

Prognostic Factors in Early Tongue Cancer: A Retrospective Review

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Abstract

Tongue cancer is biologically and epidemiologically distinct from other oral cavity tumors. This retrospective study explored figures and analyzed factors of local control and survival rates in 35 patients, who were managed for early squamous cell carcinoma of anterior tongue, between 2003 and 2015, at an Oncology Unit. Cumulative recurrence rate was 25.71%, which was associated with 50.3% survival rate compared to an overall survival rate of 76.2%. Relapse was more frequent among shamma consumers (66.7% versus 30.8%) and patients with perineural invasion (55% versus 34.6%), while mortality rate was higher in case of thin tumor margin (21.4% versus 10%) compared to their counterparts, respectively. However, due to small sample size, none of the comparisons was statistically significant. The outcomes of oral cancer can be significantly improved by promoting abstinence from shamma and enhancing early diagnosis.

Keywords: Tongue Cancer; Smoking Habits; Clinicopathological Features; Relapse; Patient Outcome

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Introduction

Oral cancer (OC) includes malignancies that develop in tissues and organs around the lip, tongue and the oral cavity. It is usually associated with alcohol or tobacco consumption as well as human papillomavirus (HPV) infection [1]. In 2018, several investigators reported the incidence (362 new cases) and prevalence (1097 cases) of oral cancer in Saudi Arabia, while greater rates were reported in the United States (incidence=4.3 per 100,000 people, prevalence=0.71%) and India (incidence 9.1 per 100,000 people, prevalence=5.6%) in the same year. Despite the low prevalence in Saudi Arabia, as suggested by these epidemiological pictures, oral cancer remains a public health risk of concern at the national level [2-4]. Indeed, OCs account for 26% of the head and neck cancers, locally, with most cases diagnosed at advanced stages requiring palliative treatment [5]. Among OCs subsites, tongue cancer represents a distinct entity both biologically and epidemiologically, compared to other tumors of the oral cavity, and is commonly associated with squamous cell carcinoma (SCC). It is often associated with non-smoking middle-aged (≤ 40 years) women [6]. Tongue cancer was also observed among non-smoking advanced-aged women as well [7]. The main lines of treatment in early carcinoma of the tongue are surgery, radiation therapy, and chemotherapy [8]. Several well-known risk factors of local recurrence in early tongue cancer have been identified. More significantly, positive surgical

margins and positive lymph nodes qualify patients for adjuvant radiation therapy as an essential treatment modality for local control and even cure of the disease [8].

In clinical practice, several concerns are raised about other eventual factors that may or may not affect disease control, which pose a dilemma when referring patients for adjuvant radiation therapy. Among these factors are the tumor's histopathological grade, depth of muscular invasion, presence of lympho-vascular and perineural invasion. Therefore, we conducted the present study to assess the level of local control and survival rates among patients treated for early tongue cancer with node negative, and to investigate the factors associated with tumor relapse [9].

Results and Discussion

Clinical Characteristics and Outcomes

Thirty-five patients fulfilled the inclusion criteria, 21 (60%) were females, mean age was 60.6 years (range=32, 91 years). Of the total patients, 9 (25.7%) used shamma and 4 (18.2%) were active smokers (Table 1). Alcohol consumption was not addressed due to religious and cultural reasons.

Baseline tumor characteristics showed mean (SD) tumor size 2.2 (1.3) mm, mean (SD) depth invasion 6.29 (4.5) mm, 25 (71.4%) average



Table 1: Patient characteristics and relapse outcomes.

Variables		Total	Relapse		P-value
			No	Yes	
Age		35	61.90 (14.1)	61.29 (20.1)	0.915
Gender	Male	14	8 (57.1%)	6 (42.9%)	0.778
	Female	21	13 (61.9%)	8 (38.1%)	
Shamma use	No	26	18 (69.2%)	8 (30.8%)	0.058
	Yes	9	3 (33.3%)	6 (66.7%)	
Smoking	No	18	12 (66.7%)	6 (33.3%)	0.746
	Yes	4	3 (75.0%)	1 (25.0%)	

grade, 2 (5.7%) high grade, and PNI were present in 9 (25.7%) (Results are not presented). Relapse occurred among 14 (40.0%) of the patients. At last follow up, 5 (14.3%) were alive with disease and 5 (14.3%) were deceased (Results are not presented).

