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Letter to the editor

Prognostic implications of pathologic lymph nodes in HPV-positive oropharyngeal cancers: Clinical validity and strategies for routine clinical practice

To the Editor,

El Asmar and colleagues have conducted and published a study regarding the prognostic impact of pathologic lymph nodes in HPV-positive oropharyngeal cancers, in a recent issue of the Oral Oncology Journal [1]. The study is aimed at propounding the clinical application of regional lymph node metastasis in HPV positive OPSCC. However, there are some aspects of the study requiring further discussion before the clinical utility of the study results can be considered.

Conceptual interpretation of HR value of the association of pathological lymph node and overall survival: The authors observed that in patients not receiving adjuvant radiotherapy, there are no significant differences in risk of death from 0 to 2 pathologic nodes, and that risk increased by 18% on average with each additional LN. Despite these marked results presented in the study by El Asmar et al. it is essential to keep in perspective that HR value is still only an indication of probability, within its 95% CI. This uncertainty of HR value (likelihood or probably) must be reflected in the statements presented by the authors [2].

Five major prognosticators of pathologic stage of HPV positive OPSCC after surgery and adjuvant radiotherapy: Furthermore, in the current clinical scenario, lymph node status is already being used as a secondary measure of assessment when other pathologic findings are unavailable. There are other factors around lymph nodes not evaluated in the paper that could have influence on prognostic capabilities of HPV positive OPSCC after surgery and adjuvant radiotherapy. With accumulating evidence-suggesting factors such as extracapsular spread (ECS), positive LN number, LN ratios and LN yield (LNY) (Table 1). While El Asmar et al. 's study focuses on LN number alone, other recently published studies put forward LN ratio as an independent prognostic factor for O/OPSCC and for predicting the benefits of adjuvant radiotherapy [3]. In clinical practice, it has been shown, that the presence of a metastatic lymph node markedly reduces the potential for a favourable prognosis. LN ratio, ECS and T-staging have also been shown through multivariate analysis, to be independent prognostic factors in 5-year DFS and DSS. Current data shows that LNR is superior to TNM staging for evaluation of prognosis, with the capacity to predict the benefits of Concurrent chemoradiotherapy (CCRT) in conjunction with LN number. However, the LN number's capacity to act as an individual marker is still being investigated, with alternatives to it being used in a panel of similar prognostic markers also being discussed. Therefore, comparison and discussion regarding these up-and-coming prognostic markers would have significantly benefited Asmar and colleagues' paper while providing better context to their results [4–6].

HPV Genotypes and Clinical decision-making: Additionally, HPV-16 DNA's presence in lymph nodes is still an ongoing research topic. The presence of HPV-16 DNA and its correlation in metastatic involvement is still under debate. In lieu of this information, we believe that it is a missed opportunity for the authors, to have not assessed the multiples types of HPV that range from low, medium and high-risk genotypes. Investigating the prevalence of infection in OPSCC after adjuvant Radiotherapy based on the HPV genotype would have provided valuable data for informing clinical decision making as well as helping future research [7,8].

Estimation of Disease Free Survival (DFS) and Disease-Specific Survival (DSS) compared Overall Survival in post-adjuvant radiotherapy patients: The authors have used Overall Survival as the survival endpoint of this study. However, considering that, this study is focused on prognosis in post-adjuvant radiotherapy patients and metastatic LN's, the endpoints of Disease Free Survival (DFS) and Disease-Specific Survival (DSS) are more accurate. Therefore, for future similar studies, we highly recommend the use of DFS and DSS as the survival endpoints being assessed. In case OS was chosen based on the availability of data, then it should explicitly be mentioned as a limitation of the study [9,10].

The points raised above are in service of scientific discussion, and we hope the authors consider these suggestions in future studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors confirmed that they have no competing interests.

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Authors' contributions

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Table 1
Comparison of survival analysis of five major prognosticators of pathologic stage of HPV positive OPSCC after surgery and adjuvant radiotherapy.

Author and year	Name of the Cancer	HR	CI lower	CI higher
Prognosis of ECS (extracapsular spread) in HPV associated oral cancer				
Maxwell et al. 2013	OPSCC	1.61	2.04	2.5
Sinha et al. 2011	OPSCC	2.54	0.88	7.34
Prognosis of Positive node in HPV associated oral cancer				
Sinha et al. 2011 > 2 Vs < 2	OPSCC	4.96	1.59	15.43
Jacobi et al. 2017 Pn1 vs Pn0	OPSCC	2.638	1.177	5.912
Prognosis of Nodal stage in HPV associated oral cancer				
Keane et al. 2015 N1	OPSCC	1.02	0.9	1.15
Keane et al. 2015 N2a	OPSCC	0.57	0.47	0.69
Keane et al. 2015 N2b	OPSCC	0.93	0.82	1.05
Keane et al. 2015 N2c	OPSCC	1.81	1.58	2.06
Keane et al. 2015 N3	OPSCC	1.76	1.47	2.09
Prognosis of pathologic lymph node in HPV associated oral cancer				
Lee et al. 2018 ≥ 5	OPSCC	5.46	2.07	14.42
Prognosis of LNR in HPV associated oral cancer				
Jacobi et al. 2017	OPSCC	3	1.297	6.936
Wang et al. 2013	OPSCC	1.27	1.03	1.579
Meyer et al. 2017	OPSCC	2.99	0.301	14.94

the final version of the manuscript.

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