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Evaluation of excisional biopsy for stage I and II squamous cell carcinoma of the oral cavity

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Abstract
Background. To reduce the risk of spreading tumor cells by incisional biopsy, we have employed excisional biopsy for early oral squamous cell carcinomas (SCCs). However, whether excisional biopsy should be adopted as a radical treatment for oral carcinomas is still controversial.
Methods. Fifty-eight patients with stage I or II SCC of the oral cavity treated by excisional biopsy were reviewed clinicopathologically to investigate treatment outcome.
Results. Eight of the 58 patients had a recurrence at the primary site and 7 had a secondary lymph node metastasis in the neck; all patients were curable by salvage treatment. We found a significant correlation between local recurrence and margin status and between tumor size and depth invasion. The absence or presence of epithelial dysplasia adjacent to the cancer was also important in predicting local recurrence. Endophytic tumors had a higher rate of neck metastasis than superficial or exophytic tumors ($P < 0.001$).
Conclusions. Excisional biopsy is an effective and less invasive treatment for small oral SCCs. For superficial tumors that are frequently accompanied by epithelial dysplasia, tumors less than 30 mm in size should be excised at a margin of 5 mm or more from the lesion, thereby including the dysplasia. Considering the positive correlation between tumor size and depth of invasion, exophytic tumors less than 20 mm in size can be treated by excisional biopsy alone. As endophytic tumors are highly aggressive and have a high propensity to metastasize to cervical lymph nodes, endophytic tumors less than 15 mm in size are indicated for excisional biopsy.

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Introduction

Early stage squamous cell carcinomas (SCCs) of the oral cavity are effectively treated by either surgery or radiotherapy. The preferred initial treatment of these early cancers at our institute is with surgery. Surgery for SCC of the oral cavity must address extirpation of the primary tumor and control of neck metastases.

Prior to surgery, an incisional biopsy is routinely performed to determine malignancy; however, incision into a neoplasm could help it to spread or could even increase its malignancy. Nevertheless, no data based on clinical surveys are available that prove a worse prognosis subsequent to certain bioptsy approaches,[1] although some experimental studies in animal models have revealed that an incision into oral cancer significantly increased the risk of regional lymph node metastasis.[2,3] Because direct inspections and digital palpations are possible for lesions of the oral cavity, close examination by surgeons makes it possible to determine the malignancy of the lesion. For these reasons, we employ excisional biopsy for small and localized oral SCCs as surgical treatment directing at controlling the primary tumor, to prevent the spreading of cancer cells by incisional biopsy.[4]

Various histopathologic parameters at the primary site have been found to have significant correlation with loco-regional recurrence and survival.[5–7] In excisional biopsy for oral cancers, however, information on their malignant potential obtained preoperatively is limited. Excisional biopsy is, therefore, still a controversial modality for oral cancer.

To evaluate excisional biopsy for early SCC of the oral cavity, we carried out a clinicopathological study of 58 patients with stage I and II oral SCC treated by excisional biopsy. We also discuss indications for the procedure and treatment strategy.

Table 1. Summary of 58 patients with stage I and II squamous cell carcinoma (SCC) of the oral cavity treated by excisional biopsy

Age (years)	mean ± SD 59.7 ± 16.2	(range, 27–90 years)
Sex	Male	37 (63.8%)
	Female	21 (36.2%)
Clinical stage	Stage I	46 (79.3%)
	Stage II	12 (20.7%)
Tumor site	Tongue	36 (62.1%)
	Gingiva	9 (15.5%)
	Floor of the mouth	8 (13.8%)
	Buccal mucosa	5 (8.6%)
Recurrence	None	43 (74.1%)
	Primary site	8 (13.8%)
	Neck	7 (12.1%)
Outcome	Alive	52 (89.7%)
	Died of cancer	0 (0.0%)
	Died of unrelated causes	6 (10.3%)

