RESEARCH ARTICLE

Survival Following Non Surgical Treatments for Oral Cancer: a Single Institutional Result

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Abstract

Aim: To report the results of radiotherapy with or without chemotherapy in the patients with oral cancer. Methods: Over the 2003-2009 periods, a total number of 69 patients with squamous cell carcinoma of the oral cavity that refused surgery or had unresectable tumor were enrolled in this study. A total dose of 60 to 70 Gy (2 Gy per day) was given to the primary tumor and clinically positive nodes. In the patients with locoregionally advanced disease (57 patients with T_3, T_4 lesions and/ or N^+) induction chemotherapy following by concomitant chemoradiation was used. Induction chemotherapy consisted of 3 cycles of Cisplatin and 5-Flourouracil with or without Docetaxel. Weekly cisplatin was used in concomitant protocol. Kaplan-Meier method was used to calculate overall survival. Log-rank test and Cox regression model were used for comparison purposes. Results: Median follow-up was 32 months. The mean age of the patients was 59.2 years. The overall response rate after induction chemotherapy was 68.4%. Actuarial overall survival rates after 2 and 3 years were 38% and 26%, respectively. Clinical stage emerged as the only independent predictor of survival. Conclusion: Outcome of the patients with oral cancer is poor. Presenting with an advanced stage lesion contributed to this result. The role of chemotherapy in advanced cases remains to be defined.

Keywords: Oral cancer - radiotherapy - chemotherapy - head and neck - survival

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Introduction

Oral carcinoma is the sixth most common cancer in the world (Effiom et al., 2008; Shah & Gil, 2009) and the most frequent cancers in the head and neck region (Montoro et al., 2008; Multidiciplinary, 2008). Squamous cell carcinoma is the most frequent histological type in oral cavity (Effiom et al., 2008). Despite improvements in treatment, the overall survival has not increased significantly for oral cancer over the past decades (Razak, et al., 1995; Larsen, 2009). Surgery is the most effective treatment for a majority of patients (Shah & Gil, 2009). The most important prognostic factor is TNM staging. Survival also may be affected by patient co-morbidity, performance status, biological and histological parameters and treatment modality (Genden et al., ????). Relatively few institutions have reported the results of non surgical treatment for oral cancer. The main aim of this study was to report the 2 and 3 year overall survival in a group of Iranian patients with oral cancer treated with non surgical modality. This is the first report of oral cancer outcome from Iran.

Materials and Methods

Between October 2003 and December 2009, a total number of 69 patients with biopsy proven diagnosis of oral squamous cell carcinoma that refused surgery or had unresectable disease (medically or surgically) were enrolled in this study. The staging workup included, computed tomographic scanning of the primary tumor and the neck and chest X-Ray. Imaging was performed as clinically indicated to rule out metastatic disease. Tumor and nodal staging were determined according to the 2010 American joint committee for cancer staging system. Normal hematological, renal and hepatic function, ECOG performance status of 0-1 and signed informed consent was required. Exclusion criteria included evidence of other synchronous tumors, surgery other than biopsy, those with incomplete treatment or evidence of distant metastasis.

A total dose of 60 to 70 Gy (according to tumor size, 2 Gy per day) was given to the primary tumor and clinically positive nodes, by external beam. The entire neck received 50 Gy. Field size was reduced after 40 Gy to separate spinal cord. The boost dose to clinical involved nodes was given by electron beam or the beam that covered the primary tumor. There was no Brachytherapy, 3-D conformal radiotherapy or IMRT facility in our institute. Conventional techniques were used to achieve treatment and to check quality.

In the patients with locoregionally advanced disease (T_3, T_4 lesions and/or N^+) induction chemotherapy following by concomitant chemoradiation was used. For the other patients radiotherapy was used, only. Induction

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chemotherapy consisted of 3 cycles of cisplatin (100 mg/m^2 on day 1) and 5-FU(1,000 mg/m^2, 24 hours infusion, on days 1-3) (PF regimen) or 3 cycles of Docetaxel (75 mg/m^2 on day 1), Cisplatin (75 mg/m^2 on day 1) and 5-FU (750 mg/m^2 24 hours infusion, on days 1-3) (TCF regimen). There was no randomization for this selection. Over the time period of the study the chemotherapy choice was changed according to reported studies. Weekly cisplatin (50 mg/m^2) was used in concomitant protocol. Kaplan-Meier analysis was used to calculate overall survival. Comparing overall survival according to treatment and patients parameters was done with log-rank test. Overall survival was defined as the time from the first day of treatment to date of death, censored at the date last known alive.

