RESEARCH ARTICLE

Survival Analysis of Oral Squamous Cell Carcinoma in a Subgroup of Young Patients

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Abstract

Oral squamous cell carcinoma (OSCC) is predominantly a disease of middle-aged men with long-term exposure to tobacco and alcohol. An increasing trend has been reported at a younger age worldwide. Clinical records of 100 patients under the age of 45 years treated specifically for oral cavity SCC in our hospital during a 10-year period were retrospectively analyzed to calculate the survival rates. An obvious male predominance coincided with smoking trend among Chinese young individuals and female patients were more likely to have no traditional risk factors such as smoking or drinking. The 5-year overall survival rate and disease-free survival rate were 61.0% and 75.5%, respectively, consistent with other published series over the decade showing a relatively better survival among the young. No significant differences clearly correlated with outcome when comparing non-smokers non-drinkers to ever-smokers and ever drinkers (*P*>0.05). Overall survival rate and disease free survival rate was found to be significantly higher in patients with early-stage disease than with advanced stage disease (*P*=0.001, *P*=0.009 respectively). The strong influence of clinical stage on prognosis emphasizes the importance of early diagnosis and treatment of oral malignancies for this unique clinical subgroup.

Keywords: Oral squamous cell carcinoma - oral cavity - survival - young patients - tobacco - alcohol

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Introduction

Oral squamous cell carcinoma (OSCC) is typically diagnosed in males in their fifth to seventh decade of life with long-term exposure to tobacco and alcohol (Iamaroon et al., 2004; Farshadpour et al., 2007; Hafkamp et al., 2008; Klozar et al., 2013; Koo et al., 2013). The incidence of OSCC in patients younger than 45 years has been reported to ranging from 0.4%-6.7% of all cases (Llewellyn et al., 2001). However, epidemiologic studies demonstrate an increasing incidence of OSCC young patients worldwide especially among young females (Myers et al., 2000; Annertz et al., 2002; Warnakulasuriya, 2009; Patel et al., 2011).

Several differences have been identified for the clinic-pathological profile of patients with early-onset OSCC, suggesting that oral cancer in the young may be distinct from that occurring in older patients with a different etiology and disease progression (Chang et al., 2013; van Monsjou et al., 2013). Nevertheless, Asian countries have distinct cultural practices such as betel chewing and varying patterns of use of tobacco and alcohol (Krishna et al., 2014). Besides, with regards to the increasing association of HPV and sexual behavior, especially for those without any traditional risk factors, it is urgent need to identify other features like oncogenic viruses mechanism and genetic predisposition, which may associate with the possible etiology in this subgroup

There are few clinical studies that examined specifically about oral cavity cancers and focused in the young age group in regard of their smoking and drinking status in a large number. The purpose of this study is to provide the information of these patients treated in our hospital during a 10-year period, as well as to describe the distinctive features and their results.

Materials and Methods

All patients referred to Peking University School of Stomatology, Beijing China between January 2001 and December 2010 with newly diagnosed and histologically confirmed OSCC were identified through medical record database (n=3820). For this study, we considered only those patients with the age younger than 45 years at diagnosis. Patients with non-oral cavity tumors, non-squamous histology, a prior history of other site malignancy, distant metastatic disease or those who received surgical treatment at another institution were excluded.

Demographic data including gender, age, family history of cancer, tobacco smoking, and alcohol consumption were recorded. Tumor and treatment characteristics, mortality data were also obtained with a

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minimum follow-up of 36 months.

Patients were classified as NSND (non-smokers and non-drinkers) or SD (smokers and/or drinkers). Non-smokers were defined as a negligible history of tobacco use and non-drinkers as nil regular alcohol consumption (<1 or more alcohol consumption/day) with no previous history of heavy alcohol intake or abuse.

Tumors were classified according to American Joint Committee on Cancer (AJCC) seventh edition system. Tumors were staged using the WHO 2005 classification system. Disease-free survival (DFS) were calculated from the date of initial pathologic diagnosis to the date of local-regional or distant treatment failure. Overall survival (OS) was defined as the time between the date of diagnosis of primary OSCC and the date of death due to any cause or date of the last follow-up or date of end of study. Follow-up data were obtained until December 2013.

