ORIGINAL ARTICLE

Clinical features of microinvasive stage I oral carcinoma

M Pentenero[1], R Navone[2], F Motta[3], R Marino[1], L Gassino[1], R Broccoletti[4], S Gandolfo[1]

[1]Department of Clinical and Biological Sciences, Oral Medicine and Oral Oncology Section, University of Turin, Orbassano (TO); [2]Department of Biomedical Sciences and Human Oncology, Pathology Section, University of Turin, Torino; [3]SCDU Odontostomatology, AOU S. Luigi Gonzaga, Orbassano (TO); [4]Department of Biomedical Sciences and Human Oncology, Oral Medicine Section, University of Turin, Torino, Italy

BACKGROUND: This study aimed to analyse a case series of microinvasive (tumour thickness <4 mm) stage I oral squamous cell carcinoma (OSCC), with an emphasis on the clinical features of the tumours.
METHODS: In total, 32 microinvasive and 67 non-microinvasive stage I lesions, which had been surgically treated, were retrospectively studied and compared. The data analysed included gender, age, risk habits, clinical appearance, lesion site, symptoms, nodal involvement and outcome.
RESULTS: The clinical features of microinvasive lesions meant that, more often than not, they resembled premalignant lesions ($P = 0.008$), and diagnosis was mainly based on accurate clinical examination rather than the presence of symptoms ($P = 0.029$). During a median follow-up of 4.5 years, one nodal involvement and one cancer-related death were observed in patients with microinvasive lesions. A significantly higher ($P = 0.044$) level of nodal involvement was observed in the non-microinvasive lesion group.
CONCLUSIONS: Stage I OSCC has a favourable prognosis overall, but nodal recurrence is more common in non-microinvasive cancers. As microinvasive lesions tend to present clinically as premalignant lesions, accurate clinical examination is essential if misdiagnosis of early lesions is to be avoided.
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Introduction

Microinvasive carcinoma is an early-stage, relatively thin tumour, without invasion of deep tissues.

Several studies (Pentenero *et al*, 2005) and a recent meta-analysis of the international literature (Huang *et al*, 2009) demonstrated how tumour thickness could affect both nodal involvement and survival. This evidence led to the proposal of a modified pathological tumour, node, metastasis (pTNM) staging system, in which three cut-offs points for tumour thickness (5, 10 and 20 mm) were combined with the largest tumour dimension to obtain the pT stage (Howaldt *et al*, 1999).

Depth of invasion (DOI) and tumour thickness (TT) are not the same. 'Depth of invasion' means the extent of cancer growth into the tissue beneath an epithelial surface. In cases in which epithelium has been destroyed, some investigators reconstruct a surface line and measure downwards from it. However, the DOI is sometimes expressed by referring to the microscopic, anatomical deep structures that are reached, rather than by referring to objective micrometer measurements in millimetres (Thompson, 1986; Breuninger *et al*, 1990; Okamoto *et al*, 2002). In this case, agreement between pathologists is less readily achieved, because a series of subjective assessments are needed to determine the level of invasion (Breslow, 1977). By contrast, 'tumour thickness' refers to the entire tumour mass; an objective parameter is needed, and the measurement can be obtained using an ocular micrometer.

Proximity to blood vessels and lymphatics determines the risk of developing nodal metastases, as close proximity facilitates the tumour's ability to disseminate. Therefore, it may be more accurate to consider the actual mass that is present beneath the theoretical reconstruction of a basement membrane (DOI), rather than the thickness of the whole tumour (TT). However, measurement of DOI implies assessments that are more subjective. The first step (subjective identification of the deepest invading tumour cell) is the same for both DOI and TT. Next, for DOI, a series of subjective assessments are needed, whereas for TT, objective measurement can be undertaken. Therefore, TT should be considered as a more objective and reproducible parameter.

Studies on microinvasive oral carcinomas have mainly focused on nodal involvement and survival, whereas, to our knowledge, no studies have examined a series of

microinvasive cancer by describing the clinical features. The clinical features of early-stage carcinomas have been already described in the literature, but have not been related to TT.

The aim of this study was to analyse a case series of early-stage (stage I) microinvasive oral carcinomas, to discover whether any clinical features could be related to the microinvasive histological status of the lesions. For this purpose, the tumours were compared with non-microinvasive stage I oral carcinomas.

Materials and methods

A retrospective study was performed on patients who were surgically treated for clinical stage I (cT1N0M0) (Sobin and Wittekind, 2002) oral squamous cell carcinoma (OSCC) at the Oral Medicine and Oral Oncology Section of the University of Turin.

