, Table I). However, no significant differences emerged when com-

Table I. Patient characteristics and treatment modalities.

Characteristic	STL after SPL (16)	STL after TLM (19)
Age		
Median	64	59
Range	39-73	36-74
Sex N (%)		
Male	15 (94)	17 (89)
Female	1 (6)	2 (11)
Disease-free interval (months)		
Median	9	13
Range	3-27	5-35
Site of primary N (%)		
Supraglottis	10 (63)	5 (26)
Glottis	6 (37)	14 (74)
pT stage N (%)		
T1	4 (25)	5 (26)
T2	12 (75)	14 (74)
T3	-	-
T4a	-	-
pN stage N(%)		
N0	14 (87)	18 (95)
N1	2 (13)	1 (5)
N2A	-	-
N2B	-	-
rT stage (on the pathology specimen) N (%)		
T3	-	3 (16)
T4a	16 (100)	16 (84)
rN stage (on the pathology specimen) N (%)		
N0	8 (50)	12 (63)
N1	4 (25)	4 (21)
N2A	2 (13)	1 (5)
N2B	1 (6)	2 (11)
N2C	1 (6)	-
Spreading pattern N (%)		
Submucosal	12 (75)	17 (89)
Undetermined	4 (25)	2 (11)
Skin removal N (%)		
Yes	8 (50)	7 (37)
No	8 (50)	12 (63)
Skin involvement N (%)		
Positive	4 (50)	4 (57)
Negative	4 (50)	3 (43)
Resection margins after SL N (%)		
Positive	2 (13)	1 (5)
Negative	14 (87)	18 (95)

STL: salvage total laryngectomy; SPL: supracricoid partial laryngectomy; TLM: transoral laser microsurgery; pT: primary tumour T stage; pN: primary tumour N stage; rT: recurrent tumour T stage; rN: recurrent tumour N stage.

paring the two groups according to pathologic staging and margin status.

Survival analysis and loco-regional control. Calculated from the date of STL, overall OS in the entire group was

Table II. Early and late sequelae, adjuvant/salvage treatment and functional endpoints.

	STL after SPL (N=16) n (%)	STL after TLM (N=19) n (%)
Early reconstructive procedures		
Myocutaneous pectoralis major flap	15 (94)	15 (79)
Myofascial pectoralis major flap	1 (6)	4 (21)
Early sequelae (within 60 days) N		
Neck bleeding	3 (19)	2 (11)
Wound infection	1 (6)	-
Salivary fistula	3 (19)	2 (11)
Dysphagia	5 (31)	4 (21)
Persistent pain	2 (13)	-
Late sequelae (after 60 days)		
Pain	4 (25)	3 (16)
Neck fibrosis	6 (38)	5 (23)
Dysphagia	4 (25)	4 (21)
Further treatments for cancer		
Adjuvant radiotherapy	3 (19)	3 (16)
Adjuvant radiochemotherapy	11 (69)	13 (68)
Feeding/nasogastric tube		
Median removal time in days (range)	14 (8-51)	15 (12-42)
Permanent (PEG)	4 (25)	4 (21)

STL: salvage total laryngectomy; SPL: supracricoid partial laryngectomy; TLM: transoral laser microsurgery.

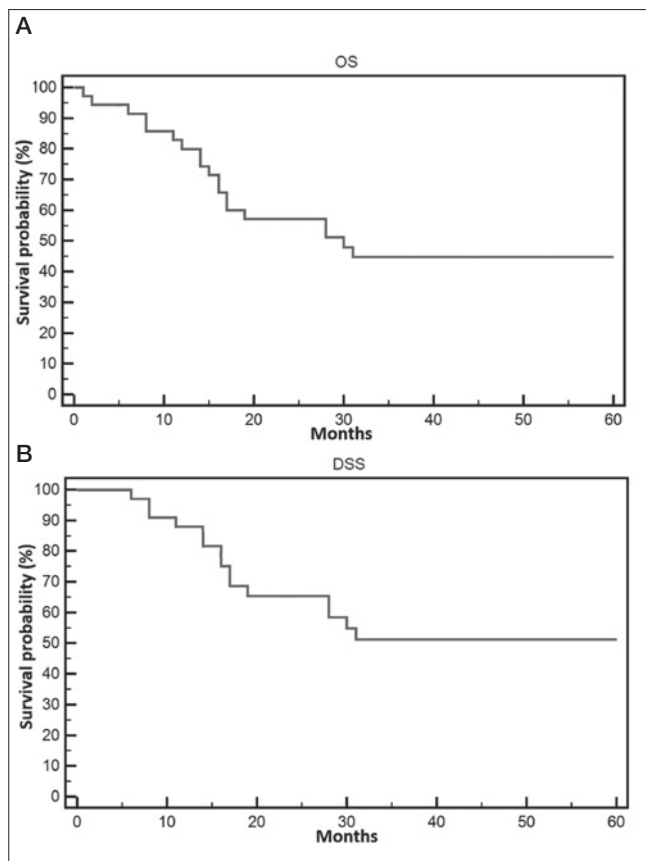


Fig. 1. Overall (a) and disease-specific (b) survival rates.

