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ORIGINAL ARTICLE

Relapse patterns and related prognostic factors in patients with mobile tongue cancer treated with postoperative radiotherapy

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Summary

Purpose: *To retrospectively assess prognostic factors and patterns of relapse in patients with oral tongue cancer treated by adjuvant radiotherapy (RT).*

Patients and methods: *Between 1995 and 2005, 65 patients with stage II-IV oral tongue cancer were treated with postoperative adjuvant RT at our institution. The influence of multiple patient- and treatment-related factors on local and regional control, and overall survival (OS), locoregional failure-free survival (LRFFS) and cause-specific survival (CSS) were evaluated. Median patient follow-up was 74 months.*

Results: *Five-year disease-free survival (DFS), LRFFS and CSS rates were 56, 60 and 58%, respectively. During the study period 27 (41.5%) patients had locoregional failures. Seventeen of the recurrences were in the primary tumor region, 4 in the neck, 6 in both regions. Most of the local failures occurred in the first year (median 13 months, range 5-15). Gender, T stage, stage (AJCC TN stage), surgical margin, localization of tumor, and hemoglobin level had predictive value for improved local-regional control in univariate analysis. In total, 35 deaths occurred: 28 patients died of progressive disease, one patient died due to another primary tumor (esophageal cancer) and 6 patients died of other causes.*

Conclusion: *Local failure was the most important problem concerning the final outcome. High local recurrence rates and poor survival rates are important issues in the management of oral tongue cancer. Further strategies should be directed to enhancing cure rates.*

Key words: prognostic factors, radiotherapy, relapse patterns, tongue cancer

Introduction

Squamous cell carcinoma of the oral tongue is a common type of oral cancer. Management of oral tongue carcinoma is difficult and depends on the size, location and growth pattern of the primary lesion and the nodal status of the neck. External RT is widely used in mobile tongue cancer with curative or palliative intent [1-3]. In early stages of oral tongue cancer, surgery and RT are the primary treatment options with similar results. Advanced disease is best managed by combined surgery and postoperative irradiation. External RT may be combined with interstitial brachytherapy according to the tumor location, stage and surgical margin status [4]. High local and regional recurrence rates due to the biological aggressiveness of the tumor make the addition of postoperative RT mandatory. Addition of postoperative RT and its impact on therapeutic results has been evaluated in a number of retrospective series [1,3]. Postoperative RT is recommended for larger lesions, close or positive margins, presence of perineural invasion and advanced nodal disease. In the published literature, the impact of postoperative RT has been evaluated for the whole group of oral cavity cancers, but it was not detailed according to tumor site (e.g. floor of the mouth, base of the tongue, oral tongue). The trials include head and neck tumors from all sites but the biological behavior of the tumor varies according to the location. Thus, the place of adjuvant RT and the prognostic factors for mobile tongue cancers remain unclear. Tumor stage, depth of invasion, nodal status, tumor location, age, sex and surgical margins are the most important prognostic factors for oral tongue cancers [5-7]. Recently Fan et al. showed extracapsular spread to be an independent prognostic factor

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[8]. Like the other head and neck cancers, oral tongue cancers also may vary according to demographical and geographical features.

The aim of the present study was to investigate prognostic factors, treatment results and failure patterns of oral tongue cancer patients treated at our institution, and to provide new perspectives for future treatment strategies.

