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Original Research Article

Survival and clinical outcomes of salvage surgery in recurrent oral cavity cancer: a single institutional experience

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ABSTRACT

Background: Oral cavity is the most common site of head and neck squamous cell carcinoma in India with more than 70% presenting in locally advanced stage. Recurrence in all stages of OCSCC occurs in up to 50% of patients, with most failures being local and/or regional relapses. The present study was done to analyze clinical outcomes of patients undergoing salvage surgery (SS) following recurrent OCSCC.
Methods: A retrospective analysis of prospectively collected data of 82 patients with recurrent OCSCC was done in the department of head and neck surgery.
Results: At the end of 1 year post SS for OCSCC 62 out of 82 (75.6%) patients were alive without disease. At the end of 2 year after SS 22 out of 45 patients were alive of which 21 were alive without disease and 1 was alive with disease (48.8%). At the end of 3 years, 10 out of 25 of which 9 were alive without disease and 1 patient was alive with disease (40%). Median disease-free survival (DFS) post SS was 13.50 months (0-47 months). DFS and overall survival (OS) post SS showed significantly better results in patients treated with surgery along with RT as primary treatment, patients with late recurrence, patients with early recurrent T stage, patients with free margins at SS and in patients who received adjuvant radiation therapy post SS.
Conclusions: Salvage Surgery is one of the best treatment options for recurrent OCSCC with acceptable survival rates.

Keywords: Salvage Surgery, Recurrent oral cancer, Survival outcomes

INTRODUCTION

Oral cavity squamous cell carcinoma is the most common cancer in India, with an estimated 135929 new cases and 75290 deaths per year.[1] It is the most common cancer in males with more than 70 percent presenting in locally advanced stage.[2] Recurrence in all stages of OCSCC occurs in up to 50% of patients, with most failures being local and/or regional relapses. Survival outcome in these patients decrease with increasing stage of the disease.[3] Surgical salvage represents the primary treatment option when recurrent disease is resectable and patient has good performance status. In literature, SS has shown better survival outcomes compared to chemo-radiation when treated with curative intent.[2] The prognosis of patients with recurrent disease depends mainly on disease free interval, subsite involved, stage at recurrence and performance status. The objectives of the study is to analyze survival and clinical outcomes of patients undergoing SS following local and/or regional recurrence of OCSCC by estimating: 1-year OS post SS as measured from time of SS of recurrent disease until the last known

follow up visit or death (any cause). DFS measured from the time of SS until the last known failure.

METHODS

A retrospective analysis was done in the department of head and neck surgery of a tertiary care cancer hospital. 82 patients with recurrent OCSCC operated from January 2016 to June 2020 were enrolled in the study. This study was approved by the institutional review board (IRB), and all participants signed an informed consent agreement. Patient demographics, staging, pathologic data, treatment details and other variables were obtained from hospital database. The study group consisted of 69 male and 13 female patients. The age ranged from 24 to 74 years with mean age of 50 yrs. Distribution of various subsites of the primary tumor was buccal mucosa 46, tongue 25, ginigivobuccal complex 9, lower lip 2 patients.

In this study, we defined treatment given after first diagnosis as primary treatment and staging as initial T and N stage. All patients were staged according to the 2018 American joint committee on cancer (AJCC) TNM staging system (8th Edition). After first surgery the tumors were classified as T1 in 19, T2 in 36, T3 in 12 and T4a in 15 patients with N staging as Nx in 8 patients, N0 48 patients, N1 18 patients, N2b 7 patients and N3b 1 patient (pathological staging). The primary treatment consisted of surgery alone in 33 patients, surgery and radiotherapy in 21 patients, surgery and CTRT in 24 patients and radical CTRT in 4 patients. Median DFS was 34.50 months.

