

## Case Report

# Surgery Following Failure of Repeated Chemotherapy for Squamous Cell Carcinoma of the Tongue can be Fatal and Futile

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## Abstract

**Introduction:** Surgery is the treatment of choice in squamous cell carcinoma of the oral cavity. Nevertheless, some patients seek alternative treatment due to concerns of surgical morbidity. We present two patients who underwent salvage surgery after failure of repeated chemotherapy for squamous cell carcinoma of the tongue.

**Methods:** All patients with squamous cell carcinoma of the oral cavity and who underwent surgery between May 1996 and February 2016 were reviewed through a departmental database. Those who had received prior chemotherapy, not as part of a neoadjuvant regime, were included in this study. Re-staging was performed before salvage surgery, and distant metastases were excluded with appropriate cross-sectional imaging.

**Results:** Two patients initially diagnosed with resectable tongue SCC defaulted surgical treatment and underwent repeated chemotherapy with poor results. They eventually returned for surgical salvage but suffered multiple major complications post-operatively including surgical wound infections, flap failure and fistula formation. They also had prolonged hospitalization at 114 days and 53 days respectively. One patient died from metastatic disease while the other had remnant disease and became lost to follow-up soon after discharge.

**Conclusion:** Tissue changes after chemo radiotherapy add to the difficulty of surgical resection and negatively impact wound healing, thereby putting patients at higher risk of positive margins and surgical complications. Both patients have had lengthy hospital stays and suffered multiple major complications. They may also have been pre-selected for more aggressive tumor biology. Surgical salvage is unlikely to be of benefit and poorer oncological outcomes are expected.

**Keywords:** Tongue cancer; Oral cavity cancer; Head and neck cancer; Squamous cell carcinoma; Salvage surgery; Chemotherapy

## Abbreviations

SCC: Squamous Cell Carcinoma; OSCC: Oral Cavity Squamous Cell Carcinoma; PET: Positron Emission Tomography; RT: Radiotherapy; HDU: High Dependency Unit; ICA: Intermediate Care Area; OS: Overall Survival; DSS: Disease-Specific Survival; UICC: Union for International Cancer Control; AJCC: American Joint Committee on Cancer

## Introduction

Squamous Cell Carcinoma of the Oral Cavity (OSCC) has a strong presence in this part of the world – with the 2012 GLOBOCAN estimates reporting the highest age-standardized rate, with respect to the world population, in the World Health Organization (WHO) South-East Asia region (6.0 per 100,000) [1]. OSCC is known to carry high mortality and morbidity, with various cohorts having described five-year Overall Survival (OS) between 36.1% to 62.5%, and complications rates ranging from 47% to 62% [2-9]. The tongue is the most common subsite in OSCC [10].

Surgery has been established as the treatment of choice in OSCC, with chemotherapy and radiotherapy largely being used in the adjuvant setting for patients with specific risk features, and in the palliative setting for patients with recurrent or unresectable disease [3,10-12]. Multidisciplinary care is imperative for ensuring favorable outcomes. Nevertheless, some patients seek alternative non-surgical treatment in the primary setting due to concerns of surgical morbidity and its impact on essential functions of eating, drinking, chewing, swallowing, and speaking.

While it is understandable that concerns arising from potential surgical morbidity may deter patients from accepting treatment upfront, non-surgical treatment in the primary setting for resectable OSCC has been associated with poorer outcomes [12]. There is little published data on the outcomes of patients who avoid surgery and instead undergo multiple cycles of non-surgical treatment for OSCC.

We present two patients who had Squamous Cell Carcinoma (SCC) of the tongue and were treated with salvage surgery after failure of repeated chemotherapy in conjunction with radiotherapy

**Table 1:** Patient Characteristics.

Case	Age	Gender	First Diagnosed	Follow-up period	UICC Stage				Histology	Treatment
					T	N	M	Over all		
1	54	Male	Mar 2014	Jun2015 -Nov 2015	YpT2	pN2a	cM0	IVA	Poorly differentiated SCC	Chemotherapy, radiotherapy
2	48	Female	Mar 2006	Jun 2009 -Sep 2009	YpT4a	PN3b	cM0		Moderate-poorly differentiated SCC	Chemotherapy, radiotherapy, photodynamic therapy

and photodynamic therapy.