Results

The characteristics of the patients and their treatment results are shown in Table 1. Median follow-up was 32 months (range: 4 to 68 months). The age of patients ranged from 27 to 87 years (mean 59.2 years, SD 16.96 years). A total of 57 patients (82.6%) were assigned to receive induction chemotherapy.

The overall response rate after induction chemotherapy was 68.4% (15.8% complete response and 52.6% partial response). No tumor progression was seen during induction treatment.

Actuarial overall survival rates of 38% and 26% were observed at 2 and 3 years, respectively.

On univariate analysis, survival differences reached statistical significance for age, tumor sub-site and T and N stage (Table 1 and Figure 1A-1F). The patients above 50 years had lower survival rate compared to younger patients (p=0.02). Overall survival was significantly reduced with advanced stage. Node positive patients had lower survival (p=0.00). survival was better for T_1/T_2 lesions compared to T_3/T_4 tumors (p=0.00) None of the patients with stage I and II died during follow up period compared to 92% death among those with stages III and IV. Tongue lesions had lower outcome compared to other locations (p=0.03). Gender was not associated with survival (p=0.74). Chemotherapy type was borderline significant (0.07). The significant variables were considered in the Cox regression model. The T (p=0.02) and N (p=0.00) stage emerged as independent predictors of survival. Age (p=0.14) and tumor site (p=0.06) were not significant.

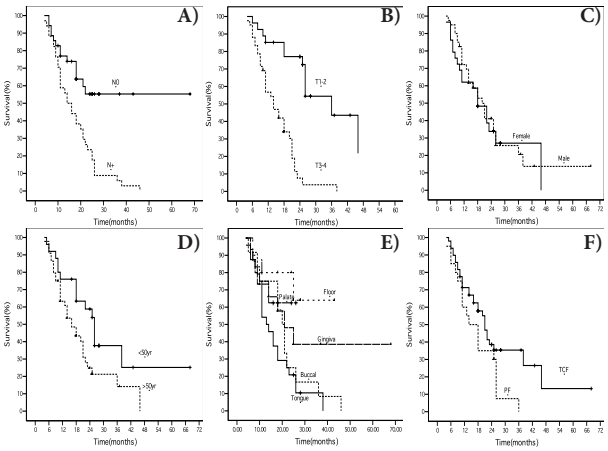

Figure 1. Kaplan-Meier Survival Curves. A) Presence (N$^+$) and absence (N0) of neck metastases (p=0.00), B) T1-T2 and T_3-T_4 patients (p=0.00), C) Male and female patients (p=0.74), D) Age factor (p=0.02), E) Different tumor location (p=0.03), F) Cisplatin + 5-Fu (PF) combination and cisplatin+5-Fu +Docetaxel (TCF) regimen (P=0.07).

Table 1. Patient Characteristics and Mean Survival by Selected Factors (Patient Numbers: 69, CTX: Chemotherapy)

Factor	No. of cases (%)	Mean survival	95%CI
Age		(X^2 (df)=5.34 (1), p=0.02)	
≤50	25 (36.2)	32.6	22.1-43.1
>50	44 (63.8)	24.0	15.7-24.3
Sex		(X^2 (df)=0.1 (1), p=0.74)	
Male	40 (58)	25.6	18.5-32.6
Female	29 (42)	22.7	16.5-28.9
T Stage		(X^2 (df)=25.8 (1), p=0)	
T_1-T_2	27 (39.1)	37.3	26.6-48.0
T_3-T_4	42 (60.9)	15.2	12.7-17.6
N Stage		(X^2 (df)=13.1 (1), p=0)	
N^0	35 (50.7)	43.5	33.7-53.3
N^+	34 (49.3)	17.1	13.8-20.4
Sub-site		(X^2 (df)=10.3 (4), p=0.03)	
Tongue	24 (34.8)	16.5	12.6-20.5
Gingiva	15 (21.7)	35.1	20.3-49.8
Buccal mucosa	12 (17.4)	21.0	14.5-27.4
Floor of mouth	10 (14.5)	32.9	23.4-42.4
Palate	8 (11.6)	20.2	14.9-25.5
CTX regimen		(X^2 (df)=3.1 (1), p=0.07)	
TCF	41 (59.4)	27.9	20.4-35.4
PF	16 (23.2)	17.1	12.9-21.3
No CTX	12 (17.4)		

Discussion

The prognosis of oral cancer is poor (Multidiciplinary, 2008). The selection of treatment is according to tumor site, clinical stage, patient performance status, physician and patient preference (Shah & Gil, 2009). For early stage oral cancer, primary surgery or definitive radiotherapy can be used. For locoregionally advanced disease, however, single treatment is not usually effective and combined modality should be considered. Surgery is generally the preferred approach in operable patients because it is typically associated with less morbidity than radiation (Genden et al., ????; Shah & Gil, 2009). Primary radiotherapy may be offered to selected patients who are medically inoperable or refused surgery. For this reason, the result of non surgical treatment is rarely reported in literature. In this study there was an opportunity to analyze the result of radiation (with or without chemotherapy) for oral cancer patients.

