

# Locally advanced oral cavity squamous cell carcinoma: Barriers related to effective treatment

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## Abstract

**Background:** Oral cavity cancer is a significant health problem in India. Majority of patients present with locally advanced disease requiring multimodality treatment. Compliance to recommended treatment is an important factor affecting outcome. **Aims:** The aim was to evaluate the outcome of locally advanced oral cavity cancer patients with regards to treatment adherence and to assess reasons of noncompliance. **Materials and Methods:** This was a prospective observational study. We included patients referred to Department of Medical Oncology for induction chemotherapy in view of locally advanced oral cavity cancer. **Results:** Only 15 (26%) patients completed planned treatment schedule. Their 1 year overall survival was 93%. The remaining 43 patients who received inadequate treatment had a dismal 21% 1 year overall survival. Illiteracy, poverty, long waiting list for surgery, prolonged delay for health scheme treatment plan approval and dissatisfaction with attitude of hospital staffs are major barriers related to effective treatment of these patients. **Conclusions:** A detailed discussion with patient and their relatives regarding recommended treatment, proper implementation of health schemes, increasing trained manpower to avoid long waiting list for surgery, provision of additional financial support for family member accompanying the patient and a sympathetic approach toward patients are needed to help these patients overcome the battle.

**Key words:** Induction, locally advanced, oral cavity

## Introduction

In India according to GLOBOCON 2012 data, oral cavity cancer was the most common cancer in men accounting for 53,842 cases (11.3% of all cancer cases). Oral cavity cancer resulted in 36,436 deaths (10.2% of all cancer-related deaths) in men and was the third most common cause of cancer-related deaths after lung and stomach cancer. In females, oral cavity cancer stood fifth in terms of incidence with 23,161 cases (4.3% of all cases) and it was fifth most common cause of cancer-related mortality in females following breast, cervix, colorectal and ovarian cancer with 15,631 deaths (4.8% of all cancer-related deaths).<sup>[1]</sup>

Although surgical excision is the mainstay of treatment for oral cavity cancers, Indian Council of Medical Research data suggests that 70–80% of oral cavity cancers present with advanced stage and are unresectable.<sup>[2]</sup> These patients are treated with nonsurgical modalities like concurrent chemoradiation, radical radiation, palliative radiation and best supportive care. However, the nonsurgical modalities rarely achieve a lasting cure. Use of induction chemotherapy in technically unresectable oral cavity cancer has been effective in down staging the tumor and enabling radical surgery.<sup>[3]</sup> Use of induction chemotherapy has been found to be safe and patients undergoing resection after induction chemotherapy had much better overall survival (median overall survival 18.0 months) than those who were treated with non-surgical local treatment (median overall survival 6.5 months). Use of induction chemotherapy was found to achieve resectability in 39% of locally advanced unresectable oral cavity cancers.<sup>[3]</sup> Following surgical resection, few patients require additional radiotherapy sometimes concurrently with chemotherapy to reduce the risk of recurrence.<sup>[4]</sup> Thus, the complete treatment schedule becomes lengthy sometimes making compliance with recommended treatment a significant issue affecting outcome.

The present study was carried out in a tertiary oncology center to analyze the scenario of locally advanced oral cavity cancer patients who received induction chemotherapy in an attempt to downstage the tumor and subsequently facilitate surgical resection. We evaluated outcome of patients receiving adequate treatment and compared it with the outcome of others not following adequate treatment schedule. We aimed to assess reasons of noncompliance with the recommended treatment schedule and hence that this significant issue can be addressed in future to improve the outcome of these patients.

## Materials and Methods

This was a prospective observational study. We obtained written informed consent from all patients. We included patients referred to the department of medical oncology for induction chemotherapy in view of locally advanced oral cavity cancer technically unresectable during July 2012 to December 2012. Patients were planned for 2–3 cycles of chemotherapy (cisplatin + 5 fluorouracil/cisplatin + paclitaxel/docetaxel + cisplatin + 5 fluorouracil) followed by surgical resection in responding patients. Sociodemographic determinants such as age, gender, tobacco/alcohol use, education, occupation, monthly family income were assessed for each patient. Socioeconomic status was determined by modified Kuppaswamy's socioeconomic scale.<sup>[5]</sup> All patients were assessed at the end of 1 year of followup with the help of patients' case files and contact information mentioned in case files. Treatment taken by patients and subsequent treatment outcome was analyzed. We also tried to analyze reasons behind inadequate treatment received by patients with the help of open-ended interview questions.

## Statistical analysis

All variables were entered on Microsoft excel/Statistical Package for Social Sciences 15 (SPSS Inc., 233 South Wacker Drive, 11<sup>th</sup> floor, Chicago). Overall survival was based on the length of time that the patient survived after being diagnosed with cancer.

