JCOMS eISSN:2783-3127 https://journalofcoms.com

Journal of

Current Oncology and Medical Sciences

Vol. 5, No. 4



Original Free Access

Impact of induction chemotherapy on resectability of borderline resectable/unresectable oral cavity carcinomas

Rajeev LK [1], Dayananda Sagar P [2]*, Lokesh KN [2], Chetan V [2], Rudresh AH [2], G V Giri [2], Smitha C Saldanha [2], Yaman Patidar [2], Suresh Babu [2]

[1] Department of Medical Oncology, Kidwai Memorial Institute of Oncology (KMIO), Bangalore, Karnataka, India

[2] Department of Medical Oncology, KMIO, Bangalore, Karnataka, India

Abstract

Introduction: To assess the impact of neoadjuvant chemotherapy (NACT) on achieving surgical resectability in patients with borderline resectable or unresectable T4a oral cavity squamous cell carcinoma (OCSCC).

Materials and methods: Patients with borderline resectable or unresectable T4a OCSCC enrolled between October 2023 and June 2025 received three to four cycles of NACT. Post-treatment, patients were assessed for response and resectability using clinical and radiological criteria.

Results: A total of 102 patients received NACT; 65.7% were male (n = 67) and 34.3% were female (n = 35). The median age was 47 years (range: 28–72). All patients received either two-weekly or three-weekly TPF regimens. Tobacco use and combined alcohol–tobacco habits were the most common (44.1% each), followed by tobacco with betel nut (4.9%), betel nut alone (2.9%), and no habits (3.9%). The buccal mucosa was the most frequent primary site (41.1%), followed by the tongue (35.2%). Other sites included the retromolar trigone (8.9%), upper alveolus (6.8%), and gingivobuccal sulcus (6.8%). Most patients presented with cT4aN1 disease (30.3%).The two-weekly TPF regimen was more commonly used (58.8%) than the three-weekly regimen (41.1%). Toxicity was manageable, with 36.3% of patients experiencing no adverse effects. The most frequent response was partial response (39.2%), followed by progressive disease and unevaluable responses (23.5% each), stable disease (8.8%), and complete response (4.9%). Surgery was considered feasible in 33 patients (32.3%), and 25 (24.5%) ultimately underwent surgery. Patients who underwent surgery demonstrated a significantly improved median overall survival (17.4 months) compared with those managed non-surgically (10.2 months; log-rank p = 0.001).

Conclusion: NACT is well tolerated and has an acceptable toxicity profile, enabling conversion to resectability in nearly one-third of patients with borderline resectable or unresectable T4a OCSCC. Surgical intervention significantly improves overall survival, underscoring the potential role of NACT in appropriately selected patients.

Keywords: Neoadjuvant chemotherapy, Borderline resectable, Unresectable, Oral cavity cancer, Overall survival

Corresponding Authors: Dayananda Sagar P

✉ Email: Psagar11011994@gmail.com

Received: 2025.8.26, Accepted: 2025.10.30

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Introduction

Squamous cell carcinoma (SCC) represents the vast majority of head and neck cancers, typically arising from the mucosa of the oral cavity, larynx, or oropharynx. In India, these cancers pose a significant health burden, ranking sixth in incidence among males and seventh among females (1). Early-stage (I–II) oral cavity cancers are usually managed with a single treatment modality, most commonly surgical resection or radiotherapy, which generally provides excellent local tumor control and favourable long-term survival outcomes (2). Stage III oral cavity tumors are typically deemed resectable, while stage IV disease is further classified into subgroups IVA and IVB. Stage IVA includes T1–T4a, N1–2, M0 tumors, whereas the IVB category comprises tumors of any T stage with N3, M0, as well as T4b tumors with any nodal status, M0. In India and other developing countries, head and neck cancers are frequently diagnosed at locally advanced stages. This presents significant treatment challenges and necessitates multimodality management under a multidisciplinary team (4). Surgical resection remains the cornerstone of therapy for resectable, locally advanced oral cavity carcinoma and is typically followed by adjuvant radiotherapy, with or without chemotherapy depending on risk factors (5).

T4a tumors represent moderately advanced local disease and are commonly described as “borderline resectable.” Although this term lacks a formal definition, it generally indicates that achieving clear (R0) surgical margins may be challenging. Radiological features defining borderline resectability include tumor or associated edema extending above the zygomatic arch, involvement of the masticator space due to infiltration of the masseter or medial pterygoid muscles, and extension into the infratemporal fossa either above or below the mandibular notch (6).

