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Research Article

DETERMINATION OF COMPLETE CLINICAL RESPONSE RATE AFTER DEFINITIVE CHEMORADIOTHERPY IN SQUAMOUS CELL CARCINOMA OF ORAL CAVITY AT A TERTIARY CARE CENTER IN KARACHI PAKISTAN

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A B S T R A C T

Objectives: To determine the complete clinical response rate after definitive chemo-radiotherapy in squamous cell carcinoma of oral cavity at a tertiary care hospital in Karachi Pakistan.
Materials & Methods: A total of 81 histologically proven cases with newly diagnosed squamous cell carcinoma of the oral cavity were enrolled in this study. The treatment protocol consisted of radiotherapy 5 days/week, 200 CG,/ fraction for 7 weeks and injection cisplatin 75 mg/m2 on day 1,22,43 day of radiation of treatment were assessed radiologically at six weeks. Information regarding various demographic data, clinical, pathological, radiation and chemotherapy, staging was entered on the study Performa. Data was entered into Stata-14 and verified by the principal researcher.
Results: Eighty one (81) patients were evaluated for the treatment response, 20 (24.7%) patients had attained complete response (CR), 23 (28.3%) patients had partial response (PR) and 38 (46.9%) showed progressive disease. Mean age of the patients were 46.72 years with ± 10.8 years SD (20-77). The objective response rate (complete response plus partial response) was 53%. There were 68(84%) males and 13(16%) females. Buccal mucosa was the commonest site identified in 44 (54.3%) patients followed by tongue in 25 (30.9%), hard palate in 7 (8.6%), floor of mouth 3 (3.7%) and lip in 2 (2.5%) respectively
Conclusion: Chemo-radiotherapy as a definitive treatment is not an effective treatment modality, as very small number of patients achieved complete clinical response and where possible surgery upfront should be offered.

INTRODUCTION

Oral cancer is found in 2 to 4 % of all cancers occurring across the globe. In some areas of the world, the occurrence of oral cancer is higher, with almost 10 % in Pakistan and almost 45 % in India[1, 2]. Between 2004 and 2009, more than 300,000 new cases of oral cancers were found around the globe. More than 7,000 people died of these cancers in the same time period[3]. Oral cancer is the type of head and neck cancer that occurs from the squamous epithelium of oral cavity. It is from the mouth that the cancer of oral cavity originates. The incidence rate of oral cancer is higher in undeveloped countries than developing countries. In high risk countries such as Sri Lanka, Bangladesh, Pakistan and India, oral cancer is the most common cancer in men and may contribute up to 25% of all new cases of cancer [4].

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Squamous cell carcinoma (SSC) amounts more than 90% of malignant tumors of oral cavity and oro-phyarynx. It is the commonest cancer in southern parts of Pakistan[5]. The well-established risk factors that are associated with this cancer are tobacco, alcohol, diet and other environmental and professional exposures[6]. These are of various types such as squamous cell carcinoma (in-situ carcinoma/invasive SCC), Verrucous carcinoma and carcinoma of minor salivary glands (adenoid cystic carcinoma, mucoepidermoid carcinoma, and polymorphous low-grade adenocarcinoma)[7]. In Pakistan, squamous cell carcinoma is the 3rd most commonly occurring solid cancer among males and females [8, 9]. The high occurrence of oral cancer is credited to oral habits of betel nuts and tobacco chewing which are widespread in this area especially among the heavily urbanized southern cities of Pakistan. The survival of oral cancer patients remains extremely low despite the availability of multimodality treatment. A large number of these oral cancers re occur in a loco regional pattern, similar to the other head and neck cancers.

In spite of the country of origin, the 5 year survival in different reports ranges from 50% to 76% [10]. Squamous cell carcinoma of oral cavity is more prevalent in the male population with a ratio of 1.5:1 for females. When it comes to the male population of the subcontinent, the cancers of the head and neck region comprise 25% of all newly diagnosed cancer [4, 11]

Loco regionally advanced oral cavity cancers are aggressive tumors with high probabilities of relapse after definitive treatment with surgery or radiotherapy (RT). Therefore, a multimodal approach combining surgery and postoperative radiotherapy or chemo radiotherapy has been proposed[12]. More than 60% of these cancers are diagnosed when the patient has already reached stages III or IV[13].In terms of oral squamous cell carcinoma, the standard of care treatment first involves surgical resection which is then in turn pursued by adjuvant radiotherapy and chemotherapy.

