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Original Research Article

Comparison between upfront surgery vs salvage surgery following definitive chemoradiation in the treatment of potentially curable locally advanced oral cavity cancer: a retrospective study

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ABSTRACT

Background: We conducted a study to compare the outcomes of upfront surgery and salvage surgery following definitive chemoradiation in locally advanced oral cavity squamous cell carcinoma. This study aims to compare the short-term outcomes (postoperative morbidity, recurrence) & long-term outcomes (overall survival, disease-free survival) between upfront surgery and salvage surgery following definitive chemoradiation in locally advanced oral cavity squamous cell carcinoma.
Methods: A total of sixty patients with locally advanced oral cavity squamous cell carcinoma (T4a, N1-N2b) were retrospectively analyzed between January 2021 and August 2023. Thirty patients underwent upfront surgery followed by adjuvant radiation (group 1) while another thirty patients underwent salvage surgery following definitive chemoradiation (group 2) (radiation dose- 66-70 Gy)
Results: Morbidity was found to be significantly higher in the salvage surgery group (group 2) when compared to the upfront surgery group (group 1) with a p value of 0.003. There was no statistical significance between the two groups in terms of disease-free survival and overall survival.
Conclusions: This retrospective study shows that there are no significant differences in overall survival and disease-free survival amongst patients of locally advanced oral cavity squamous cell carcinoma treated with upfront surgery and salvage surgery following definitive chemoradiation. Morbidity is significantly higher in the salvage surgery group.

Keywords: Upfront surgery, Salvage surgery, Definitive chemoradiation

INTRODUCTION

Oral cavity cancer is the most common cancer among men in India and the second most common malignancy overall.[1] For advanced operable cancers, a combination of surgery and RT with or without CT is often used pre- or postoperatively. Currently, there is no optimal consensus on the sequence of surgery, RT, and CT with surgery followed by adjuvant radiation considered the standard of care by many.[2] Therefore, we conducted a study to compare the outcomes of upfront surgery and salvage surgery following definitive chemoradiation in locally advanced oral cavity squamous cell carcinoma.

Aim and objectives

The aim of this study is to compare the short-term outcomes (postoperative morbidity, recurrence) & long-

term outcomes (overall survival, disease-free survival) between upfront surgery and salvage surgery following definitive chemoradiation in locally advanced oral cavity squamous cell carcinoma.

METHODS

A total of sixty patients with locally advanced oral cavity squamous cell carcinoma (T4a, N1-N2b) were retrospectively analyzed between January 2021 and August 2023 at our institution, Government Royapettah Hospital, Kilpauk Medical college Chennai. Amongst them, 30 patients who underwent upfront surgery and another 30 patients who underwent salvage surgery following definitive chemoradiation were appropriately matched for stage and analyzed.

Inclusion criteria

Inclusion criteria were; Patients with histologically confirmed squamous cell carcinoma moderately advanced i.e operable locally advanced oral cavity cancers constituted by T4a disease of lip which can be reconstructed with regional flaps, T4a diseases of buccal mucosa with induration below zygomatic arch, T4a disease of oral tongue (including lesions involving posterior 1/3 tongue but not vallecula), T4a disease of alveolar ridge with disease confined to alveolus/not crossing midline, Nodal status limited to N0, N1, N2a, N2b disease, Age 20-70 years and Karnofsky performance status of ≥70%; ECOG PS ≤2.

Exclusion criteria

Exclusion criteria were; Nonsquamous Histologies; Very advanced inoperable oral cavity lesions constituted by; T4a disease of the lip which cannot be reconstructed with regional flaps, All T4b disease, T4a disease of buccal mucosa with induration above the zygomatic arch, T4a disease of the tongue with involvement of vallecula, Nodal status -N2c, N3a, N3b and patients with recurrent disease.

Pre-treatment evaluation

History, Physical examination (Examination under anesthesia if required, to confirm stage/operability); Biopsy and complete blood analysis, Chest X-ray, ECG, 2D Echo, CECT/MRI head and neck. Patients who underwent upfront surgery (group 1) were treated with adjuvant radiation of 50-60 Gy depending on the postoperative histopathology (pT3-4, node positivity, LVI/PNI positivity, close margins (less than 5 mm).

Patients who underwent salvage surgery (group 2) had received external beam radiation with a box field technique to a total dose of 66Gy delivered in 33 fractions at a rate of 2Gy per fraction, for 5 fractions per week over 6 weeks along with weekly cisplatin 75 mg/sq.m. Only those with significant residual disease after response evaluation (done after 6 weeks), underwent surgery with appropriate reconstruction.

