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NEO-ADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED UNRESECTABLE ORAL CANCER TO IMPROVE RESECTABILITY

Oncology

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ABSTRACT

Background: Neo-adjuvant chemotherapy (NACT) in the management of locally advanced unresectable oral cavity cancers (OCC) has generated considerable discussion in recent years. We present a retrospective analysis of patients with locally advanced technically unresectable OCC who received NACT at our centre.

Objective: To evaluate impact of NACT in locally advanced unresectable OCC, who are unfit for upfront surgery.

Materials and methods: 30 patients with technically unresectable OCC were taken up for study. All the patients were subjected to 3 cycles of NACT (cisplatin+paclitaxel) after doing relevant investigations. Patients with contraindication to cisplatin were given carboplatin. After 3 cycles, patients were reevaluated for resectability and later planned for either surgery with subsequent RT or nonsurgical therapy RT or palliation depending on the response.

Results: Of 30 patients, only 27 patients were included in study as 3 patients defaulted. All patients tolerated NACT well. Clinically 5 patients (18.5%) had complete response, 20 (74%) had partial response and 2 patients (7.5%) had progressive disease. overall 25 patients underwent surgery and had R0 resection. At last follow up all patients who underwent surgery were alive and disease free.

Conclusions: Several stage IV OCC are treated with nonsurgical modality with poor outcomes. In our analysis, NACT led to successful resection with no unexpected toxicity on subsequent local treatment. NACT has shown the possibility of more limited surgery and greater achievement of resectability (R0 resection).

KEYWORDS

Neo-adjuvant chemotherapy; Locally advanced; Technically unresectable, Oral cavity cancers

INTRODUCTION:

The oral cavity is a distinct site of the head and neck region that possesses complex functional anatomy with regard to speech, swallowing, and facial projection. Anatomically, the oral cavity is composed of the mucosal lip, oral tongue, floor of mouth (FOM), mandibular and maxillary gingiva, retromolar trigone, buccal mucosa, and hard-palate subsites. Although the oropharynx is often confused as a continuous extension of the oral cavity, it is imperative to separate the two because the etiologies, management, and outcomes of cancers arising in these two head and neck sites are drastically different.

Despite advances in organ preservation and survival outcomes for oropharyngeal carcinoma (OPC) and laryngeal carcinoma, oral cavity carcinoma (OCC) remains primarily a surgical disease. In addition, despite advances in surgical techniques, adjuvant therapy, and increased understanding of the molecular mechanisms of pathogenesis, outcomes remain poor in patients with advanced cancers. This study highlights the role of neo-adjuvant chemotherapy for down staging the primary, achieving resectability and reducing morbid surgery which ultimately leads to improve quality of life.

EPIDEMIOLOGY & OUTCOMES:

India has one third of oral cancer cases in the world .Oral cancer accounts for around 30% of all cancers in India. Oral cancers in India estimated (Globocan, 2018) New cases: 1,19,992 Deaths: 72,616 annually.[1] In general, more men suffer and die from oral cancer than women. Squamous cell carcinoma (SCC) is the most common pathologic diagnosis for oral cavity malignancies and is the main focus of this article.[2] Tobacco use is the most-cited risk factor for OCC. It raises the risk of developing OCC three fold, and concomitant alcohol consumption, acting synergistically, increases the risk 10- to 15-fold.[3] Use of smokeless tobacco and betel also have high tumorigenic potential; betel quid use is highest in South East Asia and India.[4] In addition, known genetic syndromes, such as Fanconi anemia and dyskeratosis congenita, have strong associations with the development of OCC in the absence of other known risk factors.

Overall, 5-year survival (OS) for oral cavity squamous cell carcinoma (OCSCC) is 60%, but it varies from 10% to 82% depending on stage, age, race, comorbidity, and location in the oral cavity.[5] To date, data to definitively identify clinical risk factors for local recurrence are limited.[6] Despite recent advances in imaging, surgery, radiation, and systemic therapies, OS has improved only 5% in the last 20 years. Therefore, OCC remains a major clinical challenge.[5]

MATERIALS AND METHOD:

This is a retrospective analysis of patients with technically unresectable OCC treated at Saurashtra Cancer Care & Research Institute, Rajkot from May 2017 to November 2018. The data of all patients receiving NACT are prospectively maintained in our database. Total 30 patients were enrolled. Written informed consent was obtained from each patient. Detailed clinical examination was carried out. Biopsy was done and sent for histopathological examination. All patients were considered technically unresectable by a team of Radiation Oncologists and Surgical oncologist. The term unresectable has been also used to include tumors which are not staged as T4b but are known to carry poor prognosis and high morbidity after upfront surgery. Staging of the tumor was done as per the American Joint Committee on Cancer guidelines, clinically supported with relevant radiological investigations.