Now multi-disciplinary team approach is well known these days that involves close co-ordination between surgeon, medical oncologist, and radiologist and radiation oncologist. The role of definitive chemo-radiotherapy is being used to improve the outcome of unrespectable and advance cancer of oral cavity.

MATERIAL & METHODS

This prospective cohort study was conducted at Department of medical oncology, at the Jinnah postgraduate medical Centre Karachi. The study was approved by ethical review board of institute. Informed consent was taken. A total of 97 patients were enrolled out of which 16 patients died. So a total of 81 alive patients were enrolled for this study. Purposive sampling technique was applied. The study was conducted from January 2016 to June 2017.The inclusion criteria include all the patients over 16 years of age by taking histopathologically confirmed locally advanced squamous carcinoma of oral cavity (Stage III & IV), those stage III patients who were not willing for surgery, stage IV non-metastatic having no other malignancy, those stage I & II patients who were declared unrespectable by surgeon, informed consent, performance status PS (0 to 1), and normal hepatic renal function were included in the study. The exclusion criteria included previously treated (surgery/radiotherapy) patients. All patients received injection cisplatin 75 mg/m2 IV 3 weekly up to total of three cycles with concurrent radiations at a dose of 200 CG/ Fractions for 5 days a week for total of 35 days or a period of 7 weeks. During chemo-radiation patients was followed up in OPD weekly to manage any adverse effect of radiation and chemotherapy and to asses any sign of progression of disease, blood chemistry, hematological derangement. Any electrolyte imbalance, grade IV mucositis were managed in hospital.

DATA ANALYSIS

Data was entered and analyzed using Stata-14. Data was analysed for descriptive and inferential statistics. Descriptive statistics included mean ± SD for continuous variables and frequencies for categorical variables. Inferential statistics will include chi-square & fisher exact test. Complete pathological response was analyzed and generated with 95% confidence interval. All data set at 95% confidence interval and p-value<0.05 were taken as significant.

RESULTS

A total of 81 patients were included in the study. Mean age of the patients was 46.72 years with ± 10.8 years SD (20-77).Mean duration of radiotherapy were recorded 30.96 with ± 6.39 with a range (5-38). There were 68(84%) males and 13(16%) females, with a male to female ratio of 5:1 with a male predominance. Buccal mucosa was the commonest site identified in 44 (54.3%) patients followed by tongue in 25 (30.9%), hard palate in 7 (8.6%), floor of mouth 3(3.7%) and lip in 2 (2.5%). Patients with family history of oral cancer were 7 (8.2%). At the time of presentation 83.9% were in stage III and IV. Among buccal mucosa cancers, 78% were in advanced stages and among tongue cancer 63% were in advanced stages.

Table 1 Patients And Disease Characteristics

	Moderate Differentiated	**35(43.2%)**
Diagnosis Criteria	Poorly Differentiated	26(32.1%)
	Undifferentiated	1(1.2%)
	Well Differentiated	19(23.5%)
T	T1	3(3.7%)
	T2	12(14.8%)
	T3	15(18.5%)
	T4	47(58%)
	T4a	4(4.9%)
N	N0	9(11.1%)
	N1	30(37%)
	N2	36(44.4%)
	N3	6(7.4%)
M	M0	32(39.5%)
	Mx	49(60.5%)
Stage	Stage I	4(4.9%)
	Stage II	9(11.1%)
	Stage III	12(14.8%)
	Stage IV	56(69.1%)
Gender	Male	68(84%)
	Female	13(16%)
Site Involved	Buccal Mucosa	44(54.3%)
	Lip	2(2.5%)
	Floor of mouth	3(3.7%)
	Hard Palate	7(8.6%)
	Tongue	25(30.9%)