A statistical analysis was performed using the SPSS software package SPSS (Version 13.0; SPSS Inc. Chicago, IL, USA). Comparisons between baseline characteristics were performed using the chi-square tests. Curves describing disease-free survival and overall survival were generated by the Kaplan-Meier product limit method and compared by log-rank test. Statistical significance was set at $P<0.05$.

Results

Patient characteristics

A total of 100 patients who met the selection criteria were identified for this study, as shown in Table 1. There were 66 males (66.0%) and 34 females (34.0%). The mean age was 38.0 years, ranging from 22 to 44 years. Of the 100 patients, 44 reported a history of current or prior tobacco use. 33 patients reported alcohol consumption but no one was associated with heavy alcohol abuse. All the females (100%) and 20 (30.3%) of males with no exposure to tobacco or alcohol were considered as NSND group.

Eighteen patients had at least one family member with a history of cancer. Among them six were first degree relatives. Only one reported a same site oral tongue cancer as his father's. Five of patients had medical problems such as hypertension, diabetes mellitus and coronary artery disease but none had severe comorbidities.

Tumor characteristics

The most common site of oral cavity tumor was mobile tongue, with 63.0 % of patients followed by gums (14.0 %), floor of mouth (11.0 %) and buccal mucosa (7.0 %).

The staging evaluation showed that clinical status was nearly equally distributed, I, II, III and IV stage occurring in 21, 28, 26, 25 patients, respectively. Neck nodes were present in 43 patients at the time of diagnosis. 49 patients

Table 1. Clinical Characteristics of Young Patients with Oral Squamous Cell Carcinoma

Factor	No. of patients	
No. of patients		100
Median age at diagnosis, y		38.0
Gender	Male	64
	Female	34
Primary tumor site	Mobile Tongue	63
	Gums	16
	Floor of the mouth	11
	Buccal mucosa	7
	Hard palate	3
Smoking and drinking Status	SD	46
	NSND	54
Family history of cancer	Positive	18
	First degree relatives	6
	Negative	82
AJCC Stage		
Early stage	I	21
	II	28
Advanced stage	III	26
	IV	25
Histological grade	Well differentiated	51
	Moderate differentiated	46
	Poorly differentiated	3
Treatment modality	Surgery alone	40
	Surgery+RT	34
	Surgery+CHT	10
	Surgery+RT+CHT	16

Abbreviation:NSND,non-mokers and non-drinkers;therapy;CHT,chemotherapy SD:smokers and or drinkers; RT, radiation

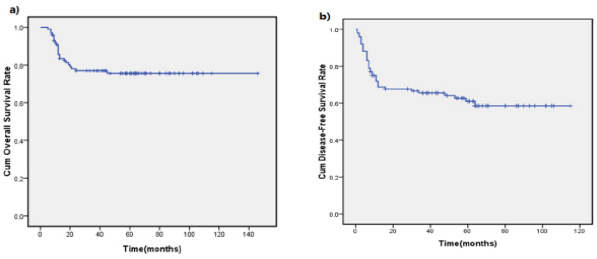

Figure 1. Kaplan-Meier Plots for Overall Survival and Disease-free Survival among 100 Young Patients with Oral Squamous Cell Carcinoma (OSCC)

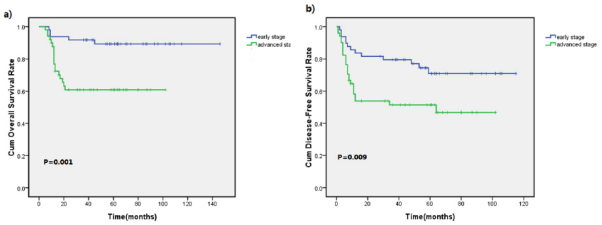

Figure 2. Overall Survival and Disease-free Survival among 100 Young Patients with Oral Squamous Cell Carcinoma (OSCC) by Clinical Stage

Table 2. Comparison of Clinical Characteristics of Young Patients with OSCCBy Smoking and Drinking Status

