



APPLICATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED ORAL CANCERS – A REVIEW

Oncology

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ABSTRACT

A major proportion of cancers in India comprise those of the oral cavity. The standard management of malignancies of the oral cavity comprises radical resection whenever feasible or radical chemoradiation in cases where the tumor is deemed unresectable. Locally advanced cases can limit the extent of surgery, thus making it difficult to achieve clear margins. Such tumors may be labelled as borderline resectable or technically unresectable. The purpose of this article was to review the current literature and determine the usefulness of Neoadjuvant Chemotherapy in downstaging a tumor in borderline resectable or technically unresectable malignancies of the oral cavity. Neoadjuvant therapies have thus shown encouraging results, however larger, well designed, and prospective studies will be needed to make meaningful.

KEYWORDS

Neoadjuvant, Chemotherapy, Downstaging, Oral cancer, Locally advanced

INTRODUCTION

A major proportion of cancers in India comprise those of the oral cavity.¹⁻³ The standard management of malignancies of the oral cavity comprises radical resection whenever feasible or radical chemoradiation in cases where the tumor is deemed unresectable.⁴ Approximately, 85% of the patients present late, when the tumor is locally advanced.¹ Due to the anatomical complexity of the structures in the head and neck, the traditionally used Tumor, Node, Metastasis (TNM) system for staging, prognosis, and treatment decisions, often misleads the tumors into the same subgroups despite differences in resectability and outcomes.⁵ A margin negative resection (R0) is the mainstay of treatment in advanced oral cancers.⁶ A high risk factor for recurrence is a close or a positive surgical margin.⁷ Resectability in oral cancers is decided upon involvement of the anatomical landmarks on clinical examination and imaging. As per the TNM guidelines, involvement of the prevertebral muscles, carotid artery, or the base of the skull are absolute contraindications to surgery.^{8,9} Other locally advanced cases can limit the extent of surgery, thus making it difficult to achieve clear margins. Such tumors may be labelled as borderline resectable or technically unresectable. In these patients, logically, a reduction in the size of the tumor may be achieved by the use of neoadjuvant chemotherapy (NACT) such that a surgical resection with adequate negative margins is attained.

The purpose of this article was to review the current literature and determine the usefulness of NACT in downstaging a tumor in borderline resectable or technically unresectable malignancies of the oral cavity.

SURGERY AS A MANAGEMENT MODALITY FOR ORAL CANCER

The most appropriate treatment for oral cancer, in order to achieve adequate surgical clearance and R0 is surgery. Various studies report surgery as having a better outcome and survival over chemoradiation in locally advanced head and neck cancers.^{10,11}

NEOADJUVANT CHEMOTHERAPY

Chemotherapy combinations such as Cisplatin with 5-Fluorouracil (5FU) show a good response rate in patients with locally advanced head and neck cancers.¹² With the advent of taxanes, induction or neoadjuvant chemotherapy has emerged as an attractive management strategy. There are several theoretical advantages of NACT such as¹³:

1. It enables tumor shrinkage
2. It optimizes the delivery of drugs through intact vasculature
3. It is useful for assessing tumor responsiveness
4. It reduces the chance of distant metastases.

A landmark study by Licitra et al. in 2003¹⁴ aimed to understand the benefit of NACT in resectable oral cancers. Their study consisted of two groups of patients, the first group being subjected to three cycles NACT followed by surgery, and the second group subjected to surgery

only. Cisplatin 100 mg/m² and 5-FU 1000 mg/m² was the standard regime used for NACT. Randomization of 195 patients was done with 97 being in the NACT group and 98 being in the surgery alone group. This study, however showed no difference in the overall survival (OS) between the two groups. Nevertheless, it was seen that mandibular resection could be avoided in 21% of the patients who received NACT. Bossi et al. conducted a long term follow-up of this study (median 11.5 years), and confirmed the same results.¹⁵ Zhong et al.¹⁶ randomized patients with locally advanced resectable oral cancer into either upfront surgery followed by post operative radiotherapy (PORT), or two cycles of NACT comprising of docetaxel, cisplatin and 5-FU (TPF) regimen, followed by surgery and PORT. Their study as well did not show a statistical difference in either the OS or disease free survival (DFS) among the two groups.

Based on this data, it would not be wrong to question the effectiveness of NACT on the OS in resectable oral cancers.

A desired outcome of surgery would be R0 resection, however this becomes a complicated task when locally advanced tumors are being dealt with, wherein R1 or R2 resections are observed.^{17,18} Borderline resectable or technically unresectable tumors are challenging. A criteria for defining such tumors has been put forward in literature¹:

1. In a case of a primary of Buccal mucosa, when either the tumor extent or the peritumoral edema reaches or crosses the level of zygomatic arch, or tumor extension into high infratemporal fossa (ITF).
2. In a case of a primary of the oral tongue, or floor of the mouth, when the tumor extent is reaching up till the vallecula or the hyoid bone or into high ITF.
3. Oral cancers with extensive skin involvement, where attainment of a negative margin is rare.
4. Frank skull base invasion, carotid artery encasement, or prevertebral fascial involvement should not be present in any of these tumors.

