

Research Article

# Squamous Cell Carcinoma of the Oral Tongue: A Single Institution Retrospective Cohort Study from Mansoura University Hospital

**Rasha Hamdy, Amal Halim**

Clinical Oncology and Nuclear Medicine Department, Mansoura University, Egypt

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### \*Corresponding author:

Amal Halim

Clinical Oncology and Nuclear  
Medicine Department, Mansoura  
University, Egypt

Email: halim43210@mans.edu.eg

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## ABSTRACT

**Background:** Egyptian hospital-based statistics showed that head & neck carcinomas represent 18% of all cancers and mostly diagnosed at advanced stages. Our Clinical Oncology & Nuclear Medicine Department of Mansoura Faculty of Medicine serves a large rural area of the Delta region of Egypt. There is no previous study in our institution that focused on oral tongue carcinoma alone. This study aims in establishing the demographics, treatment outcome and prognostic factors of oral tongue squamous cell carcinoma (SCC).

**Methods:** We retrospectively reviewed data of 50 cases with oral tongue SCC treated in our department from January 2014 to December 2016 to evaluate the demography, pathological characteristics, and therapeutic modalities. We estimated the survival rates during the entire follow-up period by the Kaplan–Meier method. The univariate and multivariate Cox proportional hazards analysis were performed for prognostic factors determination.

**Results:** The median follow-up was 30 months (range: 4-45 months). The 3-year overall survival (OS) and disease-free survival (DFS) rates were 68% and 60% respectively. By univariate analysis, both advanced stages (III, IVA) and depth of invasion >0.5 cm were statistically significant as prognostic factors for 3-year DFS and OS rates. DFS rates were 34% vs. 98% for stage III and IVA vs. stage I and II respectively ( $p = 0.001$ ); 52% vs. 78% for >0.5 cm vs.  $\leq 0.5$  cm depth of invasion ( $p = 0.003$ ). OS rates were 36% vs. 99% for stage III and IVA vs. stage I and II respectively ( $p = 0.002$ ); 52% vs. 80% for >0.5 cm vs.  $\leq 0.5$  cm depth of invasion ( $p = 0.001$ ). Multivariate analysis of prognostic factors affecting 3-year DFS and OS rates confirmed the statistical significance of the same 2 factors.

**Conclusions:** The majority of our patients were males below 60 years. Tumors were mainly found at stage III and were moderately differentiated. Vascular invasion and lymphatic permeation were uncommon. Staging and tumor invasion depth significantly affected the outcome. The 3-year OS and DFS were 68% and 60% respectively.

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## INTRODUCTION

In the Middle East, smoking rates are considerable. Egyptian hospital-based statistics showed that head & neck carcinomas represent 18% of all cancers and mostly were diagnosed at advanced stages (1). A report of the Middle-East Cancer Consortium of the National Cancer Institute in Bethesda, USA, reported that Egypt has one of the highest rates of such tumors in the Middle East (2). The Nile Delta of Egypt is the region

where the Nile River spreads out and drains into the Mediterranean Sea. It extends between Alexandria in the West to Port Said in the East and it is a rural agricultural region with poor access to dentists. Our Clinical Oncology and Nuclear Medicine Department is one of the main oncology centres in Nile Delta of Egypt. As no studies concerning oral tongue squamous cell carcinoma (SCC) have been published in our institution, this study aimed at exploring the clinico-epidemiological features of the disease as well as the prognostic factors.

## METHODS

We retrospectively reviewed the database from January 2014 to December 2016. Inclusion criteria included oral tongue SCC patients. However, exclusion criteria were: patients with other malignancies, poor performance status (Eastern Cooperative Oncology Group (ECOG)  $\geq 3$ ), end-stage renal disease, Child-Pugh C liver cirrhosis, or poor heart or lung function and lastly, patients with missing data about their staging. The data were obtained from Clinical Oncology & Nuclear Medicine Department database. Data collection was authorized by our institutional Ethical Committee (Code R.18.01.20.R1-2018/04/14).

Patient characteristics that were considered included: age, gender, staging, histological grade, pathologic descriptions and treatment modalities. Staging was according to the 7th edition of the American Joint Committee on Cancer staging (3).

