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Oncologic Outcomes After Salvage Laryngectomy for Squamous Cell Carcinoma of the Larynx and Hypopharynx: A Multicenter Retrospective Cohort Study

Jeroen Meulemans, MD[1,2], Jens Debacker, MD[3], Hannelore Demarsin, MD[1], Christophe Vanclooster, MD[4], Peter Neyt, MD[4], Tillo Mennes, MD[1,5], Tom Vauterin, MD[5], Wouter Huvenne, MD, PhD[3,6], Annouschka Laenen, MSc[7], Pierre Delaere, MD, PhD[1], and Vincent Vander Poorten, MD, PhD, MSc[1,2]

[1]Otorhinolaryngology-Head and Neck Surgery, University Hospital Leuven, Louvain, Belgium; [2]Department of Oncology, Section Head and Neck Oncology, KU Leuven, Louvain, Belgium; [3]Department of Head and Skin, Ghent University, Ghent, Belgium; [4]Otorhinolaryngology-Head and Neck Surgery, AZ Sint-Lucas, Ghent, Belgium; [5]Otorhinolaryngology-Head and Neck Surgery, AZ Sint-Jan, Brugge, Belgium; [6]Head and Neck Surgery, Ghent University Hospital, Ghent, Belgium; [7]Interuniversity Institute for Biostatistics and Statistical Bioinformatics, Louvain, Belgium

ABSTRACT

Objective. We aimed to analyze oncologic outcomes and identify patterns of failure and negative prognostic factors in patients who underwent salvage total laryngectomy (STL) for residual, recurrent, and second primary squamous cell carcinoma (SCC) of the larynx and hypopharynx.

Methods. This was a retrospective cohort study of patients who underwent STL in four major Belgian reference hospitals between 2002 and 2018 for residual/recurrent/second primary SCC in the larynx or hypopharynx after initial (chemo)radiation. Prognostic factors for oncologic outcomes were identified using univariable and multivariable analysis.

Results. A total of 405 patients were included in the final analysis. Five-year overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), and locoregional relapse-free survival (LRFS) estimates were 47.7% (95% confidence interval [CI] 42.0–53.2%), 68.7% (95% CI 63.7–73.7%), 42.1% (95% CI 36.7–47.4%), and 44.3% (95% CI 38.8–49.7%), respectively. In a multivariable model, increasing clinical tumor stage of the residual/recurrent/second primary tumor, increasing number of metastatic cervical lymph nodes retrieved during neck dissection, hypopharyngeal and supraglottic tumor location, positive section margin status and perineural invasion were independent negative prognostic variables for OS, DSS, DFS, and LRFS. The type of second tumor was identified as an additional independent prognosticator for DSS, with local recurrences and second primary tumors having a better prognosis than residual tumor.

Conclusions and Relevance. Favorable oncologic outcomes are reported after STL. Increasing clinical tumor stage, increasing number of metastatic cervical lymph nodes, hypopharyngeal and supraglottic tumor location, positive section margins, and perineural invasion are identified as independent negative prognosticators for all oncologic outcome measures.

Keywords Hypopharynx · Larynx · Oncologic outcomes · Salvage surgery · Squamous cell carcinoma · Total laryngectomy

Over the last decades, the treatment of choice for many head and neck cancers shifted from primary surgery towards primary non-surgical organ-preserving treatment strategies, including radiotherapy (RT) or concurrent chemoradiation (CRT). Landmark trials in the early 1990s and 2000s reported equivalent oncological and superior functional outcomes in patients with laryngeal and

Jeroen Meulemans and Jens Debacker contributed equally to this manuscript and are to be considered as co-first authors.

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V. Vander Poorten, MD, PhD, MSc
e-mail: vincent.vanderpoorten@uzleuven.be

hypopharyngeal squamous cell carcinoma (SCC) treated with larynx-preserving strategies, when compared with primary total laryngectomy.[1–4] As a result, (chemo)radiation is nowadays, in many cases, considered the treatment of choice for laryngeal and hypopharyngeal SCC.[5] However, the need for surgical salvage due to residual or recurrent laryngeal cancer after organ preservation is estimated to be 25–36%0.[1,2] Although this often entails the complete removal of the larynx with or without part of the hypopharynx (salvage total laryngectomy [STL] with or without partial pharyngectomy), it is a crucial step in further treatment and enhances survival to an estimated 5-year overall survival (OS) rate of 50%, with locoregional recurrence rates after STL ranging from 30% to 66% in cases of recurrent or persistent laryngeal cancer.[6] It is important to identify the prognostic factors influencing oncologic outcomes after STL, and to determine the patterns of failure, in order to optimize patient treatment and follow-up. However, studies analyzing outcomes after STL are often designed with a small cohort of patients, increasing the possible risk of bias, with consequently ambiguous results.[7–12] In the current multicenter cohort study, we retrospectively analyzed patients who underwent STL for residual, recurrent, and second primary SCC of the larynx and hypopharynx in four major institutions. We aimed at analyzing oncologic outcomes and identifying patterns of failure and negative prognostic factors for oncologic outcomes.