Factors	NSND	SD	*P* value
No. of patients	54	46	
Gender			
Male	20	46	<0.001[a]
Female		34	0
Primary tumor site			0.013[a]
Mobile Tongue	40	23	
Other sites	14	23	
Clinical Stage			0.828
Early stage (I+II)	27	22	
Advanved stage (III+IV)	27	24	
Histological grade			0.155
Well differentiated	27	27	
Moderate/poorly differentiated	20	19	
Treatment modality			0.79
Surgery alone	22	18	
Surgery+RT	17	18	
Surgery+CHT	6	3	
Surgery+RT+CHT	9	7	

Table 3. Prognostic Factors for Disease-Free Survival and Overall Survival :Univariate Analysis

Variable	No. of patients	5-year OS, %	*P*	5-year DFS, %	*P*
Gender					
Male	66	75.6	0.985	60.1	0.201
Female	34	75.3	68.2		
Smoking and drinking Status					
SD	46	73.9	0.823	60.4	0.482
NSND	54	76.7	0.822	61.4	
Primary tumor site					
Tongue	63	79.9	0.173	66.0	0.138
Other sites	37	68.1	52.3		
Clinical Stage					
Early stage (I+II)	49	89.4	0.001a	70.9	0.009[a]
Advanced Stage (III+IV)	51	60.8	51.4		
Histological grade					
Well differentiated	51	82.9	0.049a	73.1	0.026[a]
Moderate/poorly differentiated	49	67.6	49.5		
Treatment modality					
Surgery alone	40	89.5	0.004a	86.2	<0.001[a]
Surgery+RT	35	59.0	37.8		
Surgery+CHT	9	88.9	64.8		
Surgery+RT+CHT	16	67.0	41.7		

[a].significant; *P* value

had early stage disease (I+II) and 51 for loco-regional advanced stage (III+IV). 51 cases were histological confirmed well differentiated squamous cell carcinoma and 46 for moderately differentiated phenotype.

Treatment and Outcome

Surgery was used as main treatment in all patients. 34 patients received post-operative radiation therapy. 16 received radiochemotherapy due to locally advanced stage with curative intent.

The median follow-up was 68.8 months (range 36-146months), 77 patients are living without disease until their last follow up. The 3-year and 5-year overall survival rate were 77.0 % and 75.5 %, respectively as shown in Figures 1. Disease recurrence occurred in 38 young patients. The 3-year and 5 year disease free survival a rate for all patients were 65.5 % and 61.0 %, respectively. Four patient developed lung metastasis, three of them died of their disease and one patient still underwent radiochemotherpy. One reported a kidney transplant surgery 2-year after oral cancer treatment and dead of kidney failure.

Table 2 summarized the clinicopathological and treatment characteristics of NSND group and SD group. NSND patients were more likely to be women. The survival data was analysis separately between these two population (Table 3), there was no significant difference either in DFS or OS ($P>0.05$).

Potential predictive factors were calculated further, as shown in Table 3. The early stage disease (I+II) had a significantly better result compared to the advanced stage (III+IV) both in OS ($P=0.001$) and DFS analysis ($P=0.009$). A better outcome can be seen in patients with well-differentiated tumors but do not reach a significant difference.

Discussion

The incidence of oral cancer in the young is relatively low (Llewellyn et al., 2004). We retrospectively reviewed the clinical and outcome, featuring young patients with carcinoma of the oral cavity in our hospital in a 10-year period in order to determine the associated clinicopathologial characteristics among this distinct clinical subgroup in our region.

