

EFFECT OF CONCURRENT CHEMO RADIATION IN THE TREATMENT OF LOCALLY ADVANCED CARCINOMA OF TONGUE

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Summary

This quasi experimental study was conducted to observe the effects and toxicities of concurrent chemo radiation in locally advanced tongue cancer from January 2009 to December 2009 in the Radiotherapy Department of Chittagong Medical College Hospital. A total number of forty patients were purposively selected according to inclusion criteria. Among them, 30 patients presented with lesion in anterior two third & 10 patients in posterior one third. Thirty patients were male & ten were female. All of the patients having betel nut chewing habit & 90% were smoker & tobacco leaf chewer. The mean age of patient was 56.25 years. All patients received chemotherapy on D₁, D₈, D₁₅, D₂₂, D₂₉, D₃₆, D₄₃ & 66 Gy external beam radiotherapy in 200 cGy/day in six and half weeks. Pretreatment status of mean size of primary lesion of anterior two third and posterior one third of tongue cancer patients significantly decreased in last follow up. Mean size of lymph nodes significantly decreased from pretreatment to last follow up in both anterior two third and posterior one third of tongue cancer patients. Over all response of patients treated with concurrent chemo radiation only three patients of anterior two third & one patient of posterior one third showed complete response followed by seventeen patients of anterior two third & five patients of posterior one third showed partial response. Response is better in stage III than stage IV patients in both anterior two third and posterior one third of tongue cancer. The common toxicities are mucositis, skin reaction, anemia & leucopenia in both anterior two third and posterior one third of tongue cancer patients. In the treatment of locally advanced carcinoma of tongue, concurrent chemoradiation showed better symptom improvement, manageable toxicities. So, concurrent chemoradiation may be one of the treatment modality in locally advanced carcinoma of tongue patients. Period of study and number of patients were small. So, long term follow-up and large number of patients should be included to conduct more in-depth research and more specific comments.

Key words

Effect; concurrent chemoradiation; locally advanced; carcinoma of tongue

Introduction

Tongue is an organ of taste & helps in mastication, deglutition & speech. Carcinoma of the tongue is one of the most common tumors of the head & neck. Tongue cancer remains a significant health problem in terms of incidence and mortality. According to GLOBOCAN 2008 (IARC), Lip & Oral cavity represents 7.4% of all cancers and 6.9% of cancer death in Bangladesh. Lip & Oral cavity represents the second most common cancer in male and third most common cancer in female in Bangladesh. In India, Lip & Oral cavity represent second most common cancer in male and fourth most common cancer in female. Oral cavity includes tongue, gum, buccal mucosa, soft & hard palate¹.

Tongue cancer is one of the commonest cancers of the mouth. Most of the tumors occur in the fifth to seventh decades. Male: Female sex ratio is 3:1. Although the median age of onset is 60 years, tongue cancer may occur in patients younger than 30 years of age. Approximately 70% occur in the anterior two thirds, mainly on lateral or inferior aspects. Locally advanced cancers may infiltrate the musculature of tongue, the floor of the mouth & base of the tongue².

Ninety five percent of oral tongue cancers are invasive squamous cell carcinoma. A clear association has been made between cigarette smoking, pipe smoking, tobacco chewing, heavy alcohol intake, poor oral hygiene & chronic trauma from broken teeth or poorly fitting dentures, Plummer Vinson Syndrome in female, betel nut chewing³.

The treatment of oral tongue cancer depends upon the site & size of primary tumor (T), nodal status (N) & metastasis (M). The higher T & N stage at diagnosis of tongue cancers, the lower the proportion of patients will achieve complete cure, local control & lower the survival. Locally advanced tongue cancers means stage III & stage IV A & B. Management of patients with head neck cancer require a multidisciplinary approach. The goal in treating a patient with tongue cancer must be not only to cure but also to provide the best functional outcome for the patient.

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For patients with locally advanced tongue cancer, a surgical resection followed by post operative radiotherapy has been the traditional treatment. In United States, the treatment of locally advanced tongue cancer has moved from surgery towards a more conservative approach involving definitive radiotherapy & chemotherapy with extirpative surgery held in reserve for salvage. Even if the survivals are only equivalent, organ preservation approaches should be the treatment of choice for most patients⁴.

The purpose of administering chemotherapy & radiotherapy together is to take advantage of the radio sensitizing capability of many of the active drugs for tongue cancer and effect as substantial enough increase in locoregional control to significantly improve survival⁵.

Most of the patient with cancer presents themselves in a very advanced stage of his or her disease due to illiteracy, ignorance, lack of cancer awareness, religious prejudice and low socioeconomic status. Our aim should be a cost effective management of tongue cancer. In the light of above facts and figure, the study on concurrent chemoradiation in locally advanced tongue cancer was done. The study will hopefully open a new horizon in this field of oncology.

