Original Article

Outcome of Treatment of Locally Advanced Oral Cavity Cancer with Concurrent Chemo-Radiation in Comparison to Radiotherapy Alone

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Abstract

According to the World Health Report 2004, Oral cancer is more common in developing than developed countries. At least 95% of the head-neck cancers are squamous cell carcinoma and arising most commonly in the oral cavity. Non operative treatment strategies for oral cancer involving radiation and chemotherapy continue to evolve with the most current trend being that of concurrent chemoradiotherapy. The study was conducted to compare the outcome of concurrent chemo-radiation therapy and radiotherapy alone in locally advanced squamous cell carcinoma of the oral cavity. The study was designed with 62 patients of squamous cell carcinoma of oral cavity and was divided into two study groups. Concurrent chemo-radiation group (Group A) consisting 31 patients treated by radiotherapy of 66 Gy in 33 fraction for 6.5 weeks and concurrent chemotherapy with three cycles of cisplatin ($75mg/m^2$) per day 3 weeks apart . Another 31 patients (Group-B) were treated with radiotherapy alone by 66 Gy in 33 fractions for 6.5 weeks. Comparison between concurrent chemo-radiation and radiotherapy alone were studied. In this study, in chemo-radiotherapy group (Group-A) complete response (CR) was found in 20 (64.52%) cases and partial response (PR) was found in 11 (35.48%) cases. In radiotherapy group (Group-B) complete response (CR) was found in 12 (38.71%) cases and partial response (PR) was found in 19 (61.29%) cases. It was found that complete and partial response was 100%. Calculated χ^2 value was 4.14 which is greater than the table value of χ^2 i.e. 3.84. Statistically the result was significant (P<0.05). So, for better treatment outcome concurrent chemoradiotherapy can be offered for loco-regionally advanced squamous cell carcinoma originating from oral cavity region.

Keywords: Chemo-radiation, Squamous cell carcinoma, oral cavity, Cisplatin.

Introduction

Cancer is one of the major threats to public health in the developed world and increasing in the developing world. It is one of the major causes of morbidity and mortality among the non-communicable diseases in Bangladesh. Cancer is the sixth cause of mortality in Bangladesh and more than half of the cancer patients die within five years of diagnosis. In south-central Asia, cancer of the oral cavity ranks among the three most common types of cancer. At least 95% of the head-neck cancers are squamous cell carcinoma and arising most commonly in the oral cavity – about 55% are several histological types of oral cancers and around 90% are squamous cell carcinoma. Oral cancer may arise as a primary lesion originating in any tissues in the mouth or by metastasis from a distant site of origin or by extension from a neighboring anatomic structure, such as the nasal cavity[1]. The anatomical sites conventionally regarded as constituting the oral cavity are buccal mucosa, upper and lower alveolus, retro molar trigone, hard palate, tongue (anterior two thirds) and floor of the mouth [2]. As the oral cavity constitute the beginning of the upper aero digestive tract, important functions like mastication, speech, swallowing and respiration can be severely impaired by the development of a cancer in this location. A variety of etiological factors such as smoking, tobacco chewing, poor dental and oral hygiene and heavy consumption of alcohol have been linked to the development of this cancer. Tobacco use is the most important risk factor for oral cancer. In the treatment plan surgery, radiotherapy and chemotherapy play the major role[3]. Early and intermediate stage of disease can be cured with surgery and / or radiotherapy alone. Locally advanced disease required chemotherapy. For a long time, definitive radiotherapy has been standard treatment for locally advanced squamous cell carcinoma of head and neck[4]. Advances in surgical techniques continue to improve operative outcome, the overall morbidity associated with resection of advanced oral cancer remains substantial. Non operative treatment strategies involving radiation and chemotherapy continue to evolve with the most current trend being that of concurrent chemo-radiotherapy.

The main objective of the study is to demonstrate the outcome of concurrent chemo-radiation therapy in comparison to radiotherapy alone in locally advanced squamous cell carcinoma of the oral cavity.

