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RESEARCH ARTICLE

Impact of induction chemotherapy on Resectability in Locally advanced oral cavity Carcinomas

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ABSTRACT

Purpose: We aim to assess resectability in patients with locally advanced oral cavity squamous cell carcinomas with induction chemotherapy.

Methods: All stage III-IVB oral squamous cell carcinoma patients with borderline resectable (suspected R1) or unresectable disease (stage IVB, except internal carotid artery encasement or pterygoid plate or skull base involvement) recruited between January 2020 and August 2021 at a tertiary care hospital received 2-3 cycles of induction chemotherapy (standard TPF regimen) followed by a surgical assessment. The primary aim was to evaluate the proportion of patients that became resectable by induction chemotherapy.

Results: Out of 40 patients, 21 were unresectable (stage IVB disease), and 19 were borderline resectable (stage IVA disease) with doubtful resection margins as per the multi-disciplinary discussion. After chemotherapy, 21 patients became resectable (13 out of 19; and 8 out of 21). Thus, resectability was achieved in 52.5% of patients (32.5% for stage IVA and 20% for stage IVB). The median overall survival in patients who underwent surgery was 20.5 months (95% CI: 16.95-28.25 months) versus 8.0 months (95% CI: 5.74-13.46 months) in patients who remained unresectable after induction chemotherapy (p=0.0001).

Conclusions: In our study, induction chemotherapy leads to improved surgical resection rates with acceptable toxicities in a significant proportion of unresectable locally advanced oral cancers, with significant improvement in overall survival.

Keywords: Induction chemotherapy, Oral cavity, Borderline resectable, Unresectable, Masticator space, Resectability

Introduction

Lip and oral cavity carcinomas are India's second most common and seventeenth most common cancers globally. In developing countries like India, the majority of the patients present in locally advanced stages where multimodality treatment is required with a multidisciplinary team.[1,2]

Treatment of oral cancers is always a balance between morbidity and cure, factors like treatment's intent (curative/ palliative), which depends on many patients as well as tumor factors. Locally advanced oral cavity tumors are primarily treated with surgery and followed by adjuvant radiotherapy with/ without concurrent chemotherapy (depending on the post-operative histopathological features), while patients deemed unresectable are usually treated with definitive chemo-radiotherapy or sometimes with palliative cancer-directed therapies, depending on additional contributing factors.[3,4]

Locally advanced tumors are contributed by stage III and stage IV disease (excluding metastases). While stage III tumors are mostly resectable, stage IV disease is further subdivided into stages IVA and IVB. Stage IVA tumor includes either T4a or/and N2 disease, while stage IVB includes either T4b or/and N3 disease. Of these, T4a tumors are moderately advanced local diseases and primarily termed as 'Borderline resectable'.[4,5] The term 'Borderline resectable' does not have any 'formal definition' and itself means that the local extent of the disease is such that it may be difficult for the surgeons to achieve clear (R0) margins. And so, such patients are treated with definitive chemoradiotherapy. But it has been seen that the prognosis of these patients treated with non-surgical measures will remain poor while the same group, if treated with Induction chemotherapy (ICT) followed by surgery and then adjuvant (chemo)radiotherapy, has shown better outcomes and literature has been continuously showing promising results over the last two decades.[6,7]

Hitt et al. showed significant improvements in response rates in favor of the triplet ICT, that is TPF regimen.[8] Then, TAX 323 and TAX 324 studies also confirmed statistically significantly better overall survival (OS) in the long-term follow-up with an estimated 5-year survival of 52% vs. 42% in the doublet arm, and so TPF is established as the standard neoadjuvant/upfront chemotherapy regimen for locally advanced head and neck cancers.[9,10,11] Thus, this study aimed to see the feasibility of replicating the same in our practice, that is, ICT (TPF regimen), followed by surgery and adjuvant chemo-radiotherapy, to improve the prognosis of these patients.

Methods

This prospective interventional single-arm study was undertaken at a tertiary care academic university hospital in north India. The project was a collaboration between Radiation Oncology and Surgical Oncology departments. The institutional ethics board approved the protocol (registration no. ECR/262/Inst/UP/2013/RR-19, approval no. 986/Ethics/2021).

Patient and disease characteristics

The biopsy-proven non-metastatic locally advanced oral cavity squamous cell carcinoma (OCSCC) patients who may have suspected R1/ R2 and/or selected unresectable stage IVB tumors (i.e., only due to masticator space involvement) were recruited at the Department of Radiation oncology between January 2020 and August 2021. All patients must have ECOGs of ≤2 and be fit for major surgery, chemotherapy, and radiotherapy.