Patients with locally advanced, borderline resectable, or unresectable oral cavity carcinomas often experience poor outcomes when treated with non-surgical modalities alone (7). Induction chemotherapy has been shown to reduce distant metastases and improve outcomes in resectable head and neck cancers, as demonstrated by a meta-analysis from Ma et al. (8).

The pivotal TAX323 and TAX324 trials investigated induction chemotherapy for locally advanced and unresectable head and neck malignancies, reporting a 68% response rate to triple-drug regimens; however, oral cavity cancers accounted for only a small proportion (approximately 15%) of the study population (9, 10). In India, Patil VM and colleagues demonstrated that induction chemotherapy not only facilitates tumor downstaging but also contributes to organ preservation, particularly maintaining mandibular integrity (7). Similarly, Rudresha et al. reported longer overall survival in patients with T4a and T4b oral cavity cancers who underwent surgery compared to those managed non-surgically (16.9 months vs. 8.8 months) (4).

Despite these advances, a knowledge gap remains regarding the effectiveness of neoadjuvant chemotherapy in converting borderline resectable or unresectable T4a oral cavity SCC into surgically resectable disease and its impact on survival. Therefore, we evaluated patients presenting with borderline resectable or unresectable T4a oral cavity squamous cell carcinoma who received neoadjuvant chemotherapy to assess its impact on surgical resectability, toxicity, and survival outcomes.

Materials and methods

Study Design and Setting

This prospective interventional study was conducted between October 2023 and June 2025 at a tertiary care cancer hospital. Newly diagnosed patients aged ≥18 years with oral cavity squamous cell carcinoma (OCSCC) were enrolled after providing written informed consent. The study protocol was approved by the Institutional Ethics Committee (IEC No: KMIO/MEC/2024/02/PG/MO/24).

Patient Selection

Baseline evaluation included demographic data, personal habits, presenting symptoms, and medical history. A comprehensive physical examination was performed, and locoregional tumor involvement was assessed both clinically and through contrast-enhanced computed tomography (CECT). Patients with SCC of

the oral cavity and imaging suggestive of locally advanced disease were included if they were considered borderline resectable, typically corresponding to T4a tumors. The term "borderline resectable" lacks a universally accepted definition; however, it generally refers to cases in which achieving clear (R0) surgical margins is difficult.

Criteria used to define borderline resectability included:

- Tumor or edema extending above the zygomatic arch.
- Infiltration of the masseter or medial pterygoid muscles (indicating masticator space involvement).
- Extension into the infratemporal fossa, either above or below the mandibular notch (see Supplementary Appendix 1)

Additional imaging features suggestive of borderline resectability included posterior mandibular cortical erosion or marrow infiltration without gross destruction of the mandibular ramus. Final inclusion was determined through multidisciplinary team (MDT) discussion. Patients with T4b tumors or N3b nodal disease were excluded.

Chemotherapy Regimens

Eligible patients received either a three-weekly or two-weekly regimen comprising taxane, platinum, and 5-fluorouracil (TPF). The choice of regimen depended on performance status and comorbidities (details in Supplementary Appendix 2).

Parameter	Three-weekly Regimen	Two-weekly Regimen
Number of Cycles	3	4
Docetaxel	75 mg/m² over 2 hours on Day 1	50 mg/m² over 2 hours on Day 1
Cisplatin	75 mg/m² over 2 hours on Day 1	50 mg/m² over 2 hours on Day 1
Leucovorin	Not included	250 mg/m² over 2 hours on Day 1
5-Fluorouracil (5-FU)	750 mg/m²/day as continuous infusion for 4 days	2,500 mg/m² as 24-hour infusion on Day 1
Administration Interval	Every 3 weeks	Every 2 weeks

Treatment Monitoring and Dose Modification

Toxicity and clinical response were evaluated on Day 10 of each chemotherapy cycle. Chemotherapy was administered only if hemoglobin > 8 g/dL, absolute neutrophil count > 1,500 cells/µL, and platelet count > 100,000/µL. Renal function was assessed prior to every cycle using creatinine clearance.

All adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 3–4 toxicities had to recover to ≤ Grade 1 before the next cycle.