Materials and Methods

This was a randomized controlled trial from January to December 2015. Patient with oral cancer attended at the

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radiotherapy department of RMCH (Rajshahi Medical College Hospital) and DMCH (Dhaka Medical College Hospital) was included in the study according to the inclusion and exclusion criteria. Inclusion criteria: histologically proved squamous cell carcinoma of oral cavity; stage III or IV disease without distant metastasis, patients within age 18-70 years, patients having ECOG performance status score up to grade 2, both sex. Exclusion criteria: non- squamous cell carcinoma, prior treatment by radiotherapy or chemotherapy, patients with initial surgery (excluding diagnostic biopsy) of the primary site, patients dropped out or lost to follow up before completion of study, patients with double primaries, patients with uncontrolled infection, pregnant or lactating mother, prisoner. A total of 62 patients with histologically proved squamous cell carcinoma of oral cavity were selected according to the predefined inclusion/exclusion criteria and were divided into two groups. Every alternate patient was enrolled for each group. Group-A: 31 patients were treated with concurrent chemo-radiotherapy. Radiation dose of 66 Gy in 33 fractions 200 c Gy per day, 5 days in a week for 6.5 weeks by LINACmachine (6MV energy) and concurrent chemotherapy with cisplatin 75 mg/m^2 three weekly for 3 cycles. Group-B: 31 patients were treated with radiotherapy. Radiation dose of 66 Gy in 33 fractions (200 cGy per day, 5 days in a week for 6.5 weeks by LINAC machine (6MV energy). Data analysis was done by using SPSS (Statistical Package for Social Science) software program. Permissions were taken from the concerned department and institutional review board for the study.

Results

Table 1: Distribution of the respondents according Socio-demographic characteristics. n=62

Socio-demographic characteristics		Therapy	
		Chemoradiation (Group- A) %	Radiation (Group- B) %
Age (years)	Up to 50	13 (41.94)	15 (48.39)
	51-60	13 (41.94)	11 (35.48)
	Above 60	5 (16.13)	6 (19.35)
Sex	Male	15 (48.38)	15 (48.38)
	Female	16 (51.61)	16 (51.61)
Monthly family income (Tk.)	< 10000 Tk	18 (58.06)	18 (58.06)
	10000-20000	8 (25.81)	9 (29.03)
	>20000	5 (16.13)	4 (12.90)
Educational status	Illiterate	17 (54.84)	17 (54.84)
	Primary	8 (25.81)	12 (38.71)
	Up to graduate	6 (19.35)	2 (6.45)

Table 1 shows that, in case of Group A patients, mean age was 52.58 ±12 years and in Group B patients age was 52.29± 12.71 years. According to sex 48.38% patients were male and 51.61% patients were female in Group A. In

Group B 48.38% patients were male and 51.61% patients were female.

Regarding monthly family income in Group A, <10000 Tk. was 58.06%, 10000-19999 Tk. was 25.81% and >20000 Tk. was 16.13%. In Group B, <10000 Tk. was 58.06%, 10000-19999 Tk. was 29.03% and >20000 Tk. was 12.90%. Most of the patients of both groups were illiterate (54.84%). Primary passed were 25.81% in Group A and 38.71% in group B. Upto graduate patients were 19.35% in Group A and 6.45% in Group B.
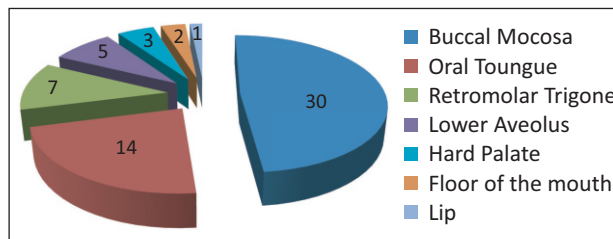

Figure1: Distribution of the respondents according to oral cavity cancer

Figure 1 shows among all the patients, 30 (48.39%) had cancer in buccal mucosa, 14 (22.58%) patients had cancer in tongue, 7 (11.29%) patients were in retromolar trigone, 5 (8.06%) patients were in lower alveolus, 3 (4.84%) patients were in hard palate, 2 (3.23%) patients were floor of the mouth, 1 (1.61%) patients had cancer in lip.
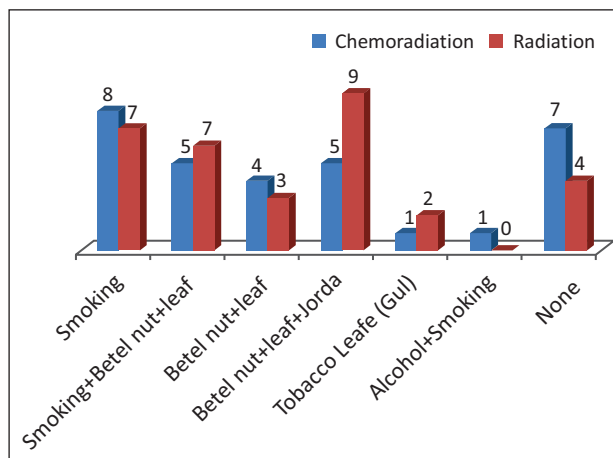