## Methods

This is a retrospective study. All consecutive OSCC patients who were seen at SGH and NCCS between May 1996 and February 2016 were reviewed through a departmental database. Patients were shortlisted for this study if they had undergone surgery after prior chemotherapy. Patients were then excluded if the chemotherapy was administered as part of a neoadjuvant regime. Both patients who were eventually included in this study underwent salvage surgery at the affiliated institutions of Singapore General Hospital (SGH) and National Cancer Centre Singapore (NCCS), where they underwent complete re-evaluation by a tumor board. Both patients had remnant or recurrent disease despite multiple attempts at chemotherapy. Unequivocal his to pathological diagnosis was ensured, re-staging was performed, and distant metastases were excluded with appropriate cross-sectional imaging. Quaternary care is provided at both SGH and NCCS by the SingHealth Duke-NUS Head and Neck Centre, a multi-sited disease-specific service led by a multidisciplinary team. The findings presented in this paper have been reported in line with the PROCESS criteria, and ethical approval from the centralized institutional review board has been obtained [13].

## Case Presentation

### Case 1

This patient is a 54-year-old Chinese male who was first diagnosed with cT4a cN2b cM0 (UICC Stage IVA) tongue SCC, and recommended surgery with adjuvant radiotherapy keep in view chemotherapy. However, he defaulted and sought out an oncologist in private practice. He subsequently underwent three chemotherapy regimes (Table 2) with poor results and returned to NCCS.

On return to NCCS, the patient was found to have persistent disease now complicated by ankyloglossia, moderate-severe oropharyngeal dysphagia and severe dysarthria. He was re-staged as cT4a cN2a cM0 (UICC IVA) and recommended salvage surgery by the tumor board.

The patient underwent total glossectomy, laryngectomy, bilateral neck dissection, and Anterolateral Thigh (ALT) flap reconstruction. Formal histopathology reported poorly differentiated SCC in the anterior tongue with perineural invasion and single left cervical level II lymph node with extranodal extension. Surgical margins were clear. The final staging was ypT2 pN2a cM0 (UICC IVA).

Post-operative recovery was complicated by surgical wound infection with collections requiring drainage, surgical site hemorrhage requiring emergency hemostasis and blood transfusion, and ALT flap infarction with complete thrombosis of the vascular pedicle. Multiple wound debridement had to be performed, with excision of the ALT flap and subsequent bilateral pectoralis major myocutaneous flap

**Table 2:** Prior treatment details.

	No.	Nature of Treatment	Drug Agents	Remarks
Case 1	1	Chemo radiotherapy	Gemcitabine Eribitux Cisplatin	
	2	Chemotherapy	Taxol Carboplatin Eribitux	
	3	Chemotherapy	Gemcitabine Eribitux Cisplatin	Did not complete treatment
Case 2	1	Photodynamic therapy	Unknown	Done in China
	2	Chemo radiotherapy	Cisplatin Thiotepa 5-fluorouracil	Done in China
	3	Chemo radiotherapy	Cisplatin Gemcitabine Cetuximab	
	4	Chemotherapy	Capecitabine Erlotinib	
	5	Chemotherapy	Gemcitabine Tegafur-uracil Nimotuzumab	

reconstruction of the oropharyngeal defects. Eventually, the bilateral pectoralis major flaps also failed, with extensive wound dehiscence and oropharyngocutaneous fistula formation. There were further complications of pseudomonas infection, chronic suppurative otitis media, and hemorrhage.

Pulmonary, cervical and mediastinal lymph node metastases were seen on a CT angiogram that was performed during a hemorrhagic episode. Palliative care was then initiated and the patient passed away from complications of metastatic disease. He spent a total of 114 days in the hospital, with 12 days in the Intermediate Care Area (ICA), 52 days in High Dependency Unit (HDU) and 50 days in the general ward.

### Case 2

This patient is a 48-year-old Malaysian Chinese female who was first diagnosed with cT3 cN0 cMX (UICC Stage III) tongue SCC, and planned for right hemiglossectomy with modified radical neck dissection and possible marginal mandibulectomy. However, she defaulted and sought alternative treatment in both China and Singapore. She underwent photodynamic therapy and repeated chemo radiotherapy (Table 2) before returning to NCCS with worsening pain, dysphagia and speech difficulties.

The patient was re-staged as cT4a cN2c cM0 (UICC Stage IVA) after appropriate cross-sectional imaging and tumor board discussion. She then underwent total glossectomy, arch segmental mandibulectomy, total laryngectomy, left radical neck dissection, right modified radical neck dissection, tracheostomy and reconstruction with left osteomyocutaneous pectoralis major flap for the mandible, right myocutaneous pectoralis major flap for the tongue and split skin graft for the neck. A mandibular plate was contoured and fixed to

**Table 3:** Summary of post-operative events.

Case	Recurrence	Post-operative Complications	Hospitalization Duration			Death	Status
			HDU	ICA	Total		
1	No	Deep wound infection*, wound dehiscence*, hematoma*, CSOM, oropharyngocutaneous fistula*, primary flap failure*, secondary flap failure*	52	12	114	Yes	Deceased
2	Unknown	Hemorrhagic shock*, myocardial infarction*, orocutaneous fistula*, superficial wound infection, wound dehiscence*, urinary tract infection	0	19	53	Unknown	Remnant disease and lost to follow-up

the remnant mandible, and the floor of mouth and buccal cavity was reconstructed with a skin paddle.

