Efficacy and Toxicity of Concurrent Chemoradiation in Inoperable Oral Carcinoma in Pakistani Population

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ABSTRACT
Objective: To evaluate the efficacy of concurrent chemoradiation in patients with locally advanced inoperable squamous cell carcinoma of oral cavity in terms of local control and toxicity.
Study Design: Case series.
Place and Duration of Study: Institute of Nuclear Medicine and Oncology (INMOL), Lahore, from January 2008 to December 2013.
Methodology: Sixty-nine patients with locally advanced inoperable oral cavity cancer, registered in INMOL hospital from January 2008 to December 2013 who fulfilled a pre-defined eligibility criteria, were enrolled in the study. Concurrent chemoradiation protocol consisted of conventional fractionation delivering 70 Gy with weekly Cisplatin (50 mg/m²) during the course of radiation. Tumor response was calculated by RECIST criteria version 1.1 along with the median overall survival and disease-free survival. Acute treatment related toxicities were graded as (G).
Results: Thirty-six (52.17%) patients showed complete response; while 19 (27.54%), 8 (11.59%) and 6 (8.7%) were observed with partial response, stable and progressive disease, respectively. Treatment response was significant (p<0.001) in terms of responders vs. nonresponders to treatment. Median overall survival was 18.00 months; whereas, median disease-free survival remained 14.00 months. Main toxicities included mucositis (G3 and G4, 71%), xerostomia (G2 and G3, 82.5%), vomiting (G3 and G4, 51%), myelosuppression (G3 and G4, 26.2%), dermatitis (G3 and G4, 49.2%), and fatigue (G3 and G4, 57.9%).
Conclusion: Platinum based CCRT remained effective for inoperable oral cancer patients.

Key Words: Chemoradiotherapy. Toxicity. Squamous cell carcinoma of head and neck. Inoperable.

INTRODUCTION
Oral cancer is the eighth most common malignancy worldwide; but unfortunately, it is the second most commonly observed cancer in Pakistan.1 A recent study, focusing on the population-based incidence of oral cavity cancer, has reported that the incidence rates of oral cancer are the highest in Pakistan and India.2
Most of the oral cancers (90-95%) are squamous cell carcinomas. Majority of patients with squamous cell carcinoma present with loco-regionally advanced disease which is associated with poor prognosis, and 5-year survival is generally low, i.e. 30-59%.3,4
Treatment approach for locally advanced oral carcinomas is surgical excision of primary tumor along with dissection of cervical lymph nodes, wherever possible.

This is followed by adjuvant radiotherapy. Adjuvant chemoradiation is reserved for cases with close or positive margins and extra-capsular extension of nodal disease. However, in cases where surgery is not possible due to non-resectable disease or medical comorbidities, concurrent chemoradiation (CCRT) is the standard option in patients with satisfactory performance status. However, in spite of using multimodality treatment, survival rate is still low and median survival has been reported as low as 2-12 months.5,6
In recent years, Cisplatin has emerged as a promising chemotherapeutic agent for the treatment of advanced oral squamous cell carcinomas (OSCC). A number of studies have reported improved 5-year survival in the patients treated with Cisplatin therapy either alone or in combination with 5 Fluorouracil in both neo-adjuvant and concurrent setting.7-9
The aim of the current study was to evaluate the efficacy of the concurrent chemoradiation therapy in locally advanced inoperable oral squamous cell carcinoma and to measure treatment-related acute toxicity in the local setting.

METHODOLOGY
The study was conducted on biopsy proven inoperable oral cavity squamous cell carcinoma patients belonging
to both genders, who were enrolled in the Institute of Nuclear Medicine and Oncology, Lahore (INMOL) for treatment from January 2008 to December 2013. Patients with Stage III, IVA and IVb were included. Exclusion criteria comprised of patients with recurrent disease, prior head and neck radiotherapy, metastatic disease or Eastern Cooperative Oncology Group (ECOG) performance status > 2.

In order to evaluate the patients according to the above mentioned selection criteria, patients’ pretreatment evaluation records were analyzed. It included biopsy report to establish diagnosis, a complete medical history along with local and general physical examination findings, computerized tomography (CT) or magnetic resonance imaging (MRI) of head and neck, to establish local extent of disease; and chest X-ray and abdominal sonogram to rule out distant metastasis and baseline fitness for chemotherapy. Basic blood chemistry included complete blood counts (CBC), liver function tests (LFTs) and renal function tests (RFTs). Glomerular filtration rate (GFR) was calculated for each patient additionally, using Cockcroft formula before giving Cisplatin.

