## The influence of mild dysplasia at the surgical margin on the prognosis of oral squamous cell carcinoma

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*Abstract.* The purpose of this study was to evaluate the clinical relevance between different margin statuses and local recurrence rate in patients undergoing primary surgical treatment for oral squamous cell carcinoma (OSCC). Five hundred and thirty-nine patients with T1-4N0M0 OSCC, who underwent surgery alone at a stomatology hospital in Nanjing, China during the years 2005-2014, were included. Tumour and margin status were assessed. Overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) were calculated by Kaplan-Meier method. Predictors of RFS, OS, and DFS were analysed. Positive or dysplastic margins were found in the initial specimen in 20.0% of the cases. On multivariate analysis, there was no significant difference between RFS (hazard ratio (HR) 1.379, P = 0.361) or DFS (HR 1.452, P = 0.183) of those with mild dysplasia and those with negative margins. However, patients with mild dysplasia who did not undergo reexcision demonstrated significantly worse RFS (HR 2.286, P = 0.010) and DFS (HR 2.070, P = 0.014) than those with negative margins. It is concluded that there appears to be a correlation between initial mild dysplastic margins that are not subjected to reexcision and inferior RFS and DFS. Additional attention should be drawn to mild dysplasia at the initial margin in OSCC, and extended excision is suggested.

For oral squamous cell carcinoma (OSCC), an overarching goal of oncologic surgery is to complete the tumour resection with histological tumour-free margins.<sup>1</sup> Adequate surgical resection is crucial for local control and the prognosis.<sup>2–4</sup> Conversely, a positive margin increases the risk of local relapse and is an indicator for postoperative adjuvant therapy.<sup>5,6</sup> In the National Comprehensive Cancer Network (NCCN) guidelines, a positive margin is defined as carcinoma *in situ* or as invasive carcinoma at the initial margin of resection. Sopka et al. reported that both severe and moderate dysplasia at the initial margin appear to be correlated with inferior local control and disease-free survival (DFS).<sup>7</sup> Additional therapy may be justi-

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fied, despite the added morbidity.<sup>3</sup> The College of American Pathologists, in its *Protocol for the Examination of Specimens from Patients with Carcinomas of the Lip and Oral Cavity*, states that keratinizing moderate and severe dysplasia should be

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viewed as a single category relative to the risk of progression to invasive carcinoma. Such a risk does not include keratinizing mild dysplasia. However, others have suggested that OSCC patients with mild dysplasia at the initial margin should be treated with re-excision,<sup>8</sup> or close observation.<sup>9</sup>

What is the correlation between different initial margin statuses and the prognosis of OSCC? Is mild dysplasia at the initial margin really irrelevant to the prognosis, or is it in fact an indicator for an extended resection?

The purpose of the present study was to perform a retrospective investigation of the clinical relevance of different margin statuses in the initial margin of surgically treated primary OSCC, especially mild dysplasia, with regard to the development of local recurrence.

#### Materials and methods

#### Patients and pathological examinations

This retrospective study included 539 patients diagnosed with primary OSCC of pT1–4N0M0 at a stomatology hospital in Nanjing, China during the years 2005–2014. Relevant clinical and pathological variables are shown in Table 1. The median age at diagnosis was 60.7 years (range 28–88 years), and the median duration of follow-up was 45.5 months (range 7–126 months). Tumours were graded as well-differentiated (52.1%) or moderately to poorly differentiated (47.9%) in accordance with the World

Table 1.	Clinical pathologic characteristics o	)
OSCC pa	atients.	

Patients and tumor characteristics	All Patients	
enaracteristics	n	%
Total	539	100.0
Gender		
Male	271	50.3
Female	268	49.7
Age		
<60	232	43.0
$\geq 60$	307	57.0
Smoking		
No	135	25.0
Yes	404	75.0
Stage		
I-II	444	82.4
III-IV	95	17.6
Differentiation		
Well	281	52.1
Medium to poor	258	47.9
Margin status		
Negative	431	80.0
Mild dysplasia	67	12.4
Moderate dysplasia	23	4.3
Severe dysplasia & positive	18	3.3

OSCC, oral squamous cell carcinoma.

Health Organization (WHO) guidelines.<sup>10</sup> T1 and T2 tumours were diagnosed in 444 patients (82.4%) and T3 and T4 tumours in 95 (17.6%).

The lesion was excised with clinically appropriate margins in all of the cases studied, and margin status was analysed by frozen section with samples taken at the tumour bed. Margins with dysplasia, positive margins, or both were observed in 20.0% of cases (mild dysplasia 12.4%, moderate dysplasia 4.3%, severe dysplasia and positive margins 3.3%). All close or positive margins (including moderate or severe dysplasia at/near the surgical margin), as well as 21 of 67 cases with mild dysplasia at the margin in the initial frozen section, were resected to gain tumour-free margins (negative or mild dysplasia). Both the primary and the permanent section were collected if an additional resection was performed. It was the initial frozen section of the separately submitted margin that was interpreted as the margin status for this retrospective analysis; however the patients with mild dysplasia were divided into two subgroups: those who underwent re-excision (with negative final margins) and those who did not (with mild dysplastic final margins).

Patients who did not undergo pre- or postoperative chemotherapy and/or radiotherapy were selected to exclude the influence of the adjuvant therapy. However, adjuvant therapy is suggested for patients with severe dysplasia at the initial margin, a positive margin, and in some cases of moderate dysplasia where there are other accompanying risk factors.<sup>11</sup>

The use of patient samples and the data inquiry were approved by the research ethics committee of the stomatology hospital. The data collected included the following variables as potential predictors of



*Fig. 1.* Univariate analysis: (a) overall survival, (b) recurrence-free survival, and (c) disease-free survival according to the margin status, including negative, mild dysplasia, moderate dysplasia, and severe dysplasia.

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