Original Article

Outcomes of Oral Tongue Cancer: Does Age Matter?

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Abstract

Introduction: This is a retrospective study aimed to analyse the outcomes of oral tongue cancer with emphasis on young people. Materials and Methods: Patients treated radically between 1998 and 2006 were included and categorised according to treatment modalities (Group A: Surgery, Group B: Surgery and adjuvant therapy, Group C: Definitive radiotherapy) and age groups (≤ 40 and > 40 years). Overall survival (OS), disease-free survival (DFS), locoregional relapse-free survival (LRS) and metastasis-free survival (MFS) were estimated using Kaplan-Meier method. Results: There were 123 patients with 32%, 53% and 15% in Group A, B and C, respectively. Of these, 17 patients (14%) were ≤40 years with 6 (15%), 8 (12%) and 3 (16%) young oral tongues in Group A, B and C, respectively. Five-year OS and DFS were 69%/72%, 41%/47% and 16%/9.5% for Group A, B and C, respectively. Young patients had similar survival as the older population with 5-year OS of 83%, 75% and 33% in Group A, B and C, as compared to the older patients (66%, 36% and 13%, respectively). Conclusion: Young oral tongue patients did not have worse outcomes.

Ann Acad Med Singapore 2010;39:897-903

Keywords: Head and neck, Squamous cell carcinoma, Young

Introduction

Oral cancer (including oral cavity and oropharynx) is the eighth most common cancer worldwide with oral cavity cancer among the 3 most common malignancies in south central Asia.[1] Oral cavity cancer, including oral tongue, is associated with a relatively high mortality rate particularly in the developing countries.[1,2] Approximately 17% of these are actually located in the base of tongue.[3] Oral tongue cancer tends to have better survival outcomes compared to base of tongue subsite and this supports the hypothesis that these 2 subsites are different entities that should be analysed separately.[4]

Different prognostic factors have been thought to influence the outcome of oral tongue cancer. Patient (age, gender), tumour (histopathological features) and treatment factors had been identified. One of the more interesting developments has been the interest in the supposedly different outcome between the younger and older patients with oral tongue cancer. The number of young patients with oral tongue cancer has been reported to be on the rise.[5-7] There is a suspicion within the oncology community that young oral tongue cancer has worse prognosis and more aggressive clinical course compared to older patients. This group of younger patients also tend to be non-smokers and non-drinkers.[8] However, the evidence for this remains inconclusive as small retrospective studies published so far have yielded contrasting results with some studies showing similar outcomes[9-14] and others confirming worse outcomes in this subgroup.[15-17] Genetic predisposition, human papilloma virus (HPV) infection and use of marijuana have all been implicated in the carcinogenesis of young oral tongue cancer.

It is questionable if we can directly extrapolate these

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results to our own patient population as our patients may have slightly different risk exposure, patient and treatment factors. Hence, we decided to embark on a retrospective study to analyse the characteristics and outcomes of patients with oral tongue cancer in our local patient population in Singapore with a subset analysis to compare young oral tongue cancer with the older population.

Materials and Methods

All patients with oral tongue squamous cell carcinoma (SCC) who received primary treatment in the National Cancer Centre between January 1998 and December 2006 were included in this retrospective analysis. Patients with base of tongue cancer or non-squamous histology, patients treated with palliative intent, foreign patients and those who received their primary treatment in another institution were excluded. Patients' medical records were reviewed. Demographic, pathological, treatment and outcome data were extracted. Tumours were staged according to the American Joint Committee of Cancer (AJCC) 6th edition system. This study was approved by our local Institutional Review Board committee.

Patients' characteristics and outcomes were analysed separately according to the treatment modality: (i) Group A – Surgery alone, (ii) Group B – Surgery and adjuvant radiotherapy (RT) or chemoradiation (CRT), and (iii) Group C – Definitive RT or CRT. Patients were also categorised into young oral tongue patients (aged ≤ 40) and older patients (> 40 years old) in each subgroup.

