



Salvage surgery in recurrent head and neck squamous cell carcinoma: Oncologic outcome and predictors of disease free survival



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ABSTRACT

Objective: Salvage surgery in recurrent SCCHN is associated with poor outcomes. This study aimed to better identify suitable surgical candidates and those at high risk of new recurrence.

Materials and methods: Single-center retrospective analysis of 109 patients undergoing salvage surgery for recurrent SCCHN. Univariate and multivariate analyses were used to identify prognostic factors affecting disease-free survival (DFS).

Results: The following factors showed a significant impact on DFS: Disease-free interval >6 months [HR 0.53; $p = 0.04$], age > 70 years [HR 0.26; $p = 0.03$], primary chemoradiotherapy [HR 2.39; $p < 0.01$] compared to radiotherapy, oropharynx [HR 5.46; $p < 0.01$] and hypopharynx [HR 3.92; $p < 0.01$] sites, compared to larynx, initial stage III [HR 7.10; $p < 0.01$] and stage IV [HR 4.13; $p < 0.01$], compared to stage I, locoregional recurrence [HR 4.57; $p < 0.01$], compared to local recurrence. Univariate analysis also identified significant postoperative predictors of poor DFS including flap reconstruction [HR 3.44; $p < 0.01$], postoperative complications [HR 2.09; $p = 0.01$], positive margins [HR 3.64; $p < 0.01$] and close margins [HR 3.83; $p < 0.01$]. On multivariate analysis, oropharynx site [HR 3.98; $p < 0.01$], initial stage III [HR 5.93; $p < 0.01$] and locoregional recurrence [HR 2.93; $p = 0.04$] were independent preoperative prognostic factors for DFS. Positive margins [HR 2.32; $p = 0.04$], close margins [HR 2.94; $p = 0.02$], extracapsular spread (ECS) [HR 4.04; $p = 0.03$] and postoperative complications [HR 3.64; $p < 0.01$] were independent postoperative prognostic factors.

Conclusions: Patients with advanced primary nonlaryngeal tumor and locoregional recurrence have limited success with salvage surgery. Because patients with positive margins and ECS are at high risk of relapse, adjuvant treatment should be discussed.

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Introduction

Treatment of recurrent squamous cell carcinoma of the head and neck (SCCHN) remains challenging. Wide local excision to achieve clear margins has to be balanced with the morbidity of the procedure and organ preservation.

Treatment with concomitant chemoradiotherapy (CRT) has progressively emerged as a gold standard in advanced tumors [1,2]. Considering that 25–48% of patients relapse after nonsurgical treatment [3,4], the role of salvage surgery is critical. Salvage surgery requires experienced surgical teams able to perform wide resections and flap reconstructions. Even then, the associated

morbidity and complication rates are high due largely to the toxicities of primary treatment and the extent of surgery required to resect often difficult to delineate tumors. It is therefore essential to establish criteria that select the best candidates for salvage surgery.

The first objective of this study was to determine whether preoperative prognostic factors influence survival to improve the selection of candidates for salvage surgery. The second objective was to identify postoperative prognostic factors on oncologic outcome to predict patients at high risk of recurrence.

Material and methods

One hundred nine patients who underwent salvage surgery for recurrent SCCHN between January 1999 and December 2012 were retrospectively analyzed. Patients selected had recurrent SCCHN,

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initially treated by radiotherapy alone (RT), CRT, surgery alone, surgery followed by postoperative RT/CRT and chemotherapy (CT) alone. Human papillomavirus (HPV) status was not investigated because p16 immunohistochemistry had not yet been routinely implemented at our institution.

Locoregional assessment included fiberoptic nasolaryngoscopy, computerized tomography or magnetic resonance imaging, and direct endoscopy under general anesthesia for biopsy purposes. Distant metastases and synchronous tumors were ruled out by FDG-PET imaging. Patients were staged or restaged according to the UICC TNM classification system, seventh edition [5].

The disease free interval (DFI) was defined as the interval between the end of the first treatment until evidence of recurrence. We defined 6 months posttreatment as the cutoff point to distinguish persistent disease from tumor recurrence. Patients with tumor present at 6 months after the end of treatment were deemed to have persistent disease.

Complications following surgery were divided into surgical and medical. Given the retrospective nature of this study, only major complications were reported. Surgical complications included complete and partial flap failure, wound breakdown, and hemorrhage. Medical complications included pneumonia, cardiac arrhythmia, myocardial infarction, congestive heart failure, thromboembolism, confusion, delirium, and stroke.

Statistics

Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were computed for all patients as the time between salvage surgery and death from any cause, death caused by SCCHN or an underlying effect, and the first relapse or death caused by SCCHN or underlying effect, respectively. Patients were right censored at the time of their last date of physical examination when they were still alive for OS and DSS and when they were still alive and without relapse for DFS. For DSS and DFS, patients who died from other causes were also right censored at the time of death. Kaplan-Meier survival curves were computed for each survival (i.e. OS, DSS and DFS) [6]. Univariate and multivariate hazard ratios were computed on DFS using univariate and multivariate Cox proportional hazard regression models [7]. The potential predictors of postoperative complications were assessed using univariate and multivariate logistic regression models. A backward selection was applied on other predictors in order to produce more parsimonious models [8]. In order to rule out confounding more effectively, a liberal criterion was used during backward selection by removing only variables with P-values > 0.2 [8]. For each multivariate analysis, predictors required for establishing the model's face validity were included, regardless of their statistical significance [8]. Generalized variance inflation factor (GVIF) implemented with the 'car' R package was used to assess multicollinearity between predictors. P-values were computed both with the Wald test and the Likelihood ratio test and their consistency was used to assess whether the number of events was sufficient to support the number of predictors in each model [8]. All statistical analyses and graphs were produced using R.3.2.4 software. A p-value < 0.05 was considered to be statistically significant.