## Results

During July 2012 to December 2012, a total of 58 patients were referred to Department of Medical Oncology for induction chemotherapy in view of locally advanced inoperable oral cavity squamous cell carcinoma. All our patients were being

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treated free of cost after being enrolled in the government scheme. Treatment approval required histopathological diagnosis and treatment requisition form filled duly by treating doctor. For each modality of treatment (chemotherapy/surgery/radiotherapy) a separate new requisition form had to be filled up by concerned treating doctor and treatment used to start after approval of that particular treatment plan. The maximum upper limit of entire treatment cost covered for an individual patient under the scheme is 1.5 lakhs.

There were 31 (53%) male patients and 27 (47%) female patients. Majority of patients were in the age group of 40–49 years (33%). Majority of patients belonged to upper lower (84%) and lower (9%) socioeconomic status as per modified Kuppaswamy's socioeconomic scale [Table 1 shows patient characteristics in study population]. Out of 58 patients, 55 (95%) were some form of tobacco users, and 33% had regular alcohol consumption along with tobacco addiction [Table 2 shows the distribution of study population according to habits]. We had planned for 2–3 cycles of induction chemotherapy, followed by surgery in responding patients. Following surgery patients with high risk of recurrence (positive surgical margins, pathological nodes positive, extracapsular extension) were planned for adjuvant radiotherapy with weekly cisplatin along with radiation. Patients with poor response to induction chemotherapy were referred for palliative radiotherapy. Only 15 (26%) patients completed planned treatment schedule of chemotherapy followed by surgery and adjuvant radiotherapy when indicated. One year overall survival for this group of patients was 93%. The median overall survival of the remaining 43 patients who received inadequate treatment was 6 months with a dismal 21% 1 year overall survival. [Tables 3 and 4 showing treatment taken by patients and treatment outcome respectively].

As majority of our patients and their relatives were illiterate and belonged to low socioeconomic status, they were unaware of prescribed treatment schedule and this contributed to low compliance to recommended treatment with patients either defaulting for surgery after achieving good response to induction chemotherapy or defaulting for necessary adjuvant radiation whenever indicated. A prolonged delay for the surgery date following good response to induction chemotherapy increasing tumor size rendering it inoperable was also a significant factor contributing to poor outcome. As these patients were awaiting approval for surgery under government health scheme, we could not ask for approval of concurrent chemoradiation in these patients. Waiting for individual treatment plan approval (approval for surgery following chemotherapy/approval for radiation following surgery or chemotherapy) led to early treatment closure by few patients. Social reasons such as nobody being available to accompany patients to receive treatment and inability to bear expense of transportation to and from the hospital also had an impact on treatment adherence and ultimate outcome. Side-effects of chemotherapy/radiotherapy made a few patients refrain from further treatment. The most common side effects experienced by patients were emesis and mucositis, whereas febrile neutropenia and aspiration pneumonia were relatively uncommon. Few (21%) patients also felt that since they were being treated free of cost, they were being treated as inferior

and hence did not continue further treatment [Table 5 shows reasons for inadequate treatment received by patients].

## Discussion

The oral cavity consists of lip, floor of the mouth, oral tongue (anterior two-thirds of the tongue), buccal mucosa, upper and lower gingiva, hard palate and retromolar trigone. Oral cavity cancer is of significant public health importance to India. It is often diagnosed at a late stage which results in inferior outcome and requires multimodality treatment incorporating chemotherapy, surgery and radiotherapy with considerable costs to the patients who typically cannot afford the treatment.<sup>[6]</sup> Lack of adequate access to trained health care providers and limited

**Table 1: Patient characteristics in study population**

Patient characteristic	Number (n=58)	Percentage
Age (in years)		
<40	14	24
40-49	19	33
50-59	13	22
60 and above	12	21
Sex		
Male	31	53
Female	27	47
Socioeconomic status as per modified Kuppaswamy's socioeconomic scale		
Upper	0	
Upper middle	0	
Lower middle	4	7
Upper lower	49	84
Lower	5	9
Duration of symptoms prior to hospital consultation		
<1-month	4	7
1-3 months	24	41
3 or more months	30	52

**Table 2: Distribution of study population according to habits**

Habit	Number (%)
Tobacco	55 (95)
Bidi	19 (33)
Cigarettes	04 (7)
Gutkha	14 (24)
Betel nut with tobacco	21 (36)
Both tobacco and alcohol	19 (33)

**Table 3: Treatment taken**

Treatment taken	Number of patients (n=58) (%)
Chemotherapy followed by surgery with adjuvant radiotherapy±chemotherapy when indicated (adequate treatment)	15 (26)
Chemotherapy followed by surgery but defaulted for necessary adjuvant treatment	04 (7)
Only chemotherapy (defaulted for surgery/ delay in surgery after having good response to chemotherapy)	19 (33)
Chemotherapy followed by palliative radiotherapy (poor response to chemotherapy and hence surgery could not be offered)	07 (12)
Did not complete planned chemotherapy cycles	09 (15)
Chemotherapy followed by palliative care	04 (7)

**Table 4: Treatment outcome**

Treatment compliance	Outcome
Adequate treatment	1-year overall survival 93% Median overall survival >1-year
Inadequate treatment	1-year overall survival 21% Median overall survival 6 months