Overall survival (OS) was measured from the date of diagnosis to the date of death due to all causes. Patients who were alive were censored on 4 March 2010 when the national Death Data Bank was queried. Disease-free survival (DFS), locoregional relapse-free survival (LRS) and metastasis-free survival (MFS) were calculated from the date of definitive treatment to the time of relapse. Survival was estimated using the Kaplan-Meier method. Multivariate analyses were performed using Cox proportional hazards model. Chi-square and Fisher exact tests were used to analyse the differences among categorical variables. A P value ≤ 0.05 was deemed as statistically significant. All tests were two-sided. SPSS version 15 was used for statistical analyses.

Results

A total of 123 patients with oral tongue SCC were treated in our centre from January 1998 to December 2006. Thirty-nine patients (32%) had surgery alone, 65 patients (53%) had surgery followed by adjuvant RT or CRT and 19 patients (15%) had definitive RT or CRT. Median age for all patients was 56 years (range, 18 to 87). The median age for patients in Group A was 53 (range, 26 to 86), Group B was 55 (range, 18 to 86) and Group C was 64 (range, 22 to 87), respectively.

Pathological Features

The majority of patients had well to moderately differentiated SCC (Group A: 87%, Group B: 77%, Group C: 79%; P = 0.445). Overall, Group A had more patients with T1/2 and N0 disease (95%/85%) compared to Group B (62%/23%) and C (16%/16%), respectively (P = 0.0001). Group A and B had pathological nodal staging whereas nodal status for Group C was determined radiologically. Table 1 shows patient characteristics.

More patients in Group B had lymphovascular invasion (LVI), perineural invasion (PNI) and extranodal extension (ENE) compared to Group A. More than half of patients in Group B had positive or close surgical margins as compared to 26% in Group A.

Treatment

All but one patient in Group A had hemiglossectomy (94%) or subtotal glossectomy (3%) with one patient (3%) undergoing wedge resection for a 0.6 cm tumour with a depth of 0.10 cm. Three patients (8%), including the patient with wedge resection, had no neck dissection (all had T1N0M0 tumours). Group B had one patient (2%) who had hemiglossectomy alone (1.5 cm tumour and depth of 1.4 cm) with all remaining patients undergoing hemi- or subtotal glossectomy and neck dissection.

Most patients in Group B (82%) and C (68%) were treated with lateral parallel-opposed 6MV photons with separate anterior neck field (midline cord shield) if the lower neck was treated. The remaining patients were treated with conformal RT or Intensity-Modulated Radiotherapy (IMRT). Most patients in Group B had Stage 3/4 disease hence requiring adjuvant RT with the remaining 8 patients with Stage 1/2 disease receiving RT due to adverse pathological factors (5) and young age (3). The majority of Group C received definitive RT because of advanced tumour stage or patients' poor general medical fitness that prevented surgery,

Nine patients (14%) in Group B had concurrent chemoRT compared to 15 patients (79%) in Group C (P = 0.0001). Chemotherapy used included Cisplatin, Carboplatin, 5-FU and Gefitinib, either as a single agent or in combination.

Outcomes of Patients According to Treatment Group

Median follow-up for all patients was 29.1 months (range, 1.2 to 150.3). Median follow-up duration for Group A, Group B and Group C were 40.4 months (range, 1.2 to 150.3), 24.7 months (range, 3.4 to 117.0) and 14.2 months (range, 2.4 to 83.9), respectively.

