

Survival Outcomes and Prognostic Factors in Oral Squamous Cell Carcinoma with Locoregional Recurrence: A Retrospective Analysis

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ABSTRACT

Introduction: Recurrence is known to occur in approximately 25% to 45% of patients treated for oral cancer. It is the most common cause of treatment failure in Oral Squamous Cell Carcinoma (OSCC), which adversely affects survival. Although recurrences in the oral cavity may be detected early, survival rates remain low.

Aim: To identify the survival outcomes and prognostic factors in OSCC with locoregional recurrence.

Materials and Methods: This retrospective study was conducted at the Malabar Cancer Centre between November 2020 to March 2021, analysing patients who were treated with curative intent between January 1997 and December 2017. It included 118 patients with OSCC who experienced recurrence-local, regional, or both-after curative treatment. Demographic variables, clinical variables, and follow-up details were analysed. Characteristics of the primary tumour, including nodal metastasis, stage, Extranodal Extension (ENE), Perineural Invasion (PNI), the extent of treatment, adjuvant therapy, and days to recurrence, were recorded. For the recurrent tumour, site, time to recurrence, and type of treatment received were noted additionally. Overall Survival (OS) was defined from the date of initial diagnosis, while the date of recurrence was determined by pathological confirmation. Statistical analysis was performed using SPSS software, version 20. All significant variables ($p < 0.05$) were then tested in a multivariate analysis using Cox regression methods. Disease-specific Survival (DSS) and OS were analysed using the Kaplan-Meier method.

Results: A total of 146 patients with OSCC (15.01%) experienced a recurrence-local, regional, or both-upon analysis of 973 OSCC patients who underwent primary curative intent surgery. One hundred eighteen patients were included in the final analysis. Salvage surgery was performed on 65 (55.08%) patients. Thirty-eight patients (32.3%) who presented with early-stage disease initially developed a recurrence, whereas recurrences were more common among patients with advanced-stage disease, accounting for 80 (67.7%) cases. The median age of patients with recurrence was 60 years, with a median follow-up period of 46 months. The median OS time for patients with recurrence was 34 months ranging from 26.343 to 42.457 months. Univariate analysis revealed that nodal stage, salvage surgery, and time to recurrence were significant factors affecting OS. On multivariate analysis, salvage surgery and time to recurrence remained significant factors impacting survival.

Conclusion: Salvage surgery and time to recurrence were identified as significant prognostic factors affecting survival outcomes in patients with OSCC experiencing locoregional recurrence. Salvage surgery significantly improves survival in oral cancer, where recurrence is usually detected more easily unlike other subsites. Patients with late recurrences demonstrated better survival outcomes. Tumours that recur early indicated poor oncological outcomes, suggesting an aggressive nature. Tumor biology is essential in guiding treatment options in recurrent settings.

Keywords: Nodal metastases, Relapse, Salvage surgery

INTRODUCTION

Head and neck cancers remain a significant burden in developing countries, with GLOBOCAN 2020 ranking lip and oral cavity cancers as the most common among men in India, and second for both sexes combined [1]. Among head and neck cancers, those of the lip and oral cavity lead in incidence (16.1%) and mortality (12.3%) in males [2]. Squamous Cell Carcinoma (SCC) is the most prevalent histological type, accounting for 90% of all oral cavity cancers [2]. Oral cavity cancer is the most common cancer in Indian males, making up 35% of total cases, and the third most common in Indian females, with 18% of total patients [2].

The OS of oral carcinoma has improved over recent decades, thanks to the judicious choice of surgical extent, understanding of tumour biology, and the employment of adjuvant postoperative radiotherapy and chemoradiotherapy [3]. Recurrences are known to occur in approximately 25% to 45% of patients treated for oral cancer [4]. Recurrence is the most common cause of treatment failure in OSCC, which in turn adversely affects survival [5]. Although

recurrences in the oral cavity may be detected early, survival rates are lower than those observed for patients with laryngeal SCCs. Recurrences in the oral cavity are reported to be equally likely to occur at local, locoregional, and regional sites [6].