Results

Salvage surgery

One hundred nine patients with a median age of 57 years (range 40–84) were included in the study (Table 1). Of these, 24 (22%) were initially treated elsewhere and referred for salvage treatment.

Table 1
Patients characteristics.

Variable	Clinical series (n = 109)
<i>Preoperative</i>	
Gender – n (%)	
Female	27 (24.8)
Male	82 (75.2)
Age at salvage surgery (years)	
Median	57
Range	40–84
≤70 years – n (%)	92 (84.4)
>70 years – n (%)	17 (15.6)
<i>Disease-free interval</i>	
Median (month)	12
Range (month)	1–228
≤3 months – n (%)	9 (8.3)
>3 months – n (%)	100 (91.7)
<i>Treatment</i>	
RT alone	61 (56.0)
CRT	26 (23.8)
Surgery alone	10 (9.2)
Surgery + RT/CRT	10 (9.2)
CT alone	2 (1.8)
<i>Primary site – n (%)</i>	
Larynx	45 (41.3)
Oropharynx	38 (34.9)
Hypopharynx	21 (19.3)
Oral cavity	5 (4.6)
<i>Initial staging – n (%)</i>	
I	24 (23.1)
II	23 (22.1)
III	25 (24.0)
IVa	31 (29.8)
IVb	1 (1.0)
Missing	5
<i>Site of recurrence – n (%)</i>	
Local	85 (78.0)
Locoregional	12 (11.0)
Regional	12 (11.0)
<i>Postoperative</i>	
<i>p staging – n (%)</i>	
I	19 (17.4)
II	26 (23.9)
III	11 (10.1)
IVa	51 (46.8)
IVb	2 (1.8)
<i>Surgery T/N/T + N</i>	
N	12 (11.0)
T	29 (26.6)
T + N	68 (62.4)
<i>Perineural infiltration</i>	
No	80 (73.4)
Yes	17 (15.6)
Not applicable	12 (11.0)
<i>Extracapsular spread</i>	
No	68 (62.4)
Yes	12 (11.0)
Not applicable	29 (26.6)
<i>Reconstruction with distant flap</i>	
No	52 (47.7)
Yes	57 (52.3)
<i>Complication</i>	
No	70 (64.2)
Yes	39 (35.8)
<i>Margins</i>	
R0	79 (72.5)
R0 with close margins	10 (9.2)
R1–R2	20 (18.3)

Abbreviations: n, number of patients; RT, radiotherapy; CRT, chemoradiotherapy; CT, chemotherapy; T, tumor; N lymph node(s); R0, clear margins; R1, margin(s) microscopically invaded; R2, margin(s) macroscopically invaded.

Previous treatments were RT in 61/109 patients (56%), concomitant CRT in 26/109 (23.8%), surgery in 20/109 (18.4%); surgery alone in 10/109 (9.2%), followed by RT in 9/109 (8.2%), followed by CRT in 1/109 (0.9%) and CT alone in 2/109 (1.8%).

Primary tumors were located in the larynx in 45/109 (41.3%), in the oropharynx in 38/109 (34.9%), in the hypopharynx in 21/109 (19.3%) and in the oral cavity in 5/109 (4.6%). Among 104 patients for whom initial staging was available, 47/104 (45.2%) had stage I/II disease, while 57/104 (54.8%) had stage III/IV. Twenty-six of the 109 patients (23.9%) had a DFI of less than six months and were considered as having persistent disease, while 83/109 (76.1%) had a DFI greater than six months and were considered as having recurrent disease. Median DFI was 12 months (range 1–228).

Eighty-five of the 109 patients (78%) had local recurrence, 12/109 patients (11%) were diagnosed with locoregional recurrence, and 12/109 (11%) had an isolated regional recurrence. Salvage surgery was performed on the tumor site exclusively in 29/109 patients (26.6%), while 68/109 patients (62.4%) had surgery on the tumor site coupled with neck dissection (ND), and 12/109 patients (11%) had ND alone.

Surgical procedures for tumors included glossectomy/oropharyngectomy (37/109), partial laryngectomy/laryngopharyngectomy (15/109), total laryngectomy (24/109), and total pharyngolaryngectomy (21/109). In patients who underwent ND alone, modified radical ND was performed in four, radical ND in three, extended radical ND in two and selective ND in three. Reconstruction using distant pedicled and microvascular free flaps was performed in 57/109 patients (52.3%).