Figure 2: Distribution of patients according to risk factors

In group A as risk factor of smoking was found in 8 patients; smoking, betel nut and leaf in 5 patients; betel nut and leaf in 4 patients; betel nut, leaf and jorda in 5 patients; tobacco leaf (gul) in 1 patient; alcohol and smoking in 1 patient.7 patients were found with no risk factor. In group B as a risk factor of smoking was found in 7 patients; smoking, betel nut and leaf in 6 patients; betel nut and leaf in 3 patients; betel nut, leaf, and jorda in 9 patients; tobacco leaf (gul) in 2 patients; alcohol and smoking in 0 patient. 4 patients were found with no risk factor (Figure-2)
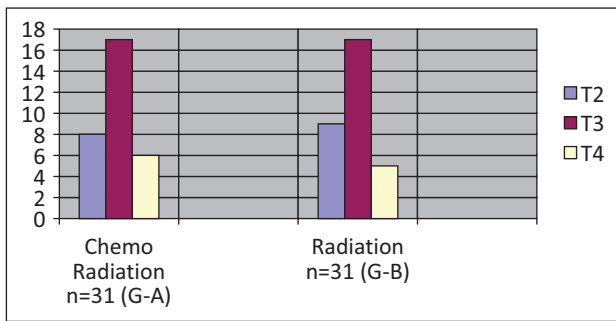
Figure 3: Distribution of the patient by the treatment group and tumor category (n=62)

Figure 3 shows- Out of patients 31 in Group A, 8 (25.80%) patients had T2, 17 (54.83%) patients had T3 and 6 (19.35%) had T4 tumour category. Out of patients 31 in Group B, 9 (29.03%) patients had T2, 17 (54.83%) patients had in T3 and 5 (16.13%) patients had T4 tumour category
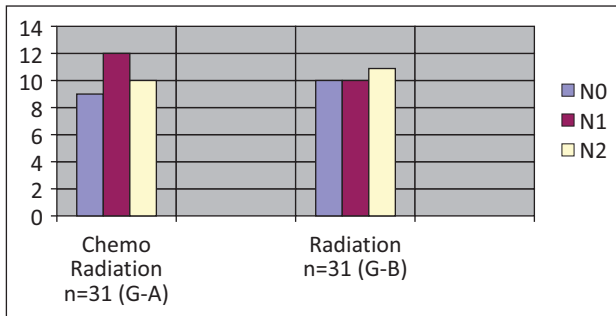

Figure 4: Distribution of the patient by the treatment Group and nodal category (n=62)

Figure 4 shows- In Group A, nodal status were 9 (29.03%), 12 (38.70%), 10 (32.25%) for N0, N1, N2 respectively and in Group B, nodal status were 10 (32.45%), 10 (32.45%), 11 (35.48%) for N0, N1, N2 respectively (Figure- II)
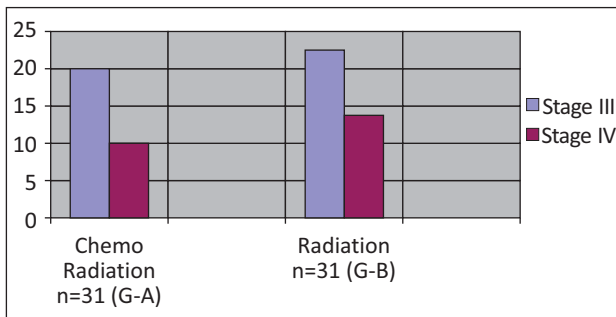

Figure 5: Distribution of the patient by the treatment group and tumour stage

Figure 5 shows that, most of the patients presented with stage III oral cancer in both groups. In group A, 20 (64.51%) patients were in stage III and 11 (35.48%) patients were in stage IV. In group B, 22 (70.96%) patients were in stage III and 9 (29.03%) patients were in stage IV.