The criteria used for considering patients as borderline resectable/unresectable were: buccal mucosa primary with disease/edema reaching above the level of the zygoma, or/and masticator space involvement due to either masseter muscle or medial pterygoid muscle infiltration, infratemporal fossa (ITF) involvement either below/ above the level of the mandibular notch. Patients who qualified for masticator space involvement either due to temporalis or lateral pterygoid muscle involvement or disease having skull base invasion or ICA encasement or pterygoid plate involvement were not taken in the study. The primary tongue disease involving the posterior part also makes it challenging to resect with clear (R0) margins and was hence included in the study.

Baseline clinical staging was established with contrast-enhanced computed tomography (CECT)/ Magnetic Resonance Imaging (MRI) (for tongue primary) of the face and neck other than routine history and examination. To rule out metastases, CECT Thorax was done. Routine hematological

investigations were done to assess the patient's general well-being. The staging used was AJCC 8th Edition Cancer Staging Manual. Patients provided written informed consent before accrual in the study.

Study design

Selected patients received two or a maximum of three cycles of ICT (Inj. Docetaxel 75 mg/m2 Day 1, Inj. Cisplatin 75 mg/m2 Day 1, Inj. 5-Fluorouracil 750mg/m2 Day 1-5 continuous infusion) at an interval of three weeks. Primary prophylaxis with granulocyte colony-stimulating factor was planned. Chemotherapy tolerability and toxicity are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Response to ICT is assessed by radiological and clinical examination. RECIST 1.1 criteria were used.

All patients were evaluated clinically as well as radiologically for surgical resectability (R0 margins) after two-three weeks of the last chemotherapy cycle, and patients who were deemed operable after ICT will undergo radical resection of the primary tumor with neck dissection (functional or radical) and appropriate reconstruction (pedicle or free flap) within 3-5 weeks of the last cycle of ICT. Adjuvant Radiation therapy was initiated within 4 to 6 weeks after surgery with concurrent chemotherapy in the form of Injection Cisplatin 40 mg /m2 per week (total of six cycles with 240mg/m^2).

While patients who did not become operable even after ICT were treated either with definitive chemoradiotherapy or with palliative measures based on the final extent of the disease and response to upfront chemotherapy. All patients were followed up every month for the first year, two-monthly for the second year, and three months thereafter.