The presence of recurrent disease was ascertained in all patients radiologically by either PETCT or CECT and pathologically by biopsy. Local recurrence was found in 69 patients, regional (nodal) in 6 patients and locoregional in 7 patients. On surgical salvage primary site was addressed in 10 patients, primary and neck in 66 and only neck 6 in patients. Out of 72-neck dissection, ipsilateral neck was addressed in 26, contralateral in 33, bilateral in 13 patients. The defect post SS was reconstructed with pedicled flaps in 45 patients (43 were pectoralis major myocutaneous flap (PMMC), PMMC and deltopectorial flap in 2 patients) and microvascular free flaps in 7 patients (4 anterolateral thigh flap, 2 free radial artery forearm flap, 1 free fibula osteomyocutaneous flap). In 13 patients' defect was reconstructed with split thickness skin graft and primary closure in 10 patients. The pathological T stage after SS was Tx in 6, T1 in 5, T2 in 20, T3 in 16, T4 in 35 patients with N stage Nx: 11, N0: 47, N1: 3, N2a-2, N2b-3, N2c-4 and N3 in 12 patients. 3 patients received NACT before SS. Histopathological reports post SS were evaluated showing free margin in 60 and involved in 16 patients. 20 patients were treated by surgery alone, post-operative adjuvant therapy was given in 57 patients with PORT in 20, CTRT in 35 and chemotherapy in 2 patients (as reirradiation was not possible, decision of institutional MDT). Five patients refused adjuvant treatment post SS.

Post SS failure was seen in 23 patients in form of 7 local recurrence, 11 nodal, 1 locoregional recurrence, skin nodule in 1 patient and distant metastasis in 3 patients. Mean disease free interval post SS was 13.5 months.

Patients were followed up in the clinic or telephonically. 62 patients were alive and 20 patients died at the end of 1 year after SS. In final follow up of all patients, 38 were Alive (33 alive without disease, 5 alive with disease and on palliative CT) and 44 Death (4 deaths not due to disease). Patient characteristics are shown in Table 1.

Table 1: Patient characteristics.

Parameters	N
Site	
Buccal mucosa	46
Tongue	25
Lower alveolus	4
Lower or upper GBS	5
Lower lip	2
Site addressed	
Local	10
Nodal	6
Both	66
Neck addressed	
Ipsilateral	26
Contralateral	33
Bilateral	13
Margin status	
Free	60
Involved	16
Reconstruction post SS	
PMMC	43
PMMC + DP	2
Free flaps	7
STSG	13
Primary closure	10
Failure (recurrence) post SS	
Local recurrence	7
Nodal recurrence	11
Local+ nodal	1
Skin nodule	1
Distant metastasis	3
Status post SS	
Alive without disease	33
Alive with disease	5
Death due to disease	40
Death not due to disease	4

Statistical analysis

Kaplan Meier statical analysis was used to determine the survival and clinical outcome of patients. DFS was measured from date of SS until the last known failure. OS was measured from date of SS until last follow up date/

death. Disease free interval as taken from date of primary treatment till date of confirmed recurrence. IBM SPSS statistics version 23.0 was used for analysis. Cox proportional hazard and regression models were used for the multivariate analysis.

RESULTS

At the end of 1 year post SS for OCSCC 62 out of 82 (75.6%) patients were alive without disease and 20 patients died due to disease. At the end of 2 year after SS 22 out of 45 patients were alive of which 21 were alive without disease and 1 was alive with disease (48.8%), 22 patients died due to disease and 1 patient died due to other cause. At the end of 3 years 10 out of 25 (40%) patients were alive (9 were alive without disease and 1 patient was alive with disease) and 15 patients died due to disease and is shown in Table 2. The Median OS post SS was 16.50 months (0-47 months). Post SS, 23 patients developed recurrence.

Various clinico-pathological factors were evaluated to determine prognosis and outcomes post SS. Effect of disease-free interval across various cutoff points on OS was analyzed and we found that cut off point at 2 years had significant effect on OS and is shown in Table 3. Hence, disease free interval was divided into 2 groups, early recurrence (≤2 years) and late recurrence (>2 years). The late recurrence group showed significantly increased OS post SS.

Univariate analysis of OS at the end of 1 year post SS showed significantly better results in patients treated with surgery followed by PORT as primary treatment (p=0.023, surgery alone 78.8%, surgery + RT 81%, surgery + CTRT 75%), patients with late recurrence (p=0.010, early recurrence: 64.3%, late recurrence: 87.5%), patients with early recurrent T stage (p=0.012 on univariate analysis; T1 80%, T2:95%, T3 68.8, T4 74.3%), patients with free margins at SS (p=0.006, free margins 81.7%, involved margins 68.8%) and in patients who received adjuvant radiation therapy post SS (p=0.033, surgery alone 60%, surgery + RT 90%, surgery + CTRT 82.9%, surgery + CT 50%). Multivariate analysis at the end of 1 year post SS showed late recurrence (p=0.028) was significantly associated with better OS as shown in Table 4 and 5.

