Impact of Clinical and Histo-Pathological Prognostic Factors on T1-2N0-1 Oral Tongue Carcinoma

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Abstract To determine predictive factors which affect local and regional recurrence of T1-2N0-1M0 oral tongue carcinoma (OTC). Records of 42 patients with T1-2N0-1 M0 OTC were reviewed. The clinical characteristics, histo-pathological data, disease recurrence and survival rate were analyzed. Descriptive statistics and Kaplan–Meier survival analysis were used. The median follow up was 38 months. The 2-year overall survival and disease-free survival rates were 85.7 and 55.6 % respectively. At the 2 year analysis, there were surgical margin <5 mm (p value = 0.01), tumor thickness >7 mm (p value = 0.03), perivascular and perilymphatic invasion (p value = 0.01) affected on local recurrence and perivascular and perilymphatic invasion were also predictors for regional recurrence (p value = 0.04). The surgical margin status, tumor thickness, perivascular and perilymphatic invasion represented significant predictive factors for local recurrent OTC. Postoperative adjuvant therapy should be considered in these groups.

Keywords Tongue carcinoma · Early stage · Clinical prognostic factor · Histo-pathological prognostic factor

Introduction

Oral tongue carcinoma (OTC) is one of the most common sites of cancer in the head and neck area [1, 2]. A combined modality of either surgery with postoperative radiotherapy or chemoradiotherapy is well documented in the treatment of advanced head and neck cancer and a single modality of either surgery or radiotherapy is usually recommended in the early-stage of the disease [3, 4]. Transoral surgical resection is the preferred treatment in T1-2 OTC but the management of clinically N0 neck remains controversial between elective ipsilateral selective neck dissection and observation [3, 4]. In N1 disease, comprehensive neck dissection is indicated and post-operative adjuvant therapy is not required if pathological staging remains N1 without extracapsular extension [4–6]. There are reports of low overall and disease-specific survival rate compared with an early stage of other subsites of oral cavity cancer and also late-stage oropharyngeal cancer [1, 2]. The cause of poor survival is related to locoregional recurrence. Adjuvant radiotherapy with or without chemotherapy has been used to improve the outcome in “high risk” squamous cell carcinoma of the head and neck [1, 7]. The frequently identified high-risk pathologic features are close or positive surgical margins and extracapsular nodal extension which are usually not found in early-stage OTC [5, 6]. Other pathological as well as clinical risk factors have been reported but there is still uncertainty [3, 8–10].

The objective was to determine a specific group of patients with T1-2N0-1M0 OTC who would benefit from adjuvant therapy after having surgical resection with intent to cure. The specific indicators other than histo-pathological data are clinical features which will be achieved before surgery and the surgeon can establish an appropriate treatment plan and pre-treatment counseling to gain the

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optimal results and decrease side effects of unnecessary additional treatment. The other objective was to assess the result of elective treatment versus observation in N0 neck.

Material and Method

Clinical records of patients with oral tongue squamous cell carcinoma who underwent surgical treatment at the Department of Otolaryngology, Chiang Mai University Hospital between January 2002 and December 2009 were reviewed. All patients had previously untreated T1-2 N0-1 M0 disease according to TNM staging of AJCC cancer staging manual, 6th ed. Patients who had synchronous or metachronous second primary cancers were excluded.

The patients were treated with surgical resection (partial glossectomy/hemiglossectomy) for the primary tumor and elective neck dissection or observation for N0 and modified radical neck dissection for N1 disease. Contralateral supraomohyoid neck dissection was done for a primary tumor which closed or crossed the midline. Tumor thickness was assessed by palpation preoperatively and if the thickness could be felt between fingers, prophylactic neck dissection was planned. In clinical N0 neck if intraoperative frozen section for suspected lymph node was reported as a positive result, modified radical neck dissection was indicated. Postoperative radiotherapy would be assigned for a pathologic report of closed or positive surgical margin (≤ 5 mm), extracapsular spreading of lymph node, multiple lymph node metastasis (≥ 2 nodes) and multiple level of lymph node metastasis (≥ 2 levels). After the year 2007, chemoradiotherapy has been applied when there were closed or positive surgical margin and/or extracapsular spread (ECS).

