



## Outcome of heavily pretreated recurrent oral squamous cell carcinoma after salvage resection: A monocentric retrospective analysis



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### ABSTRACT

**Purpose:** The goals of the present study were to analyze survival data of patients who received salvage surgery due to recurrent oral squamous cell carcinoma (OSCC) of the oral cavity with curative intent, and to investigate the feasibility of microvascular flap reconstruction in a heavily pretreated patient cohort. **Material and methods:** A total of 32 patients who received salvage surgery due to recurrent OSCC were included. The cohort was analyzed in regard to relevant clinical and pathological features. Survival was estimated by using Kaplan–Meier analysis and verified in a multivariate Cox regression model.

**Results:** All patients recovered well from surgery. The most common severe complication was free flap failure in 7 patients (24.1%). R0-resection was achieved in 16 patients (50%). Univariate Kaplan–Meier analysis showed that the estimated overall survival and disease-free survival of all patients after 24 months were 37.8% and 30.9%, respectively. Multivariate testing identified R1-resection was the only independent predictor of treatment failure.

**Conclusion:** Salvage surgery is the only potential curative treatment option in recurrent OSCC. Microvascular reconstruction is feasible in heavily pretreated patients, but it is associated with a higher free flap failure rate. Recurrent OSCC in heavily pretreated patients shows different biological behavior. Further prospective clinical and molecular studies are needed to develop a better molecular understanding of recurrent OSCC and the best and safest individual therapeutic strategy.

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### 1. Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common cancers worldwide. In 2008, approximately 260,000 new cases were diagnosed, and 120,000 patients died of their disease (Bray et al., 2012). For the treatment of OSCC, surgery is still the primary option for resectable OSCC, followed by adjuvant radiation with 50–60 Gy in advanced stages (Licitra et al., 2009). Platinum-based chemotherapy is frequently concomitantly applied in the case of histopathological risk factors such as incomplete resection or extracapsular lymph node spread, to increase local and distant control (Bernier et al., 2005). Thanks to

those combined treatment approaches, a 5-year-survival rate of stage IVA OSCC of up to 60% is currently achieved (Siegel et al., 2014). Nevertheless, despite such aggressive therapeutic regimens, local or loco-regional progressive disease is a frequently observed phenomenon in OSCC. In the absence of distant metastases, salvage resection of the recurrent tumor after previous radiation remains the only potentially curative treatment option (Agra et al., 2006). Since microvascular free flap surgery to reconstruct major defects in the head and neck region has been established in large cancer centers in the last 30 years, therapeutic options for this difficult group of patients have widely increased in the hands of experienced surgeons. Nowadays, not only ablating the recurrent tumor but also maintaining patients' speech and swallowing ability are key aims of surgical therapy (Cordeiro, 2008). Therefore, it is of the utmost importance to apply these established techniques in the setting of salvage surgery of the oral cavity. The current literature provides little information about the

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outcome of heavily pretreated OSCC patients in the salvage setting (Agra et al., 2010; Chen et al., 2014; Kostrzewa et al., 2010), with overall survival rates between 20% and 50% after 3 years. To supplement the available information with substantial data in order to correctly judge the outcome of this difficult-to-treat patient collective, we retrospectively analyzed a patient cohort with progressive OSCC after several therapeutic approaches that was treated with ablative salvage surgery with curative intent and microvascular free flap reconstruction, with regard to morbidity, mortality, and postoperative functional outcome as well as for overall survival and disease-free survival. We used the term “heavy pretreatment” in patients who had undergone at least 2 therapeutic modalities at the primary site and the neck, including definitive radiotherapy of the tumor and the lymphatic drainage pathways as well as surgery, chemotherapy, or cetuximab therapy, respectively (Table 2).

## 2. Material and methods

### 2.1. Patient collective and clinical staging

In the present study, we retrospectively analyzed 32 patients who underwent salvage surgical treatment at the Department of Oral and Craniomaxillofacial Surgery of the University Hospital Heidelberg between 2010 and 2013, after approval by the local institutional review board (ethic vote S-186/2015). The mean age of the patients was 60.3 years (range 32.4–79.7 years). Of the patients, 23 were male and 9 were female. All patients had an extensive medical history of oral squamous cell carcinoma (OSCC) treatment with 2.7 (range 1–5) different treatment approaches including surgery, and/or radiotherapy/chemotherapy in all cases. The mean time between the first-line treatment and salvage resection was 48 months (range 10–256 months). For all patients, salvage surgery presented the only remaining potentially curative treatment option. A total of 17 patients experienced local recurrence in the oral cavity, 6 patients had a second primary carcinoma in the oral cavity, and 9 patients showed loco-regional soft-tissue metastases.

