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# Oncologic outcomes after salvage laryngectomy for squamous cell carcinoma of the larynx and hypopharynx: a multicenter retrospective cohort study

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**Key words:** hypopharynx, larynx, oncologic outcomes, recurrence, salvage surgery, second primary carcinoma, squamous cell carcinoma, total laryngectomy

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## Synopsis

In this cohort study of 405 patients, favorable oncologic outcomes are reported after salvage total laryngectomy. Tumor stage, number of metastatic cervical lymph nodes, tumor location, section margin status and perineural invasion are identified as independent prognosticators for oncologic outcomes.

## Abstract

***Purpose:*** We aimed at analyzing oncologic outcomes and identifying 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:*** Retrospective cohort study of patients who underwent STL in 4 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 with uni- and multivariable analysis.

***Results:*** A total of 405 patients were included into final analysis. Recurrence after STL occurred in 35.5% of patients. Five-year OS, DSS, DFS and 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.

## Introduction

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 hypopharyngeal squamous cell carcinoma (SCC) treated with larynx-preserving strategies, when compared to 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 in many cases.[5] However, the need for surgical salvage due to residual or recurrent laryngeal cancer after organ preservation is estimated to be 25-36%.[1,2] Although this often entails the complete removal of the larynx with or without a part of the hypopharynx (salvage total laryngectomy or 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) 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 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 consequentially ambiguous results.[7-12] In the current multicenter cohort study, we retrospectively analyzed patients who underwent STL for residual, ~~,~~ recurrent and second primary ~~and~~ SCC of the larynx and hypopharynx in ~~4~~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 ~~4~~ four reference centers for head and neck cancer surgery in Belgium: University Hospital Leuven, University Hospital 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 a salvage total laryngectomy (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. (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 a STL with circumferential pharyngectomy necessitating reconstruction with free jejunal transfer, colon interposition, tubulated (myo)cutaneous free flap or gastric transposition, or an 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 SEER, local recurrent SCC of the

larynx/hypopharynx was defined as SCC developing less than 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 diagnosis was made less than 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 UICC/AJCC TNM classification. All data were pseudonymized in the participating centers and eventually gathered in one central database with the University Hospitals Leuven as data-controller.

***Statistics***

Statistical analyses were performed using SAS software (version 9.4 of the SAS System for Windows). The Kaplan-Meier method was used for estimating potential follow-up, overall survival (OS), disease free survival (DFS) and locoregional relapse-free survival (LRFS).[15] The cumulative incidence function was used for DSS, accounting for non disease-related death as 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 as a competing event. Patients alive were censored at last follow-up. DFS was defined as the time between STL and the earliest among 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 among 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, LRFS. Results are presented as hazard ratios (HR) with 95% confidence intervals. A backward selection procedure was used for the selection of a multivariable model of independent prognostic variables for OS, DSS, DFS, LRFS,

with a 5% significance level for removal of variables. During the selection of the multivariable model, missing values were accounted for by adding a subcategory '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 uni- and multivariable analyses are presented in ***table 1***.

Margin status ~~is~~was defined as ~~either~~ the status of the ~~permanent margin~~surgical margin ~~as observed~~ on the resected specimen by standard histopathological analysis. ~~or the definitive status of the intraoperative frozen section in case of margin positivity on the specimen.~~

***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 case of a cN+ neck. However, the decisions to perform prophylactic selective neck dissection ~~(~~of the lateral ~~and/or central 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 more limited dissection of trachea-esophageal nodes, depending on the institution, surgeon and pathology. The use of per~~intra~~operative frozen sections ~~analysis of the~~ to analyse the surgical margins ~~also~~ depended on the intraoperative findings and surgeon's preferences. In case of positive ~~intra-~~peroperative 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

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**Met opmerkingen [JD1]:** Ik vermoed dat elk centrum de finale marge bepaalt door histopathologie, ook bij positieve vriescoupes. Ik zou vriescoupes hier dan ook weglaten.