Adjuvant chemotherapy was advised for patients with significant residue in the postoperative specimen. Patients were monitored for complications diligently and were managed appropriately. The follow-up protocol included clinical examination monthly for 1 year, 2- 3 monthly for 1-5 years, and 6 monthly thereafter. Chest X-rays will be performed every 6 months for 2 years and once a year thereafter.

Statistical analysis

The analysis will be done on an “Intention to treat basis” using appropriate statistical tools. A two-tailed $p<0.05$ will be taken as statistically significant. Survival analysis will be done using the Kaplan- Meier Curve and Cox regression analysis. SPSS version 22 was used for statistical analysis.

RESULTS

Age distribution

The mean±SD age distribution of patients belonging to group 1(upfront surgery) was 52.57±9.85. The median (IQR) age was found to be 52 (45-59.25). The minimum and maximum ages were 34 years and 70 years respectively with a range of 36 years. The mean±SD age distribution of patients belonging to group 2 (salvage surgery) was 49.33±11.10. The median (IQR) age was found to be 47.50 (39.75-58.50). The minimum and maximum ages were 32 years and 70 years respectively with a range of 38 years.

Sex distribution

Out of 60 study participants, 50 (83.3%) were males and 10 (16.7%) were females. The distribution of males and females in the two groups of patients is given in (Table 1).

Table 1: Sex distribution among the study participants.

Sex	Upfront surgery group (group 1) N (%)	Surgery following chemoradiation group (group2) N (%)	X^2	P value
Females	6 (60)	4 (40)	0.480	0.488
Males	24 (48)	26 (52)		

Primary site of cancer

In patients who underwent upfront surgery, the primary sites of cancer are presented in (Table 2). Buccal mucosa was the most common primary cancer site, accounting for 43.3% of cases, followed closely by the lateral tongue at 36.7% and alveolus at 20%.

Table 3 shows the distribution of primary cancer sites among patients who underwent surgery following chemoradiation (group 2). Among the participants, the most prevalent primary cancer site was the buccal mucosa, accounting for 60.0% of cases, followed by the tongue at 23.3 and alveolus at 16.7%.

Table 2: Primary site of cancer among the upfront surgery group of study participants.

Primary cancer site	N	%
Buccal mucosa	13	43.3
Tongue	11	36.7
Alveolus	6	20.0

Table 3: Primary site of cancer among the study participants in the surgery followed by chemoradiation group.

Primary cancer site	N	%
Tongue	7	23.3
Buccal mucosa	18	60.0
Alveolus	5	16.7

Morbidity

Complications were present in a total of 23 (38.3%) study participants. The distribution of complications among the study participants in the two groups of patients is given in (Table 4). In the upfront surgery group, complications were absent in 80% of cases, while in the surgery followed by the chemoradiation group, only 43.3% had no complications. This discrepancy was statistically significant, with a chi-squared value of 8.531 and a p value of 0.003. Recurrence was absent in most cases in both groups, with 93.3% in the upfront surgery group and 76.7% in the surgery followed by the chemoradiation group. Although there was a numerical difference, the chi-squared test did not show statistical significance (p=0.071). Notably, the absence of death was observed in 100% of the upfront surgery group, but only in 86.7% of the surgery followed by the chemoradiation group, resulting in a significant Chi-squared value of 4.286 and a p value of 0.038. This data underscores the varying morbidity outcomes between the two treatment groups, with particular significance regarding complications and mortality.

Wound dehiscence was the most common complication in group 1 (upfront surgery) found in 3 patients. Carotid blowout, chyle leak, and SSI (surgical site infections) were present in one patient each. Flap dehiscence was the most common complication in group 2 (salvage surgery) found in 5 patients. Chyle leak occurred in 4 patients, followed by carotid blowout and wound dehiscence in 3 patients each and SSI in 2 patients.

Table 4: Morbidity among the study participants.

Morbidity variables		Upfront surgery group (group1) N (%)	Surgery following chemoradiation group (group 2) N (%)	X2	P value
Complications	Absent	24 (80)	13 (43.3)	8.531	0.003*
	Present	6 (20)	17 (56.7)		
Recurrence	Absent	28 (93.3)	23 (76.7)	3.268	0.071
	Present	2 (6.7)	7 (23.3)		
Death	Absent	30 (100)	26 (86.7)	4.286	0.038*
	Present	0 (0)	4 (13.3)		

*Significant p value

Table 5: Disease-free survival analysis model among the study participants.