After pathological analysis, margins were considered negative in 89/109 patients (81.7%), but 10 of those had close margins of less than 0.5 mm. Margins were microscopically positive in 20/109 patients (18.3%). Perineural infiltration was reported in 17/109 patients (15.6%). In patients who underwent ND, extracapsular spread (ECS) was reported in 12/80 (15%). After salvage, 64/109 patients (58.7%) had stage III and IV disease, whereas 45/109 patients (41.3%) had stage I and II.

Thirty-nine of the 109 patients (35.8%) experienced major complications. Surgical complications occurred in 30/39 (76.9%). Pharyngocutaneous fistula occurred in 16/97 patients (16.5%), five had postoperative hemorrhage requiring intervention, and partial or total flap necrosis requiring reintervention occurred in nine. Major medical complications were reported in 9/39 patients (23.1%). General infectious complications and hemodynamic com-

plications were reported in five and four patients, respectively. One patient died postoperatively due to hemodynamic complications.

Oncologic outcome

The median time of follow-up after salvage surgery was 30 months (range 1–198 months). At two and five years, OS of all patients was 59% and 42%, DSS was 66% and 56.5%, and DFS was 56% and 47%, respectively (Fig. 1).

Survival was analyzed according to tumor site (Fig. 2, Table 2). The 2- and 5-year OS of patients with larynx cancer, oral cancer, hypopharynx cancer and oropharynx cancer recurrences were 85.3% and 64%, 60% and 60%, 38.8% and 15.5%, and 51.9% and 29.3%, respectively. The 2- and 5-year DSS of patients surgically salvaged for larynx cancer, oral cancer, hypopharynx cancer and oropharynx cancer recurrences were 90.4% and 80.7%, 60% and 60%, 55.5% and 44.4%, and 56.2% and 41.2%, respectively. The 2- and 5-year DFS of patients salvaged for larynx cancer, oral cancer, hypopharynx cancer and oropharynx cancer recurrences were 83% and 76.9%, 60% and 40%, 50% and 41.7%, and 30.3% and 27.6%, respectively.

Prognostic factors

Preoperative predictors having a significant impact on DFS were first identified on univariate analysis (Table 3). Tumor site was a strong predictor with significant hazard ratios for the oropharynx [HR5.46; $p < 0.01$] and hypopharynx [HR3.92; $p < 0.01$], both compared to the larynx. Other preoperative predictors included DFI > 6 months [HR 0.53; $p = 0.04$], age > 70 years [HR0.26; $p = 0.03$], initial advanced stage [HR7.10; $p < 0.01$ for stage III; HR = 4.13; $p = 0.01$ for stage IV, both compared to stage I], primary CRT [HR 2.39; $p < 0.01$, compared to RT alone], and locoregional recurrence [HR4.57; $p < 0.01$, compared to local recurrence]. The multivariate analysis was then performed in order to obtain adjusted HR and consequently decrease the biases generated by confounding effects. The high number of predictors included in the full multivariate model did not affect its reliability, as measured by the consistency between p-values obtained both with the Wald test and likelihood ratio test and by the consistency between HR obtained before and after backward selection. Perineural infiltration was highly correlated with site of recurrence and was therefore not included in the multivariate models in order

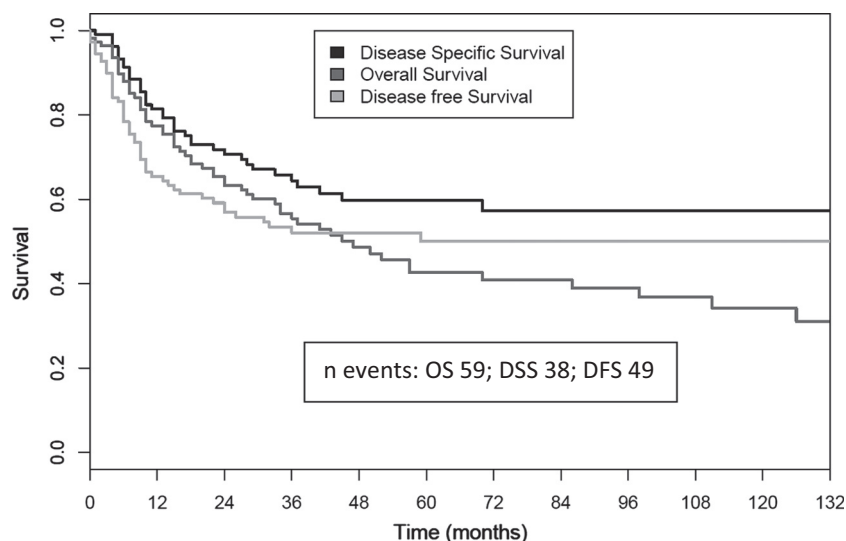


Fig. 1. Overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS) rates for all patients. OS at 2 years and 5 years: 59% and 42%; DSS at 2 years and at 5 years: 66% and 56.5%, DFS at 2 years and at 5 years: 56% and 47%.

