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LETTER TO THE EDITOR

Ki-67 expression in non-tumour epithelium adjacent to oral cancer as risk marker for multiple oral tumours

We have read with great interest and would like to take the opportunity to comment on the recently published article 'Ki-67 expression in non-tumour epithelium adjacent to oral cancer as risk marker for multiple oral tumours' (González-Moles *et al*, 2010). There is a lack of consensus on the duration on which the lesion would be classified as synchronous or metachronous e.g. 6 or more months (Hong *et al*, 1990), 1 month (Liao *et al*, 2007) and 2 months (Van der Haring *et al*, 2009). Such classification appears irrelevant as the treatment and prognosis depend ultimately on clinical and histopathological prognosticators. The criteria for secondary primary tumours (SPTs) were erroneously attributed to Billroth (1889), but it was revealed that he did not state such unrealistically rigid criteria (Moertel *et al*, 1961). The established criteria which are widely used include (i) each of the tumours must present a definite picture of malignancy; (ii) each must be distinct; and (iii) the probability that one was a metastatic lesion from the other must be excluded (Warren and Gates, 1931). Histopathological examination often solves the issue of whether the tumour is malignant, but the other two criteria remain confusing and debatable.

We agree with the author on choosing 1 cm as cut-off point, considering the fact that 2-cm criteria had been proposed (Hong *et al*, 1990). But there is no agreement in the literature on what distance should lie between the tumours e.g. 2 cm (Hong *et al*, 1990), 3 cm (Tabor *et al*, 2002) and 1.5 cm (Scholes *et al*, 1998). We also opine that the possibility of undermining of single OSCC beneath the clinically normal looking mucosa and its presence at another area (simulating synchronous OSCC) cannot be ignored. Conversely, it is also possible that two closely associated sites in case of synchronous/metachronous OSCCs can invade underneath the normal mucosa towards each other and collide. In both the situations, malignant epithelial cells will be present beneath the clinically normal oral mucosa. It is impossible to confirm whether OSCC is synchronous/metachronous or single primary. Hence, we propose that the cases showing presence of malignant epithelial cells beneath the normal mucosa should be excluded. This situation is quite possible as authors have considered areas in close proximity in many cases in their study as shown in Table 2.

Another point which we would humbly like to question is the criteria used for calibrating the 1-cm distance by counting the basal cells. Considering the distance in which the basal cell counting was done, the presence/absence of rete ridges would render the situation tricky and may hamper the calibration standardization leading to inaccurate results. It appears that the authors have failed to take notice of it and included areas with and without rete ridges in their sample size (as evident in Figure 1 showing Ki-67 staining). For better standardization of the results, we propose that the distance should be measured using an image analysing software or oculometer grid by keeping the post-operative shrinkage of tissue in mind.

It is proposed that an SPT should occur at least 3 years after diagnosis of the primary tumour (Leong *et al*, 1998). With respect to the issue of discriminating an SPT from a metastasis to the lungs, oesophagus, larynx, a discussion may arise concerning what criteria should be used: should the time interval between the occurrence of the lesions and/or the histological examination of both the lesions be the criteria? Thus, because of the subjective decision making, the clinical definitions of multiplicity carried the risk of misclassification. Hence, a novel classification of the secondary tumours based on the molecular analysis of the tumours and the genetically altered mucosal field in between was described in the literature (Braakhuis *et al*, 2002). Braakhuis *et al* (2002) proposed definitions for a 'true SPT', a local recurrence, a 'second field tumour' (second field tumour derived from the same genetically altered mucosal field as the primary tumour), and a metastasis. Hence, we posit that future studies on SPTs should follow this classification as it will increase the authenticity of the study and help us in better understanding the nature and the behaviour of the true SPTs. But we also agree with the author that a reliable diagnosis of premalignant fields requires the use of molecular techniques (mutational and LOH analysis), although they are not routinely applied because of their cost and complexity.

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Reply to letter to the editor

Dear Editor,

We sincerely appreciate the comments given by Sarode *et al*. on our published work in Oral Diseases. We think it is due to in some extent to the growing interest in relation to premalignant changes in the oral cavity.

Nevertheless we would like to make some brief points:

1. We agree with the possible existence of malignant cells which lie beneath the mucosal layer that have an apparent normal clinical aspect. We think that analysis of some oral cancer cases can be just as more complex as the illness itself. For cataloguing multiple tumours, we have used the World Health Organisation System which is referred to in our article.
2. In order to count basal cells approximately 1 μ in diameter, to measure 1 cm from the point of the beginning of the invasion, regardless of the existence of rete ridges or no, could be a good system. Our belief is that something important in the growth of the field is the expansion of malignant cells without the ability to invade even with a higher proliferative activity along the parabasal layers, which in our opinion, continues the contours of the deeper zones of the epithelium, regardless of the form of the epithelium borders.
3. To raise a molecular distinction between a 'true SPT', a local recurrence, a 'second field tumour' (second field tumour derived from the same genetically altered mucosal field as the primary tumour), and a metastasis is the goal of future studies. Not only for investigational purposes, but also clinical and even medicolegal problems can be solved with these techniques. However, because of their cost and complexity some time will be needed.

In any case, we are truly grateful for the interesting commentaries of the authors.

Best regards

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