Patients and methods

This study was carried out under the control of the institutional ethics committee. Between 1995 and 2005, 65 consecutive patients were treated in our department for squamous cell carcinoma of mobile tongue with postoperative RT. None of the patients was known to have distant metastasis at the time of diagnosis. The extent of surgical resection was determined by the intraoperative findings with the intent being to resect the disease completely with negative surgical margins if possible. The indications for neck dissection included existence of clinically palpable lymph nodes, or radiologically suspicious lymph nodes, and tumor size greater than 2 cm. Contralateral neck dissection was performed when ipsilateral cervical nodal metastasis was found or when the tumor extended across the midline. Surgical resection consisted of partial glossectomy alone in 4 patients. Fifty-two patients underwent unilateral and 9 patients bilateral neck dissection in addition to partial glossectomy. Most of the patients were initially treated with standard 3-field RT technique, covering the surgical bed and the areas at risk for nodal disease. The shrinking field technique was used. The first field reduction excluded the spinal cord after 46 Gy. The posterior cervical lymphatic fields were then treated with electron fields overlying the spinal cord with energy selection according to the depth at risk and spinal cord. The lower anterior neck field was shielded in the midline to spare the spinal cord, thyroid and laryngeal tissues. Median radiation dose was 6000 cGy (range 5400-6600). All patients received postoperative RT consisting of a conventional fractionated dose of 2 Gy, 1 fraction per day, 5 days per week. Median time to RT after surgery was 4 weeks (range 3-8). Patients also had to have a Karnovsky performance status greater than 70 before RT, no distant metastasis, and one or more of the following risk factors reported in the histopathological examination of the surgical specimen: extension of primary disease to the floor of the mouth, buccal mucosa, and bone; positive or close margins of resection (defined as tumor within 5 mm from the resection edge); invasion of lymphatics and/or blood vessels; perineural invasion; more than one metastatic lymph node (pN2b-3); single metastatic node larger than 3 cm in diameter (pN2a); extracapsular extension of at least one node.

Follow-up visits were performed at one month post-RT, every 2 to 3 months for the first 2 years and every 6 months thereafter. Physical examination and radiologic evaluation were performed at each follow-up. In patients with suspicious findings on physical examination, biopsies were obtained to confirm or exclude recurrence. If biopsies were positive, salvage treatment including surgery, RT or chemotherapy were performed if the patient was in good condition.

We started using of radiochemotherapy in the adjuvant setting in high risk patients after 2002. Chemotherapy with weekly cisplatin (40 mg/m^2) during RT was administered to patients with positive surgical margins and/or nodal involvement who had adequate hematologic, hepatic and kidney functions and performance status. After 2002, 20% of the patients (4 of 20) were treated with radiochemotherapy.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 10.0, SPSS Inc., Chicago, Illinois, USA). OS was calculated from the date of diagnosis to the date of the last follow-up or death from any cause, and CSS from the date of diagnosis to the date of the last follow-up or death from tongue cancer. Patients dead of causes not related to tongue cancer were censored on the date of death. LRFFS and DFS were calculated from the date of diagnosis to the date of local or regional failure or distant metastasis. Survival curves were constructed using the Kaplan and Meier method and univariate analysis was performed using the log-rank test. A p-value of 0.05 or less was considered statistically significant.

Results

Patients

Median age was 54 years (range 26-79), 40 (61.5%) patients were men and 25 (38.5%) women. The tumor originated from the lateral side in 57 (87%) patients, from the dorsal surface in 5 (8%) patients, and was unspecified or unclear in the remaining 3 (5%) patients. Histopathological diagnosis was squamous cell carcinoma in all patients. The median tumor size was 4 cm (range 1.2–6). Twenty-five (39%) patients had microscopically positive resection margins, and 40 (61%) had negative margins. Pathological T stages were as follows: T1 20%, T2 52%, T3 14%, and T4 14%. Clinical characteristics are summarized in Table 1.

Table 1. Patient characteristics

Characteristic	*n (%)*
Age, years	
median (range)	54 (26-79)
Gender	
Male	40 (61.5)
Female	25 (38.5)
Type of surgery	
Primary tumor resection	4 (6.2)
Primary tumor resection and unilateral neck dissection	52 (80)
Primary tumor resection and bilateral neck dissection	9 (13.8)
AJCC 1997 T stage	
T1	13 (20)
T2	34 (52.3)
T3	9 (13.8)
T4	9 (13.8)
AJCC 1997 N stage	
N0	26 (40)
N1	24 (37)
N2	12 (18.2)
N3	1 (1.5)
NX	2 (3)
AJCC stage	
2	18 (28)
3	28 (43)
4	17 (26)
X	2 (3)
Margin status	
Negative	40 (61.5)
Positive	25 (38.5)

Table 2. Patterns of relapse

Relapse site	*n (%)*
No relapse	36 (55)
Primary tumor	17 (26)
Neck	4 (6)
Neck+primary	4 (6)
Distant failure	2 (3)
Distant+primary+neck	2 (3)
Total	65 (100)