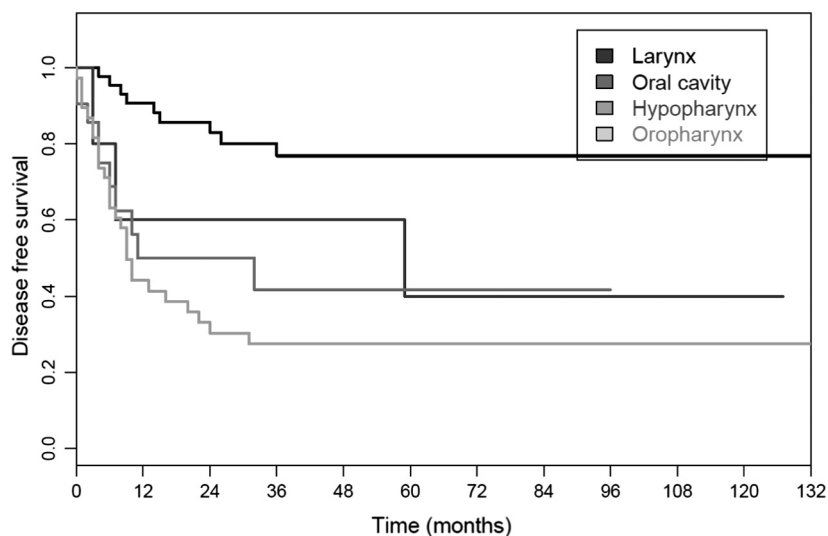


Fig. 2. Disease-free survival (DFS) probabilities according to tumor site: larynx, oral cavity, hypopharynx and oropharynx.

to avoid a collinearity problem. After backward selection of the predictors in the multivariate model, oropharynx primary site [HR 3.98; $p < 0.01$], initial stage III [HR 5.93; $p < 0.01$] and locoregional recurrence [HR 2.49; $p = 0.04$] were independent preoperative prognostic factors for DFS (Table 3). It is worth noting that DFI did not produce a significant adjusted HR but this predictor was not removed during backward selection to preserve the model's face validity [8]. Although the impact of the hypopharynx primary site was not statistically significant on multivariate analysis resulting from the limited number of patients with this primary site, the HR of 2.36 suggests a strong adverse effect on DFS. The multivariate analysis invalidated the unfavourable effect of primary CRT which was identified with univariate analysis. This unadjusted unfavourable effect was mainly attributable to the high proportion of hypopharynx primary (42%) and of advanced initial staging (87.5%) site among patients with primary CRT (compared to 15% of hypopharynx primary site and 50% of advanced initial staging among patients with primary RT alone).

We built a survival prediction score incorporating three independent preoperative prognostic factors, locoregional failure, tumor site (larynx vs. non larynx), and initial stage (stage I/II vs stage III/IV) to test for survival. Patients with none, one, two or

three poor prognostic factors had a 2-year DFS of 96.2%, 62.5%, 35.5%, and 28.6%, respectively (Fig. 3).

Regarding postoperative variables as potential predictors of poor outcome, the univariate analysis identified reconstruction with distant flap [HR 3.44; $p < 0.01$], occurrence of postoperative major complications [HR 2.09; $p = 0.01$], positive margins [HR 3.64; $p < 0.01$] and close margins [HR 3.83; $p < 0.01$] as significant factors influencing DFS (Tables 3 and 4). On multivariate analysis, positive margins [HR 2.32; $p = 0.04$], close margins [HR 2.94; $p = 0.02$], ECS [HR 4.04; $p = 0.03$] and occurrence of postoperative complications [HR 3.64; $p < 0.01$] were independent postoperative prognostic factors for DFS (Table 3).

Complications

After backward selection, the adjusted odds ratio from the multivariate logistic regression model reveal a statistically significant association between reconstruction with distant flap and the occurrence of postoperative complications [OR 3.35 ($p = 0.02$)]. A strong association was found in patients undergoing surgery on the recurrent tumor combined with ND [OR 4.48 ($p = 0.01$)] compared to patients undergoing surgery on tumor alone (Table 4).

Discussion

The emergence of organ preservation strategies has limited the role of primary surgery in advanced SCCHN. Despite aggressive combinations of CT and RT, 40% to 60% of patients still relapse [4]. Salvage surgery is generally regarded as the primary option for most patients with resectable recurrent SCCHN, however it remains associated with high morbidity and poor oncologic outcomes [9]. The availability, therefore, of preoperative criteria capable of accurately predicting suitable patients for salvage surgery would greatly assist decision-making. After surgery, the ability to identify patients at high risk of another recurrence is also essential.

Surgical outcomes in our study were similar to those reported in the literature. Distant pedicled and microvascular free flaps were necessary in 52.3% of our patients, which is comparable to other salvage procedure reports [3,10].

Prior RT influences wound healing and increases the risk of wound complications following salvage surgery. While it is difficult to compare complications data across trials in the absence of accepted guidelines, major complications arose in 35.8% of our

Table 2

2-year and 5-year disease-free survival, disease specific survival and overall survival of patients according to tumor site: larynx, oral cavity, hypopharynx and oropharynx.