Each patient received primary G-CSF prophylaxis (300 µg daily for five days). A 20% dose reduction was applied in subsequent cycles for patients who developed febrile neutropenia or severe (Grade 3–4) toxicities.

Patients on the three-weekly regimen were reassessed after three cycles, and those on the two-weekly regimen after four cycles, using clinical and radiological evaluation to determine response and resectability.

Assessment of Response

Radiological response was evaluated using RECIST 1.1 criteria (18):

- Complete Response (CR): disappearance of all target lesions.
- Partial Response (PR): ≥ 30% decrease in the sum of target lesions.
- Progressive Disease (PD): ≥ 20% increase or new lesions.
- Stable Disease (SD): neither sufficient shrinkage nor growth to qualify as PR or PD.

Patients with CR or PR were considered responders; others were categorized as non-responders.

Definitive Treatment and Follow-up

Patients who achieved downstaging after NACT underwent surgery, followed by adjuvant radiotherapy ± weekly cisplatin, based on histopathology. Those who remained unresectable were treated with definitive chemoradiotherapy, radical or palliative radiotherapy,

or best supportive care, depending on performance status and disease extent. All patients were regularly followed up for survival and treatment outcomes.

Statistical Analysis

Data were analysed using SPSS version 23.0 (IBM, Chicago, IL, USA). Categorical variables were expressed as frequencies and percentages, and continuous variables as mean ± standard deviation or median (range), depending on distribution.

The primary endpoint was conversion to resectability following NACT. Secondary endpoints included response rate, toxicity, and overall survival (OS) among surgical versus non-surgical patients. Kaplan–Meier analysis estimated survival probabilities, and log-rank tests compared OS across groups. Associations between categorical variables were examined using the Chi-square test. Multivariate Cox proportional hazards modelling identified independent predictors of OS.

Results

Patient Demographics

A total of 102 patients who met the eligibility criteria were enrolled and analysed. The cohort was predominantly male, comprising 65.7% (n = 67) males and 34.3% (n = 35) females. The median age at diagnosis was 47 years (range: 28–72), representing a younger cohort compared to global head and neck cancer populations.

Habits and Risk Factors

Tobacco use and alcohol consumption were highly prevalent. Tobacco alone was reported in 44.1% of patients, while combined alcohol–tobacco use was seen in another 44.1%. Betel nut use alone occurred in 2.9%, and tobacco with betel nut in 4.9%. Only 3.9% of patients reported no high-risk habits.

Primary Tumor Site

The buccal mucosa was the most common primary site (41.1%), followed by the tongue (35.2%). Other less frequent sites included the retromolar trigone (8.9%), upper alveolus (6.8%), and gingivobuccal sulcus (6.8%).

Clinical Stage at Presentation

Most patients presented with advanced disease. The most frequent stage was cT4aN1 (30.3%), followed by cT4aN2c (16.7%), cT4aN2a (15.6%), cT4aN2b (14.7%), and cT4aN3a (2%). This pattern highlights the late stage at diagnosis typical in this region.

Neoadjuvant Chemotherapy Regimens

All patients received TPF-based induction chemotherapy. The two-weekly TPF regimen was more common (58.9%) than the three-weekly regimen (41.1%).

Toxicity Profile

The treatment was generally well tolerated. The most frequent adverse effect was Grade 1–2 diarrhea ± nausea (17.6%), followed by Grade 3–4 neutropenia or febrile neutropenia (13.7%), and Grade 3–4 diarrhea/nausea (10.8%). Mucositis occurred in 7.8%, while other toxicities accounted for 13.7%. Overall, toxicity was observed in 63.7% of patients, with the majority being mild to moderate.

Response to Neoadjuvant Chemotherapy

Treatment response assessment showed that partial response (PR) was the most common outcome (39.2%), followed by progressive disease (PD) (23.5%), stable disease (SD) (8.8%), and complete response (CR) (4.9%). Response evaluation was not possible in 24 patients (23.5%), primarily due to non-compliance with follow-up or early treatment discontinuation. These cases were likely related to disease progression, toxicity, or socioeconomic barriers. Outcome data were unavailable for five patients despite follow-up attempts.

