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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.

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)
Preoperative	
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)
Disease-free interval	
Median (month)	12
Range (month)	1–228
⩽3 months - n (%)	9 (8.3)
>3 months - n (%)	100 (91.7)
Treatment	
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)
Primary site – n (%)	
Larynx	45 (41.3)
Oropharynx	38 (34.9)
Hypopharynx	21 (19.3)
Oral cavity	5 (4.6)
Initial staging - n (%)	
I	24 (23.1)
II	23 (22.1)
III	25 (24.0)
IVa	31 (29.8)
IVb	1 (1.0)
Missing	5
Site of recurrence - n (%)	
Local	85 (78.0)
Locoregional	12 (11.0)
Regional	12 (11.0)
Postoperative	
p staging - n (%)	
I	19(17.4)
II	26 (23.9)
III	11 (10.1)
IVa	51 (46.8)
IVb	2 (1.8)
Surgery T/N/T + N	
N	12 (11.0)
T	29 (26.6)
T + N	68 (62.4)
Perineural infiltration	
No	80 (73.4)
Yes	17 (15.6)
Not applicable	12 (11.0)
Extracapsular spread	
No	68 (62.4)
Yes	12 (11.0)
Not applicable	29 (26.6)
Reconstruction with distant flap	
No	52 (47.7)
Yes	57 (52.3)
Complication	
No	70 (64.2)
Yes	39 (35.8)
Margins	
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.