Table 2: Distribution of the oral cavity cancer patients by local examination findings of the tumour and the treatment Groups before treatment. n=62

Local examination findings of lump		Therapy	
		Chemoradiation (Group- A) N%	Radiation (Group- B) N%
Tenderness	Present	25 (80.7%)	23 (74.1%)
	Absent	06 (19.3%)	08 (25.8%)
Bleeding	Present	12 (38.7%)	10 (32.2%)
	Absent	19 (61.2%)	21 (67.4%)
Fixation	Present	11 (35.4%)	08 (25.8%)
	Absent	20 (64.5%)	23 (74.1%)

Table 2 shows that, in Group A tenderness was present in (80.7%) of patients and in Group B tenderness was present in (74.1%) of patients. Bleeding was present in (38.7%) of patients in Group A and in (32.2%) of patients in Group B. In case of fixation, (35.4%) patients in Group A and (25.8%) patients in Group B had fixity of tumour.

Table 3: Comparison the effects of concurrent chemo-radiation and radiation on oral cavity tumour size by weekly

Time of treatment	Comparison group	Mean tumour (cm)	Mean differences (cm)	t value	p valuep <0.05
Before treatment	Chemo-radiation	3.60	-0.08	-0.279	Not significant
	Radiation	3.68			
1st week	Chemo-radiation	3.31	-0.15	-0.543	Not significant
	Radiation	3.46			
2nd week	Chemo-radiation	3.03	-0.17	-0.69	Not significant
	Radiation	3.20			
3rd week	Chemo-radiation	2.61	-0.24	-0.98	Not significant
	Radiation	2.85			
4th week	Chemo-radiation	2.12	-0.34	-1.52	Not significant
	Radiation	2.46			
5th week	Chemo-radiation	1.58	-0.48	-2.16	Significant
	Radiation	2.06			
6th week	Chemo-radiation	0.94	-0.64	-2.97	Significant
	Radiation	1.58			
6 weeks after treatment	Chemo-radiation	0.46	-0.55	-2.77	Significant
	Radiation	1.01			

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Before the treatment mean tumour size in Group A was 3.60 cm and 3.68 cm in Group B. No significant differences were seen before treatment. It was noted that, P value decreases weekly and at 5th week, it tend to become significant. At 6th week and 6 weeks after treatment the reduction of tumour size between two groups became statistically significant (Table- 3)

Table 4: Overall treatment response on oral cavity cancer (n=62)

Type of treatment	Treatment response		Total N (%)
	Complete response N (%)	Partial response N (%)	
Chemo-radiation	20 (64.5%)	11 (35.5%)	31 (50%)
Radiation	12 (38.7%)	19 (61.3%)	31 (50%)
Total n (%)	32 (51.6%)	30 (48.4%)	62 (100%)

χ^2=4.14, df=1, p = <0.05

Table 4 shows that among the patient of Group A (concurrent chemo-radiation), 64.5% of them had complete response and 35.5% had partial response by concurrent chemo-radiotherapy. Among the patients of Group B (radiotherapy), 38.7% of them had complete response and 61.3% had partial response by radiotherapy alone. This table also showed that the response by chemo-radiotherapy in Group A was much better than radiotherapy alone in Group B, which was statistically significant (p<0.05).
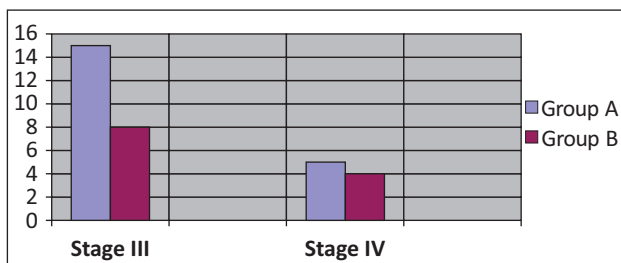

Figure 6: Complete response according to stage

Figure 6 shows that it was found that in case of stage III patients 15 (48.38 %) complete response found in Group A and 8 (25.80 %) complete response found in Group B patients. For stage IV 5 (16.12%) complete response found in Group A and 4 (12.90%) in Group B patients.

Discussion

The study was done to compare the effects of concurrent chemo radiotherapy and radiotherapy alone, and to observed the loco-regional control and early side effects in treating locally advanced oral cavity cancer.

In this study most of the patients in the both groups are between the ages of 30-60 years. In Group-A mean age was 52.58 ±12.42 years and in Group-B mean age was 52.29 ± 12.71 years respectively. This observation correlates with Perez et al (2013) and DeVita et al (2014)[5,6].

