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RESEARCH ARTICLE

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Role of neo-adjuvant chemotherapy in locally advanced oral squamous cell carcinoma

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ABSTRACT

Introduction: The aim of this study was to compare the outcome of patients with locally advanced squamous cell carcinoma of buccal mucosa who underwent neoadjuvant chemotherapy (NACT) followed by surgery to that of those who underwent primary surgery.
Materials and Methods: Total 50 patients with locally advanced buccal squamous cell carcinoma were randomly divided into in two groups with 25 patients in each. Patients in group I received neoadjuvant chemotherapy followed by surgery and radiotherapy, while patients in group II were only treated by surgery followed by radiotherapy. All the patients were assessed for demographic details, habit, clinical and histological grading of the tumour. Chemotherapy drug details, side effects, complications and response rate to NACT was studied. Type of surgery in terms of respectability, neck dissection and reconstruction modality was documented. Study of recurrence pattern in terms of local, regional and distant spread was evaluated.
Result: age group of patient ranged from 30-60 years, with median age of 52, with a male to female ratio of 2:1 in group I and 3:1 in group II. Moderately differentiated SCC was the most common grade in both the groups. Post NACT, partial response was seen in 76% cases and complete response was seen in 8% cases. Study of recurrence pattern showed; 36% (9) local, 16% (4) regional and 8% (2) both local and regional in group I. In group II 16% (4) local, 16% (4) regional, 4% (1) both local and regional recurrence and 4% (1) distant metastasis was seen.
Conclusion: NACT induces a high response rate that may facilitate definitive surgery in a borderline case or where margin identification is difficult due to wet edematous borders of disease. In the present study NACT showed partial response rate of 76% and complete response in 8% cases.

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Introduction

Head and Neck carcinoma constitutes 30-40% of all adult malignancies in India [1]. The buccogingival complex is the most common sub-site of oral cancer. It is closely linked with the habit of chewing betel quid and gutkha containing tobacco. Squamous cell carcinoma of buccal mucosa is an aggressive cancer, reported to have worse survival and higher recurrence rate [2]. Close proximity of these tumors to the mandible and skin makes the latter susceptible to early tumor invasion. Most patients with squamous cell carcinoma of the head and neck present with locally advanced stage of III or IV. Traditional therapy for these patients has consisted of surgical resection, reconstruction and postoperative radiation. Although this approach is often effective in loco-regional control of disease, there can be devastating effects on personal appearance and critical function, such as speech and swallowing. In patients treated with surgical resection and postoperative radiation, long term survival rates are generally low, ranging from 30% to 40% [3]. Despite the diversity of these patients, loco-regional recurrence patterns are more often than distant metastasis. To improve surgical

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resection, to have better locoregional control, to minimize distant micro-metastasis and to maintain critical functions, induction chemotherapy has been investigated [4]. Frequently Cisplatin and 5 Fluorouracil, along with taxanes and mitomycin have been used in neo-adjuvant chemotherapy (NACT) [5]. Induction chemotherapy is highly active in this setting, inducing partial remission in 60% to 90% of previously untreated patients. However randomized trials have failed to demonstrate a clear impact on local tumor control or overall survival. The induction treatment format also provides a useful instrument to evaluate a novel drug regimen. The use of chemotherapy provides the potential for better regional and distant tumor control. The aim of this study was to compare the outcome of patients with locally advanced squamous cell carcinoma of buccal mucosa who underwent neoadjuvant chemotherapy followed by surgery to that of those who underwent primary surgery.

The aim of the prospective randomized clinical study included

- To study clinical profile of locally advanced squamous cell carcinoma of buccal mucosa.
- To study response to neo-adjuvant chemotherapy in locally advanced squamous cell carcinoma of buccal mucosa.
- To study the patterns of recurrence following the multimodality therapy.

Materials and Methods

The present study was a prospective, randomized study conducted at Department of Surgical Oncology. Krishna Hospital, Karad, India from period of November 2015 to January 2018 after due approval of institutional ethical committee. Total 50 patients with locally advanced buccal squamous cell carcinoma were included in the study. All patients underwent thorough clinical examination by joint committee of surgical, medical and radiation oncologist. Patients were screened for tumor staging, complete blood and serum profile, chest x-ray, ECG and computed tomography scan of the head and neck (whenever necessary). Clinical staging of the lesion was done according to the International Union against Cancer (UICC) TNM classification.