Regarding histologic diagnosis of the tumors, 35(43.2%) were moderately differentiated while 26 (32.1%) were poorly differentiated, 19(23.5%) patients were found well differentiated and 1 (1.2%) patient was undifferentiated. Clinical "T" staging was recorded in 81 patients; Most of the cases were recorded in T4 stage 47 (58%) while the second most recorded stage was T3 15(18.5%).Clinical "N" staging was recorded out of which 9(11.1%) cases were in the N0 category, 30(37%) were in N1 category, 36 (44.4%) were in N2 category only 6(7.4%) were found in N3. Eighty one (81) patients were evaluated for the treatment response, 20 (24.7%) patients achieved complete clinical response (cCR), 23 (28.3%) patients achieved partial response (PR) and 38 (46.9%) showed progressive disease. The objective response rate (complete response plus partial response) was 53%.

Response of concurrent chemo-radiation with respect to different demographical variable is shown in Table-2. Partial and complete response was high in age groups 51-70 statistically significant (p=0.007*).Male patients found to have high objective response rate as compare to female (P-value=0.018*). Insignificant association were found in T-staging with respect to response of treatment.

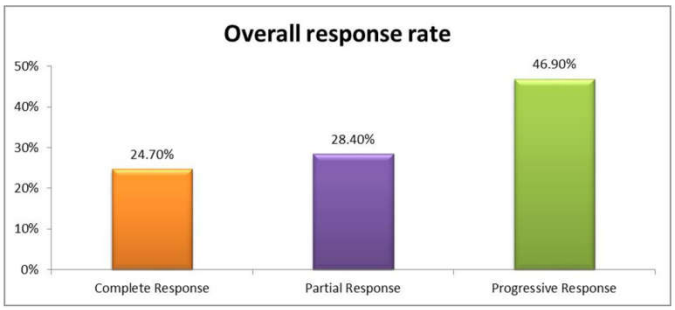

Figure I

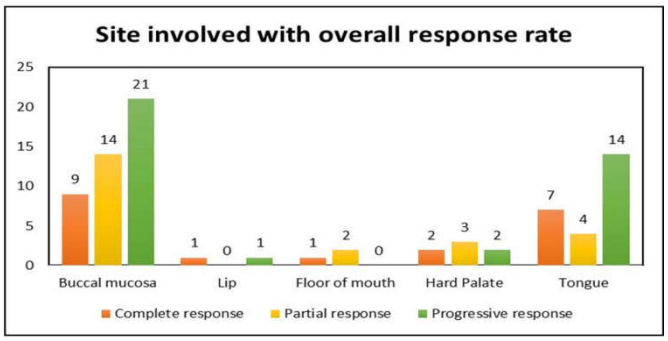

Figure II

In our study mean age of the patients was 46.72±10.8 which is in their 5th decade which indicates that Oral Cancer is mostly found in old age individuals. Though, there have been a few cases found with oral cancer among young age groups, however, the ratio is relatively low. Maximum incidence was observed in the age range of 40 to 60 years (67.9%) patients. However, most of the western studies have shown that carcinoma is affecting the older population without any risk factors.[16]

Cisplatin is considered to be a very powerful Chemotherapy agent. Mostly it is prescribed to patients of head and neck cancer. In this study used the Cisplatin 75mg/m2. However, there have been other international studies where the dose of 50mg/m2 and 100 mg/m2 is used [17]. This study injection cisplatin 75 mg/m2 IV 3 weekly up to total of three cycles with concurrent radiations at a dose of 200 CG/ Fractions for 5 days a week for total of 35 days or a period of 7 weeks is used.

According to this Study, complete response 20(24.7%), Partial 23(28.4%) and 38(46.9%) patients were progressive. On the other hand, if we look at other international and national studies e.g. we found that Zenda *et al* [18] shows 50%, Kim *et al*.54% [19], Adelstein *et al* shows 40.2%[20] and vokes *et al*.[21] has 67%.