Patients with previous upper-aero digestive tract cancer, or those who had been treated by adjuvant or neo-adjuvant therapies other than surgery to the neck, were excluded.

Preoperative staging was based on clinical examination (palpation) and imaging data. Each patient was assessed by ultrasonography (US) and by at least one other imaging technique [computed tomography (CT) or magnetic resonance (MRI)]. Lymph nodes with abnormal appearance suggestive of metastases were diagnosed by established criteria (Sakai *et al*, 2000), including nodal size (>15 mm for levels I and II, >10 mm for levels III–V). In addition, any lymph node with a central lucency that suggested necrosis was considered malignant, regardless of its size; conversely, lymph nodes of border line size (10–15 mm for levels I and II and 8–10 mm for levels III–V) were considered positive if there were other signs suggestive of malignant involvement such as nodes spherical in shape (rather than being flat or bean-shaped), rim enhancement with central necrosis or cystic degeneration and presence of abnormally grouped lymph nodes.

Assessment of tumour thickness
To devise a more objective measurement procedure, it was decided to define microinvasiveness using TT rather than DOI. Various cut-off values for TT and DOI have been proposed in the literature, with 4 and 5 mm being the most frequently used. In the absence of an international consensus on the cut-off value to be used, in this study, a cut-off value of 4 mm for TT was used to define microinvasive lesions. To obtain a standardized assessment of the TT, an experienced pathologist blindly reviewed the histological slides of all the selected cases. Thickness was measured by an optical micrometer, measuring from the surface to the maximum depth of the tumour (Figure 1). Using the cut-off value of 4 mm, a subgroup of microinvasive lesions was identified.

Clinical data
Data such as gender, age, risk habits (tobacco and/or alcohol), clinical appearance of the lesion/s for example, flat or patches, plaques, verrucous lesions and/or
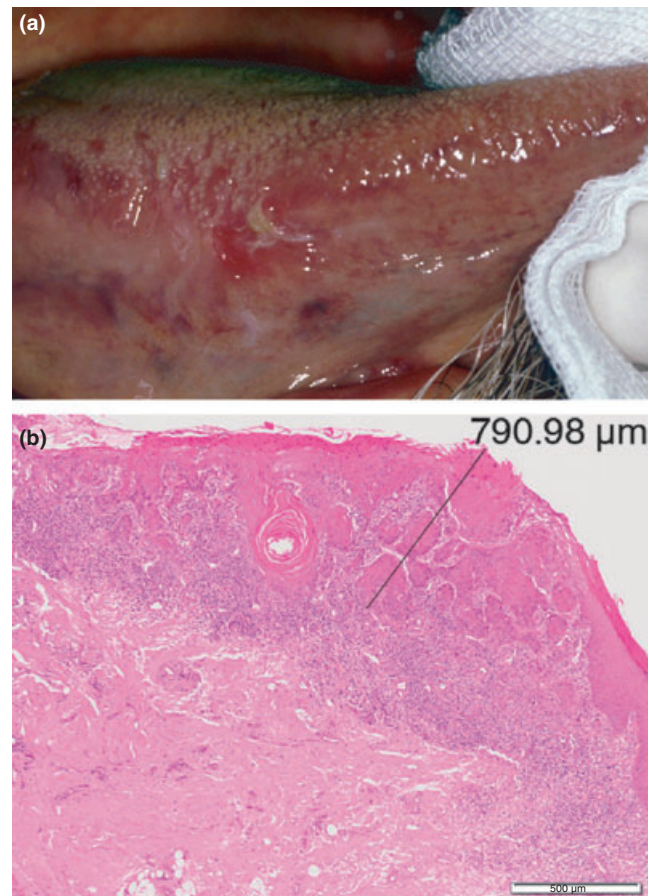
Figure 1 Microinvasive carcinoma: clinical aspect resembling a non-homogeneous premalignant lesion (a) and tumour thickness measurement (b) (Haematoxylin–Eosin, 30×)

erosions/ulcers and lesion site were collected from the patients' records. The histological type of the mucosa (thin, vestibular or masticatory), location in the oral cavity (anterior/posterior), symptoms and outcome, were all recorded. Lesions were considered symptomatic if there was any sensation inducing the patient to visit a doctor. The anterior/posterior location was defined by referring to an imaginary coronal plane passing through the premolar area. The motivation for the visit was defined as 'referred by dentist' in cases of incidental findings of asymptomatic lesions, which were occasionally observed during routine dental visits or treatments and prompted a referral.

Smoking habit was recorded as positive for both active and former smokers. The use of smokeless (e.g. chewing) tobacco was not considered, as the practice is almost non-existent in Italy. The consumption of at least one alcoholic unit per day (1 unit = 8–10 g of ethanol = 1 glass of wine = ¼ l of beer = 1 measure of liqueur) was considered alcohol exposure.