Inclusion criteria

- All previously untreated, biopsy proven, resectable but locally advanced, non-metastatic SCC of buccal mucosa (cT4a). 40 mm
- Eastern Co-operative oncology group (ECOG) performance status <2.
- WBC Count >4000/mm^3 and platelet count >1,00,000/mm^3, normal serum creatinine
- Adequate nutritional, cardiac and pulmonary status

Exclusion criteria

- Previously treated patients with recurrence or second primary.
- Patients with inadequate nutritional, cardiac, pulmonary status.

Patients enrolled for the study randomly were divided in two groups using computer generated table (free random number generator) with 25 patients in each group. After explaining the study protocol, written consent was taken from the patient. Patients in group I received neoadjuvant chemotherapy followed by surgery and radiotherapy, while patients in group II did not receive NACT and were treated by surgery followed by radiotherapy.

Chemotherapy

Patients received single or combination drug chemotherapy. The major deciding factor was performance and the socioeconomic status of the patients. Cisplatin was the first choice for all patients with normal renal parameters. Docetaxel was administered at a dose of 75 mg/m^2 over 2 hours on day 1, cisplatin was administered at a dose of 75 mg/m^2 over 1 hour on day 1 and 5FU was administered at a dose of 750 mg/m^2/day as continuous infusion for 3 days. Patients were administered standard premedication prior to chemotherapy. Patients also received G-CSF prophylaxis and oral antibiotics prophylaxis. In 2 drug combination, either

Docetaxel at a dose of 75 mg/m^2 over 2 hours or Paclitaxel at a dose of 175 mg/m^2 over 3 hours was administered on day 1 with either Cisplatin at a dose of 75 mg/m^2 or Carboplatin at a dose of AUC (area under curve) of 6 on the same day. Standard premedication was used. The regimen was given on outpatient basis in the day-care. The chemotherapy was once given every 21 days for total of 2 or 3 cycles

on the basis of operating surgical team evaluation.

Surgery

All patients in the both the groups were operated with composite resection of buccal tumours, marginal, segmental or hemi mandibulectomy with or without lower partial maxillectomy. Comprehensive neck dissections with MND type I, II or RND performed (bilateral neck dissection was performed when required). Reconstruction was performed with various flaps, including the pectoralis major myo-cutaneous flap, delto-pectoral, cervico-facial and forehead flaps.

Radiotherapy

All patients in both the groups were treated with megavoltage adjuvant radiation using linear accelerator. Treatment was delivered in fraction of 1.8 to 2 Gy/day, five fractions per week to a total dose of 60 Gy to 66 Gy. Toxicity to radiotherapy was assessed every month for three months after the end of radiotherapy, then every two months thereafter. Adjuvant concurrent CT and RT was given in extra capsular spread and in close or positive margin.

Follow-up and Parameters assessed

All patients were examined clinically and radiologically (if required) every 2 to 3 months for first 2 years and 6 monthly thereafter. All the patients were assessed for demographic details, habit, clinical and histological grading of the tumour. Chemotherapy drug details, side effects, complications and response rate to NACT was studied. Type of surgery in terms of neck dissection and reconstruction modality was documented. Study of recurrence pattern in terms of local, regional and distant spread was evaluated.

Results

In this study 50 patient were enrolled with 25 patients in each group, after fulfilling the inclusion criteria. Most common age group was 30-60 years, with median age of 52 years in both the groups. Most commonly involved gender was male, with a male to female ratio of 2:1 in group I and 3:1 in group II. Ulcer and truisms were the most common symptoms in both the groups, accounting for 95% and 60% presentation respectively, with median duration of 3 months. All patients had habit of tobacco consumption in chewing or smoking forms in both the groups. All the patients in both the groups were clinically and histologically graded. According to Borders classification moderately differentiated SCC (Grade II) was the most common grade in both the groups.