Our present study showed a male preponderance (66.0% vs 34.0%) in OSCC which is in agreement with some earlier studies (Manuel et al., 2003; Sherin et al., 2008; Chang et al., 2013). While increasing number of studies suggest that the proportion of oral cavity cancer cases in women increased worldwide especially among young white individuals in western countries (Patel et al., 2011; Durr et al., 2013). The alteration of the sex distribution is likely due to the gap is narrowing as habits such as smoking and drinking are seen as more socially acceptable amongst women (Llewellyn et al., 2001; Li et al., 2013). Although the rising mortality in Europe and the US has been placed on the use of smokeless tobacco products (Warnakulasuriya, 2009), smokeless tobacco is virtually unavailable in Mainland China. A significant gender differences in our corhort is coincide with the current smoking trend according to Global Adult Tobacco Survey (GATS) data from Chinese states and WHO conducted during 2009-2010, indicating a prevalence smoking younger males (age group of 24-44y) was approximately 50 times higher than Chinese female (59.3% to 0.6%) and the proportion of smoking female was far less than in the USA (24.3% to 19.8%), UK (29.0% to 25.0%), India (54.4% to 19.0%) and some other countries in the world (Li et al., 2011). That is notable in our study for all the OSCC young female patients declared as non-smokers and non-drinkers.

Tobacco and alcohol are well-established etiologic agents in oral squamous cell carcinoma (Dahlstrom et al., 2008). Prolonged tobacco carcinogens exposure leads to genetic mutation in the oral epithelia that can ultimately result in cancer. Alcohol consumption is regarded as a cancer promoter and has a markedly synergistic effect with smoking. Some researchers proposed the NSND status had a positive effect on long-term survival for young patients. Harris et al (2010) compared 28 NSND younger patients and 50 SD patients found no difference in 10-year disease free survival rate but an improved 10 year overall survival rates for NSND patients (71% vs. 46%). Durr's study (2013) also concluded the similar trend towards increased survival for never smokers (78.8 months in never smokers vs. 44.7 months in ever smokers). However, the case number was limited and their study included more early stage cases in NSND group and consequently better survival outcome. Moreover, it has been assumed that the exposure to carcinogens such as alcohol and tobacco might be too short a duration for malignant transformation to occur in younger patients (Siebers et al., 2008), thus the usual high-risk behavioral patterns were not likely a significant predictor. In our analysis, we did not observe any difference of 5-year OS and DFS between NSND and SD groups ($P>0.05$) even when adjust to clinical stage and treatment modality, which is of great important to take into account other predict factors for this unique clinical subgroup.

Hereditary factors was questioned by Lynch et al (1995). Due to the phenomenon that a higher familial risks for the same site of cancer in first degree relative if the index cancer was diagnosed in younger age. Our study reported 18% patients with family history of cancer. Nevertheless, whether these intrinsic susceptibility may play a role in carcinogenesis still need a large population-based study and genetic component in the development of OSCC at a younger age are also needed a further investigation.

It has been speculated that patients with human papillomavirus (HPV)-mediated oropharyngeal cancers is strongly associated with therapeutic response and survival compared to patients with HPV-negative carcinoma (Kaminagakura et al., 2012). However, high rates of HPV infection have rarely been demonstrated in the oral cavity and are an unlikely explanation for the increased incidence and impact the survival rate of younger patients (Isayeva et al., 2012). Goot-Heah et al. (2012) indicated a low viral load of high-risk HPV in Malaysian OSCC by analysing virus PCR product from saliva samples, suggesting the prevalence of HPV infection may not be important in Malaysian OSCC. Thai patients investigation by Khovidhunkit et al. (2008) also found low infection rate in their region (1.54% of 65 patients). However, their study included combination of sites of cancer, type of specimen and detection method. since HPV infection various from site by site, it presence in the lesional tissue may be casual or disappear as the result of treatment. Moreover, population-based cohort studies about natural history of oral infection suggest that the average clearance rate of HPV is about 6.9 months among healthly people (Kreimer et al., 2013). From this prospective, even infected, merely HPV tumorgenesis proteins are insufficient for malignant transformation, so a potential positive prognostic effect of HPV infection would be small.