INCLUSION CRITERIA

1. Loco regionally advanced (T4a-b,N0-3,M0) oral cavity carcinoma
2. Biopsy proven Squamous cell carcinoma
3. Technically unresectable tumors (ie, high probability of R1 or R2 resection),
4. Age > 18 years and < 70 years

EXCLUSION CRITERIA

1. Very poor general condition (Karnofsky Performance Scale <50)
2. Histology other than squamous cell carcinoma

All patients received 2 drug combination (Platinum + Taxane) neoadjuvant chemotherapy. Paclitaxel was administered at a dose of 175 mg/m^2 over 3 hours on day 1 with cisplatin at a dose of 75 mg/m^2 with adequate hydration. In patients with contraindications to cisplatin , carboplatin at a dose of AUC (area under curve) of 5 was administered on the same day. Standard premedication was used. The chemotherapy was given once every 21 days on outpatient basis in the day care.

Chemotherapy was administered only if hemoglobin was above 9.0 mg/dl, absolute neutrophil count was more than 1500/cu.mm and platelet count was more than 100000/cu.mm. Those patients without any uncontrolled co-morbidity and with adequate hematological, renal and hepatic reserve parameters were included in study.

All patients after the completion of the 2nd/3rd cycle of chemotherapy were reassessed by radiological and clinical examination. The total number of cycles received in all patients was 3. More than 2 cycles were required in all patients on account of delay in dates of local treatment (operative waiting list). The response and potential for resectability was decided by team of Radiation Oncologists and Surgical Oncologist. Patients who were considered to have resectable disease underwent surgical resection. Patients who did not achieve resectability after chemotherapy, underwent radical radiation, palliative radiation, palliative chemotherapy or best supportive care depending on response. Surgery was planned as per the site, stage of the disease, and patient general condition as well as patient willingness for surgery. The various surgical procedures performed included wide local excision of the soft tissue and bony components, selective, modified or radical neck dissection, and/or flap reconstruction. RT treatment was given by conventional two-dimensional planning on Cobalt 60 Tele-therapy unit by shrinking field technique or by intensity modulated radiotherapy on Linear Accelerator. Total dose given was 60 Gy in postoperative and 66 Gy in inoperable patients over 6–7 weeks duration (200cGy/fraction). Usually, postoperative adjuvant RT was started after 21–40 days of surgery. This usually takes 6–7 weeks (42–49 days).

The maximum grade of toxicity in all cycles according to the Common Terminology Criteria for Adverse Effects (CTCAE) was reported. The response rates and percentage of patients achieving resectability at the end of the second or third cycle were calculated.

OBSERVATION & RESULTS:

Our study involved locally advanced tumors. The stage wise distribution was carried out.10 patients were in stage IVA and 17 patients in stage IVB. The baseline characteristics are shown in Table-1. Out of 30 patients, only 27 patients were included in study as 3 patients defaulted after the completion of NACT and didn't turn up for surgery. Planned chemotherapy was completed in all patients. 2 patients had disease progression after the 3rd cycle. Dose reduction was not required in any patient.

Table-1: Baseline Characteristics

Patients Characteristics	Patient No.
Age (Years)	
21-30	3
31-40	10
41-50	8
51-60	6
Male / Female	21 / 6
Site of Cancer	
Buccal alveolar complex	11
Tongue / Floor of mouth	10
Upper Alveolus-Hard Palate	3
Others	3
T Stage	
T4a	10
T4b	17
N Stage	
N0	8
N1	13
N2	6
Reason for NACT	
Masticator space involvement	14
Extrinsic muscle of tongue involvement	10
Pterygoid plate and maxillary sinus involvement	3