All of following clinical data and histo-pathological data were recorded: gender, age, smoking, alcohol drinking, site of primary lesion (lateral side/dorsum/ventral/tip/midline), gross lesion character (ulceroinfiltrative-infiltrative/ulcerative/exophytic), clinical TNM staging, treatment of primary site and neck, timing of local recurrence (LR), timing of regional recurrence (RR), tumor differentiation, surgical margin status, tumor thickness, perineural invasion (PNI), perivascular invasion (PVI), perilymphatic invasion (PLI) and ECS.

All categorical variables were reported in percentage. Fisher's exact test and Chi-square test were used to compare between categorical variables and recurrent disease. LR, RR, disease-free survival (DFS) and overall survival (OS) rates were determined by a median follow-up time of 38 months. The 2-year survival was analyzed by an actuarial curve of Kaplan–Meier survival analysis. Statistic analysis was performed by using SPSS (15.0), p value of <0.05 was considered statistically significant. This study

was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, Thailand.

Result

Clinical and Histo-Pathological Characteristics

Forty-two patients were enrolled in the study. The median time of follow-up was 38 months (range, 3–114 months). There were 22 male and 20 female with a ratio of 1.1 to 1. The median age was 54 years (range, 31–75 years) and only two patients were younger than 40 years of age. The most common location and gross character of the primary lesions were the lateral tongue and infiltrative-ulceroinfiltrative lesions respectively (Table 1).

In 36 of the clinical (c) N0 patients, 16 had elective neck dissection which turned out to be nine of pathological (p) N0, four of pN1 and three of pN2. All of six cN1 patients had therapeutic neck dissection and only one patient was upstaged to pN2. The rate of occult lymph node metastasis in T1 was 40 % (2/5) and T2 was 44.5 % (5/11).

Table 1 Patient characteristics

Patient characteristics	Number of patient (%)
Gender	
Male	22 (52.4)
Female	20 (47.6)
Age (31–75 years, median age = 45 years)	
>60 years	13 (31.0)
≤ 60 years	29 (69.0)
Smoking ^a	
Yes	25 (71.4)
No	10 (28.6)
Drinking ^b	
Yes	23 (74.2)
No	8 (25.8)
Location of primary lesion	
Lateral	33 (78.6)
Others (ventral, dorsum, tip)	9 (21.4)
Gross lesion character	
Infiltrative-ulceroinfiltrative	33 (78.6)
Others (ulcerative, exophytic)	9 (21.4)
Staging classification	
T1N0	19 (45.2)
T2N0	17 (40.5)
T1N1	1 (2.4)
T2N1	5 (11.9)

^a Missing data in 7 patients

^b Missing data in 11 patients

Table 2 Treatment

	T1N0 (<i>n</i> = 19)	T2N0 (<i>n</i> = 17)	T1N1 (<i>n</i> = 1)	T2N1 (<i>n</i> = 5)
Treatment modalities				
Surgery alone	17 (89.4)	3 (17.6)	1 (100)	–
Surgery + RT/CRT	2 (10.6)	14 (82.4)	–	5 (100)
Neck dissection				
Yes	5 (26.3)	11 (64.7)	1 (100)	5 (100)
SOHND	5 (100)	9 (81.8)	–	–
MND/RND	–	1 (9.1) ^a	–	5 (100)
Bilateral ND	–	1 (9.1) ^b	1 (100) ^c	–
No	14 (73.7)	6 (35.5)	–	–

RT radiotherapy, CRT chemoradiotherapy, SOHND supraomohyoid neck dissection, MND modified radical neck dissection, RND radical neck dissection, ND neck dissection

^a Only patient with positive pathological lymph node metastasis on frozen section

^b Bilateral SOHND

^c Ipsilateral MND and contralateral SOHND

Half of the studied patients received postoperative adjuvant therapy (radiotherapy or chemoradiotherapy) (Table 2). All of the histo-pathological data of primary tumors and lymph nodes were presented in Table 3.