Definitive Treatment Modalities

Following NACT, surgery was considered feasible in 33 patients (32.3%), but only 25 (24.5%) ultimately underwent resection. Definitive chemoradiotherapy (CTRT) was administered to 19 patients (18.6%). The

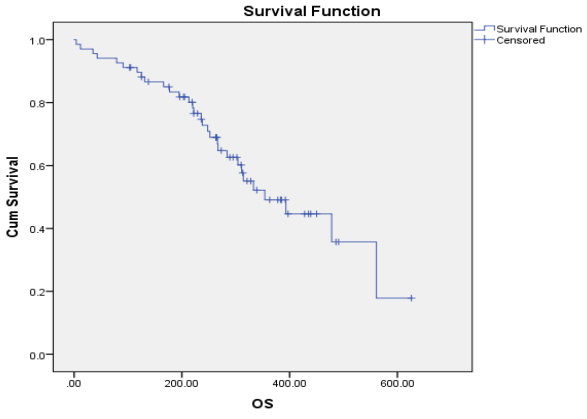
remaining patients were either ineligible for radical treatment or non-compliant with further therapy.

Survival Outcomes

The median follow-up period was 15 months. At the last follow-up, 67.6% (n = 69) of patients were alive, and 32.4% (n = 33) had died. At one year, patients who received definitive treatment had a higher median overall survival (OS) than those managed non-surgically. The median OS was not reached in the definitive treatment group, indicating prolonged survival, while it was 10.1 months (95% CI: 7.7–12.6) in others (Figure 1). The overall median survival for the cohort was 11.8 months (95% CI: 10.2–13.4). This difference was statistically significant (log-rank test: $\chi^2 = 13.337$; $p < 0.001$), indicating a survival advantage with definitive treatment. Kaplan–Meier analysis showed a median OS of 17.4 months for patients who underwent definitive surgery, compared with 10.2 months for those treated non-surgically.

The Cox proportional hazards model, adjusted for age, sex, and stage, revealed a hazard ratio (HR) of 3.896 (95% CI: 0.684–22.189; p = 0.126) for non-surgical versus surgical treatment, suggesting a non-significant trend favouring surgery. Younger age was associated with better outcomes (p = 0.076).Certain staging subgroups also correlated significantly with survival, though some had wide confidence intervals due to smaller sample sizes.

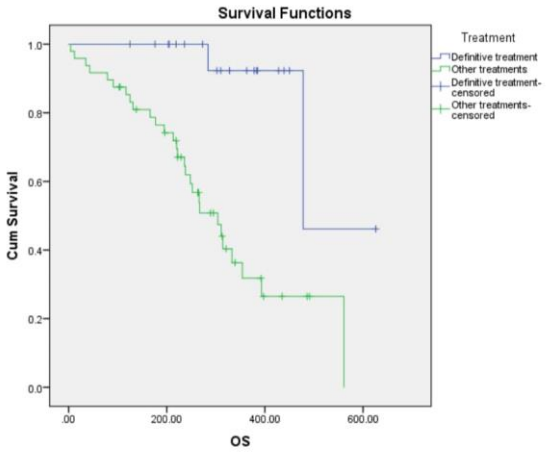
Figure 1. Kaplan–Meier survival curve showing overall survival (OS) for the full patient cohort. The x-axis represents time in days, while the y-axis indicates cumulative survival probability. Censoring events are denoted by vertical tick marks along the survival curve.



Subgroup Analysis

Patients on the two-weekly TPF regimen demonstrated a higher response rate (53.3%) than those on the three-weekly regimen (30.9%), suggesting greater efficacy. However, Grade 3–4 toxicities were more frequent with the two-weekly regimen (31.7% vs. 19.0%). The median survival for the two-weekly group was not reached, whereas for the three-weekly group it was 9.3 months (Figure 2) (95% CI: 5.4–13.4). Although direct comparison is limited due to censored data in the two-weekly group, the unreached median suggests a potential survival advantage with the dose-dense regimen.

Fgure 2. The x-axis represents time in days, and the y-axis shows cumulative survival probability. Patients receiving definitive treatment (blue line) demonstrated superior survival compared to those receiving other treatments (green line). Censoring events are indicated by vertical tick marks along each curve.



Parameter	2-Weekly TPF (n = 60)	3-Weekly TPF (n = 42)
Response Rate (PR + CR)	32 patients (53.3%)	13 patients (30.9%)
Grade 3–4 Toxicity	19 patients (31.7%)	8 patients (19.0%)
Median Survival	Not reached	9.3 months (95% CI: 5.4–13.4)

Discussion

Oral cavity squamous cell carcinoma involving regions such as the masticator space (via masseter or medial pterygoid infiltration), the infratemporal fossa (above or below the mandibular notch), or with disease or edema extending above the zygoma, presents significant surgical challenges. The anatomical complexity and extent of tumor spread make it difficult to establish a standardized surgical approach.

