*The Journal of Laryngology & Otology (2009), **123**, 114–120.*

doi:10.1017/S0022215108003186

Main Article

Squamous cell carcinoma of the oral tongue: a 25-year, single institution experience

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Abstract

Aim: To report the characteristics, prognostic factors and treatment outcomes of 102 patients with squamous cell carcinoma of the oral tongue treated and followed up at a single institution over a 25-year period.

Patients and methods: This retrospective study was carried out by auditing the medical records of 102 patients diagnosed with squamous cell carcinoma of the oral tongue and treated at our institution between 1982 and 2007. Patient follow up ranged from nine to 310 months (median 35 months). Fifty per cent of the patients were treated with surgery followed by a combination of chemotherapy and radiotherapy (43.1 per cent received concurrent chemoradiation and 6.9 per cent received sequential chemotherapy and radiotherapy), whereas 29.4 per cent received surgery followed by adjuvant radiotherapy alone. The remaining patients (20.6 per cent) did not undergo surgery and were treated with definitive radiotherapy with or without chemotherapy.

Results: There were 48 men and 54 women. The age at presentation was 19–85 years (median 57 years). The peak incidence was observed between 60 and 70 years. Resection margins were clear in 75 per cent of patients and involved in 25 per cent. Stage I disease was found in 11.8 per cent of patients, stage II in 34.3 per cent, stage III in 22.5 per cent and stage IV in 31.4 per cent. The five-year disease-free survival and overall survival were 65.7 and 72.5 per cent, respectively. Thirty-five patients suffered recurrence after treatment, 74.0 per cent of them at the site of initial cervical nodal involvement. Univariate analysis for overall survival revealed the following as prognostic factors: treatment schedule (surgical *vs* non-surgical; $p < 0.001$); age (<60 years *vs* ≥ 60 years; $p = 0.038$); extent of cervical lymph node involvement ($p = 0.015$); primary tumour stage ($p < 0.001$); node stage ($p = 0.034$); and disease stage ($p = 0.013$). However, on multivariate analysis, only non-surgical treatment ($p = 0.001$) and advanced disease stage ($p = 0.05$) were found to have a negative influence on survival.

Conclusions: Our limited data suggest that, in Iran, squamous cell carcinoma of the oral tongue tends to present at a locally advanced stage, with a high frequency of locoregional failure and a poor outcome. Combined modality therapy should be considered for the majority of patients with squamous cell carcinoma of the tongue.

Key words: Tongue Neoplasms; Squamous Cell Carcinoma; Prognosis; Surgery; Radiotherapy; Iran

Introduction

Tongue cancer is the most common oral cavity neoplasm, with a remarkable geographic distribution worldwide. The highest tongue cancer rate has been found in India, where the incidence is roughly 9.4/100 000/year.[1] Tongue cancer is a major health problem in many parts of the world, with poor prognosis despite aggressive combined treatment. This cancer usually affects men more than women, with the highest incidence occurring in the sixth to eighth decades.[2]

More than 80 per cent of tongue cancers arise from the oral tongue (i.e. the anterior two-thirds of the tongue).[3] Squamous cell carcinoma (SCC) constitutes the vast majority (more than 95 per cent) of oral tongue neoplasms.[4]

Over recent decades, the incidence of tongue cancer has increased in patients younger than 40 years.[1] There are conflicting reports regarding the prognostic impact of age on the clinical outcome of oral tongue cancer.[5]

This is the first report from Iran which specifically describes the characteristics, prognostic factors and treatment outcome of SCC of the oral tongue. Herein, we investigate the influence on survival of various prognostic factors, in particular age at presentation, in 102 patients with SCC of the oral tongue.

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Accepted for publication: 14 May 2008. First published online 30 June 2008.

Materials and methods

Patients

This retrospective study was carried out by auditing patients' notes from our departmental computer databases or (for older data) from written patient lists. To overcome possible disease coding errors, over 1500 sets of patient notes with similar diagnoses were reviewed. The study included all patients with a diagnosis of oral tongue SCC treated between 1982 and 2007 at our radiotherapy and oncology department, a total of 102 patients. The patients had been followed up until they chose otherwise or expired. During follow up, any side effects, relapse and patient complaints had been noted.

Chemotherapy

The chemotherapy regimen consisted of cisplatin 80 mg/m^2 on day one and 5-fluorouracil 1000 mg/m^2 on days one to three. Fifty per cent of the patients received a median two (range one to six) cycles of chemotherapy.