Treatment modalities that were applied by different physicians and documented in the records were performed according to the National Comprehensive Cancer Network Guidelines. The technique of delineation for conformal radiotherapy was according to the Radiation Therapy Oncology Group Guidelines. Following the treatment, patients were subjected to regular follow-up. Follow-up was in the form of clinical examination plus magnetic resonance imaging or computerized tomography scan of head and neck every 3 months in the first year, every 6 months in the second year, yearly in the third year and then every 2 years till death.

Generally, in cases of documented relapse or disease persistence, the patient was reassessed by a multidisciplinary treatment board to decide the suitable salvage treatment. Death was considered to be related to tongue cancer if it was documented in the file or it occurred within one month after the treatment ends.

Descriptive analysis was performed to characterize the patient's demographic variables, pathological characteristics and therapeutic modalities by reporting them as frequencies and proportions. The follow-up periods for each patient was calculated from treatment end date until the date of death or last follow up. Disease-free survival was calculated from treatment start date to the date of recurrence. Overall survival was calculated from date of diagnosis to date of death or last follow up. We estimated the survival rates during the entire follow-up period by the Kaplan–Meier method. The univariate and multivariate Cox proportional hazards analysis was performed for prognostic factors that influence survival. For all tests, significance was defined at  $p < 0.05$ . The statistics were accomplished through Statistical Package Version 16 (SPSS, INC., Chicago, IL, USA).

## RESULTS

**Table 1.** Patients, tumor, and treatment characteristics

Characteristics	N (%)
Age (years)	
$\leq 60$	45 (90%)
$> 60$	5 (10%)
Gender	
Male	30 (60%)
Female	20 (40%)
Performance status	
ECOG 0	12 (24%)
ECOG 1	38 (76%)
T-category	
T1	5 (10%)
T2	9 (18%)
T3	35 (70%)
T4a	1 (2%)
N-category	
N0	32 (64%)
N1	13 (26%)
N2	5 (10%)
N3	0 (0%)
Stage	
I	1 (2%)
II	10 (20%)
III	38 (76%)
IVA	1 (2%)
Histological grade	
Low grade	16 (32%)
Moderately grade	22 (44%)
High grade	12 (24%)
Depth of invasion (cm)	
$\leq 0.5$	28 (56%)
$> 0.5$	22 (44%)
Resection margin	
Negative	49 (98%)
Close ( $< 0.5$ cm)	1 (2%)
Positive	0 (0%)
Lymphovascular invasion	
Yes	3 (6%)
No	47 (94%)
Perineural invasion	
Yes	4 (8%)
No	46 (92%)
Surgery of primary site	
Simple excision	4 (8%)
Wide excision	8 (16%)
Hemiglossectomy	38 (76%)
Neck dissection	
Yes	38 (76%)
No	12 (24%)
Radiotherapy	
Yes	38 (76%)
No	12 (24%)
Concurrent chemotherapy	
Yes	28 (56%)
No	22 (44%)

### Patients, tumor, and treatment characteristics

Patient, tumor, and treatment characteristics of 50 cases of SCC of the oral tongue are shown in Table 1. The age was ranged from 40 to 72 years old (mean: 52 years  $\pm$  12.3), 45 (90%) patients were  $\leq$  60 years and 5 (10%) patients were  $>$  60 years. There were 30 (60%) males and 20 (40%) females. Thirty-eight (76%) patients had ECOG 1 performance status. Smoking habit was documented in 20 (40%) patients, while documentation of delayed diagnosis because of lack of dentists' awareness was documented in 3 cases. There were 38 (76%) patients with clinical stage III. Pathologic specimens were assessed. Twenty-two patients (44%) patients had moderately differentiated disease and 28 (56%) patients had disease with depth of invasion  $\leq$  0.5 cm.

Among the total of 50 patients, 4 (8%) patients underwent simple excision, 8 (16%) patients underwent wide excision while hemiglossectomy was performed in 38 (76%) patients. Neck node dissection was performed in 38 (76%) patients. Thirty eight patients (76%) received radiotherapy with the median dose of 62.7Gy to the primary tumor, 60.1Gy to positive neck node, and 45Gy to electively treated neck node. All patients received 3-dimensional conformal radiation therapy. Weekly concurrent chemotherapy was administrated in 28 (56%) of patients (26 cases received cisplatin and 2 cases received carboplatin). Range of chemotherapy weekly cycles was 2 to 6 cycles (median was 3 cycles).

