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Treatment Results and Prognostic Factors for Advanced Oral Tongue Cancer

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Abstract

Objective: The aim of this study was to retrospectively analyze advanced oral tongue cancer to determine tumor characteristics, treatment patterns and any other prognostic factors that may influence the survival of patients with the disease.

Patients and Methods: The records of 70 patients with stage III to IVA oral tongue cancer (TNM system) seen between December 1999 and December 2005 at one institution were reviewed. One group of patients had been treated with surgery plus adjuvant therapy (Group A), while the other group of patients had undergone definitive concurrent chemoradiotherapy (CCRT) without surgery (Group B). The chemotherapy protocol consisted of two monthly courses of cisplatin and fluorouracil as a concurrent regimen followed by another 2-month course as an adjuvant systemic regimen. The regimen was cisplatin (20 mg/m^2/d) on day 1 and fluorouracil (1000 mg/m^2/d) on days 1 to 5.

Results: The 3-year overall survival, disease-free survival, local recurrence and distant metastasis rates in Groups A/B were 76%/18%, 75%/22%, 14%/33% and 13%/27%, respectively. Significant differences were observed in the overall and disease-free survival in the two groups. Multivariate analysis for predictors of overall survival across all patients, treatment types and local recurrence were significant. Furthermore, multivariate analysis to discover predictors of overall survival showed that a positive pathological finding for the margin or a margin < 1 mm in size, and extracapsular spread were significant.

Conclusion: Among the patients who were not candidates for surgery, the effect of definitive CCRT was not satisfactory. A higher dose of radiation was found to result in significantly better survival and local control in Group A. However, in Group B, while local control was better with higher doses, survival did not differ significantly. The effectiveness of radiotherapy might be increased with the use of brachytherapy, the use of more effective drugs such as a radiosensitizer or other recently introduced chemotherapy drugs. [*Tzu Chi Med J* 2009;21(1):52–58]

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1. Introduction

Oral tongue cancer is one of the more common intraoral malignancies. The spread of a tumor may occur by local invasion, through lymphatic involvement to regional lymph nodes or via the bloodstream to distant sites. Surgical excision has been the primary treatment for early disease. However, the tumor may be deeply infiltrating or have an ill-defined edge, which makes it difficult to decide where the resection margin should be placed. Furthermore, lymphatic metastases from oral tongue cancer are frequently seen and occur in between 15% and 80% of cases dependent on the stage [1,2]. Because of the difficulties of surgical excision and the high incidence of neck failure, most clinicians would agree that a multidisciplinary approach should produce optimal curative results and provide quality of life for a patient with advanced oral tongue cancer. Surgery with postoperative adjuvant radiotherapy is the standard treatment for advanced oral tongue cancer and this approach has a 5-year survival rate that varies between 30% and 50% [2–4]. The value of adding chemotherapy to definitive surgery and/or radiation when treating head and neck cancer has been extensively evaluated over the past 20 years. However, a survival advantage has been difficult to demonstrate, particularly after neoadjuvant or sequential treatment. More recently, two large-scale randomized trials by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research Treatment of Cancer (EORTC) have demonstrated the benefits of adjuvant concurrent chemoradiotherapy (CCRT) after radical surgery in high-risk head-and-neck cancer patients [5,6]; this infers that adjuvant CCRT should be used when there is extracapsular spread (ECS) and/or an unclear margin [7]. However, these two trials included head-and-neck tumors from all sites, which may have blurred the differences in survival at different sites. In addition, these two trials used different inclusion criteria and had no subgroup analyses. The aim of this retrospective case analysis of advanced oral tongue cancers was to determine tumor characteristics, treatment patterns or any other prognostic factors that influence disease survival.

2. Patients and methods

The records of 86 patients with stage III to IVA oral tongue cancer (TNM system) [8] seen between December 1999 and December 2005 in one institution were reviewed. Of these, 16 patients were excluded from the analysis because they were either treated with surgery alone (10 patients), were lost to follow-up (4 patients) or had a synchronous second primary (2 patients); all were diagnosed histologically with oral tongue cancer by pathologists and none had a prior cancer. All patients were informed about their disease treatment, including potential benefits and possible side effects. One group of patients was treated with surgery plus adjuvant therapy (Group A), while the other group of patients had definitive CCRT without surgery (Group B); the treatment regimen of the patients in the latter group was chosen for medical reasons (4 suffered from chronic liver disease, 2 suffered from chronic lung disease, 2 had heart disease and the remainder refused surgery (14 patients)). All patients were treated by a multidisciplinary team group including a head and neck surgery team, radiation oncologists, medical oncologists and dieticians.