Formal histopathology reported moderate to poorly differentiated tongue SCC with involvement of the poster lateral resection margin. The tumor involved the left internal jugular vein, left accessory nerve and was associated with extensive vascular emboli.

Intra-operatively, there was significant blood loss requiring transfusion and this was further complicated by type 2 myocardial infarction. Post-operatively, the patient required inotropic support, and there were other complications including pseudomonas urinary tract infection, surgical wound infection, and orocutaneous fistula formation. Multiple debridement was necessary, and a nasolabial rotation flap and split skin graft were later performed for closure of further defects.

The patient was eventually discharged after a total duration of 53 days in hospital, out of which 19 days were spent in the ICA. Final staging was  $\gamma pT4a$   $pN3b$   $cM0$  (UICC Stage IVB), and the tumor board recommended close observation in view of remnant disease. Unfortunately, she became lost to follow-up soon after discharge (Table 3).

## Discussion

The five-year Disease-Specific Survival (DSS) and five-year OS in tongue SCC have been reported to be 78% and 64% respectively [13]. The same study also reported rates of local only recurrence, regional only recurrence, and combined locoregional recurrence at 6%, 8% and 3% respectively. The overall risk of developing any non-distant recurrence within 5 years is approximately 16%. Unfortunately, owing to the unique nature of patients and small sample size in this study, we do not have sufficient data to make meaningful comparisons with the above historical series.

Of particular interest, however, were the subset analysis results of a randomized controlled trial showing superior survival in OSCC patients treated with primary surgery versus those treated with concurrent chemo radiotherapy [12]. The five-year DSS was 68% in the surgery arm versus 12% in the chemo radiotherapy arm. The risk of distant metastases was also lower in the surgery arm with distant recurrence-free survival of 92% compared to 50% in the chemo radiotherapy arm. These findings were specific to UICC stages III and IV OSCC, and similar trends were not observed in other head and neck cancer subsites. It clearly establishes primary surgery as the treatment of choice in resectable OSCC.

Salvage surgery has also been associated with significantly higher complication rates, as reported by a multiple studies [14-16]. A retrospective analysis conducted at the Cleveland Clinic demonstrated an overall complication rate of 60% in patients who underwent

salvage surgery, as compared to 31% in those who underwent planned surgery after neoadjuvant therapy [17]. The major complication rate of 20% in the salvage surgery group was also significantly higher than that of 3.4% in the planned surgery group. The increased risk of complications has largely been attributed to tissue changes such as fibrosis, edema and increased friability. These tissue changes add to the difficulty of surgical resection and negatively impact wound healing, which may explain the multiple severe complications that the two patients in this study suffered [14-16,18,19]. At the same time, there remains significant risk of incomplete oncological resection, with reports of positive margins in up to 41% of patients after salvage surgery [20-23].

Most OSCC patients do not require prolonged hospitalization following surgery. One study analyzing a retrospective cohort of 408 patients in an American College of Surgeons database reported median and mean hospital stay durations of 3.0 and 4.8 days respectively [24]. Naturally, it was found that patients who experienced adverse events had significantly longer hospital stays. The same study reported an overall adverse event rate of 20.3% with neck dissection being a strongly associated factor. Both patients in this study underwent neck dissections which had already put them at higher risk of adverse events and longer hospital stays. The occurrence of complications would also hinder recovery and contribute to poorer outcomes.

In addition, the combination of both local and regional treatment failure in these two patients may have contributed to the poor outcomes. A large stratified analysis of head and neck cancer patients who underwent salvage surgery at the Institute Gustave Roussy showed that patients with both local and regional treatment failure had poorer survival compared to those who had either local or regional failure only [22]. The median survival for former group was 13.3 months, which compares poorly to 36.3 months in the latter group. Initial stage IV was also identified as a significant predictor of poor survival. Therefore, patients should undergo the best definitive treatment upfront, and that comprises primary surgery in the context of OSCC. Less-than-optimal treatment results in greater risk of disease progression, which forebodes poorer outcomes even with surgical salvage.

## Conclusion

Both patients in this study have had lengthy hospital stays and suffered multiple major complications. Case 1 died from metastatic disease while case 2 had remnant disease. Chemotherapy in the primary setting is not the standard of care in OSCC, and salvage surgery following failure of repeated chemotherapy can be futile and fraught with danger even at a high volume centre. These patients may have been pre-selected for more aggressive tumor biology, and are at greater risk of positive margins, poor healing and major complications. Surgical salvage is unlikely to be of benefit and poorer

oncological outcomes are expected. A multi-centre study pooling together a larger experience from different institutions may better prove this point.

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