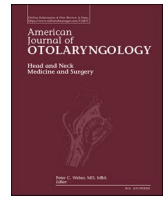


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## Peri-tumoral infiltrate in OSCC: “The simpler, the better” temptation

### ARTICLE INFO

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 Peri-tumoral inflammatory infiltrate  
 Human papillomavirus  
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#### Dear Editor,

Our esteemed colleagues Ai et al. published a study entitled “Peri-tumoral infiltrate associates with postoperative prognosis of patients with OSCC: Stronger association in HPV negative patients [1]”. The authors investigated the density in inflammatory cells on hematoxylin-eosin-stained (HES) slides from paraffin-embedded tumor specimens of oral squamous cells carcinomas (OSCC). They distinguished human papillomavirus (HPV)-associated tumors by detecting the p16 protein by immunohistochemistry. They concluded that peri-tumoral infiltrate (PTI) (present vs absent) was associated with a dissemination of tumor cells in lymph nodes and paradoxically that a moderate PTI was associated to a better overall survival (OS) in HPV-independent patients only. These results seem to contradict each other and raise more questions than they answer. They suggested that PTI was better assessed with their four-grades score that permitted to find an association between moderate PTI and a better OS. According to them, moderate PTI should be in the middle range to avoid the drawbacks of insufficient (no PTI or low PTI) or excessive (excess in immunosuppressive factors production) interactions between tumor and inflammatory cells. According to us, this assessment is too far from a precise description of the tumoral micro-environment and data from the literature are too heterogeneous [2–4] to be other than a mere conjecture. Several limitations should be highlighted with regard to the state of the art. No distinction is made between the different immune cells considered as constituting PTI. It is generally accepted that CD8<sup>+</sup>T cells and especially resident memory cells are associated with a good prognosis [5], while macrophages, especially M2 type (CD163+), are correlated with a poor prognosis [6]. The differences in the ratio of these immune cells cannot be defined by the simple measurement of PTI by HES. Besides, the score used by the authors corresponds to a double reading quantitative assessment and classification in four categories on the basis of a direct examination under the optical microscope. This score has not been the subject of a previous methodological validation. Finally, detection of p16 protein is not the most specific method for assessing HPV involvement and confirmation PCR analysis is required as about 10 % of p16 positive specimens revealed to be HPV negative in PCR [7].

Moreover, this valuable contribution in the immune understanding

of the Head and Neck Squamous cells tumors reflected a tendency towards increasing dichotomy that should be considered with attention. Since Dunn et al.'s work in 2002 and their description of the concept of immunoediting [8], research in cancer immunology has progressed considerably and gained insight into interactions and effectors in the tumor microenvironment. Head and neck cancers have been affected by this movement and immunotherapy has emerged as a treatment for these diseases based on immune checkpoint PDL1 inhibitors [9]. Nevertheless, the search for immune prognostic elements that will allow to define the best therapeutic strategy is still a current imperative. On the one hand, there is a tendency towards the use of increasingly sophisticated, innovative, expensive and advanced techniques such as mass spectrometry, metabolomics, molecular studies, gene sequencing, tumor infiltrating T-cells RNA sequencing [10] or *in situ* analysis of the tumor microenvironment by multiplex imaging. At present, no markers other than the TPS and CPS scores have been developed based on the assessment of PDL-1 expression by means of immunostaining in the tumor and its stroma [11]. On the other hand, the research is moving towards much simpler markers, such as neutrophils to lymphocytes ratio analysis [12] or, here, visual appreciation of the peri-tumor infiltrate on HES staining slides by a couple of cytologists. An extreme change in depth of field thus characterizes the immune assessment of cancers. But let's not fool ourselves. If the description of these distant photographs of tumor immunity sustains publications that repeat and decline the association between inflammation and tumor progression, they do not make it possible to implement therapeutic strategies or to glimpse real possibilities for patient selection. Only a much finer understanding of the tumor microenvironment really opens up a field of therapeutic possibilities. Such research is slow, costly in time, money and energy. Please, dear editor, consider this text as an appeal to the esteemed authors of this work and other potential ones to complete and extend their analysis of tumor microenvironment at the cellular and molecular levels.

#### Declaration of competing interest

None.

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