The Significance of Surface Ulceration as a Sign of Malignancy in Exophytic Oral Mucosal Lesions: Myth or Fact?

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Abstract To compare the spectrum of pathologies in ulcerated versus non-ulcerated exophytic oral mucosal lesions and explore the significance of surface ulceration as an indication of malignancy. Retrospective analysis of exophytic lesions of the oral mucosa, 2009–2011. 713 biopsies of exophytic lesions of oral mucosa were included, of which 9.4 % were ulcerated. Significant differences were found between ulcerated and non-ulcerated lesions. Of the ulcerated lesions 67.2 % were reactive, 31.3 % malignant and 1.5 % benign, compared to 86, 8.4 and 5.6 % respectively in non-ulcerated lesions ($p < 0.0001$). Malignancies were most prevalent in ulcerated lesions, in patients over 50. Malignancies presented the highest ulceration rate (36.8 %, $p < 0.001$), compared to reactive (7.5 %) and benign neoplasia (1.8 %), however, the majority of oral mucosal malignancies (63.2 %) presented

as non-ulcerated masses. Squamous cell carcinoma presented the highest ulceration rate among malignancies, but even these were only ulcerated in 50 % of cases. Non-epithelial malignancies were non-ulcerated in all cases. One-third of all malignancies were not suspected as such clinically, however, there was a better agreement between the clinical and microscopic diagnosis of malignancy in ulcerated lesions. Although the statistical likelihood of ulcerated masses to represent malignancy was higher than non-ulcerated lesions, especially in patients over 50, the majority of malignancies presented as non-ulcerated masses. Thus, all exophytic lesions should be submitted for microscopic analysis, and the status of ulceration should not be regarded neither as a factor in the decision to biopsy, nor a reliable indicator for malignancy.

Keywords Ulcerated · Mucosal mass · Exophytic · Reactive · Benign · Malignant · Squamous cell carcinoma · Clinical diagnosis

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Introduction

Exophytic lesions of the oral mucosa are common in the clinical practice of oral surgery and oral medicine [1, 2]. Most frequently these masses are reactive, resulting from local irritation or trauma, including fibrous overgrowth, pyogenic granuloma, mucous extravasation and others [2–9]. However, the complete pathological spectrum of mucosal exophytic masses also includes developmental anomalies, infections with various microorganisms, granulomatous inflammatory reactions, cysts and pseudo-cysts, malformations, hamartoma, as well as benign and malignant neoplasia [1, 10, 11]. Surface ulceration of the oral mucosa may arise from a diverse list of etiological factors

of which malignancy is but one [1, 12, 13]. Although the presence of surface ulceration in an exophytic mucosal mass is not pathognomonic for any specific condition, ulcerated masses are conventionally treated with a higher degree of suspicion for malignancy than non-ulcerated mucosal masses. A search of the English literature yielded several studies analyzing the prevalence of oral lesions based on either clinical or of pathologic findings [2–9, 14–18], but studies relating specifically to the significance of surface ulcerations as an indicator for malignancy in mucosal exophytic lesions were not found.

The purpose of the present study was to compare the spectrum of findings in biopsies of oral mucosal exophytic masses, compare ulcerated and non-ulcerated lesions and explore the significance of surface ulceration as a clinical indicator of the risk of malignancy in these types of lesions. In addition, the degree of agreement between pre-biopsy clinicians' classification and final microscopic diagnosis were compared between ulcerated and non-ulcerated lesions.

Patients and Methods

The study was conducted as a retrospective analysis in a referral center for oral and maxillofacial surgery (OMS) and ear nose and throat (ENT) surgery, where biopsies were diagnosed by a certified oral pathologist. The study was approved by the institutional review board. All the oral biopsy reports between the years 2009 and 2011 at the Rabin Medical Center were retrieved and only intra-oral lesions presenting as exophytic mucosal masses were included in the study. Lesions that were flat, intra-bony, or extra-oral such as masses from the sub mandibular, mental and temporomandibular regions, surgical resection specimens and extensions of excisions were all excluded, as were cases with severe thermal or mechanical artifacts. Clinico-pathological data, including the presence of clinical and microscopic ulceration were included in the analysis.

