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 smoking 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% (283/453) followed by exophytic pattern in 23.5% (108/453). Grade II lesion was seen in 25.3% (283/453). Grade I lesion in 25.3% (108/453). There was no significant association of tobacco related habits and alcohol abuse. Tobacco associated chewing was seen in 22.7% (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 was 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).

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 was 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 (1.72) | 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 (13.63) | 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

| 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 user | 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 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 (Warrnakulamuriya, 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 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 (Sankaranarayanan 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 epidemiologically 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.
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.

References
Andre K, Schraub S, Mercier M, Bontemps P (1995) Role of alcohol and tobacco in the aetiology of head and neck cancer: a case-control study in the Doubs region of France. Eur J Cancer B Oral Oncol, 31, 301-9.
Annertz K, Anderson H, Birkelund A, et al (2002). Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer, 101, 95-9.
Bachar G, Hod R, Goldstein DP, et al (2011) Outcome of oral tongue squamous cell carcinoma in patients with and without known risk factors. Oral Oncol, 47, 45-50.
Davidson BJ, Root WA, Trock BJ (2001). Age and survival from squamous cell carcinoma of the oral tongue. Head Neck, 23, 273-9.
Dickman PW, Hakulinen T, Luostarinen T, et al (1999). Survival of cancer patients in Finland 1955-1994. Acta Oncol, 38, 1-103.
El-Husseiny G, Kandil A, Jamshed A, et al (2000) Squamous
cell carcinoma of the oral tongue: an analysis of prognostic factors. *Bri J Oral Maxillofac Surg*, 38, 193-9.

Elango JK, Gangadharan P, Sumithra S, Kuriakose MA (2006). Trends of head and neck cancer in urban and rural population. *Asian Pac J Cancer Prev*, 7, 108-12.

Friedlander PL, Schantz SP, Shah AR, Yu G, Shah JP (1998). Squamous cell carcinoma of the tongue in young patients: a matched-pair analysis. *Head Neck*, 20, 363-8.

Garavello W, Spreafico R, Gaini RM (2007). Oral tongue cancer in young patients: a matched analysis. *Oral Oncol*, 43, 894-7.

Gupta PC, Murti PR, Bhonsle RB, Mehta FS, Pindborg JJ (1995). Oral squamous cell carcinoma: increasing trends in the US population ages 20-44 years. *Cancer*, 103, 1843-9.

Siegelmann-Danieli N, Hanlon A, Ridge JA, et al (1998). Oral tongue cancer in patients less than 45 years old: institutional experience and comparison with older patients. *J Clin Oncol*, 16, 745-53.

Silverman S Jr (2001). Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. *J Am Dent Assoc*, 132, 7-11.

Soudry E, Preis M, Hod R, et al (2010). Squamous cell carcinoma of the oral tongue in patients younger than 30 years: clinicopathologic features and outcome. *Clin Otolaryngol*, 35, 307-12.

Turati F, Garavello W, Tramacere I, et al (2010). A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 2: results by subsites. *Oral Oncol*, 46, 720-6.

Veness MJ, Morgan GJ, Sathiaseelan Y, Gembki V (2003). Anterior tongue cancer: age is not a predictor of outcome and should not alter treatment. *Anz J Surg*, 73, 899-904.

Vijayalakshmi R, Krishnamurthy A (2012). Human papilloma virus in head and neck cancers? Role and relevance in clinical management. *Indian J Surg Oncol*, 12, 196-205.

Wallner PE, Hanks GE, Kramer S, McLean CJ (1986). Patterns of Care study: analysis of outcome survey data: anterior two thirds of tongue and floor of mouth. *Am J Clin Oncol*, 9, 50-7.

Warnakulasuriya S (2009) Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*, 45, 309-16.

Warnakulasuriya S (2009). Causes of oral cancer—an appraisal of controversies. *Brit Dent J*, 207, 471-5.

Zheng Y, Kiriti T, Kurumatani N, Sugimura M, Yonemasu K (1999). Trends in oral cancer mortality in Japan: 1950-1993. *Oral Dis*, 5, 3-9.