Radiotherapy

All patients received external beam radiotherapy (RT) using cobalt-60 units and/or 9 MV X-ray photons or electrons from a linear accelerator. A mean dose of 55.5 Gy (median 60 Gy) was delivered via a daily fraction of 2 Gy, with five fractions per week. The primary site and upper cervical lymph nodes were treated with two lateral parallel-opposed fields; the lower cervical lymph nodes were treated with a separate en face anterior field. The spinal cord was excluded from the radiation fields after 46 Gy. After 50 Gy, RT was continued to the primary tumour, using reduced size fields, up to 60–70 Gy. Metastatic cervical lymph nodes were boosted through anterior and posterior neck fields with a central block and a dose of 15–20 Gy.

Measures

The following parameters were noted for every patient: age, sex, clinical findings at diagnosis, tumour stage, pathological grade, tumour margin, haemoglobin level, treatment mode, RT dose, operation date, relapse date (if applicable) and date of patient's death (if applicable).

Statistical analysis

Disease-free survival was calculated from the date of registration to the date of disease relapse at any site. Overall survival was calculated from the date of registration to the date of death due to any cause. Univariate analysis for disease-free survival and overall survival rates was performed using the Kaplan–Meier method, and prognostic factors were compared using the log-rank test. Multiple-covariate analysis was performed using the stepwise Cox's proportional hazards regression model. The hazard ratio for death, with the 95 per cent confidence interval (CI), was calculated for the treatment groups. The stratified log-rank test was used to compare treatment results in each disease group. A p value of 0.05 or less was considered to be statistically significant.

Results

Age and sex distribution

The age at presentation was in the range 19–85 years with a median of 57 years. Fifty-eight patients were $\leq$60 years old at presentation and 44 patients were $>$60 years old. The peak incidence was observed between the sixth and seventh decades of life. Follow up ranged from nine to 310 months (median 35 months). There were 48 men and 54 women. The distribution of men and women with ages greater or less than 50 years was similar.

Stage distribution

Twelve patients (11.8 per cent) had stage I disease, 35 (34.3 per cent) had stage II disease, 23 (22.5 per cent) had stage III disease and 32 (31.4 per cent) had stage IV disease, as detailed in Tables I and II.

Treatment distribution

Surgery was undertaken in 81 (79.4 per cent) patients, 50 per cent of whom were treated with a combination of surgery, chemotherapy and RT (seven (6.9 per cent) received surgery followed by sequential chemotherapy and RT, and 44 (43.1 per cent) received surgery followed by concurrent chemo-radiotherapy), whereas 30 (29.4 per cent) received RT alone following surgical resection. The remaining 21 (20.6 per cent) patients did not undergo surgery and were treated with definitive RT with or without chemotherapy. The distribution

TABLE I

CLINICAL STAGING OF 102 ORAL TONGUE SCC PATIENTS

Clinical T stage	Clinical node stage (n (%))				Total (n (%))
	N_0	N_1	N_2	N_3	
T_1	12 (11.8)	2 (2.0)	0	0	14 (13.7)
T_2	34 (33.3)	12 (11.8)	5 (4.9)	1 (1.0)	52 (51.0)
T_3	7 (6.9)	13 (12.7)	8 (7.8)	1 (1.0)	29 (28.4)
T_4	0 (0.0)	4 (3.9)	1 (1.0)	2 (2.0)	7 (6.9)
Total	53 (52)	31 (30.4)	14 (13.7)	4 (3.9)	102 (100)

SCC = squamous cell carcinoma; T = tumour; N = node

https://doi.org/10.1017/S0022215108003186 Published online by Cambridge University Press

TABLE II

PATIENTS' DISTRIBUTION OF TREATMENT BY DISEASE STAGE

Stage	RT alone (*n* (%))	Surgery + RT (*n* (%))	Surgery + RT then CT (*n* (%))	Surgery + concurrent RT & CT (*n* (%))
I	1 (8.5)	7 (58)	1 (8.5)	3 (25)
II	3 (8.5)	13 (37)	2 (6)	17 (48.5)
III	6 (26)	4 (17)	3 (13)	10 (44)
IV	11 (34)	6 (19)	1 (3)	14 (44)

RT = radiotherapy; CT = chemotherapy

of treatment choice by disease stage is shown in Table II.

Response and survival rates

A complete response was achieved in 91 patients (89.2 per cent) during or after completion of treatment. All non-responding patients had been treated with definitive RT.

After a median follow up of 35 months for surviving patients, the five-year disease-free survival and overall survival rates were 65.7 and 72.5 per cent, respectively (Figures 1 and 2).

Various prognostic factors were analysed to establish their effect on response rates and patient survival.