	2 years survival (95% CI)	5 years survival (95% CI)
DFS		
Larynx	0.830 (0.723–0.954)	0.769 (0.645–0.916)
Oral cavity	0.600 (0.293–1.000)	0.400 (0.137–1.000)
Hypopharynx	0.500 (0.311–0.803)	0.417 (0.230–0.755)
Oropharynx	0.303 (0.186–0.495)	0.276 (0.163–0.466)
DSS		
Larynx	0.904 (0.818–0.998)	0.807 (0.685–0.950)
Oral cavity	0.600 (0.293–1.000)	0.600 (0.293–1.000)
Hypopharynx	0.555 (0.354–0.868)	0.444 (0.237–0.831)
Oropharynx	0.562 (0.421–0.750)	0.412 (0.269–0.631)
OS		
Larynx	0.853 (0.752–0.969)	0.640 (0.489–0.838)
Oral cavity	0.600 (0.293–1.000)	0.600 (0.293–1.000)
Hypopharynx	0.388 (0.221–0.683)	0.155 (0.046–0.522)
Oropharynx	0.519 (0.381–0.707)	0.293 (0.171–0.501)

Abbreviations: CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; OS, overall survival.

Table 3

Prognostic factors for Disease Free Survival (DFS) on univariate and multivariate analysis.

Variable	Univariate hazard ratio (95% CI)	P value	Multivariate (Full model) hazard ratio (95% CI)	P value	Multivariate (Backward selection) hazard ratio (95% CI)	P value
<i>Pre-operative</i>						
Gender (ref: Female)		0.15*		0.99*		
Male	1.66 (0.80–3.43)	0.17	1.00 (0.43–2.32)	0.99	–	–
Age at salvage surgery (ref: ≤70 yrs)		0.01*		0.30*		
>70 yrs	0.26 (0.08–0.84)	0.03	0.45 (0.10–2.14)	0.32	–	–
Disease-free interval (ref: ≤6 months)		0.05*		0.19*		0.22*
>6 months	0.53 (0.29–0.97)	0.04	0.57 (0.25–1.32)	0.19	0.62 (0.29–1.33)	0.22
Treatment (ref: RT alone)		0.05*		0.34*		
CRT	2.39 (1.27–4.50)	<0.01	0.71 (0.28–1.78)	0.46	–	–
Surgery alone	1.02 (0.35–2.97)	0.96	0.77 (0.16–3.73)	0.74	–	–
Surgery + RT/CRT	1.62 (0.61–4.27)	0.32	2.73 (0.62–12.1)	0.18	–	–
CT alone	–	–	–	–	–	–
Primary site (ref: Larynx)		<0.01*		0.32*		0.01*
Oropharynx	5.46 (2.56–11.7)	<0.01	2.62 (0.92–7.46)	0.07	3.98 (1.65–9.62)	<0.01
Hypopharynx	3.92 (1.58–9.67)	<0.01	2.26 (0.70–7.29)	0.17	2.36 (0.85–6.59)	0.10
Oral cavity	3.46 (0.93–12.8)	0.06	2.70 (0.44–16.7)	0.28	3.84 (0.91–16.2)	0.07
Initial staging (ref: I)		<0.01*		<0.01*		<0.01*
II	2.41 (0.74–7.83)	0.14	2.13 (0.52–8.80)	0.30	1.97 (0.50–7.71)	0.33
III	7.10 (2.39–21.1)	<0.01	7.36 (2.04–26.6)	<0.01	5.93 (1.80–19.5)	<0.01
IV	4.13 (1.37–12.4)	0.01	2.16 (0.62–7.56)	0.23	2.58 (0.81–8.27)	0.11
Site of recurrence (ref: Local)		<0.01*		0.10*		0.02*
Locoregional	4.57 (2.21–9.45)	<0.01	2.92 (0.94–9.04)	0.06	2.93 (1.02–8.39)	0.04
Regional	0.86 (0.31–2.43)	0.78	0.49 (0.08–2.92)	0.43	0.34 (0.07–1.67)	0.18
<i>Post-operative</i>						
Perineural infiltration (ref: no)		0.20*		–		–
Yes	1.84 (0.93–3.66)	0.08	–	–	–	–
Not applicable						
Extracapsular spread (ref: no)		0.21*		0.33*		0.13*
Yes	1.44 (0.60–3.45)	0.41	2.81 (0.76–10.4)	0.12	4.04 (1.12–14.6)	0.03
Not applicable	–	–	–	–	–	–
Reconstruction with distant flap (ref: no)		<0.01*		0.67*		
Yes	3.44 (1.84–6.42)	<0.01	1.24 (0.46–3.35)	0.67	–	–
Complication (ref: no)		0.01*		<0.01*		<0.01*
Yes	2.09 (1.19–3.67)	0.01	4.10 (1.87–8.99)	<0.01	3.64 (1.85–7.17)	<0.01
Margins (ref: R0)		<0.01*		<0.01*		0.03*
R0 with close margins	3.83 (1.72–8.51)	<0.01	4.13 (1.48–11.5)	0.01	2.94 (1.19–7.27)	0.02
R1–R2	3.64 (1.92–6.91)	<0.01	3.37 (1.34–8.48)	0.01	2.32 (1.03–5.22)	0.04

Abbreviations: CI, confidence interval; yrs, years; RT, radiotherapy; CRT, chemoradiotherapy; CT, chemotherapy; R0, clear margins; R1, margin(s) microscopically invaded; R2, margin(s) macroscopically invaded. * Indicates overall p-values computed for each variable with the likelihood ratio test. All other p-values were computed with the Wald test.