Data on treatment methods and delayed nodal involvement or cancer-related deaths were obtained from the follow-up clinical charts.

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Statistical analysis

Comparisons between dichotomous variables were assessed by using the chi-square test with Yates correction or the Fisher's exact test, and analysis of variance (ANOVA) was used to test for comparability of age (having proved normal distribution of values). Survival was calculated by Kaplan–Meier analysis using the log-rank test. All the statistical procedures were performed using the SPSS 17.0 software package (Apache Software Foundation, Chicago, IL, USA). A P-value of ≤0.05 was considered significant.

Results

In total, 99 patients (56 men and 43 women), surgically treated for stage I OSCC, were retrieved from the computerized patient database. Mean age at diagnosis was 64.2 years (range 30–92 years, median 67 years). Gender was a significant parameter for risk habits: both tobacco ($P = 0.007$) and alcohol ($P = 0.002$) consumption were more common in men, but no differences were observed in age ($P = 0.892$) or presence of symptoms ($P = 0.596$).

Lesions were located on the ventral tongue/tongue border (54/99; 54.5%), buccal mucosa (18/99; 18.2%), floor of the mouth (16/99; 16.2%), gingiva (6/99; 6.1%), lip (4/99; 4.0%) and hard palate (1/99; 1.0%). These locations meant that there were 70/99 (70.7%) lesions on thin mucosa, 22/99 (22.2%) on vestibular mucosa and 7/99 (7.1%) on masticatory mucosa. Anterior lesions were present in 35/99 (35.4%) cases, median lesions in 22/99 (22.2%) and posterior lesions in 42/99 (42.4%).

Using the TT measurement, the lesions were divided into 32 microinvasive and 67 non-microinvasive lesions (Table 1). Microinvasive OSCC were not significantly related to gender ($P = 0.141$), age ($P = 0.204$), tobacco ($P = 0.904$) or alcohol ($P = 0.071$) habit, presence of symptoms ($P = 0.351$), mucosal type ($P = 0.889$), site ($P = 0.583$) or location ($P = 0.480$) of the lesions. Microinvasive lesions had distinctive clinical features, present more frequently as patches, plaques or erosions rather than as ulcers or verrucous lesions ($P = 0.008$). They were also more likely to be diagnosed either as the results of an incidental finding during routine dental visits or during follow-up visits for premalignant disorders, rather than because of presence of symptoms ($P = 0.029$).

Treatment and follow-up

To plan for surgical resection, clinical, histological and imaging (US, CT, MRI) data were used. The traditional policy at our unit for management of the clinically negative neck in T1 OSCC has generally been a 'wait-and-see' policy, thus in the present series, elective neck dissection (END) was performed only in cases with borderline nodal features and/or tumour size at preoperative staging or in the presence of poorly differentiated lesions. END (levels I–III) was performed in 18/99 (18.2%) patients, corresponding to six microinvasive and 12 non-microinvasive lesions: five cases (all non-

Table 1 Clinical features related to tumour thickness

	Tumour thickness		
	< 4 mm	≥4 mm	P-value
Motivation for the visit[a]			
Referred by dentist	11 (34.4)	4 (10.5)	0.029
Follow-up of PMD	10 (31.3)	11 (28.9)	
Symptoms	11 (34.4)	23 (60.5)	
Site			
Tongue	15 (46.9)	39 (58.2)	0.583
Buccal	7 (21.9)	11 (16.4)	
Floor of the mouth	7 (21.9)	9 (13.4)	
Other	3 (9.4)	8 (11.9)	
Clinical aspect			
Erosion	7 (21.9)	3 (4.5)	0.008
Plaques	9 (28.1)	12 (17.9)	
Patch	4 (12.5)	2 (3.0)	
Ulcer	6 (18.8)	29 (43.3)	
Verrucous lesions	5 (15.6)	18 (26.9)	
Node	1 (3.1)	3 (4.5)	
Location			
Anterior	14 (43.8)	21 (31.3)	0.480
Median	6 (18.8)	16 (23.9)	
Posterior	12 (37.5)	30 (44.8)	
Mucosal type			
Thin	22 (68.8)	48 (71.6)	0.889
Vestibular	8 (25.0)	14 (20.9)	
Masticatory	2 (6.3)	5 (7.5)	
Symptoms[b]			
Yes	15 (46.9)	22 (61.1)	0.351
No	17 (53.1)	14 (38.9)	
Tobacco			
Yes	15 (46.9)	29 (43.3)	0.904
No	17 (53.1)	38 (56.7)	
Alcohol			
Yes	8 (25.0)	31 (46.3)	0.071
No	24 (75.0)	36 (53.7)	

Values given in parentheses are percentages.
[a]Data available for 70 patients.
[b]Data available for 68 patients.

microinvasive) were diagnosed as pN+. As stated above, none of the remaining 81 patients had undergone adjuvant or neo-adjuvant therapies other than surgery to the neck.