Univariate analysis. Univariate analysis for overall survival revealed the following as significant prognostic factors: surgical treatment (five-year overall survival was 28.6 per cent for non-surgical patients *vs* 81.1 per cent in surgical patients; $p < 0.001$); age (five-year overall survival 58.7 per cent for age <60 years *vs* 79.2 per cent for age ≥ 60 years; $p = 0.038$); extent of cervical lymph node involvement (five-year overall survival rates for uninvolved, unilaterally involved and bilaterally involved nodes were 78.4, 59.3 and 25 per cent, respectively; $p = 0.015$); tumour (T) stage (five-year overall survival rates for patients with T_1, T_2, T_3 and T_4 lesions were 88.9, 80.6, 38.5 and 42.9 per cent, respectively; $p < 0.001$); node (N) stage (five-year overall survival rates for patients with N_0, N_1, N_2 and N_3 involvement were 77.9, 57.3, 70.1 and 25.0 per cent, respectively; $p = 0.034$); and disease stage (five-year overall survival rates were 85.7 per cent for stage I patients, 81.2 per cent for stage II, 60.8 per cent for stage III and 49.2 per cent for stage IV; $p = 0.013$).

Sex ($p = 0.602$), RT dose ($p = 0.79$), resection margin status ($p = 0.28$) and tumour grade ($p = 0.443$) were found not to be prognostic factors for overall survival.

Univariate analysis revealed that age, T stage, extent of cervical lymph node involvement and node stage were independent prognostic factors for overall survival. Patients younger than 60 years of age at the time of diagnosis were found to have a significantly poorer outcome compared with those older than 60 years ($p = 0.038$). However, this difference was not statistically significant ($p = 0.53$) when comparing patients younger and older than 40 years. Univariate analysis for disease-free survival showed similar results (Tables I and III).

Multivariate analysis. Multivariate analysis revealed that non-surgical treatment (hazard ratio = 3.816; 95 per cent CI = 1.728–8.430; $p = 0.001$) and advanced disease stage (hazard ratio for death =

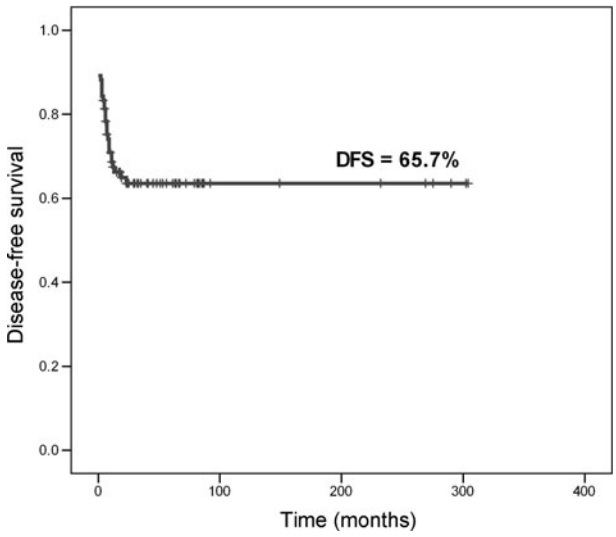

FIG. 1

Five-year disease-free survival (DFS) for 102 patients with oral squamous cell carcinoma.

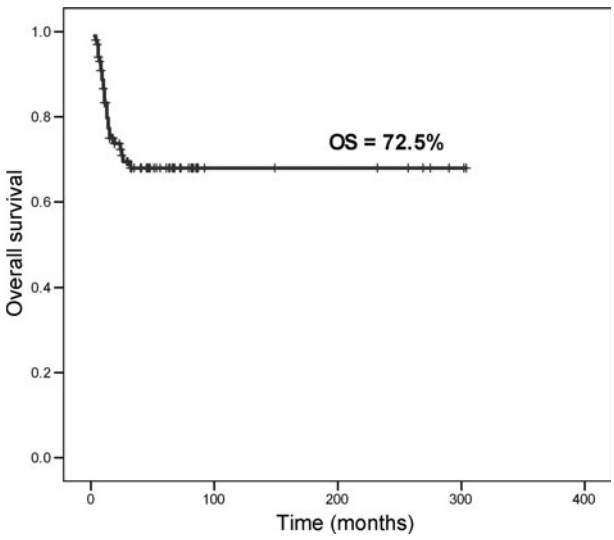

FIG. 2

Five-year overall survival (OS) for 102 patients with oral squamous cell carcinoma.

https://doi.org/10.1017/S0022215108003186 Published online by Cambridge University Press