Analysis by site showed that 63.0 % of cancers arose on the mobile tongue in our young patients, followed by the gums. This finding is in agreement with the previous literature on the subject (Sherin et al., 2008; Koo et al., 2013). Conversely, studies in some other Asian countries such as Taiwan, India and Thailand have found that buccal mucosa was a common location which has strongly associated with betel quid chewing habit regionally (Iamaroon et al., 2004; Khovidhunkit et al., 2008; Kaminagakura et al., 2012; Chang et al., 2013; Krishna et al., 2014)

Historically, young patients with oral cancers were believed to be particularly aggressive and carry a poor prognosis (Dahlstrom et al., 2008). Sarkaria et al. (2013) said that even early stage patients below the age of 40 years showed high rate loco-regional failure and poor prognosis. They further review 14 reports of 152 cases in English literature indicated 57% of patients developed loco-regional failure and 47% of patients died secondary of their cancers. Chun et al. (2013) in Taiwan concluded that younger subgroups experienced a higher distant failure in oral tongue cancer ,indicating that the prognosis factors is due to the unique and more progress process of the disease. However, data regarding prognosis are conflicting. Some investigators have proposed that a more favorable clinical outcome of young adults should be expected, with an average 5-year survival rate of 65 % or even better (van Monsjou et al., 2013). Moreover, this subset of patients may benefit form more aggressive surgical resections facilitated by modern reconstructive methods in recent decades and better tolerance of radiotherapy and chemotherapy with less side effects (Kies et al., 2012).

Our own observations indicate a 75.5% 5-year overall survival rate and a 61.5 % 5-year local-regional control rate, which consistent with some other published series over the decade showing the relatively better survival rate among young group (Llewellyn et al., 2001; van Monsjou et al., 2013). However, it would be take into account tumour stage and site, type of treatment and a more comprehensive examination of risk factors when considering true better survivial rate difference among studies. The 5-year DFS rate was found to be significantly higher in patients with early stage disease than with advanced stage (P=0.001). Its effect on OS was still statistically significant (P=0.009).

Several other studies on the subject confirm our finding (Sherin et al., 2008). Ganly et al. in the US (2012) evaluated a cohort with a higher proportion of T1 and T2 tumors young patients experienced better survival. Manuel et al. (Manuel et al., 2003) furthermore found that lymphatic invasion was associated with decreased survival. The 5-year OS in patients with a pathologically negative node was significantly higher compared to patients with histologically positive nodes (P=0.006). The strong influence of clinical stage on prognosis emphasizes the importance of early diagnosis and treatment of oral malignancies.

Reviewed of pathologic parameters and evaluated their relationship to clinical outcomes yielded a better outcome in patients with well-differentiated ones (P=0.049). However, this finding was questioned by Sherin et al. (Sherin et al., 2008), suggesting that survival among young patients was more related to the TNM stage of the disease at diagnosis rather than the histologic grade. A recent Japanese study also evaluated the clinical-pathological features of OSCC among young people under 40 years of age, grading of different pathological parameters on degree of keratinization, number of mitoses, mode of invasion, depth of invasion and lympho-plasmacytic infiltration, which showed some variations but failed to explain the worse outcome in their younger group (Sasaki et al., 2005).

Strengths of our study, therefore, include relatively large size cohort analysis for unique group of young patients and the outcome data with adjustment for tobacco and alcohol exposure as well as all relevant clinical variables specifically for oral cavatiy squmaous cell carcinoma.

We acknowledge several limitations to our study. First, because this was a retrospective analysis, we often encountered missing data and inconsistent reporting of clinicopathologic information. Second, we did not perform survival analysis between our younger individuals with older counterparts, because in China, older generation tend to postpone their treatment for their oral tumors

and concurrently high risks factors such as second malignancies and mortality related to other comorbidities like cardiovascular and chronic pulmonary disease which severely affect the overall survival rate. Third, information on HPV infection was not available, although a continuous change in the epidemiological and biological profile of HPV-positive cancer associated with possibly better prognosis, the accurate rate of HPV infection among Chinese young OSCC patients has never been calculated.

In conclusion, the rarity of OSCC in young patients limits our understanding of its etiology, optimal therapeutic management and prognosis factors .In our study, we found an obvious male predominance in OSCC coincide with smoking trend among Chinese young individuals, with all the female patients has no traditional risk factors such as smoking or drinking. Furthermore, no significant differences in DFS and OS were identified when comparing NSND group to SD group with OSCC. The strong influence of clinical stage on prognosis emphasizes the importance of early diagnosis and treatment. Speculations abound regarding the possible etiology in this subgroup and long-term follow-up should be the area needs further confirmation and evaluation.

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