### Patterns of failure

Recurrence was reported in 20 cases which include 10 local failures, 8 regional failures, and 4 distant metastases. Locoregional failure occurred in 18 patients. There were 16 (32%) patients with locoregional failure in stage III, 1 (2%) patient in stage II, and 1 (2%) patient in stage IVA.

Local failure was reported in 1 (2%) patient with T2, 8 (16%) patients with T3 and 1 (2%) patient T4a disease. Salvage surgical resection was done in 30% (3 out of 10) of patients who had local failure, while 7 patients did not undergo operation due to locally unresectable disease in 2 patients and 5 patients refused surgical resection. Eight patients reported regional failure: One (2%) patient with N0, 1 (2%) patient with N1, and 6 (12%) patients with N2. Two patients had salvage neck dissection, while 4 patients declined the surgery, and 2 had distant metastases.

Distant metastases (lung metastases) were reported in 4 patients. Chemotherapy was received and tolerated by 2 patients with distant metastases (1 patient received cisplatin + 5-fluorouracil and the other one received carboplatin + paclitaxel).

### Survival and prognostic analysis

The median follow-up was 30 months (range: 4-45 months). A total of 16 patients died. Causes of death were due to tongue cancer in 10 patients, cardiac event in 1 patient, end stage renal disease in 1 patient, and unknown cause in 4 patients. The median OS was 41 months. The 3-year OS and DFS were 68% and 60% respectively (figure 1 and 2).

By univariate analysis (Table 2.), both advanced stages (III and IVA) and depth of invasion  $>$  0.5 cm were statistically significant prognostic factors for 3-year DFS and OS rates. DFS rates were 34% vs. 98% for stage III and IVA vs. stage I and II respectively ( $p = 0.001$ ); 52% vs. 78% for  $>$ 0.5 cm vs.  $\leq$ 0.5 cm depth of invasion ( $p = 0.003$ ). OS rates were 36% vs. 99% for stage III and IVA vs. stage I and II respectively ( $p = 0.002$ ); 52% vs. 80% for  $>$ 0.5 cm vs.  $\leq$ 0.5 cm depth of invasion ( $p = 0.001$ ). Multivariate analysis of prognostic factors affecting 3-year DFS and OS rates revealed the statistical significance of the 2 factors (Table 3).

