Research Article

Neoadjuvant chemotherapy: role in locoregionally advanced oral cancers

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Abstract

Background: Oral cancers are the most predominant cancers in our region due to the habit of betel nut chewing. The treatment protocols available have not given satisfactory results. Neoadjuvant chemotherapy has been tried out successfully in other cancers like cancer of larynx.

Objectives: Our study aimed to assess the response of neoadjuvant chemotherapy in locally advanced oral cancer.

Materials and Methods: A total of 40 patients were taken up for the study; 20 patients each in both study and the control groups. In the study group, patients were subjected to three cycles of neoadjuvant chemotherapy (cisplatin and 5-fluorouracil) after doing relevant investigations, later evaluated for resectability, and later taken up for surgery or radiotherapy depending on the response. In the control arm, all the patients were directly taken up for surgery.

Results: The results showed that among the 20 patients who underwent neoadjuvant chemotherapy no one had complete response, 55% had partial response, 35% had stable disease, and 2 had progressive disease and were advised palliative radiotherapy only. Two patients in study arm were lost for follow-up. The remaining 16 patients in study arm and all 20 patients in control arm were taken up for surgery. The specimens were assessed histopathologically for positive margins. Almost equal incidence of positive margins was found in both arms. The patients were followed up for 2 years after surgery. The results showed marginally better disease-free survival in stage III disease patients who underwent neoadjuvant chemotherapy followed by surgery compared to those who had direct surgery; however, no major difference in patient with stage IVA disease was seen.

Conclusion: Neoadjuvant chemotherapy in locally advanced oral cancers delays the progression of disease and gives partial response macroscopically. There was no significant improvement in locoregional control, disease-free survival, and overall survival of the patients.

KEY WORDS: Betel nut chewing, cisplatin, 5-fluorouracil, neoadjuvant chemotherapy, oral cancers

Introduction

Oral cancer ranks the sixth most common cancer worldwide. Head and neck cancer in India constitutes 40% of all malignancies.[1] The oral cavity is the predominant location in head and neck region for primary malignant tumors. In spite of the advances made in the diagnosis, surgery, radiotherapy, chemotherapy, and reconstruction over the past 50 years, oral cancers continue to pose a challenge to the surgeon. In India, the buccal mucosa and retromolar trigone are the most frequently encountered primary sites.[2]

India has the highest rate of cancer of the oral cavity in the world, with male/female ratio of 2:5. The major difference in occurrence rates between males and females in India could be attributed to the differences in practice of tobacco habits. In a case–control study of the oral cavity, it was found (among controls) that compared to 39% tobacco chewers among women, there were only 9.6% tobacco chewers among men, whereas 63% of males were smokers but <1% women were smokers.[3]

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As survival rates were poor in advanced cancers even after surgery and postoperative radiotherapy, neoadjuvant chemotherapy was tried. Neoadjuvant chemotherapy is used before surgery. Two-to-three cycles of chemotherapy are given. The two most commonly used regimes are cisplatin and 5-fluorouracil and cisplatin and bleomycin.[4] Overall response rates of 80% are frequently achieved, complete response rates are 30%. Some of these are confirmed histopathologically following surgery. Toxicity is moderate to severe, though the rate of distant metastasis is decreased, survival rate is not constantly improved, only in 1 out of 10 studies it is found to be improved.[5]

The benefits of neoadjuvant chemotherapy, according to studies, are tumor reduction, local control, decreased recurrence, decreased distant metastasis, organ preservation in resectable tumors, less need of postoperative radiotherapy, less need for mandibulectomy, and 4%–6% increase in survival rate.[6] The adverse effects are myelosuppression (thrombocytopenia, anemia, leukopenia), nausea, vomiting, stomatitis, alopecia, and facial edema.[6]

In this study, we propose to assess the impact of neoadjuvant chemotherapy in locally advanced oral cancer T_3 and T_4, and N_1 and N_2 in patients who attended the Otorhinolaryngology and Head and Neck Department of RL Jalappa Hospital, Kolar, Karnataka, India.