Variables	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Study group	-0.353	0.398	0.375	0.703	0.322	1.533
Age	0.000	0.016	0.979	1.000	0.969	1.031
Sex	-0.034	0.511	0.946	0.966	0.355	2.632
T stage	-	-	0.822	-	-	-
T1	-0.614	1.194	0.607	0.541	0.052	5.616
T2	-0.882	0.870	0.310	0.414	0.075	2.277
T3	-0.030	0.477	0.950	0.971	0.381	2.473
T4	-0.262	0.377	0.487	0.769	0.368	1.610
N stage	-	-	0.017*	-	-	-
N1	0.573	0.411	0.164	1.774	0.792	3.974

Continued.

Variables	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
N2	1.436	0.515	0.005*	4.204	1.532	11.534
Complications	-0.069	0.399	0.862	0.933	0.427	2.038
Recurrence	-0.838	0.441	0.058	0.433	0.182	1.028

*Significant p value

Table 6: Overall survival analysis model among the study participants.

Variables	B	SE	P value	OR	95.0% CI for OR	
					Lower	Upper
Group	-3.386	8.766	0.699	0.034	0.000	979643.750
Age in years	-0.277	0.458	0.545	0.758	0.309	1.860
Sex	2.492	11.701	0.831	12.085	0.000	110280062731
T stage	-	-	0.990	-	-	-
T1	4.333	98.967	0.965	76.206	0.000	1.328E+086
T2	-5.899	47.568	0.901	0.003	0.000	8.469E+037
T3	-4.977	14.787	0.736	0.007	0.000	26637188653
T4	-2.803	6.702	0.676	0.061	0.000	30733.405
N	-	-	0.692	-	0.000	-
N1	-2.862	3.893	0.462	0.057	0.000	117.802
N2	-7.576	9.221	0.411	0.001	0.000	36222.104
Complications	-1.593	6.567	0.808	0.203	0.000	78993.311
Recurrence	6.412	8.400	0.445	609.148	0.000	8605333981

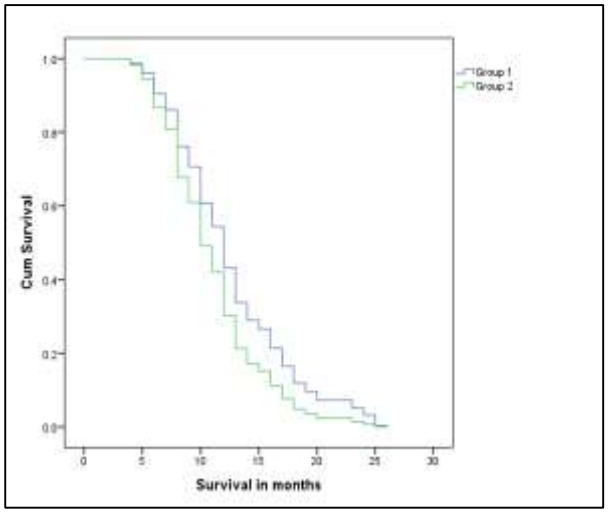

Figure 1: Disease-free survival among the study participants.

Survival analysis

The mean±SD survival in months among patients belonging to the upfront surgery group (group 1) was 13.03±6.87 months. The median (IQR) was found to be 12 (6.75-18.25) months. The minimum and maximum were 4 months and 26 months respectively with a range of 22 months. The mean±SD survival in months among patients belonging to the salvage surgery group (group 2) was 10.75±3.85 months. The median (IQR) was found to be 11 (8-13) months. The minimum and maximum were 2 months and 18 months respectively with a range of 16 months. There is no significant difference in survival between the two groups with a p value of 0.128. For the disease-free survival, the N2 stage was found to be a significant predictor with a p value of 0.005 (Table 5, Figure 1), and for the overall survival, there were no significant predictors (Table 6).

DISCUSSION

The optimal management of locally advanced oral squamous cell carcinoma remains uncertain. Currently, upfront surgery followed by adjuvant radiation is considered the standard of care. However, definitive chemoradiation followed by salvage surgery is also a viable alternative.