Out of the 27 patients who were on chemotherapy, 15 (55%) had nausea, 10 (37%) had vomiting which were controlled with antiemetics and did not have major dehydration. Among them, 12 (44%) had fatigue; 2 (7%) had diarrhea after administering chemotherapy, which subsided within 3–4 days. None of them had had febrile neutropenia. All the patients tolerated NACT well. None of the patient had grade 3-4 toxicity. The details of grade1-2 toxicity can be seen in Table-2. 5 patients (18.5%) had complete response and 20 (74%) had partial response clinically till they were taken for surgery. Details of clinical response can be seen in Figure-1. 25 patients underwent surgery followed by post operative radiotherapy. However, two patients had progressive disease in spite of chemotherapy and were treated with radical radiation therapy. Overall response rate to NACT was 92%. The median duration between completion of chemotherapy and date of surgery was 3 weeks. Pathological downgrading in staging was achieved in all 25 patients who underwent surgery, with 1 tumor being ypT0, 9 being ypT1, 13 being ypT2 and 2 being ypT3 respectively. All patients had R0 resection with good cosmesis in view of less morbid surgery. Details of pathological downstaging can be seen in Table-3. The patients were followed up routinely after treatment (3-15months). At last follow up all patients were alive. All (25) patients who underwent surgery were disease free. 2 patients treated with radiotherapy after NACT for progressive disease had residual disease.

Table-2: Details of Adverse effects (all grade 1-2 only)

Adverse effects	No. of Patients (grade-1)	No. of Patients (grade-2)
Anorexia	14 (51%)	-
Nausea	15 (55%)	4 (14%)
Vomiting	10 (37%)	4 (14%)
Fatigue	12 (44%)	-
Diarrhea	2 (7%)	-
Mucositis	4 (14%)	1 (3.7%)
Anemia	4 (14%)	2 (7%)
Febrile neutropenia	-	-
Impaired hearing	1 (3.7%)	1 (3.7%)
Paresthesia	6 (22%)	-
Peripheral Neuropathy	3 (11%)	1 (3.7%)

Figure 1: Clinical response achieved after NACT (According to RECIST 1.1 criteria)

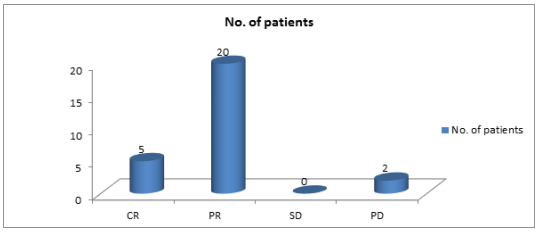

Table-3: Pathological downstaging after NACT

Pathological response after NACT	No of Patients
yPT0N0	1
yPT1N0	5
yPT1N1	4
yPT2N0	7
yPT2N1	6
yPT3N1	2

DISCUSSION:

Surgery remains the main-stay of treatment for oral cavity carcinoma even in advanced stages.[7] Despite advances in surgical and reconstructive techniques, complete clearance of infratemporal fossa and masticator space which are the frequently involved anatomical sites in oral carcinoma, is extensive and extremely morbid. The existing treatment options in the patients with locally advanced technically unresectable OCC are limited. The usual therapeutic options include concurrent chemoradiation, radical radiation, palliative radiation and best supportive care.[8,9] However, the nonsurgical modalities rarely achieve a lasting cure.

Paccagnella *et al*. showed in their study that patients with either stage III or IV SCC tumors of the head and neck without distant metastasis who were not candidates for surgery had a 21% OS rate at 5 years when they underwent 4 cycles of neoadjuvant cisplatin and 5-FU (PF) followed by radiotherapy as opposed to an 8% OS rate in similar patients who received radiotherapy alone. The participants in the study who were deemed resectable after treatment underwent surgical resection. These patients did not have any survival benefit with the

addition of chemotherapy, however, showed significantly lower rates of distant metastasis.[10]

Hitt *et al*. published the first randomized trial comparing PF to PF plus paclitaxel (TPF). They included 384 patients with resectable and unresectable disease. The trial showed significant improvements in terms of response rates and time to treatment failure in favor of TPF regimen. A clear OS advantage was however observed only in unresectable disease.[11]

TAX 323 trial, compared TPF versus PF (4 cycles) followed by radiotherapy in 358 patients with locally advanced HNSCC (LAHNSCC). The primary endpoint was progression-free survival (PFS). It was observed that patients in TPF group had statistically significant PFS and OS. The proportion of oral cavity cancer patients in this study was about 17 %.[12]

TAX 324 trials, a randomized, open-label phase 3 trial consisting of 501 patients with LAHNSCC compared three cycles of TPF induction chemotherapy with three cycles of PF. Both regimens were followed by 7 weeks of chemoradiotherapy with concomitant weekly carboplatin. TPF group showed 3 years OS was 62% versus 48% in the PF group. However, oral cavity patients consisted only 13% in TPF and 15% in PF group.[13]