Materials & methods

Type of study

Quasi experimental study

Duration of study

1st January 2009 to 31st December 2009.

Sampling technique

A total of forty patients attending in outpatient and indoor department of Radiotherapy of CMCH with stage III & stage IV A, B tongue cancer (without distant metastasis) were selected purposively from the patient selection criteria & all of them were treated with concomitant chemoradiotherapy.

Selection of patient

Inclusion criteria

- Histologically diagnosed squamous cell carcinoma of tongue.
- Without distant metastasis.
- Karnofsky performance scale status score 100 to 60.
- Minimum laboratory criteria required to include:
 - Haemoglobin should be 10gm/dl or more or 60%
 - An absolute WBC count more than or equal to 4000 cell/ml.
 - A platelet count of more than or equal to 100,000 cells/ml.

iv) Bilirubin level of less than or equal to 1.5 mg/dl.

v) An AST level not more than 2.5 times the upper limit of normal.

vi) A serum creatinine level of less than or equal to 1.5mg/dl.

Exclusion criteria

- Patients with other than squamous cell carcinoma.
- Previously treated patients and or patients who were treated with radiotherapy or chemotherapy.
- Patients with distant metastasis
- Karnofsky performance status scale <60.
- Age over 70 years.

Pretreatment evaluation

Following procedures were followed to evaluate the patient's condition before treatment:

- Complete history and physical examination
- Histopathological examination reports which had already been done by taking biopsy.
- Laboratory studies-
 - CBC
 - Kidney function test
 - Liver function test
- Radiologic studies-
 - Chest X-ray P/A view
 - Ultrasonogram of whole abdomen
 - CT scan of neck
 - MRI of neck
- Dental evaluation with management was done prior to the start of treatment.

Management

a) General

Patients were managed symptomatically with antibiotics, oral mouth wash, steroids, antiemetic, vitamins, blood transfusion, and nasogastric tube feeding etc. according to their need throughout the treatment period. All patients were advised to take proper skin care during treatment. Dental care was taken before starting of radiotherapy.

b) Specific treatments

Chemotherapy

Concurrent chemotherapy was given by injection Cisplatin 30mg/m²/day IV infusion on Day1 (the day on the start of the radiotherapy treatment), Day8, Day15, Day22, Day29 and Day36 with sufficient pre and post hydration.

Radiotherapy

All the patients were treated by Co₆₀ machine in following ways:-

Tumor dose	: 66 Gy
Number of fields/day	: 3 fields /day
Dose/ fraction	
Right faciocervical	: 100cGy/day
Left faciocervical	: 100cGy/day
Dose limit to Spinal cord	: 44 Gy
Tumor dose at lower anterior neck	= 50 Gy
Dose/fraction	: 200cGy/day

Evaluation

Evaluation of treatment included patients complete history, physical examination (tumour response, symptom improvement), toxicity of treatment, lab studies like CBC, kidney function test, liver function test etc. Size of primary lesion & lymph node were measured by scale three weeks and six weeks during treatment & again at six weeks and three months after completion of treatment.

Response criteria⁶

Responses were classified by four parameters

- Complete Response (CR) - Complete disappearance of measurable and palpable disease for at least 4 weeks with no lesions appearing.
- Partial Response (PR) - Tumour reduction of at least 50% in measurable disease maintained for 4 weeks in the absence of any progressive or new lesion.
- No change or stable disease (SD) - Less than 50% reduction in measurable disease or less than 25% increase in measurable disease.
- Progression - An increase of 25% or more in an area of measurable disease or the development of new lesion.

Data analysis

Data obtained from the study was compiled and analyzed with computer by SPSS (Statistical package for social science). Results were presented in tables and figures. Response of treatment and evaluation of toxicity were calculated with standard statistical method. A P-value of <0.05 was taken as significant.

Results**Distribution of patients according to age**

Age ranged from 40-69 years. Mean age was 56.25 years (SD± 8.13). The peak age incidence of disease was found in the age group of 60-69 years.

Size of primary lesion in anterior two third of tongue patients from pretreatment to last follow up

Size of primary lesion in anterior two third of tongue patients gradually decreases from pretreatment to last follow up which is significant ($p < 0.001$; paired t test). Result is shown in Table I.

Indirect laryngoscopic findings of posterior one third of tongue cancer patients from pretreatment to last follow up.

In indirect laryngoscopic findings size of primary lesion in posterior one third of tongue patients gradually decreases from pretreatment to last follow up which is significant ($p < 0.001$; paired t test). Result is shown in Table II.

Mean distributions of patients by pre and post treatment size of lymph node.