Patients and methods

Patients

Were reviewed 58 patients who received excisional biopsy among 113 surgically treated patients with stage I or II SCC of the oral cavity at the Department of Oral and Maxillofacial Surgery, Kurume University Hospital. Forty-six (67.6%) of 68 stage I tumors and 12 (26.7%) of 45 stage II tumors were treated by excisional biopsy. The clinical profiles of the 58 patients are summarized in Table 1. Excisional biopsy was performed for small and localized tumors i.e., when the vertical palpated induration did not exceed half of the maximum tumor size. Fifty-five (94.8%) of the 58 tumors were locally excised with at least a 5-mm of surgical safety margin and alveolectomy was also performed for 3 tumors of the gum. When an induration was palpated in a lesion, a concave excision with deep margins was done. Preoperatively, exfoliative cytology was performed for 74.1% of the 58 patients, with 83.7% accuracy of diagnosis obtained. In addition, intraoperative rapid frozen section diagnoses were also performed to confirm margin status. Neither elective neck dissection nor adjuvant radiotherapy was done. Peplomycin was administered preoperatively and tegafur was given for 6 months postoperatively, with 43 of the 58 patients (74.1%) receiving chemotherapy. Follow-up ranged from 28 to 237 months (median, 56 months).

Excised oral tissue specimens were serially sectioned into 3-mm-thicknesses after fixation with 10% buffered formalin. The sections were embedded in paraffin and stained with hematoxylin and eosin. Each section was examined microscopically. Four of the 58 surgical specimens revealed carcinoma in situ (CIS), and the remaining 54 specimens revealed invasive SCC.

Clinicopathologic data

The following clinicopathological parameters were utilized in the study: patient age and sex, tumor site, clinical growth pattern, tumor size, tumor thickness, histologic grade, mode of invasion at the tumor-host borderline, degree of dysplasia of the pericancerous epithelium, and margin status. The clinical growth pattern of the tumor was divided into three types by palpation and macroscopic appearance: superficial, an erosive, erythroplakic or leukoplakic lesion without induration; exophytic, a lesion with papillary or granular appearance; and endophytic, an ulcerative or indurative lesion.[8] Tumor thickness was measured from the mucosal surface to the point of furthest penetration into the underlying tissue, using an ocular micrometer. Surface keratin, parakeratin, inflammatory exudate, and glandular involvement were excluded from the measurements. Histologic grade was classified as "well differentiated," "moderate," or "poor" according to the degree of differentiation, based on the degree of keratinization, presence or absence of intracellular bridges, and degree of nuclear pleomorphism. Mode of invasion at the tumor-host borderline was classified into three types (W, M, and D) as described previously.[9] Briefly, type W had a well-defined borderline, type M exhibited groups of tumor cells and had no distinct borderline, and type D spread in small aggregates with finger-like projections or invaded diffusely without forming nests of tumor cells. The degree of dysplasia of the pericancerous epithelium was graded as "slight," "moderate," or "severe" based on the *General rules for clinical and pathological studies on head and neck cancer* established by the Japan Society for Head and Neck Cancer in 1991. Margin status was evaluated in all directions in each section, and was described as "free," "close," and "positive". Specimens with dysplasia or carcinoma at the margin were classified as "positive". Specimens in which the tumor was less than 5 mm from the margin were classified as "close". Only for tumors 5 mm or more distant from the margin was the margin classified as "free".

The data were analyzed for treatment outcome with respect to the clinicopathologic factors. The data obtained were analyzed by either χ^2-square test, Mann-Whitney's test, or unpaired Student's *t*-test.

Results

The cancer recurred in 15 (25.9%) of the 58 patients; 8 (13.7%) at the primary site and 7 (12.1%) in the neck. All patients with local or regional recurrent tumors were cured by salvage treatment. Of the 58 patients evaluated, 52 were alive and clinically free of disease at the time of analysis, and 6 were free of disease when they died of unrelated causes. Thus, the 5-year cumulative survival rate was 88.0% for the patients with stage I and II oral SCC treated by excisional biopsy.

As shown in Table 2, margin status was the only factor affecting local recurrence of locally excised tumors. Thirty-one patients had *free* margins (53.4%); 23, *close* margins (39.7%); and 4, *positive* margins (6.9%). Positive margins occurred at the lateral margins, not in the deep margins. All patients with positive margins were observed carefully; 3 of them showed recurrence at the primary site. Patients who

Table 2. Locoregional recurrence in the 58 patients with stage I and II SCC of the oral cavity treated by excisional biopsy