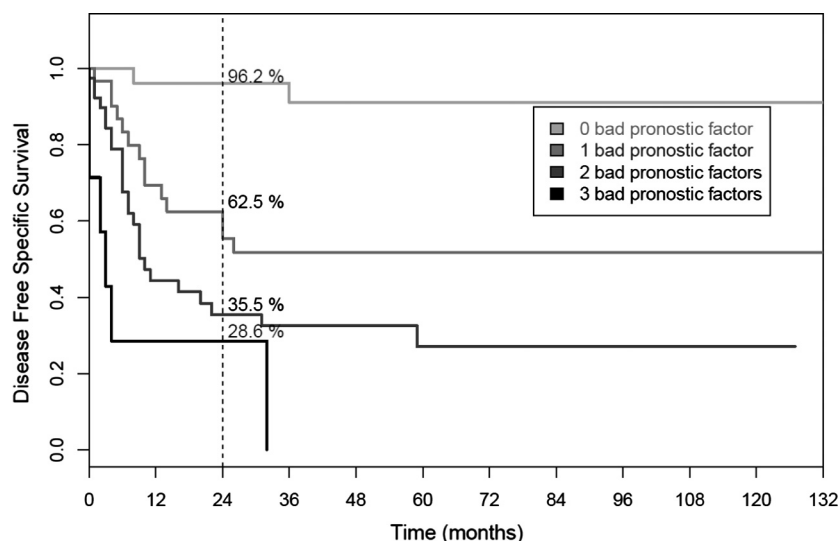


Fig. 3. DFS rates in patients with 0 vs. 1 vs. 2 vs. 3 predictors of salvage, respectively. Preoperative prognostic factors: locoregional failure, tumor site (larynx vs. non larynx), and initial stage (stage I/II vs. stage III/IV).

Table 4
Univariate and multivariate odds-ratio to develop complication after salvage surgery. Considering that no major complications were reported in all patients who had neck dissection alone (n = 12), these patients were excluded from the logistic regression analysis to avoid a category that was homogeneous with respect to the outcome.

Variable	Univariate odds ratio (95% CI)	P value	Multivariate odds ratio (95% CI) full model	P value	Multivariate odds ratio (95% CI) backward selected	P value
Disease-free interval (ref: ≤6 months)		0.05*		0.50*		
>6 months	0.38 (0.14–1.00)	0.05	0.66 (0.20–2.18)	0.50	–	–
Primary treatment (ref: RT alone)		0.35*		0.42*		0.43*
CRT	1.62 (0.60–4.35)	0.34	0.76 (0.21–2.69)	0.67	1.02 (0.34–3.10)	0.98
Surgery alone	0.80 (0.11–4.48)	0.81	0.76 (0.09–6.49)	0.80	0.74 (0.11–4.90)	0.76
Surgery + RT/CRT	0.27 (0.01–1.72)	0.24	0.14 (0.01–1.77)	0.13	0.19 (0.02–1.88)	0.15
CT alone	–	–	–	–	–	–
Primary site (ref: Larynx)		0.43*		0.75*		
Oropharynx	0.97 (0.37–2.51)	0.95	2.61 (0.13–53.5)	0.54	–	–
Hypopharynx	2.32 (0.76–7.39)	0.15	0.74 (0.07–7.85)	0.80	–	–
Oral cavity	1.86 (0.07–49.4)	0.67	6.36 (0.07–595)	0.43	–	–
Reconstruction with distant flap (ref: No)		<0.01*		0.03*		0.02*
Yes	3.90 (1.57–10.4)	<0.01	4.90 (1.11–21.7)	0.04	3.35 (1.19–9.49)	0.02
Surgery T/T + N (ref: T)		<0.01*		0.07*		0.01*
T + N	5.81 (1.99–21.5)	<0.01	3.42 (0.85–13.9)	0.08	4.48 (1.34–15.0)	0.01
Type of surgery (ref: Glossectomy/oropharyngectomy)		0.04*		0.24*		
P. laryngectomy/pharyngolaryngectomy	0.57 (0.11–2.25)	0.44	3.86 (0.20–74.4)	0.37	–	–
T. pharyngolaryngectomy	3.71 (1.22–11.9)	0.02	9.21 (0.54–156.0)	0.13	–	–
T. laryngectomy	1.75 (0.59–5.26)	0.31	10.3 (0.45–235.1)	0.14	–	–

Abbreviations: CI, confidence interval; yrs, years; RT, radiotherapy; CRT, chemoradiotherapy; CT, chemotherapy; T, tumor; N lymph node(s); P, partial; T, total. * Indicates overall P-values computed for each variable with the likelihood ratio test. All other P-values were computed with the Wald test.

patients in line with previous reports [3,10–17]. The importance of accurately collecting postoperative complications data using a widely accepted classification system [18] was recently highlighted in Head & Neck [19]. A comprehensive review of the complications following salvage total laryngectomy including 50 studies and 3293 patients recently reported an overall complications rate of 67.5% when pharyngocutaneous fistula was the commonest complication with a pooled incidence of 28.9% [20]. Because our study was unpowered for this issue, we were not able to demonstrate any relationship between a patient's characteristics and the occurrence of postoperative complications. Beside, it was not the primary objective of our study.