PATIENTS AND METHODS

Study Design

A retrospective multicenter cohort study was performed at four reference centers for head and neck cancer surgery in Belgium: University Hospital Leuven, Leuven; University Hospital Ghent, Ghent; General Hospital Sint-Lucas, Ghent; and General Hospital Sint-Jan, Bruges. The study was approved by the local Institutional Review Boards, accepting a waiver of informed consent given the retrospective nature of the study (registration numbers S61749 and B670201938931). The medical records of patients treated with STL between 2002 and 2018 were screened and analyzed for eligibility. Patients were eligible for inclusion when they fitted one of the following criteria: (1) STL with or without partial pharyngectomy for a local recurrent/residual SCC of the larynx or hypopharynx, primarily treated with RT or CRT; and (2) STL with or without partial pharyngectomy for a second primary SCC located in an irradiated larynx or hypopharynx after primary RT or CRT for a head and neck cancer in a different subsite. Patients receiving STL with circumferential pharyngectomy necessitating reconstruction with free jejunal transfer, colon interposition, tubulated (myo)cutaneous free flap or gastric transposition, or STL for a non-SCC, were excluded. Total laryngectomies performed for persistent aspiration after primary (chemo)radiation without evidence of malignancy were also excluded.

Clinical Data Collection

Retrospective review of the identified patients and their electronic files was performed at each participating institution between November 2018 and November 2019. According to the criteria of Warren and Gates, and its modification by the Surveillance, Epidemiology, and End Results (SEER) program, local recurrent SCC of the larynx/hypopharynx was defined as SCC developing < 60 months after the index diagnosis in the same anatomical subsite, with cancers in the same subsite diagnosed later than 60 months considered a second primary carcinoma.[13,14] If a diagnosis was made < 12 months after the index diagnosis, the tumor was considered to be a residual tumor. Tumor staging was reviewed and performed according to the most recent 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) TNM classification. All data were pseudonymized in the participating centers and eventually gathered in one central database, with the University Hospital Leuven as the data controller.

Statistics

Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The Kaplan–Meier method was used for estimating potential follow-up, OS, disease-free survival (DFS), and locoregional relapse-free survival (LRFS).[15] The cumulative incidence function was used for disease-specific survival (DSS), accounting for non-disease-related death as a competing event. OS was defined as the time between STL and death by any cause. Patients alive were censored at last follow-up. DSS was defined as the time between STL and disease-related death; non-disease-related death was considered a competing event. Patients alive were censored at last follow-up. DFS was defined as the time between STL and the earliest recurrence of any type or death of any cause. Patients alive and disease-free were censored at last follow-up. LRFS was defined as the time between STL and the earliest locoregional recurrence or death of any cause. Patients alive and locoregional relapse-free were censored at last follow-up. The Cox proportional hazards model was used to analyze prognostic effects of patient or treatment characteristics on OS, DSS, DFS, and LRFS. Results are presented as hazard ratios (HRs) with 95% confidence

intervals (CIs). A backward selection procedure was used for the selection of a multivariable model of independent prognostic variables for OS, DSS, DFS, and LRFS, with a 5% significance level for the removal of variables. During the selection of the multivariable model, missing values were accounted for by adding a subcategory of 'missing value' for analysis of categorical variables, and by using a 'dummy' variable for analysis of continuous variables. As a result, all records could be included in the final analysis.

The selected variables used for univariable and multivariable analyses are presented in Table 1.

Margin status is defined as either the status of the permanent margin as observed on the resected specimen, or the definitive status of the intraoperative frozen section in case of negative intraoperative frozen sections that unexpectedly turn out positive in the final pathology report.

Surgery and Follow-Up

STL was performed in all centers according to a standardized and well-described surgical technique.[16] Neck dissections were always performed in the case of a cN +

TABLE 1 Variables (continuous and categorical), with their possible values (for categorical variables), used for univariable and multivariable analyses

Variable	Values
Years between first and second tumor	
Type of second tumor	Local recurrence
	Residual tumor
	Second primary tumor
Initial location of the second tumor	Glottis
	Subglottis
	Supraglottis
	Transglottis
	Hypopharynx
pT classification second tumor (8th edition UICC/AJCC)	pT1/pT2/pT3/pT4
pN classification second tumor (8th edition UICC/AJCC)	pN0/pN1/pN2/pN3
Tumor stage second tumor (8th edition UICC/AJCC)	I/II/III/IVa/IVb/IVc
Preoperative active smoking	Yes/no
Preoperative tracheotomy	Yes/no
Type of thyroid surgery	None
	Total thyroidectomy
	Partial thyroidectomy
Extent of lateral neck dissection	None
	Ipsilateral
	Bilateral
Number of positive (pN +) lymph nodes	
Location of positive (pN +) lymph nodes	Central compartment (levels VI/VII)
	Ipsilateral lateral compartment (levels II/III/IV)
	Contralateral lateral compartment (levels II/III/IV)
Section margins	Free (> or = 5 mm)
	Close (< 5 mm)
	Positive
Lymphovascular invasion	Yes/no
Perineural invasion	Yes/no
Extracapsular extension metastatic lymph node	Yes/no
Histology second tumor	SCC poorly differentiated
	SCC moderately differentiated
	SCC highly differentiated

