PROGNOSTIC FACTORS OF CLINICALLY STAGE I AND II ORAL TONGUE CARCINOMA—A COMPARATIVE STUDY OF STAGE, THICKNESS, SHAPE, GROWTH PATTERN, INVASIVE FRONT MALIGNANCY GRADING, MARTINEZ-GIMENO SCORE, AND PATHOLOGIC FEATURES

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Abstract: *Purpose*. This study aims at evaluation of the different prognostic models, including stage, tumor thickness, shape, malignancy grading of tumor invasive front, Martinez-Gimeno score, and pathologic features in the prediction of subclinical nodal metastasis, local recurrence, and survival of early T1 and T2 oral tongue squamous cell carcinoma. The results will have important implication for the management of patients.

Patients and Methods. Seventy-two clinically T1 and T2 glossectomy specimens of oral tongue carcinoma were serially sectioned in 3-mm thickness for the evaluation of various pathologic features. The prognostic value in the prediction of subclinical nodal metastasis, local recurrence, and survival of different models were compared.

Results. Among all the tumor parameters and predictive models being evaluated, tumor thickness was the only significant factor that had significant predictive value for subclinical nodal metastasis, local recurrence, and survival. With the use of 3-mm and 9-mm division, tumor of up to 3-mm thickness has 8% subclinical 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 had 44% subclinical nodal metastasis, 7% local recurrence, and 76% 5-year actuarial disease-free survival; tumor of more than 9 mm had 53% subclinical nodal metastasis, 24% local recurrence, and 66% 5-year actuarial disease-free survival.

Conclusions. Tumor thickness should be considered in the management planning of patients with early oral tongue

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Oral tongue carcinoma is well known for its propensity of subclinical nodal metastasis in stage I and II tumors. Micrometastasis could be found in 36% of early T1–2 oral tongue carcinoma. Locoregional recurrences are the main cause of treatment failures of oral tongue carcinoma.[2–4] Nodal recurrence as result of undetectable subclinical nodal metastasis is, however, the main management problem of early stage I and II carcinomas.[5] These micrometastasis are not detectable by the best contemporary diagnostic technology.

Subclinical nodal metastasis is not a management problem for large size tumors, because these tumors require free flap or pedicle flap reconstruction of the large defect after resection. In this situation, the neck has to be assessed, and therefore elective neck dissection is usually done. The large size tumor also warrants postoperative radiotherapy to improve local control, and the neck can therefore also be irradiated together with the oral cavity. Elective neck dissection or neck irradiation is, however, an option that is not mandatory after partial glossectomy and primary closure of the small defect in early T1–2 carcinoma.

Although there is no doubt about the significant reduction of nodal recurrence with prophylactic neck dissection of early oral tongue carcinoma, there is, however, controversy on the long-term benefit.[5–8] Prophylactic treatment of the clinically node-negative neck based on a reliable prognostic evaluation model has been the main focus of research for many years. The indications for elective neck dissection will still rely on prognostic parameters in the near future until technology is available to detect the micrometastasis.

The AJCC and UICC TNM staging systems are international standards for cancer reporting, prognosis evaluation, and treatment planning.[9,10] T1 is up to 2 cm, and T2 is more than 2 cm and up to 4 cm. T stage alone, however, cannot distinguish high risk from low risk of subclinical nodal metastasis. We have previously reported the significant prognostic value of tumor thickness in the prediction of both clinical and subclinical nodal metastasis.[11] Tumor thickness can also predict the risk of local recurrence and survival of oral tongue carcinoma.[11] Other predictive models have been reported for head and neck cancers over the years, including tumor shape (reductive or expansive), tumor growth pattern (exophytic or endophytic), various pathologic features, various invasive front malignancy grading scores, and Martinex-Gimeno score.[12–28] Many of these studies used pooled data from heterogeneous sites, stage, and treatment. There is no consensus on the best prognostic model for early stage I and II oral tongue carcinoma.