Patients were followed up with clinical evaluation and US every 3 months for the first 36 months, every 6 months for the following 36 months and then once a year. Chest X-ray was performed once a year. Further assessments (CT, MRI, US-guided fine-needle aspiration biopsy) were performed in cases of positive or suspicious results at routine evaluations. The median follow-up was 4.5 years (mean 5.3, range 0.3–13.3); during that period, nine regional recurrences (9.1%) and five cancer-related deaths (5.1%) were recorded. Regional recurrence occurred in 1/32 patients (3.1%) with microinvasive lesions and in 8/67 (11.9%) with non-microinvasive lesions; cancer-related death occurred in 1/32 patients (3.1%) with microinvasive lesions and in 4/67 (6.0%) with non-microinvasive lesions. Kaplan–Meier curves gave a 5-year disease-specific survival rate for stage I OSCC of 95%; 96% for microinvasive lesions and 94.5% for non-microinvasive lesions ($P = 0.550$). Conversely, a recurrence time (mean ± s.d.) of

2.3 ± 2.5 years for nodal involvement was observed and the Kaplan–Meier curves showed a 5-year survival rate of 86.1%; 96.4% for microinvasive lesions and 81.5% for non-microinvasive lesions (log-rank test, $P = 0.044$), thus corresponding to a negative predictive value of 96.9% for microinvasive lesions.

Discussion

This retrospective study offers an original contribution about microinvasive oral cancer, as it evaluates the clinical features and factors related to diagnosis in a homogeneous sample of lesions (all stage I).

In agreement with data from international literature (Kim *et al*, 1993; Fukano *et al*, 1997; O-charoenrat *et al*, 2003; Gandolfo *et al*, 2006), we observed OSCC lesions more frequently in thin mucosa, with the tongue and the floor of the mouth being the most frequently affected sites. Notably, the buccal mucosa was also a relatively frequently affected site in the present series.

The present data confirmed that TT is significantly related to the clinical appearance of early-stage lesions: 'thin' lesions were similar to premalignant lesions, presenting as erosions, patches and plaques, whereas the 'thick' lesions were more likely to be ulcerated, with a low prevalence of erosions and/or patches. This stresses the importance of careful diagnostic evaluation of any apparently premalignant lesions.

Reports in the literature indicate that symptoms are uncommon in the earlier stages, and thus early diagnosis of asymptomatic OSCC requires a high clinical index of suspicion. Conversely, symptomatic lesions are more readily diagnosed, because a patient experiencing any discomfort will direct the clinician to the primary lesion (Mashberg and Samit, 1995).

In the present series of 99 patients with stage I OSCC, it was possible to identify the basis of diagnosis in 70 cases: the correct diagnosis was reached for almost half the patients, through an accurate clinical examination.

In total, 36/70 diagnoses (51.4%) were made during the follow-up for potentially malignant disorders, or occasionally, through detection of asymptomatic lesions. The issue of early diagnosis is even more important for microinvasive lesions; in the present series, only 11/32 (34.4%) diagnosed lesions produced symptoms ($P = 0.029$). It is noteworthy that 11/32 (34.4%) lesions were referred to us as an incidental finding during dental visits, thus highlighting the importance of dental practice as an essential aid in the early detection of suspicious intraoral lesions. Nevertheless, symptoms must be interpreted with care. As early cancer has frequently been reported to be asymptomatic, the presence of symptoms that are not strongly indicative of carcinoma (such as those indicating non-specific inflammation, trauma or other benign conditions) might induce general practitioners to interpret the symptoms incorrectly and consequently, fail to refer the patients for investigation, resulting in diagnostic delay.

The international literature reports significant links between the delay in diagnosis and location of the lesion on the less visible surfaces of the oral cavity (Kowalski *et al*, 1994; Gorsky and Dayan, 1995). In the present series, the microinvasive lesions occurred more frequently on the anterior sites, but this did not reach significance ($P = 0.480$). However, it is noteworthy that when anterior or posterior cases were considered separately, the presence of symptoms was frequently related to a diagnosis of anterior lesions ($P = 0.055$; data not shown). Consequently, the presence of symptoms did not seem to be helpful in achieving an early diagnosis in posterior (less visible) tumour lesions.