UICC Union for International Cancer Control, *AJCC* American Joint Committee on Cancer, *SCC* squamous cell carcinoma

neck. However, the decision to perform prophylactic selective neck dissection of the lateral compartment, thyroidectomy (non, partial or complete), and reconstruction (pectoralis major muscle [PM] onlay, PM myocutaneous inset or primary closure) were left at the surgeon's discretion and depended on the case/defect and institutional practice. Central neck dissection was routinely performed and varied from a formal bilateral level VI and VII dissection to a more limited dissection of the tracheaesophageal nodes, depending on the institution, surgeon, and pathology. The use of intraoperative frozen section analysis of the surgical margins also depended on the intraoperative findings and the surgeon's preferences. In case of positive intraoperative frozen sections, an immediate additional resection was performed when reasonable, aiming at a radical resection by pursuing negative margins on further frozen section analysis. However, when definitive pathologic examination of frozen sections, initially considered 'free', eventually revealed invasive SCC, no additional resections were performed during a second procedure.

Postoperatively, a 'nil per os' policy was maintained until the upper gastrointestinal tract radiograph, using aqueous low osmolar non-ionic iodine contrast (Ultravist® or iopromide) [postoperative day 10], showed favorable healing without pharyngocutaneous fistula (PCF) formation, whereupon patients gradually started oral intake. The decision to submit the patient to adjuvant therapy after STL (e.g. re-irradiation) always resulted from a multidisciplinary oncological board discussion. Postoperatively, clinical follow-up was organized at 2-month intervals during the first 2 years, 3-month intervals during the third year, 4-month intervals during the fourth year, and at 5-month intervals during the fifth year. Baseline imaging (usually computed tomography [CT] of the neck) was routinely performed 4 months postoperatively and was repeated 1 and 2 years after treatment. Chest imaging (plain chest radiograph and, for more recent patients, CT chest) was performed annually to exclude metachronous lung malignancies or distant disease. If indicated, a positron emission tomography (PET)/CT scan was performed during follow-up.

RESULTS

Patient Characteristics

In total, 405 patients treated with STL for SCC of the larynx or hypopharynx after initial (chemo)radiotherapy were identified. Indication for STL was residual tumor after organ-preserving treatment (40.2%) and local recurrence of the initial tumor (40.4%). Laryngeal/hypopharyngeal second primary SCC necessitated STL in 19.4% of cases. The population consisted of 378 males (93.3%) and 27 females (6.7%). Mean age at the time of diagnosis was 65.3 years. Active smoking prior to STL was reported by 30.6% of patients.

Tumor Characteristics

Patients' initial tumors were most frequently located in the glottis (64.7%), followed by the supraglottis (23.9%). When looking at tumor classification (cTNM), a shift was observed from locally limited disease (cT1 and cT2 in 41.4% and 31.4% of cases, respectively) for the initial tumor, to locally advanced disease for the second tumor (cT3 and cT4a in 35.9% and 26.8% of cases, respectively). Location of the second tumor frequently remained in the glottis (43.5%), followed by the supraglottis (29.6%). Transglottic extension was apparent in 12.2% of cases. A minority of patients had a history of a hypopharyngeal primary tumor (n = 19/402, or 4.7%) or underwent STL for a residual/recurrent/second primary tumor in the hypopharynx (n = 24/402, or 5.97%). Detailed data on initial and second tumor characteristics are reported in Table 2.

Treatment Characteristics

The treatment characteristics of the included patients are depicted in Table 3. All patients were primarily treated with initial (chemo)radiotherapy, with 76.4% receiving definitive RT and 14.1% receiving CRT. Surgical salvage included total laryngectomy in 35.9% of cases and total laryngectomy with partial pharyngectomy in 64.1% of cases. Concurrent neck dissection was performed in 69.8% of patients, of whom 48.8% and 51.2% received ipsilateral and bilateral neck dissection, respectively. Total, partial, or no thyroidectomy was performed in 20.0%, 63.7%, and 16.2% of cases, respectively. Flap reconstruction of the neopharynx was performed in 57.0% of cases, with reconstruction consisting of onlay PM muscle flap in 57.2%, PM myocutaneous inset flap in 41.1%, radial forearm free flap in 1.3%, and unspecified reconstruction in 0.4% of patients. Nearly all patients (95.5%) received definitive STL as a single salvage treatment modality without any subsequent adjuvant therapies. Upon pathologic examination of the STL specimen, section margins were considered free ($\geq$ 5 mm) in 80.9% of cases, close ($<$ 5 mm) in 11.5% of cases, and positive in 7.7% of the included cases. Lymphovascular invasion was observed in 33.2% and perineural invasion was present in 35.5%. pN + status was observed in only 15.1% of cases, with most of the pN + patients (67.9%) harboring nodal metastasis in the ipsilateral lateral compartments of the