(Table 1 and 2) The chemotherapy regimen in group I, was TPF (n=7), P+T (n=7), P+MTX (n=7), P+F (n=1) and PMF (n=2) (Table 3). Response rate to NACT was studied based on response evaluation criteria in solid tumours (RECIST). Complete Response (CR) meant disappearance of all known lesion(s) confirmed at 4 weeks, Partial response (PR) meant at least 30% decrease confirmed at 4 weeks, while Stable disease (SD) implied neither PR nor PD criteria met. Progressive disease (PD) meant a 20% increase with no CR, PR, or SD documented before increased disease or new lesion(s) Post NACT, partial response (PR) was seen in 76% cases and complete response (CR) was seen in 8% cases (Table 4). In this study the chemotherapy induced nausea and vomiting were the most common toxicity (40%), followed mucositis, diarrhoea and neutropenia (Table 5). Neck dissections done in the form of MND I most frequent, followed by MND II. Resection of primary lesion was performed most commonly with segmental, distal or hemi-mandibulectomy. In our series in both the groups the pedicled pectoralis major myo-cutaneous flap (PMMC) was most commonly used for reconstruction. For skin replacement either double flaps like PMMC and delto-Pectoral (DP) or bilobed PMMC, spiral PMMC and cervico-facial rotation flaps were used. Study of recurrence pattern showed; 36% (9) local, 16% (4) regional and 8% (2) both local and regional recurrence. Distant metastasis was not seen in any patient of group I. Patients in group II showed 16% (4) local, 16% (4) regional and 4% (1) both local and regional recurrence. Distant metastasis was seen in 4% (1) cases (Table 6).

Grade	Group I	Group II
Well differentiated	7(28%)	9 (36%)
Moderate differentiated	17(68%)	15(60%)
Poorly differentiated	1(4%)	1(4%)

Table 1. Histopathological grading of Tumour

	Clinical Staging		Pathological Staging	
N Stage	Group I	Group II	Group I	Group II
N0	3 (12%)	4 (16%)	11 (44%)	12(48%)
N1	8 (32%)	12 (48%)	06(24%)	4(16%)
N2a	3(12%)	1(4%)	01(4%)	2 (8%)
N2b	9(36%)	5(20%)	06(24%)	6(24%)
N2c	2(8%)	3(12%)	01(4%)	1(4%)

N3	-	-	-	-

Table 2. Clinical and pathological nodal staging

Regimen	No. of Patients
TPF (Docetaxel, cisplatin and fluorouracil)	07(28%)
P+T	07(28%)
P+MTX	07(28%)
PF	01(04%)
PMF	02(08%)
F=5-Fluorouracil , MTX=Methotrexate, P=cisplatin, T= Docetaxel,	

Table 3. Chemotherapy regimen

Response	Percentage
Complete response (CR)	08%
Partial Response (PR)	76%
Stable disease (SD)	12%
Progressive disease (PD)	04%

Table 4. Response to chemotherapy

Toxicity	No. of patients (%)
Vomiting	10(40%)
Diarrhea	3(12%)
Hematological	2 (8%)
Infections	2(8%)
Mucositis	8(32%)
Pulmonary	1(4%)
Renal	1(4%)
Cardiac	-

Table 5. Side-effects associated with chemotherapy

	Group I%(n)	Group II%(n)
Local	36% (9)	16% (4)
Regional	16% (4)	16% (4)
Both	8% (2)	4% (1)
Distant	0%	4% (1)