Patients undergoing surgery on tumor combined with ND are more at risk, however, of developing complications than patients undergoing surgery on tumor alone or ND alone. Previous studies have identified ND as an independent factor for postoperative morbidity. In series combining primary and salvage surgery, complication rates of 33%–67.5% in patients undergoing ND in combination with tumor resection have been reported [19–22]. The occurrence of surgical complications was reported as an independent predictive factor of poor prognosis after salvage surgery [16]. Previous studies have successfully identified greater primary tumor and nodal stage, short DFI, positive margins, nonlaryngeal cancer site, and history of RT as oncologic risk factors of poor outcome [23–26].

We report a 5-year OS, DSS and DFS of 42%, 56.5% and 47%, respectively. Comparison with other studies is difficult. Some studies address salvage treatment for specific subsites [15,16,27,28], others analyze the results of all salvage modalities [22], or report results after failure of a specific primary treatment [3,17]. Considering these remarks, our results are in line with the results of previously reported series [3,10,16]. Goodwin reported a 5-year OS of 39% in a large multicenter retrospective series of 1080 patients [9]. Taguchi reported a 5-year OS of 61% for patients who had salvage surgery [17]. Of note, salvage surgery was performed in only a third of failing patients and, of those, one third had ND alone, suggesting stringent selection criteria.

Oropharyngeal primary site, primary advanced stage, locoregional recurrence, positive and close margins, ECS and postoperative complications are independent postoperative prognostic factors for DFS. Although hypopharynx recurrence is not statisti-

cally significant, there is a strong suggestion it correlates with poor outcome. Several authors have reported that resection margin status and ECS are significantly related to survival [3,10,29].

Recurrence after non-surgical treatment is related to the site of the primary tumor. In patients with larynx SSC, a 36% relapse rate is reported, while around half of advanced oropharyngeal cancer patients relapse [1,2]. In a study analyzing salvage treatment in recurrent oropharynx cancer, patients treated with palliative treatment had a 5-year OS of 0%, compared to 28% after salvage surgery and 32% after reirradiation [15]. Gañán et al. reported a series of 1088 patients presenting with local and/or regional recurrence. Half of them had salvage treatment with curative intent. Salvage surgery was performed in 89.5% of the patients, and salvage RT or CRT in 10.5%. Salvage surgery was associated with adjuvant RT or CRT in 22.5% of the patients. The 5-year DSS of patients treated with salvage RT/CRT was 26.4%, while the 5-year DSS was 58.3% for patients treated with salvage surgery [30]. It is unknown whether patients salvaged by RT/CRT were initially treated by surgery or RT.

The site of recurrence has great impact on outcome. In our study, the patients salvaged for a recurrent larynx cancer or oral cancer had a 5-year OS of 64% and 60% respectively, contrasting with 29.3% and 15.5% for patients with recurrence in the oropharynx or hypopharynx. Laryngeal recurrence is associated with favourable survival outcomes relative to other sites. Typically, salvage total laryngectomy enables wide resection and clear margins in most recurrent larynx cancers, and offers 5-year OS rates from 57% to 70% [28,31,32].

Although oral cavity recurrences are easily detected, survival rates are generally lower than those occurring in the larynx. Oral cavity recurrences have been reported to be equally likely to occur among local, locoregional, and regional sites. In contrast to laryngeal recurrences, a high rate of oral cavity failures occur at distant sites [33]. In our study, the limited number of patients salvaged for oral cancer did not enable any conclusions to be drawn.

Survival rates after surgical salvage for recurrent oropharyngeal cancer are generally poor and range from 13% to 28% at five years [14,15]. The complex anatomy of the oropharynx and its proximity to the skull base leads to difficulties in tumor control [12]. Patients in our study had a 5-year DFS of only 27.6%, confirming the difficulty in achieving local control in these patients.

Salvage laryngopharyngectomy for hypopharynx recurrence carries a high risk of major wound complications and perioperative mortality [34,35]. Recurrent hypopharyngeal cancer has been reported as resectable in only 29% of patients [34]. This underscores the need to realistically frame the potentially severe consequences of surgical salvage within the lower rate of cure. Nevertheless, when possible, salvage surgery remains the best chance of disease control and survival. In our study, patients undergoing salvage surgery for recurrent hypopharynx cancer had a 5-year DFS of 44.4%. This is in line with the 5-year DFS results of 40–50% reported from other experienced centers [35,36].

The presence of positive margins, reported in 18.3% of our patients, is a strong independent factor for recurrence as also reported in previous studies [15]. Tan reported invaded margins in 22% of patients [3]. Nichols reported a 5-year OS of 43.4% when clear margins were achieved [27]. A study on 352 SCCHN patients who underwent salvage surgery without postoperative RT found that 47% of those considered to have clear margins nonetheless developed subsequent local recurrence [37]. Of interest, our patients with clear but close margins are also at risk of developing a new recurrence.

In our series, patients with initially stage III tumors had a poor oncologic outcome, but not patients with stage IV tumors. Stage III patients were six times more likely to develop early recurrence compared to stage I. This result could be the consequence of more stringent selection of stage IV patients for salvage surgery. Many authors have reported decreased survival in patients with advanced initial tumors because of more locoregional recurrences and distant metastasis after salvage [3,16,17,38]. Studies have shown that the stage of disease at the time of recurrence is of substantial importance in predicting prognosis [9,12,39]. Like us, Gleich could not show, however, that stage at the time of recurrence influences outcome [38].