Median DFS post SS was 13.50 months (0-47 months). On univariate analysis failure post SS was significantly associated with primary treatment modality (p=0.008, surgery alone: 54.5%, surgery + RT: 47.6%, surgery + CTRT: 37.5%), disease free interval (p=0.015, early recurrence: 28.6%, late recurrence: 62.5%), recurrent T (p=0.000, T1: 80%, T2: 70%, T3: 31.3%, T4: 37.1%) and N stage (p=0.005, N0: 57.4%, N1: 33.3%, N2: 22.2%, N3: 16.7%), margin status (p=0.000, free margins: 53.3%, involved margins: 25%) and adjuvant treatment taken post SS (p=0.007, surgery alone: 45%, surgery+ RT: 75%, Surgery + CTRT: 34.3%, surgery + CT: 0%). On multivariate analysis early disease-free interval (p=0.019) was independently associated with worse DFS post SS as shown in Table 4 and 5.

Table 2: Year wise follow up of patients post salvage surgery.

Follow up post SS	N	Alive without disease	Alive with disease	Died due to disease	Died due to other causes
1 year	82	62	0	20	0
2 years	45	21	1	22	1
3 years	25	9	1	15	0

Table 3: Effect of disease-free interval across various cutoff points on OS.

DFS (in months)	N	OS	DFS (in years)	N	OS	DFS (in years)	N	OS
0-6	3	0.0%	0	10	0.0%	≤2 (early recurrence)	42	23.80%
13-18	5	0.0%	1	14	21.4%	>2 (late recurrence)	40	70%
19-24	9	22.2%	2	18	38.9%			
25-30	2	100.0%	3	11	72.7%			
31-36	16	37.5%	4	10	60.0%			
37-42	8	75.0%	5	9	77.8%			
43-48	2	100.0%	6	1	100.0%			
49-54	5	60.0%	7	6	50.0%			
55-60	6	66.7%	9	1	100.0%			
61-66	4	100.0%	10	1	100.0%			
67-72	3	33.3%	11	1	100.0%			
7-12	9	11.1%						
73-78	1	100.0%						
>80	9	66.7%						

Table 4: Statistical analysis of various clinicopathological factors (Initial treatment) influencing 1 year OS and DFS post salvage surgery.

Parameters	No. of cases	1 year OS post SS (in months), % (n)	DFS post SS, % (n)	P value (univariate)		P value (multivariate)		HR 1 year OS post SS
				1 year OS post SS	DFS post SS	1 year OS post SS	DFS post SS	
Age (in years)								
<55	53	69.8 (33.61)	41.5 (22.43)	0.134	0.159	0.167	0.106	0.353
≥55	29	86.2 (41.24)	51.7 (29.33)					
Initial T stage								
T1	19	78.9 (30.79)	63.2 (25.57)	0.913	0.114	0.639	0.291	2.628
T2	36	72.2 (31.34)	33.3 (17.65)					
T3	12	75.0 (37.25)	33.3 (26.22)					
T4	15	80.0 (37.27)	60.0 (30.99)					
Initial N stage								
Nx	8	100.00	75.00 (26.50)	0.385	0.543	0.962	0.477	14.590
N0	48	72.90	43.8 (22.69)					
N1	18	77.80	44.4 (28.11)					
N2	7	57.10	28.6 (18.07)					
N3	1	100.00	0.0 (25.00)					
Initial treatment								
Surgery alone	33	78.8 (33.87)	54.5 (23.18)	0.023	0.008	0.717	0.363	2.364
Adjuvant RT	21	81.0 (39.43)	47.6 (27.58)					
Adjuvant CTRT	24	75.0 (35.35)	37.5 (24.85)					
Time of recurrence (in years)								
Early ≤2	42	64.3 (32.45)	28.6 (20.69)	0.010	0.015	0.028	0.019	2.053
Late >2	40	87.5 (40.33)	62.5 (29.97)					

Table 5: Statistical analysis of various clinicopathological factors (Post SS) influencing 1 year OS and DFS post salvage surgery.

