

Neo-adjuvant chemo-radiation therapy in T4 resectable oral cavity cancer

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Abstract

Purpose: Primary objective is to evaluate clinical and pathological response at both primary and neck and margin status and postoperative morbidity in T4 resectable oral cavity cancer patients treated with neo adjuvant chemo-radiotherapy.

Methods: 30 patients, presenting with T4 resectable oral cavity cancers were randomly assigned to Arm A (Neo-adjuvant chemo-radiotherapy followed Surgery was performed after 2 to 6 weeks) and Arm B (Definitive Surgery followed by adjuvant radiotherapy with or without chemotherapy).

Results: In our study, out of fifteen patients in neo-adjuvant chemo-radiation, who underwent surgery in which 7(46.7%) had pathological complete response with no residual disease, 6(40%) with partial response with negative margins and negative nodes. No significant difference observed in margin positivity compared with standard arm (p=0.88). Postoperative morbidity was comparable. Some of the patients could undergo limited resections.

Conclusion: Our study concludes that neo adjuvant chemo-radiotherapy followed by surgery is feasible with good pathological complete responses. Since response to chemo radiotherapy is an important prognostic factor, results may translate in better disease-free survival in the future.

Introduction

Although progress has been achieved in radical surgical resection with reconstruction and use of postoperative radiotherapy/chemo-radiotherapy, the 5-year survival rate has not improved substantially in recent years, remaining at 50% to 60% [1,2]. Statistics of surgical departments indicate most of them recur regionally or distantly in the first two years in spite of initial surgery and radiotherapy [3].

To improve local-regional control and to allow better functional and cosmetic results after surgery, neo-adjuvant protocols have been developed during the last decade implementing radio-chemotherapy prior to selective surgery. Currently there is no well-established protocol for neo-adjuvant chemo-radiotherapy for resectable oral cavity cancers. Hence this study is undertaken. We have chosen resectable T4 oral cancers because of high incidence of close margins (especially in tumors of retromolar trigone and upper bucco-gingival region extending posteriorly) reported higher local recurrence rates in Indian population.

Objectives

1. To evaluate clinical and pathological response at both primary and neck and margin status in T4 resectable oral cavity cancer patients treated with neo adjuvant chemo-radiotherapy. 2.To evaluate postoperative morbidity.

Methods

The source of data for the study were patients presenting to the department of oncology, Vydehi Institute of Medical Sciences, Bangalore with stage T4 resectable oral cavity cancers. Patients recruited from Jan 2014 to June 2015.

The sample size chosen was 30. This was estimated based on data obtained with the historical studies.

ARM A: Neo adjuvant chemo radiotherapy.

ARM B: Surgery and adjuvant chemo and/or radiotherapy.

Inclusion Criteria: 1. Age 20 to 65 years, 2. Performance Status-0-2 (ECOG Criteria). 3. Primary-T4 resectable invasive squamous cell carcinoma of the oral cavity (According to AJCC 7th edition) 4. Neck -N0, N1, N2b and N2c (Nodal size less than 3 cm, mobile).

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Exclusion Criteria: 1. Metastatic disease, 2. Performance status more than 2, 3. Previous irradiation to head and neck area, 4. Patients with fixed nodes and nodal size more than 3 cm.

Informed and written consent of the patient taken.

Treatment

Out of 30 patients, presenting with stage IV oral cavity cancers 15 patients were randomly assigned to neo-adjuvant chemo radiation (Arm A). Radiotherapy was delivered to a dose of 4600cGy in 23 fractions, 200cGy per fraction, 5 fractions per week to primary and neck, using 3-dimensional conformal radiation therapy (3DCRT) with 6 MV photons. Chemotherapy drug was Inj. Cisplatin (70 mg/m²) which was delivered concurrently with radiation therapy on day 1 and day 21. Surgery was performed after 4-6 weeks and 15 patients in (Arm B) definitive Surgery followed by adjuvant radiotherapy with or without chemotherapy (Positive margin/Extra nodal extension). Radiation was delivered to a dose of 6000cGy in 30 fractions, 200cGy per fraction, 5 fractions per week to primary and neck, using 3 dimensional conformal radiation therapy (3DCRT) with 6 MV photons and Chemotherapy was delivered with Inj. Cisplatin (70mg/m²) concurrently with radiation therapy on day 1 and day 21. All patients were intravenously pre medicated with dexamethasone, ranitidine and standard antiemetic agents.

During treatment

The patients were explained about the care of irradiated site, precautions, and diet modifications. The weight of the patient was checked on a weekly basis. Acute reactions were recorded using RTOG Acute Reaction Morbidity Criteria. The patients were managed according to the toxicity profile.

