

RESEARCH ARTICLE

Early Stage Oral Tongue Cancer among Non-Tobacco Users - An Increasing Trend Observed in a South Indian Patient Population Presenting at a Single Centre

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Abstract

Background: Oral tongue squamous cell carcinoma (OTSCC) is the most common cancer diagnosed within the oral cavity worldwide. Many studies in India report OTSCC ranking among the top two most common subsites within the oral cavity. India is often labeled the oral cancer capital of the world. The incidence of tongue cancers in the population-based cancer registry (PBCR) of Chennai is showing an increasing trend. A majority of the oral cavity cancers (85%) in our cancer center present in advanced stages (III and IV). In contrast, early tongue cancers (stages I and II) constitute nearly 45% of all OTSCCs. **Aim:** The aim of this study was to analyze the clinical profile and epidemiological trends in our early stage tongue cancer patients with an emphasis on tobacco and alcohol habits. **Materials and Methods:** This retrospective analysis was based on a prospectively collected database of 458 consecutive early stage OTSCC in-patients at a tertiary care oncology centre in Chennai between 1995 and 2008. **Results:** Our study suggests that the earlier trends have clearly changed whereby nearly half of our patients are now never-tobacco users. The findings of the study indicate that a majority of the patients were never alcohol users (86.4%) and nearly half of them were never tobacco users (49.3%), and they had the best survival outcomes. This increasing trend of OTSCC among non-tobacco users is in contrast to our earlier experience of tongue cancer more than five decades ago. The median age of patients in our study was 53.3 years; the male to female ratio was approximately 2:1. The median follow up for the 458 patients was 53 months. **Conclusions:** Our study importantly as well as interestingly shows a conspicuous absence of association with the traditional risk factors, tobacco and alcohol.

Keywords: Oral tongue cancer - tobacco chewers - never smokers - alcohol - overall survival

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Introduction

Oral carcinomas are the sixth most common cancers in the world (Warnakulasuriya et al., 2009). Oral tongue squamous cell carcinoma (OTSCC) is the most common cancer diagnosed within the oral cavity worldwide. In India, oral cancer is one of the most common cancers and continues to be a major public health problem. OTSCC has been reported to be among the top two most common subsites among the oral cavity cancers across many studies in India. The incidence of OTSCC although showing a slightly decreasing trend in India, is clearly showing an increasing trend in Chennai over the past 25 years as per the data of the National Cancer Control Program.

A majority of the oral cavity cancers (85%) in our cancer center present in advanced stages (Stages III and IV), on the contrary early tongue cancers (Stages I and II) constitute nearly 45% of all OTSCCs. The aim of this study was to analyze the clinical profile and the epidemiological trends in our early staged tongue cancer patients with an emphasis on the tobacco (chewing and

smoking habits) and alcohol related practices. Majority of the epidemiological studies have focused on oral cancers as a whole, there have been very few studies in literature which has specifically looked specifically into OTSCC.

Materials and Methods

This is a retrospective analysis of a prospectively collected database of 458 consecutive OTSCC patients with clinical stages I and II at a tertiary care oncology centre in Chennai between 1995 and 2008. All patients underwent the routine evaluation for tongue cancer, which apart from the comprehensive history and physical examination of the upper aero-digestive tract included a chest X-ray and a biopsy for pathologic confirmation of cancer. An ultrasound of the neck was incorporated as a part of the staging protocol during the later part of the study. Standard treatment consisting of either surgery (wide excision glossectomy) or brachytherapy with or without selective neck dissection (Levels I to IV) was performed as per the decision of the head and neck

multi-disciplinary tumor board of the Institution. Patient, tumor, and treatment related characteristics were captured. Disease-free survival and overall survival were calculated using SPSS Statistical package and depicted as Kaplan-Meier survival curves. Cox Proportional hazard regression analysis was done to obtain the hazard ratio. The predictors of outcome were identified using multivariate analysis. Statistical methods also included the Fischer exact chi square tests for the evaluation of significant associations.