A variable range of overall survival has been reported for oral cancer (Yeole, 2003; Warnakulasuriya, 2007; Brandizzi, 2008; Effiom et al., 2008; Montoro et al., 2008; Rogers et al., 2009). In Australia an overall survival rate of 83.3% has been reported (Chandu, 2005). In United Kingdom the 5-year overall survival was 64% (Woolgar et al., 1999). In India a survival rate of 30.5% has been reported (Yeole et al., 2003). In Brazil the survival rate

was 28.6% (Oliveira et al., 2008). In Malay the 5- year survival has been 18% (Razak et al., ????). The global variation in the overall survival of oral cancer may be due to geographic differences in data collection, differences in patient characteristics (stage, age and genetic and environmental risk factors) and variation in treatment modality (Yeole et al., 2003). It is difficult to compare our outcomes directly with others because of variations in patient characteristics, treatment modality and report of outcome data. The 2-year and 3–year survival rates in this study were 38% and 26%, very much lower compared with other studies using surgery (Chandu et al., 2005; Rogers et al., 2009). This finding may be due to higher percentage of the patients with advanced stages in this study compared to the other studies. This series contained 60.9% of T_3/T_4 tumors and 49.3% of node involved lesions. In a study in which the majority of patients were treated with primary radiotherapy (73% of the patients) the overall survival was 33% (Langdon et al., 1977). In another study none of the patients treated with radiotherapy alone survived at 5 years (Razak et al., ????).

Many prognostic factors have been studied in oral cancer. Some of these factors have been studied in the present report. Metastasis to neck node is the most important prognostic factor for oral cancer. Tumor size and T stage is another factor (Woolgar et al., 1995; Lee, 2005; Murthy et al., ????). In this study the T (p=0.02) and N (p=0.00) stage emerged as independent predictors of survival, which was in agreement with most published results (Montoro et al., 2008; Murthy et al., ???? ; Razak et al., ????). None of the patients with stages I and II died within 3 years compared to 92% death among those with stages III and IV. This finding highlights the importance of early detection and screening for oral cancer. The prognostic importance of age and sex is not clear in literature. In some studies young patients had better outcome (Yeole et al., 2003; Oliveira et al., 2008). In one study radiotherapy outcome was inferior in those patients below the age of 40 years (Murthy et al., ????). In this study log-rank test showed better survival for patients below 51 years (p=0.02). But on multivariate analysis the role of age in treatment outcome was not significant (p=0.14). Also, the association between sex and survival is controversial. In some reports there is no difference between male and female patients (Chandu et al., 2005; Montoro et al., 2008) whereas in some others male patients have lower survival (Yeole et al., 2003; Oliveira et al., 2008). In the present study survival between male and female gender was not significant (p=0.74). There is no consensus in literature with regard to association between tumor sub site and overall survival. Some series reported inferior outcomes in patients with tongue lesions (Murthy et al.) where others have failed to demonstrate this finding (Bell, 2007). In this report tongue lesion had lower survival (p=0.03). But Cox regression test showed no independent predictor value for tumor location in oral cancer (p=0.06).

Conventional treatment for locoregionally advanced head and neck cancer has included either radical surgery and adjuvant radiotherapy or radiotherapy alone. Recently, combined modality regimens (for example induction chemotherapy followed by chemoradiation) have shown that non surgical treatment increases the probability of organ preservation without jeopardizing survival outcomes in these patients (Forastiere et al., 2003; Posner, 2007; Adelstein, 2008). Cisplatin and fluorouracil combination chemotherapy, as the oldest induction regimen, was developed in the late 1970s. Recent studies suggest that induction chemotherapy with taxane, cisplatin and fluorouracil provides better outcomes without greater toxicity (Posner et al., 2007; Vermorken et al., 2007; Pointreau et al., 2009). In this study TCF regimen was marginally better than PF regimen (p=0.07).

After three cycles of induction chemotherapy, complete response and partial response were seen in 15.8% and 52.6% of the patients. This result is lower than our previous published result for induction chemotherapy in laryngeal cancer (Larizadeh & Damghani).

In conclusion, outcome of the patients with oral cancer is poor. Presenting with an advanced stage lesion contributed to this result. Detecting in early stages offers the best chance of long term survival. The role of chemotherapy in advanced cases remains to be defined.