This study aims at comparison of the prognostic value, including subclinical nodal metastasis, recurrence, and survival of the different models that have been reported in the literature. By use of stringent homogenous patient selection criteria in this study with uniform histologic findings (squamous cell carcinoma), pathologic evaluation method (using entire specimen serial section), site (oral tongue only), stage (only cT1N0M0 and cT2N0M0), and treatment (primary surgical treatment without prior radiotherapy or chemotherapy), we hope to resolve the question on the best prognostic model on the basis of readily available clinical and pathologic parameters of early oral tongue carcinoma. The data will be useful guide to the management planning for each individual patient.

METHODS AND PATIENTS

Patients with squamous cell carcinoma of oral tongue who had glossectomy treatment from 1987 to 1998 were recruited in this prospective study. Only patients with clinically T1N0M0 or T2N0M0 who had primary surgical treatment without prior radiotherapy or chemotherapy were recruited. Patients with carcinoma of tongue base or other sites of oral cavity were all excluded. Patients with excision biopsy before glossectomy were excluded, because the tumor thickness and invasive front malignancy grading could not be measured in the glossectomy specimen.

A total of 72 patients were included in this study. There were 47 male and 25 female patients. The median age was 60 years (range, 16–86 years). The median follow-up duration excluding patients who died of tumor was 43 months. The preoperative clinical AJCC/UICC TNM stages (1997) were 30 cT1N0M0 and 42 cT2N0M0. All patients received glossectomy as the primary treatment, and 41 patients had elective neck dissections.

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. Histologic section of each block with hematoxylin and eosin staining for microscopic examination was carried out. The tumor border was outlined on each slide. The images on the slides were analyzed by use of a computerized image analyzer (Metamorph Imaging System, Universal Imaging Corporation, PA). The software of the image analyzer can measure the tumor size, including width, thickness, and area. The tumor thickness was measured from the surface of the tumor to the deepest point of invasion using the method published previousely.[11] The largest tumor thickness was taken among all the blocks. Tumor thickness was divided into three groups: group I was up to 3 mm, group II was more than 3 mm and up to 9 m, and group III was more than 9 mm.[11] The exophytic/endophytic ratio of tumor was calculated by the ratio of tumor thickness above and below a straight line joining the tumor edge to mucosal junction in a representative coronal section. Figure 1 illustrates the coronal section of the glossectomy specimen. The Anneroth et al[20] and Bryne et al[26] malignancy grading scores were calculated according to their original descriptions. The Martinez-Gimeno score was calculated according to the formula in the original publication.[27]

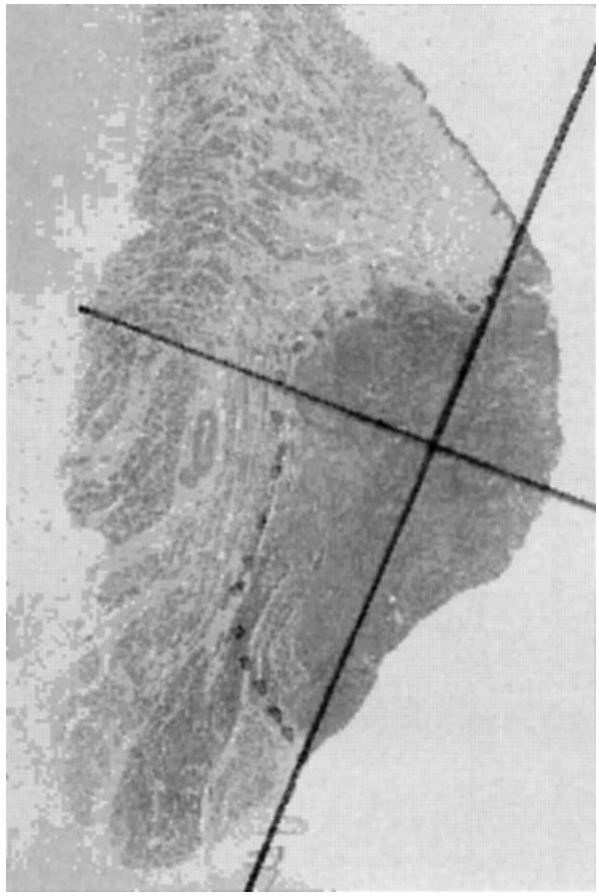

FIGURE 1. Coronal section of surgical specimen. The tumor is outlined with dotted line. The shape of the tumor is reductive. A horizontal straight line is drawn crossing the tumor edge mucosal junction. Another vertical line perpendicular to the horizontal line is drawn to measure the tumor thickness. The exophytic/endophytic ratio is the proportion of tumor above and below the horizontal line.