TABLE 2 Patient and tumor characteristics

Variable	Primary tumor *n/N* (%)	Second tumor *n/N* (%)
Sex		
Male	378/405 (93.33)	–
Female	27/405 (6.67)	–
Smoking		
Non-smoker	18/363 (4.96)	
Active smoker	279/363 (76.86)	106/347 (30.55)
Past smoker	66/363 (18.18)	241/347 (69.45)[a]
Unknown	42	58
Alcohol use		
Never	19/341 (5.57)	–
Occasional	201/341 (58.94)	–
Active heavy drinking	99/341 (29.03)	–
Past heavy drinking	22/341 (6.45)	–
Unknown	64	
Clinical tumor classification		
cTx	2/401 (0.50)	2/373 (0.54)
cT1	166/401 (41.40)	45/373 (12.06)
cT2	126/401 (31.42)	89/373 (23.86)
cT3	87/401 (21.70)	134/373 (35.92)
cT4a	19/401 (4.74)	100/373 (26.81)
cT4b	1/401 (0.25)	3/373 (0.80)
Unknown	4	32
Clinical nodal classification		
cN0	325/401 (81.05)	319/376 (84.84)
cN1	30/401 (7.48)	25/376 (6.65)
cN2	5/401 (1.25)	2/376 (0.53)
cN2a	7/401 (1.75)	14/376 (3.72)
cN2b	19/401 (4.74)	10/376 (2.66)
cN2c	15/401 (3.74)	6/376 (1.60)
Unknown	4	29
Clinical metastases classification		
M0	401/401 (100)	374/376 (99.47)
M1	0/401 (0.00)	2/376 (0.53)
Unknown	4	29
Clinical tumor stage		
I	160/401 (39.90)	33/373 (8.85)
II	103/401 (25.69)	79/373 (21.18)
III	86/401 (21.45)	137/373 (36.73)
IVa	51/401 (12.72)	113/373 (30.29)
IVb	1/401 (0.25)	8/373 (2.14)
IVc	0/401 (0.00)	3/373 (0.80)
Unknown	4	32
Tumor location		
Oropharynx	18/402 (4.48)	0/402 (0.00)
Hypopharynx	19/402 (4.73)	24/402 (5.97)
Supraglottis	96/402 (23.88)	119/402 (29.60)
Glottis	260/402 (64.68)	175/402 (43.53)
Subglottis	6/402 (1.49)	22/402 (5.47)
Transglottis	0/402 (0.00)	49/402 (12.19)
Other head/neck site	3/402 (0.75)	0/402 (0.00)
Combination	0/402 (0.00)	13/402 (3.23)
Unknown	3	3
Type of second tumor		
Local recurrence	–	163/403 (40.45)
Second primary	–	78/403 (19.35)
Residual tumor	–	162/403 (40.20)
Unknown	–	2

Details on the primary and secondary tumors (which necessitated salvage total laryngectomy) are depicted in the respective columns

[a]Including non-smokers

neck (levels II/III/IV). In the subgroup of cN0 patients receiving prophylactic neck dissection (221/314 cases), 96.8% proved pN0, with only 3.2% of cN0 patients showing positive nodes upon pathologic examination. In 50% of these cN0/pN + patients, only one metastatic lymph node was found. Half of these positive nodes could be found in the ipsilateral lateral compartment. Patients with occult lymph node metastases tended to have locally advanced disease (cT3 − and cT4a in 2/9 and 5/9 cases, respectively).

Oncologic Outcomes and Patterns of Failure

Mean and median follow-up after STL, based on the Kaplan–Meier estimate of potential follow-up, was 8.28 and 7.94 years, respectively. Evolution to disease recurrence after STL was apparent in 39.5% of cases; patients developed local and/or regional relapse, distant metastases, or both, in 58.5%, 29.9%, and 11.6% of cases, respectively. If local relapse (isolated or in combination with regional/distant disease) occurred, these were (para)stomal recurrences (44.9%), followed by neopharyngeal recurrences (39.7%), of which 64.5% were located proximally, close to the base of the tongue. The estimated LRFS (plotted in Fig. 1a) at 5 and 10 years was 44.3% (95% CI 38.8–49.7%) and 29.3% (95% CI 23.8–35.0%), respectively. During follow-up, death occurred in 54.6% of patients, with 52.0% of these deaths considered disease-related. Only one early death within the first 30 postoperative days was identified (0.25%; myocardial infarction). More in-depth information about oncologic outcomes is