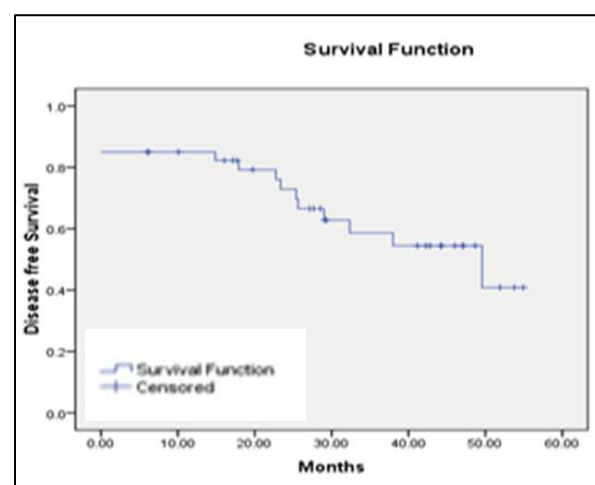


Figure 1. Disease-free survival of 50 patients with SCC of oral tongue

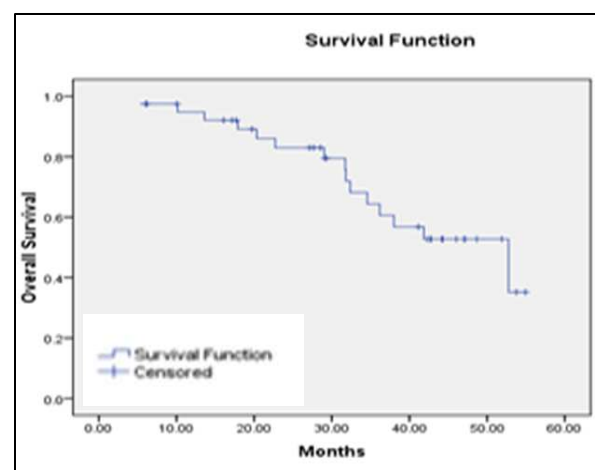


Figure 2. Overall survival of 50 patients with SCC of oral tongue

**Table 2.** Univariate analysis of prognostic factors affecting DFS and OS

Variable	3-year DFS (%)	HR (95%CI)	p-value	3-year OS (%)	HR (95%CI)	p-value
Age						
≤ 60	64	1.83	0.96	64	2.19	0.98
> 60	56	(0.94-1.92)		56	(0.45-9.65)	
Gender						
Male	58	3.07	0.65	60	4.99	0.32
Female	62	(0.98-8.7)		62	(0.95-10.65)	
Performance status						
ECOG 0	66	2.83	0.98	66	4.19	0.43
ECOG 1	54	(0.45-20.65)		56	(0.85-11.05)	
T-category						
T1,T2	58	1.07	0.67	59	3.19	0.65
T3, T4a	30	(0.89-8.7)		31	(0.45-9.75)	
N-category						
N0	66	3.11	0.3	68	3.99	0.34
N +ve	54	(0.08-8.32)		56	(0.95-7.65)	
Stage						
I, II	98	3.09	<b>0.001</b>	99	3.39	<b>0.002</b>
III, IVA	34	(1.02-7.33)		36	(1.95-9.25)	
Histological grade						
Low, Intermediate grade	62	2.63	0.7	64	2.87	0.42
High grade	44	(0.45-10.65)		40	(0.45-10.65)	
Depth of invasion						
≤ 0.5	78	3.73	<b>0.003</b>	80	4.19	<b>0.001</b>
>0.5	52	(2.45-12.65)		52	(1.45-11.65)	
Resection margin						
Negative	64	1.83	0.97	66	2.19	0.87
Close, Positive	31	(0.84-1.92)		34	(0.45-9.65)	
Lymphovascular Invasion						
Yes	44	2.07		46	4.99	
No	66	(0.98-8.2)	0.43	68	(0.95-10.65)	0.63
Perineural invasion						
Yes	46	3.83	0.65	46	4.19	0.85
No	62	(0.45-9.65)		66	(0.85-11.05)	
Surgery of primary site						
Simple excision	54	2.07	0.43	54	5.19	0.93
Wide excision, Hemiglossectomy	69	(0.89-3.7)		71	(0.45-9.75)	
Neck dissection						
Yes	62	2.11	0.46	64	3.99	0.76
No	56	(0.08-5.32)		58	(0.95-9.65)	

Radiotherapy						
Yes	62	4.83	0.43	68	2.15	0.23
No	58	(0.94-11.92)		58	(0.45-5.65)	
Chemotherapy						
Yes	68	3.44	0.32	70	1.99	0.32
No	52	(0.98-8.7)		52	(0.95-2.65)	

**Table 2.** Multivariate analysis of prognostic factors affecting DFS and OS

Variable	DFS			OS		
	HR	(95%CI)	p-value	HR	(95%CI)	p-value
Stage ( I,II Vs. III, IVA)	7.09	(3.45-20.65)	0.001	3.99	(1.45-9.65)	0.004
Depth of invasion ( $\leq 0.5$ Vs. $>0.5$ )	3.83	(3.45-20.65)	0.01	4.19	(1.45-11.65)	0.01

## DISCUSSION

In Africa, the incidence rate of oral carcinomas is 2.6/100.000 people and the rate is higher in males. Male to female ratio is 3,3:2 (4). In India, the incidence is one of the highest in the world due to the popularity of betel and areca nuts with male to female ratio of 2,3:1 (5). In USA the incidence is 1,6-2,9/100.000 (6). In England, as a European example, the yearly mean incidence is 1,4/100.000 population with male to female ratio of 1,6:1 (7).

In our institution, the incidence of tongue cancer was 50% of oral cavity carcinomas but less than 1% of all cancers received during the study period. The functions of tongue as regard mastication, swallowing, taste and speech are very much affecting quality of life but unfortunately, the access to optimum oral health care is limited in rural areas. Consequently, this work aimed at exploring the clinic –epidemiological characteristics of oral tongue SCC which was not studied before in our institution.

The role of tobacco in development of oral cavity carcinomas is well documented (8). Smoking habit was documented in the records of 20 patients in this study (40%). Unfortunately, tobacco awareness programs are still deficient especially in rural areas with existence of wrong beliefs about the positive correlation between smoking habit and personal prestige.

The mean age in the present study was  $52 \pm 12$  years similar to the large Indian study (124 patients) of Shukla et al. ( $50 \pm 12$ ) (9). No ages below 20 years old was recorded in our study and this parallels with the published fact of paucity of these patients worldwide (10). In our study, males exceeded females. This result agrees with results of other publications in different parts of the world as the American paper of Tota et al. (11), the Spanish paper of Garcia-Kass et al. (12),

Dhanuthai et al. (13) from Thailand and the Turkish study of Duzlu et al. (14).