Table 3. Causes of death

	n (%)
Progressive disease	28 (40.9)
Other causes	
Myocardial infarction	1 (1.5)
Acute abdomen	1 (1.5)
Esophageal cancer	1 (1.5)
Pneumonia	2 (3)
Other*	2 (3)
Total	35 (54.4)

*unspecified

Survival and patterns of failure

Median follow-up time was 74 months (range 26-144) for surviving patients. Five-year DFS, LRFFS and CSS (Figure 1) rates were 56, 60 and 58%, respectively. During the study period 27 (41.5%) patients had locoregional failures. Seventeen of the recurrences were in the primary tumor region, 4 of them were in the neck, 6 of them were in both regions. Nineteen of 27 (71.4%) locoregional failures occurred in the first year (median 13 months, range 5-15). Distant failures were detected in 4 (6.1%) patients during follow-up (lung metastasis in 2 patients, bone metastasis in 2 patients). Relapse patterns are shown in Table 2. A total of 35 deaths had occurred: 28 patients died of progressive disease, one patient died due to another primary tumor (esophageal cancer) and 6 patients died of other causes. Causes of deaths are shown in Table 3. Second primary cancers were detected in 3 (5%) patients during follow-up (esophageal, prostate and lung cancer).

Prognostic factors

A significantly higher 5-year CSS rate was observed among patients with tumors located in the lateral side of the tongue compared to those with dorsally located tumors (72 vs. 27%, $p < 0.01$; Figure 2), and in those with hemoglobin levels greater than 12 g/dl compared to those with lower hemoglobin levels (71 vs. 32%, $p < 0.01$). Surgical margin status ($p=0.01$), stage of disease ($p=0.01$; Figure 3) and T stage ($p=0.00$) had also adverse impact on CSS. According to univariate analysis, prognostic factors influencing LRFFS were surgical margin status ($p < 0.01$), tumor localization ($p < 0.01$), T stage ($p < 0.01$), TN stage ($p < 0.01$), initial hemoglobin level ($p < 0.01$) and gender ($p=0.04$).

Detailed results of the univariate analysis are shown in Table 4.

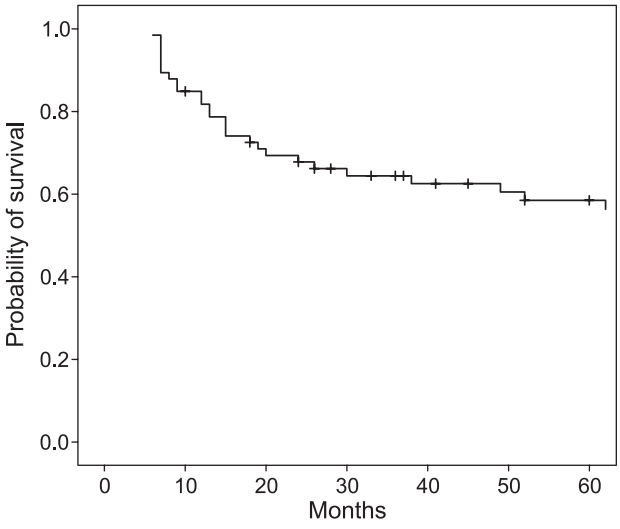

Figure 1. Overall cause-specific survival.

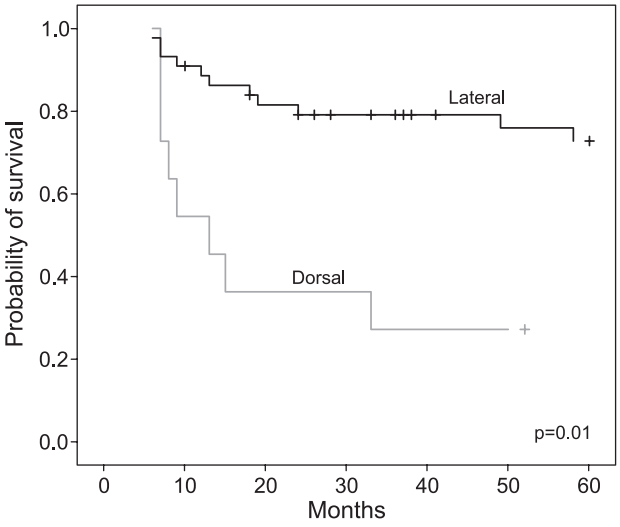

Figure 2. Importance of localization on cause-specific survival.