TABLE III

UNIVARIATE ANALYSIS OF PROGNOSTIC FACTORS FOR CLINICAL OUTCOME

Prognostic factor	Pts (*n*)	5-yr OS		5-yr DFS	
		%	*p*	%	*p*
Age (yrs)					
≤60	58	58.7		53.6	
>60	44	79.2	0.038	76.0	0.024
Sex					
Female	54	70.1		62.3	
Male	48	66.3	0.60	65.5	0.65
Cervical node involvement					
None	53	78.4		76.7	
Unilateral	44	59.3		49.6	
Bilateral	5	25.0	0.015	30.0	0.006
Primary T stage					
T_1	14	88.9		84.4	
T_2	52	80.6		71.7	
T_3	29	38.5		42.9	
T_4	7	42.9	<0.001	42.9	0.006
N stage					
N_0	53	77.9		76.3	
N_1	31	57.3		46.3	
N_2	14	70.1		76.2	
N_3	4	25.0	<0.034	48.3	0.006
Disease stage					
I	12	85.7		91.7	
II	35	81.2		76.3	
III	23	60.8		53.9	
IV	32	49.2	0.015	48.3	0.013
Treatment					
Surgical	81	81.1		73.0	
Non-surgical	21	28.6	<0.001	28.6	<0.001
Histological grade					
I	78	66.1		60.9	
II	20	68.8		64.4	
III	4	100	<0.443	100	<0.296
Margin status					
Clear	58	73.0		64.3	
Involved	19	60.2	0.284	56.4	0.54
RT dose					
≥60 Gy	54	67.4		61.5	
<60 Gy	48	68.3	0.791	69.4	0.513

Pts = patients; yr = year; OS = overall survival; DFS = disease-free survival; T = tumour; N = node; RT = radiotherapy

1.521; 95 per cent CI = 0.986–2.346; $p = 0.002$) had a negative influence on survival.

Recurrence

Thirty-five patients (34.3 per cent) suffered recurrence after treatment. Of these patients, 26 (74.3 per cent) had recurrence at the site of initial cervical node involvement (the most common site of recurrence), five (14.3 per cent) had recurrence at the primary site and the initial cervical node involvement site, two (5.7 per cent) developed distant metastasis, and two (5.7 per cent) developed regional (cervical nodes) and distant failure. Six recurrences occurred in the 14 patients younger than 40 years, 17 in the 40 patients aged between 40 and less than 60 years, and 12 in the 48 patients aged 60 years and older. The mean and median times to recurrence were both five months. All recurrences occurred within 23 months (range zero to 23 months).

Resection margins

Resection margin information was available in 75.5 per cent (77/102) of patients treated with surgery. Resection margins were clear in 75 per cent and involved in 25 per cent of patients.

Treatment complications

Most of the patients developed some degree of treatment-related complications during and/or after RT. Complication rates increased in patients receiving concurrent chemo-radiotherapy. Mucositis was the most frequently observed acute complication, encountered in almost all patients. Xerostomia was the most common and major late sequela, followed by dental caries and neck soft tissue fibrosis each in a remarkable 25–50 per cent of patients.

Discussion

Squamous cell carcinoma of the oral tongue constitutes the majority of tongue cancers. In most reported series, men represent a higher proportion of oral tongue cancer sufferers than women.[6–12] However, consistent with our series, a few reports have found a preponderance of female compared with male cases.[13–16]

https://doi.org/10.1017/S0022215108003186 Published online by Cambridge University Press

Squamous cell carcinoma of the oral tongue occurs commonly in the sixth to eighth decades.[2] In the present study, the peak incidence was observed between the sixth and the seventh decades, with a median patient age of 57 years. Fourteen per cent of our patients were younger than 40 years at the time of diagnosis. We found an equal distribution by disease stage, comparing patients younger and older than 40 years of age. In previous studies, the proportion of patients younger than 40 years has been reported as 1–10 per cent.[11,17–19] Sargeran *et al.* reported a similar age distribution among 470 Iranian patients with cancer of the oral cavity.[20]

This neoplasm usually presents early, with two-thirds of patients being diagnosed with stage I and II disease.[8,11,12] In the present study, the majority of patients presented with locally advanced disease, and 55 per cent had stage III or IV disease. The small percentage of patients diagnosed with stage I may be due to the initial lesion being missed or ignored. Sargeran *et al.* described a similar disease stage distribution among 470 Iranian patients with oral cavity cancer.[21]