Stages III & IV represented more than two thirds of our cases similar to a large Brazilian population-based study (15) and a respectable Japanese report (16). This observation is really strange because tongue is an accessible organ. Population in our rural areas cannot afford the high cost of dental care since very few of them are covered by insurance. As a result, they rarely seek the advice of dentists. Unfortunately, the exact role for dentists in the disease scenario of each of our patients, if any, was not documented in all the records. However, it was frankly reported that delayed diagnosis of the cancer in 3 of our cases was due to deficiency in the dentists' knowledge. This agrees with the interesting review of Stoykova (17). Increasing awareness of dentists about oral carcinomas can help detecting oral carcinomas at earlier stages.

Surgery alone is the treatment of early stage tongue carcinoma. Adjuvant therapy is used when pathologic adverse features exist (18). Multidisciplinary treatment in the form of surgery, external radiotherapy, and chemotherapy was the main focus of our institutional policy in treating tongue cancer especially in advanced stages. High dose brachytherapy was proven to be beneficial for control in T1 tumor (19). However, it was not among our treatment policies due to unavailability. Similarly, neo adjuvant chemotherapy was reported to give favorable results (20, 21) and so was the retrograde super selective intra-arterial chemo radiotherapy (22). These techniques have not yet been investigated in our department.

Our 3-year overall survival figure seems similar to other publications like the respectable paper of Spiotto et al. (23) who studied 2803 cases. Their 3-year overall survival was from 67%-73%. However, the 3-year overall survival rate of Mroueh et al. (24) from Finland who studied 360 patients was 80%. This may be attributed to

the very high socioeconomic standard in Finland. The non-satisfactory survival rates of tongue cancer make identification of early serum markers for tumor detection, such as N-glycopeptides, urgent (25).

Regarding the prognostic factors, age was not among our prognostic factors. However, Jeon et al. (26) concluded in his study of 117 patients that tongue cancer prognosis in ages less than 40 years is worse than those above 40 years. On the other hand, Tsai et al. (27) reported that ages above 75 years had worse survival rate in the group of advanced stage. In our study, patients above 60 years were just 5 in number so we could not test the effect of very advanced age on prognosis. Staging and depth of invasion were proven to be our independent statistically significant prognostic factors. This parallels with the results of Cariati et al. (117 cases) (28). However, extra nodal extension, nerve and vascular invasion were other significant factors reported by Cariati and his group. Depth of invasion was of prognostic significance in other several studies as that of Tarsitano et al. (67 patients) (29) and Hori et al. (48 patients) (30). Inclusion of the depth of invasion in the recent 8th version of TNM Classification of the AJCC was worthy as clarified by Almangush et al. (31). Determination of the tumor depth has a significant aspect other than the prognosis. Intraoral sonography applied before surgery to determine the depth leads to minimizing the chance of occurrence of surgical margin positivity as clarified by the respectable review of Klein Nulent et al. (32). Intraoral sonography has not yet been applied in the routine preoperative policy of tongue cancer management in our institution. Cassidy et al. (33) studied 180 N0 tongue cancers and found that lymphatic permeation is of poor prognostic impact and consequently he highlighted the need to include it among the indications of adjuvant radiotherapy in radically resected N0 tongue cancer. Pathologic grading in the present work was of no prognostic significance. Dik et al. (34) in his study that included 145 early oral squamous cell carcinoma (mainly tongue carcinomas) patients reported a similar observation. The limited independent prognostic factors in the present study may be due to the limited number of patients.

The retrospective nature of the study with missing of some data beside the small patient number represents limitations of the study.

## CONCLUSIONS

The majority of patients of our institution were males below 60 years with stage III moderately differentiated tumors. Vascular invasion and lymphatic permeation were uncommon. Tumor staging and tumor invasion depth significantly affected the outcome. The 3-year OS and DFS were 68% and 60% respectively. Tobacco awareness programs and periodic oral

examination by well-trained dentists could help in early detection of tongue carcinoma.

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## DECLARATIONS

### Ethical approval

This study was approved by the ethical committee of Faculty of Medicine, Mansoura University.

### Competing of Interest

The authors declare that they have no competing interests.

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