Results

Demographic profile

There were 458 cases of histologically proven OTSCC in Stages I and II from January 1995 to December 2008. The median follow up was 53 months (Range: 24-88 months) The mean age was 53.3 years (Range: 24-88 years). Majority of patients were in the age group of 51-70 years (226/458; 49.3%). There was no significant association between early age (<40 years) and older age (>40 years) and tobacco habits. Majority of patients were males (313/458; 68%). The male to female ratio was about 2:1.

A majority of the tongue cancers occurred in the lateral border (416/458; 90.8%). The growth pattern was ulcerative in 61.7% (283/416) followed by exophytic pattern in 23.5% (108/453). Grade II lesion was seen in 61.7% of patients followed by grade I lesion in 25.3% (116/453) There was no significant association of tobacco usage with the above mentioned parameters.

Tobacco and alcohol use

Interestingly, our study results showed that 49.3% (226/458) of OTSCC patients had no tobacco related habits. Tobacco associated chewing was seen in 22.7% (104/458) and smoking was seen in 16.8% (77/458) of patients. The patient population constituting both chewers and smokers were 11.1% (51/453). Non-alcoholics constituted a majority of the study population constituting 86.4% (396/458). We found a very significant association between tobacco related habits and alcohol abuse. (p=0.0001) Among the tobacco users, 85.3% (198/232) belonged to the male sex and this association of male sex and tobacco use was found to be statistically significant (p=0.0001). Similar trend was seen among alcoholics as well, with 80%, (108/135) belonging to male sex (p=0.0006). More than 99% (224/226) of the non-tobacco users were also found to be non-alcoholics compared to 25.8% (60/232) having both the habits of using tobacco and alcohol (Table 1).

Analysis of prognostic factors

The 5-year-overall survival of the entire cohort was found to be 63.6%. There was no significant difference in survival pattern among males and female sexes. Evaluation of patient survival based on the distribution of the growth pattern showed that the infiltrating type of lesions showing a poorer survival pattern compared to the exophytic and ulcerated types. Survival was predictably better for lower grade I tumors as compared to grade II and III lesions. Lesions in the lateral border and dorsum

Table 1. Patient Demographic Profile Based on Tobacco Habits

		Tobacco user (n=232)	Non-Tobacco user (n=226)
Age	≤40	36 (15.5)	39 (17.2)
	>40	196 (84.4)	187 (82.7)
Site	Lateral border	208 (89.6)	208 (92.0)
	Tip	5 (2.15)	4 (1.76)
	Dorsum	4 (1.724)	5 (2.21)
	Ventral	15 (6.46)	9 (3.98)
Pattern	Exophytic	59 (25.4)	49 (21.6)
	Infiltrating	141 (60.7)	142 (62.8)
	Ulcerated	32 (13.7)	35 (15.4)
Grade	I	52 (22.4)	64 (28.3)
	II	149 (64.2)	134 (60.19)
	III	31 (13.36)	28 (12.3)
Clinical stage	I	110 (47.4)	126 (55.7)
	II	122 (52.5)	100 (44.2)
Alcohol habit	Yes	60 (25.8)	2 (0.8)
	No	172 (74.1)	224 (99.1)*

*p=0.0001

Table 2. Mean Probability of Survival at the End of Five Years

		Mean Probability of survival at the end of 5 years
Site	Lateral border	0.59999
	Tip	0.8889
	Dorsum	0.5444
	Ventral Aspect	0.732
Pattern	Exophytic	0.6667
	Infiltrating	0.5635*
	Ulcerated	0.7139
Tobacco usage	Tobacco chewer	0.5877
	Tobacco smoker	0.5826
	Both chewer and smoker	0.4201
	Non - tobacco user	0.664
Clinical Stage	I	0.7026
	II	0.5103