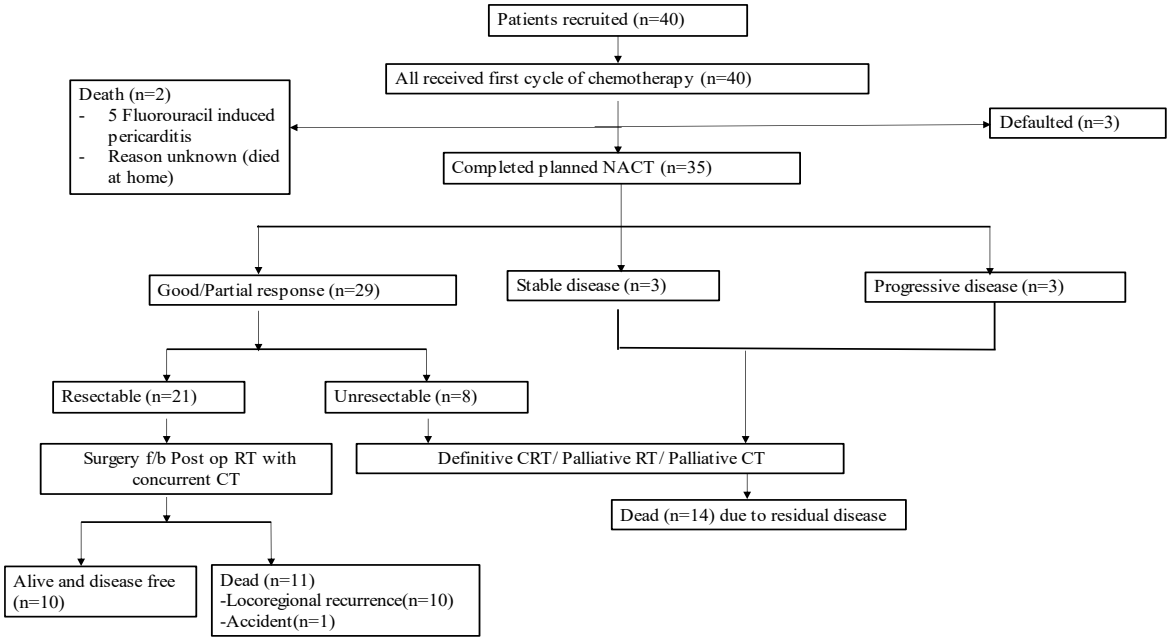


Figure 1: Consort diagram showing patients included in the study

Statistical analysis: The data were analyzed with IBM SPSS Statistics software version 29. Descriptive statistics were applied for patient profiles and response rates. The comparison of response rates with different regimens was done with Fisher's exact test. Overall survival (OS) was calculated from the biopsy date to the date of death or last contact. Kaplan Meir analysis was done to estimate OS, and Bivariate analysis was done by Cox regression analysis to identify the factor of OS.

Results

(I) Baseline characteristics and staging details with reasons for unresectability

Between January 2020 and August 2021, a total of 40 patients were recruited from the outdoors after MDT board discussions (Figure 1). Their baseline characteristics are shown in Table 1.

Table 1: Baseline characteristics of all included patients

Particulars	**Number (n:40)**	**Percentage**
Male	37	92.5
Tobacco usage	38	95
Alcohol usage	17	42.5
ECOG: 1	40	100
Median Age (interquartile range)	38.5 years (31.25-49 years)	
Location of primary		
Tongue	6	15
Buccal mucosa	30	75
Lower alveolus	3	7.5
RMT	1	2.5
Differentiation		
Well-differentiated	29	72.5
Moderately differentiated	11	27.5
Poorly differentiated	0	0
Grade of trismus		
0	9	22.5
1	7	17.5
2	7	17.5
3	17	42.5
Clinical T stage		
T3	6	15
T4A	15	37.5
T4B	19	47.5
Clinical N stage		
N0	4	10
N1	14	35
N2a	3	7.5
N2b	5	12.5
N2c	5	12.5
N3b	9	22.5
Composite clinical stage		
IVA	19	47.5
IVB	21	52.5

The most common primary site was buccal mucosa in 30 (75%) patients. The median age of patients was 38.5 years, with an interquartile range (IQR) of 31.25 - 49 years. The staging details are shown in Table 1. An almost equal number of composite stage IVA (47.5%) and IVB (52.5%) patients were recruited. The reasons for unresectability are listed in Table 2.

Table 2: Reasons for unresectability at the baseline and after ICT

Reason for unresectability	Total patients n: 40 (%)	The proportion of patients who underwent surgery after ICT
Medial Pterygoid muscle involvement	16	4
Abutting Medial Pterygoid muscle with loss of a fat plane	10	8
Disease/edema reaching above the zygoma	2	1
Disease involving the posterior part of the oral tongue	6	4
Low ITF	5	4
High ITF	1	0
Total	40 (100%)	21 (52.5%)

Overall, masticator space involvement was present in twenty (50%) patients either due to medial pterygoid or masseter involvement or both.

(II)Chemotherapy details

The median number of chemotherapy cycles received was two. Two patients died after the first chemotherapy; one had 5-Fluorouracil-induced fatal pericarditis, confirmed on ECG, and the second died due to an unknown reason at home. Three patients withdrew their consent from the study after the first cycle of ICT.

(III) Response assessment and post-chemotherapy treatment with histopathological details

After ICT, a response assessment was done by RECIST 1.1 criteria. Twenty-one (52.5%) out of baseline forty patients became resectable after receiving ICT. Table 2 shows the baseline details of unresectability for these 21 patients.

The response could not be assessed in another five patients for the abovementioned reasons in the chemotherapy detail section. Surgery performed was wide local excision with appropriate neck dissection and reconstruction in all 21(100%) patients (Table 3).