TABLE 3 Treatment characteristics

	n/N (%)
Treatment of the primary tumor	
Surgery and adjuvant RT	22/403 (5.46)
Surgery and adjuvant CRT	6/403 (1.49)
Definitive RT	308/403 (76.43)
Definitive CRT	57/403 (14.14)
Induction chemotherapy + definitive CRT	3/403 (0.74)
Induction chemotherapy + definitive RT	1/403 (0.25)
Other	6/403 (1.49)
Unknown[a]	2
Type of RT for the primary tumor	
Conventional	108/216 (50.00)
3D	3/216 (1.39)
IMRT standard	77/216 (35.65)
IMRT accelerated	4/216 (1.85)
IMRT hyperfractionated	24/216 (11.11)
Unknown	189
Type of salvage operation	
Total laryngectomy	145/404 (35.89)
Total laryngectomy with partial pharyngectomy	259/404 (64.11)
Unknown	1
Extent of lateral neck dissection	
None	121/400 (30.25)
Ipsilateral	136/400 (34.00)
Bilateral	143/400 (35.75)
Unknown	5
Type of thyroidectomy	
No thyroidectomy	39/240 (16.25)
Total	48/240 (20.00)
Partial	153/240 (63.75)
Unknown	165
Adjuvant treatment after STL	
No adjuvant treatment	380/398 (95.48)
Adjuvant RT (re-irradiation)	14/398 (3.52)
Adjuvant CRT (including re-irradiation)	2/398 (0.50)
Adjuvant treatment unspecified	2/398 (0.50)
Unknown	7
Histology of the second tumor	
Highly differentiated SCC	42/373 (11.26)
Moderately differentiated SCC	180/373 (48.26)
Poorly differentiated SCC	151/373 (40.48)
Unknown	32
Section margins	
Free ($\geq$ 5 mm)	317/392 (80.87)
Close ($<$ 5 mm)	45/392 (11.48)
Positive	30/392 (7.65)
Unknown	13
Lymphovascular invasion	
No	255/382 (66.75)
Yes	127/382 (33.25)
Unknown	23
Perineural invasion	
No	247/383 (64.49)
Yes	136/383 (35.51)
Unknown	22
Extracapsular extension lymph node[b]	
No	283/312 (90.71)
Yes	29/312 (9.29)
Unknown[c]	93
Number of positive lymph nodes (pN +)[b]	
0	259/316 (81.96)
1	24/316 (7.59)
2	15/316 (4.75)
+ 3	18/316 (5.70)
Unknown[c]	89

RT radiotherapy, *CRT* chemoradiotherapy, *IMRT* intensity-modulated radiotherapy, *STL* salvage total laryngectomy, *SCC* squamous cell carcinoma

[a]The primary tumor was treated with at least radiotherapy but no further details could be retrieved

[b]Including lymph nodes from the central (levels VI and VII) and lateral (ipsilateral and/or bilateral) compartments

[c]Including patients with no lymph node yield due to omission of (central and lateral) neck dissection, as well as true missing data regarding the cervical nodes

reported in Table 4. The 5-year OS, DSS, and DFS were estimated at 47.7% (95% CI 42.0–53.2%), 68.7% (95% CI 63.7–73.7%), and 42.1% (95% CI 36.7–47.4%), respectively (Fig. 1b–d). The time between STL and recurrence after STL is plotted in a cumulative incidence curve of recurrence (Fig. 1e). Within the first 2 postoperative years, the cumulative recurrence rate (CRR) after STL rises to 34.4% (29.7–39.2%) and stagnates afterwards, with only a modest increase to 38.2% (33.2–43.1%) at 5 years after salvage treatment.

Prognostic Factors for Oncologic Results

In multivariable analysis, multiple factors were found to be significantly and independently associated with oncologic outcomes in patients treated with STL (Table 5). Increasing tumor stage of the second tumor and increasing number of metastatic lymph nodes retrieved during neck dissection were associated with an increased risk of an