	Total no. of patients (tumors)	No. of local recurrences (%)	*P* value	No. of neck metastases (%)	*P* value
Tumor site					
Tongue	36	7 (19.4%)		5 (19.4%)	
Gingiva	9	0 (0.0%)		1 (11.1%)	
Floor of the mouth	8	1 (12.5%)		1 (12.5%)	
Buccal mucosa	5	0 (0.0%)	NS	0 (0.0%)	NS
Tumor size (mm)					
0–10	11	2 (18.2%)		1 (9.1%)	
11–20	35	4 (11.4%)		4 (11.4%)	
21–30	8	1 (12.5%)		1 (12.5%)	
31–40	4	1 (25.0%)	NS	1 (25.0%)	NS
Clinical growth pattern					
Superficial	15	3 (20.0%)		0 (0.0%)	
Exophytic	25	4 (16.0%)		0 (0.0%)	
Endophytic	18	1 (5.6%)	NS	7 (38.9%)	<0.0001
Histologic grade					
In situ	4	1 (25.0%)		0 (0.0%)	
Well differentiated	43	6 (14.0%)		4 (9.3%)	
Moderate	9	1 (11.1%)		2 (22.2%)	
Poor	2	0 (0.0%)	NS	1 (50.0%)	NS
Mode of invasion					
W	20	2 (10.0%)		0 (0.0%)	
M	23	5 (21.7%)		1 (4.3%)	
D	15	1 (6.7%)	NS	6 (40.0%)	0.0001
Depth of invasion (mm)					
In situ	4	1 (25.0%)		0 (0.0%)	
≤1.50	19	3 (15.8%)		0 (0.0%)	
1.50–3.00	18	0 (0.0%)		1 (5.6%)	
3.00–6.00	14	4 (28.6%)		4 (28.6%)	
>6.00	3	0 (0.0%)	NS	2 (66.7%)	0.0004
Epithelial dysplasia					
Absent	29	2 (6.9%)		5 (17.2%)	
Present Slight	14	2 (14.3%)		1 (7.1%)	
Moderate	13	3 (23.1%)		0 (0.0%)	
Severe	2	1 (50.0%)	NS	1 (50.0%)	NS
Margin status					
Free	31	2 (6.5%)		6 (19.4%)	
Close	23	3 (13.0%)		1 (4.3%)	
Positive	4	3 (75.0%)	0.007	0 (0.0%)	NS

NS, Not significnt. For definitions of "free", "close", and "positive", and W, M, and D, see text

had positive margins had a significantly higher incidence of recurrence than those who had free or close margins ($P < 0.05$). With regard to pericancerous epithelial dysplasia, 2 (6.9%) of 29 tumors without epithelial dysplasia had recurred at the primary site, whereas 6 (20.7%) of 29 tumors with pericancerous dysplasia had recurred; however, this difference was not significant. Concerning the clinical growth pattern, the 58 tumors were classified as 17 superficial type (29.3%), 23 exophytic type (39.7%), and 18 endophytic type (31%). Local recurrence was present in 3 of 17 superficial tumors (17.6%), 4 of 23 exophytic tumors (17.4%), and 1 of 18 endophytic tumors (5.6%); however, the differences were not significant.

Factors significantly predicting the risk of neck metastasis were the clinical growth pattern ($P < 0.001$), mode of invasion ($P = 0.01$), and depth of invasion ($P = 0.002$). None of the superficial and exophytic tumors showed neck metastasis; all tumors which subsequently developed neck metastasis showed an endophytic growth pattern. Thus endophytic tumors metastasized in the neck with a significantly higher incidence than superficial or exophytic tumors ($P < 0.001$). In addition, 6 of 7 tumors with neck metastasis (85.7%) showed a diffuse invasive mode and invaded more than 3 mm in depth. As tumors increased in size, the incidence of neck metastasis increased as well. Tumor size alone, however, was not a reliable parameter for predicting the risk of neck metastasis. As tumors increased in size, the depth of invasion also increased. In particular, both the exophytic and endophytic types showed a positive correlation between tumor size and depth of invasion (exophytic type, $R^2 = 0.679$; endophytic type, $R^2 = 0.465$) (Fig. 1).