2.1. Treatment

Surgery consisted of partial glossectomy, hemiglossectomy or subtotal glossectomy with unilateral or bilateral radical neck dissection. Pathology reports were reviewed for evidence of size, grade, type, surgical margins, lymph nodes involved, perineural invasion, vascular permeation, lymphatic permeation and ECS. Subclavian venous-access catheters were placed for nutritional support and administration of chemotherapy. Adjuvant treatment was started 4–6 weeks after surgery.

Radiation therapy was delivered using the intensity-modulated radiation technique (IMRT) via an inverse planning system (PLATO, Nucleotron Inc., Veenendaal, The Netherlands). The radiation field encompassed the primary tumor bed and neck lymph nodes. Treatment was delivered with a 6-MV multileaf collimator system (Precise, Elekta, Crawley, UK) using a step-and-shoot method with seven coplanar beams. Gross tumor volume (GTV) was defined as the gross disease as shown by imaging with the clinical target volume (CTV) defined as GTV plus margin of 3–10 mm, depending on the proximity of critical structures. The critical normal structures used for optimization included the brainstem, spinal cord, parotid glands, optic nerves, chiasm, lenses, eyeballs, temporal lobes, temporomandibular joints, neck muscle, mastoid air cells and oral mucosa. Verification of the treatment plan and dose was carried out before treatment; a weekly machine-check film involving electronic portal imaging was performed to ensure set-up accuracy during treatment. The prescribed doses delivered by external beam radiotherapy were: 70–72 Gy to the GTV and positive neck nodes; 60–66 Gy to the CTV together with 50–60 Gy to clinically negative neck. For the adjuvant setting, these were 60–72 Gy to GTV and positive neck nodes, 50–60 Gy to CTV and 50 Gy to pathologically negative neck. Doses were delivered at 1.8 Gy/day for 5 consecutive days by a linear accelerator with the patients lying supine wearing a mask. GTVs received a higher dose per fraction, which ranged from 1.8–2.16 Gy per day.

The dose delivered to the neck nodes was a dose per fraction ranging from 1.7–2.0 Gy per day. The spinal cord dose was limited to 45 Gy.

Chemotherapy was given as a definitive or adjuvant setting and is a regime routinely used in advanced oral cancer patients. The adjuvant setting was delivered 4–6 weeks after surgery. Patients received radiotherapy alone if they refused or were unfit for chemotherapy. The chemotherapy protocol consisted of two monthly courses of cisplatin and fluorouracil (5-FU) as a concurrent regimen followed by another 2-month course as an adjuvant systemic regimen. The regimen consisted of cisplatin (20 mg/m^2/d) on day 1 and 5-FU (1000 mg/m^2/d) on days 1–5. All consenting patients were eligible for chemotherapy if they met the following criteria: ECOG performance status ≤2, serum creatinine level <1.5 mg/dL, absolute neutrophil count >2000 cells/μL, platelet count >10,000/μL. Toxicity was evaluated using the common toxicity criteria of the National Cancer Institute [9]. Cisplatin and 5-FU were withheld if the absolute neutrophil count dropped below 1500 cells/μL or the platelet count dropped below 75,000 cells/μL. For grades 3 and 4 renal toxicity, cisplatin was withheld until the patient's creatinine level was <1.5 mg/dL. Cisplatin and 5-FU were administered at 70% of the initial dose thereafter. Radiotherapy was withheld only if the neutrophil count dropped below 1000 cells/μL or the platelet count dropped below 50,000 cells/μL.

2.2. *Patient follow-up and patterns of failure*

Patients were assessed at 3, 6 and 12 months and then every 6–12 months for 5 years, or more often if clinically indicated. Survival was calculated from the date of diagnosis to the most recent follow-up or date of recurrence or death. Treatment responses to CCRT were defined according to the response evaluation criteria in solid tumors (RECIST) and classified as complete response, partial response, progressive disease or stable disease [10]. Briefly, complete response was defined as an absence of carcinoma on biopsy or the disappearance of radiographic evidence of the disease. Partial response was defined as a reduction of at least 30% in the size of the tumor as assessed by radiography. Progressive disease was defined increase in the size of the tumor by at least 20%. Stable disease was defined as neither sufficient shrinkage to qualify for a partial response nor a sufficient increase to qualify for progressive disease. The pattern of failure for both groups was defined according to the first site of failure. Local failure was defined as recurrence of the primary tumor or metastasis to the regional lymph nodes. Distant failure was defined as metastasis to any site beyond the primary tumor and to the regional lymph nodes. After recurrence or metastasis, patients were given salvage therapy as determined by their physicians.