Induction chemotherapy is increasingly being used as a strategy to downstage locally advanced head and neck cancers, aiming to improve surgical feasibility, preserve organ function, and reduce metastatic risk, thereby improving treatment outcomes. Drug delivery is often more effective when administered prior to local therapy, as well-vascularized, untreated tumors allow more uniform drug distribution, supporting the rationale for early systemic therapy.

Although several randomized clinical trials have not shown a statistically significant overall survival (OS) benefit for induction chemotherapy in head and neck squamous cell carcinoma (HNSCC) (11,12), many have reported clinically meaningful advantages, such as higher pathological complete response rates, tumor shrinkage, and improved organ preservation (13,14). Retrospective studies from India have also suggested a survival advantage for induction chemotherapy in locally advanced or technically unresectable oral cavity cancers (4,15).

There are limited prospective studies assessing the impact of induction chemotherapy on borderline resectable or unresectable oral cavity carcinomas. In the present study, induction chemotherapy resulted in a moderate response rate, with surgery deemed feasible in about one-third of patients. However, only one-fourth eventually underwent resection, mainly due to treatment non-compliance, disease progression, or socioeconomic barriers.

Survival outcomes were significantly better among patients who underwent definitive surgical treatment compared with those managed non-surgically. Although the Cox proportional hazards model indicated a trend toward improved survival with surgery, this did not reach statistical significance, likely due to the limited sample size. Younger patients were found to have better outcomes, consistent with previous observations. In the study by Rudresha et al., partial response was achieved in 21.3% of patients, resectability in 23.8%, and median OS was 16.9 months for surgical versus 8.8 months for nonsurgical patients.

In comparison, 44.1% of patients in the current study achieved a response, and surgery was feasible in 32.3%. Median OS was 17.4 months for surgical and 10.2 months for nonsurgical treatment, showing a modest improvement in resectability and survival (4).

Dandekar et al. reported a 38% partial response in locally advanced oral cavity cancers (16), comparable to the 44% combined response (PR + CR) observed here. However, despite achieving downstaging in 33 patients (32.3%), only 25 (24.5%) underwent surgery, primarily due to non-compliance.

This surgery rate was lower than that reported by Patil et al. (~40%), likely due to socioeconomic limitations, treatment toxicity, or disease progression. The toxicity profile in this cohort was acceptable, with most events being mild to moderate, and more than one-third of patients experiencing no significant toxicity. These results reinforce the feasibility of NACT in carefully selected patients with borderline resectable OCSCC.

No phase-III RCT has shown 2-weekly TPF superior to 3-weekly in borderline-resectable oral cavity cancer. In our study, 2-weekly TPF achieved higher response (53.3% vs. 30.9%) and longer survival (median not reached vs. 9.3 months) but with increased Grade 3–4 toxicity (31.7% vs. 19.0%).

Limitations of this study include its single-center design, lack of randomization, and absence of a control group, which restrict the ability to draw definitive conclusions. Patient attrition and noncompliance may have also introduced bias. Future large-scale randomized trials are warranted to validate these findings.

Future directions

Future research should focus on large, multicenter randomized trials to confirm these findings. Enhancing

patient adherence and support, while addressing socioeconomic barriers, is vital. Incorporating immunotherapy alongside or after induction chemotherapy may provide new treatment options, especially for those unsuitable for surgery. Identifying predictive biomarkers will further improve patient selection and personalized therapy.

Conclusion

NACT enables conversion to resectability in nearly one-third of patients with borderline resectable or unresectable oral cavity squamous cell carcinoma. Surgical treatment is associated with significantly improved overall survival. However, the study's single-center design, lack of randomization, and absence of a control group limit the generalizability of these findings. Larger, randomized trials are necessary to validate the benefits of NACT and refine patient selection..

Author contribution

LKR and **SB** conceptualization and project administrator.
LKR methodology and supervision
DSP data curation and investigation, resources and software
RAH, **LKN**, **SCS** and **GVG** formal analysis
LKR, **DSP GS**, **DRS**, **KA** manuscript writing and figures.

Conflicts of interest

There are no conflicts of interest.

Funding

There is no funding.

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