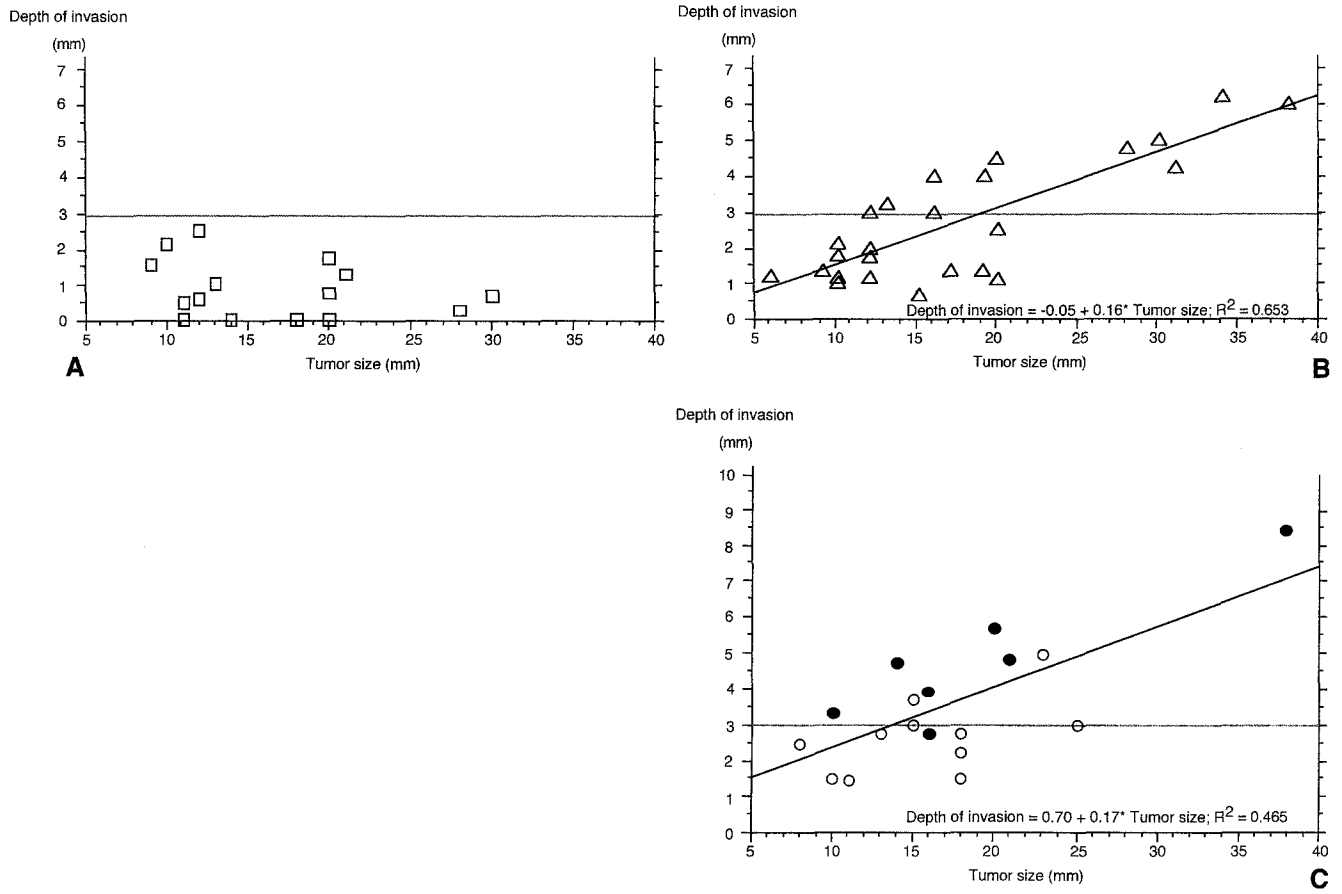

Fig. 1A–C. Correlation between tumor size and depth of invasion. The tumor size and depth of invasion of each tumor was plotted according to the clinical growth pattern. **A** All 15 superficial tumors showed less than 3-mm depth of invasion, and there was no relation between tumor size and depth of invasion. **B** Exophytic tumors showed a positive correlation between tumor size and depth of invasion ($R^2 = 0.653$). **C** Endophytic tumors also showed a positive correlation between tumor size and depth of invasion ($R^2 = 0.465$). Six of eight tumors showing over 3-mm depth of invasion developed neck metastasis (•)

Table 3. Correlation between clinical growth pattern and pathologic parameters in 58 patients with stage I and II SCC of the oral cavity treated by excisional biopsy