Salvage treatment may be considered for patients with locoregional recurrence, but the decision must be weighed against the associated morbidity. Salvage surgery has shown significantly better outcomes than salvage radiotherapy/chemoradiotherapy for late relapsed oral cancers, compared to those that relapsed early [6]. Salvage surgery cure rates range from 15% to 67% [7]. It is crucial to identify the most important patient and tumour factors that can predict reasonable outcome expectations, considering the functional and cosmetic morbidity imposed by salvage surgery. The literature review showed limited data from the Indian subcontinent analysing the outcomes of patients with locoregional recurrences in OSCC without distant metastasis. Therefore, this study was designed to evaluate the survival outcomes of patients with OSCC who developed locoregional recurrences. It also aimed to identify prognostic factors predicting

favourable survival outcomes that could help oncologists identify which patients may benefit from intensified treatment.

MATERIALS AND METHODS

This retrospective observational study was conducted at the Malabar Cancer Centre, Kerala, India, between November 2020 and March 2021. The medical records of 973 patients with OSCC who underwent primary curative intent surgery from January 1997 to December 2017 were evaluated.

Information was collected using a case proforma from the patient records registered at the Malabar Cancer Centre through the medical records library, after obtaining permission from the Institutional Review Board (IRB No: 0632).

Inclusion criteria: Patients identified with OSCC recurrence, either local, regional, or both, were included in the study.

Exclusion criteria: Those patients with distant metastasis, those who underwent incomplete treatment elsewhere, those with a history of neoadjuvant chemotherapy for the primary tumour, and patients who received best supportive care for the recurrence due to performance status were excluded from the study.

Recurrence was defined inversely, representing a modification of the definition given by Warren and Gates [8]. A total of 146 patients with OSCC recurrence were identified, of which 118 were included in the final analysis.

Procedure

Demographic variables, clinical variables, and follow-up details were analysed. All patients were staged according to the American Joint Committee on Cancer (AJCC) staging, seventh edition [9].

The characteristics of the primary tumour included pathological T stage, pathological nodal status, stage, ENE, PNI, adjuvant therapy, and time to recurrence. For the recurrent tumour, parameters similar to those of the primary tumour, including time to recurrence and treatment received, were noted. OS was defined from the date of diagnosis. The date of recurrence was established as the date of confirmation by pathological test. The status of the patient at the time of the last follow-up was recorded as per the case sheet, except for those with a follow-up date more than three months prior, who were contacted by phone.

STATISTICAL ANALYSIS

The data were entered into the EpiData entry software and validated by the principal and co-investigators. Statistical analysis was performed using SPSS Statistics software, version 20.0. Variables for univariate analysis were selected based on their clinical relevance and on what has been described in the literature. Univariate analysis was conducted using the chi-square test. All significant variables ($p < 0.05$) were subsequently tested using multivariate analysis with Cox regression methods. DSS and OS survival were analysed using the Kaplan-Meier method.

RESULTS

Among the patients diagnosed with OSCC who received treatment with curative intent, 146 (15.01%) were identified with recurrence-local, regional, or locoregional. Of these, 15 patients were lost to follow-up. Thirteen patients who were given best supportive care were excluded from the analysis.

One hundred eighteen patients were included in the final analysis. Salvage surgery was performed on 65 (44.5%) patients. Five patients received salvage radiotherapy. Forty-eight patients underwent palliative radiotherapy followed by low-dose oral metronomic chemotherapy.

The cohort consisted of 84 (70%) male patients, as shown in [Table/Fig-1]. The pathological tumour stage T4 was the most common, observed in 37 (30.8%) patients, followed by the T2 stage in 35 (29.6%). Pathological node positivity was seen in 47 (56%)

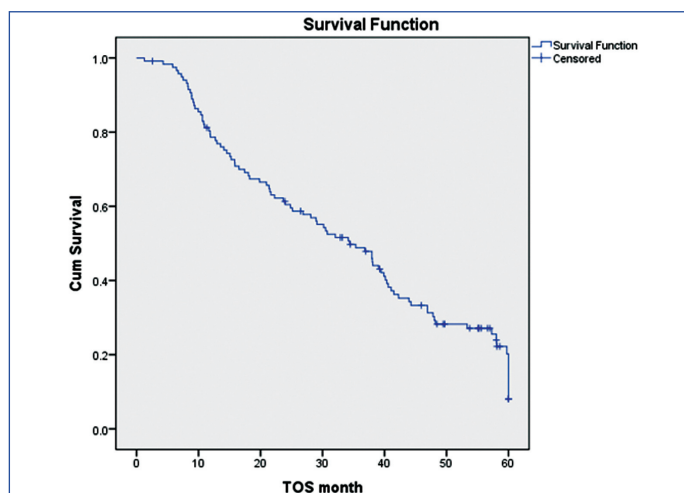
patients. Thirty-eight (32.3%) patients initially presented with early-stage disease and developed recurrence, while a larger number, 80 (67.7%), had advanced disease at recurrence. Eighteen (15.7%) patients with ENE on the final histopathology report developed recurrence, and perineural invasion was noted in 28 (24.7%) patients. Seventy-six patients received adjuvant therapy, with 16 undergoing chemoradiotherapy as adjuvant. Ten patients did not receive adjuvant therapy, although it was indicated, whereas it was not indicated for 32 patients with early-stage disease. Sixty-five (44.5%) patients underwent salvage surgery for recurrence, while 53 (36.3%) received other cancer-related treatments. Fifty-nine (50%) patients who had early recurrence (within one year), with an equal number having late recurrence.

