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

INTRODUCTION

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. Approximately, 85% of the patients present late, when the tumor is locally advanced. Due to the anatomical complexity of the structures in the head and neck, 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. A margin negative resection (R0) is the mainstay of treatment in advanced oral cancers. A high risk factor for recurrence is a close or a positive surgical margin. Resectability in oral cancers is decided upon involvement of the anatomical landmarks on clinical examination and imaging. As per the TNM classification, involvement of the prevertebral muscles, carotid artery, or the base of the skull are absolute contraindications to surgery.

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. 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. Borderline resectable or technically unresectable tumors are challenging. A criteria for defining such tumors has been put forward in literature: 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 the zygomatic arch, or tumor extension into high infratemporal fossa (ITF).

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.

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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. NACT followed by resection for surgery seems like a logical approach in such cases. This is substantiated by a recent retrospective study conducted by Patil et al. 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. Joshi et al. 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 only. Cisplatin 100 mg/m$^2$ and 5-FU 1000 mg/m$^2$ was the standard regimen 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. Zhong et al. 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.

KEYWORDS

Neoadjuvant, Chemotherapy, Downstaging, Oral cancer, Locally advanced

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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.
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 60% of the patients with the 18 month 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 tumours, thus making this approach inadequate in downstaging high T4E tumors. Another study by Fang et al 5 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 41% and DFS of 44.3%. Pathological downstaging was observed in 7/27 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. Kum et al 6 investigated the use of NACT 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 metastases. 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. 7 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 fluorouracil (5-fluorouracil) to paclitaxel and docetaxel which included in the same group. This study reflected that NACT was categorized into supra-notch and infra-notch disease, while being prospective 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 tumours, thus making this approach inadequate in downstaging high T4E tumors. Another study by Fang et al 5 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 41% and DFS of 44.3%. Pathological downstaging was observed in 7/27 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. Kum et al 6 investigated the use of NACT 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 metastases. They reported no chemotherapy related deaths.

**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. 2,10 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 borderlineline resectability technically unresectable in order to achieve a better response rate and OS with the TPF regimen. 2,10 Paccagnella et al. 9 have shown that the response to NACT continues up to 4 cycles, when being treated with the Cisplatin and 5-FU regimen. TAX 323 and 324 8 studies used 4 cycles of TPF, the PARADIGM 7 study used 3 cycles of TPF and the DeCIDE 5 study used 2 cycles of TPF, as a result of which it may seem that atleast 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. 2,10

**REFERENCES**

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