The mean size of lymph node was significantly ($p < 0.001$; paired t test) decrease from pre-treatment status to final follow up in both anterior two third and posterior one third of tongue. Results are shown in table III.

Distribution of patients by treatment response

Complete response is found in two patients of stage III & one patient of stage IV in anterior two third & one patient of stage III in posterior one third of tongue. Significant difference was noted between stage III & stage IV of anterior two third of tongue patients ($\chi^2 = 9.71$; $P < 0.05$). Significant difference was also noted between stage III & stage IV of posterior one third of tongue ($\chi^2 = 7.62$; $P < 0.10$). Results are shown in table IV.

Distribution of treatment related toxicities in anterior two third and posterior one third of tongue Treatment related hematological & non-hematological toxicities of the studied patients are described in table V.

Table I: Size of primary lesion in anterior two third of tongue patients from pretreatment to last follow up

Size of primary lesion	Mean Score in cm	P Value
Pre-treatment	3.3	<0.001
After 3 Weeks of treatment	3.0	<0.001
After 6.5 Weeks of treatment	2.6	<0.001
6 weeks after treatment	2.0	<0.001
3 months after treatment	1.9	<0.001

Table II: Indirect laryngoscopic findings of posterior one third of tongue patients from pretreatment to last follow up

Size of primary lesion	Mean Score in cm	P Value
Pre-treatment	3.5	<0.001
After 3 Weeks of treatment	3.2	<0.001
After 6.5 Weeks of treatment	2.8	<0.001
6 weeks after treatment	2.2	<0.001
3 months after treatment	2.0	<0.001

Table III: Mean size of lymph node in anterior two third and Posterior one third of tongue patients from pretreatment to last follow up

Anterior two third of tongue		
Size of lymph node	Mean Score in cm	P Value
Pre-treatment	3.8	<0.001
After 3 Weeks of treatment	3.4	<0.001
After 6.5 Weeks of treatment	3.0	<0.001
6 weeks after treatment	2.6	<0.001
3 months after treatment	2.0	<0.001

Posterior one third of tongue		
Size of lymph node	Mean Score in cm	P Value
Pre-treatment	4.4	<0.001
After 3 Weeks of treatment	4.0	<0.001
After 6.5 Weeks of treatment	3.6	<0.001
6 weeks after treatment	3.2	<0.001
3 months after treatment	3.0	<0.001

Table IV: Distribution of patients by treatment response in anterior two third and posterior one third of tongue

Anterior two third of tongue						
Stage	No. of Patients	Complete Response (%)	Partial Response (%)	Stable Disease (%)	No Response (%)	Chi Square Test
Stage III	20	2 (10%)	15 (75%)	2 (10%)	1 (5%)	$\chi^2=9.71$;
Stage IV A	6	1 (16.66%)	1 (16.66%)	3 (50%)	1 (16.66%)	$P<0.05$
Stage IV B	4	0 (0%)	1 (25%)	1 (25%)	2 (50%)	

Posterior one third of tongue

Stage	No. of Patients	Complete Response (%)	Partial Response (%)	Stable Disease (%)	No Response (%)	Chi Square Test
Stage III	7	1 (14.28%)	5 (71.43%)	1 (14.28%)	0 (0%)	$\chi^2=7.62$
Stage IV A	2	0 (0%)	0 (0%)	1 (50%)	1 (50%)	$P<0.10$
Stage IV B	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	

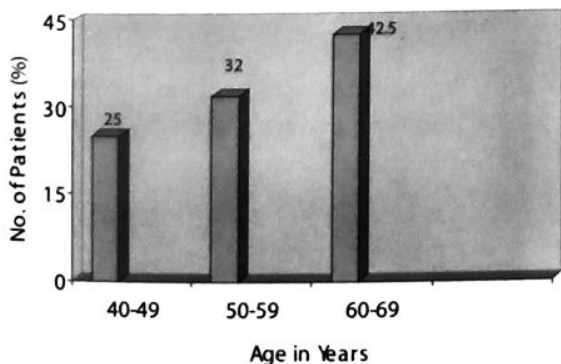


Fig 1: Distribution of Patients according to Age

Table V: Distribution of treatment related toxicities in anterior two third and posterior one third of tongue.

