SCIENTIFIC PAPER

A Comparison of the Prognostic Significance of Tumor Diameter, Length, Width, Thickness, Area, Volume, and Clinicopathological Features of Oral Tongue Carcinoma

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BACKGROUND: The present study aims at evaluation of the prognostic value of tumor size including diameter, length, thickness, width, area, and volume in the prediction of nodal metastasis, local recurrence, and survival of oral tongue carcinoma. The results will have important implications for the management of patients.

METHODS: Eighty-five glossectomy specimens of oral tongue carcinoma were serially sectioned in 3 mm thickness for the tumor size evaluation with computer image analyzer.

RESULTS: Among all the tumor size parameters being evaluated, tumor thickness was the only significant factor for the prediction of local recurrence, nodal metastasis, and survival. With the use of 3 mm and 9 mm division, tumor of up to 3 mm thickness has 10% nodal metastasis, 0% local recurrence, and 100% 5-year actuarial disease-free survival; tumor thickness of more than 3 mm and up to 9 mm has 50% nodal metastasis, 11% local recurrence, and 77% 5-year actuarial disease free survival; tumor of more than 9 mm has 65% nodal metastasis, 26% local recurrence, and 60% 5-year actuarial disease-free survival.

CONCLUSIONS: Tumor thickness should be considered in the management of patients with oral tongue carcinoma. *Am J Surg.* 2000;180:139–143. © 2000 by Excerpta Medica, Inc.

The American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC) TNM staging systems are important international standards for cancer reporting, prognosis evaluation, formulation of treatment strategy, and comparison of treatment results.[1,2] Tumor size is an important TNM staging parameter in many solid cancers, and the largest tumor diameter has been used for many years in the AJCC and UICC TNM staging systems. Solid cancer is, however, a three-dimensional structure in which cancer cells spread in different planes at various rates to invade the surrounding structures. Owing to the unequal rate of cancer spread in different planes and the presence of tumor necrosis, tumor will never conform to a perfect spherical shape. The largest tumor diameter therefore cannot reflect perfectly the total tumor volume and total number of cancer cells.

Tumor diameter alone may not be the best prognostic factor to reflect the extent of cancer invasion, response to treatment, and prognosis. Other tumor size parameters such as thickness of invasion has been used in the T-staging of cutaneous melanoma, colorectal cancer, gastric cancer, and bladder cancer.[1,2] Tumor thickness has also been found to be an important prognostic factor in head and neck cancers.[3–10] Tumor volume is also another tumor size parameter that has been found to be a better prognostic factor compared with tumor diameter in the prediction of radiosensitivity in laryngeal cancer.[11]

Except in T4 stage, the largest tumor diameter is the only parameter used in the classification of stage T1 to T3 oral cavity cancer. T1 is up to 2 cm, T2 is more than 2 cm and up to 4 cm, and T3 is more than 4 cm.[1,2] Reports in the literature showed that tumor thickness was a better prognostic parameter compared with the T stage or largest diameter in the prediction of nodal metastasis in oral cavity carcinomas.[3–10] Apart from the prediction of nodal metastasis, the prognostic value of tumor thickness on local recurrence and survival was not well documented, particularly in oral tongue carcinoma. The prognostic value of other tumor size measurements including tumor width, area and volume has not been reported. Although there was proposal of using tumor thickness as T-staging parameter,[5] there was a lack of consensus on what should be the optimal thickness in the proposed revised T-stage classification.

The present study aims at comparison of the prognostic value of tumor size parameters including diameter, length, thickness, width, area, and volume in the prediction of nodal metastasis, local recurrence, and survival. The results may have important implications for the management of patients.

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This study was supported by a research grant from the University of Hong Kong.

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Manuscript submitted March 21, 2000, and accepted in revised form June 25, 2000.