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**Met opmerkingen [JD2]:** Klopt dit? Ik meen me te herinneren dat er in Gent nogal weinig uitruimingen gebeurden. Dit zou ik nuanceren

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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 with aqueous low osmolar non-ionic iodine contrast (~~Ultravist® or~~ iopromide) ~~low osmolar iodine contrast (Gastrografin®)~~ (postoperative day 10) showed favourable 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 organised at 2-month intervals during the first 2 years, at 3-month intervals during the third year, at 4-month intervals during the fourth year and at 5-month intervals during the fifth year. Baseline imaging (usually 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 PET-CT scan was performed during follow-up.

**Met opmerkingen [JD3]:** Ik zou de merknaam weglaten, weinig meerwaarde

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## 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 is observed from locally limited disease (cT1 and cT2 in 41.4% and 31.4% of cases) for the initial tumor to locally advanced disease for the second tumor (cT3 and cT4a in 35.9% and 26.8% 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 tumor in the hypopharynx (n=24/402 or 5.97%). Detailed data on initial and second tumor characteristics are reported in ***table 2*** .

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### *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 which 48.8% and 51.2% of patients received ipsi- and bilateral neck dissection, respectively. Total, partial, or no thyroidectomy was performed in 20.0%, 63.7% and 16.2% of the respective cases. 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 (≥ 5mm) in 80.9%, close (<5mm) in 11.5% 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 neck (levels II-III-IV). In the subgroup cN0 patients receiving prophylactic neck dissection (221 out of 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 1 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%; 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 (43.244.9%), followed by neopharyngeal recurrences (38.339.7%) of which 64.5% were located proximally, close to the base of tongue. The estimated LRFS, plotted in ***figure 1.A***, at 5 and 10 years were 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 (0.253%; myocardial infarction). More in-depth information about oncologic outcomes is reported in ***table 4***. The 5-year OS, DSS and DFS were estimated at 47.7% (95% confidence interval [CI]: 42.0%-53.2%), 68.7% (95% CI: 63.7%-73.7%) and 42.1% (95% CI: 36.7%-47.4%) respectively (***figure 1.B-D***). The time between STL and recurrence after STL is plotted in a cumulative incidence curve of recurrence (***figure 1.E)***. Within the first two 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 the 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 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 to free margins, no significant difference was found in OS, DFS and LRFS, but significance was found for DSS

(p=0.026). Also location of the residual/recurrent/second primary carcinoma was found to be related to oncologic outcomes, with tumor locations in the ~~glottis~~ hypopharynx and supraglottis implying ~~better~~ worse survival as compared to ~~hypopharyngeal and or supraglottie~~glottic locations. The presence of perineural invasion was an independent negative prognostic factor for OS, DSS, DFS and LRFS. Residual tumors had worse DSS when compared to 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 & 0.10), nor in the group of patients with second tumor in the (supra)glottis neither in patients with hypopharyngeal, trans-, 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 radiotherapy-based larynx-sparing treatment. We show 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 to ~~the~~ 5-year DSS rates ~~reported in the literature,~~ ranging from 52% to 78%, reported in several case series including STL cases for recurrent or persistent laryngeal cancer.[6,17] With its 5-year DSS and OS as low as 40% and 31% respectively, the ~~O~~oncologic outcomes of salvage laryngopharyngectomy for radiation failure of hypopharyngeal cancer ~~are~~is known to be much worse than average~~, with 5-year DSS and OS 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 contribute~~s~~d to the favorable oncologic outcomes

~~This~~ Our favorable 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.[18] 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

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average local control of 67% with scarce serious complications, short hospitalization times and favorable functional outcomes when compared to open conservation laryngeal surgery.[19]

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 local recurrences having a better prognosis than residual and second primary tumors. In accordance with previous studies, tumor stage, nodal involvement, section margin status and the presence of perineural invasion were confirmed as important negative prognosticators for survival after multivariable analysis.[9,20] The identification of solid negative prognosticators for all oncological outcome measures in this study does raise the question 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 pre-operatively 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 to ours.[21,22] However, similarly 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.[6,21] 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 out of 27 patients undergoing END (4% occult metastasis rate) but observed 3 regional recurrences in 59 patients (5%) who did not receive END during STL[23] Their suggestion to keep END into 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 to be 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 pre-operative workup, 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 tumor. 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 bio-endoscopy during follow-up. Moreover, in our cohort, CRR after STL displays an important stagnation after approximately 2 years (**figure 1.E)**. Based on these findings, we suggest highly intensive follow-up during the first two years after STL including regular neopharyngoscopy and imaging