Table 2

		Complete Response	Partial Response	Progressive Response	
Diagnosis Criteria	Moderate Differentiated	8(9.9%)	13(16%)	14(17.3%)	0.001*
	Poorly Differentiated	3(3.7%)	2(2.5%)	21(25.9%)	
	Undifferentiated	0(0%)	0(0%)	1(1.2%)	
	Well Differentiated	9(11.1%)	8(9.9%)	2(2.5%)	
T Stage	T1	3(3.7%)	0(0%)	0(0%)	0.001*
	T2	8(9.9%)	3(3.7%)	1(1.2%)	
	T3	4(4.9%)	4(4.9%)	7(8.6%)	
	T4	5(6.2%)	15(18.5%)	27(33.3%)	
	T4a	0(0%)	1(1.2%)	3(3.7%)	
N Stage	N0	4(4.9%)	1(1.2%)	4(4.9%)	0.28
	N1	5(6.2%)	13(16%)	12(14.8%)	
	N2	10(12.3%)	8(9.9%)	18(22.2%)	
	N3	1(1.2%)	1(1.2%)	4(4.9%)	
M Stage	M0	5(6.2%)	8(9.9%)	19(23.5%)	0.155
	Mx	15(18.5%)	15(18.5%)	19(23.5%)	
Stage	Stage I	3(3.7%)	1(1.2%)	0(0%)	0.003*
	Stage II	6(7.4%)	2(2.5%)	1(1.2%)	
	Stage III	4(4.9%)	3(3.7%)	5(6.2%)	
	Stage IV	7(8.6%)	17(21%)	32(39.5%)	
Gender Distribution	Male	15(18.5%)	16(19.8%)	37(45.7%)	0.007*
	Female	5(6.2%)	7(8.6%)	1(1.2%)	
Site Involved	Buccal Mucosa	9(11.1%)	14(17.3%)	21(25.9%)	0.473
	Lip	1(1.2%)	0(0%)	1(1.2%)	
	Floor of mouth	1(1.2%)	2(2.5%)	0(0%)	
	Hard Palate	2(2.5%)	3(3.7%)	2(2.5%)	
	Tongue	7(8.6%)	4(4.9%)	14(17.3%)	

DISCUSSION

The oral cavity is the most common site of head and neck squamous cell carcinoma, a disease which results in significant morbidity and mortality worldwide. According to this study the male patients were more as compared to female 84% (n=68) and 16% (n=13).The incidence of oral cancer was found to be more prevalent in male as compared to female (P<0.007*). The reason for this higher incidence was observed to be due to greater use of tobacco in our male population. Merchant, Anwar, *et al*. Published in international journal of cancer in this study the proportion of oral cavity observed mainly in men because of tobacco usage in Pakistan[14, 15].

However, they have used other chemotherapeutic agent than cisplatin.

In addition, one more study showed that treatment result was better with weekly Cisplatin along with radiation. Study included 45 patients. Complete response was noted in 26 patients (57.7%), partial response in 14 (31.1%), and in 5 (11.1%) disease remain stable. Overall response rate were to 88.8%[22]. These outcomes are different from our study.

Out of 81 patients, most of them were either stage III and Stage IV. Stage I patient's complete response rate was (3/4=75%) and Stage II complete response rate were (6/9=66.6%) p and stage III (4/12=33.3%) and in stage IV were (7/56=12.5%)[23-25].

Among Total evaluable 81 patients complete response seen in 24.7% of patients, among those in Buccal mucosa CCR seen in 9(11.1%), tongue 7(8.6%), hard palate 2(2.5%) and the lowest CCR seen in floor of the mouth and lip i.e 1(1.2%) [26, 27].

CONCLUSION

Definitive chemo radiation in locally advance squamous cell carcinoma of oral cavity in our population shows disappointing results and in contrast to other studies complete clinical response rate is lower i.e. 25% as opposed to 51% in west. This difference in response rate could be due to many reasons including etiology of cancer, viral vs tobacco chewing, as in former case prognosis is good than latter case, performance status of patients, racial differences and difference in radiation technologies.

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