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References

Adelstein D J (2008). Redefining the role of induction chemotherapy in head and neck cancer. *J Clinical Oncol*, **26**, 3117-9.

Bell R B, Kademani D, Homer L, et al (2007). Tongue cancer: Is there a difference in survival compared with other subsites in the oral cavity? *J Oral and Maxillofacial Surg*, **65**, 229-36.

Brandizzi D, Gandolfo M, Velazco M L, et al (2008). Clinical features and evolution of oral cancer: A study of 274 cases in Buenos Aires, Argentina. *Age (in years)*, **40**, 9.

Chandu A, Adams G, Smith A (2005). Factors affecting survival in patients with oral cancer: an Australian perspective. *Int J Oral and Maxillofacial Surg*, **34**, 514-20.

Effiom O A, Adeyemo W L, Omitola O G, et al (2008). Oral squamous cell carcinoma: a clinicopathologic review of 233 cases in Lagos, Nigeria. *J Oral and Maxillofacial Surg*, **66**, 1595-9.

Forastiere A A, Goepfert H, Maor M, et al (2003). Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *New England J Med*, **349**, 2091-8.

Genden E M, Ferlito A, Silver C E, et al (????). Contemporary management of cancer of the oral cavity. *Eur Archives of Oto-Rhino-Laryngology*, **267**, 1001-17.

Langdon J D, Harvey P W, Rapidis A D, et al (1977). Oral cancer: The behaviour and response to treatment of 194 cases*. *J Maxillofacial Surg*, **5**, 221-37.

Larizadeh M H, Damghani M A (????). Sequential chemoradiotherapy in advanced laryngeal cancer: An institutional experience. *Asian Pac J Clinical Oncol*, **6**, 106-10.

Larsen S R, Johansen J, SÃ¸rensen J A, et al (2009). The prognostic significance of histological features in oral squamous cell carcinoma. *J Oral Pathol & Med*, **38**, 657-62.

Lee K, Veness M, Pearla Larson T, Morgan G (2005). Role of combined modality treatment of buccal mucosa squamous cell carcinoma. *Australian Dental J*, **50**, 108-13.

Montoro J R M C, Hicz H A, Souza L, et al (2008). Prognostic factors in squamous cell carcinoma of the oral cavity. *Revista Brasileira de Otorrinolaringologia*, **74**, 861-6.

Multidiciplinary A O F (2008). Oral cancer: the current status and strategies of its management. *Chinese Med J*, **121**, 1859-60.

Murthy V, Agarwal J, Laskar S G, et al (????). Analysis of prognostic factors in 1180 patients with oral cavity primary cancer treated with definitive or adjuvant radiotherapy. *J Cancer Res and Therapeutics*, **6**, 282.

Oliveira L R, Ribeiro-Silva A, Costa J P O, et al (2008). Prognostic factors and survival analysis in a sample of oral squamous cell carcinoma patients. *Oral Radiol & Endodontol*, **106**, 685-95.

Pointreau Y, Garaud P, Chapet S, et al (2009). Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J National Cancer Institute*, **101**, 498-506.

Posner M (2007). Evolving strategies for combined-modality therapy for locally advanced head and neck cancer. *The Oncologist*, **12**, 967-74.

Posner M R, Hershock D M, Blajman C R, et al (2007). Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *New England J Med*, **357**, 1705-15.

Razak A A, Saddki N, Naing N N (????). Oral cancer survival among Malay patients in Hospital Universiti Sains Malaysia, Kelantan. *Asian Pac J Cancer Prev*, **11**, 187-91.

Rogers S N, Brown J S, Woolgar J A, et al (2009). Survival following primary surgery for oral cancer. *Oral oncology*, **45**, 201-11.

Shah J P, Gil Z (2009). Current concepts in management of oral cancer-surgery. *Oral oncology*, **45**, 394-401.

Vermorken J B, Remenar E, van Herpen C, et al (2007). Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *New England J Med*, **357**, 1695-704.

Warnakulasuriya S, Mak V, Maller H (2007). Oral cancer survival in young people in South East England. *Oral Oncology*, **43**, 982-6.

Woolgar J, Rogers S, West C, et al (1999). Survival and patterns of recurrence in 200 oral cancer patients treated by radical surgery and neck dissection. *Oral oncology*, **35**, 257-65.

Woolgar J A, Scott J, Vaughan E, et al(1995). Survival, metastasis and recurrence of oral cancer in relation to pathological features. *Annals of the Royal College of Surgeons of England*, **77**, 325.

Yeole B B, Ramanakumar A V, Sankaranarayanan R (2003). Survival from oral cancer in Mumbai (Bombay), India. *Cancer Causes and Control*, **14**, 945-52.