All the clinical and final (histopathological) diagnoses were classified into 3 diagnostic groups: Group 1: Reactive/developmental: lesions that are known to develop as a result of local irritation, trauma, infection with microorganisms, or lesions that are considered developmental; Group 2: Benign neoplasia; Group 3: Malignant neoplasia; When there was more than a single clinical diagnosis present in the chart, the diagnostic group included in the analysis was the most severe one, thus, whenever a request to rule-out malignancy was submitted by the clinician, the clinical diagnostic classification was included under malignant neoplasia. This was decided since there was no consistent way to evaluate whether the suspicion of malignancy was low or high.

Statistical analysis was carried out by a biostatistician using the SPSS15.00 software. Chi square test was applied and the threshold for significance was set at $p < 0.05$.

Results

A total of 69,764 biopsies were processed at the institute of pathology between 2009 and 2011, of which 1,482 (2.1 %) were oral biopsies. Of these, 713 (48.1 %) were exophytic mucosal lesions meeting the study inclusion criteria. The final study population therefore included 313 males and 397 females (for 3 the gender was not recorded), reflecting a general female predominance of 55.9 % ($p = 0.02$).

The age was known for 709 cases, with a range of 0.5–94 years. When classifying the patients into three age groups, 435 (61 %) lesions occurred in the above 50 age group, 206 (29 %) in the 20–50 age group and 68 (10 %) in the under 20 age group.

The exact site of the lesions was specified in 701 cases. The most frequent locations involved were the tongue 159 (22.7 %), buccal mucosa 157 (22.4 %) and the gingiva/alveolar ridge 136 (19.4 %). The lips were involved in 152 (21.6 %) cases, of which 125 (82.2 % of lip lesions) involved the lower lip. Table 1 presents the distribution of microscopic diagnoses and classification to diagnostic groups of all lesions included in the study.

The majority of the exophytic lesions, 601 (84.3 %), were classified in the reactive/developmental group. Neoplasia represented 112 (15.7 %) of lesions, 55 (7.7 % of total, 49.1 % of neoplasm) were benign, 57 (8 % of total, 50.9 % of tumors) were malignant.

Although reactive lesions were by far the most common in all the age groups, their prevalence decreased in the older age group (86.6, 87.9 and 77.2 % in below 20, 20–50 and above 50 groups, respectively). The prevalence of benign neoplasms also changed between age groups (11.9 %, 8.3 and 9.5 respectively). Notably, there was a significant increase in the prevalence of malignancy, especially in the over 50 age group (1.5, 2.9 and 11.3 % respectively) ($p < 0.001$).

Surface ulceration was clinically recorded in 67 (9.4 %) lesions, and was confirmed by microscopic evidence of ulceration in 100 % of these cases, whereas 3.5 % of the clinically non-ulcerated lesions had microscopic ulceration.

Significant differences were found in the distribution of lesion groups between the ulcerated and non-ulcerated groups. Malignancies accounted for 31.3 % of the ulcerated group and only of 5.6 % of the non-ulcerated group, indicating a six fold higher prevalence of malignancy in the ulcerated group. Benign neoplasms represented 1.5 % of the ulcerated and 8.4 % of the non-ulcerated group ($p < 0.0001$) (Table 2).