Parameters	N	1 year OS post SS (in months), % (n)	DFS post SS, % (n)	P value (univariate)		P value (multivariate)		HR 1 year OS post SS
				1 year OS post SS	DFS post SS	1 year OS post SS	DFS post SS	
Recurrent T stage								
Tx	6	33.3 (9.00)	16.7 (6.67)	0.012	0.000	0.430	0.288	1.326
T1	5	80.0 (37.60)	80.0 (37.00)					
T2	20	95.0 (44.95)	70.0 (37.52)					
T3	16	68.8 (27.56)	31.3 (18.02)					
T4	35	74.3 (35.01)	37.1 (20.79)					
Recurrent N stage								
Nx	11	90.90	45.5 (22.42)	0.061	0.005	0.987	0.388	1.705
N0	47	80.90	57.4 (30.53)					
N1	3	100.00	33.3 (17.33)					
N2	9	55.60	22.2 (14.56)					
N3	12	50.00	16.7 (10.75)					
Margin status								
Free	60	81.7 (33.33)	53.3 (29.52)	0.006	0.000	0.428	0.114	0.547
Involved	16	68.8 (22.09)	25.0 (12.11)					
Na	6	33.3 (9.00)	16.7 (25.27)					
Salvage treatment								
Surgery alone	20	60.0 (30.45)	45.0 (25.06)	0.033	0.007	0.162	0.074	0.667
Surgery + RT	20	90.0 (41.35)	75.0 (36.31)					
Surgery + CT	2	50.0 (16.50)	0.0 (10.50)					
Surgery + CTRT	35	82.9 (38.56)	34.3 (20.34)					
Surgery (defaulted CTRT)	5	40.0 (11.80)	20.0 (8.80)					

DISCUSSION

Garcia in his meta-analysis of 1,692 oral cancer patients showed a mean local recurrence rate of 47.3%, regional recurrence rate of 35.1%, and loco-regional recurrence rate of 10.9.[4] Locoregional recurrence remains the most frequent cause of failure in patients treated with SCC of the oral cavity and the incidence depends primarily on the site of the tumor, clinical stage, and histo-pathological characteristics.[2] SS remains the primary treatment option

when recurrent disease is resectable and the patient has good performance status. However, extensive surgery is frequently required which may be associated with permanent functional loss, cosmetic deformities, high rate of complications, and even mortality.[5] Hence, various clinicopathological factors need to be identified for successful SS.

The 3-year OS in our study is 36% with the literature reporting between 30-50%. In present study, OS post SS was significantly associated with factors such as primary treatment with surgery + radiotherapy, late recurrence, early recurrent T stage, free margins, and adjuvant treatment taken after SS on univariate analysis. In multivariate analysis, the time interval to recurrence (early recurrence) was independently associated with worse OS and DFS post SS.

In our study we found that OS and DFS was significantly associated with primary treatment modality. Patients who underwent surgery as the initial treatment had a significantly improved DFS (p=0.008 on univariate analysis, surgery alone: 54.5%, surgery + RT: 47.6%, surgery + CTRT: 37.5%) and patients who underwent surgery + PORT had a significantly better OS post SS (p=0.023 on univariate analysis, surgery alone 78.8%, surgery + RT 81%, surgery + CTRT 75%). Brown et al in his study found improved salvage rate for recurrent disease in surgery group (53%) in comparison to surgery + RT group (13%).[6] Chung et al in his study has shown that patients who underwent surgery as primary treatment had significantly improved DFS (69.6% vs. 41.2%; p=0.015) and OS (73.9% vs. 47.1%; p=0.021) than patients who received multi-modality treatment.[7] Tam et al found that patients who received adjuvant therapy at time of primary treatment had worst outcomes with 5-year OS of 10%.[3] Kernohan et al also demonstrated similar results with patients who were treated initially with single modality have better prognosis than those treated with combined modality therapy.[8]

Disease-free interval has a significant impact on survival outcomes post SS (Figure 1). There is consensus in literature that recurrence in first year of primary treatment has poor prognosis post SS. In present study, we found that late recurrence (>2 years) was significantly associated with better OS and DFS post SS both on univariate and multivariate analysis. Liao et al in series of 272 recurrent OSCC patients, found that cutoff point at 10 months from the initial treatment has the worst prognosis in terms of 5-year disease-specific survival (DSS) and OS.[9] Stell et al in series of 515 recurrent OSCC patients treated with salvage treatment, showed that patients with early recurrence had worse prognosis.[10] Agra et al showed that patients recurring less than a year after primary treatment had significant worse prognosis.[11]