Response assessment

At 4 weeks patients were assessed by clinical and radiological examination with contrast CT of the Head and neck. Responses were categorized according to RECIST criteria 1.1.

After surgery, post op histo-pathological response was assessed at primary and nodes, any other positive risk features were documented. Adjuvant radiation/chemotherapy was given ONLY for positive margins/positive nodes with ECE.

Follow up

Patients were assessed for post treatment morbidity and were followed up at 6wks, 3 months ,6 months.

Statistical analysis

Our study is a randomized, prospective interventional study.

Statistical Methods:

Data were analyzed using SPSS version 20 for windows. Frequency distribution of response and categorical variables were determined. Chi square test for proportions to compare differences between neoadjuvant chemoradiation arm and standard treatment arm for site, stage, surgery type, positive margins, and postoperative morbidity was determined. P value <0.05 was considered statistically significant.

Results

All the patients had T4a resectable oral cavity cancers, Sub sites were comparable in both arms, but the nodal status was higher in the

neo-adjuvant arm as shown in the Table 1. Response assessment was done at 4weeks of post CTRT by clinical and radiological examination which showed 70.6% partial response and 17.6% complete response (Figures 1 and 2). Fifteen patients underwent surgery within 4-9 weeks. Thirteen patients underwent composite resection and 2 patients wide local excision (Figure 3). Histologically 46.7% patients shows complete response at primary and 100% at nodes (Figure 4). There was one treatment related mortality in Neo-adjuvant chemo-radiation arm. Margin status and morbidity was comparable in both the arms (Figures 5 and 6).

Discussion

To our best knowledge, this is the first prospective study in India to compare Neo-adjuvant chemo-radiotherapy (CRT) and surgery followed by radiotherapy with/without chemotherapy in the treatment of resectable T4 oral cavity cancer.

Although surgery is the mainstream of therapy in oral cavity Squamous cell carcinoma, most patients in stage IV with bone and deep

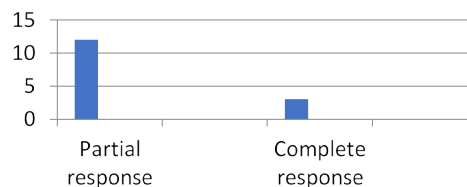


Figure 1. Bar diagram showing clinical and radiological response –Primary

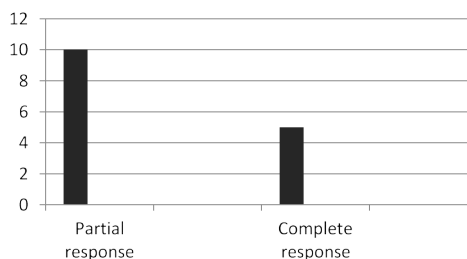


Figure 2. Bar diagram showing clinical and radiological response - Node

Table 1. Patient and tumour characteristics

	NEOADJUVANT ARM	STANDARD ARM	P Value
Age			
20-39	2	1	
40-59	10	12	
60-65	3	2	
Sex			
Male	6(40%)	7(43%)	0.74
Female	9(60%)	8(53%)	
Sub site			
Buccal mucosa extending to Retromolar trigone	9 (60%)	10 (66%)	0.4
Buccal mucosa	1(10%)	2(13%)	
Lower alveolus	2(13%)	1(10%)	
Retromolar trigone	3 (20%)	1(10%)	
Tongue	-	1(15%)	
Upper Alveolus	-	-	
N STATUS			
N0	0	8(53%)	0.001
N1	12(80%)	5(33%)	
N2	3(20%)	2(13%)	