The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) included 63 randomized trails published from 1965 to 1993, all of which compared loco-regional treatment with or without chemotherapy, here survival benefit diminished with patient age and , on subset analysis, was not significant in patients over 70 years of age. Head and neck cancers are very rare below 18 years of age, so 18 to 70 years age group was considered in this study.

Regarding the site of involvement in both groups, it revealed that buccal mucosa and oral tongue were major primary sites. Buccal mucosa cancer was found in 30 (48.39%) patients and oral tongue cancer in 14(22.58%) patients. In USA, The most common subsite for squamous cell carcinoma of the oral cavity cancer is the oral tongue. In a review of 3,308 cases of oral cavity cancer treated at the University of Texas M.D. Anderson Cancer Center between 1970 and 1999, 32% involved the oral tongue. The floor of the mouth is the second most common subsite where oral cavity carcinomas may arise. Similarly, carcinoma of the buccal mucosa is rare in the United States but it is the most common carcinoma of the oral cavity in South east Asia because of the widespread use of betel nut[5]. This reflects that there is a little bit variation of disease distribution in this study due to random sampling.

In the study in both groups 25.8% patients had long history of smoking with or without habit of betel nut and leaf, 16.12% of them had habit of betel leaf, nut and jorda. 3.22% of patient gave history of consuming tobacco leaf (gul). Consumption of alcohol is only in 1.5% patient due to rate of alcohol consumption in Bangladesh is lower than Western countries. There is a strong causal relationship between smoking and cancer of the oral cavity. Smoking is identified as an independent risk factor in 80% to 90% of patients. Tobacco users have a fivefold to 25-fold higher risk of oral cavity and oropharyngeal cancer. Cessation of smoking is associated with a decline in the risk of cancer of the oral cavity. Abstaining from the use of cigarettes results in a 30% reduction in the risk of cancer in those who quit after 1 to 9 years; the risk is reduced by 50% in those who quit for more than 9 years. In India the habit of chewing betel nut leaves rolled with lime and tobacco (mixture known as "pan"), which results in prolonged carcinogen exposure to the oral mucosa, is thought to be the leading cause of oral cancer. The practice of "reverse smoking" (smoking with the lighted end of the cigar in the mouth, also known as Chutta), peculiar to certain parts of India, is associated with an increase in cancer of the hard palate. The combined use of alcohol and tobacco may have a synergistic effect on carcinogenesis[5].

In this study most of the patients of both groups came from lower socioeconomic class. In Group-A 58.06 % came from lower socioeconomic class, 25.81% from middle class and 16.13% from upper class. In Group-B 58.06% patients came from lower socioeconomic class, 29.03% from middle class and 12.90% from upper class. The reason more number of low to middle class patients were may be

due to that, higher class patients can go to private sector or aboard to get treatment by cost of money which is not possible for low to middle class patients.

In case of oral cancer male: female ratio is 2:1[7]. In my study, Male: Female ratio of oral cancer is 2: 2.1. In our country smoking is less in female and habit of ignorance of disease is high. So very few poor female patients came to hospital for treatment.

After clinical staging it has been observed that patients of group A 20 (64.51%) patients were in stage III and the remaining 11(35.48%) patients were in stage IV. In arm B, 22(70.96%) patients were in stage III and 9(29.03%) patients were in stage IV. In this study it was found that in case of stage III patients 15 (48.38%) complete response found in group A and 8(25.80%) complete response found in group B patients. For stage IV 5 (16.12%) complete response found in group A and 4 (12.90%) in group B patients.

In group-A, patients treated with concurrent chemo radiotherapy, complete response (CR) observed in 20 (64.5%) out of 31 patients. In Arm-B, treated with radiotherapy, complete response (CR) observed in 12 (38.7%) out of 31 patients. the response by chemo-radiotherapy in group A was much better than radiotherapy alone in group B, which was statistically significant ($p<0.05$).

Conclusion

Oral cavity squamous cell carcinoma is relatively common, curable and controllable disease. Radiotherapy gives good control with preservation of organ function and cosmetic outcome. Result of treatment with concurrent chemo-radiotherapy is comparable to surgical management. Platinum based cytotoxic agents; Cisplatin gave better result providing significant local control of disease in this study. Significant better result was noted in primary cancer developed from oral cavity of stage III and IV disease. So for better treatment outcome concurrent chemo-radiotherapy can be offered for loco-regionally advanced squamous cell carcinoma originating from oral cavity region. In conclusion it may be said that concurrent chemo-radiotherapy is more effective than radiotherapy alone in loco-regional control of oral cavity cancers.

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