Table 1 The distribution of microscopic diagnoses (in descending order of prevalence) and classification to diagnostic groups

Spectrum of microscopic diagnosis	No. of lesions (%)	Diagnostic group ^a
Fibrous/fibro-epithelial overgrowth, giant cell fibroma	360 (50.5)	1
Mucocoele, ranula	46 (6.5)	1
Pyogenic granuloma	36 (5)	1
Squamous cell carcinoma	36 (5)	3
Vascular proliferations and tumors	32 (4.5)	2
Epithelial hyperplasia (focal, papillary, psoriasiform)	30 (4.1)	1
Peripheral giant cell granuloma	22 (3.1)	1
Ulcer	20 (2.8)	1
Mesenchymal non-vascular benign tumors	18 (2.5)	2
Papilloma, verruca	18 (2.5)	1
Inflammation and lymphoid reactive changes	12 (1.7)	1
Cysts of soft tissues	10 (1.4)	1
Malignant salivary gland tumors	10 (1.4)	3
Hamartoma or choristoma	10 (1.4)	1
Other malignancies: lymphoid, BCC, metastases, sarcoma	8 (1.1)	3
Granulomatous inflammation no pathogen identified	7 (1.0)	1
Bacterial, leishmaniasis, actinomycosis, zygomycosis	7 (1.0)	1
Peripheral ossifying fibroma	6 (0.8)	1
Benign salivary gland tumors	5 (0.7)	2
Varicose vein, thrombus, hematoma	5 (0.7)	1
Necrotizing sialometaplasia	4 (0.6)	1
Adenomatoid hyperplasia	3 (0.5)	1
Verrucous carcinoma	3 (0.5)	3
Traumatic granuloma with stromal eosinophilia	3 (0.5)	1
Amyloidosis	2 (0.2)	1
Total	713 (100)	

BCC Basal cell carcinoma

^a 1—Reactive/developmental; 2—benign neoplasia; 3—malignant neoplasia

The effect of the age group was evident when comparing between ulcerated versus non-ulcerated lesions: while none of the ulcerated masses was malignant in the below 20 age group, 12.5 % of the ulcerated lesions in the 20–50 age group and 38 % in the over 50 age group were malignant ($p < 0.001$) (Fig. 1a, b).

In the reactive/developmental group there were 601 lesions, the majority were fibrous overgrowths (Table 1). Within the ulcerated lesions, the largest number were reactive (67 %) (Table 2), however, of all the reactive/developmental lesions only 7.5 % were ulcerated (Table 3).

Table 2 The distribution of the diagnostic groups in clinically ulcerated versus non-ulcerated exophytic lesions

	Reactive-developmental no. (%)	Benign no. (%)	Malignant no. (%)	Total no. (%)
Ulcerated ^a	45 (67.2)	1 (1.5)	21 (31.3)	67 (100)
Non-ulcerated ^a	556 (86)	54 (8.4)	36 (5.6)	646 (100)
Total	601 (84.3)	55 (7.7)	57 (8)	713 (100)

^a $p < 0.0001$

The benign neoplasia group consisted of 55 tumors, with an equal male to female ratio and an age range of 0.5–86 years. These included 32 vascular tumors, 18 mesenchymal non-vascular tumors (11 lipomatous and 7 tumors of neural origin), and 5 salivary gland tumors. The majority of the benign tumors were found in the tongue 23 (35.4 %), lower lip 14 (21.5 %) and gingiva/alveolar ridge 10 (15.4 %). Only one (1.5 %) of the benign tumors was ulcerated.

The malignant group included 57 tumors, with an equal gender distribution and a wide age range of 9–90 years, but only 2 of these were in the below 20 age group, both were non-ulcerated.

There was a predominance of malignant neoplasia of epithelial origin (carcinoma), accounting for 52 (91.2 %) cases, while only 5 (8.8 %) were tumors of non-epithelial origin. The epithelial malignancies consisted of 36 (63.2 %) squamous cell carcinoma (SCC) and 3 (5.2 %) verrucous carcinoma. Other carcinomas included 10 (17.5 %) malignant salivary gland tumors, 2 (3.6 %) oral metastasis from non-oral primary tumors, and 1 (1.8 %) rare case of intra-oral basal cell carcinoma. The non-epithelial tumors consisted of 1 (1.8 %) metastatic angiosarcoma, 3 (5.2 %) lymphoid malignancies, and 1 (1.8 %) primary low-grade fibromyxoid sarcoma. The most common site of malignancy was the gingiva/alveolar ridge with 17 (29.8 %) cases, tongue 11 (19.3 %) and buccal mucosa 8 (14 %). Other locations included hard palate, floor of mouth and lower lip 6 (10.5 %) each, and upper lip 3 (5.4 %).