Clinico pathological details		(N=118)	Percentage
Sex	Male	84	70
	Female	34	30
Pathologic tumour stage	T1	31	25.8
	T2	35	29.6
	T3	13	10.8
	T4	37	30.8
Pathological nodal status	N0	62	52.5
	N+	56	47.5
Stage	Early	38	32.2
	Advanced	80	67.7
ENE	Present	18	15.25
	Absent	100	84.7
PNI	Present	28	24.2
	Absent	90	75.8
Adjuvant therapy	Received	76	63.3
	Not received	42	36.6
Treatment received	Salvage surgery	65	44.5
	Others*	53	36.3
Time to recurrence	Early (<1 year)	59	50.0
	Late (>1 year)	59	50.0

[Table/Fig-1]: Clinicopathological details of the patients with recurrent Oral Squamous Cell Carcinoma (OSCC).

*Others included those who received alternative treatment in the form of chemotherapy or radiotherapy; PNI: Perineural invasion; ENE: Extranodal extension

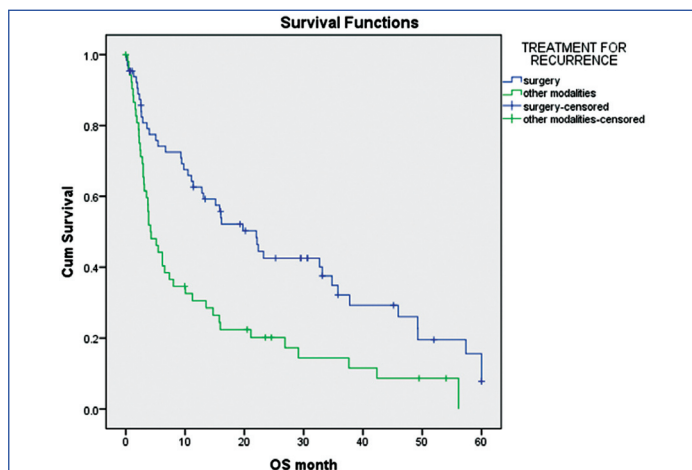
Patients with recurrence had a median age of 60 and a median follow-up of 46 months. The median OS time for these patients was 34 months, ranging from 26.343 to 42.457, as shown in [Table/Fig-2].



[Table/Fig-2]: Overall Survival (OS) for the patients with Recurrent OSCC-34 months (OS in months plotted in X axis, survival percentages in Y axis).

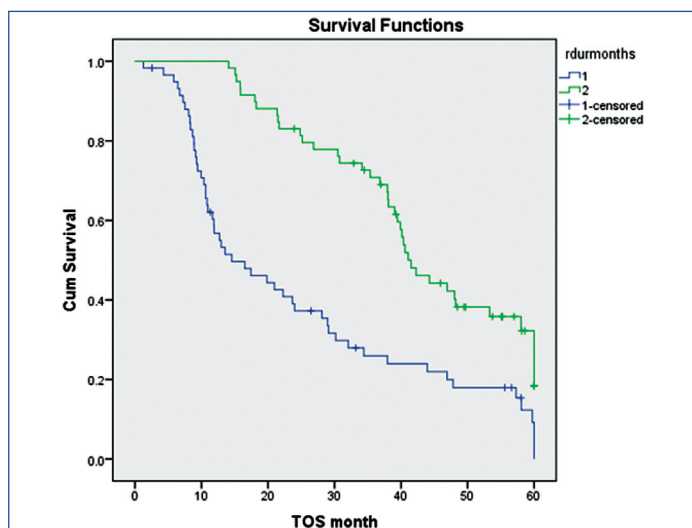
Univariate analysis revealed that nodal stage, salvage surgery, and time to recurrence were significant factors affecting OS. Patients who underwent salvage surgery had a significantly better OS (40.6 months)

compared to those who received other modalities (24 months) ($p=0.001$), as shown in [Table/Fig-3].