Sixty-nine patients fulfilled the selection criteria. Following informed consent, they received a total dose of 70 Gy in 35 fractions in around 7 weeks. Patients were radiated by parallel opposed lateral beams and bilateral low anterior neck field, using energy of 6MV on LINAC. They were administered weekly Cisplatin during the course of radiation, starting from the first day of radiation at a dose of 50 mg/m². No radiation dose corrections were applied, if treatment gap did not extend the overall treatment time beyond 8 weeks. Some patients, who could not be treated with CCRT immediately due to treatment machine burden, were administered 2 to 3 cycles of neoadjuvant chemotherapy. Regimen selected for this purpose was Cisplatin (100mg/m²) given intravenously on day 1 with adequate pre-hydration and post-hydration, and 5-Fluorouracil (1000mg/m²) given through continuous intravenous infusion on days 1 to 5, every 3-4 weeks depending upon bone marrow recovery.

Clinical response to treatment was assessed through physical examination, both during treatment and 12 weeks after completion. In case of no-disease signs on physical examination, complete response was verified by post-treatment CT or MRI imaging. Response was stratified according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 in complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Complete response was characterized as the absence of visible disease by physical examination and radiographic investigation, both in the primary site and neck.

Data were analyzed using SPSS V.16. Chi-square test was applied for measuring significance of categorical variables. P-values <0.05 were considered significant. Median overall survival (OS) and disease-free survival (DFS) were estimated through follow-up record applying Kaplan-Meier method. Median values were calculated because of small sample size. Data was not normally distributed; therefore, parametric analysis was not performed.

Tolerance to treatment was determined by the patients’ ability to complete treatment as per above mentioned protocol. Treatment time extending beyond 8 weeks for study was considered an unacceptable major deviation; and inferred as poor tolerance to treatment.

For the purpose of study, acute and subacute toxicities of CCRT only were focused. Acute toxicities were defined as treatment, related side effects observed during the course of CCRT until 6 weeks post-treatment. Subacute toxicities were defined as treatment-related side effects that developed any time between 6 weeks to 6 months following treatment. All patients who stopped coming for scheduled follow-up visits for at least a year were assumed dead for the purpose of study.

Treatment-related toxicities were graded according to Common Toxicity Criteria (CTC) version 4. Grade 1 and 2 toxicities were managed by supportive treatment alongside CCRT, while grade 3 and 4 toxicities were managed more aggressively by withholding CCRT and managing with indoor supportive care.

**RESULTS**

The study included 69 patients with oral squamous cell carcinoma. Maximum incidence was observed in the age range of 51 to 60 years comprising of 25 (36.23%) patients. It was followed by fifth decade (41-50 years) comprising of 18 patients (26.09%), while seventh decade (61-70 years) was the third most common age group comprising of 12 patients (17.39%).

Patients population comprised of 66.7% (n=46) male and 33.3% (n=23) female patients in our study. Male patients were predominantly high (p=0.006).

As regards of the subsite involvement, tongue remained the most common site of primary disease comprising 37.7% of all cases with majority of lesions in midline (35%) followed by right sided tongue lesions (23.3%). Buccal mucosa was the second common site with an incidence of 20.3%. Alveolar ridge (n=11; 15.9%) was the third most common site of primary disease.

Response to treatment in the subjects under study was calculated. It was observed that 79.7% (n=55) patients had shown response to treatment with 52.17% (n=36) having complete response (CR) and 27.5% (n=19) showing partial response (PR). 11.59% (n=8) patients had stable disease (SD), and progressive disease (PD) was observed in 8.7% (n=6) patients.
Stage- and site-wise treatment response was also evaluated. Eleven out of 69 patients were staged as III, making 15.9% of patient population. Stage IVa was present in 52 (75.4%) and IVb in 6 (8.7%) of the patients at presentation.

Stage III patients had shown maximum response to treatment and 10 out of 11 had shown complete response to treatment, i.e. 90.9%. Only one patient had shown partial response to treatment (9.1%), and stable and progressive disease was not observed in this stage.