Table 1. Patient and Tumour Characteristics for All Patients

Patient Characteristics		Group A (n = 39) No. (%)	Group B (n = 65) No. (%)	Group C (n = 19) No. (%)	*P* value
Age groups	≤ 40	6 (15%)	8 (12%)	3 (16%)	0.821
	>40	33 (85%)	57 (88%)	16 (84%)	
Gender	Male	22 (56%)	47 (72%)	14 (74%)	0.210
	Female	17 (44%)	18 (28%)	5 (26%)	
Smoker	Yes	18 (46%)	23 (37%)	10 (53%)	0.732
	No	17 (44%)	32 (49%)	8 (42%)	
	Unknown	3 (10%)	9 (14%)	1 (5%)	
Alcohol	Yes	10 (26%)	20 (31%)	9 (47%)	0.039
	No	15 (38%)	35 (54%)	9 (47%)	
	Unknown	14 (36%)	10 (15%)	1 (6%)	
Grade	Well	9 (23%)	11 (17%)	4 (21%)	0.445
	Moderate	24 (64%)	39 (60%)	11 (58%)	
	Poor	2 (5%)	10 (15%)	1 (5%)	
	Mixed	0	3 (5%)	1 (5%)	
	Unknown	3 (8%)	2 (3%)	2 (11%)	
T stage	1	28 (71%)	15 (24%)	0	0.0001
	2	9 (23%)	25 (37%)	3 (16%)	
	3	1 (3%)	10 (15%)	3 (16%)	
	4	1 (3%)	15 (24%)	13 (68%)	
N stage	0	33 (85%)	15 (23%)	3 (16%)	0.0001
	1	1 (3%)	11 (17%)	6 (32%)	
	2	5 (12%)	36 (55%)	9 (47%)	
	3	0	3 (5%)	1 (5%)	
TNM stage	1	26 (66%)	3 (5%)	0	0.0001
	2	7 (18%)	6 (9%)	1 (5%)	
	3	1 (3%)	12 (18%)	2 (11%)	
	4	5 (13%)	44 (68%)	16 (84%)	
Lymphovascular invasion	Yes	2 (5%)	13 (22%)	N/A	0.023
	No	36 (92%)	51 (78%)	N/A	
	Unknown	1 (3%)	0	N/A	
Perineural invasion	Yes	6 (15%)	19 (29%)	N/A	0.094
	No	32 (82%)	46 (71%)	N/A	
	Unknown	1 (3%)	0	N/A	
Surgical margins	Positive	2 (6%)	7 (11%)	N/A	0.016
	Negative	29 (74%)	30 (46%)	N/A	
	Close	7 (18%)	28 (43%)	N/A	
Extranodal extension	Yes	3 (8%)	15 (23%)	N/A	0.0001
	No	3 (8%)	35 (54%)	N/A	
	Unknown	33 (84%)	15 (23%)	N/A	
RT parameters	Median dose (range)	N/A	60 (30-70)	70 (45-80)	
	Dose per fraction (Gy)	N/A	2 (2.0-2.2)	2 (2.0-2.5)	
	Duration (days)	N/A	44 (23-85)	48 (28-66)	

Median OS for all patients was 36.9 months (95% CI, 5.6 to 68.2). Two- and 5-year OS were 74%/69%, 54%/41% and 32%/16% for Group A, B and C, respectively (P = 0.0001) (Fig. 1). Univariate analysis showed that more advanced T, N and tumour stages, older age, LVI, PNI, ENE and definitive RT/CRT were negative predictors for OS. Multivariate analysis revealed that T (P = 0.028) and N (P = 0.007) stages were the only significant prognostic indicators.

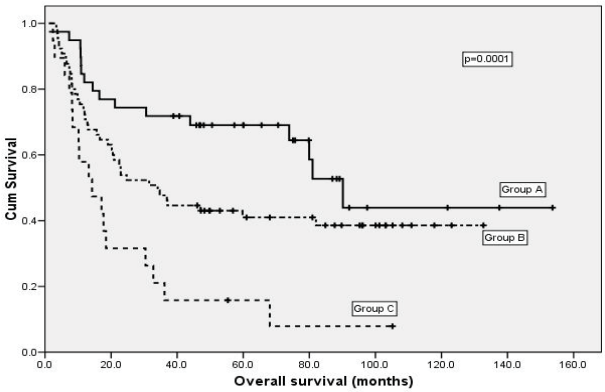

Fig. 1. Overall survival according to treatment groups.

Median DFS for all patients was 71.3 months (95% CI, 18.5 to 124.1). Two- and 5-year DFS were 75%/72%, 49%/47% and 9.5%/9.5% in Group A, B and C, respectively (P = 0.0001) (Fig. 2). Univariate analysis revealed that definitive RT, advanced T, N and tumour stages as well as ENE were all negative prognostic indicators for DFS. However, multivariate analysis showed that only T stage retained its significance as a prognostic indicator for DFS (P = 0.033).