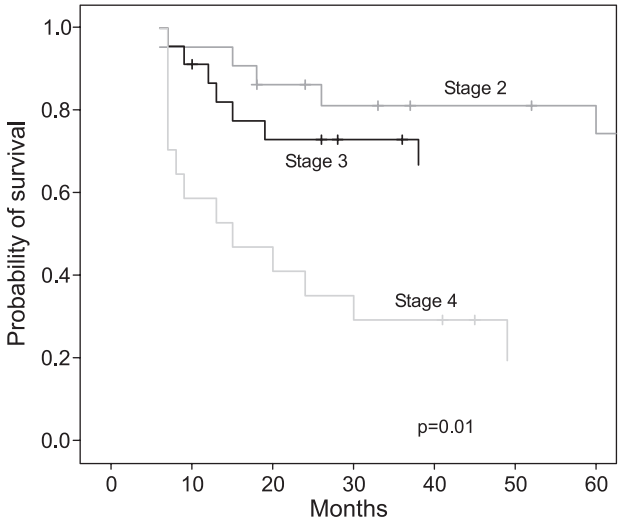

Figure 3. Importance of stage on cause-specific survival.

Discussion

Oral tongue cancer is a common type of oral cancer. The treatment of oral tongue cancer firstly aims to cure the cancer itself, and secondly to preserve anatomy and to minimize the therapeutic sequelae. Traditionally, patients with mobile tongue cancer have been treated with surgical resection and, when indicated, postoperative adjuvant RT. The purpose of prescribing postoperative RT is to reduce the risk of locoregional

Table 4. Univariate analysis of prognostic factors

	5-year cause specific survival			*5-year locoregional failure free survival*		
Factor	*Patients, n*	*%*	*p-value*	*Patients, n*	*%*	*p-value*
Age (years)						
<40	4/5	40		4/5	40	
≥40	24/60	59	0.33	23/60	62	0.08
Gender						
Male	15/40	66		14/40	68	
Female	13/25	44	0.09	13/25	46	0.04
Hb level (g/dl)						
< 12	14/20	32		14/20	33	
> 12	13/44	71	0.00	12/44	74	0.00
T stage						
T1	5/13	69		5/13	61	
T2	11/34	66		10/34	74	
T3	3/9	66		3/9	66	
T4	9/9	0	0.00	9/9	0	0.00
N stage						
N0	11/26	65		9/26	69	
N1	8/24	63		8/24	65	
N2-3	8/13	35	0.43	9/13	36	0.27
TN stage						
II	6/18	77		4/18	83	
III	8/28	69		8/28	70	
IV	13/17	19	0.00	14/17	22	0.00
Localization						
Lateral	13/44	72		12/44	75	
Dorsal surface	8/11	27	0.00	8/11	27	0.00
Surgical margin						
Negative	13/40	70		11/40	73	
Positive	15/25	37	0.01	16/25	38	0.00

Table 5. Patterns of relapse in the literature

First author [reference]	*Number of patients*	*Stage*	*Treatment*	*Locoregional relapse %*	*Distant metastases %*
Fan [8]	201	III-IV	OP followed by RT±CT	50.2	13.90
Sessions [10]	332	All stages	OP±RT or RT	41.2	5.70
Greenberg [11]	266	All stages	OP±RT	32.5	7.00
Al-Rajhi [7]	85	T1-2 N0	OP±RT	39.0	0.00
Current study	65	II-III-IV	OP followed by RT±CT	41.5	6.06

OP: operation, RT: radiotherapy, CT: chemotherapy

recurrence and improve OS. This study questioned the prognostic factors, relapse patterns and the impact of postoperative RT on oral tongue cancer.