Table 6. Recurrence pattern

Discussion

The gingivo-buccal complex is the most common subsite of oral cancer in Indian Sub-continent [6]. The gingivo-buccal complex consists of buccal mucosa, alveolus, and both upper and lower gingivo-buccal sulcus and retromolar trigone. A habit of chewing betel quid containing tobacco is closely linked to the etiology of SCC involving this region. The presence of nodal metastasis is single most prognostic factor for determination for survival. Large gingivo-buccal mucosa cancers represent a diverse and challenging group, with virtue of skin and soft tissue infiltration in addition to associated mandible and/or maxilla (bone) invasion. The primary treatment modality for squamous cell carcinoma of buccal mucosa is either surgery or radiotherapy. Despite the use of aggressive multimodality managements, patients with locally advanced buccal mucosa cancer still suffer poor local control, poor quality of life and survival [7]. The rationale underlying the use of NACT in locally advanced buccal mucosa cancer is the possibility of better drug delivery in well vascularised tumours, tumour shrinkage and sterilization of initial edematous wet margins that would allow better results when surgery and/or radiation therapy is given [8]. NACT also help to eradicate micro-metastasis [9]. Though the NACT seems to be promising, but loco-regional control, survival benefits and appropriate NACT regimen are still to be defined and assessed. In oral cavity cancer patients, surgery entails mandibulectomy, which translates into significant functional impairment. Although not formally assessed, some effect on quality of life is plausible [10] .This could justify the incorporation of chemotherapy in the treatment strategy, at least in selected patients. Patients treated NACT with significant pre-operative down staging can be benefitted with less demolitive surgery. This would be in line with the organ- and function-preserving approaches currently used in other head and neck cancers. In oral cavity cancer, the benefit would essentially be functional, in terms of better mastication and cosmetic. Based on this principle the current study was designed to assess the outcome of patients with locally advanced squamous cell carcinoma of buccal mucosa who underwent neoadjuvant chemotherapy followed by surgery and compare them with control group. The standard induction regimen consists of Cisplatin and continuous infusion fluorouracil. In this study following neo-adjuvant chemotherapy 19 out of 25 patients (76%) had partial response, 2 patients (8%) had complete response to NACT, 3 patients (12%) had stable disease and 1 patient (4%) had progression of disease despite two/three cycles of NACT. NACT was tolerable in this study group. Grau et al. reported a 50% partial response and 16% complete response following NACT [11]. Khalife et al. reported a 45% complete response, 23% partial response, 22% stable disease and 10% progressive disease following NACT in their study [12]. Adequacy of excision and achieving oncological resection

margins is an important fundamental in the head and neck squamous cell carcinoma. In our study patients, no had a positive resection margin in both the groups. In this present study, recurrence rate of 60% (15/25), in the group I (NACT followed by surgery and RT) and 40% (10/25) in the group II (Surgery followed by RT) has been noted, consistent with other series recurrence rates in the range of 20-80% [5]. Higher occurrence of loco-regional recurrences in group 1 may be indicative of more aggressive clinical disease, presence of patchy response to NACT or may be result of bias. However, there were no distant recurrences in group 1 as compared to group II. This observation needs further evaluation on larger studies. Chun –Shu-Lin et al. reported a recurrence rate of 57%, and Lee et al. reported a recurrence rate of 25% following NACT followed by surgery and RT in their study [13]. A large number of NACT studies using both single and combination agents have been conducted. The results of these trials have been consistent and failed to demonstrate a survival advantage for the NACT schedule. The largest of these meta-analysis from meta-analysis of chemotherapy in Head and Neck cancer Collaborative group based in France, reviewed 63 randomized trials, including more than 10,000 patients with updated data [14]. Loco-regional treatment was compared with some chemotherapy for locally advanced head and neck SCC. The median follow-up period was 6 years. An absolute survival benefit of 4% was seen in patients given chemotherapy with concomitant regimens. Data from more than 5000 patients treated with NACT regimens were analysed and no statically significantly survival advantage was found when compared with loco-regional treatment alone. It has been suggested that in the advent of newer chemotherapy molecules and regimens and more aggressive drug combinations might result in survival benefit after NACT schedule. This study demonstrated the feasibility of induction chemotherapy with acceptable results. However elaborate studies are necessary from surgical, medical and radiation oncologist community before this NACT approach could legitimately be incorporated into standard care.

Conclusion

Surgical excision is the mainstay of treatment of oral cancers. The aim of the surgery is to completely excise tumor with wide margins. However, the achievement of pathologically negative margins is significantly decreased with increasing T stage of the tumor, especially in tumors with extensive skin edema, extensive soft tissue involvement and involvement of pterygoid muscles. NACT induces a high response rate that may facilitate definitive surgery in a borderline case or where margin identification is difficult due to wet edematous borders of disease. In our study NACT had partial response rate of 76% and complete response in 8% cases. The likelihood of chemotherapy induced response increases with taxane based regimen. Due to short available follow up survival analysis is not possible. Large scale multicenter randomized, controlled trials and meta-analysis are necessary to evaluate the efficacy of NACT in locally advanced buccal mucosal cancer as this approach may be worth for further exploration.

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