Materials and Methods

This was a prospective comparative study conducted in the Department of Otorhinolaryngology at RL Jalappa Hospital, Kolar, from April 2008 to March 2010, coordinated by a multidisciplinary team including a head and neck surgeon, a medical oncologist, and a radiation oncologist to evaluate all eligible patients. Well-informed consent was taken explaining the patients the benefits and side effects of the study. The permission of institutional ethics committee was taken. Detailed clinical examination was carried out, and patients were staged accordingly and biopsy was done and sent for histopathological examination. Other required tests such as complete blood examination, X-ray mandible, liver and renal function tests, chest X-ray, electrocardiogram, and detailed ear examination were carried out. Then patients were randomized into groups by single blind method eliminating the bias of age and staging. Twenty patients each were taken in study and control groups. The patients in study group were given neoadjuvant chemotherapy—cisplatin 80 mg/m^2 over 2 days and 5-fluorouracil 750 mg/m^2 for 4 days along with hydration and anti-emetics (3 cycles for every 4 weeks), and later, if resectable, were taken for surgery or else for radiotherapy. The patients belonging to the control group were directly taken for surgery without neoadjuvant chemotherapy. Postoperative radiotherapy was given to all the patients. Follow-up was done for 2 years.

Inclusion criteria included histologically proven oral squamous cell carcinoma $T_3T_4N_1N_2$ disease, previously untreated cases, age between 20 and 80 years, no distant metastasis, normal renal and hepatic functions, patients ready for written informed consent for above study, and resectable tumors. In case of females, inclusion criteria were nonpregnant females and willing for contraceptives for 8 months.

Results

The age group of patients varied from 35 to 71 years in the study arm, and 35 to 75 years in the control arm, with majority of the patients being in age group between 35 and 60 years. This shows the relatively early presentation of malignancy in this region due to the tobacco chewing habit [Table 1]. The majority of patients were females in both arms.

Duration of symptoms in study arm within 6 months was seen in three patients (15%), between 6 and 12 months was seen in eight patients (40%), and >12 months was seen in nine patients (45%) . In control arm, the duration of symptoms within 6 months was seen in five patients (25%). Most of the patients presented late due to illiteracy, ignorance, and poor socioeconomic conditions.

As the study involved locally advanced tumors, the stage-wise distribution was carried out. The majority of patients were in stage IVA (borderline operable); four in study arm, seven in control arm had stage III disease as their tumor was extensively extending to retromolar trigone with no involvement of bone or skin. 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 [Table 2], and majority had either bone or skin involvement. The study group that was subjected to neoadjuvant chemotherapy (cisplatin and 5-fluorouracil), the response was assessed 3 weeks after each cycle. All of them had three cycles of neoadjuvant chemotherapy.

Table 1: Age distribution of patients

Age (in years)	Study arm, *n* = 20		Control arm, *n* = 20	
	No. of patients	%	No. of patients	%
21–30	0	0	0	0
31–40	6	30	5	25
41–50	5	25	6	30
51–60	7	35	4	20
61–70	1	5	4	20
>70	1	5	1	5

Table 2: Tumor size before and after NAC

Size (cm)	Before NAC, *n* = 20	%	After NAC, *n* = 20	%
<2	0	0	0	0
2–4	0	0	2	10
>4	20	100	18	90

Of 20 patients, 11 had partial response and 7 had no progression of disease till they were taken for surgery. However, two patients had progressive disease in spite of chemotherapy and needed palliative radiation therapy. Of the four patients with stage III, three showed partial response. Of the 16 patient with stage IVA, 8 had partial response. Both the patients with progressive disease had stage IVA [Table 3].

Of the 20 patients who were on chemotherapy, 18 (90%) had nausea, 15 (75%) had vomiting, 3 or more episodes per day, which were controlled with antiemetics and did not have major dehydration. Among them, 60% had severe fatigue; 40% had diarrhea after administering chemotherapy, which subsided within 3–4 days; 6 of them had extensive mucositis, out of them 1 needed steroids; 3 patients (15%) had neutropenia (total count <3000/mm^3), however it subsided within 7–10 days and none of them needed granulocyte-stimulating factor [Table 4].

All patients in the control arm were taken for surgical resection. Of them, 16 patients in the study arm (80%) were taken for surgical resection. Two patients who had progressive disease (10%) were referred for palliative radiotherapy as they were found to be inoperable. Two patients had partial response and were planned for surgery but defaulted and lost to follow-up (10%).

Surgical resection involved wide excision of the tumor in all plains with hemimandibulectomy with modified radical/radical neck dissection along with reconstruction using pectoralis major myocutaneous flap [Figures 1 and 2]. All patients in both groups were advised postoperative radiotherapy. The histopathological report of the resected specimen revealed positive margins (R1 resection) in 7 out of 16 patients in the study arm (44%) and 8 of 20 patients in the control arm (40%).

