Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

De-intensification of treatment in human papilloma virus related oropharyngeal carcinoma: Patient choice still matters for de-escalation and for the COVID era

Dear Sir/Madam,

We read "De-intensification of therapy in human papillomavirus associated oropharyngeal cancer: A systematic review of prospective trials" by Patel et al. [1] with interest. This systematic review included eight trials in total [2–9]; four [2–5] of these involved induction chemotherapy which actually prolonged the treatment course and by true definition, this does not qualify as 'de-intensification'. The two trials [6,7] which replaced cisplatin with cetuximab as de-intensification strategy were proven to be inferior.

Only two trials [8,9], of reduced dose chemoradiotherapy (60 Gy with weekly cisplatin) showed 3-year distant metastasis-free survival and overall survival (OS) ranging from 91 to 100% and 95%, respectively. Both trials were non-comparative single arm trials, and, in both trials, 84–89% patients had early T-stage disease (T1/T2) and only 16% had > N2b disease and the long-term results of these studies are still awaited to make any firm conclusions. Authors of one of the other trials [2] stated that small sample size impaired analysis of the statistical significance of acute toxicity between the 2 groups of patients receiving 54 Gy and 69.3 Gy. Other studies showed, patient reported acute toxicity scores consistently higher than clinician reported scores [8,9], and the question also arises whether 2-year progression free survival is an adequate measurement endpoint? None of the eight trials under examination reviewed differences in late toxicity, secondary to de-intensification.

Another factor known to effect outcomes is smoking history which was not incorporated into the eighth edition of the UICC/AJCC classification of oropharyngeal carcinoma. Mirghani et al. [10] published analysis on 282 HPV positive patients and 56% of patients had a smoking history. This smoking history (either more than 20 pack-years or smoking at the time of diagnosis) was the strongest prognostic factor of survival as smoking history was associated with local and distant relapse.

HPV-associated oropharyngeal carcinoma typically responds very well to the initial therapy however the distant metastases rates are not different to HPV negative disease though the occurrence of distant metastases is typically later than HPV negative disease [11]. There is evidence that human papillomavirus (HPV) DNA can be detected in the plasma of patients with HPV-positive oropharyngeal carcinoma [12] and that plasma circulating tumor human papillomavirus DNA in two consecutive plasma samples during post-treatment surveillance has a high positive predictive value and negative predictive value, for identifying disease recurrence in patients with HPV-associated oropharyngeal cancer and may facilitate earlier initiation of salvage therapy [13]. Whether viral load at the time of diagnosis can help risk stratification of patients for de- or intensification remains a question. The potential for utilising serological markers to predict suitability of patients for treatment de-intensification may have a role in future studies.

For patients (independent of age) with head and neck cancer (HNC) including HPV-associated, cure remains the highest priority for survivors and regret over decision making increased with additional treatment modalities [14,15]. Reduction of toxicity while preserving antitumour efficiency of treatment is a laudable aim but it is important to remember that HNC is a relatively treatment resistant group of malignancies, unlike for example some lymphomas where a significant reduction in total radiotherapy dose has allowed the reduction in treatment morbidity while maintaining very similar survival targets. This is not always the case in head and neck cancer and an example of this is the quoted De-ESCALaTE study [7], where toxicity was similar between cisplatin and cetuximab, but the cetuximab arm showed worse 2-year survival and had higher two-year recurrence rates. Although starting with equipoise, some patients appeared to have died because they went into the study rather than had standard of care treatment.

De-escalation of treatment intensity in HNC context, where not all patients are cured with the present standard of care, may carry a risk of more residual or recurrent disease with more patient deaths, in any de-escalation arm. This emphasises the need for full discussion and information giving to patients so that they can make an informed decision about entering a de-escalation trial, knowing there may be a less chance of cure than if they had a standard of care treatment outside of a trial. This is even more important in present COVID-19 era, where radiotherapy hypofractionation regimens, and reduced or abandoned concomitant chemotherapy regimens, are being introduced [16], for the best possible motives, to reduce hospital visits and potential immunosuppression, but in general without input from individual patients or patient groups. It should be remembered that advanced HNC can kill patients as well as COVID, and some of the patients may wish to accept a potential risk from contracting coronavirus, while keeping their chances of cure for HNC as high as possible. The case fatality rates in younger age groups have been reported as quite low; 0.32% (95%CI 0.25–0.41%) for 20–49 years, 1.3% (95%CI 1.1–1.5%) for age 50–59 years and 3.6% (95%CI 3.2–4.0%) for age group 60–69 years [17].

Patients should be able to make a fully informed decision and choice about their treatment, both with regard to de-escalation treatments to improve morbidity and de-escalation treatments, put in place to decrease hospital visits and potential immunosuppression during this COVID emergency.

Declaration of Competing Interest

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 paper.

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