Chemoradiation or palliative radiation is usually the classical treatment for such tumors, however the results are usually grim with the reported median survival being less than a year.¹⁹⁻²² NACT followed by reassessment for surgery seems like a logical approach in such cases. This is substantiated by a recent retrospective study conducted by Patil et al.¹ wherein, 721 patients matching the aforementioned criteria received two cycles of NACT after which they were reassessed for surgery. Out of them 43% underwent surgery after NACT due to sufficient reduction in tumor size, thus achieving a successful R0 resection and an improved median OS of 19.6 months. To downstage a primary tumor NACT has been advocated by a few studies.²³⁻²⁴ Joshi et al.²³ in their study demonstrated the use of two cycles of NACT following which, the patients who responded were operated upon and the other group was offered palliative radiation or chemoradiation. About 20% of a total of 110 patients with masticator space involvement included in their study, received a 3-drug regimen, with

the others receiving a 2-drug regimen. The final analysis comprised about 100 patients of which 28 showed partial response, 49 had a stable disease and the tumor progressed in 23 patients. Resectability was achieved in 30% of the patients with the OS being 18 months in the surgery group, thus formulating a conclusion that NACT is feasible. A prospectively collected data underwent a retrospective analysis in this study. The patients with masticator space involvement were categorized into supra-notch and infra-notch disease, while being placed in the same group. This study reflected that NACT was unsuccessful in downstaging a majority (85%) of the supra-notch tumors, thus making this approach inadequate in downsizing high ITF tumors. Another study by Fang et al.²⁴ included 79 patients with masticator space involvement, all of whom received NACT and 65 (82%) of them showed partial or complete response. Of these 65 patients, 33 underwent surgery with an OS of 75% and DFS of 72.6% as compared to the remaining patients who underwent chemotherapy (on patient discretion) with an OS of 47.7% and DFS of 44.3%. Pathological downstaging was observed in 27 of the 33 cases. Out of a total of 79 patients, 52 had a supra-notch disease which got converted to infra-notch in 27 patients following NACT. The induction chemotherapy had a statistically significant higher chance of achieving a complete response, thus making the results of this study quite encouraging and the concept of downstaging these tumors appealing. Kina et al.²⁵ in their study aimed to investigate the OS in tongue carcinoma patients with metronomic NACT with bleomycin as compared to those subjected to surgery alone. It was a retrospective study, wherein 117 patients who underwent surgery were divided into the "surgery group"- 54/117 or the "metronomic NACT with bleomycin (15 mg x 6 group)"-63/117. NACT increased the OS (76 vs 90%) along with having significantly lower rates of distant metastasis. They reported no chemotherapy related deaths.

NACT Regimen for Oral Cancer

The 3-drug combination of TPF appears to be the most appropriate regimen for NACT in oral carcinomas. A retrospective study by Noronha et al.²⁶ compared patients receiving either a 2-drug combination which included taxanes (paclitaxel or docetaxel) and platinum (cisplatin or carboplatin), or a 3-drug combination of TPF. A significantly better response rate was observed with TPF (50% versus 22%). Amongst the taxanes, docetaxel had a 30.3% response rate while paclitaxel had the same of only 17.2%. The TAX 323 and 324 studies compare cisplatin and 5-FU based combinations with TPF, as induction chemotherapy before definitive radiotherapy and chemoradiation and reveal a better response rate and OS with the TPF regimen.²⁷⁻²⁸ Paccagnella et al.²⁹ have shown that the response to NACT continues until 4 cycles, when being treated with the Cisplatin and 5-FU regimen. TAX 323 and 324²⁷⁻²⁸ studies used 4 cycles of TPF, the PARADIGM³⁰ study used 3 cycles of TPF and the DeCIDE³¹ study used 2 cycles of TPF, as a result of which it may seem that at least 2 cycles of NACT are required with TPF, which may go up to a maximum of 4 cycles.

The TPF is a well tolerated NACT regimen and only 1-2% of the patients may not be able to sustain a second cycle due to toxicity.⁵

SUMMARY

In countries with limited resources, and even in some western countries, there is a huge concern related to a long waiting period and a delay of 1-2 months before the patient may be taken up for surgery.³²⁻³³ NACT, logically and theoretically, could be useful in preventing disease progression in such cases. Considering the prevalent review of literature, after adequate examination and appropriate planning, NACT may have a role in downstaging borderline resectable and technically unresectable oral carcinomas in order to achieve R0 resection. However, there is a dire need for more prospective studies which might aid us in understanding the feasibility of such an approach.

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