Although the majority of lesions in all three diagnostic groups were non-ulcerated, the highest frequency of ulceration was recorded in the malignant group (36.8 %, $p < 0.001$). However, this reflects a ratio of approximately 2/3 of the exophytic malignant tumors which were non-ulcerated at presentation. Lesions diagnosed as SCC exhibited the highest ulceration rate, reaching 50 % of cases, thus, an equal fraction was not ulcerated at presentation. Only 1 of the 3 (33.3 %) cases of verrucous

Fig. 1 The distribution of the diagnostic groups according to age groups. **a** Ulcerated lesions: in the <20 years group all the lesions were reactive. Malignant neoplasia significantly rise in the >50 age group ($p < 0.001$). **b** Non-ulcerated lesions: malignant neoplasia increase and the benign neoplasia decline in the >50 age group ($p < 0.001$)

Table 3 The percentage of exophytic lesions presenting with surface ulceration according to the diagnostic group

	Clinically ulcerated lesions (% of cases in group)	
Reactive	7.5 ^a	
Benign	1.8	
Malignant		
Squamous cell carcinoma	50	All malignancies 36.8 % ^a
Verrucous carcinoma	33.3	
Salivary gland malignancy	10	
Non-epithelial malignancies	0	

^a $p < 0.001$

carcinoma and only 1 (10 %) of the salivary gland malignancies were ulcerated. In addition, all of the non-epithelial malignancies were not ulcerated (Table 3). The site distribution of ulcerated and non-ulcerated malignant tumors was similar.

When referring to the clinical diagnosis in the pre-biopsy stage, 33.3 % of the malignancies were not clinically suspected to be malignant. Rather, they were thought to be either reactive or benign and did not even include a request to rule out a malignancy. The percentage of clinically unsuspected malignancies was significantly lower in the ulcerated (23.8 %) than the non-ulcerated group (36.7 %), ($p = 0.03$), reflecting a somewhat better agreement between clinical and microscopic diagnosis in the cases where the lesions were ulcerated.

Discussion

The rational of this study was to seek evidence for the validity of a common practice, in which ulcerated exophytic masses of the oral mucosa are treated with a high degree of suspicion for malignancy, while non-ulcerated lesions are labeled as a low or no risk lesions.

The grouping and classifications employed in the present study are similar to the ones used by Flaitz and Coleman [17] of exophytic soft tissue entities in children. Weir et al. [15] studied oral tissue specimens and found that neoplasia constituted nearly 15 % of all the specimens, with approximately 18 % of these being malignant, whereas in the present study the prevalence of neoplasia was similar, but the rate of malignancy was higher, comprising nearly half of all neoplasms.

There may be a drawback in the classification of the vascular tumors under benign neoplasia in the present study, since these included hemangioma variants, lesions diagnosed as non-specific vascular proliferations and malformations. Vascular malformations would have been better classified in the reactive/developmental group, however, the classification schemes of vascular lesions have changed in recent years, and although there are current markers that can differentiate vascular neoplasms from malformations (such as Glut-1 and WT-1), these were not available at the time, and thus the original diagnosis as either neoplasia or malformation may not hold true according to newer standards. Neither were there enough clinical details available in the files to confidently re-classify each individual vascular lesion, which was also beyond the objectives of the present study. Thus, being aware of these limitations, but taking into account the low number of cases in this group, a decision was made to include for analysis all 32 vascular lesions in the benign neoplasia group. A possible mistake in classification in a

small number of these cases is certainly possible, but it does not seem to significantly influence the results of the entire study.