Pretreatment staging such as clinical examination, panoramic tomographic imaging, and computed tomography (CT) scanning of the head and neck region and the chest, as well as panendoscopy including bronchoscopy and esophagoscopy, were performed to

asses loco-regional spread and to identify second primary carcinomas and distant metastases.

### 2.2. Therapy regimen and follow-up

After informed consent was provided by patients and after complete microscopic resection (R0) was found to be feasible, the patients were surgically treated with curative intent. Microvascular free flap reconstruction was performed in 29 patients using the antero-lateral thigh flap (n = 20), the free fibular flap (n = 5), the radial forearm flap (n = 3), and the scapula flap (n = 1). In 3 cases, loco-regional flaps were used for defect coverage. Overall hospital stay, surgical complications, and postoperative dependency on tracheostomy and permanent gastric feeding tube at discharge from hospital were assessed to evaluate the morbidity during and after surgery. The histological charts of the patients were examined to evaluate definitive resection margins and further histological risk factors.

After completion of the therapy, patients had to undergo a monthly clinical monitoring in the first year after salvage surgery. Afterward, clinical evaluation was performed every 8 weeks and was combined with regular ultrasound examinations (every 4–6 months). Computed tomography (CT) and/or magnetic resonance imaging (MRI) was performed every 12 months or earlier if clinical examination showed conspicuities. Lesions suspicious for recurrent or second primary carcinoma were biopsied if necessary.

### 2.3. Statistical analyses

Kaplan–Meier curves were used to calculate univariate overall survival and disease-free survival. Different Kaplan–Meier curves stratified according to clinical or histological criteria were compared by the log-rank test. To further detect the impact of clinical and histopathologic parameters on overall and disease-free survival of the patients, a Cox proportional hazard model was constructed. P values of  $\leq 0.05$  were considered to be significant. All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Perioperative complications, morbidity and follow-up

All patients recovered well from extensive salvage surgery. No major intraoperative complications were observed. Postoperatively, a total of 26 secondary stage procedures were necessary due to postoperative complications. The most common severe postoperative complication was unsalvageable free flap failure in 7 cases (7/29, 24.1%) due to arterial or venous hemostasis of the vascular pedicle. Five of those patients subsequently underwent successful soft-tissue reconstruction using the antero-lateral thigh flap (ALT). In 2 other patients, pedicled pectoralis major musculocutaneous flap and latissimus dorsi flap were applied for loco-regional reconstruction, respectively. Eight patients presented with minor complications such as postoperative bleeding, hematoma, and/or partial tissue necrosis that required surgical intervention. In 4 cases, an additional free flap approach was necessary to close an orocervical fistula and/or to cover the carotid artery by using the fibula flap (n = 1), the osteomyocutaneous iliac crest flap (DCIA, n = 2), or the ALT (n = 1). One DCIA in a secondary procedure failed, resulting in a permanent defect situation. The average hospital length of stay in all patients was 28 days (range 11–55 days). After this time, 12 patients (37.5%) were able to consume a soft diet; 19 patients were dependent long term

**Table 1**  
Clinical and pathological characteristics of patient cohort.

Variable	Subgroup	n (%)
Age, y	<60	12 (37.5%)
	>60	20 (62.5%)
Number of previous therapies	1	3 (9.4%)
	2	14 (43.8%)
	3	8 (25%)
	4	4 (12.5%)
	5	3 (9.4%)
Reconstruction	Microvascular	29 (90.6%)
	Local	3 (9.4%)
Free flap failure	Yes	7 (24.1%)
	No	22 (75.9%)
Minor complications	Yes	9 (28.1%)
	No	23 (71.9%)
Gastrostomie feeding tube	Yes	20 (62.5%)
	No	12 (37.5%)
Permanent tracheotomy	Yes	14 (43.8%)
	No	18 (56.3%)
R-status	R0	16 (50%)
	R1/Rx	16 (50%)
Pathological risk factors	Yes	5 (15.6%)
	No	27 (84.4%)

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