RESULTS

There were 31 (43%) patients who had subclinical nodal metastasis as evidenced by the presence of either pathologic finding of nodal metastasis in the elective neck dissection specimens or the development of nodal metastasis on follow-up not associated with local recurrence. The correlation of subclinical nodal metastasis with the different prognostic models is shown in Table 1. Both tumor thickness and Martinez-Gimeno score were significant in the univariate analysis. In the multivariate analysis, use of the logistic regression model showed that tumor thickness was the only significant independent prognostic factor for subclinical nodal metastasis. When the Martinez-Gimeno score was recalculated with the points contributed by tumor thickness taken out, this modified Martinez-Gimeno score was not found to be significantly correlated with subclinical nodal metastasis (t test, $p = .121$). It showed that the predictive value of the Martinez-Gimeno score was mainly contributed by the element of tumor thickness in oral tongue carcinoma.

There were seven (10%) patients who developed local recurrences after treatment. The correlation of local recurrences with various prognostic factors is shown in Table 2. Tumor thickness and perineural infiltration were both significant prognostic factors. Multivariate analysis by use of the logistic regression model showed that both tumor thickness and perineural infiltration were significant independent prognostic factors for local recurrence.

At the last follow-up, there were 12 patients who died of recurrences and another 2 patients who were still alive with recurrences. Multivariate analysis by use of the Cox-regression model

Table 1. Correlation of subclinical nodal metastasis with prognostic factors.

Prognostic factors	Number	Nodal metastasis	Mean score	Significance
T stage				
T1	30	9 (30%)		chi-square,
T2	42	22 (52%)		$p = .059$
Broder's grade				
Well	42	16 (38%)		Spearman's
Moderate	28	13 (46%)		correlation,
Poor	2	2 (10%)		$p = .238$
Thickness				
≤ 3 mm	12	1 (8%)		Spearman's
> 3 mm, ≤9 mm	43	21 (44%)		correlation,
> 9 mm	17	9 (53%)		$p = .031$
Vascular invasion				
Absent	68	30 (44%)		Fisher,
Present	4	1 (25%)		$p = .629$
Lymphatic vessel invasion				
Absent	28	28 (41%)		Fisher,
Present	3	3 (100%)		$p = .075$
Perineural invasion				
Absent	56	22 (39%)		chi-square,
Present	16	9 (56%)		$p = .227$
Shape				
Reductive	24	8 (33%)		chi-square,
Expansive	48	23 (48%)		$p = .239$
Exophytic/endophytic ratio	41	−ve node	0.56	*t* test,
	31	+ve node	0.39	$p = .200$
Anneroth malignancy score	41	−ve node	13.1	*t* test,
	31	+ve node	13.8	$p = .267$
Bryne malignancy score	41	−ve node	8.5	*t* test,
	31	+ve node	8.9	$p = .444$
Martinez-Gimeno score	41	−ve node	14.1	*t* test,
	31	+ve node	15.9	$p = .02$

showed that both tumor thickness and perineural infiltration were significant independent prognostic factors for survival. The actuarial 5-year tumor-free survival rates were 100% for thickness group I, 76% for thickness group II, and 66% for thickness group III. The actuarial 5-year tumor-free survival rates were 86% without perineural infiltration and 52% with perineural infiltration.

DISCUSSION

Locoregional recurrences are the main causes of treatment failure of oral tongue carcinoma. By use of the TNM staging system, there is no significant difference in the risk of subclinical nodal metastasis, local recurrence, and survival between T1 and T2. A better prognostic evaluation system is therefore necessary to guide the clinical management, particularly in the prediction of subclinical nodal metastasis.