Maximum patient population had stage IVa at presentation. This stage had CR in 24 (46.2%) and PR in 16 (30.8%) patients; while SD and PD was observed in 8 (15.4%) and 4 (7.7%) patients, respectively.

Patients presented at stage IVb had CR, PR and PD in 2 (33.3%) patients each; while no patients was observed with stable disease.

Site-wise treatment response was also evaluated. Tongue was the most commonly observed site with 26 (37.7%) patients. Complete response to treatment in tongue was observed in 13 (50.0%) patients. Maximum CR was observed in floor of mouth where CR was 100%. Only one patient had disease in floor of mouth and showed complete response to treatment. In retromolar trigone (RMT), 90.0% patients had shown complete response to treatment; while poorest response was observed in gingiva, showing 0% and hard palate with 16.7% CR (Table I).

Median overall survival was calculated for all 69 patients and turned out to be 18.00 months with IQR (Q3-Q1, 9.00-24.00, Figure 1).

Median disease-free survival was 14.00 months with IQR (Q3-Q1, 9.00-18.00) in locally advanced inoperable oral cancer. It was calculated using data for 38 patients who had shown complete response to CCRT. Thirty-one patients experienced either partial response, stable disease or progressive disease. They were thus excluded from data, while calculating disease-free survival.

Toxicities and grading of toxicities were assessed in reference with Common Toxicity Criteria (CTC) version 4. None of the 69 patients had to discontinue treatment.

### Table I: Stage- and site-wise treatment response in study population.

<table>
<thead>
<tr>
<th>Treatment outcomes</th>
<th>Complete response (CR) N (%)</th>
<th>Partial response (PR) N (%)</th>
<th>Stable disease (SD) N (%)</th>
<th>Progressive disease (PD) N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-wise outcome:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>10 (90.9)</td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Stage IVa</td>
<td>24 (46.2)</td>
<td>16 (30.8)</td>
<td>8 (15.4)</td>
<td>4 (7.7)</td>
<td>52 (100)</td>
</tr>
<tr>
<td>Stage IVb</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>2 (33.3)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Site-wise outcome:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>13 (50.0)</td>
<td>10 (38.5)</td>
<td>1 (3.8)</td>
<td>2 (7.7)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>8 (57.1)</td>
<td>4 (28.6)</td>
<td>1 (7.1)</td>
<td>1 (7.1)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Hard palate</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>3 (50.0)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Alveolar ridge</td>
<td>4 (36.4)</td>
<td>3 (27.3)</td>
<td>4 (36.4)</td>
<td>0 (0)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Gingiva</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Retromolar trigone (RMT)</td>
<td>9 (90.0)</td>
<td>0 (0)</td>
<td>1 (10.0)</td>
<td>0 (0)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

### Table II: Grade-wise acute and sub-acute toxicities of CCRT observed in patients of oral cavity carcinoma.

<table>
<thead>
<tr>
<th>Side effects (n=69)</th>
<th>G0 n (%)</th>
<th>G1 n (%)</th>
<th>G2 n (%)</th>
<th>G3 n (%)</th>
<th>G4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>24 (34.8)</td>
<td>36 (52.2)</td>
<td>7 (10.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0)</td>
<td>3 (4.3)</td>
<td>26 (37.7)</td>
<td>31 (44.9)</td>
<td>9 (13.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>4 (5.8)</td>
<td>30 (43.5)</td>
<td>31 (44.9)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0 (0)</td>
<td>6 (8.7)</td>
<td>14 (20.3)</td>
<td>29 (42.0)</td>
<td>20 (29.0)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2 (2.9)</td>
<td>3 (4.3)</td>
<td>30 (43.5)</td>
<td>31 (44.9)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23 (33.3)</td>
<td>46 (66.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysphagia / Odynophagia</td>
<td>0 (0)</td>
<td>11 (15.9)</td>
<td>26 (37.7)</td>
<td>28 (40.6)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>0 (0)</td>
<td>5 (7.2)</td>
<td>40 (58.0)</td>
<td>24 (34.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myelosuppression (Neutropenia)</td>
<td>0 (0)</td>
<td>11 (15.9)</td>
<td>40 (58.0)</td>
<td>14 (20.3)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>0 (0)</td>
<td>12 (17.4)</td>
<td>37 (53.6)</td>
<td>20 (29.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>0 (0)</td>
<td>26 (37.7)</td>
<td>37 (53.6)</td>
<td>6 (8.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0 (0)</td>
<td>14 (20.0)</td>
<td>36 (52.1)</td>
<td>19 (27.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>62 (89.8)</td>
<td>3 (4.3)</td>
<td>1 (1.4)</td>
<td>3 (4.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Oral Candidiasis</td>
<td>0 (0)</td>
<td>4 (5.8)</td>
<td>7 (10.1)</td>
<td>27 (39.1)</td>
<td>31 (44.9)</td>
</tr>
</tbody>
</table>