Table 3: Clinical response after neoadjuvant chemotherapy

Response	No. of patients, *n* = 20	%
Complete	0	0
Partial	11	55
Stable disease	7	35
Progressive disease	2	10

Table 4: Toxicities

Toxicities	No. of patients	%
Nausea	18	90
Vomiting	15	75
Fatigue	12	60
Diarrhea	8	40
Mucositis	6	30
Neutropenia	3	15

Table 5: Histopathology findings

Arm	Total no. of patients	Margins positive	%
Study	16	7	44
Control	20	8	40

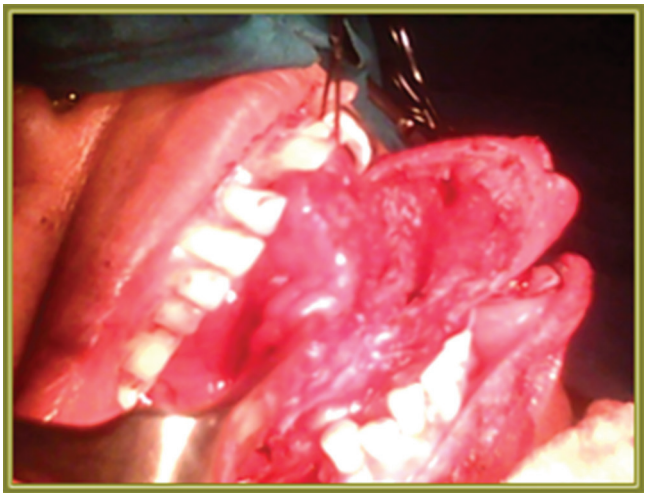

Figure 1: Excision of primary tumor.

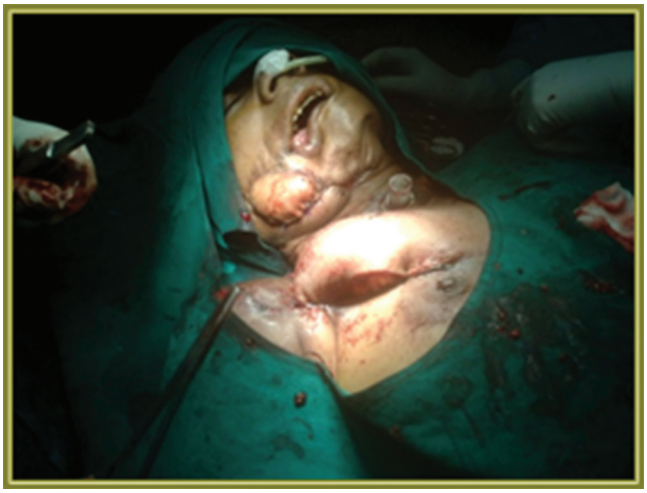

Figure 2: Flap division after reconstruction.

This could mean that though the tumor regressed macroscopically after neoadjuvant chemotherapy, there could have been microscopic disease (diluted margins) [Table 5].

The patients were followed up routinely for 2 years after treatment. At the last follow-up, 4 patients with stage III disease and 6 out of 16 patients with stage IVA disease in the study arm were alive and disease free. In control arm, 6 out of 7 patients with stage III disease and 4 out of 13 patients with stage IVA disease were alive and disease free. In study arm, out of 16 patients who had stage IVA disease, 4 had only local recurrence, 1 had regional recurrence (metastatic neck nodes), 2 had locoregional recurrence, and 1 patient died due to other causes (myocardial infarction) more than 6 months after surgery. All the patients with positive margins

Table 6: Condition at last follow-up

Follow-up	Study arm		Control arm	
	Stage III	Stage IVA	Stage III	Stage IVA
Alive and disease free	4	6	6	4
Alive with local recurrence	0	4	1	4
Alive with regional recurrence	0	1	0	1
Alive with locoregional recurrence	0	2	0	2
Lost to follow-up	0	2	0	2
Death (due to other causes)	0	1	0	0

had recurrences. In the control arm, those who had been directly taken up for surgery without neoadjuvant chemotherapy, one patient with stage III disease and four patients with stage IVA disease had local recurrence. One patient with stage IVA disease had regional recurrence (metastatic neck disease). Two patients had locoregional recurrence. Two patients were lost to follow-up 3 months after the surgery [Table 6].