TABLE I
Prognostic Significance of Tumor Thickness

Tumor Thickness	Patient Number	Nodal Metastasis	Local Recurrence	Tumor-related Death
≤3 mm	10	1 (10%)	0	0
>3 mm, ≤6 mm	24	10 (42%)	2 (8%)	5 (21%)
>6 mm, ≤9 mm	20	12 (60%)	3 (15%)	3 (15%)
>9 mm, ≤12 mm	12	7 (58%)	4 (33%)	5 (42%)
>12 mm	19	13 (68%)	4 (121%)	6 (32%)
Spearman correlation		$P = 0.003$	$P = 0.037$	$P = 0.042$

PATIENTS AND METHODS

Patients with squamous cell carcinoma of oral tongue who had glossectomy treatment from 1987 to 1998 were recruited in the present prospective study. Patients with carcinoma of tongue base, other sites of oral cavity, or T4 stage were all excluded. Patients with excision biopsy prior to glossectomy were excluded because the tumor size could not be measured in the glossectomy specimen. One patient who died of the postoperative immediate complication of chest infection was also excluded because of the short follow-up. A total of 85 patients were included in the present study. There were 53 male and 32 female patients. The median age was 59 years (range 16 to 86). The median follow-up duration excluding patients who died of tumor was 27 months. The preoperative clinical AJCC TNM stages (1997) were 32 cT1 (30N0, 1 N1,1N2a) M0, 44 cT2 (40N0, 4 N1) M0, and 9 cT3 (6N0, 1 N1, 2 N2b) M0. The differentiations were 48 well, 33 moderate, and 4 poor. Of the 9 cN+ patients, radical neck dissections were done. Elective neck dissections were not done routinely in this study period and were decided by the individual surgeon. Of the 76 cN0 patients, 58 elective neck dissections were done including 6 modified radical neck dissections, 48 selective I, II, III neck dissections, 2 modified radical neck dissections and contralateral selective I, II, III neck dissections, and 2 bilateral selective I, II, III neck dissections. The pathological nodal examinations had upstaged the clinical nodal staging of 21 cN0 to become 15 pN1 and 6 pN2, and another 4 clinical cN1 were upstaged to pathological pN2.

The glossectomy specimen was fixed by pins on a foam board during formalin fixation to prevent shrinkage of tissue. The preserved specimen was cut into 3 mm blocks in the coronal plane. Histological section of each block with hematoxylin and eosin staining for microscopic examination was carried out. The tumor border was outlined on each slide. The image on the slides were analyzed by using a computerized image analyzer (Metamorph Imaging System; Universal Imaging Corporation, Pennsylvania). The software of the image analyzer can measure the tumor size including width, thickness, and area. The length of the tumor is calculated by counting the number of blocks containing the tumor multiplied by 3 mm. The tumor thickness was measured from the surface of the tumor to the deepest point of invasion. The largest tumor thickness, width, and area was taken among all the blocks. The diameter was defined as the largest measurement among length, width, and thickness. The tumor volume was calculated by adding all areas from each block multiplied by 3 mm.

RESULTS

Nodal metastasis was present in 43 (51%) patients including 30 patients who had pathological evidence of nodal metastasis in the neck dissection specimens (9 therapeutic neck dissections for clinically N+ neck and 21 neck dissections for cN0 neck, 6 of them also had regional recurrences after neck dissections) and 13 patients who had nodal recurrences not associated with local recurrence (11 cN0 without elective neck dissection and 2 contralateral neck of pN0 patients after elective ipsilateral I,II,III neck dissections). Of the 9 cN+ patients with therapeutic neck dissections, 2 patients had regional recurrences without associated local recurrence. Of the 58 cN0 patients who had elective neck dissections, 2 of the 37 pN0 patients developed contralateral neck recurrences and 4 of the 21 pN+ patients developed regional recurrences. Of the 18 cN0 patients without elective neck treatment, 11 developed nodal recurrences without associated local recurrence.

The correlation of nodal metastasis with tumor diameter, length, width, thickness, area, volume, sex, age, differentiation, clinical T-stage, pathological T-stage, lymphocyte infiltration, vascular invasion, and perineural infiltration were evaluated by appropriate univariate analysis method. Statistical significant ($P \leq 0.05$) or close to significant level ($P > 0.05$ and ≤ 0.1) were found for 4 parameters including tumor thickness (t test, $P = 0.005$), area (t test, $P = 0.03$), width (t test, $P = 0.052$), and perineural infiltration (chi-square test, $P = 0.038$). Logistic regression multivariate analysis recruiting these four parameters showed that tumor thickness was the only significant independent risk factor ($P = 0.0089$). The mean tumor thickness of patients without nodal metastasis was 7 mm compared with 11 mm for patients with nodal metastasis. The risk of nodal metastasis increased progressively with increasing tumor thickness as shown in **Table I**. Of the 76 clinically N0 patients, the risk of subclinical nodal metastasis also increased with tumor thickness as shown in **Table II**.