45% at 3 years; the DSS was 51% at 3 years (Fig. 1 a-b). No significant differences emerged comparing SPL vs. TLM for OS and DSS. However, a trend showing a worse survival was seen in SPL cases (3-year OS = 38% vs. 52%, $p = 0.16$; HR, 1.84, 95% CI, 0.72-4.66; 3-year-DSS = 40% vs. 61%, $p = 0.057$; HR, 2.57, 95% CI, 0.90-7.34, Fig. 2 a-b). This trend was confirmed if we consider locoregional control (LRC) as the endpoint. In fact, the SPL group showed worse LRC than the TLM group (3-year LRC = 40% vs. 54%, $p = 0.056$; HR, 2.44, 95% CI, 0.91-6.53) (Fig. 3).

Comparing the SPL and TLM groups using Cox univariate and multivariate regression analyses, we found no significant associations between clinical parameters (i.e., age, gender, time to first recurrence, cT, rT, nodal involvement at diagnosis and at recurrence, primary site, primary treatment, and margin status after STL) with DSS rates (Table III).

Discussion

STL is an aggressive surgical technique characterised by removing the larynx/neo-larynx in addition to prelaryngeal soft tissue, strap muscles and, when subcutaneous lymphangitis is suspected, a skin area overlying the larynx (wide field laryngectomy)⁷⁻⁹. Because the surgical removal is large, the surgical defect must be filled. There-

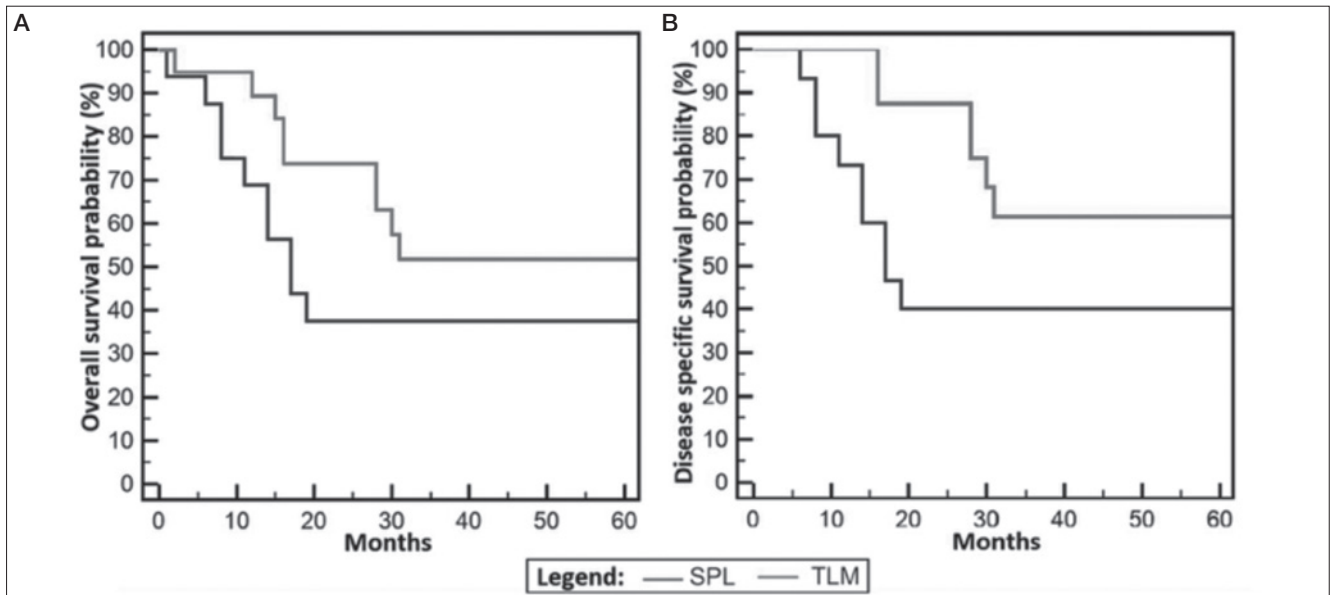


Fig. 2. Comparison between salvage wide field laryngectomy after supracricoid partial laryngectomy group (SPL) and salvage wide field laryngectomy after transoral laser microsurgery group (TLM) for overall (A) and disease-specific (B) survival.