Clinical Factors Associated with Relapse

Shamma usage was associated with higher rate of relapse (66.7%) compared to non-use (30.8%); however, the difference was not statistically significant (P=.058). No notable association of relapse was found with the other baseline clinical characteristics.

Tumor Characteristics Associated with Relapse

Mean (SD) tumor size was 2.08 (1.4) cm among patients without relapse versus 2.37 (1.2) cm among those with relapse. Mean (SD) depth of invasion was 6.29 (5.1) mm among patients without relapse, and 6.29 (3.5) mm among patients with relapse. Mean (SD) duration of radiotherapy was 47.00 (4.5) days for patients without relapse and 45.63 (18.6) days for those with relapse. Relapse showed no statistically significant association with other tumor characteristics such as tumor grade (P=.475), closest margin (P=.588) or PNI (P=.269) (Table 2).

Clinical Factors Associated with Last Follow-Up Status

Shamma users had higher rate of disease (33.3% versus 7.7%) at last follow up but not relatively lower mortality (11.1% versus 15.4%) compared to nonusers; however, the comparison was not statistically significant (P=.166). Mortality rate was higher among smokers (25.0% versus 5.6%) and the difference was not statistically significant (P=.400).

Tumor Characteristics Associated with Status at Last Follow-Up

Tumor characteristics did not have a significant association with

Table 2: Tumor characteristics and relapse outcomes.

Variables		Total	Relapse		P-value
			No	Yes	
Tumor size (cm)		34	2.08 (1.4)	2.37 (1.2)	0.543
Invasion depth (mm)		35	6.29 (5.1)	6.29 (3.5)	1
Radiotherapy duration		12	47.00 (4.5)	45.63 (18.6)	0.889
Grade	Low	7	4(57.1%)	3(42.9%)	0.475
	Average	25	14(56.0%)	11(44.0%)	
	High	2	2(100.0%)	0(0.0%)	
Closest margin (mm)	≤2	14	9(64.3%)	5(35.7%)	0.588
	>2	20	11(55.0%)	9(45.0%)	
PNI	Negative	26	17(65.4%)	9(34.6%)	0.269
	Present	9	4(44.4%)	5(55.6%)	
LVI	Negative	35	21(60.0%)	14(40.0%)	N/A ^a
Site of lymph node dissection	Uni	13	9(69.2%)	4(30.8%)	0.482
	Bi	4	2(50.0%)	2(50.0%)	
Extranodal extension	No	17	11(64.7%)	6(35.3%)	N/A ^a

follow-up status; however, some observations are worth to be noted. The two patients who had high-grade tumor were alive and disease-free at last follow up. The rate of disease-free survival was higher among patients with closest tumor margin >2 mm (78.6% versus 65.0%) and those with negative PNI (80.8% versus 44.4%) compared to their counterparts, respectively. The depth of tumor invasion was relatively lesser in the group of patients who were alive without disease (mean [SD] = 6.0[4.7] mm) compared to those who were alive with disease (mean [SD] = 7.6 [4.7] mm) and those who were deceased (mean [SD] = 6.4 [3.6] mm) (Table 3).

Patient Survival Rates

Based on the survival table and function (Figure 1), more than 70% of the patients survived from 2004 to 2019. From 2004 to 2010, there has been 100% survival rate. It remained above 90% for the next three years until 2013, where the survival rate changed to 88.7%. Another patient died in 2014, decreasing the survival rate to 83.8%. By 2016 onwards, the cumulative survival rate is at 76.2%. The recurrence rate for this group was at 25.71%. Among patients that went into relapse, five patients died from 2010 to 2016, bringing their survival rate to 50.3% (Table 4).

Table 3: Tumor characteristics and status at last follow up.

Variables		Total	Status at last follow up			P-value
			Alive	Alive with disease	Died	
Tumor size (cm)		34	2.22 (1.4)	2.42 (0.6)	1.88 (1.5)	0.82
Invasion depth (mm)		35	6.00 (4.7)	7.60 (4.7)	6.40 (3.6)	0.775
Radiotherapy duration		12	48.00 (4.5)	44.00 (0.0)	43.25 (27.7)	0.892
Grade	Low	7	4(57.1%)	0(0.0%)	3(42.9%)	0.133
	Average	25	18(72.0%)	5(20.0%)	2(8.0%)	
	High	2	2(100.0%)	0(0.0%)	0(0.0%)	
Closest margin (mm)	≤2	14	11(78.6%)	0(0.0%)	3(21.4%)	0.108
	>2	20	13(65.0%)	5(25.0%)	2(10.0%)	
PNI	Negative	26	21(80.8%)	2(7.7%)	3(11.5%)	0.089
	Present	9	4(44.4%)	3(33.3%)	2(22.2%)	
LVI	Negative	35	25(71.4%)	5(14.3%)	5(14.3%)	N/A ^a
Site of lymph node dissection	Uni	13	10(76.9%)	3(23.1%)	0(0.0%)	0.124
	Bi	4	3(75.0%)	0(0.0%)	1(25.0%)	
Extranodal extension	No	17	13(76.5%)	3(17.6%)	1(5.9%)	N/A ^a
	Yes	0	0(0.0%)	0(0.0%)	0(0.0%)	