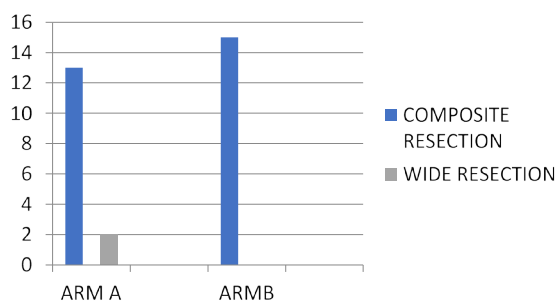


Figure 3. Bar diagram showing type of surgery done

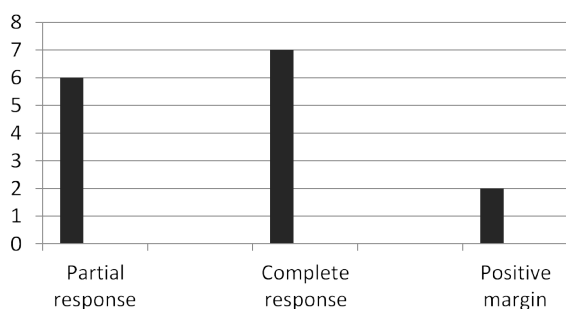


Figure 4. Bar diagram showing pathological response: ARM A

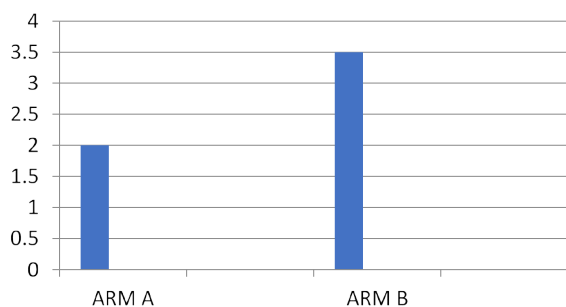


Figure 5. Bar diagram positive margins status

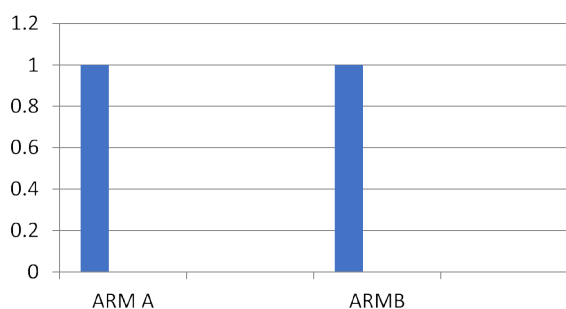


Figure 6. Bar diagram showing postop morbidity

muscles of tongue end up with severe morbidity and are more likely to have positive margins. Adjuvant chemo-radiotherapy is associated with acute mucositis, dysphagia, nausea, vomiting, hoarseness and long term complications such as esophageal stenosis, hypothyroidism, osteoradionecrosis, xerostomia and subcutaneous fibrosis [4].

Sum studies on preoperative radiation in locally advanced head and neck cancer was reportedly associated with more toxicity than postoperative RT by the results of RTOG multicenter phase 3 trial 7303 [5-7].

Studies on preoperative chemo-radiation followed by surgery showed improved disease free survival and overall survival and acceptable toxicity [8-14].

Cisplatin has been studied most extensively, achieving significantly greater regression of experimental tumors when combined with radiation than did either technique alone [15,16], with partial and complete tumor responses in many patients with non resectable squamous cell carcinoma of head and neck [17,18].

Addition of cisplatin to preoperative radiotherapy did not enhance OS, but significantly improved 5-year DMFS and also borderline significance in PFS when compared to preoperative radiotherapy alone [19].

One of the most significant findings of our study was the large number of pathologically complete responses at primary (46.7%) and node (100%) after neo-adjuvant CT/RT. The drawback here was that these nodes were detected on clinical and radiological examination and were not proven with histopathology before starting neo-adjuvant chemo radiation. Also the inclusion criteria was to include nodes up to 3cm. But considering the fact that 30% of the clinically N0 nodes show microscopic disease, neo-adjuvant chemo radiation has definitely helped to treat these cases.

In the literature, studies have reported that response to neo-adjuvant chemotherapy was the most important prognostic factor [9,10]. Our study has shown high pathological complete responses, this may translate in to better disease free survival and overall survival though long term follow up would be required to document these findings. Adjuvant radiation was needed in only one patient with positive margin.

Our results showed that neo-adjuvant CT/RT followed by surgery was well tolerated with acceptable toxicity similar to previous study [9]. During neo-adjuvant CT/RT, mucositis of grade 3 was observed in 9(45%) patients and were managed symptomatically. Two patients had radiation treatment interruption of two days. Only one patient developed grade 3 neutropenia. One patient in neo-adjuvant arm died in the postoperative period due to septicemia. No other major complications were observed. Though statistically not significant, two patients could undergo wide local excision after neo-adjuvant chemo radiation. The use neo-adjuvant chemo-radiation in achieving limited resections needs to be addressed further. Postoperative morbidity was comparable with standard arm. Only one patient in the neo-adjuvant chemo-radiation arm developed fistula. One patient in standard arm had graft failure. Long term follow up will be required to further assess the effectiveness of neo-adjuvant therapy.

Conclusion

1. A higher pathological complete response could be achieved at both primary and selected neck nodal disease by neo-adjuvant chemo-radiotherapy in patients with resectable T4a squamous cell carcinoma oral cancers.
2. The higher pathological response could be a predictor of better disease-free survival and overall survival.
3. The neo-adjuvant chemo-radiation did not increase toxicity and post op morbidity.

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