Studies in the literature comparing these two regimens are very limited. A single randomized controlled trial (RCT) published by Soo et al and later updated by Iyer et al compared surgery with adjuvant RT to radical concurrent chemoradiotherapy (CCRT).[3,4] The trial involved 119 patients with locally advanced (stage III/IV) resectable head and neck cancers, who were randomized into two groups: surgery with adjuvant RT versus CCRT. Patients in the surgery followed by radiation group underwent radical resection of the primary tumor, with neck dissection as needed, followed by adjuvant RT of standard fractionation to a total of 60 Gy in 30 fractions. Patients in the CCRT group received 2 cycles of cisplatin and 5-fluorouracil (5-FU) (PF) concurrently given with 66 Gy in 33 fractions over 6.5 weeks. Only 27% (32 patients) had oral cavity primaries. At a median follow-up of 13 years, patients with oral cavity cancers who underwent surgery had significantly improved 5-year disease-specific survival (DSS; 68% vs. 12%, P¼ 0.038) and distant recurrence-free survival (92% vs. 50% P¼ 0.05). However, there were no statistically significant

differences in overall survival (OS) and DSS of the entire cohort between the two groups. Head and neck oncologists have been hesitant to use chemoradiotherapy (CRT) as the primary treatment for patients with oral cavity tumors. This is mainly due to the high risk of complications caused by the anatomic limitations of the oral cavity, as well as the limited effectiveness of radiation therapy (RT) in cases of bone invasion. According to the National Comprehensive Cancer Network guidelines, both surgery and multimodality treatment such as CRT are equally effective options for managing patients with locally advanced oral SCC. The study conducted by Gore et al involved 104 patients with oral cavity SCC.[5] Among them, 54 patients underwent surgical excision followed by postoperative RT while 50 patients received concurrent CRT. The results showed that the surgically treated group had significantly higher rates of overall survival (OS) and disease-specific survival (DSS) compared to the CRT group ($p<0.001$).

The study concluded that treatment with surgery followed by adjuvant RT was more effective in controlling advanced oral cavity SCC than treatment with CRT. This study is one of the few that directly compares outcomes after treatment for oral cavity SCC. In fact, patients who underwent primary surgery had a 94% lower risk of disease-specific death rate than those who received concurrent CRT, even after adjusting for stage and comorbidity. Spiotto et al reported that patients undergoing primary surgical resection had significantly better 3-year overall survival compared to those receiving definitive chemoradiotherapy, in propensity-score matched cohorts controlling for comorbidity, T-stage, N-stage, and tumor subsite.[6]

Definitive chemoradiation is an essential treatment option for patients who either refuse surgery or are unable to undergo surgery. In a study conducted by Stenson et al patients with advanced oral cavity cancer who received chemoradiation therapy as their primary treatment had a high survival rate, with a 66.9% PFS at 3 years.[7] Similarly, Cohen et al studied 39 patients with T4 tumors of the oral cavity treated with primary chemoradiation.[8] They reported an overall 5-year survival of 56% and a 3-year PFS of 51%, with an 18% incidence of osteoradionecrosis (ORN). A frequently raised concern against using definitive chemoradiotherapy (CRT) to treat oral cavity squamous cell carcinoma (OCSCC) is the potential risk of osteoradionecrosis (ORN). Foster et al updated the findings of Stenson et al and reported a 20.7% rate of ORN over a period of twenty years while treating locally advanced OCSCC using intensity-modulated radiation therapy (IMRT).[9] However, it is interesting to note that in our series, we did not encounter any cases of ORN. Wound healing remains a significant cause of concern post-irradiation. In the post-chemoradiation group, we had 17 patients (56.7) % with wound morbidity as compared to six patients (20%) in the upfront surgery which was statistically significant with a p value of 0.003. Several studies have demonstrated that radiation can have a negative impact on wound healing.[10,11] A total of four patients died in the salvage surgery group compared with none in the upfront surgery group which was statistically significant with a p value of 0.038. The rate of salvage surgery following definitive chemoradiation is significantly high although the exact rates have not been definitively addressed in the literature. Hosni et al in a study of 108 patients with oral cavity squamous cell carcinoma treated with definitive chemoradiation reported that amongst the 26 patients who experienced local failure, seventeen (65%) underwent subsequent salvage surgery.[12] Our study did not show a statistically significant difference in survival between upfront surgery and salvage surgery groups (13.03 m vs. 10.75 m; $p=0.128$ respectively). For the disease-free survival, the N2 stage was found to be a significant predictor with a p value of 0.005 and for the overall survival, there were no significant predictors. The retrospective nature of our study is the major drawback which has the potential to introduce bias. The limited sample size is also a concern.

CONCLUSION

This retrospective study shows that there are no significant differences in overall survival and disease-free survival amongst patients of locally advanced oral cavity squamous cell carcinoma treated with upfront surgery and salvage surgery following definitive chemoradiation. Morbidity is significantly higher in the salvage surgery group. Whether definitive chemoradiation is equally effective in comparison to upfront surgery in locally advanced oral cavity squamous cell carcinomas is a question that can be better addressed in further large-scale randomized control studies.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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