including 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 the fact that 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 2002-2018 where much has changed in terms of oncologic therapy, for example the change from conventional to intensity modulated radiotherapy, the introduction of immunotherapy and change in institutional practices and surgeons performing STL over the years. Moreover, we collected data from 4 different hospitals and although these hospitals have a similar general approach and philosophy, there was no standardization in decision-making nor in 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 is, to our knowledge, the largest cohort described at the moment of manuscript submission. To address these limitations mentioned 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. A prospective (randomized) trial is needed to validate the identified prognosticators.

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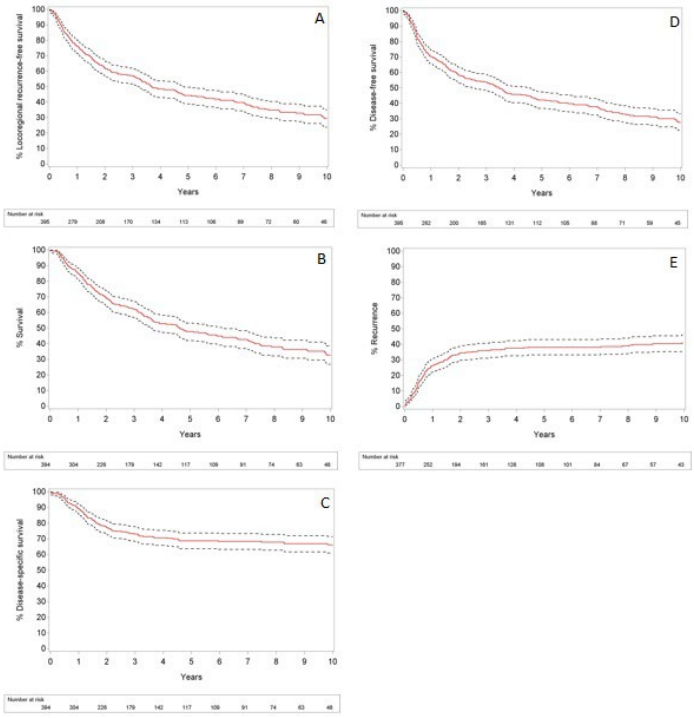
## Figure Legend

***Figure 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.

## Figures

***Figure 1***



## Table legend

***Table 1*** – Variables (continuous and categorical) with their possible values (for categorical variables) used for uni- and multivariable analyses.

***Table 2*** - Patient and tumor characteristics. Details on the primary tumor as well as on the second tumor (which necessitated salvage total laryngectomy) are depicted in respective columns.

***Table 3*** – Treatment characteristics.

*Abbreviations:* RT: radiotherapy; CRT: chemoradiotherapy; IMRT: intensity modulated radiotherapy; STL: salvage total laryngectomy; SCC: squamous cell carcinoma

***Table 4*** – Oncologic results after salvage laryngectomy

*Abbreviations:* STL: salvage total laryngectomy

***Table 5*** – Overview of independent prognostic variables for OS, DSS, DFS, LRFS as identified upon multivariable analysis.

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

## Tables

***Table 1***

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

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*Table 2*

| Variable | Primary Tumor n/n (%) | Second Tumor n/n (%) |
|---|---|---|
| **Gender** | | |
| 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)* |
| 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 cassification** | | |
| 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 |

**: including non-smokers*

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*Table 3*

| | n/n (%) |
|---|---|
| **Treatment primary tumor** | |
| surgery & adjuvant RT | 22/403 (5.46) |
| surgery & 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) |
| o~~O~~ther | 6/403 (1.49) |
| unknown* | 2 |
| **Type RT 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 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 (reirradiation) | 14/398 (3.52) |
| adjuvant CRT (including reirradiation) | 2/398 (0.50) |
| adjuvant treatment u~~U~~nspecified | 2/398 (0.50) |
| unknown | 7 |
| **Histology 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 |