Discussion

This is a prospective study of 40 patients of locally advanced oral squamous cell carcinoma in which 20 patients (control group) were taken up directly for surgery followed by postoperative radiotherapy. Another 20 patients (study group) were subjected to three cycles of neoadjuvant chemotherapy using cisplatin and 5-fluorouracil and were later evaluated for resectability. Sixteen patients of the study group underwent surgery followed by radiotherapy, two had progressive disease and were subjected to palliative care. One patient was lost to follow-up and one died due to other causes. The age of patients in this study varied from 35 to 75 years, with maximum number of patients being in 35 to 60 years. And the majority of patients were women (75%–80%). This can be explained by the fact that the women in this region (Kolar and adjoining areas) have the habit of using tobacco or betel leaf with slaked lime cud in their mouth.

The onset of malignancy in this area is relatively at an early age (30s and 40s) owing to the above habit. And this area has a high incidence of oral cancer.[7] Most of the patients presented with locally advanced disease in this area. This is because of illiteracy and ignorance in this region and poor socioeconomic conditions. Lack of awareness among local medical practitioners is also a contributing factor for late presentation of the patients. As can be deduced from the stage-wise distribution of patients, 80% of patients in study group and 65% of patients in control group had stage IVA disease (involvement of skin or bone). In the majority of patients in addition to buccal mucosa, the mandible was involved as evidenced by clinical and radiological examinations. And the tumor was extending to upper alveolus in 11 patients in the study group and 8 patients in the control group. Retromolar trigone was involved in 50% of patients in both arms. Skin involvement was 80% in the study group and 65% in the control arm. The late presentation of patients in this region indicates lack of awareness.

The patients in study arm (20 patients) were subjected to three cycles of cisplatin 80 mg/m^2 and 5-fluorouracil 750 mg/m^2, administered once in 3 weeks and response was assessed after each cycle. The patients were also evaluated for adverse reaction and their blood count was taken after each cycle of chemotherapy. Most of these patients tolerated neoadjuvant chemotherapy well; however, the reactions seen were nausea and vomiting (2–3 episodes per day) in most of the patients (75%–90%), generalized weakness, and fatigue in 60% of patients. And in 30%–40% patients, extensive mucositis and diarrhea were observed and 15% presented with neutropenia. However, none of these patients had adverse effects severe enough to require intervention with granulocyte-stimulating factor. The nausea, vomiting, mucositis, and diarrhea could be easily controlled with injectable antiemetics, supportive care, delaying the next cycle of chemotherapy by 5–7 days; in occasional case one or two doses of steroids were given. Most of the studies in literature have shown extensive mucositis wherever high-dose 5-fluorouracil (500 mg/day days 2–6) was used[8] and reduced toxicity was seen in various studies using neoadjuvant chemotherapy whenever the dose of 5-fluorouracil was reduced and additive drug like paclitaxel was added.[9] However, in our study the low incidence of toxicity can be explained to the slightly lower dose of 5-fluorouracil (750 mg/m^2 per cycle) and good supportive care. The neutropenia was transient and did not require intervention. The toxicities showed increased severity in various studies wherever concurrent chemoradiation has been used.[4] Among the 20 patients who underwent neoadjuvant chemotherapy, no one had complete response, 55% of patients had partial response as evidenced by reduction in size of tumor and 35% had stable disease without any progression till they were taken up for surgery. Two patients had progressive disease and were advised only palliative radiotherapy.

Most of the other studies had equal number of stage III and stage IV cases. So in other series involving neoadjuvant chemotherapy, quoted complete response rates vary from 14% to 30%.[6] However, it was not seen in our series as only cisplatin and 5-fluorouracil with a lower dose of 5-fluorouracil was used. And most of our patients had stage IV disease.

Partial response was seen in majority of our patients and 35% had stable disease with no progression. The other series in literature have also shown better locoregional control rates and better resectability till patients were taken up for surgery whenever neoadjuvant chemotherapy was used.[10] The two patients who had progressive disease were subjected to palliative radiation.