Predictive Factors and Locoregional Recurrence

None of clinical characteristics including: gender, age, smoking, alcohol drinking, tumor location, gross lesion character, T staging and N staging were significant for LR or RR. Histo-pathological predictors which were analyzed at 2 year, the local control rate was 64.3 % and the LR was predicted by a surgical margin <5 mm (*p* value = 0.01) (OR 0.18; 95 % CI 0.04–0.69), tumor thickness >7 mm (*p* value = 0.03) (OR 0.21; 95 % CI 0.05–0.87), PVI and PLI (*p* value = 0.01) (OR 20.8; 95 % CI 0.99–434). The regional control rate at 2 years was 54.8 % while the PVI and PLI were also predictors of RR (*p* value = 0.04) (OR 11.2; 95 % CI 0.55–231) (Table 4, 5). The median time of recurrence was 36 months (range, 1–114 months) for the primary site and 24 months (range, 1–114 months) for the neck.

Overall Survival and Disease Free Survival

There were eight patients who died during the study and they all died within the first 3 years after treatment (median time, 13 months, range, 3–36 months). Local aggressiveness of the disease was the cause of death in seven patients and only one patient died from a pulmonary embolism. The 2-year OS rate was 85.7 % and DFS rate was 55.6 %.

Table 3 Histo-pathological characters

Histo-pathological characters	Number of patient (%)
Tumor differentiation	
MD + PD	8 (19.0)
WD	34 (81.0)
Surgical margin	
Positive/close	17 (40.5)
Negative	25 (59.5)
Tumor thickness	
<4 mm	6 (15.0)
≥4–7 mm	15 (37.5)
>7 mm	19 (47.5)
PNI ^a	
Yes	13 (33.3)
No	26 (66.7)
PVI ^b	
Yes	4 (10.0)
No	36 (90.0)
PLI ^c	
Yes	4 (10.0)
No	36 (90.0)
ECS	
Yes	6 (30.0)
No	14 (70.0)

MD moderate differentiation, PD poor differentiation, WD well differentiation, PNI perineural invasion, PVI perivascular invasion, PLI perilymphatic invasion, ECS extracapsular spread

^a Missing data in three patients

^b Missing data in two patients

^c Missing data in two patients

Treatment of N0 Neck: Elective Treatment Versus Observation

In 36 N0 patients, 23 had elective treatment with either surgery (*n* = 16) or radiotherapy (*n* = 7) and 13 underwent close observation. Between elective treatment and observation, there was no statistical significance in the 2 year RR rate (*p* value = 0.12) (OR 0.33; 95 % CI 0.08–1.36), DFS rate (*p* value = 0.12) (OR 0.31; 95 % CI 0.07–1.43), and OS rate (*p* value = 0.61) (OR 1.21; 95 % CI 0.18–8.39) (Table 6).

Discussion

Although surgical resection is the preferred single treatment modality for early stage OTC, locoregional recurrence is still the most significant cause of treatment failure [1, 2]. To improve the result, radiotherapy or chemoradiotherapy is often added postoperatively [1, 7]. However,

Table 4 Clinical and histo-pathological risk factors for local and regional recurrence at 2 years

Risk factors	<i>p</i> Value	
	LR	RR
Gender: male vs female	0.46	0.52
Age: >60 years vs ≤60 years	0.47	0.45
Smoking: yes vs no	0.13	0.11
Drinking: yes vs no	0.28	0.09
Location: lateral vs others	0.16	0.37
Gross lesion: infiltrative-ulceroinfiltrative vs others	0.60	0.34
cT: T1 vs T2	0.46	0.23
cN: N0 vs N1	0.64	0.57
Tumor differentiation: MD/PD vs WD	0.09	0.07
Surgical margin: positive/close vs negative	0.01	0.85
PNI: yes vs no	0.10	0.07
PVI: yes vs no	0.01	0.04
PLI: yes vs no	0.01	0.04
ECS: yes vs no	–	0.18
Neck treatment: elective vs observation	0.45	0.12

LR local recurrence, RR regional recurrence, cT clinical T staging, cN clinical N staging, PNI perineural invasion, PVI perivascular invasion, PLI perilymphatic invasion, ECS extracapsular spread

Table 5 Relationship between different tumor thickness and local and regional recurrence at 2 years

Tumor thickness (mm)	<i>p</i> Value	
	LR	RR
≤2 vs >2	0.65	0.53
≤3 vs >3	0.65	0.38
≤4 vs >4	0.41	0.59
≤5 vs >5	0.11	0.46
≤6 vs >6	0.12	0.73
≤7 vs >7	0.03	0.99
≤8 vs >8	0.004	0.37

LR local recurrence, RR regional recurrence

toxicities of the adjuvant therapy are considerable, predictive factors in each patient should be identified and taken to evaluate risk and benefit.