2.3. *Statistical analysis*

The baseline characteristics of the two groups were compared using a *t* test for the continuous variables and a χ^2 test for the categorical variables. The Kaplan-Meier method was used for the survival analysis [11]. The difference between the survival curves was determined using the log-rank test [12]. Multivariate analysis to identify significant prognostic factors was done using Cox's regression model. Covariates were selected in a forward fashion using their maximum likelihood ratio. A matched-pair analysis was used to compare radiotherapy doses. The matching variables were performance, T status, N status and stage. SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis of all data. A statistical significant difference was defined by a *p* value of less than 0.05.

3. Results

Seventy patients were evaluated. There were 48 were in Group A and 22 were in Group B. There was no significant difference in the T and N staging between the two groups (Table 1). The most frequent symptom at diagnosis, present in over 90% of individuals, was an ulcer, an exophytic mass or a neck mass. Other common symptoms included bleeding, speech difficulties or pain. The patient characteristics are presented in Table 2.

3.1. *Treatment outcome*

Median patient follow-up at the commencement of the analysis was 18 months (range, 5–63 months). Among the patients in Group A, 21 patients received adjuvant radiation alone while the others received adjuvant CCRT. The patients received 3960–7020 cGy of radiation (median, 6120 cGy). Forty of the 48 patients received the full planned dose of radiation and

Table 1 — Tumor (T) and nodal (N) staging

Group A						Group B					
	T1	T2	T3	T4A			T1	T2	T3	T4A	
N0			4	16	20	N0			1	5	6
N1	1	7	4	6	18	N1	0	4	2	4	10
N2	0	2	3	5	10	N2	0	1	2	3	6
	1	9	11	27			0	5	5	12	

There was no significant difference in T and N stages between the two treatment groups.

Table 2 — Patient characteristics*

	Group A	Group B
Sex		
All	48	22
Male	41 (85)	20 (91)
Female	7 (15)	2 (9)
Age (yr)		
Median	48	51
Range	27–77	45–79
Histological differentiation		
Well	3 (7)	2 (9)
Moderate	37 (77)	16 (73)
Poor	4 (8)	2 (9)
Missing	4 (8)	2 (9)
Performance status (ECOG)		
0	21 (44)	7 (32)
1	17 (35)	10 (45)
2	10 (21)	5 (23)
AJCC 1997 stage group		
3	16 (33)	7 (32)
4	32 (67)	15 (68)

*Data presented as *n* (%). ECOG = Eastern Cooperative Oncology Group; AJCC = American Joint Committee on Cancer.

Table 3 — Site of recurrence in oral tongue cancer

Site of recurrence	Group A patients (*n*)	Group B patients (*n*)
Local	1	3
Regional	2	1
Distant	1	2
Local and regional	0	1
Local and distant	0	0
Regional and distant	1	1
All three sites	0	1

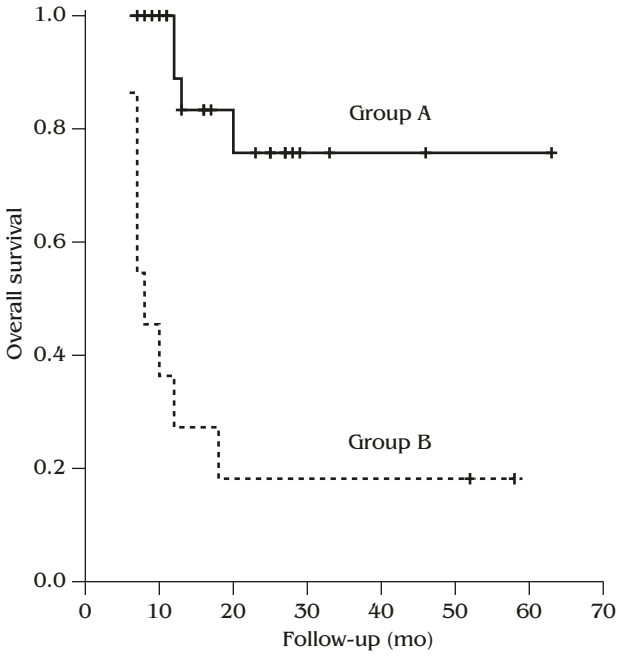

Fig. 1 — Kaplan-Meier survival curves for overall survival for two different treatment modalities.