Pathology parameters	Clinical growth pattern			
	Superficial type ($n = 15$)	Exophytic type ($n = 25$)	Endophytic type ($n = 18$)	P value
Histologic grade				
In situ	4 (26.7%)	0 (0.0%)	0 (0.0%)	
Well differentiated	9 (60.0%)	21 (84.0%)	13 (72.2%)	
Moderate	2 (13.3%)	4 (16.0%)	3 (16.7%)	
Poor	0 (0.0%)	0 (0.0%)	2 (11.1%)	0.010
Mode of invasion				
W	9 (60.0%)	11 (44.0%)	0 (0.0%)	
M	6 (40.0%)	10 (40.0%)	7 (38.9%)	
D	0 (0.0%)	4 (16.0%)	11 (61.1%)	0.0001
Depth of invasion (mm)				
≤3.00	15 (100%)	16 (64.0%)	10 (55.6%)	
>3.00	0 (0.0%)	9 (36.0%)	8 (44.4%)	0.013
Epithelial dysplasia				
Absent	4 (26.7%)	13 (52.0%)	12 (66.7%)	
Present	11 (73.3%)	12 (48.0%)	6 (33.3%)	0.070
Margin status				
Free	8 (53.3%)	9 (36.0%)	13 (72.2%)	
Close	5 (33.3%)	14 (56.0%)	5 (27.8%)	
Positive	2 (13.3%)	2 (8.0%)	0 (0.0%)	0.127

Table 4. Correlation between margin status and dysplasia in 58 patients with stage I and II SCC of the oral cavity treated by excisional biopsy

Dysplasia	Margin status				
	Free	Close	Dysplasia	Invasive cancer	Total (%)
None	0/20	1/8 (9m)	–	1/1 (12m)	2/29 (6.9%)
Mild	1/7 (24m)	1/7 (5m)	–	–	2/14 (14.3%)
Moderate	1/2 (36m)	0/8	2/3 (5.20m)	–	3/13 (23.1%)
Severe	0/1	1/1 (16m)	–	–	1/2 (50.0%)
Total (%)	2/30 (6.7%)	3/24 (12.5%)	2/3 (66.7%)	1/1 (100%)	8/58 (13.8%)

m, month
*($P = 0.023$), Significant correlation

Histologically, four of the 43 well-differentiated SCCs (9.3%), 2 of 9 moderately differentiated SCCs (22.2%), and 1 of 2 poorly differentiated SCCs (50%), exhibited neck metastasis. However, the number of patients with poorly differentiated SCC was too small to predict neck metastasis.

The relationship between tumor site, tumor size, depth of invasion, degree of histological differentiation, mode of invasion, and local recurrence was also analyzed, but no significant correlations were shown. Similarly, we found no correlation between tumor site, pericancerous dysplasia, margin status, and neck metastasis.

Among the clinical parameters, clinical growth pattern was the only parameter that was well correlated with pathologic parameters, including mode of invasion ($P = 0.001$), degree of histological differentiation ($P = 0.01$), and depth of invasion ($P = 0.013$) (Table 3).

Discussion

Complete resection of a malignant tumor can eliminate recurrence and secure local control of the disease.[10] Jones et al.[11] reported a 20% incidence of positive margins and a 24.5% incidence of local recurrence in patients with stage I and II oral SCC treated by surgical excision. Similarly, Loree and Strong[12] reported a 29.0% incidence of positive margins and a 29.5% local recurrence rate. Compared with these two studies' results, we found a lower incidence of positive margins and local recurrence, of 6.9% and 13.8%, respectively. However, our 39.7% incidence of close margins cannot be disregarded. The factor most affecting margin status is the presence of pericancerous epithelial dysplasia, which makes it more difficult to define the extent of the tumor. In fact, we found that 67.9% of tumors with close or positive margins were accompanied by pericancerous epithelial dysplasia, whereas the rate among tumors with free margins was 33.3%. Table 4 shows the correlation between margin status and pericancerous epithelial dysplasia. Tumors with close or positive margins were associated with a local recurrence rate of 21.4%, while tumors with free margins recurred 6.7% of the time. These results suggest that the margins should be at least 5mm distant from the lesion, to include any epithelial dysplasia.