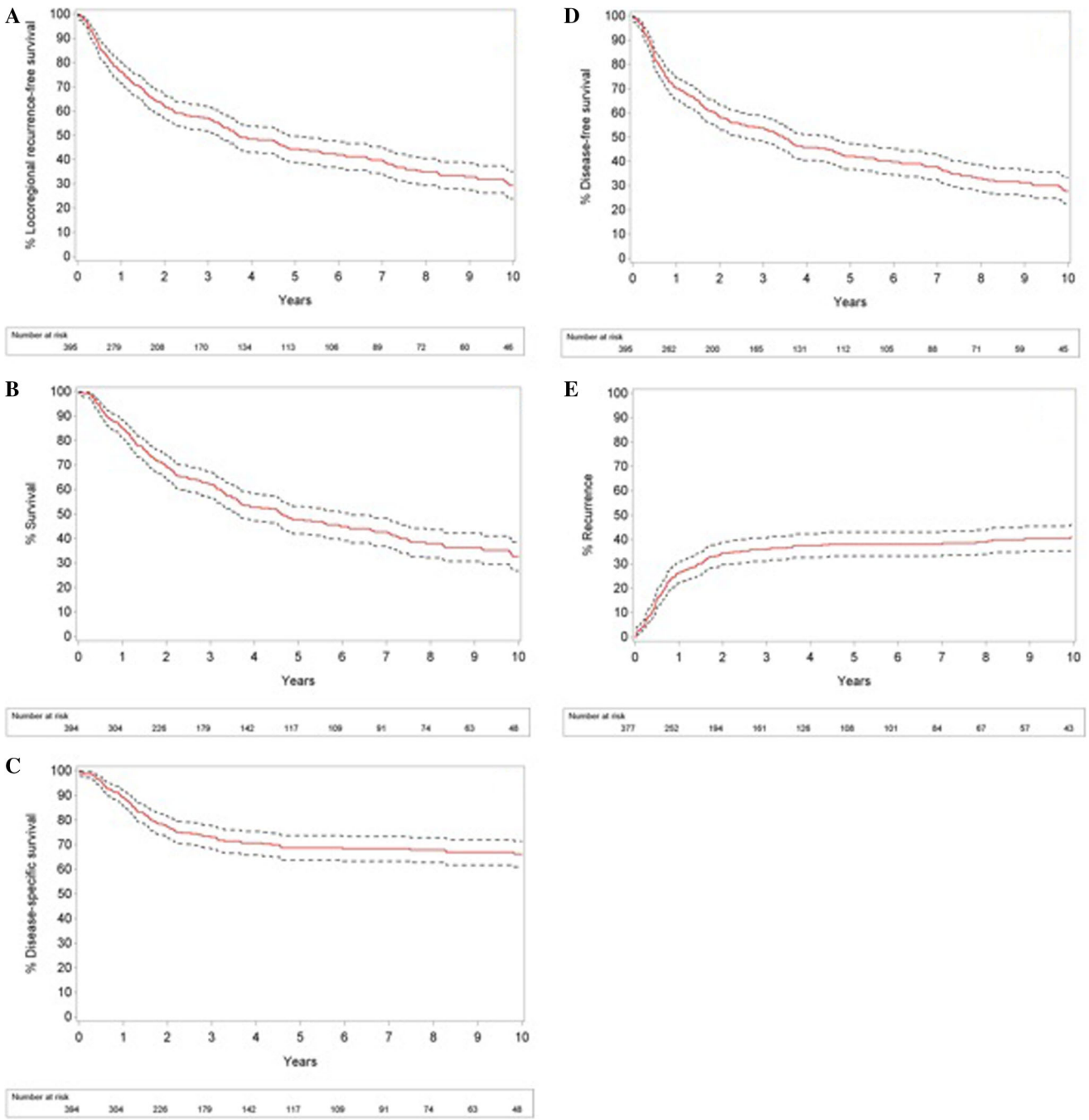

FIG. 1 Kaplan–Meier survival curves and cumulative incidence curve of recurrence with 95% confidence interval: (**a**) locoregional recurrence-free survival; (**b**) overall survival; (**c**) disease-specific survival; (**d**) disease-free survival; and (**e**) cumulative incidence of recurrence after salvage total laryngectomy

undesirable oncologic event. These variables were identified as independent negative prognostic variables, consistent for all oncologic outcomes (OS, DFS, DSS, and LRFS). Moreover, a significant correlation was observed between all oncological outcomes and the presence of positive versus free section margins and positive versus close section margins. When comparing close margins with free margins, no significant difference was found in OS, DFS, and LRFS, but significance was found for DSS ($p = 0.026$). In addition, location of the residual/recurrent/second primary carcinoma was found to be related to oncologic outcomes, with tumor locations in the hypopharynx and supraglottis implying worse survival compared with glottic locations. The presence of perineural invasion was an independent negative prognostic factor for

TABLE 4 Oncologic results after salvage laryngectomy

	n/N (%)
Evolution to disease after STL	
No	234/387 (60.47)
Yes	153/387 (39.53)
Unknown	18
Recurrence type after STL (n = 153)	
Local	27/147 (18.37)
Regional	21/147 (14.29)
Locoregional	38/147 (25.85)
Distant	44/147 (29.93)
Distant and local/(loco)regional	17/147 (11.56)
Unknown	6
Treatment of recurrence after STL	
No treatment	37/153 (24.18)
Chemotherapy	52/153 (33.99)
Re-irradiation	25/153 (16.34)
Re-irradiation and chemotherapy	14/153 (9.15)
Immunotherapy	5/153 (3.27)
Chemotherapy + later immunotherapy	12/153 (7.84)
Not specified	9/153 (5.88)
Location local recurrence after STL[a]	
Tracheostoma	35/78 (44.87)
Neopharynx proximal (to base of the tongue)	20/78 (25.64)
Neopharynx distal (to the esophagus)	5/78 (6.41)
Neopharynx not specified	6/78 (7.69)
Recurrence in flap	3/78 (3.84)
Oropharynx	8/78 (10.26)
Not specified	1/78 (1.28)
Death	
No	184/405 (45.43)
Yes	221/405 (54.57)
Disease-related death	
No death	184/405 (45.43)
Death disease-related	115/405 (28.40)
Death non-disease-related	106/405 (26.17)
Early death (≤ 30 days after STL)	
No	404/405 (99.75)
Yes	1/405 (0.25)

STL salvage total laryngectomy

[a]Including local recurrence locations in patients with local recurrence, locoregional recurrence, and distant disease combined with local or locoregional recurrence

OS, DSS, DFS, and LRFS. Residual tumors had worse DSS when compared with recurrences or second primaries.