Less than 10 % of all exophytic lesions in the study were ulcerated. This finding is higher than 6.6 % reported by Cebeci et al. [14], in a study that included all types of oral ulcers, and a low number of malignant neoplasms. Although most of the ulcerated masses of the present study were reactive, exophytic malignancies were found to be more prone for ulceration than both reactive lesions and benign neoplasms. Malignancy was found to be statistically about 6 times more prevalent in the ulcerated group than in the non-ulcerated. However, in absolute numbers, due to the fact that the non-ulcerated group comprised 90 % of all lesions, the majority of malignant tumors were not ulcerated. In other words, although the likelihood for malignancy is higher in ulcerated masses, in absolute terms 2 of every 3 oral malignant tumors is not ulcerated at presentation. Thus, the common concept that ulceration is typical for oral malignancy is proved to be at least partially inaccurate.

The age of the patient certainly plays a role when evaluating the significance of surface ulceration. In the below 20 age group all of the ulcerated exophytic lesions were found reactive/developmental, whereas in the over 50 age group the percentage of malignancy was significantly higher, predominately so within the ulcerated lesions. Of the various malignancies in the oral mucosa, SCC are more likely to present as ulcerated lesions, while non-epithelial malignancies were not ulcerated in this series.

When trying to explain what makes malignancies, and in particular SCC more prone for ulceration, a few possible explanations can be raised: size-related, site-related and biological aspects. Regarding the size, it is possible that as lesions grow they interfere with anatomical structures, compromise the blood supply, or combined with functional movements such as mastication and speech may be traumatized and therefore ulcerate. Regarding the site, it is possible that lesions appearing in specific sites may be traumatized easily and therefore ulceration is not related to their reactive or malignant nature but to their location. In this study, the most common sites for ulceration were identical when comparing the reactive/developmental to the malignant group (in the benign group only one ulceration was recorded), with the tongue and gingiva/alveolar ridge being the most common locations in both groups. This may support a site-related etiology, possibly in areas more exposed to trauma. Nevertheless, it may not suffice to explain the clear propensity of SCC to ulcerate. It may be a combination of the tendency of SCC to develop in the tongue and alveolar ridge with biological aspects of the tumor which are responsible for the higher frequency of ulceration in comparison with benign tumors and reactive lesions. Moreover, a similar site distribution of ulcerated

and non-ulcerated malignant tumors was observed, a finding that is not supportive of a site-related etiology.

Notably, although the biopsies were performed by trained specialists or residents of the OMS and ENT departments, their ability to provide a correct provisional diagnosis on a clinical basis (only as far as malignant or non-malignant grouping) was found to be limited, with 1/3 of malignancies not suspected as such, not even as a request to rule out malignancy. An improved match between clinical diagnosis and microscopic results was found for ulcerated lesions, indicating that the study hypothesis (e.g. clinicians treat ulcerated raised lesions with higher degree of suspicion) is in fact true. While in a dentist in the community setting, a low index of suspicion towards non-ulcerated masses may result in delayed diagnosis [19], this should not be accepted in a setting of a referral center. The results of the present study suggest that clinical judgment, even in a specialty clinic environment has limitations in predicting the nature of oral exophytic lesions. Relying on the factor of surface ulceration can be misleading, and therefore non-ulcerated mucosal masses should be treated as potentially malignant.

In conclusion, although the statistical likelihood of ulcerated masses to represent malignancy is higher than non-ulcerated lesions, especially in patients over 50, the majority of malignancies of the oral mucosa present initially as non-ulcerated masses. Thus, all lesions should be submitted for microscopic analysis, and the status of ulceration should not be regarded neither as a factor in the decision to biopsy, nor as a reliable indicator for malignancy. Future studies relating to the complete spectrum of clinical presentation of malignancies of the oral mucosa, and in particular SCC, should confirm this observation.

Conflict of interest The authors declare no conflict of interest.

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