*RR=1.49

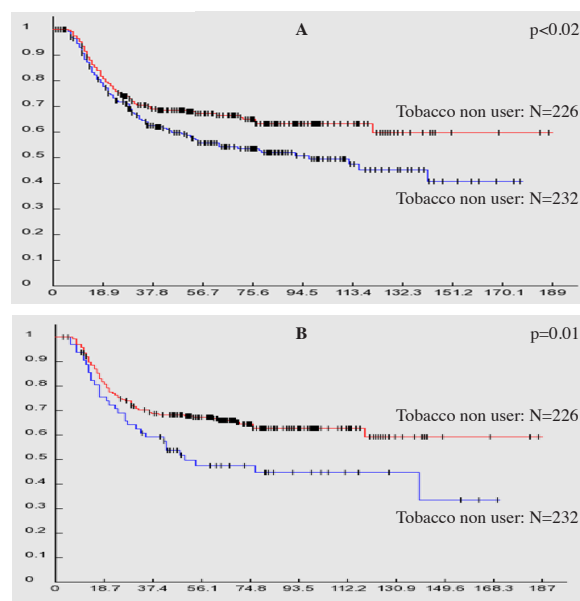


Figure 1. Kaplan Meier Survival. A) Showing survival among the tobacco users and non-tobacco users p<0.02. **B)** Showing survival among the tobacco and alcohol users and non-tobacco, non alcohol users p=0.01

tongue had a poorer survival than the patients with lesions on the tip of the tongue.

Survival comparisons based on tobacco usage showed that tobacco users, smokers and/or chewers had a significantly poorer survival when compared to the never tobacco users (Figure 1A). Similar was the observation among alcohol users, showing a poorer survival when compared to the never alcohol users. Patients with habits of both tobacco and alcohol use showed poorer survival compared to the patients with no habits ($p=0.01$) (Figure 1B). Among the patients with and without tobacco habits, predictably stage II patients had a poorer overall survival compared to stage I ($p=0.0005$; $p=0.0001$) respectively. This reiterates the significance of clinical 'T' stage being an independent risk factor in determining overall survival. We also found among the patients with Grade I tumors, the overall survival was significantly better among the non-tobacco users ($p=0.028$) however this difference was not observed for grade II and Grade III tumors (Table 2).

Discussion

Oral cancers are heterogeneous group of cancers that arise in various sub sites of the oral cavity with differing predisposing factors, prevalence and outcomes. It is the sixth most common cancer reported globally with an annual incidence of over 300,000 cases, of which 62% arise in developing countries. The age-adjusted rates (AAR) of oral cancer is over 20 per 100,000 populations in India, this is in contrast to the AAR of 10 per 100,000 in the United States, 2 per 100,000 in the Middle East and as low as 0.2 per 100,000 in Japan. In comparison with the population in the United States, wherein oral cancers constitute only about 3% of malignancies, oral cancers account for over 30% of all cancers in India and up to 40% of all cancers in South Asia. Oral cancer is one of the most common cancers in India; it is ranked as the most common cancer in males with an annual incidence of 45,455 and a mortality of 31,102. It is the fourth most common cancer in females, with an annual incidence of 24,375 and a mortality of 16,551. India is often labeled, the oral cancer capital of the world. Oral cancer has remained in the list of the top ten cancers in both men and women in the PBCR Chennai. According to PBCR Chennai- 2003-2005, the number of cases per year indicated a male preponderance in the ratio of 420 females to 1000 males.

The etiology of oral cancer is associated with well established risk factors such as tobacco, betel quid chewing and alcohol (Warnakulasuriya, 2009). Genetic susceptibility and dietary factors may enhance the effect of these carcinogens. There are suggestions of a reduction in the overall global incidence of oral cancer from 1990 to 2005 paralleling with decreased consumption of tobacco and alcohol. A comparison of oral cancer incidence in India and the United States has shown a declining trend in both the countries. The impact of this decline is much more dramatic in India, where there is a significantly higher prevalence of oral cancer. However, there are epidemiologic studies demonstrating an increase in the incidence of carcinomas in specific sub sites of the oral cavity i.e. tonsil and oral tongue (Shiboski 2005; Elango,

2006). During the past three decades, data supporting human papilloma virus (HPV) as a causative agent in the development and progression of head and neck cancer, particularly that of oropharynx has accumulated (Vijayalakshmi et al., 2012).