Due to the high locoregional relapse rates oral tongue cancer prognosis is poor. Locoregional relapse rates were between 30-50% in the published literature which is similar to the findings of the current study (Table 5). The main cause of death in tongue cancer is locoregional recurrence. As shown in Table 5, distant metastases rates were not so high despite high locoregional relapse rates. This biological behavior of oral tongue cancer calls for finding solutions in order to improve locoregional control rates. In regard to improving locoregional control rates, RT dose escalations, radiosensitizers, more effective chemotherapy agents and targeted therapies might be evaluated.

Postoperative recurrence of tongue cancer is not uncommon, mostly occurring within 1 or 2 years [8,9]. The majority of our recurrences (71.4%) occurred within the first year, indicating the need for regular follow-up at short intervals during that period. The relevant literature shows that most of the recurrences developed in 2 years [8,10,11].

In our study, median age was 55 years and 80% of the patients were above 40 years of age at the time of diagnosis. In the last few years, the incidence of the onset of tongue cancer in young individuals has been increasing [12,13]. Likewise, the percentage of patients below 40 years of age at the time of diagnosis rose from 2 to 6% during the last 5 years in our series. Younger age has been defined as an important prognostic factor in oral tongue cancer by some authors [13,14]. However, other authors did not confirm differences in relapse rates, CSS and OS rates between younger and older patients [15]. Age was not found to be a significant prognostic factor in our study.

Hemoglobin (Hb) level has been defined as an important prognostic factor for head and neck cancers. It is known that oxygenation is related to the therapeutic effects of RT. In the published literature, especially in head and neck cancers, the importance of Hb level on the RT outcome has been defined [16-18]. In the present study, initial Hb level had a significant impact on LRFFS and OS. Based on these data, improving anemia before and during RT may improve the outcomes of RT. But there are lot of controversies in the management of anemia in patients with cancer [19].

In oral squamous cell carcinomas, surgery is the mainstay of treatment. The status of the surgical margins is known as another important prognostic factor for these cancers. Positive surgical margins with tumor cells within the margin, not only result in a high risk of local recurrence [10,20-22], but also have a negative effect on survival [21]. This was also the case in the study of Al-Rajhi et al., where the tumor resection margin was an important prognostic determinant for recurrence with statistically significant higher recurrence rate for distance from the resection margins smaller than 5 mm as compared to those greater than 5 mm [7]. This led to disease-specific survival (DSS) advantage for patients with distance from the resection margin greater than 5 mm [7]. The importance of tumor-free margins in the outcome of cancer surgery is well known [7,20, 22-24]. Obtaining tumor-free surgical margin is of paramount importance in patients with carcinoma of the oral cavity. Although the risk of recurrence is not completely eliminated even with pathological evidence of complete excision it is still desirable to achieve the same, as the prognosis with residual microscopic disease is much worse both in terms of higher recurrence rates and shorter overall survival [7,13]. In our study, the status of the surgical margin has an impact on either locoregional control and DSS.

Generally, for tongue cancer, the location of the tumor is defined as anterior or posterior portion of the tongue. In our series we only included patients with anterior 2/3-located mobile tongue cancers. We have also evaluated the outcomes of the lesions by localization. Originally in this study, the location of the tumor, whether laterally or centrally, affected local control and survival. Localization of the tumor may impact the outcome in this tumor group of patients.

Previous investigations have also indicated that survival rates for oropharyngeal carcinoma are lower in males than in females. Chen et al. showed significantly higher 5-year survival rates for females compared with males [25]. After adjustment for clinical factors, males had a risk of 1.54 and 1.44 times higher than females for death of oropharyngeal carcinoma and all-cause death, respectively. The authors concluded that this might be related with the use of betel quid being much more common among males than among females [25]. In this present study DSS was worse in females.

Stage is the most important factor affecting prognosis in mobile tongue cancers as in other types of head and neck cancers [10]. In our study T stage and stage were determined as the most important factors on survival. Screening and early detection protocols will provide better treatment results than minor outcome improvements in locally advanced lesions.

In conclusion, head and neck cancer is an important health problem in the developing countries such as Turkey. Most of the cases are in advanced stage at diagnosis and most of them need adjuvant RT after surgery. High local recurrence rates and poor survival are important issues in the management of oral tongue cancers. Further strategies should be directed at the enhancement of cure rates.

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