Local recurrence was found in 13 (15%) patients. The correlation of local recurrence with tumor diameter, length, width, thickness, area, volume, sex, age, differentiation, cT-stage, pT-stage, cN-stage, pN-stage, lymphocyte infiltration, vascular invasion, perineural infiltration, and pathological resection margin (inadequate pathological resection margin was defined to be less or equal to 2 mm, clear resection margin was defined for more than 2

TABLE II
Subclinical Nodal Metastasis of cN0 Patients

Tumor Thickness	Patient Number	Nodal Metastasis
≤3 mm	10	1 (10%)
>3 mm, ≤6 mm	22	8 (36%)
>6 mm, ≤9 mm	20	12 (60%)
>9 mm, ≤12 mm	12	7 (58%)
>12 mm	12	6 (50%)
Spearman's correlation		$P = 0.023$

mm) were evaluated by univariate analysis method. Three factors were found to be significant or close to significant level, including pathological resection margin (*t* test, $P = 0.038$), perineural infiltration (chi-square test, $P = 0.059$), and tumor thickness (*t* test, $P = 0.082$).

Logistic regression multivariate analysis showed that only pathological resection margin was significant independent risk factor for local recurrence. The local recurrence rate of inadequate pathological resection margin was 27% (9 of 34) compared with 8% (4 of 51) of clear pathological resection margin. There were 34 (40%) patients who had inadequate pathological resection margin. The sites of inadequate resection margin were in deep margin (17 patients), mucosal margin (10 patients), and both sites (7 patients). The risk of having inadequate deep resection margin increased progressively with increasing tumor thickness, 9% (1 of 10) for tumor thickness of ≤3 mm, 21% (9 of 44) for tumor thickness of >3 mm and ≤9 mm, 45% (14 of 31) for tumor thickness of >9 mm (Spearman's correlation, $P = 0.007$). The risk of local recurrence increased with increasing tumor thickness due to its association with inadequate resection margin. The local recurrence rates increased significantly with increasing tumor thickness as shown in Table I.

There were 19 (22%) patients who died of oral tongue carcinoma. The correlation of tumor related death with tumor diameter, length, width, thickness, area, volume, sex, age, differentiation, cT stage, pT stage, pN stage, lymphocyte infiltration, pathological resection margin, vascular invasion, and perineural infiltration were evaluated by appropriate univariate analysis. Four factors were found to be significant or close to significant level including pN stage (chi-square test, $P = 0.001$), tumor thickness (*t* test, $P = 0.049$), perineural infiltration (chi-square test, $P = 0.051$), and area (*t* test, $P = 0.094$).

Logistic regression multivariate analysis recruiting these four factors showed that only pathological pN stage was significant independent factor for tumor-related death. The risks of tumor-related death increased with increasing pN stage, 13% (7 of 55) for pN0, 35% (6 of 17) for pN1, and 46% (6 of 13) for pN2 (Spearman's correlation, $P = 0.003$). The risk of tumor related death increased with increasing tumor thickness due to its association with nodal metastasis, inadequate resection margin, and local recurrence. The tumor related death rate increased with increasing tumor thickness as shown in Table I. The actuarial disease-free survival curves with respect to the tumor thickness is shown in **Figure 1**. The actuarial 5-year disease-free survival rates were 100% for tumor thickness ≤3 mm, 77% for tumor thickness >3 mm and ≤9 mm, and 60% for tumor thickness >9 mm (log rank test, $P = 0.028$).