*Shows qualitative evaluation of the side effects in terms of Yes or No (n represents the frequency of patients in each sub-group, G0 - G4 is indicative of grades of toxicity).
altogether as a result of severe toxicity. None of the patients suffered from treatment breaks that extended the overall treatment period beyond 8 weeks. Therefore, we can safely say that CCRT was well tolerated. Objective analysis of specific acute and sub-acute CCRT induced toxicities are tabulated in Table II.

**DISCUSSION**

Oral cancers are more frequently observed in men as compared to women. We have observed 66.7% (n=46) male and 33.3% (n=23) female patients in our study. Disease incidence was observed to be significantly high (p=0.006) in male subjects as compared to females (Table I). Higher incidence in males may be due to greater use of tobacco in our society.

Oral cancer, commonly affects patients in the sixth to seventh decades of life. However, some recent studies have suggested that carcinoma is affecting the younger population without any risk factors. In this present series, most of the patients were in sixth followed by fifth decade of life. Age related incidence in our study remained 46.4% (n=32) for the patients below 50 years and 53.6% (n=37) for the patients older than 50 years.

Many studies have reported tongue as the major site affected by oral cavity carcinomas comprising of almost 42% of the reported cases, buccal mucosa and gingiva being the next commonly observed sites of involvement. Tongue was the most common site of involvement in the study population, comprising 37.7% of all cases, followed by buccal mucosa (20.3%) and alveolar ridge (n=11; 15.9%).

Multiple studies have demonstrated CCRT to be highly effective in increasing the survival of patients with unresectable disease and it has long been established as an appropriate standard of care for many patients with locally advanced squamous cell carcinoma of head and neck (SCCHN). Addition of chemotherapy to radiotherapy is believed to have a synergistic effect in terms of tumor control. Cisplatin depletes intracellular glutathione reserves as well as proteins involved in Base Excision Repair (BER) and Nucleotide Excision Repair (NER) pathways. Both these effects result in decline in tumor cells’ ability to repair radiation induced damage. Furthermore, tumor repopulation which is a common observation during radiotherapy causing decrease in local control can be inhibited by addition of chemotherapy. Similarly, chemotherapy aids to kill the hypoxic cells and additionally targets the micro-metastatic disease, which is out of radiation field.

Many previous studies have explored the efficacy of concurrent chemoradiation in SCCHN. One such study has reported the response rate of 93% in concurrent chemoradiotherapy, and 78% in chemotherapy followed by radiation. No difference was observed in CR between the two groups (52% in concurrent chemoradiotherapy and 50% in chemotherapy followed by radiation). The study concluded that the concurrent chemoradiation with Cisplatin and 5FU achieved improved disease control, predominantly of regional disease, compared with Chemotherapy followed by radiation. These results correlate with our findings showing 52.17% (n=36) complete response. However, overall response in their study was 93% with concurrent chemoradiotherapy, which is 79% (n=55) in this study.

Comparison of responders vs. nonresponders of the treatment in our study showed that 79% (n=55) had shown response to the treatment either in the form of complete response (52.17%, n=36) or partial response (27.54%, n=19). Whereas, patients who had shown no
response to the treatment or nonresponders were either having stable disease (11.59%, n= 8) or having disease progression (8.7%, n=6). Nonresponders were 20.29% of patient population (n=14). Treatment response remained significant (p < 0.001) in the study population. In another study, treatment outcome was measured with weekly Cisplatin concurrent with radiation therapy in locally advanced SCCHN. Study included 45 subjects. Complete response was observed in 26 patients (57.7%), partial response in 14 (31.1%), and in 5 (11.1%) the disease remained stable. Overall response to the treatment remains 88.8%.15 These findings are also in close agreement with this study.

Median survivals, including overall and median disease-free survival, are important indicators which give a measure of the efficacy of a treatment protocol. As inoperable oral cancer remains a challenge in cancer treatment several trials are being carried out to compare different treatment regimens for better treatment outcome.