eight had incomplete radiation because of treatment-induced complications. Thirteen of the 27 patients who received adjuvant CCRT completed the full course of monthly chemotherapy; the others received less than four cycles at a reduced dose. The median survival for Group A was 23 months (range, 7–63 months). The estimated 3-year overall survival was 76%. The 3-year disease-free survival, local recurrence and distant metastasis rates were 75%, 14% and 13%, respectively. The 22 patients in Group B received 5220–7200 cGy of radiation (median, 7020 cGy). Of these 22 patients, 11 completed the full course of monthly chemotherapy, while the others received fewer than four cycles at a reduced dose. The full planned dose of radiation was given to 16 patients in the CCRT group and six patients did not complete course because of treatment-induced complications. Of the 16 patients who completed definitive CCRT, 10 achieved a complete response; three a partial response; two showed stable disease and one showed progressive disease when assessed at the 3-month follow-up. Eight patients developed recurrence and/or metastasis after follow-up (Table 3). The median survival was 18 months (range, 6–58 months), with an estimated 3-year overall survival of 18%. The 3-year disease-free survival, local recurrence and distant metastasis rate were 22%, 33% and 27%, respectively. In addition, if we excluded the suboptimal dose patients from analysis, the 3-year overall, disease-free survival, local recurrence and distant metastasis rates were 38%, 42%, 26% and 22%, respectively.

Significant differences were observed in the overall and disease-free survival between the two groups ($p<0.05$; Fig. 1). Marginal significance was also observed when local control ($p=0.07$) and distant metastasis-free rate ($p=0.06$) were assessed in the two groups. Furthermore, significant differences were also observed in the overall and disease-free survival between the two groups ($p<0.05$) if we excluded the suboptimal dose Group B patients from the analysis. Using multivariate analysis for the predictors of overall survival with all patients, only treatment type and local recurrence were significant (Table 4). However, multivariate analysis for the predictors of overall survival showed that a positive pathological examination for the margin, a margin <1 mm and ECS were significant in Group A (Table 5).

3.2. Radiotherapy dose

There was no significant difference in performance, T status, N status and stage between the two groups.

Table 4 — Factors associated with overall survival

	3-yr survival rate (%)	Univariate analysis (*p*)	Multivariate analysis (*p*)
Treatment type			
Group A	76	<0.001*	0.009*
Group B	18		HR=0.11 (95% CI, 0.02–0.57)
Locoregional recurrence		<0.001*	<0.001*
Present	10		HR=9.88 (95% CI, 3.2–26.8)
Absent	82		
Age (yr)			
<45	92	0.02*	Not significant
≥45	50		
Tumor size			
<4 cm	80	0.02*	Not significant
≥4 cm	44		
Stage			
III	66	0.02*	Not significant
IV	31		
T stage			
T3	76	0.05*	Not significant
T4	62		
Nodal status			
Positive	52	0.04*	Not significant
Negative	80		

*Statistically significant difference. HR = hazard ratio; CI = confidence interval.

Table 5 — Multivariate regression analysis of histological findings

Variable	*p*
Positive or margin <1 mm	0.032
Extracapsular spread	0.046
Perineural invasion	0.164
Two or more lymph nodes involved	0.126
Vascular permeation	0.586
Grade	0.968
Size	0.984

Nonetheless, a higher dose of radiation resulted in significantly better survival and local control in Group A ($p<0.05$), with a total dose of >65 Gy yielding both better local control at 3 years (95% *vs.* 67%; $p<0.05$) and better 3-year survival (88% *vs.* 61%; $p<0.05$) than treatment with <65 Gy. In Group B, 3-year local control in patients receiving >70 Gy was better than in those receiving <70 Gy (50% *vs.* 16%) but survival did not differ significantly.