Numerous studies have evaluated various potential prognostic factors for oral tongue SCC, in order to establish their influence on response rates and patient survival.[3,4,10,16,19,22–27] Advanced tumour and nodal stages and the use of radiotherapy as primary treatment modality have been associated with reduced survival rates.[6,11,12,18,19,21] Thus far, nodal status at presentation has been seen as the most important prognostic factor. If the nodes are affected, then the chance of cure reduces by half.[28] However, the use of surgery for treatment of the primary tumour, including neck dissection, has been found to improve survival.[7,8,12]

In the current study, the disease stage and the use of non-surgical treatment significantly influenced outcome for patients with SCC of the oral tongue. However, in this and most previous reports, there was a selection bias in the use of RT alone or combined with chemotherapy in oral tongue cancer patients, because in most of these studies non-surgical treatment (RT alone or combined with chemotherapy) was used for advanced, inoperable or unresectable disease.[7,19,21,26] In our study, the treatment received by the majority of patients was surgery and concurrent chemoradiation (43.1 per cent), followed by surgery and RT (29.4 per cent). Treatment was chosen according to the tumour stage and the patient's general condition. Radiotherapy alone or in combination with chemotherapy was given in the case of unresectable or inoperable disease, hence the higher percentage of stage IV tumours being treated with this regime (52 per cent in the non-surgical group *vs* 26 per cent in the surgical group) (Table II).

There is no consensus regarding the impact of age at presentation on clinical course and outcome in patients with oral tongue cancer. Few reports have found a more aggressive clinical course in younger patients with oral tongue cancer.[29–31] Other reports have found no difference in the clinical course and prognosis for younger patients with oral tongue cancer, compared with older such patients.[12,21,32,33] In contrast, some reports have found better survival rates in oral tongue SCC patients younger than 40 years compared with older patients.[5,7,8,11,12]

In the current study, patients younger than 60 years had poorer survival rates compared with older patients; however, no statistically significant difference was found when patients younger and older than 40 years were compared.

Rates of regional failure are remarkable, even in the early stages of the disease, and in locally advanced disease this is the most frequent type of treatment failure and the leading cause of death.[12,34] Once regional recurrence occurs, prognosis is poor and long-term survival is rare.[34,35] In addition, elective or therapeutic neck management, even in the early stages of the disease, significantly improves regional control and overall survival rate in these patients.[34,36–38] In published series, the rate of locoregional recurrent disease has been reported as 28–37 per cent.[12,24] In the current study, 34 per cent of patients developed recurrent disease, the vast majority of which comprised locoregional failure (89 per cent); isolated regional failure comprised 74 per cent of all recurrences and was the major cause of death. This finding strongly suggests the need for further improvement in the treatment of cervical nodes, and also highlights the importance of cervical neck dissection. The majority of recurrences occur within the first and second year of treatment.[24,32] In our series, if the patients had not relapsed by 30 months, then the risk of subsequent relapse was minimal.

- **This report suggests that, in Iran, squamous cell carcinoma of the oral tongue tends to present at a locally advanced stage, with a high frequency of locoregional failure and a poor outcome**
- **Non-surgical treatment and advanced disease stage were the most important prognostic factors, and had a negative influence on survival**
- **Combined-modality therapy should be considered for the majority of such patients**
- **Public health strategies should be planned to facilitate continuing education of oral health and general medical practitioners regarding the early detection and diagnosis of this aggressive cancer**

Over the past 20 years, better locoregional control of tongue carcinoma has been achieved, together with some improvement in survival.[1] This improvement may have resulted from a combination of, firstly, elective neck dissection for the N_0 neck, and, secondly, the use of adjunctive RT for stage III and IV disease, close or involved margins, multiple nodal metastases, poor differentiation, extracapsular spread, and vascular or perineural involvement.[23,39–41]

Comparison between our results and those of previous studies is difficult, because our patients

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had more advanced disease and shorter follow-up periods. Nevertheless, our treatment results are comparable with those of previous studies in terms of response and survival rates,[8,11,12,23,26,27] and are better than those of some reported series.[19,21]

However, as the majority of oral tongue cancer cases in our study presented as locally advanced disease, we highly recommend action to enhance public awareness of oral cancer and to continue oral health professionals' education in this field, in order to increase early detection rates and to improve treatment outcome in such patients.

Conclusions

This report suggests that, in Iran, SCC of the oral tongue tends to present at a locally advanced stage, with a high frequency of locoregional failure and a poor outcome. Non-surgical treatment and advanced disease stage are the most important prognostic factors and have a negative influence on survival. Combined-modality therapy should be considered for the majority of these patients. Public health strategies should be planned in order to continue educating oral health and general medical practitioners regarding early detection and diagnosis of this aggressive neoplasm.

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Dr M Mohammadianpanah takes responsibility for the integrity of the content of the paper.
Competing interests: None declared