[Table/Fig-3]: Overall Survival (OS) for the patients who underwent salvage surgery (blue line) significantly better than those who received other modalities (green line). (OS in months plotted in X axis, survival percentages in Y axis).

Patients with late recurrence (41.07 months) had significantly better OS ($p<0.001$) compared to those with early recurrence (14.57 months), as indicated in [Table/Fig-4]. Multivariate analysis identified salvage surgery and time to recurrence as significant factors affecting survival, as shown in [Table/Fig-5].



[Table/Fig-4]: Overall Survival (OS) for the patients who had early recurrence (blue line) was significantly worse than those who recurred late (green line). (X axis represents OS in months, survival percentages in Y axis).

	p-value	HR	95.0% CI	
			Lower	Upper
Stage	0.428	0.842	0.550	1.288
PN	0.096	1.403	0.942	2.089
PT	0.081	1.273	0.971	1.670
PNI	0.650	0.879	0.503	1.535
Grade	0.111	1.413	0.924	2.161
Adjuvant	0.735	0.986	0.909	1.069
Salvage surgery	0.04	0.492	0.303	0.765
Time to recurrence	0.002	0.434	0.282	0.668

[Table/Fig-5]: Summary of multivariate analysis showing salvage surgery and duration to recurrence significant effect on Overall Survival (OS). Bold p-values are significant

Salvage surgery was associated with a reduced risk of death, with a hazard ratio of 0.492 (CI: 0.303-0.765) and a p-value of 0.04. Similarly, patients with early recurrence had significantly poorer survival outcomes, as demonstrated in [Table/Fig-5], with a hazard ratio of 0.434 (CI: 0.282-0.668) and a p-value of 0.002.

DISCUSSION

Despite advances in surgery in terms of function and reconstruction and multimodality treatment for advanced cases, the chances of locoregional recurrence remain significant in head and neck cancer. The locoregional recurrence rate for OSCC of 15% in the present study was similar to the range described in the literature following primary treatment [4]. The duration to recurrence and the availability of salvage surgery were found to be key prognostic factors affecting the survival outcomes of patients with locoregionally recurrent OSCC.

Differences in biological aggressiveness, barriers to spread, and lymphatic drainage pathways have been attributed to the poor survival outcomes in oral cavity recurrences [6]. A higher number of oral cavity failures occur at distant sites, whereas the incidence is found to be similar in terms of local, locoregional, and regional sites [6].

Kernohan MD et al., did a retrospective analysis of 77 patients with recurrent OSCC from 1988 to 2006. The overall DSS for the surgical salvage group was 50% at five years. Initial treatments involving more than one modality (surgery and radiotherapy) and shorter times to recurrence were associated with worse outcomes. The hazard ratio associated with the site of recurrence (primary site and neck) and time to recurrence was found to be dynamic due to the interaction between both factors. Early recurrences (<6 months) were associated with the worst outcomes when associated with primary site recurrences, and vice versa [10].

Matsuura D et al., did a retrospective study of 46 patients with relapsed OSCC among those treated for primary oral cancer from 2009 to 2017. Positive surgical margins and the presence of lymph node metastasis affected the OS rate and Disease-Free Survival (DFS). The OS rate for surgically salvaged patients with no further relapse (19) was found to be similar to that of patients with previously untreated cancers (199), showing 54.7% versus 70.7% ($p=0.158$, log-rank test) [4]. This study's results were similar to those of a larger cohort.

Tam S et al., analysed 59 patients (20%) with recurrence of OSCC from 1999 to 2011, of whom 39 underwent surgical salvage. They identified adjuvant therapy after the first surgery and age under 62 as the most important negative prognostic factors. The five-year OS for patients who underwent surgery followed by adjuvant therapy as initial treatment was 10%, versus 54% for those who did not receive adjuvant treatment [8]. Age and adjuvant therapy were not found to be significant on univariate analysis in the current study.