Table 3- yp TNM for patients who underwent surgery

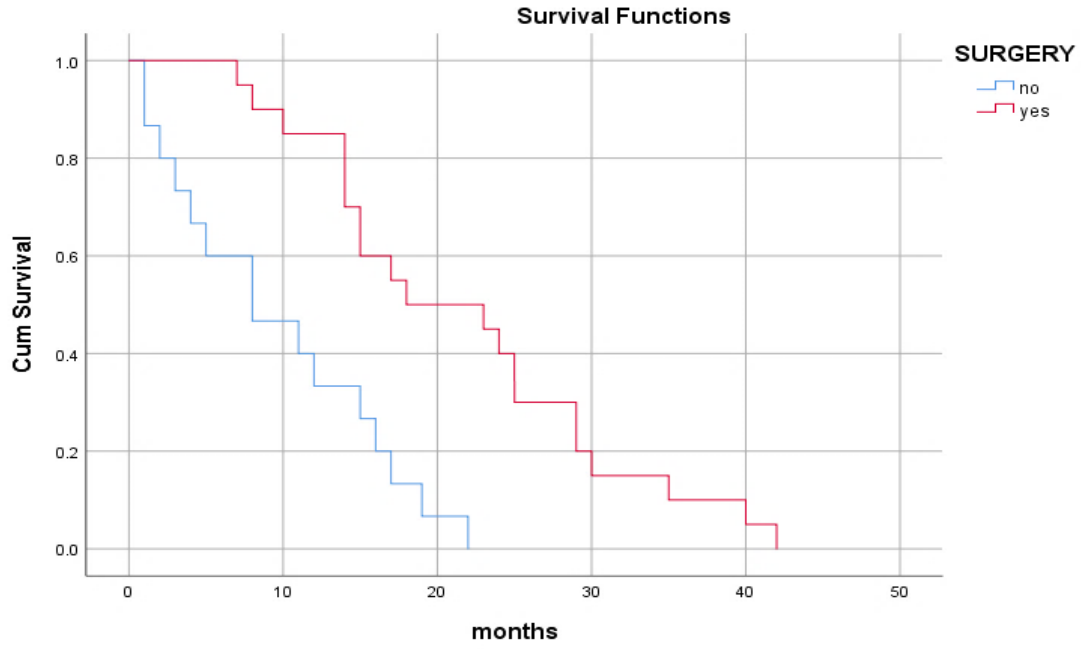
yp T stage	**Number, n=21**	%
T2	5	23.8
T3	7	33.3
T4a	9	42.9
yp N stage	**Number, n=21**	%
N0	9	42.9
N1	4	19
N2a	1	4.8
N2b	3	14.3
N3a	0	0
N3b	4	19
Yp Composite stage	**Number, n=21**	%
II	4	19
III	3	14.3
IVA	10	47.6
IVB	4	19

The post-operative histopathological examination report showed the median (range) tumor size was 0.85 (0.7- 4.3) cm; thirteen patients had a depth of invasion (DOI) of >10mm; bone involvement was present in nine patients; margins (close: free=1:20), Lymphovascular invasion (LVI) was present in 4 patients (19%), and Peri-neural invasion (PNI) was seen in 5 patients (23.8%). The median (IQR) number of lymph nodes harvested was 25 (19.5-28), and the median (IQR) lymph node positivity was one (0-2). The extra-nodal extension (ENE) was present in seven (33.3%) patients. Table 3 shows detailed pathological TNM staging of these 21 operated patients. All resected (twenty-one) patients completed postoperative radiation therapy with planned concurrent chemotherapy without any treatment gap or unexpected delays.

(IV) Overall survival:

The median overall survival (OS) for patients who underwent surgery was 20.5 months (95% CI: 16.95-28.25 months), while it was 8.0 months (95% CI: 5.74-13.46 months) in patients who remained unresectable even after ICT (p=0.0001) (figure: 2).

Figure 2: Kaplan Meir survival analysis of patients who underwent surgical resection as opposed to those who remained unresectable after induction chemotherapy.



(V) Outcome:

On a follow-up of 42 months, out of twenty-one patients who underwent surgery, ten are disease free and alive; ten had died due to the locoregional recurrence of disease; and one died in a road traffic accident. All the patients who did not undergo surgery due to poor or no response to upfront chemotherapy succumbed to their primary disease due to locoregional recurrence/ residual disease.

Discussion

Locally advanced oral squamous cell carcinoma (OSCC) is a heterogeneous group and has stage combinations ranging widely from T1N1 (composite stage III) to T4bN3 disease (composite stage IVB). Stage III tumors are considered resectable with adjuvant chemo-radiotherapy.[12,13] While management of stage IV disease varies from 'definitive chemoradiotherapy'/ 'upfront surgery followed by (chemo) radiotherapy'/ 'trial of induction chemotherapy (ICT) in borderline resectable patients'/ 'palliative treatment' or/up to 'best supportive care (BSC) only.