Table 4: Survival table among patients with relapse.

Time	Status	Cumulative Proportion Surviving		Cumulative Events	Remaining Cases
		Estimate	Std. Error		
2010	Died	0.929	0.069	1	13
2010	Alive	.	.	1	12
2012	Died	0.851	0.097	2	11
2012	Alive	.	.	2	10
2013	Died	0.766	0.119	3	9
2013	Alive	.	.	3	8
2014	Died	0.67	0.137	4	7
2015	Alive	.	.	4	6
2015	Alive	.	.	4	5
2015	Alive	.	.	4	4
2016	Died	0.503	0.178	5	3
2018	Alive	.	.	5	2
2018	Alive	.	.	5	1
2019	Alive	.	.	5	0

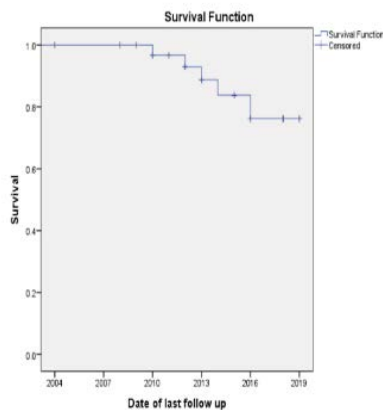


Figure 1: Kaplan-Meier survival function for tongue cancer patients.

The purpose of this study was to evaluate local control of early tongue cancer among patients treated at a referral center in Western Saudi Arabia, by assessing relapse and mortality rates and exploring the associated clinical and pathological factors. Identifying such factors would be of great interest in the decision making for adjuvant radiotherapy. Goodman M, et al. (2009) stated the importance of reporting tumor characteristics among tongue cancer patients [9]. Analysis of the findings suggest that the use of shamma, presence of PNI and small tumor margin at baseline are associated with poor outcomes including relapse, persistence of the disease and or death.

Although the crude rates of both relapse and mortality were increased in presence of the previously mentioned risk factors, the results were not statistically significant. This is probably due to the small sample size of the study population leading to type II error. Shamma is a form of smokeless tobacco, a combination of tobacco powder, lime carbonates, ash, black pepper, oils and flavoring. It is also known as Yemeni snuff, a frequently used chewing material that is used in Yemen and in the southern regions of the Kingdom of Saudi Arabia. It is reported to be most commonly used in Jizan province, as it shares borders with Yemen [10-15]. Studies have shown that early exposure to shamma in Jizan can begin as early as 10 to 13 years old, and is even used on infants to lessen the pain caused by erupting teeth [10,16]. As per Allard WF, et al. (1999) shamma continues to contribute in the development of oral cancer up to the present [17].

Microscopic measurement for depth of invasion (DOI) or tumor thickness is a crucial parameter that is associated with regional lymph nodes metastasis and duration of disease-free survival. Proper sections taken at grossing, with 2-3 mm slice thickness will facilitate accurate microscopic examination of DOI [18]. There are slight differences between DOI and tumor thickness. DOI is measured from the adjacent normal basement membrane to the deepest point of tumor invasion, while tumor thickness is measured from tumor mucosal surface to the deepest point of tumor invasion (Figure 2) [19]. In our study, the mean tumor depth was 6.29 mm in the study population, while it was increased to 6.40 mm and 7.60 among those who deceased and those who were alive with disease at the last follow-up, respectively. Although it was not statistically significant, this may be indicative of an association between increased tumor depth and poor prognosis. This is consistent with Tarsitano A, et al. (2006), who demonstrated that increased tumor depth was associated with mortality [20].