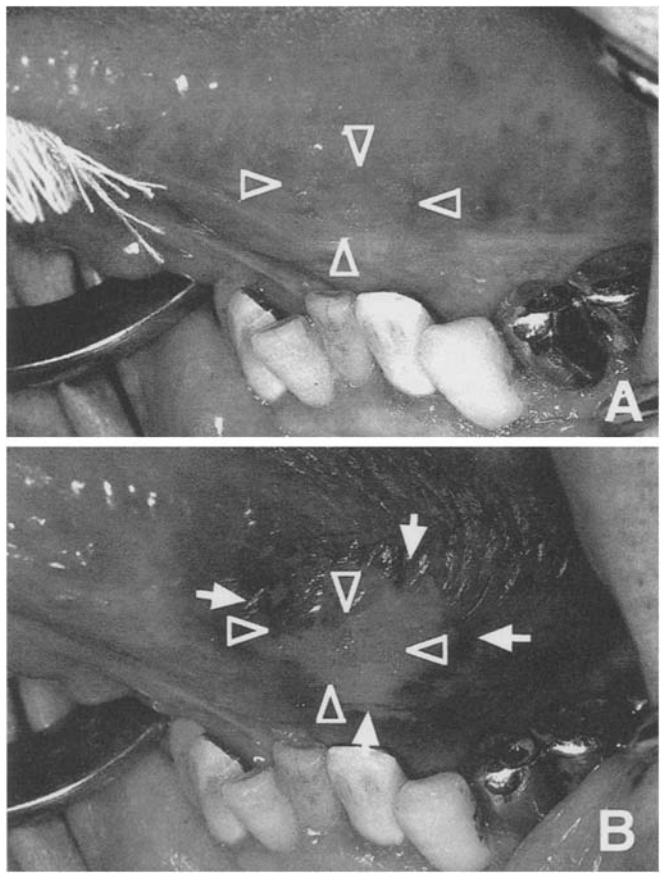

Fig. 2. **A** Before and **B** after vital staining with iodine glycerin (Lugol). Dental iodine glycerin was applied for microinvasive squamous cell carcinoma of the tongue. Macroscopically detectable lesion (*arrowheads*) and undetectable dysplastic epithelium (*arrows*) showing as lack of staining with iodine

Although it is difficult to distinguish precancerous lesions from CIS and early invasive carcinoma clinically, precancerous mucosa adjacent to carcinoma, if present, should be excised simultaneously at the primary operation. Exfoliative cytology alone is not sufficient to determine whether the lesion is malignant; however, our latest study revealed that accuracy was improved from the 83.7% shown in the present study to 94.7% by using an interdental brush

for sample collection.[13] Vital staining combined with exfoliative cytology should be useful to detect dysplastic epithelium (Fig. 2).[14–16]

The results of our present study revealed that factors predicting the risk of neck metastasis were clinical growth pattern, mode of invasion, and depth of invasion. The clinical growth pattern was well correlated with pathologic parameters associated with neck metastasis, such as mode of invasion and depth of invasion.

As endophytic tumors invade diffusely and deeply, they should be excised, taking into account their deep margins.[6,17] The cutoff point we found most strongly associated with neck metastasis was when the depth of invasion was categorized as greater or less than 3 mm. As shown in Fig. 1, there was a positive correlation between tumor size and depth of invasion in both the endophytic type ($R^2 = 0.465$) and exophytic type ($R^2 = 0.653$) of tumor. According to the clinical growth pattern, the regression lines of exophytic and endophytic types were expressed as "depth of invasion (mm)" = 0.16 × "tumor size (mm)" − 0.05 and "depth of invasion (mm)" = 0.17 × "tumor size (mm)" + 0.70, respectively. Based on these formulae, exophytic tumors exceeding 20 mm in size and endophytic tumors 15 mm or more in size would invade 3 mm or more in depth. Because excisional biopsy should be limited to localized tumors, in which neck metastasis has not occurred, exophytic tumors less than 20 mm in size and endophytic tumors less than 15 mm in size can be treated with excisional biopsy. However it is difficult to know how tumors should be excised in the deep portion. In this series, we performed concave excision combined with intraoperative rapid frozen section diagnosis to confirm cancer-free margins, and with all of these excisions we obtained cancer-free margins in the deep portion. Intraoral ultrasound examination of lesions should also be helpful to evaluate the depth of invasion.

Superficial tumors did not exceed 3 mm in depth of invasion, regardless of tumor size; however, 73.3% of superficial tumors were accompanied by epithelial dysplasia adjacent to the carcinoma. In superficial tumors, lesions including epithelial dysplasia of 30 mm less in size can be treated by excisional biopsy alone.

The need to treat the neck in patients with a small primary oral cancer remains controversial. In our literature review, we found that some authors recommended elective neck dissection for stage I and II tumors, particularly those showing a high risk of neck metastasis on histology, because of a significant incidence of occult metastases and low salvage rates.[18–21] In our series, however, seven patients (12.1%) who developed neck metastasis were salvaged by subsequent neck dissection. We adopt a policy of "wait and see" for these tumors to avoid unnecessary surgical intervention.

In conclusion, excisional biopsy is an effective treatment for patients with a small and localized SCC tumor of the oral cavity which does not exceed 3 mm in depth of invasion.

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