To date, there are no universally accepted guidelines for the treatment of clinically negative nodes in early-stage OSCC, and use of END is a continuing controversy (Fakih *et al*, 1989; Kligerman *et al*, 1994; Shah and Gil, 2009; Yuen *et al*, 2009), particularly in stage I lesions (Haddadin *et al*, 1999; Dias *et al*, 2001). In the present series, the improved 5-year disease-specific

Table 2 Nodal involvement related to tumour thickness/depth of invasion in stage I-II lesions

Author	TNM	Site	Cut-off value (mm)	Nodal involvement	
				N+/Total	%
Asakage *et al* (1998)	$T_{1,2}N_0$	Tongue	< 4	2/17	11.76
Fakih *et al* (1989)	$T_{1,2}N_0$	Tongue	< 4	1/12	8.33
Hayashi *et al* (2001)	$T_{1,2}N_0$	Tongue	< 5	0/6	0.00
Kim *et al* (1993)	$T_{1,2}N_0$	Oral cavity	< 3	8/59	13.56
Kurokawa *et al* (2002)	$T_{1,2}N_0$	Tongue	< 4	1/34	2.94
Lim *et al* (2004)	$T_{1,2}N_0$	Tongue	< 4	17/38	44.74
Matsuura *et al* (1998)	T_1N_0	Tongue	< 8	13/75	17.33
Mohit-Tabatabai *et al* (1986)	T_1N_0	Floor	≤3.5	2/43	4.65
Morton *et al* (1994)	$T_{<3cm}N_0$	Tongue	< 4	2/9	22.22
Nakagawa *et al* (2003)	$T_{1,2}N_0$	Tongue	< 4	38/191	19.90
O'Brien *et al* (2003)	T_1N_0	Oral cavity	< 4	0/27	0.00
O-charoenrat *et al* (2003)	$T_{1,2}N_0$	Tongue	≤5	4/25	16.00
Okamoto *et al* (2002)	$T_{1,2}N_0$	Tongue	< 4	2/22	9.09
Po Wing *et al* (2002)	$T_{1,2}N_0$	Tongue	≤3	1/12	8.33
Ross *et al* (2004)	$T_{1,2}N_0$	UADT	≤5	7/22	31.82
Sheahan *et al* (2003)	$T_{1,2}N_0$	Oral cavity	≤5	0/13	0.00
Shintani *et al* (1997)	$T_{1,2}N_0$	Tongue	< 5	2/19	10.53
Yamazaki *et al* (1998)	$T_{1,2}N_0$	Tongue	< 5	27/91	29.67

survival rate observed with END did not reach significance (100% *vs* 94%; *P* = 0.344), thus these data are not able to support a recommendation for END in stage I OSCC.

In the full series of 99 stage I OSCC cases, most of the regional recurrences (8/9; 88.9%) occurred within 2.2 years after surgery. The incidence of nodal recurrences detected during follow-up at 1–2 years after surgery is confirmed by the literature (Morton *et al*, 1994; Al Rajhi *et al*, 2000; Merkx *et al*, 2006) and confirms the effectiveness of follow-up in very early-stage tumours also.

The survival analysis for nodal involvement confirms the importance of TT in prognosis. The literature data on TT and nodal involvement in early-stage OSCC generally groups patients with stage I and II lesions together, making it difficult to carry out a comparison with the present results. Although numerous studies have assessed the role of TT in nodal involvement (Pentenero *et al*, 2005), it is rarely possible to extract data from these reports for stage I lesions alone. We found a slightly lower overall incidence of nodal involvement in stage I OSCC compared with the studies in the literature (Table 2). This may be a result of pooling stage I and II lesions as mentioned previously. Although the literature (Pentenero *et al*, 2005; Huang *et al*, 2009) generally seems to validate the link between TT and nodal involvement, not all authors agree on this issue; a recent study comparing TT and Sentinel Node Biopsy (SNB) found that SNB was more reliable than TT in predicting occult disease(Goerkem *et al*, 2010). However, this study was based on a series of stage I and II tumours with a prevalence of SNB-proven nodal involvement of 35.9%; this is not comparable with our study, which assessed stage I series with a prevalence of nodal involvement of 14.1%. Nevertheless, the cut-off value of 4 mm gave, in the present series, a lower prevalence of nodal involvement (either at diagnosis or during follow-up).

This study confirms the favourable prognosis overall of stage I OSCC. The evaluation of clinical appearance of microinvasive compared with non-microinvasive lesions is the most important issue of this study, and it does emphasizes the risk, during clinical examination, of underestimating the malignancy of early lesions that resemble premalignant disorders.

Acknowledgements

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