Of interest, in multivariable analysis, prophylactic lateral selective neck dissection during STL did not have a significant impact on DSS, DFS, or LRFS for cN0 patients (p = 0.79). Moreover, performing partial or total thyroidectomy during STL did not entail a significant oncological benefit (p = 0.86, 0.17, and 0.10, respectively), neither in the group of patients with a second tumor in the (supra)glottis or in patients with hypopharyngeal, transglottic, or subglottic tumor location. In univariable analysis, increasing tumor stage of the initial (primary) head and neck tumor had a negative prognostic impact on DSS, DFS, and LRFS after STL in the subgroup of patients with residual and recurrent tumors ($p < 0.0001$), but this could not be confirmed in multivariable analysis (p = 0.06).

DISCUSSION

The current study retrospectively analyzed a cohort of 405 patients treated with STL after initial RT-based larynx-sparing treatment. We report favorable oncologic outcomes, confirming the importance of STL in cases of recurrent, residual, and second primary laryngeal/hypopharyngeal SCC. Multiple previous studies retrospectively analyzed the oncologic outcome in patients treated with STL.[6] To the best of our knowledge, the current study includes the largest cohort described in the literature. We observed a 5-year DSS of 68.7%, which is comparable with 5-year DSS rates ranging from 52% to 78% reported in several case series including STL cases for recurrent or persistent laryngeal cancer.[6,17] Oncologic outcomes of salvage laryngopharyngectomy for radiation failure of hypopharyngeal cancer are known to be much worse, with 5-year DSS and OS rates as low as 40% and 31%, respectively.[18] As such, the small portion of patients who underwent salvage surgery for a hypopharyngeal cancer (5.97%) in our cohort contributes to these favorable oncologic outcomes.

The observed high DSS stresses the importance of STL in the treatment of recurrent or residual laryngeal and hypopharyngeal SCC, as well as second primary SCC emerging in the irradiated laryngopharynx. Although STL remains an important procedure, other surgical salvage techniques are currently at the surgeon's disposal. Salvage open partial laryngectomy procedures, such as supracricoid partial laryngectomy, have shown to combine excellent oncologic outcomes with a larynx preservation rate of 85%, when applied in well-selected cases.[19] In selected early-stage radiorecurrent or second primary laryngeal carcinomas, minimally invasive transoral approaches (transoral laser microsurgery [TLM] and transoral robotic surgery [TORS]) are increasingly emerging as alternative surgical options. A review on salvage TLM reported an average local control of 67%, with scarce serious complications,

TABLE 5 Overview of independent prognostic variables for overall survival, disease-specific survival, disease-free survival, and locoregional relapse-free survival, as identified on multivariable analysis

Variable	OS		DSS		DFS		LRFS	
	HR	95% CI; *p* value	HR	95% CI; *p*-value	HR	95% CI; *p*-value	HR	95% CI; *p*-value
Tumor stage								
+1 stage	1.260	1.065–1.490; 0.0070	1.315	1.023–1.690; 0.0328	1.363	1.164–1.596; 0.0001	1.319	1.124–1.547; 0.0007
Positive lymph nodes								
+1 node	1.557	1.381–1.754; <0.0001	1.626	1.382–1.913; <0.0001	1.374	1.234–1.529; <0.0001	1.427	1.280–1.590; <0.0001
Location of recurrence (glottis as the reference)								
Supraglottis	2.102	1.484–2.978; < 0.0001	1.888	1.087–3.277; 0.0240	2.024	1.450–2.826; < 0.0001	2.197	1.575–3.064; < 0.0001
Hypopharynx	2.240	1.154–4.345; $p = 0.0171$	3.165	1.394–7.189; 0.0059	1.873	1.007–3.482; 0.0474	2.333	1.265–4.305; 0.0067
Subglottis	NS		NS		NS		NS	
Section margins								
Close (< 5 mm) vs. free (≥ 5 mm)	NS		1.981	1.087–3.610; 0.0256	NS		NS	
Close (< 5 mm) vs. positive	0.536	0.290–0.991; 0.0467	0.446	0.207–0.958; 0.0383	0.435	0.246–0.769; 0.0042	0.525	0.296–0.930; 0.0272
Free (≥ 5 mm) vs. positive	0.384	0.233–0.634; 0.0002	0.225	0.120–0.422; <0.0001	0.320	0.199–0.514; < 0.0001	0.408	0.256–0.648; 0.0001
Perineural invasion								
Yes vs. no	1.597	1.178–2.166; 0.0026	2.201	1.421–3.409; 0.0004	1.561	1.169–2.086; 0.0026	1.548	1.154–2.077; 0.0036
Type of second tumor (residual tumor as the reference)								
Local recurrence	NA		0.493	0.296–0.821; 0.0066	NA		NA	
Second primary	NA		0.568	0.328–0.982; 0.0428	NA		NA	