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**Met opmaak:** Regelafstand: 1,5 regel

| | |
|---|---|
| **Section margins** | |
| Free (≥5mm) | 317/392 (80.87) |
| Close (<5mm) | 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**** | |
| No | 283/312 (90.71) |
| Yes | 29/312 (9.29) |
| unknown*** | 93 |
| **Number positive lymph nodes (pN+)**** | |
| 0 | 259/316 (81.96) |
| 1 | 24/316 (7.59) |
| 2 | 15/316 (4.75) |
| +3 | 18/316 (5.70) |
| unknown*** | 89 |

*Primary tumor was treated with at least radiotherapy but no further details could be retrieved

**Including lymph nodes from central compartment (levels VI and VII) and lateral compartments (ipsi-and/or bilateral)

***Including patients with no lymph node yield due to omission of (central and lateral) neck dissection as well as true missing data concerning the cervical nodes

*Table 4*

| | n/n (%) |
|---|---|
| **Evolution to disease after STL** | |
| no | 234/387 (60.47) |
| y~~Y~~es | 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 & local/(loco)regional | 17/147 (11.56) |
| unknown | 6 |
| **Treatment of recurrence after STL** | |
| no treatment | 37/~~154~~ 153 (24.~~03~~18) |
| chemotherapy | 52/153~~154~~ (33.99~~77~~) |
| reirradiation | 25/153~~154~~ (16.~~23~~34) |
| reirradiation & chemotherapy | 14/153~~154~~ (9.15~~09~~) |
| Immunotherapy | 5/153~~154~~ (3.2~~75~~) |
| chemotherapy + later immunotherapy | 12/153~~154~~ (7.~~79~~84) |
| Not specified | 9/153 ~~154~~ (5.884) |
| **Location local~~oregional~~ recurrence after STL*** | |
| tracheostoma | 35/~~81~~ 78 (~~43.21~~44.87) |
| neopharynx proximal (to base of tongue) | 20/78~~81~~ (~~24.69~~25.64) |
| neopharynx distal (to esophagus) | 5/78~~81~~ (6.~~17~~41) |
| neopharynx not specified | 6/78~~81~~ (7.~~41~~69) |
| recurrence in flap | 3/78~~81~~ (3.~~70~~84) |
| ~~regional recurrence in neck~~ | ~~2/81 (2.47)~~ |
| ~~mediastinal recurrence~~ | ~~1/81 (1.23)~~ |
| oropharynx | 8/78~~81~~ (~~9.88~~10.26) |
| Not specified | 1/78~~81~~ (1.2~~83~~) |
| **Death** | |
| no | 184/405 (45.43) |
| yes | 221/405 (54.57) |
| **Disease-related death** | |

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| | |
|---|---|
| no | 184/405 (45.43) |
| death disease-related | 115/405 (28.40) |
| death non disease-related | 106/405 (26.17) |
| ~~**Disease-free survival (event)**~~ | |
| ~~no~~ | ~~148/405 (36.54)~~ |
| ~~yes~~ | ~~257/405 (63.46)~~ |
| ~~**Locoregional recurrence-free survival (event)**~~ | |
| ~~no~~ | ~~163/405 (40.25)~~ |
| ~~yes~~ | ~~242/405 (59.75)~~ |
| **Early death (≤30d after STL)** | |
| no | ~~391/392~~404/405 (99.7~~54~~) |
| Yes | 1/~~392~~ 405 (0.2~~56~~) |

*Including local recurrence locations in patients with local recurrence, locoregional recurrence and distant disease combined with local or locoregional recurrence