In the present study, DFS and OS post SS did not differ significantly with initial T or N stage, but was significantly associated with recurrent T (p=0.012 on univariate analysis for OS; T1 80%, T2:95%, T3 68.8, T4 74.3%, p=0.000 on univariate analysis for DFS, T1: 80%, T2: 70%, T3: 31.3%, T4: 37.1%) and N stage (p=0.005, N0: 57.4%, N1: 33.3%, N2: 22.2%, N3: 16.7%). Agra et al in his study has shown that staging at SS is a significant predictor of SS (43.6% in early stage versus 29.1% in advanced stage).[11]

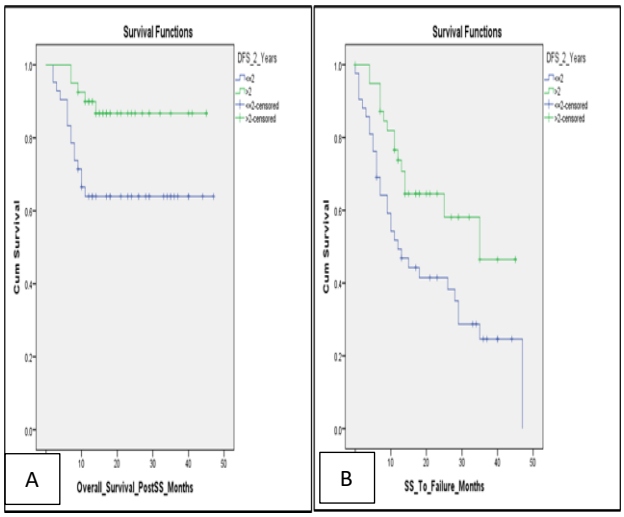

Figure 1 (A and B): Kaplan-Meier overall survival curve and DFS curve according to early versus late recurrence.

Surgical margin is a known prognostic predictor of oral cavity cancers. In our study free margins post SS was statistically significant for both OS and DFS. Matsuura et al in his study has shown that the presence of positive surgical margins after the SS were associated with worse OS rate in patients with OCSCC.[12] Haque et al in his study of 73 patients has shown that adverse pathological features at the time of SS had worse prognosis.[13] Similar results were shown by Chung et al with free margins at salvage surgery having better survival outcomes.[7]

Chang et al in his data review of 4839 patients of recurrent HNSCC found that advanced clinical stage at first diagnosis, and recurrence-free interval <1 year were significant independent prognostic risk factors for OS.[14]

Reirradiation has shown better survival outcomes in advanced stage OCSCC patients post SS. However patient selection is very important for calculation of benefit risk ratio due to high toxicity, impaired quality of life and complications associated with re-irradiation. According to NCCN guidelines 2020 re-irradiation can be given within a gap of 6 months but more the duration from previous radiation better is the tolerability of the patient. In present study we found that patients who had received adjuvant radiotherapy post SS have significantly better OS and DFS. Koo et al in a retrospective study of 36 recurrent OCSCC found that patients who underwent SS with or without postoperative radiotherapy had significantly improved salvage rate and OS.[15]

Failures post SS was seen in our study in the form of local and/or regional recurrence which has shown to strongly affect the survival outcomes. In our study, free margin and adjuvant treatment post SS had low failure rates than patients with positive margins and defaulters and was statistically significant.

Microvascular free flaps are a reliable method of reconstructing complex oral cavity defects after SS with acceptable functional and cosmetic outcome. Reconstruction with vascularized tissues like free flaps can reduce the toxicity of irradiation following SS.[16,17] In our study microvascular reconstruction was done in 7 patients with acceptable quality of life.

The limitations of this study include small sample size, retrospective data and short follow up period.

CONCLUSION

SS is one of the best treatment options for recurrent OSCC, either local, regional or loco-regional, with the highest rates in terms of survival and with an acceptable morbidity. Patients who received initial treatment as surgery + PORT (OS) and surgery alone (DFS), late recurrence (≥2 years), early recurrent T and N stage, free margins at the time of SS and who were treated with adjuvant treatment post SS had a better OS and DFS.

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