The long-term follow-up of 5 years of TAX 324 study showed that the OS was significantly better with TPF versus PF (hazard ratio [HR] = 0.74, 95% confidence interval [CI]: 0.58-0.94), with an estimated 5-year survival rate of 0.52 and 0.42 in the TPF and PF arms, respectively. Median survival time was 70.6 months (95% CI: 49.0-89.0 months) with TPF versus 34.8 months (the 95% CI: 22.6-48.0 months) in the PF group ($P = 0.014$). PFS was also significantly better with TPF (38.1 months; 95% CI: 19.3-66.1 months vs. 13.2 months, 95% CI: 10.6-20.7 months; HR = 0.75, 95% CI: 0.60-0.94). The results in the TPF group were better for laryngeal and hypopharyngeal cancers.[14]

None of these trials was designed exclusively for oral cavity cancers and only had a small proportion of patients with OCC. The outcomes were also not compared with the outcomes with the standard of care which is surgery. Therefore, direct extrapolation to OCC patients may not be possible. These studies clearly demonstrate the advantage of using three drugs over two drug regime for induction. However, feasibility of using TPF chemotherapy in this setting remains low in the Indian context.

In the present analysis, we attempted to downstage the malignancy with neo-adjuvant chemotherapy so that surgical resections with negative margins could be achieved. Majority of the patients were in age group between 31 and 50 years. This shows the relatively early presentation of malignancy in this region due to the tobacco chewing habit. The youngest patient was of 24 years old. Male preponderance indicates males more often involve themselves with various addictions which is a known risk factor for OCC. Most of the patients presented late due to illiteracy, ignorance, and poor socioeconomic conditions. The majority of our patients had buccal alveolar complex as the primary site followed by tongue/fom. The tumor involving buccal mucosa was found to be extending to skin, upper and lower alveolus, and retromolar trigone. All the patients had tumor size more than 4 cm in diameter and majority had either bone or skin involvement. Most of them were N1 staging. Reason for giving NACT includes involvement of masticator space, involvement of extrinsic muscle of tongue, extensive skin infiltration, pterygoid plate involvement etc. Most of these patients tolerated neo-adjuvant chemotherapy well. The reaction seen were anorexia, nausea, vomiting, fatigue etc. grade (1-2 toxicity) only in most of patients. None of them had grade 3-4 toxicities. Febrile neutropenia was not reported in any patient. Clinically partial response was observed in majority of patients (74%) and 18.5% had complete response according to RECIST 1.1 criteria. Pathological downstaging was observed in all 25 patients who underwent surgery out of 27. All patients had R0 resection. The two patients who had progressive disease were subjected to radiation.

Several inferences can be drawn after follow up range of 3-15 months in term of response to NACT, achievement of resectability and acute or immediate toxicity. This study has shown the possibility of more limited surgery after NACT and greater achievement of resectability (R0 resection). Taxane + platinum based (2 drug regimen) NACT did not increase perioperative morbidity. Overall favorable response was seen with no unexpected toxicity or adverse effect on subsequent local treatment (surgery + radiotherapy). But considering the limitations of the study such as limited number of patients and lack of long term follow up, the results are not applicable to all patients with advanced oral cavity squamous cell carcinoma, proper patient selection is necessary.

CONCLUSION:

Challenges are still ahead in treating locally advanced oral cavity carcinoma in spite of using multimodality treatment approach. More and more cases of oral cancer are reported in younger individuals in India due to various addictions, poor diet, poor oral hygiene, and carelessness toward various oral pathologies. Massive health promotion and awareness programs are required to target the risk population. Several stage IV OCC are considered unresectable due to anatomical spread and are treated with nonsurgical modality with poor outcomes. In our analysis, NACT led to successful resection and effective in converting technically unresectable oral cavity cancers to resectable disease in approximately 92% of patients. The use of taxanes in two drug regimen (Cisplatin + Paclitaxel) in our study led to greater degree of achievement of resectability without risk of increased adverse effects or acute toxicity as compared to three drug regimen (DCF). Late sequels, disease free survival and overall survival cannot be assessed because of short follow up. However more multi-institutional trials are required to arrive at a definite conclusion or protocol with neo-adjuvant chemotherapy that may make a difference in locally advanced oral malignancies.

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