**Table 5: Reasons for inadequate treatment**

Reason	Number of patients (%)
Lack of understanding of recommended treatment	11 (26)
Nobody available to accompany patients to receive treatment	7 (16)
Delay in getting surgery date	14 (33)
Delay in approval of health scheme	17 (34)
Side effects of treatment	8 (18)
Preference to seek alternative treatment (homeopathy, ayurveda)	8 (18)
Inability to bear expense of transportation to and from the hospital	9 (21)
Not happy with care received at the center	9 (21)

health services in rural areas leads to delay in diagnosis of these cancers leading to the advanced stage at presentation.<sup>[7]</sup> Our study also had similar findings with 30 (52%) of our patients presenting to a cancer hospital after more than 3 months of symptom onset. As noted in our study oral cavity cancer affects people from the lower socioeconomic strata of society due to a higher exposure to risk factors such as the use of tobacco.<sup>[8]</sup> The concomitant use of alcohol and tobacco has been shown to significantly increase the risk of head and neck cancers.<sup>[9]</sup> It is also found that men who both smoke and drink are nearly 38 times more likely to develop head and neck cancers than men who do neither.<sup>[10]</sup> The risk for a second primary tumor in patients with a previous upper aerodigestive tract tumor is augmented by alcohol and smoking.<sup>[11]</sup> Among Asian population, a significantly higher risk of cancer of upper aero-digestive tract, oral cavity, oropharynx and hypopharynx were found in moderate or heavy drinkers carrying the ADH1B \*1 allele or ADH1C\*1/\*2 or ADH1C\*2/\*2 genotypes.<sup>[12]</sup> In our study, 33% patients were addicted to both tobacco and alcohol.

Early detected oral cavity cancers (stages I and II) are usually treated with surgery or radiotherapy with equivalent 5-year survival of approximately 80%. Surgical resection is technically not possible in locally advanced oral cavity cancer as the oral cavity is anatomically close to the infra-temporal fossa and masticator space, explaining the frequent involvement of these spaces in the oral cavity primaries.<sup>[13]</sup> These patients are usually treated with radical radiotherapy with or without chemotherapy with an estimated 5-year survival of 50–60% according to western literature. However, treatment outcomes have generally been poor in Indian patients. Ghoshal *et al.*<sup>[14]</sup> reported that the 2-year disease free survival for buccal mucosa cancer patients was 48%, and patients with advanced stage who were treated with palliative intent had much worse outcome. Nair *et al.* reported 3-year disease free survival of 41% for stage III and 15% for stage IV buccal mucosa patients treated with radiotherapy.<sup>[15]</sup> Agarwal *et al.* found 55% 1 year progression free survival for advanced head and neck cancer patients treated with radiotherapy.<sup>[16]</sup>

Different approaches have been tried to improve outcome of these patients. Use of induction chemotherapy has been

found effective to downstage the tumor and facilitate surgical resection in patients whose tumors are deemed unresectable at presentation. Patients undergoing resection after induction chemotherapy had much better overall survival (median overall survival 18.0 months) than those who were treated with non-surgical local treatment (median overall survival 6.5 months).<sup>[3]</sup> Induction chemotherapy is generally given for 2–3 cycles every 3 weeks and then patient is assessed for surgery. Following surgery patients with high risk of recurrence (positive surgical margins, pathological nodes positive, extracapsular extension) need adjuvant radiotherapy with weekly cisplatin along with radiation. Postoperative radiation dose is 60–66 Gy (2.0 Gy/fraction daily Monday–Friday in 7 week).

Thus compliance with recommended treatment is an important factor contributing to treatment outcome in these patients. Although poverty and nonaffordability for treatment is often looked as the major culprit for poor outcome in Indian patients, our patients were being treated free of cost under government health insurance scheme and we found that there are several other things contributing to ultimate outcome of these patients. As majority of our patients were illiterate, they were unaware of prescribed treatment schedule, and this led to patients either defaulting for surgery after achieving good response to induction chemotherapy or defaulting for necessary adjuvant radiation whenever indicated. Social reasons such as nobody being available to accompany patients to receive treatment and inability to bear expense of transportation to and from the hospital also had an impact on treatment adherence. As there are only a few government funded cancer centers which are often overburdened with patients and have a long waiting list, a prolonged delay for surgery date following good response to induction chemotherapy increasing tumor size rendering it inoperable was also a significant factor contributing to poor outcome in our patients. Proper implementation of health scheme is also important as delay in approval of individual treatment plan (approval for surgery following chemotherapy/approval for radiation following surgery or chemotherapy) can be annoying for patients and their relatives who later on prefer for alternative treatment such as homeopathy or ayurvedic treatment.

## Conclusions

Public health officials, private hospitals, and academic medical centers within India have recognized oral cavity cancer as a grave problem and improving the outcome of locally advanced oral cavity cancer poses a major therapeutic challenge. A detailed discussion with patient and their relatives regarding recommended treatment, proper implementation of health schemes, increasing trained manpower to avoid long waiting list for surgery, provision of additional financial support for family member accompanying the patient and a sympathetic approach towards patients are needed to help these patients overcome the battle.

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