Locoregional relapse occurred in 13 patients (33%) in Group A compared to 25 (38%) and 6 (32%) patients in Group B and C, respectively (P = 0.001). In Group C, there were 5 patients (26%) who had persistent disease after definitive CRT. All 5 patients had Stage IV tumours (four with cT4a and one with cT4b disease). Three of these patients underwent salvage surgery with or without further adjuvant treatment while the other two patients each receiving chemotherapy and supportive care, respectively. Two- and 5-year LRS were 75%/72%, 57%/55% and 19%/19% in Group A, B and C, respectively (P = 0.001). Univariate analysis showed that definitive RT, advanced T and N stages, male gender and ENE were significantly associated with poorer LRS. However, only male gender and N stage continued to be significant factors in multivariate analysis.

There were 4 (10%), 9 (14%) and 5 (26%) patients in Group A, B and C, respectively who developed distant relapse (P = 0.262). Two- and 5-year MFS were found to

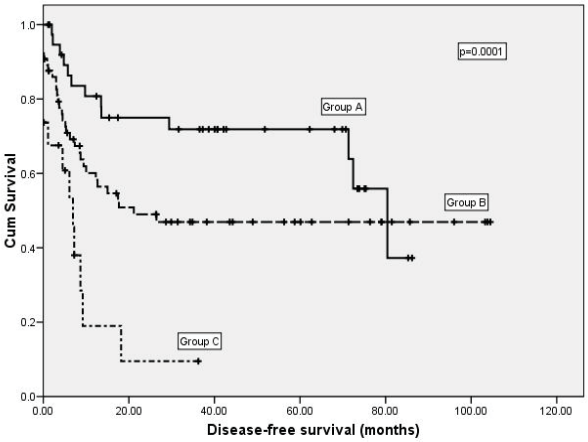

Fig. 2. Disease-free survival according to treatment groups.

be 88%/88%, 84%/84% and 57%/57% in Group A, B and C, respectively. Univariate analysis showed that advanced T, N and tumour stages, LVI and ENE were significant negative prognostic factors but none were found to be significant factors in multivariate analysis.

Young Oral Tongue Cancer

There were 17 patients (14%) aged 40 years old and younger in the entire cohort with 6 (15%), 8 (12%) and 3 (16%) young oral tongues in Group A, B and C, respectively. They were less likely to be smokers and drinkers although these differences were not statistically significant (Table 2).

Young oral tongues tend to have well to moderately differentiated SCC with T1/2 and N0 disease. They also present with less advanced disease except for all 3 patients who received definitive RT who had Stage 3/4 tumours. However, these differences were not statistically significant.

Adverse pathological factors such as PNI and ENE were found more frequently in the older patients although not statistically different.

Overall survival was significantly better in the young patients across all groups with 2/5-year OS for younger and older patients as follow: Group A – 83%/83% vs 70%/66%, Group B – 75%/75% vs 51%/36% and Group C – 33%/33% vs 31%/13% (P = 0.012).

The differences in DFS, LRS and MFS were not statistically significant between the different age groups across all treatment groups. In the larger Group B, there was a trend towards better 2- and 5-year DFS (86%/86% vs 44%/42%) and LRS (86%/86% vs 53%/50%) among younger patients (P = 0.601).