Broder's tumor grading system of well, moderately, and poorly differentiated tumors have been used in routine pathologic reporting. Broders[16] found progressively increasing rate of metastasis of lip carcinoma from well-differentiated tumor to poorly differentiated tumor. Tumor grade was found to correlate with subclinical nodal metastasis in our previous study of laryngeal carcinoma.[29] Byers et al[30] found a significant association of nodal metastasis with tumor differentiation in a mixed group of T1−T4, N0 and N+ oral tongue carcinoma; there was, however, no data analysis of subclinical nodal metastasis in clinically node negative T1 and T2 carcinomas in their study. In this study, subclinical nodal metastasis was found to have no correlation with tumor grade. The prognostic value of tumor grade therefore varies in different head and neck cancers and may account for the variable results in studies using pooled data in the literature.

Shintani et al[17] reported the significant relationship of tumor shape (reductive or expansive), growth pattern (endophytic or exophytic), depth (not equivalent to thickness), and neck metasta-

Table 2. Correlation of local recurrence with prognostic factors.

Prognostic factors	Number	Local recurrence	Mean score	Significance
T stage				
T1	30	1 (3%)		Fisher's exact,
T2	42	6 (14%)		$p = .227$
Broder's grade				
Well	42	3 (7%)		Spearman's
Moderate	28	4 (14%)		correlation,
Poor	2	0		$p = .444$
Thickness				
≤ 3 mm	12	0		Spearman's
> 3 mm, ≤ 9 mm	43	3 (7%)		correlation,
> 9 mm	17	4 (24%)		$p = .025$
Vascular invasion				
Absent	68	7 (10%)		Fisher,
Present	4	0		$p = 1$
Lymphatic vessel invasion				
Absent	69	6 (8%)		Fisher,
Present	3	1 (33%)		$p = .268$
Perineural invasion				
Absent	56	3 (5%)		chi-square,
Present	16	4 (25%)		$p = .019$
Shape				
Reductive	24	0		Fisher,
Expansive	48	7 (15%)		$p = .087$
Exophytic/endophytic ratio	65	–ve recur	0.52	*t* test,
	7	+ve recur	0.22	$p = .241$
Anneroth malignancy score	65	–ve recur	13.42	*t* test,
	7	+ve recur	13.29	$p = .895$
Bryne malignancy score	65	–ve recur	8.65	*t* test,
	7	+ve recur	8.71	$p = .935$
Martinez-Gimeno score	65	–ve recur	14.66	*t* test,
	7	+ve recur	17.00	$p = .093$

sis of T1 and T2 tongue carcinomas. Shintani et al found higher frequencies of nodal metastasis with deeper infiltrating tumor. The tumor shape was also found to be related to tumor depth in their study; expansive shape was more commonly found in deeply infiltrating tumor. There was, however, no multivariate analysis to evaluate whether the tumor shape itself was an independent predictive factor for nodal metastasis. There was also exceptionally low frequency of subclinical nodal metastasis of only 12.8% (5 of 39) of the clinically N0 patients in their study, and therefore the samples might not be representative. In this study, there was no significant correlation of reductive or expansive shape with subclinical nodal metastasis, local recurrence, or survival. There was also no significant correlation of exophytic or endophytic pattern of growth with subclinical nodal metastasis, local recurrence, and survival. The higher incidence of subclinical nodal metastasis and poor prognosis found in endophytic and expansive tumors in some studies was probably caused by their association with thicker tumors.

Jakobsson et al[31] reported the application of a multifactorial malignancy grading system using eight features of the tumors, including tumor cell structure, differentiation, nuclear polymorphism, mitotic count, mode of invasion, depth of invasion, vascular invasion, and inflammatory cellular response in the prognostic evaluation of laryngeal carcinoma. Each feature was given 1 to 4 points according to their degree of malignancy, and the total points were added to give the final total malignancy grading score. The points in some of the features were not clearly defined in Jakobsson's original description (eg, the use of moderate number, great number, and numerous in the definition of mitoses without definitive objective number of mitotic count). A number of modifications of the Jakobsson malignancy grading were subsequently reported in the prognostic evaluation of oral cavity carcinoma.