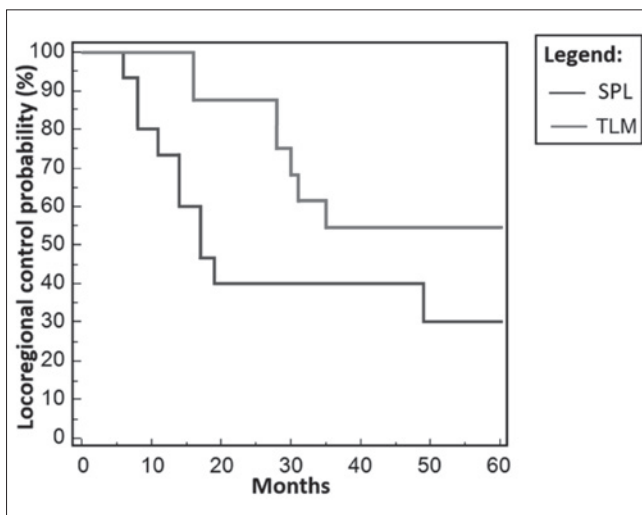


Fig. 3. Comparison between salvage wide field laryngectomy after supracricoid partial laryngectomy group (SPL) and salvage wide field laryngectomy after transoral laser microsurgery group (TLM) for locoregional control.

fore, in our centre, we prefer to use a pedicled myocutaneous or myofascial pectoralis major flap, which reliably provides an adequate amount of well-vascularised tissue and is particularly useful in patients who have previously undergone surgery and are candidates for adjuvant radio and/or chemotherapy¹⁰. Furthermore, the pectoralis major flap has been demonstrated by several reports to significantly reduce local complications such as salivary fistula¹¹. In our study, the pectoralis major flap was used for reconstruction purposes in all cases.

In this study, we investigated the results of STL in LSCC recurrences after SPL or TLM. To our knowledge, no

similar studies evaluating a large series of STL have been previously published in the international literature. OS and DSS, post-operative morbidity, and mortality appear to be acceptable, especially considering the fact that we included only recurrent cases that by definition are characterised by poor survival¹².

We divided patients into two groups according to the primary tumour treatment: SPL or TLM. This allowed comparison of oncological data for salvage surgery following widely differing surgical techniques. Indeed, SPL is an 'open' procedure that involves the opening of the laryngeal box, removal of the thyroid cartilage, false cords, true vocal cords, epiglottis (or part of it) and, when necessary, one arytenoid. Furthermore, a pexy between the cricoid cartilage and the hyoid bone is performed¹³. TLM is an endoscopic technique that does not violate the laryngeal osteocartilaginous frame and the procedure does not involve communications between the laryngeal box and laterocervical spaces²⁴. In our opinion, the main advantage of SPL is the oncological radicality in LSCC with suspected or minimal cartilage invasion¹³. Indeed, the oncological radicality of SPL in selected locally advanced LSCC is increasingly being confirmed in the recent literature¹³⁻¹⁵. The main advantage of TLM seems to be linked to the possibility of treating LSCC without excluding further therapeutic options in cases of new recurrences²¹⁶¹⁷. Furthermore TLM is repeatable in the case of local early recurrence¹⁸.

Comparing the two groups according to OS and DSS, some trends were evident: SPL cases showed worse survival (OS = 38% vs. 52%, DSS = 40% vs. 61%), but there were no statistically significant differences ($p = 0.16$ and 0.057 , respectively). This trend was also confirmed when

Table III. Univariate and multivariate analysis of prognostic covariates for DSS (calculated from the time of salvage).

Characteristic	Univariate Analysis			Multivariate Analysis		
	HR ^a	95% CI ^b	p	HR ^a	95% CI ^b	p
Age						
Over 65 years	1			1		
≤65 years	1.6	0.54 to 4.65	0.39	5.37	0.87 to 33.23	0.07
Sex						
Female	1			1		
Male	1.51	0.34 to 6.68	0.59	3.76	0.38 to 37.28	0.25
Time to first recurrence						
Before 10 months	1			1		
After 10 months	1.14	0.40 to 3.19	0.8	1.58	0.48 to 5.14	0.44
cT						
cT1	1			1		
cT2	1.39	0.39 to 4.88	0.61	5.12	0.61 to 42.88	0.13
rT						
rT3	1			1		
rT4a	2	0.26 to 15.14	0.5	0.25	0.01 to 5.25	0.37
Nodal involvement at first diagnosis						
No	1			1		
Yes	0.65	0.08 to 4.87	0.67	0.51	0.04 to 5.60	0.59
Nodal involvement at recurrence						
No	1			1		
Yes	1.45	0.80 to 2.61	0.22	1.96	0.81 to 4.74	0.13
Primary site						
Glottis	1			1		
Supraglottis	2.43	0.86 to 6.88	0.09	0.88	0.23 to 3.28	0.85
Primary Treatment						
Supracricoid laryngectomy	1			1		
Transoral laser microsurgery	0.383	0.13 to 1.07	0.07	0.23	0.05 to 1.08	0.06
Skin involvement						
positive	1			1		
negative	2.43	0.83 to 7.14	0.10	3.56	0.65 to 19.26	0.14
Salvage resection margins						
Negative	1			1		
Positive	1.92	0.42 to 8.64	0.4	5.92	0.71 to 49.39	0.1