Table 2. Patient and Tumour Characteristics according to Age Groups

Patient Characteristics	**Group A (n = 39) No. (%)**		**Group B (n = 65) No. (%)**		**Group C (n = 19) No. (%)**	
	≤ 40 (n = 6)	**40 (n = 33)**	**≤ 40 (n = 8)**	**> 40 (n = 57)**	**≤ 40 (n = 3)**	**> 40 (n = 16)**
Gender (*P* value)	1.000		0.032		1.000	
Male	3 (50%)	19 (58%)	3 (38%)	44 (77%)	2 (67%)	12 (75%)
Female	3 (50%)	14 (42%)	5 (62%)	13 (23%)	1 (33%)	4 (25%)
Smoker (*P* value)	0.439		0.287		0.628	
Yes	2 (33%)	16 (48%)	1 (13%)	23 (40%)	1 (33%)	9 (56%)
No	4 (67%)	13 (40%)	6 (74%)	26 (46%)	2 (67%)	6 (38%)
Unknown	0	4 (12%)	1 (13%)	8 (14%)	0	1 (6%)
Alcohol (*P* value)	0.624		0.531		1.000	
Yes	2 (33%)	8 (24%)	1 (13%)	19 (33%)	1 (33%)	8 (50%)
No	3 (50%)	12 (36%)	6 (74%)	29 (51%)	2 (67%)	7 (44%)
Unknown	1 (17%)	13 (40%)	1 (13%)	9 (16%)	0	1 (6%)
Grade (*P* value)	0.404		0.336		1.000	
Well	0	9 (27%)	0	11 (19%)	1 (33%)	3 (19%)
Moderate	6 (100%)	19 (58%)	5 (62%)	34 (60%)	2 (67%)	9 (56%)
Poor	0	2 (6%)	3 (38%)	7 (12%)	0	1 (6%)
Mixed	0	3 (9%)	0	3 (5%)	0	1 (6%)
Unknown	0	0	0	2 (4%)	0	2 (13%)
T stage (*P* value)	0.729		0.135		0.705	
1	4 (67%)	24 (73%)	3 (38%)	13 (23%)	0	0
2	2 (33%)	7 (21%)	5 (62%)	19 (33%)	1 (33%)	2 (13%)
3	0	1 (3%)	0	10 (18%)	0	3 (19%)
4	0	1 (3%)	0	15 (26%)	2 (67%)	11 (69%)
N stage (*P* value)	0.636		0.320		0.777	
0	6 (100%)	27 (82%)	4 (50%)	11 (19%)	1 (33%)	2 (13%)
1	0	1 (3%)	1 (13%)	10 (18%)	1 (33%)	5 (31%)
2	0	5 (15%)	3 (37%)	33 (58%)	1 (33%)	8 (50%)
3	0	0	0	3 (5%)	0	1 (6%)
TNM stage (*P* value)	0.598		0.021		0.422	
1	4 (67%)	22 (67%)	1 (13%)	2 (4%)	0	0
2	2 (33%)	5 (15%)	3 (37%)	3 (5%)	0	1 (6%)
3	0	1 (3%)	1 (13%)	11 (19%)	1 (33%)	1 (6%)
4	0	5 (15%)	3 (37%)	41 (72%)	2 (67%)	14 (88%)
LVI (*P* value)	0.020		0.185			
Yes	2 (67%)	0	0	14 (25%)	N/A	
No	4 (67%)	32 (97%)	8 (100%)	43 (75%)		
Unknown	0	1 (3%)	0	0		
PNI (*P* value)	0.630		0.420			
Yes	0	6 (18%)	1 (13%)	18 (32%)	N/A	
No	6 (100%)	26 (79%)	7 (87%)	39 (68%)		
Unknown	0	1 (3%)	0	0		
Surgical margins (*P* value)	1.000		0.288			
Positive	0	3 (9%)	0	7 (12%)	N/A	
Negative	5 (83%)	24 (73%)	6 (75%)	24 (42%)		
Close	1 (17%)	6 (18%)	2 (25%)	26 (46%)		

Table 2. Patient and Tumour Characteristics according to Age Groups (Cont'd)

ENE (*P* value)	1.000		0.219		
Yes	0	3 (9)	1 (13)	14 (25)	NA
No	0	3 (9)	3 (37)	32 (56)	
Unknown	6 (100)	27 (82)	4 (50)	11 (19)	

Discussion

This was a retrospective study of patients with oral tongue SCC in Singapore over a period of 8 years. Although our patient cohort was not large, it provided important information regarding demographics and treatment outcomes of oral tongue cancer in our local population. However, this study was limited by the caveats of a retrospective analysis, small number of patients and also by the short median follow-up duration.