In one such randomized trial with three arms, authors compared radiotherapy alone (arm A), radiotherapy with Cisplatin (arm B), and third arm (C) having radiotherapy (split course) and Cisplatin/5FU in unresectable head and neck cancers. The results showed median survival of 12.6 months, 19.1 months, and 13.8 months in arm A, B and C, respectively. Median overall survival (OS) in our case remained 18.00 months (95% CI, 15.13-20.87); whereas, median disease-free survival (DFS) was 14.00 months (95% CI, 11.07-14.62).16 So, the treatment outcome in this study was comparable with the published data in terms of overall and median disease-free survival.

Concurrent use of Cisplatin not only radiosensitizes tumor cells, but also sensitizes the normal cells. The normal cells in close proximity to tumor cells, upon inadvertent exposure to radiation, are likely to develop exaggerated toxicity to radiation. Furthermore, specific chemotherapy-related toxicities are also likely to be seen in patients who are administered chemoradiation. So, the patients treated with combined treatment (CCRT) are under threat of radiation hazards as well as experiencing the toxic effects of chemotherapy. This may sometimes lead to discontinuation of treatment or significant treatment breaks. Toxicity, therefore, is the prime concern for the concurrent treatment and is still under trial.

Increased incidence of acute grade 3 and 4 toxic effects has been reported in CCRT trials. Most commonly observed toxic effects include mucositis and dermatitis. However, a number of studies have reported that the long term side effects are not increased as compared to the radiotherapy alone.17,18 Commonly observed radiation induced toxicities include mucositis, which becomes adverse with chemoradiation. Prominent mucositis (grade 3 or 4, 40-98%) has been reported with CCRT in the previously published data. Severe mucositis is observed when Cisplatin/5-FU regimen is applied. Therefore, the regimen is suggested to be used with the patients having good performance status.19 In the current study, mucositis was observed in all patients. Grade 3 or 4 mucositis was observed in 71% (Table II).

Xerostomia has a reported incidence of 77% in the patients treated with CCRT. Xerostomia along with odynophagia has shown to have a worse effect on the quality of life of the patients. According to the reported data, 50% of the patients cannot take their normal diet after therapy. Odynophagia has a reported incidence of 50% in the patients receiving CCRT. Huguenin et al. have stated xerostomia as the cause of poor hygiene and social interaction in the patients receiving CCRT.20 In this study, grade 2 xerostomia was observed in 53.6% (n=37) of patients followed by grade 3 in 29% of patients. However, grade 1 was observed in 17.4% of patients. Grade 2 odynophagia/dysphagia was observed in 26 (37.7%) patients and grade 3 in 40.6% (n=28), while absolute dysphagia was observed in 4 patients only. G3 oral candidiasis was observed in 27 (39.1%), G4 in 31 (44.9%), and G0 ototoxicity was most commonly observed being 62 (89.8%, Table II). Myelosuppression, alopecia, anorexia, vomiting, fatigue, dental caries, hoarseness of voice, hypothyroidism and skin pigmentation were other commonly observed toxicities.

Hematologic toxic effects of grade 3 or 4 are observed in approximately 30-40% of the patients taking CCRT.21 Nausea and vomiting are also reported to increase with Cisplatin therapy.22 In this study, grade 3 or 4 myelosuppression (neutropenia) was observed in 26.2% cases. Severe (G3 or 4) vomiting was seen in about 51% cases (Table II).

In spite of the toxicities experienced by the combined treatment, CCRT has been declared as superior modality over the conventional treatment for advanced carcinomas in long term survey reports.23 Cisplatin is most commonly used drug for chemoradiotherapy in head and neck cancer. Platinum-containing regimens are reported to provide increased survival rates as compared to the non-Cisplatin-containing regimens.24 Adelstein et al. reported that the addition of 5-fluorouracil to Cisplatin therapy increases its efficacy and better survival is attained.25

**CONCLUSION**

Present study, focusing on the treatment outcome with Platinum based CCRT, remained effective for inoperable oral cancer patients. Significant treatment response (p <0.001) was obtained and 55 (79.7%) patients had shown response to the treatment with only 6 (8.7%) having progressive disease. Median OS remained 18.00 months and DFS was 14.00 months with tolerable toxicities.
REFERENCES