In terms of overall survival, 68% of the patients were alive without

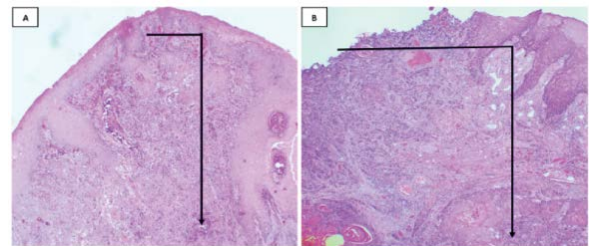


Figure 2: Depth of invasion (DOI) measurement, using the horizon from adjacent basement membrane relative to the closes intact squamous mucosa lining. The greatest DOI is measured by dropping a line from the horizon to the deepest point of invasion.

disease at last follow-up, which is relatively higher compared to the overall survival reported by Rusthoven K, et al (2008) (60.9%) [21]. The cumulative survival rate of the 35 patients is higher compared to the Surveillance, Epidemiology and End Results' (SEER) latest established five-year survival rate (76.2% vs. 66.4%) by Howlader N, et al. (2019) [22]. Among the patients that relapsed, cumulative survival rates after six years were 50.3% (Table 4), whereas Kernohan MD, et al. (2010) [23], reported that 50% out of 77 patients survived in five years. On the other hand, Gonçalves Agra IM, et al. (2006) [24] reported that only 32.3% survived in five years after salvage surgery.

In terms of tumor margins, no remarkable difference in relapse rate was observed in this study, possibly due to the small sample size. Smaller margins increase the likelihood of local recurrence as compared to wider margins [25]. In a study by Jang et al. smaller margins were a significant risk factor for local recurrence in advanced stages but not in early stages [26]. While there is no established cut-off point relating close surgical margins with local recurrence, a study by Wong LS, et al. (2012) [27] reported that there is a significant adverse association between surgical margins less than or equal to 1.6 mm and disease-specific survival. For shamma usage, the percentage of those who admitted the use of shamma was lower compared to another study (25.7% vs. 49%), however the actual number of people using shamma could be different as it could be possible that some of the participants would not disclose its usage as shamma is illegal.

Experimental

A retrospective study was carried out by extraction and review of clinical data that was obtained from the Oncology Department in Western Saudi Arabia. It included all patients who underwent initial surgical resection of early SCC of the anterior tongue from January 2003 to December 2015. Only patients with tumor Stage I & II, absence of lymph nodes invasion (N_0), and having undergone tumor +/- lymph nodes resection were included. Patients may or may not have received postoperative irradiation, depending on pathological risk factors. Patients who were diagnosed at advanced stage (T3,4; N+) and those who were treated primarily with radiotherapy without initial surgical resection were excluded.

Collected data were divided into 3 categories:

- Clinical features such as age, sex, smoking habits, etc.,
- Pathological characteristics including tumor size, histopathological grade, T stage, extent of negative surgical margins status in mm, depth of invasion, presence or absence of perineural invasion, lymph vascular invasion, extent of nodal dissection unilateral Vs bilateral;
- Treatment modalities (surgery only versus surgery and postoperative radiation therapy). The primary outcome of this study



consisted of tumor recurrence or relapse, which was defined as any local (tongue itself) and or regional (oral cavity excluding tongue, or neck nodes) tumor regrowth during the postoperative follow up period.

Data was collected, coded, and processed with confidentiality, after concealment of all identifying details such as names, contact details, etc., and was shared securely with different collaborators. The study was approved by the institutional review board of the hospital.

Statistical Methods

Statistical analysis was done with IBM SPSS version 23 (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize the population characteristics and other study variables; data was presented as frequency and percentages or means and standard deviations, as applicable. The relationship of relapse and status at last follow-up with the explored clinical and pathological factors was analyzed using chi-square test for categorical variables and independent t-test or One-way ANOVA, as appropriate for numerical variables; these tests were carried out with the assumption of normal distribution. The null hypothesis was rejected for a P-value < 0.05 and the Least Significant Difference (LSD) was used as a post hoc test for more than two groups comparison.

Conclusion

Early tongue cancer is associated with 40% relapse and 14.3% mortality after surgery, in Western Saudi Arabia. The use of shamma continues to contribute significantly in morbidity related to oral cancer and is highlighted as a major determinant of therapeutic success in early tongue cancer. Other tumor characteristics such as the presence of perineural invasion and increased tumor size are associated with poor postoperative outcomes including relapse or progression and mortality. Further studies with larger sample size are warranted to identify clinical and pathological predictors of therapeutic success in early tongue cancer, which would be crucial for the indication of adjuvant radiotherapy.

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