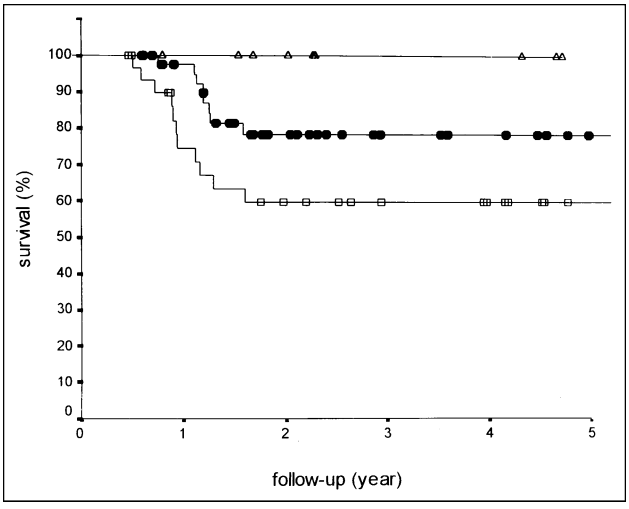

Figure 1. Actuarial survival related to tumor thickness by using the revised T stage, revised T1 (**triangle**, thickness ≤3 mm), revised T2 (**circle**, thickness >3 mm and ≤9 mm), revised T3 square, thickness >9 mm).

Since tumor thickness is a more important prognostic factor for nodal metastasis, inadequate resection margin, local recurrence, tumor-related death, and tumor-free survival compared with the tumor diameter, a proposal of the revised staging system for T1 to T3 stages by using tumor thickness is recommended. The revised T-staging will be T1 for tumor thickness ≤3 mm, T2 for tumor thickness >3 mm and ≤9 mm, and T3 for tumor thickness >9 mm. By using the proposed new staging system, 26 (31%) patients should be up-staged and 6 (7%) patients should be down-staged to reflect their true prognosis of nodal metastasis, local recurrence, and survival.

COMMENTS

Carcinoma of oral tongue is known to have high incidence of nodal metastasis even in the early T1 and T2 stages.[12,13] Nodal metastasis is in fact the most common site of recurrence and treatment failure of tongue carcinoma. The prognostic significance of tumor thickness in head and neck carcinomas had been reported consistently in the literature.[3–9] Tumor diameter and T-staging were consistently found to be not significant prognostic factors in most reports.[3–9] The failure of the currently used T-staging system on using tumor diameter on T1 to T3 to differentiate the high risk from low risk of nodal metastasis, local recurrence, and survival indicates that tumor diameter alone in not the best parameter used in designing the best treatment plan of oral cavity cancer despite its simplicity.

In the study of tumor thickness, most reports included mixed group of head and neck carcinomas from multiple sites.[3–9] Tumor thickness is found to be the most consistent prognostic factor in these reports. The results of the present study confirmed the findings of other reports in the litera-

ture that tumor thickness is the most important prognostic factor for nodal metastasis in oral tongue carcinoma. The prognostic value of other tumor size measurements including length, width, area and volume had not been reported in the literature.

Our results indicated that tumor thickness was the only tumor size measurement that had prognostic significance for nodal metastasis, local recurrence, and survival. Despite our knowledge of significant correlation of tumor volume with radiotherapy and chemotherapy, it is out of our original expectation to find that tumor volume has no predictive value for surgical treatment. It is however reasonable because we do see tumors of the same volume with different thickness. Those tumors that have large surface diameter and are thin will have lower risk of nodal metastasis and higher chance of clear surgical resection compared with those tumors of the same volume but with smaller surface diameter and more deeply infiltrating.

Tumor thickness was found to be able to predict the risk of nodal metastasis. The pathophysiology of nodal metastasis in relation to tumor thickness is unknown. In the microscopic examination of the serially sectioned specimens, lymphatic vessels are found to be abundant in the submucosa of oral tongue. This histological feature may account for the nodal metastasis in very small tongue carcinoma. The incidence of nodal metastasis, however, increased rapidly when the tumor invaded the tongue muscle more deeply. The postulated reasons for the higher nodal metastatic rate of deeply infiltrating carcinoma may be related to the more invasive behavior of the deeply infiltrating cancer, and the other possibility is the contraction of the tongue muscle, which may promote the entry of cancer cells into the lymphatics.