There has been no change in the incidence rates of OTSCC in the Population Based Cancer Registries (PBCRs) of Bangalore, Bhopal and Delhi. However, the PBCR of Chennai is showing an increasing trend, and Mumbai is showing a decreasing trend. The Annual Percentage Change (APC) for Chennai was 1.3, where as the APC for Mumbai was - 2.0. OTSCC has been one of the top ten cancers in males ever since the inception of the PBCR- Chennai. It was the seventh most common cancer (4.3% of all cancers) in PBCR- Chennai 1982-83 report; the increasing trend has brought it to occupy the fifth position (5.4% of all cancers) in the PBCR- Chennai 2005-2006 report. The Age adjusted incidence rates (AAR) for carcinoma tongue has increased from 3.6 to 5.7 per 100,000 persons over the above 25 years.

Oral tongue is among the top two most common sub-sites to be affected by carcinoma of the oral cavity in a majority of the Indian studies, the buccal mucosa along with the gingivo-buccal sulcus being the most common. The scenario in our hospital based cancer registry is no different. A majority of the oral cavity cancers (85%) in our cancer center present in advanced stages (Stages III and IV), on the contrary early tongue cancers (Stages I and II) constitute nearly 45% of all OTSCCs

The mean age in our study group was 53.4 years. Majority of patients were in the age group of 51-70 years (226/458; 49.3%). This is in agreement with many other Indian series show that the peak-age frequency of occurrence of oral cancers (including OTSCCs) in India is in the fifth decade, at least a decade earlier than that described in the western literature (Sankaranarayan et al., 1990; Gupta et al., 2001; Mathew Iype et al., 2001).

Some studies have shown increased incidence of oral cancers among younger patients, (<40 years) although the incidence of oral cancers among the younger patients is still lower than the older patients. (>40 years) According to our data, only 16% of patients with OTSCCs were <40 years old. It was also believed that oral carcinoma in younger patients was etiologically distinct from oral cancers in older patients owing to less significant exposure to risk factors such as tobacco and alcohol. There was however no significant association between younger age (<40 years) and older age patients (>40 years) with relation to the use of tobacco in our patient cohort.

There is no consensus in literature about the prognostic value of age in patients with OTSCC. It was traditionally believed and also reported in some studies that younger patients (<40 years) had an increased frequency of tumor recurrences and disease specific mortality as compared to their older counterparts (Wallner et al., 1986, Sarkaria et al., 1994; Hyam et al., 2003; Liao et al., 2006, Garevello et al., 2007., Bachar et al., 2011). However several other studies have reported that prognosis of younger patients (<40 years) is in fact better (Kantola et al., 2000; Annertz et al., 2002). Some investigators have found no difference between age and prognosis as was seen in our study

(Friedlander et al., 1998; Siegelmann-Danieli et al., 1998; Pitman et al., 2000; Manuel et al., 2003; Veness et al., 2003; Soudry et al., 2010). The Surveillance Epidemiology and End Result (SEER) tumor registry data report has suggested that old age is more likely to be associated with poor survival (Davidson et al., 2001).

The male to female ratio sex distribution from an earlier study in our center (Shanta et al., 1959) was 3:1. Several other studies have also reported that the incidence of OTSCCs is increasing and that the increasing trend was significantly greater in women compared with that of men (Moore et al., 2000; Patel et al., 2011).