The OS rate at 2 years was 85.7 % which is comparable to other study (77 %) [1], however a 2-year DFS rate was only 55.6 %. These explained the median time of 24 months for RR and 36 months for LR. Concerning about risk factors for local and regional recurrence in OTC it was found that mean and average time of recurrences were within 2 years [1, 3, 7–9, 14, 16–18] and the mean follow-up time of 3 years could be used for statistical analysis in deciding for adjuvant treatment in this particular patient group [1, 3].

Table 6 Elective neck treatment vs observation affected on regional recurrence and survival

	Elective neck treatment (ND or RT) <i>n</i> = 23 (%)	Observation <i>n</i> = 13 (%)
2-year RR	8 (34.8)	8 (61.5)
2-year OS	20 (87.0)	11 (84.6)
2-year DFS	13 (65.5)	4 (36.4)

ND neck dissection, RT radiotherapy, RR regional recurrence, OS overall survival, DFS disease-free survival

Previous studies have attempted to identify clinical risk factors of tumor recurrence such as gender, age, tobacco consumption, alcohol drinking and clinical stage [2, 5, 8, 11–13] and there were reports of gender [2], age >60 years [13], alcohol consumption [12], and T stage [2] which significantly affected recurrence or survival. All those features and also included tumor location (lateral vs ventral/dorsum/tip) and gross character of the tumor (infiltrative-ulceroinfiltrative vs ulcerative/exophytic) were investigated in the present study but disappointingly, no clinical feature was determined as a risk factor.

The prognostic significance of surgical margin for LR of head and neck cancer and oral tongue cancer has been reported [1, 14–16] and it was confirmed as a risk factor when <5 mm of margin status was encountered even though the patients had postoperative adjuvant therapy. Tumor thickness has been considered to correlate with cervical lymph node metastasis but there is no clear consensus of how to measure depth or thickness and also the decisive cut-off level for elective neck treatment. Measurement of tumor thickness by using the distance between the maximum depth of the tumor and the imaginary mucosal line by using optical micrometer as previously described in a study [17] which represent the aggressiveness of the tumor in vertical growth plane was used. From the statistic evaluation, the thickness of >7 mm is the cut point which significantly affected LR and interestingly, there was no correlation with RR. The postulation is when the tumor depth increases, the possibility of clear deep surgical margin may be affected and there is a study which has reported the status of deep surgical margins as a risk of LR [16].

The presence of PVI, PLI and PNI are identified as predictors of occult neck metastasis [16] and the clinical trial published in 2004 [14] has demonstrated benefits in the locoregional control of adjuvant therapy in patients with these histo-pathological features. The results of the present study revealed PVI and PLI have statistical significance in both LR and RR but PNI has not. ECS had no effect on RR, this may be because all patients had postoperative adjuvant therapy.

Many histo-pathologic features have been previously investigated as risk factors for occult cervical lymph node metastasis in early OTC but there is no consensus [9, 10, 18] and there is still controversy regarding the management of clinical N0 neck [19]. The PVI and PLI are identified as the factors of RR but no statistical difference in DFS or OS between elective treatment and observation groups in the present study.

Conclusion

Almost all patients died from recurrence of the primary tumor and the prognostic indicators of LR are tumor thickness (>7 mm), PVI and PLI, the patients who have these features may have benefited from postoperative radiotherapy or chemotherapy. Close/positive surgical margin status (<5 mm) still has an effect on LR although postoperative adjuvant therapy was added, these patients need to obtain clear surgical margin. There is no difference in elective neck treatment and observation, patients with PVI and PLI which may be reported preoperatively from tissue biopsy should be considered to have elective neck dissection at the time of the primary tumor resection.

Conflict of interest We have not received all of the funding sources and no conflicts of interests.

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