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Editorial

"Are some green apples less green than others?"☆

The oropharynx belongs to the upper aerodigestive tract including the base of tongue and vallecula, the posterior pharyngeal wall, the tonsillar region and lateral oropharyngeal walls, and the soft palate and uvula. Most oropharyngeal cancers are squamous cell carcinoma (OPSCC). Similar to other head and neck cancers, OPSCCs were traditionally more often diagnosed in heavy smokers/heavy drinkers with lower income, lower socioeconomical background and frequent comorbidities related to their lifestyle. However, the last two decades have witnessed an increase in the incidence of OPSCC related to the emergence of human papillomavirus (HPV) -positive tumours mainly observed in high-income countries. Typically, HPV-positive OPSCC occurs in younger, healthier and nonsmoking patients with a higher socioeconomic status. In the United States, the incidence of HPV-positive OPSCC has exceeded the one for cervical cancer with more than 13 000 new HPV-positive OPSCC cases diagnosed per year [1]. As for alcohol- and tobacco-related OPSCCs, HPV-driven tumours are more commonly seen in men. At similar stage and for identical treatments, HPV-driven OPSCCs have a much better outcome, and these tumours must then be considered as a distinct entity different from their alcohol- and tobacco-related counterparts [2].

Retrospective outcome analyses have shown that the 7th edition of the UICC/AJCC TNM classification was not discriminative for HPV-driven OPSCCs, and have prompted the introduction of the 8th edition, with a different staging system for this new clinical entity identified by the overexpression of the p16 protein [3,4]. For example, in accordance with the new classification, a p16+ patient with a less than 2-cm oropharyngeal SCC with two ipsilateral lymph node metastases, previously classified as T1-N2b (stage IV), is now classified as T1-N1 (stage I). It should be emphasised that the patients included in the retrospective analyses were most likely treated similarly whether they were p16-positive or p16-negative, and that the HPV status is just a prognostic indicator for outcome and not a predictive factor for a particular treatment.

In this issue of the European Journal of Cancer, Maklund *et al.* retrospectively reviewed an institutional database of 932 patients with OPSCC treated with curative intent by surgery and/or radiotherapy or concomitant chemoradiotherapy, and analysed the prognostic value of p16 positivity as a function of the location of the primary subsite [5]. Of these 932 patients, most patients had tumours (>90%) located in the tonsil areas and/or in the base of tongue, whereas only 91 patients (9.8%) presented with another OPSCC, mainly a soft palate or a posterior pharyngeal wall tumour. In the total patient population, 655 (70%) had an HPV-driven tumour as identified by the p16 protein expression. Only 13 of these patients had a p16-positive other-OPSCC. Overall, the study confirmed the prognostic value for overall survival of p16-positivity, but only in patients with tonsil or base-of-tongue OPSCCs (stage I/II and stage III/IV). The survival of p16-positive patients with other-OPSCC was identical to that of patients with p16-negative OPSCC. The study also confirmed the absence of the discriminative power of the UICC/AJCC 7th edition of the TNM staging for base-of-tongue and tonsil OPSCCs, which were mainly p16-positive. On the other hand, for the other-OPSCCs, which were mainly p16-negative, the 7th edition of the TNM staging retained its discriminative property. As a conclusion of their study, Maklund *et al.* underscored the potential risk of misclassifying patients with p16-positive other-OPSCC when applying the TNM-8

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staging system, and suggested that those patients should be staged as patients with p16-negative OPSCC and that p16 should only be used for prognosis in tonsil and base-of-tongue SCCs [5].

The study of Maklund *et al.* is definitely thought provoking. Why would some p16+ OPSCC tumours have a worse prognosis than other p16-positive OPSCC tumours? Are some green apples less green than others? Several comments can be made.

First, one needs to stress that very few patients were p16-positive other-OPSCC in the study, and some of these patients were even staged as M1 disease, which may have influenced their overall survival. The statistical power of such finding is likely to be low and the finding definitely needs to be confirmed by other and larger series. For example, the International Collaboration on Oropharyngeal cancer NetWork for Staging (ICON-S), which gathered a large data set from five North American and two European Centers, could be an ideal platform to validate the data of Maklund et al [4].

Second, HPV-related carcinomas are caused by high-risk (HR)-HPV colonising the reticulated epithelium lining the crypts of the palatine and lingual tonsils. This unique microenvironment specific to these subsites probably explains why the incidence of HPV infection is much higher than in other oropharyngeal locations, as also reported in the study of Maklund et al. Moreover, the tonsil and base of tongue are known to be rich in lympho-epithelial tissue, which may play a role in triggering a local immune response possibly adding its efficacy to the local treatments [6,7]. Along this line, the different lining of the soft palate and the posterior pharyngeal wall may not be as potent to trigger an immune response, thus potentially explaining the different clinical outcome reported for OPSCC arising from these locations, although HPV-driven.

Third, interestingly, the TNM-8 manual clearly mentioned that p16 overexpression is context-specific, and currently is only applicable to the tonsillar and base-of-tongue regions of the oropharynx [8]. The reason why nontonsil or non−base-of-tongue tumours were finally also included in the separate staging for HR-HPV-driven cancer of the oropharynx remains unknown. But, in the same manual, in the chapter dedicated to p16-positive OPSCCs, it is mentioned that HPV-mediated cancers most commonly arise in the lymphatic tissue of the palatine and lingual tonsil, but may also arise in any of the regions of the oropharynx, suggesting that all oropharyngeal sites need to be staged differently in accordance with the p16 status [9].

Finally, as already mentioned previously, the TNM staging system is only a prognostic factor, and the results of the study of Maklund *et al.* illustrating possible different outcome in various p16+ oropharyngeal subsites clearly underline that it is not a predictive factor justifying different treatment intensities. Although possibly performed by some physicians under medical fashion pressure, as of today, outside of adequately designed clinical research trials, there is no argument to de-escalate treatment in stage I or II p16-positive OPSCCs. Two recently published de-escalation trials in p16-positive OPSCCs (i.e. De-ESCALaTE and RTOG 1016 trials) clearly demonstrated that radiotherapy and concomitant cisplatin high dose (100 mg/m^2 every 3 weeks) remained the standard of care in locoregionally advanced p16-positive OPSCCs [10,11]. In addition, these trials support the notion that outcome of HPV-positive OPSCC patients strongly depends on the type of treatment received.

To conclude, TNM staging should only be modified when it allows better categorising patients into different validated prognostic classes; in other words, when some apples are definitely less green than other green apples!

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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