Hogmo et al[21] used seven features by deleting the tumor cell structure in the study of 56 oral tongue carcinomas. They found significant correlation between total malignancy score with clinical stage and clinical nodal metastasis. Their study, however, included patients from different subsites of oral cavity, stages, and treatment, and there was no mention about the predictive value on early oral tongue carcinoma. Bryne et al[26] proposed the invasive front grading system (IFG) in which the features at the most invasive part of the tumor, including degree of keratinization, nuclear polymorphism, pattern of invasion, and host inflammatory response, were scored. They found prognostic significance in a group of 68 patients with buccal and tongue carcinoma. Odell et al[25] found significant correlation of Bryne's IFG score with nodal metastasis in 47 T1 oral tongue carcinomas undergoing radiotherapy. The problem with this study is the doubtful accuracy of IFG score in the biopsy specimen, because biopsy material was usually taken at the tumor edge rather than at the most invasive front of the tumor. The incidence of subclinical nodal metastasis could not be evaluated in their study because all patients had radiotherapy treatment of the node-negative neck already. There were other modifications of the original Jakosson's malignancy grading system by Lund et al[33] in carcinoma of lip and tongue, Willen et al[32] in gingival carcinoma, Anneroth et al[20] in oral cavity carcinoma, and Crissman et al[34] in floor of mouth carcinoma. The large number of modifications in the literature may reflect the problem of inconsistency of these complicated malignancy grading systems in their predictive value. There was no correlation between the different malignancy grading scores with subclinical nodal metastasis, local recurrence, and survival in this study.

Martinez-Gimeno et al studied the risk of nodal metastasis of 126 patients with oral cavity and oropharynx carcinoma. The risk of nodal metastasis was found correlate with seven parameters, including T stage, intravascular invasion, tumor grade, tumor thickness, tumor host interphase, inflammatory infiltrate, and perineural spread. A weighted scoring system was designed on the basis of the relative importance of the predictive value of each factor.[27] The Martinez-Gimeno scoring system is based on data from mixed group of tumors from both oral cavity and oropharynx, and patients were also of different stages. It is unknown whether this scoring system can be applied specifically to early T1 and T2 oral tongue carcinoma. The Martinez-Gimeno score was found to correlate with subclinical nodal metastasis in univariate analysis in this study. In multivariate analysis recruiting both Martinez-Gimeno score and tumor thickness together, only tumor thickness was found to be the independent factor in the prediction of subclinical nodal metastasis. Repeating the univariate analysis of the Martinez-Gimeno score with the tumor thickness taken out showed that there was no more significant correlation. It indicates that the predictive value of the Martinez-Gimeno score is mainly contributed by the tumor thickness in early oral tongue carcinoma. There were also no significant predictive values of the Martinez-Gimeno score with local recurrence and survival in this study.

Tumor thickness has been found to be a reliable prognostic marker for subclinical nodal metastasis, local recurrence, and survival in our previous report.[11] This study showed that tumor thickness is superior to other prognostic parameters and models in the prediction of subclinical nodal metastasis, local recurrence, and survival. A revised T-staging system based on tumor thickness is proposed to replace the tumor diameter of the present UICC/AJCC system. The management could be modified according to the tumor thickness rather than the largest diameter. The revised T1 (group I) is tumor thickness of up to 3 mm, revised T2 (group II) is thickness more than 3 mm and up to 9 mm, and revised T3 (group III) is more than 9 mm. Tumor thickness can be measured accurately by intraoral ultrasonography or immediate section of the tumor specimen intraoperatively.[35]

Of the patients with revised T1 stage tumor based on tumor thickness, the risk of subclinical nodal metastasis is 8%. Elective neck dissection is therefore not indicated. Partial glossectomy alone is a sufficient primary treatment, with nearly 100% local control and survival. Of the revised T2 stage tumor, the risk of subclinical nodal metastasis was 44%; elective neck dissection may be considered to improve nodal control. Elective neck dissection is particularly essential for those patients who cannot be followed up regularly. Of those patients with revised T3 stage tumor, there were high risk of both subclinical nodal metastasis and local recurrence. Postoperative adjuvant radiotherapy to oral cavity is recommended to improve local control, and the irradiation field should cover the neck.