Tan developed a model stratifying patients into distinct prognosis groups for postsalvage survival based on initial stage IV tumors and concurrent local and regional failures as independent predictors for decreased survival [3]. Two-year OS rates for patients with none, one and two of these predictive factors were 83%, 49% and 0%, respectively. We applied a comparable model using our independent preoperative predictive factors. Patients with none, one, two and three predictive factors of poor outcome had 96.2%, 62.5%, 35.5%, and 28.6% respectively to be successfully salvaged. Patients with none or only one predictive factors have a good chance to be successfully treated by salvage surgery whereas patients with more than one predictors have limited chance to be successfully salvaged by surgery. Such information should be helpful for clinicians to better decide on whether or not with salvage surgery, in particular when voice-mutilating surgery is considered, and to counsel patients facing recurrent SCCHN and its subsequent management decisions.

A short DFI has been reported to have significant negative prognostic impact [15,40,41]. In our study, short DFI was not an significant independent prognostic factor. This is probably explained because our study is underpowered. Many authors proposed a period of six months up to two years [27,29,42] when a shorter period of six weeks was sometimes proposed in patients treated with RT alone [15]. These differences may explain the contradictory results.

The occurrence of postoperative complications was significantly correlated with poor outcome. Patients who had postoperative complications were three times more at risk for relapse compared to those without complications. Postoperative complications occur more frequently in patients with comorbidities, tobacco and alcohol addiction and malnutrition [21,22]. A correlation between initial concomitant CRT and postoperative complications has been reported [43]. In our study, patients undergoing surgery requiring

reconstruction with distant flap and surgery on the tumor site with ND were more likely to have postoperative complications.

A limitation of our study is the absence of performance status data when the recurrence was diagnosed. This variable is a significant factor in determining outcomes in the recurrent setting [33,42]. With increasing numbers of SCCHN in elderly patients, factors that can negatively affect the postoperative outcome are essential for making treatment decisions. A recent study concluded that medical comorbidities and age must be strongly considered when selecting candidates for salvage surgery [42] as survival is adversely affected.

Salvage surgery remains the standard of care but is not always possible in patients with recurrent disease. Reirradiation could play a role in selected patients and results are sometimes better, than with salvage surgery. Encouraging 5-year OS results of 32% have been reported in highly selected salvage patients treated with reirradiation [15]. However, reirradiation seems of limited clinical interest because of high toxicity, impaired quality of life and strict limitations on irradiation dose [44,45]. Intensity-modulated RT could have an emerging role in the treatment of selected recurrences, delivering higher and more conformal doses while minimizing radiation to normal tissue [46]. When reirradiation is considered, if the patient can tolerate it, a chemotherapeutic agent, preferably to which the patient is naïve, should be administered to sensitize the tissues, but toxicity remains a major issue. Two multi-institutional Radiation Therapy Oncology Group (RTOG) trials prospectively examined the role of hyperfractionated reirradiation and CT in patients with recurrent unresectable SCCHN [47,48] with encouraging 2-year OS rates. However, the incidence of grade 4–5 acute toxicity was 25% and 28% in both studies, with 8–9% treatment-related mortality. Reirradiation studies have shown long-term OS rates of 36–60% if surgery was performed first, compared with 9–17% in the nonsurgical arms [44,48,49].

The role of postoperative reirradiation or concomitant chemoreirradiation after salvage surgery in patients treated by primary RT is still up for debate. In patients with adverse pathologic features on the pathologic specimen, a randomized study has shown that DFS and locoregional control, but not OS, was prolonged when surgery was followed by concomitant CRT compared to surgery alone [50]. The regimen employed was not common and toxicity was substantially increased with 8% of treatment-related death in the group of patients randomized in the chemoreirradiation arm and 39% of late grade 3–4 toxicity in patients surviving 24 months.

In recurrent deemed unresectable patients, immunotherapy could play an increasing role. Recently, Ferris et al. reported that Nivolumab, a fully human IgG4 anti-programmed death 1 (PD-1) monoclonal antibody prolonged survival as compared with standard single-agent systemic therapy, among patients with platinum-refractory SCCHN. Beside, Nivolumab was associated with fewer toxic effects than standard therapy and with maintenance of quality of life among patients with a treatment-refractory cancer that otherwise has serious adverse effects on quality of life as it leads to death [51].

Conclusion

In recurrent SCCHN, salvage surgery is only effective in highly selected patients. According to a prediction modelling based on preoperative information, patients with none or one predictive factors have a good chance to be successfully treated by salvage surgery whereas patients with two and three predictors have limited chance to be successfully salvaged by surgery. Such information is paramount for clinicians to decide on whether or not with salvage surgery and to better counsel patients facing recurrent SCCHN. Patients with advanced primary tumor in a nonlaryngeal localiza-

tion and both local and regional recurrence have very limited success with salvage surgery and should be considered for palliative treatment. Patients with positive or close margins and ECS on the surgical specimen should be strongly considered for clinical trials with adjuvant therapy.

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Conflict of interest statement

The authors declared that there is no conflict of interest.

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