***Table 5***

| **Variable** | **OS** HR (95%CI, p-value) | | **DSS** HR (95%CI, p-value) | | **DFS** HR (95%CI, p-value) | | **LRFS** HR (95%CI, p-value) | |
|---|---|---|---|---|---|---|---|---|
| **Tumor stage** | | | | | | | | |
| +1 stage | 1.260 | 1.065;1.490; p=0.0070 | 1.315 | 1.023;1.690; p=0.0328 | 1.363 | 1.164;1.596; p=0.0001 | 1.319 | 1.124;1.547; p=0.0007 |
| **Positive lymph nodes** | | | | | | | | |
| +1 node | 1.557 | 1.381;1.754; p=<.0001 | 1.626 | 1.382;1.913; p=<.0001 | 1.374 | 1.234;1.529; p=<.0001 | 1.427 | 1.280;1.590; p=<.0001 |
| **Location of recurrence** (glottis as reference) | | | | | | | | |
| Supraglottis | 2.102 | 1.484;2.978; p=<.0001 | 1.888 | 1.087;3.277; p=0.0240 | 2.024 | 1.450;2.826; p=<.0001 | 2.197 | 1.575; p=<.0… |
| Hypopharynx | 2.240 | 1.154;4.345; p=0.0171 | 3.165 | 1.394;7.189; p=0.0059 | 1.873 | 1.007;3.482; p=0.0474 | 2.333 | 1.265; p=0.00… |
| Subglottis | NS | | NS | | NS | | NS | |
| ~~glottic vs hypopharynx~~ | ~~0.447~~ | ~~0.230;0.866; p= 0.0171~~ | ~~0.316~~ | ~~0.139;0.718; p=0.0059~~ | ~~0.534~~ | ~~0.287;0.993; p=0.0474~~ | ~~0.429~~ | ~~0.233;…~~ |
| ~~glottic vs supraglottic~~ | ~~0.476~~ | ~~0.336;0.674; p=<.0001~~ | ~~0.530~~ | ~~0.305;0.920; p=0.0240~~ | ~~0.494~~ | ~~0.354;0.690; p=<.0001~~ | ~~0.455~~ | ~~0.326;…~~ |
| ~~hypopharynx vs subglottic~~ | ~~4.590~~ | ~~1.661;12.681; p=0.0033~~ | ~~10.005~~ | ~~2.078;48.181; p=0.0041~~ | ~~4.196~~ | ~~1.567;11.236; p=0.0043~~ | ~~5.214~~ | ~~1.882;…~~ |
| ~~subglottic vs supraglottic~~ | ~~0.232~~ | ~~0.100;0.540; p=0.0007~~ | ~~0.168~~ | ~~0.040;0.709; p=0.0152~~ | ~~0.220~~ | ~~0.095;0.512; p=0.0004~~ | ~~0.204~~ | ~~0.082;…~~ |
| ~~subglottic vs transglottic~~ | ~~0.330~~ | ~~0.134;0.812; p=0.0158~~ | ~~0.177~~ | ~~0.039;0.811; p=0.0258~~ | ~~0.315~~ | ~~0.129;0.765; p=0.0108~~ | ~~0.309~~ | ~~0.124;…~~ |
| **Section margins** | | | | | | | | |
| Close (<5mm) vs Free (>5mm) | NS | | 1.981 | 1.087;3.610; p=0.0256 | NS | | NS | |
| Close (<5mm) vs Positive | 0.536 | 0.290;0.991; p=0.0467 | 0.446 | 0.207;0.958; p=0.0383 | 0.435 | 0.246;0.769; p=0.0042 | 0.525 | 0.296;0.930; p=0.0272 |
| Free (>5mm) vs Positive | 0.384 | 0.233;0.634; p=0.0002 | 0.225 | 0.120;0.422; p=<.0001 | 0.320 | 0.199;0.514; p=<.0001 | 0.408 | 0.256;0.648; p=0.0001 |
| **Perineural invasion** | | | | | | | | |
| Yes vs No | 1.597 | 1.178;2.166; p=0.0026 | 2.201 | 1.421;3.409; p=0.0004 | 1.561 | 1.169;2.086; p=0.0026 | 1.548 | 1.154;2.077; p=0.0036 |
| **Type of second tumor** | | | | | | | | |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (residual tumor as reference) | | | | | | | |
| Local Recurrence | NA | | 0.493 | 0.296;0.821; p=0.0066 | NA | | NA |
| Second Primary | NA | | 0.568 | 0.328;0.982 p=0.0428 | NA | | NA |
| ~~Local recurrence vs Residual tumor~~ | ~~NS~~ | | ~~0.493~~ | ~~0.296;0.821; p=0.0066~~ | ~~NS~~ | | ~~NS~~ |
| ~~Residual tumor vs Second primary~~ | ~~NS~~ | | ~~1.762~~ | ~~1.019;3.049; p=0.0428~~ | ~~NS~~ | | ~~NS~~ |

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