Because elective radiotherapy of the neck is an effective treatment of subclinical nodal metastasis in these patients, elective neck dissection is not necessary.

In conclusion, tumor thickness is the most reliable predictive factor for subclinical nodal metastasis, local recurrence, and survival in the surgical management of stage I and II oral tongue carcinomas. A revised T-staging system is recommended based on tumor thickness rather than the largest tumor diameter. Management of patients should be based on tumor thickness to get the best cost-benefit treatment result. With the implementation of tumor thickness in the management planning, unnecessary elective neck dissection can be avoided in 40 T1–2 patients who had either thin tumor of up to 3 mm or thick tumor of more than 9 mm. Adjuvant radiotherapy should be given selectively for patients with thick tumor of more than 9 mm who had high risk of both local and regional recurrence.

REFERENCES

1. Yuen APW, Lam KY, Chan ACL, et al. Clinicopathological analysis of elective neck dissection for N0 neck of early oral tongue carcinoma. Am J Surg 1999;177:90–92.
2. Yuen APW, Lam KY, Chan ACL, et al. Clinicopathological analysis of local spread of carcinoma of tongue. Am J Surg 1998;175:242–244.
3. Yuen APW, Wei WI, Wong SHW, Ng RWM. Local recurrence of carcinoma of tongue: patient prognosis. Ear Nose Throat J 1998;77(3):181–184.
4. Yuen APW, Wei WI, Wong YM, Tang KC. Comprehensive analysis of results of surgical treatment of oral tongue carcinoma in Hong Kong. Chinese Med J 1997; 110(11): 859–864.
5. Yuen APW, Wei WI, Wong YM, Tang KC. Elective neck dissection versus observation in the surgical treatment of early oral tongue carcinoma. Head Neck 1997;19: 583–588.
6. van den Brouck C, Sancho-Garnier H, Chassagne D, et al. Elective versus therapeutic radical neck dissection in epidermoid carcinoma of oral cavity, results of a randomized clinical trial. Cancer 1980;46:386–390.
7. Fakih AR, Rao RS, Borges AM, Patel AR. Elective versus therapeutic neck dissection in squamous cell carcinoma of tongue: a prospective randomized study. Semin Surg Oncol 1989;158:327–330.
8. Franceschi D, Gupta R, Spiro RH, Shah JP. Improved survival in the treatment of squamous carcinoma of oral tongue. Am J Surg 1993;166:360–365.
9. American Joint Committee of Cancer. Cancer staging manual, 5th ed. Philadelphia: Lippincott Raven; 1997.
10. Sobin LH, Wittekind CH, editors. International Union Against Cancer: TNM classification of malignant tumor, 5th ed. New York: John Wiley & Sons; 1997.
11. Yuen APW, Lam KY, Wei WI, Ho WK. A comparison of prognostic significance of tumor diameter, length, width, thickness, area, volume and clinicopathological features of oral tongue carcinoma. Am J Surg 2000;180:139–143.
12. Spiro RH, Huvos AG, Wong GY, et al. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of mouth. Am J Surg 1986;152:345–350.
13. Morton RP, Ferguson CM, Lambie NK, Whitlock RML. Tumor thickness in early tongue cancer. Arch Otolaryngol Head Neck Surg. 1994;120:717–720.
14. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. Arch Surg 1986;121:1410–1414.
15. Mohit-Tabatabal MA, Sobel HJ, Rush BF, Mashberg A. Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. Am J Surg 1986;152:351–353.
16. Broders AC. Squamous cell epithelioma of the lip; a study of five hundred and thirty-seven cases. JAMA 1920;74: 656–664.