Variables	Anterior two third of tongue No. (%)	Posterior one third of tongue No. (%)
Skin Reaction		
Grade I	16 (60%)	4 (40%)
Grade II	4 (13.33%)	2 (20%)
Grade III	8 (26.67%)	4 (40%)
Mucositis		
Grade I	20 (66.67%)	4 (40%)
Grade II	5 (16.67%)	4 (40%)
Grade III	5 (16.66%)	2 (20%)
Stomatitis		
Grade I	21 (70%)	5 (50%)
Grade II	6 (20%)	2 (20%)
Grade III	3 (10%)	3 (30%)
Diarrhoea		
Grade I	18 (60%)	4 (40%)
Grade II	8 (26.67%)	4 (40%)
Grade III	4 (13.33%)	2 (20%)
Hematological		
Leucopenia		
Grade I	6 (20%)	3 (30%)
Grade II	12 (40%)	3 (30%)
Grade III	7 (23.33%)	2 (20%)
Grade IV	5 (16.67%)	2 (20%)
Anemia		
Grade I	20 (66.67%)	6 (60%)
Grade II	10 (33.33%)	4 (40%)

Discussion

The study was carried out with an aim to observe the effects and toxicities of concurrent chemoradiation in locally advanced carcinoma of tongue. The present study findings were discussed and compared with the previously published relevant studies. Carcinoma of tongue is common particularly in older age group⁷. The present study showed that the patients with carcinoma of tongue were mostly at advanced age. Peak age was between 60-69 years. This study coincides with the study of Brizel D.M.et. al⁸. The study showed that, 30% of patients with cancer of oral tongue present with palpable nodes at presentation. For the posterior third of the tongue, 75% of patients have palpable nodes. All the patients in this study were with cervical lymph nodes because of advanced disease⁹. The study showed that ulceration, painful swallowing or drinking, otalgia are common symptoms of anterior two third of tongue. Sore throat, difficulty in swallowing, otalgia is common symptoms of posterior one third of tongue. The patients in this study shows similar clinical presentation¹⁰.

Highest percentage of patients was habituated with betel nut chewing followed by smoking 90% and tobacco leaf 90%.

Among thirty patients of anterior two third of tongue cancer, twenty patients were stage III, six patients were stage IVA & four patients were stage IVB. Among ten patients of posterior third of tongue cancer, seven were stage III, two were stage IVA & one was stage IVB. Pre-treatment status of mean size of primary lesion in anterior two third of tongue cancer patients is 3.3 cm which is reduced to 2.0cm six weeks and 1.9 cm three months after completion of treatment. On the other hand, pre-treatment status of mean size of primary lesion in posterior one third of tongue cancer patients is 3.5cm which is reduced to 2.2cm in six weeks and 2.0 cm in three months after completion of treatment. Analysis revealed that severity of pain significantly decrease from initial treatment to final follow up in both anterior two third and posterior one third of tongue. The mean size of lymph nodes was significantly decreased from pretreatment status to final follow up in both anterior two third and posterior one third of tongue.

In response to concurrent chemoradiotherapy complete response was observed in 10% of stage III, 16.66% of stage IVA of anterior two third of tongue cancer. Partial response was observed in 75% of stage III, 16.67% of stage IVA & 25% of stage IVB. In posterior third of tongue only 14.28% was observed with complete response and partial response shows 71.43% of stage III. In stage IVA 50% shows stable disease and 50% shows no response. In stage IVB one patient shows no response. This is similar to study of Chen Y. et al.¹¹

It is to be noted that stage III patients showed better treatment response than stage IV patients in both anterior two third and posterior third of patients. Adverse effects are mainly mucositis, stomatitis, skin reaction, nausea and vomiting. Eight patients of anterior two-third and four patients of posterior one-third show grade III skin reaction.

Treatment of these patients had to be stopped. After giving seven days rest and proper treatment, concurrent chemoradiation was started. Five patients of anterior two-third and two patients of posterior one-third show grade III mucositis reaction. Treatment of these patients had to be stopped. After giving proper management, treatment was continued. In anterior two-third of tongue cancer patients seven show grade III and five show grade IV leucopenia and in patients of posterior one-third two show grade III and two show grade IV leucopenia. These patients were treated with Inj. G-CSF. Ten patients of anterior two-third and four patients of posterior one-third show grade II anemia.

These patients were treated with appropriate amount of fresh blood transfusion. Mucositis and skin reaction gradually decrease from third week of treatment to final follow up. This observations correlate with the observation of Chen Y. et al.¹² It is now said that concurrent chemoradiation is effective and tolerable in locally advanced carcinoma of tongue. However further studies are recommended to determine the efficacy of concurrent chemoradiotherapy.

Limitations of study

There were several limitations encountered in this study. Forty patients were not at all representative of total population. Poverty and lack of literacy of studied patients worked as a potential barrier against scheduled follow up. Short duration of research made the effort less conclusive. Randomization of patients cannot be done. Retreatment, duration of response & developing new metastasis could not be taken into account in this study.

Conclusion

In the treatment of locally advanced carcinoma of tongue, concurrent chemoradiation showed better symptom improvement, manageable toxicities, better tumor response, and organ preservation. So, concurrent chemoradiation may be one of the treatment modality in locally advanced carcinoma of tongue patients.

Disclosure

All the authors declared no competing interestes

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