4. Discussion

In the present study, locoregional recurrence and treatment with definitive CCRT were found to be adverse prognostic factors in the multivariate analysis. It is generally considered that surgery and radiotherapy are equivalent when treating early disease. However, with advanced deeply infiltrative lesions the best management is considered to be a primary surgical approach with postoperative therapy. When radiotherapy alone was used for T1 and T2 tumors, 5-year survival rates of 61% and 74%, respectively, could be achieved, but the results for larger tumors were poor [13]. In addition, Kramer et al reported that the overall survival was significantly better in stage II patients who received combined therapy compared with radiotherapy alone (73% *vs.* 30%) [14]. In another study by Aksu et al, the 5-year overall survival, the relapse-free survival and the disease-specific survival rates were all significantly better in the surgery plus postoperative radiotherapy group than in the radiotherapy alone group, and this was true for all stage patients [4]. Even with combined chemotherapy and definitive radiation, the estimated 5-year survival rates range from 50% to 70% for stages I and II and from 15% to 30% for stages III and IV [14,15]. In this study, when we evaluated the whole group or excluded the suboptimal dose patients from analysis, the overall survival and disease-free survival were all significantly better in Group A than in Group B. In advanced patients who are not candidates for surgery, the effect of definitive CCRT was not satisfactory.

Surgery with postoperative adjuvant radiotherapy is the standard treatment for patients with advanced oral tongue cancer, and the 5-year survival reportedly varies between 30% and 50% [2–4]. From recent studies, adjuvant CCRT is indicated in ECS and/or when there are unclear margins [5–7]. With surgery, an adequate margin would seem to be crucial to local control because of the high rate of occult disease (41%). Local recurrence was observed in 15% of patients

with close margins (< 1 cm) and in 9% of patients with adequate margins (> 1 cm) [16]. In another study of oral tongue cancer treated with surgery alone, it was found that a distance of > 5 mm from the resection margin was a significant prognostic factor for both local control and survival [17]. ECS is also another important significant factor. The extent of ECS on histopathological review of the involved lymph nodes was measured from the capsular margin to the farthest perinodal extension in mm. As the ECS increased, the recurrence rate increased in oral tongue cancer from 20.4% to 83.8%, respectively [18]. ECS was also significantly associated with higher rates of locoregional recurrence, distant metastasis and decreased survival in oral tongue cancer patients. The 5-year disease-specific and overall survival rates for pN0 patients were 88% and 75%; for pN+/ECS– patients were 65% and 50%; and for pN+/ECS+ patients were 48% and 30%, respectively. The patterns of failure for the pN0, pN+/ECS– and, pN+/ECS+ groups showed overall recurrence rates of 19.8%, 34.2% and 51.1%, respectively. The regional failure rates were 11.5%, 19.2% and 28.9%, respectively. Furthermore, the distant metastases rates were 3.3%, 8.2% and 24.4%, respectively [19]. However, adjuvant CCRT, as opposed to adjuvant radiotherapy alone, appeared to benefit patients with ECS [2]. The present study produced similar results and the significant factors affecting survival in Group A were positive pathological finding for the margin or a margin < 1 mm and extracapsular spread.

Different radiation doses have also been shown to be associated with differences in tumor control. One randomized trial study reported a dose of < 57.6 Gy was associated with a higher risk of recurrence. Doses > 63 Gy did benefit patients with ECS [20]. Furthermore, a close surgical margin requires high doses, such as 70 Gy, because of the difficulty in eradicating the tumor [21]. In our study, a higher dose of radiation in Group A resulted in significantly better survival, together with better local control. This differed from Group B in which a higher dose was only associated with better local control.

Toxicity is often a concern in combined chemotherapy, and a recent study showed a 74% incidence of moderate-to-severe acute toxicity when using a combined modality treatment [22]; another study found that CCRT-treated patients had a higher incidence of acute grade 3 and acute grade 4 toxicity compared with those treated with radiation alone (71% *vs.* 39%) [23]. In the present study, nearly half of our patients had severe toxicity during therapy that required treatment modification. More effective and safer drugs such as radiosensitizers or modern chemotherapy drugs should be considered when carrying out a multimodal treatment strategy.

Because this is a retrospective study, a number of factors in terms of patients and tumor characteristics could not be controlled and may have biased the results. However, when we consider the advanced patients who were not candidates for surgery, the effect of definitive CCRT was not satisfactory. Another important finding was that a higher dose of radiation resulted in a significantly better survival and improved local control. Thus, it may be possible to increase the effectiveness of radiotherapy by the use of brachytherapy or more effective drugs.

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