Liao CT et al., conducted a retrospective review of 212 patients with relapsed OSCC from 1996 to 2005. A total of 134 patients underwent salvage surgery (65 with early relapse and 69 with late relapse). Late relapse was associated with better survival than a relapse occurring within the first 10 months. Patients with late-relapsed OSCC may benefit from salvage therapy, especially those with local recurrence. The five-year DSS rate was 53.5% for late relapse versus 13.8% for early relapse [11]. This was similar to the findings in the present study.

Accordingly, early-onset relapse is associated with a poor prognosis, indicating the tumour's biology and aggressiveness. In the study by Liao CT et al., patients with late-relapsed OSCC who were salvaged with surgery had significantly better outcomes compared with those salvaged with RT/CCRT [11].

Schwartz GJ et al., analysed 99 patients with recurrent OSCC treated between 1956 and 1992, of whom 38 underwent salvage surgery. Twenty-seven patients underwent salvage surgery, and the overall salvage cure rate was 21%. The group of patients who underwent salvage surgery approached a statistically significant improvement in cure rate ($p=0.08$) [7].

Consistent with the literature, salvage surgery offered to the patients analysed in this study leads to a substantial improvement in OS in oral cancer recurrence, similar to outcomes seen in other head and neck surgery subsites [12]. Goto M et al., reviewed 69 patients

with recurrent Oral Tongue Squamous Cell Carcinoma (OTSCC) who underwent salvage surgery to identify prognostic factors and outcomes. Univariate analysis indicated that survival was significantly worse in patients with recurrent stage III or IV tumours, two or more positive cervical lymph nodes, levels IV or V positive cervical lymph nodes, Extracapsular Spread (ECS) of positive cervical lymph nodes, and a disease-free interval from initial treatment of less than 12 months. On multivariate analysis, ECS was an independent prognostic factor for OS after salvage surgery. In all, 36 patients (52%) developed a second recurrence or died, of which 21 (58%) occurred within 12 months of salvage surgery [13]. The subset of patients with extracapsular extension in the present study may have shown an improvement in survival owing to the adjuvant concurrent chemoradiotherapy protocol.

For patients with resectable recurrence and favourable performance status, surgery offers the best chance of achieving Locoregional Control (LRC) and prolonged survival [6]. The current study also concurs with the authors' observation that significant selection bias unavoidably occurs against chemoradiation salvage arms: These non-surgery cohorts typically comprise advanced-stage or poor surgical candidates who are expected to have worse outcomes, regardless of treatment modalities, and a judicious interpretation of results is required when compared against one another [6]. The same results shown in this study owe to the multi-disciplinary consensus, as only those patients with resectable tumours and good performance status end up in the salvage arm.

Although salvage surgery is the best option available for surgically fit patients, it must be weighed against the functional consequences and quality of life outcomes. The combination of treatment toxicity and patients' co-morbidities leads to a higher rate of postoperative complications. These side effects must be balanced against the chances of cure so that the most suitable candidates may be offered surgical salvage. In view of all these factors, it is essential that multidisciplinary teams involved in the management of these patients establish criteria based on functional and oncological outcomes to select the best candidates for salvage surgery [14].

Limitation(s)

The limitations of the present study include its retrospective nature and the fact that it is based on single-center data. Salvage surgery cannot be directly compared with other modalities, as the other group comprises more cases of advanced disease and inoperable cases.

Additionally, the present study is limited by the lack of available data on surgical morbidity and quality of life outcomes in salvage settings.

CONCLUSION(S)

In the present study, locoregional recurrence in OSCC was found to have unfavourable outcomes on OS. The study identified salvage

surgery and time to recurrence as significant prognostic factors predicting survival outcomes in patients with OSCC experiencing locoregional recurrence. Patients who underwent salvage surgery had better OS compared to those who received other treatment modalities. This difference could be attributed to the fact that patients with advanced-stage disease and poor performance status were not considered for surgical salvage. Time to recurrence was identified as a prognostic factor, aiding clinicians in the judicious selection of patients for salvage surgery. Patients with early recurrences had significantly poorer survival outcomes compared to those with late recurrences. This information could assist in deciding the intent and treatment modality in recurrent settings, taking into account the morbidity of the procedure. The tumours with early recurrences are biologically aggressive with the potential for relapse and poor survival outcomes, where salvage options must be chosen judiciously, balancing their impact on quality of life.

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