Tumor thickness is also found to be associated with local recurrence. The most important risk factor of local recurrence was in fact the histological resection margin. The deep margin was frequently the site of positive or inadequate resection margin. During resection of tongue carcinoma, the deep margin is more difficult to be assessed accurately with palpation compared with mucosal margin at the surface. It is therefore more likely to have inadequate resection margin when the tumor becomes more deeply infiltrating. The incidence of inadequate resection margin increased with increasing tumor thickness. It is important to achieve clear histological resection margin because local recurrence has a poor prognosis and can rarely be salvaged.[14,15]

The association of tumor thickness with nodal metastasis and local recurrence ultimately led to tumor-related death. Tumor size is most important in the staging of T1 to T3. T4 stage is related to invasion of adjacent structures outside oral tongue rather than tumor size. Although tumor thickness is the most consistent prognostic factor, there is no unanimous agreement on how to group thickness into different stages in order to guide the treatment as shown in Table I. In the design of treatment strategy, we need to consider the prognosis of local recurrence, nodal metastasis, and survival all together. In the classification of T1 to T3 lesions, we should aim at stratifying T1 lesions to have low risk, T2 lesions to have moderate risk, and T3 lesions to have high risk of nodal metastasis, local recurrence, and tumor-related death. With the better prognosis prediction, we would be able to design an oncologically sound management protocol.

In our proposed staging system, T1 lesions is defined to be up to 3 mm in thickness. The revised T1 stage has 10% nodal metastasis, 0% local recurrence, and 100% 5-year actuarial disease-free survival. These T1 patients do not require elective treatment of the neck if they are clinically N0 because the risk of nodal metastasis is very low. Glossectomy treatment alone based on tumor depth irrespective to the size of tumor diameter is an adequate treatment with good prognosis of nearly 100% cure rate.

T2 lesions with more than 3 mm and up to 9 mm thickness have 50% nodal metastasis, 11% local recurrence, and 77% 5-year actuarial disease-free survival. These T2 patients have a high incidence of nodal metastasis and may benefit from elective neck dissection even if they are clinically N0. Although elective neck dissection has been shown to improve long- term survival of early oral tongue carcinoma in our previous retrospective study,[12] the benefit of elective neck dissection versus observation needs verification by further prospective randomized study. Primary surgical treatment alone without radiotherapy for T2 N0 lesions should be an adequate treatment with low local recurrence rate and high survival rate. Postoperative adjuvant radiotherapy is, however, recommended for T1-T2 N0 lesions when there are other indications including histologic inadequate margin or presence of metastatic nodes in the electively dissected neck specimens of clinically node negative T2 lesion.

T3 lesions with more than 9 mm thickness have 65% nodal metastasis, 26% local recurrence, and 60% 5-year actuarial disease-free survival. These patients should be treated with combined surgery and postoperative radiotherapy in view of the high local recurrence and poor survival rate. Although there was high incidence of subclinical nodal metastasis in this deeply infiltrating tumor, elective neck dissection of N0 neck of T3 lesion may not be necessary if postoperative radiotherapy is given for better local control in which the radiotherapy field can cover the neck as well. With the use of tumor thickness in the design of treatment protocol, elective neck dissection should be considered only necessary in patients with tumor thickness between 3 and 9 mm. The real benefit of elective neck treatment in this group of patients, however, needs further verification by a prospective randomized study.

There is also a problem of documentation of tumor thickness if it is to be used in the treatment of patients. Since we are using pathologic tumor thickness in the study, the management of the neck needs to wait for the glossectomy pathologic report before the decision of a second stage neck treatment. The best is to be able to have accurate preoperative measurement of thickness with the help of radiologic imaging or intraoperative sectioning. The accuracy of these methods needs further study.

In conclusion, tumor thickness is found to be the most important tumor size parameter in the prediction of nodal metastasis, local recurrence, and survival. A revised management protocol is recommended based on tumor thickness to replace tumor diameter. The treatment is based on a more accurate prognostic system with T1 for tumor

thickness of up to 3 mm, T2 for tumor thickness of more than 3 mm and up to 9 mm, and T3 for tumor thickness of more than 9 mm. The currently used T4 will remain unchanged as it does not depend on tumor size measurement. With the use of the revised T-staging system, we should be able to better manage our patients according to their prognosis. The proposal is worth further prospective study.

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