In our series, partial response was seen in three of four patients who had stage III disease only. However 8 out of 16 had partial response with stage IVA disease. This concurs with other series where the response rate was better whenever neoadjuvant chemotherapy was used. However, addition of taxanes in the studies abroad, especially European studies in Spain and Italy, has shown better response rates.[11] All 20 patients in the control arm and 16 patients in the study arm were taken up for surgery, which was wide excision of primary tumor along with hemimandibulectomy and neck dissection. The specimen was assessed by histopathology for positive margins. Among the control group, 8 of 20 (40%) had margins positive and 7 of 16 (44%) in study group had margins positive. This shows that though the macroscopic size of tumor reduced after neoadjuvant chemotherapy and borderline inoperable tumors looked more resectable, there was underlying microscopic disease. So, the resection must be as radical as it would have been without neoadjuvant chemotherapy. Though the tumors were made more assessable for resection, there was no obvious improvement in locoregional control following neoadjuvant chemotherapy. The studies abroad have also shown no significant improvement in locoregional control following neoadjuvant chemotherapy.[12]

All the patients in both study and control arms who had positive margins had recurrence. And the other patients had no recurrence till the end of the study. Having followed up for a minimum period of 2 years, among the stage III patients 6 of 7 in the control group (direct surgery) were alive and disease free, and 4 of 13 stage IVA patients in the control group were alive and disease free. In study group, four of four patients with stage III disease who underwent neoadjuvant chemotherapy followed by surgery were alive and disease free. Of the 12 patients, 6 with stage IVA disease who underwent neoadjuvant chemotherapy followed by surgery were alive and disease free (2 patients had progressive disease and were subjected to palliative radiotherapy and were not operable). Two patients were lost to follow-up and could not be taken up for surgery after partial response with neoadjuvant chemotherapy. This shows marginally better disease-free survival in patients with stage III disease who underwent neoadjuvant chemotherapy followed by surgery compared to those who had direct surgery. However, neoadjuvant chemotherapy did not show a major difference in patients who had stage IVA disease.

Among the patients with stage IVA disease who underwent neoadjuvant chemotherapy followed by surgery, 3 of 12 patients had local recurrence and all of them had positive margins. One patient had regional recurrence and one patient had locoregional recurrence. The patient with locoregional recurrence also had positive margins. One patient died 6 months after surgery due to other causes did not have any recurrence till the last follow-up. Among the patients with stage IVA disease who were directly taken up for surgery followed by postoperative radiotherapy 4 of 13 had local recurrence, 1 had regional recurrence (neck nodes), and 2 patients had locoregional recurrence. Two patients were lost to follow-up soon after postoperative radiotherapy. Among the patients with stage III disease taken up directly for surgery, only one of seven had local recurrence. There was no locoregional or regional recurrence. This shows almost similar locoregional control and disease-free survival rate among the control and study arms. So, there was no significant benefit on disease-free survival rate and overall survival rate after administering neoadjuvant chemotherapy in stage IVA disease. The studies abroad also show no significant benefit of using neoadjuvant chemotherapy on overall survival and disease-free survival.[13] However, organ preservation (mandible) has been achieved in T_2 and T_3 disease in abroad studies[14] but not in our study as most of the patients had lower alveolus involvement. The studies abroad quote low incidence of metastasis whenever neoadjuvant chemotherapy is used.[15] None of our patients had distant metastasis till 2 years.

Conclusion

Neoadjuvant chemotherapy in locally advanced oral squamous cell carcinoma delays the progression of disease and gives partial response macroscopically. However, in a significant number of patients there is microscopic disease. So extent of resection cannot be compromised after neoadjuvant chemotherapy. The borderline inoperable tumors were made more assessable to resection following neoadjuvant chemotherapy. There was marginal benefit whenever neoadjuvant chemotherapy was used in stage III disease. However, it was not so in stage IVA disease. There was no significant metastasis in the entire series. There was no significant improvement in locoregional control, disease-free survival, overall survival when neoadjuvant chemotherapy was used in locally advanced squamous cell carcinoma. This correlates with most of the studies conducted abroad. However, response rates can be improved by increasing the dose of cisplatin and 5-fluorouracil or by adding paclitaxel to neoadjuvant chemotherapy, as shown in the studies conducted abroad. However, our patients were relatively undernourished and might not tolerated such high-dose chemotherapy, and taxanes are still too costly for a patient with head and neck squamous cell carcinoma in a rural setup in our country.

More multi-institutional trials are required to arrive at a definite conclusion or protocol with neoadjuvant chemotherapy that may make a difference in locally advanced oral malignancies.

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