OS overall survival, *DSS* disease-specific survival, *DFS* disease-free survival, *LRFS* locoregional relapse-free survival, *HR* hazard ratio, *CI* confidence interval, *NA* not applicable (variable not selected in the multivariable model), *NS* not statistically significant

short hospitalization times, and favorable functional outcomes when compared with open conservation laryngeal surgery.[20]

Increasing clinical tumor stage of the salvaged tumor, increasing number of metastatic cervical lymph nodes retrieved during neck dissection, hypopharyngeal and supraglottic tumor location, positive section margin status, and perineural invasion proved independent negative prognosticators for OS, DSS, DFS, and LRFS in multivariable analysis. The type of second tumor was identified as an additional independent prognosticator for DSS, with residual tumors having a worse prognosis compared with local recurrences or second primaries. These findings are in accordance with previous studies that identified tumor stage, nodal involvement, section margin status, and the presence of perineural invasion as important negative prognosticators for survival after multivariable analysis.[9,21] The identification and/or confirmation of solid negative prognosticators for all oncological outcome measures in this study raises the question as to whether patients with one or more negative prognostic factors could benefit from adjuvant therapy after STL. This question could guide later prospective clinical trials on the matter.

As a result of multiple contradictory results, the added value of elective prophylactic neck dissection (END) during STL remains a matter of debate. An interesting finding in our study was the very low probability (3.18%) of occult lymph node metastases upon pathologic examination after prophylactic neck dissection in patients with a preoperative cN0 neck. Moreover, the positive nodes were scattered over the different neck levels, without a straightforward high-risk region. Performance of an END in this cN0 group

did not result in better oncologic outcomes upon multivariable analysis. Two recent meta-analyses covered the role of END during STL, specifically describing a significantly higher rate of occult metastasis (11–14%) when compared with our rate.[22,23] However, similar to the current results, both manuscripts could not show a significant improvement in survival related to END. Interestingly, multiple authors described higher occult metastasis in T3/4 and supra- and transglottic recurrences, indicating a role for END in these settings.[6,22] In our small cohort of patients with occult nodal metastases, we could confirm the higher rate of occult nodal metastasis in locally advanced (T3/T4) disease. However, selection bias needs to be taken into account as most STL procedures are performed for locally advanced disease. Bernard et al. advised consideration of an END in patients undergoing STL. They reported one cT3 patient with an occult lymph node metastasis, of 27 patients undergoing END (4% occult metastasis rate), but observed three regional recurrences in 59 patients (5%) who did not receive END during STL.[24] Their suggestion to keep END in consideration was mainly based on their finding of a significantly higher OS in patients with END, which could not be confirmed by our results. Moreover, their study population was limited ($n = 86$) and DSS proved not significantly different between patients with or without END. In our opinion, the increased risk of occult metastases in patients staged cT3/4N0 needs to be taken into account during the preoperative work-up, stressing the need for staging examinations with high sensitivity for cervical nodal metastasis, rather than performing END as a standard of care in all STL patients.

Interestingly, our cohort showed a significant increase in cT and cN classification between the primary and secondary tumors. This increase suggests that early (locoregional) recurrences and second primaries after initial (chemo)radiation are frequently missed during standard follow-up, stressing the important role of highly sensitive techniques such as PET/CT and bioendoscopy (e.g. narrow band imaging [NBI]) during follow-up. Moreover, in our cohort, CRR after STL displays an important stagnation after approximately 2 years (Fig. 1e). Based on these findings, we suggest highly intensive follow-up during the first 2 years after STL, including regular neopharyngoscopy and imaging such as PET/CT and CT or MRI of the neck. In our centers, initial follow-up includes clinical examination and neopharyngoscopy every 2 months; CT or MRI of the neck 4, 12, and 24 months after STL; and PET/CT or CT of the chest and abdomen 12 and 24 months after STL.

We acknowledge there are some limitations in the current study. As the current study analyzed data retrospectively, selection bias is inherent to the design. We analyzed patients in a broad time period from 2002 until 2018, during which much has changed in terms of oncologic therapy over the years, for example the change from conventional to intensity-modulated RT, the introduction of immunotherapy, and the change in institutional practices and surgeons performing STL. Moreover, we collected data from four different hospitals and although these hospitals have a similar general approach and philosophy, there was no standardization in decision making nor therapy. As a result of the multitude of variables, missing data are present for important secondary endpoints, which might bias the results. However, our study resulted in a large study population of 405 patients, which, to our knowledge, is the largest cohort described at the time of manuscript submission. To address these limitations and to validate the retrospectively identified prognosticators, a multicenter, observational, prospective study is warranted to confirm the retrospectively identified prognostic factors and patterns of failure.

CONCLUSION

Favorable oncologic outcomes are reported after STL, with a 5-year DSS of 68.7%. This confirms the important role STL plays in the salvage treatment of patients diagnosed with residual, recurrent, or second primary cancers in the larynx or hypopharynx after initial radio(chemo)therapy. Increasing clinical tumor stage, increasing number of metastatic cervical lymph nodes, hypopharyngeal and supraglottic tumor location, positive section margins, and perineural invasion are identified as independent negative prognosticators for all oncologic outcome measures.

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