^a Hazard ratio; ^b Confidence interval.

we compared the two groups according to LRC: SPL was related to worse LRC (40% vs. 54%), albeit non-significantly ($p = 0.056$). Furthermore, comparing the SPL and TLM groups using Cox univariate and multivariate regression analyses, we found no significant correlations of clinical parameters with DSS rates (Table III). Although no significant differences emerged, we cannot exclude the possibility that a larger series would have obtained more representative data, which may have yielded statistically significant differences for OS, DSS and LRC. Note that LSCC cases with anterior extralaryngeal extension and candidates for surgery are rare and, in the literature, there are few data concerning the surgical treatment of this peculiar LSCC. Moreover, we should consider that,

although extralaryngeal extension was radiologically strongly suspected in all cases, final pathological staging in TLM group was T3 in 3 cases (16%), while the SPL group included only T4a. Although the difference in staging was not significant, this could represent a potential bias.

The different clinical behaviours observed in the two groups and the better salvageability of TLM can be explained by the characteristics of the primary operation. In recurrences after SPL, the complete absence of thyroid cartilage allows the tumour to spread more directly, faster and (potentially) with no clinical manifestation in the anterior regions of the neck in the absence of a mechanical barrier until extensive anterior involvement occurs.

Conversely, TLM offers the great advantage of leaving the osteocartilaginous laryngeal frame, a valuable tumour spread barrier, largely intact (albeit by resecting the internal perichondrium). Preservation of the osteocartilaginous frame is the main factor underlying the better salvageability of recurrences as well as the better tolerance to adjuvant radiotherapy observed in cases treated endoscopically; this treatment triggered the progressive replacement of traditional open operations with endoscopic laser homologues, such as cordectomy, and (later) horizontal supraglottic laryngectomy^{18 19}. Therefore, the present results indirectly confirm the advantages of TLM in terms of recurrence salvageability.

In our opinion, the above delineated salvageability issues associated with primary SPL should not prevent the use of SPL. In fact, although there are conflicting data on the oncologic efficacy of TLM in the treatment of locally advanced LSCC, there is increasing evidence supporting the use of SPL in the primary treatment of advanced LSCC and as salvage treatment in early recurrent LSCC after radiotherapy with high organ preservation rates and survival^{13 15 20-23}.

Finally, in the majority of cases it is possible to classify LSCC anterior relapse into three categories: 1) local recurrent tumour inside the neolarynx (visible as submucosal recurrence) in continuity with extralaryngeal spread; 2) extra-laryngeal only pattern: no tumour inside the neolarynx, fully extra-laryngeal recurrence. This is probably a regional recurrence due to ECS from Delphian lymph node or level VI nodes; 3) undetermined recurrence pattern: tumour involving and destroying the remnant laryngeal framework with extralaryngeal extension. This is probably related to vascular or lymphatic permeation. We did not include extra-laryngeal only pattern in our study since in our opinion it could not be considered as a pure laryngeal relapse.

We observed that median time from primary treatment to first recurrence was 8 months in the submucosal recurrent pattern (29 patients, 83%) and 14 months for the undetermined recurrence pattern (6 patients, 17%), with a mean of 7.83 and 14 months, respectively ($p < 0.001$). This result should be strongly emphasised since endoscopic early detection of LSCC relapse with undetermined pattern is very difficult and, in our opinion, a higher level of caution in the follow-up is recommended after salvage laryngectomy in SPL patients.

Globally, our results suggest that longer follow-up periods with stricter intervals (2 months for the first 2 years) using different imaging techniques (MRI and PET scan) can be useful in early detection of relapse. Moreover, the routine use of adjuvant chemoradiation (in case of favourable performance status) after STL should be considered in all cases to improve survival. Finally, further research is warranted to confirm our findings and to validate our speculations.

Conclusions

To the best of our knowledge, the present study is the first to investigate the salvageability of recurrent LSCC with anterior suspected extralaryngeal extension after SPL or TLM. Although our results did not reach statistical significance, there was a trend indicating lower survival and locoregional control in patients who had undergone STL for LSCC recurrence after SPL. This was probably due to the complete absence of thyroid cartilage in SPL patients.

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