Letter to Editor

The AJCC/UICC eighth edition for staging head and neck cancers: Is it wise to de-escalate treatment regimens in p16-positive oropharyngeal cancer patients?

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Conflict of Interest

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Dear Editor,

High risk alpha human papillomaviruses (HPVs), and in particular HPV type 16, have been causally associated to a subset of oropharyngeal squamous cell carcinomas (OPSCCs) arising from the crypt epithelium of the palatine and lingual tonsils to which they confer a highly significant favorable prognosis [1].

The Tumor Nodes Metastases (TNM) classification of malignant tumors, which is the internationally recognized standard for cancer staging, was developed by and continues to undergo the scrutiny of the concerted efforts of the Unio Internationalis Contra Cancrum (UICC) and the American Joint Committee on Cancer (AJCC). Its main objectives are to provide an indication of individual prognosis and aid treatment planning.

Initially the 8th edition of the AJCC/UICC TNM staging system, which was released in December 2016, was set to be clinically applicable beginning in January 2017, but the AJCC decided to delay its implementation until January 1, 2018. Seeking to provide a more accurate prediction of survival based on retrospective analysis of data sets of mainly North American patients[2], the latest edition of the staging system for OPSCC incorporated several significant changes including a separate staging algorithm for p16-positive tumors. Positive immunostaining for cyclin-dependent kinase inhibitor p16 is, in fact, considered a surrogate marker for active HPV involvement in oropharyngeal carcinogenesis [3].

These major changes proposed by the latest edition raise some concerns. Standard treatment options for stages I and II OPSCC are surgery or radiation therapy which are both equally

successful in controlling an early disease stage. Conversely, internationally recognized guidelines advocate multidisciplinary strategies consisting in up-front surgery followed by radio(chemo)therapy or induction/concurrent radiochemotherapy followed by surgery in non-responders to manage stage III-IV OPSCC [4]. Most evidence suggesting that HPV-positive OPSCCs have a considerably better prognosis with respect to their HPV-negative counterparts is based on retrospective analyses of archival tumor specimens from patients enrolled in phase II and III trials then receiving multidisciplinary treatment for advanced stage disease [1,5].

The most significant changes in the 8th with respect to the precedent edition involve N category definitions and stage groupings. According to the latest edition, for example, a patient with a 3 cm in diameter, p16-positive OPSCC as well as ipsilateral lymph nodes with a maximum diameter of 6 cm, would find him/herself in an early stage (T2N1, Stage I, according to 8th edition) instead of in an advanced stage (T2N2b, stage IV, according to 7th edition).

Although the main goal of TNM staging system is *not* to indicate how patients should be treated, treatment guidelines for head and neck cancers are mainly based on TNM classification. We are, therefore, concerned that implementation of the latest edition could lead to treatment de-escalation in p16-positive OPSCC patients who would be down-staged from an advanced to an early stage disease status (e.g. from radiochemotherapy to radiotherapy alone). Numerous ongoing clinical trials aiming to reduce toxicity without loss in efficacy will hopefully lead to treatment de-escalation in HPV-positive OPSCC. For the time being, however, de-escalation strategies have not yet been established in the real clinical arena [6].

In addition, in view of its impact on prognosis in p16-negative cancers, extranodal extension (ENE) has now been incorporated into the N classification of that subset. There is nevertheless evidence that ENE lacks prognostic significance in HPV-positive cases. [7]. Should this be considered an element against the use of post-operative adjuvant radiochemotherapy in patients with p16-positive OPSCC with ENE? Interestingly, a large study recently provided evidence that ENE is an independent risk factor for worse prognosis also in patients with HPV-positive OPSCC, despite the fact that adjuvant radiochemotherapy was not associated to a better overall survival rate compared with radiotherapy alone [8].

Using positive immunostaining for p16 as a stand-alone test to define an OPSCC as HPV-driven also raises concerns. p16 immunostaining has shown suboptimal sensitivity and insufficient specificity with 10-20% of p16-positive OPSCC resulting HPV-DNA/RNA negative [9–13]. Prognostic stratification based on p16 immunostaining alone has, in fact, been found unsatisfactory with respect to one based on more accurate biomarkers of transforming HPV infections [13,14]. The geographic prevalence of HPV-related OPSCC is extremely heterogeneous and estimates of the HPV-attributable fraction derived from a recent pooled analysis have been quantified as approximately 60% in USA, 20-30% in Europe, and 18% in Asia [10,11]. Assuming that its sensitivity and specificity are the same, it means that the diagnostic positive predictive value of p16 immunostaining will drop considerably if the *a priori* probability of having a HPV-positive OPSCC is lowered by 30-40%. Furthermore, associated tobacco and alcohol intake seems to be diverse in North America with respect to Europe [14]. The majority of HPV16-positive patients thus show combined risk situations according to the intermediate and high risk profile defined by Ang [1].

In conclusion, all prognostic models may need to be adapted to different populations and geographic areas. Until scientific evidence from ongoing clinical trials investigating various de-intensification strategies in different populations becomes available, we recommend that the major changes proposed by the 8th edition of the AJCC/UICC staging system for head and neck cancers be used *only* for prognostication purposes. The wise decision to delay its implementation until January 1, 2018, will allow interested parties to develop and update their protocols and guidelines so that its application will not lead to premature de-escalation of treatment in HPV-positive OPSCC. Additionally, we strongly recommend aiming for the positivity to both p16 immunostaining and HPV-DNA to define an OPSCC as HPV-driven in order to obtain more accurate prognostic information, particularly in geographic areas with a low prevalence of HPV-positive OPSCC.

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