To differentiate between resectable versus unresectable patients, the AJCC 6th TNM staging manual subdivided the T4 stage into T4a- locally advanced resectable and T4b- locally advanced unresectable disease. However, this division seems too rigorous as few T4b tumors (masticator space

involvement only) could be operated on. Considering this, the AJCC 7th TNM staging manual renamed T4 oral cancers as T4a- moderately advanced local disease and T4b- very advanced local disease. The current AJCC 8th edition also follows the same. And so, when selecting the appropriate treatment protocol for locally advanced oral cancers, patients should be categorized into either of the two groups- operable or inoperable.[4]

The terms resectable and operable are often used interchangeably, but actually, both differ in clinical use.[4] Resectability depends on the anatomical location of the tumor and its relation to the critical structures. At the same time, operability also considers the morbidity associated with surgery and the chances of achieving a favorable oncological outcome, like survival with each morbid surgery. Thus, locally advanced oral cancer may be technically resectable, but its high morbidity or unchanged poor outcome (may make it inoperable). Disease involving temporalis or lateral pterygoid muscle is difficult to resect with clear margins even after an excellent response to ICT. It was analyzed in earlier studies that most patients who became operable after ICT had disease infiltrating or abutting to medial pterygoid muscle only as the criteria for baseline unresectability. Thus, a disease with masticator space involvement (stage IVB) can still be considered resectable following ICT if it's only due to either masseter or medial pterygoid muscle infiltration. A study by Trivedi et al. showed a reasonable locoregional control rate, which improved overall survival using compartmental resections for selected tumors with masticator space involvement.[14] Our study also showed improvement in resectability after induction chemotherapy in nearly half of the patients and improvement in OS as well. In contrast, none survived at the last follow-up in a group treated with a non-surgical modality. There is another term, "borderline resectable," which does not have a formal definition. According to the surgeon, the possibility of having a positive margin is higher in these patients, which is also at the cost of a very high functional and cosmetic morbidity. And so, such patients can usually be taken up for definitive chemoradiotherapy. As per the literature, the prognosis of patients treated with non-surgical modalities is always poor compared to surgery.[5,6,7,15] The locoregional control rates for patients treated with definitive chemoradiation are between 16-30%.[16] Thus, surgery should be preferred wherever feasible, even for locally advanced stages.[17] ICT in highly selected fit patients with a borderline resectable disease can be given with the hope that it may downstage the tumor and make R0 resection possible and hence improve the overall prognosis and survival.[18,19] Our study also showed a significantly better median overall survival of resected patients than those who received non-surgical treatment due to poor or no response to ICT, as previously mentioned, i.e., 20.5 months vs. 8.0 months.

In our study, 29 (72.5%) patients had a good/partial response, and 13 patients with stage IVA disease and 8 patients with stage IVB disease finally became resectable. Thus, resectability was achieved in 52.5% of patients and is 20% exclusively for stage IVB unresectable disease. Four out of five patients with low ITF involvement became operable after induction chemotherapy. Liao et al., in a single institution study, also reported promising results of upfront surgery in T4b oral cavity cancers below the mandibular notch (i.e., same as in those four patients in our study) with five years locoregional control rate of 47%.[20] Our study also showed nearly the same locoregional control for patients who underwent surgery after ICT at a three-and-a-half-year follow-up.

Various other studies also have been conducted previously to establish the role of induction chemotherapy. Of those, the three most prominent are by Patil et al., Joshi et al., and Mishra et al., and they published retrospective data on patients with technically unresectable locally advanced oral cavity cancers.[21,22,23] At the same time, the study by Rudresha et al. conducted a prospective study of giving induction chemotherapy in patients with T4a and T4b oral cavity cancers.[24,25] They all combinedly demonstrated neoadjuvant chemotherapy's effectiveness in enabling surgery and ultimately improving overall survival rates. In the study by Rudresha et al., for stage T4a cancers median overall survival of patients who underwent surgery was 16.9 months versus 8.8 months for those treated with nonsurgical local therapies.[24] Whereas for stage T4b cancers, the median overall survival was 19.7 months versus 7.1 months, respectively,

i.e., nearly double the median overall survival in resected patients.[25] Our study also showed a similar median OS of 20.5 months for patients who underwent surgery versus 8.0 months in patients who remained unresectable after induction chemotherapy (p=0.0001) (Figure: 1).

On the other hand, the results of the previous few other studies remained inconclusive.[10.11.26.27] And this may be because of having a heterogeneous group and the majority of patients belongs to other sites like oropharynx, larynx, hypopharynx instead of oral cavity tumors, which is only 10-20% of out of the total patient population. And so, these do not qualify as a reference for oral cavity primaries.

Conclusion: Based on the results of our study, it is feasible to deliver the standard TPF regimen in well-selected patients, thus improving not only the resectability but also significant survival advantages. However, we need big multi-institutional RCTs on this topic to further make a final evident practice-changing statement.

All authors declare no conflict of interest.

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