Our 5-year OS (46%) for all patients did not differ greatly compared to some of the other reported retrospective studies (5-year OS of 40% to 50%).[4,18,19] Direct comparison of these results can be difficult as some studies analysed all patients with oral tongue cancers treated with definitive and palliative intent while others grouped all oral cavity cancers together for analysis. One retrospective study showed 5-year disease-specific survival rates of between 44% and 65% for patients who underwent surgery followed by adjuvant RT.[20]

Much attention had been given to the characteristics and prognosis of young oral tongue cancer despite the relative rarity of this disease in young patients. However, its incidence has increased in recent years. The definition of young age oral tongue SCC has variously been described as below 35 to 45 years old. For the purpose of this study, we arbitrarily defined young tongue patients as 40 years old and below. The incidence of young oral tongue SCC in our cohort was 14%, which was comparable to other studies.[11,13,21] There was a female predominance in the younger group and these patients tend to be non-smokers and non-drinkers. This is consistent with previous published findings. However, the proportion of patients with adverse pathological features was not significantly different between the younger and older groups. Our study showed that the overall survival for the young oral tongues was significantly better compared to the older patients. However, this difference could be attributed to the better general medical status of these patients to tolerate the rigorous treatment and fewer deaths due to concurrent illnesses. Although our study did show a trend of improved disease-specific survival (DSS) in the younger patients (5-yr DSS in patients aged ≤ 40 and > 40: Group A – 33% vs 16%; Group B – 75% vs 42%; Group C – 83% vs 76%), these differences were not statistically significant ($P = 0.123$). Also interestingly, our study failed to show significant differences in the disease-free survival, locoregional and distant relapse rates among the young and old patients. Although our number of young oral tongue patients was small, it did provide additional information regarding the characteristics and survival outcomes in our local Asian population that would help to guide future management of this group of patients.

Previous retrospective studies had shown contrasting results regarding the outcome of young oral tongue cancer. A literature review of 14 studies published between 1968 and 1993 revealed a 57% locoregional failure rate.[16] A subsequent meta-analysis by Pitman showed a 3-year disease-free survival of 53.3% in patients younger than 40.9 A few recent publications demonstrated 5-year OS rates of 64% to 77.7% for this cohort. A multicentre retrospective study over a 10-year period showed that majority of the 52 young oral tongue patients (≤ 35 years) had T1/2 and N0 disease with a 5-year OS of 64% and a 5-year DFS of 52%.[22] A Japanese retrospective analysis of young oral tongue cancer patients treated over a 25-year period with low-dose rate brachytherapy did not demonstrate a worse outcome compared to the older population, with 5-year cause-specific survival of 80% and 5-year local failure rate of 22%.[13] Another matched-pair analysis in Taiwan showed excellent survival rate (more than 90% at 4 years) and less than 30% recurrence rate in the younger cohort.[12] A small retrospective study from Thailand analysing 20 patients younger than 45 years old with oral cavity cancer (75% with oral tongue tumour) showed a 3-year overall survival and disease-free survival rate of 62% and 60%, respectively.[23] Thus, no definite conclusion could be drawn regarding the outcome of young oral tongue cancers based on these results.

A few hypotheses have been put forward to explain the biological differences in young oral tongue patients. Although HPV has been implicated in the pathogenesis of head and neck SCC, it is more strongly associated with oropharyngeal SCC (particularly tonsillar cancers) than oral tongue tumours.[24,25] Thus, there is currently not enough evidence to suggest a similar entity of HPV-associated oral tongue cancer.

Conclusion

Our study showed that the survival rates for oral tongue SCC in Singapore were comparable to other series although locoregional failure remained a major problem. Our study did not support the hypothesis that young oral tongue patients had worse biological features and clinical outcomes. Hence, we should adopt more aggressive locoregional treatments for all patients with oral tongue cancer irrespective of the patients' age, assuming that they are fit to receive therapy. Perhaps the wider use of concurrent chemoradiation or other radiotherapy techniques such as IMRT or brachytherapy that enable the delivery of higher radiation dose to areas at risk may help to improve local control. Meanwhile, young oral tongue cases should be discussed at multidisciplinary meetings for the best possible management option with close observation after that to detect any evidence of disease recurrence.

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