The current study also showed a decrease of male to female ratio in sex distribution (2:1) in OTSCCs. The male-preponderance in our study was similar to that reported in many other studies and was largely attributed to the increasing use of tobacco (Schmidt et al., 2004; Polesel et al., 2008) and alcohol (Rao et al., 1998; Turanti et al., 2010) by men. Our study confirmed the fact that a significantly higher proportion of males were addicted to tobacco and alcohol use than females.

Some studies have reported that the survival outcomes in males with OTSCC were poorer than in females (Dickman et al., 1999; Zheng et al., 1999) while some others have found no such association (Mathew Iype et al., 2000). In the current study gender did not have a prognostic significance.

A significant etiological association between tobacco and alcohol usage and oral cancer was first reported in a large survey of 347 patients from the author's institute in 1959 (Shanta and Krishnamurthi, 1959). The study found the association of betel nut and tobacco chewing habit in the OTSCC patients to be as high as 80.5%. Further the tobacco smoking habit was seen in 69% and alcohol usage was seen in 22% of the OTSCC patients. The incidence of dental sepsis in anterior tongue cancers was reported as 100%. Further the study showed a negative association of OTSCC with religion, environment, diet, pre-existing illness like anemia, syphilis, tuberculosis, diabetes and hypertension. A similar strong association was seen in a larger survey of over 10,000 patients of the Chengelpet district of the then Madras state. This study reported a relative risk of developing oral cancer to be 84 times higher in a tobacco chewer than a tobacco nonuser (Shanta and Krishnamurthi, 1974).

Our study suggests that the earlier trends have clearly changed where in nearly half of our patients are never-tobacco users. 13.6% of the patients in our cohort were alcohol users in contrast to around 22.2% of the patient in earlier study. This study suggests involvement of other co-factors and a possible different etiology in the tumorigenesis of OTSCC. A similar view was echoed in a retrospective descriptive study of patients under the age of 35 years with cancer of the oral cavity, only about half of the cases in this series, including about 49% of the OTSCC patients were found to have no addictions to tobacco and alcohol (Iype et al., 2000). The authors went on to suggest that OTSCC seemed to have a different etiology at younger age. Our study for the first time suggests that OTSCC patients having a different etiology, other than traditionally believed tobacco habits regardless of age.

Another aspect of the study is the poorer survival among the tobacco as well as alcohol users. Tobacco usage in any form (chewing or smoking) found to have a significant adverse effect on survival similar to the earlier reports (El-Husseiny et al., 2000). Alcohol usage was also significantly associated with a decreased survival in our patients similar to earlier studies (Andre et al., 1995). Our study reiterates the killer potential of tobacco and alcohol and also the need for a complete cessation of tobacco usage and alcohol consumption in order to improve the survival outcomes. Although the analysis of the patient cohort was retrospective, the maintenance of a prospective data base ensured an accurate capture of all the clinico-epidemiological parameters. The study also suggests that the risk factors involved in OTSCC other than tobacco and alcohol should be evaluated. Although the tumor, node, metastasis (TNM) staging of tumors has long been used in the treatment planning of OTSCC and still remains the most important tool for the clinician in predicting disease outcomes, our study illustrates that the clinico-epidemiological factors not only provide vital clues as to the etiology of OTSCC, but also has a prognostic significance.

In conclusion, the incidence of tongue cancer in the PBCR of Chennai is showing an increasing trend. Importantly as well as interestingly, our study shows a conspicuous absence of association with the traditional risk factors of tobacco and alcohol habits in our early staged OTSCC patients. We report possibly for the first time that this association, contrary to the popular belief is independent of age. The never tobacco users and the never alcohol users in fact had the best overall survivals. Although the tumor, node, metastasis (TNM) staging of tumors remains the most important tool for the clinician in predicting disease outcomes, our study suggests that a review of the clinico-epidemiological factors not only provides vital clues as to the etiology of OTSCC, but also has a prognostic significance. This information will help clinicians better understand the etiology and biology of OTSCC and can also potentially aid the policy makers to channelise the resources better for effective public health interventions.

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