17. Shintani S, Matsuura H, Hasegawa Y, Nakayama B, Fujimoto Y. The relationship of shape of tumor invasion to depth of invasion and cervical lymph node metastasis in squamous cell carcinoma of the tongue. Oncology 1997;54: 463–467.
18. Shingaki S, Suzuki I, Nakajima T, Kawasaki T. Evaluation of histopathological parameters in predicting cervical lymph node metastasis of oral and oropharyngeal carcinomas. Oral Surg Oral Med Oral Pathol 1988;66:683–688.
19. Rasgon SM, Cruz RM, Hilsinger RL, Sawicki JE. Relation of lymph node metastasis to histopathologic appearance in oral cavity and oropharyngeal carcinoma: a case series and literature review. Laryngoscope 1989;99:1103–1110.
20. Anneroth G, Batsakis J, Luna M. Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinoma. Scand J Dent Res 1987;95:229–249.
21. Hogmo A, Kuylenstierna R, Lindholm J, Munck-Wikland E. Predictive value of malignancy grading systems, DNA content, p53, and angiogenesis for stage I tongue carcinomas. J Clin Pathol 1999;52:35–40.
22. Hiratsuka H, Miyakawa A, Nakamori K, Kido Y, Sunakawa H, Kohama G-I. Multivariate analysis of occult lymph node metastasis as a prognostic indicator for patients with squamous cell carcinoma of the oral cavity. Cancer 1997;80:351–356.
23. Nason RW, Castello NB, Sako K, Shedd DP. Cervical node metastasis in early squamous cell carcinoma of the floor of the mouth: predictive value of multiple histopathologic parameters. World J Surg 1990;14:606–609.
24. Piffko J, Bankfalvi A, Ofner D, et al. Prognostic value of histological factors (malignancy grading and AgNOR content) assessed at the invasive tumour front of oral squamous cell carcinomas. Br J Cancer 1997;10:1543–1546.
25. Odell EW, Jani PJ, Sherriff M, et al. The prognostic value of individual histologic grading parameters in small lingual squamous cell carcinomas—the importance of the pattern of invasion. Cancer 1994;74:789–794.
26. Bryne M, Boysen M, Alfsen CG, et al. The invasive front of carcinomas. The most important area for tumor prognosis. Anticancer Res 1998;18:4757–4764.
27. Martinez-Gimeno C, Rodriguez EM, Vila CN, Varela CL. Squamous cell carcinoma of the oral cavity: a clinicopathologic scoring system for evaluating risk of cervical lymph node metastasis. Laryngoscope 1995;105:728–733.
28. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. Head Neck 1995;17:463–472.
29. Yuen APW, Lam KY, Choy JTH, Ho WK, Wei WI. Bcl-2 expression of laryngeal carcinoma. Clin Otolaryngol 2001; 26(2):129–133.
30. Byers RM, El-Naggar AK, Lee YY, et al. Can we detect or predict the presence of occult nodal metastasis in patients with squamous cell carcinoma of the oral tongue? Head Neck 1998;20:138–144.
31. Jakobsson PA, Eneeroth CM, Killander D, Moberger G, Martensson B. Histologic classification and grading of

malignancy in carcinoma of the larynx (a pilot study). Acta Radiol Ther Phys Biol 1973;12:1–8.
32. Lund C, Sogaard K, Elbrond O, Jorgensen K, Pedersen. Epidermoid carcinoma of the lip. Histologic grading in the clinical evaluation. Acta Radiol Ther Biol 1975;14: 464–474.
33. Willen R, Nathanson A, Moberger G, Anneroth G. Squamous cell carcinoma of the gingiva. Histological classification and grading of malignancy. Acta Otolaryngol 1975;79:146–154.
34. Crissman JD, Gluckman J, Whiteley J, Quanelle O. Squamous cell carcinoma of the floor of mouth. Head Neck Surg 1980;3:2–7.
35. HelbigM, Flechtenmacher C, Hansmann J, Dietz A, Tasman AJ. Intraoperative B-mode endosonography of tongue carcinoma. Head Neck 2001;23:233–237.