EDITORIAL

Radiographic Extranodal Extension in Human Papillomavirus-Associated Oropharyngeal Carcinoma: Can it Help Tailor Treatment?

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Received Apr 16, 2019. Accepted for publication May 12, 2019.

Because of the excellent prognosis of patients with human papillomavirus—associated (HPV+) oropharyngeal carcinoma (OPC), there has recently been great interest in treatment de-escalation for these patients to reduce toxicity. This could be accomplished by using a less toxic concurrent chemotherapy regimen, reducing radiation dose or fields, or using transoral surgical resection with de-escalated adjuvant therapy. Two recent phase 3 trials testing substitution of cetuximab for cisplatin with radiation therapy in HPV+ OPC disappointingly showed inferior results with the cetuximab regimen.2,3 Smaller trials will soon report on the results of alternative de-escalation strategies (eg, NRG-HN002 [NCT02254278] and ECOG-ACRIN E3311 [NCT01898494]). As we move forward with trying to find successful de-escalation strategies, it will be important not only to pick the right strategy but also to identify a group of patients who are likely to have a low risk of disease recurrence with de-escalated treatment. Therefore, development of effective prognostic models is vital.

In this context, the article by Billfalk-Kelly and colleagues in the current issue of the Red Journal is intriguing because it suggests value of a prognostic factor, radiographic extranodal extension (rENE), that is not included in American Joint Committee on Cancer (AJCC) staging for HPV+ OPC.4 The authors retrospectively examined 280 patients with AJCC 8th edition stage I, node positive HPV+ OPC treated with definitive radiation therapy with or without concurrent chemotherapy. Detailed information on involved nodes was recorded by a neuroradiologist, including nodal number, location, and rENE (defined as an “unequivocal ill-defined nodal border”). Patients with rENE had inferior 5-year disease-free survival (58% vs 90%), and this effect persisted in multivariable analysis accounting for other known prognostic factors. When a multivariable model was constructed to predict disease-free survival, inclusion of rENE improved discrimination performance (c-index increased from 0.67 to 0.74).

This study has several strengths, including the use of modern staging imaging and treatments, the use of prospectively collected clinical data, and the uniform scoring of rENE, which was validated by assessing interrater reliability. Using rENE, the authors identified a subgroup of stage I patients who had high recurrence rate but would otherwise be predicted to have low recurrence risk; these patients may be less suitable for future de-escalation trials.

The study fits into a larger discussion about the value of ENE in prognostication of OPC, considering the many changes with the new AJCC 8th edition staging system. For HPV+ OPC and other head and neck subsites, extranodal extension (ENE) is now part of both clinical and pathologic staging. For clinical staging, the ENE must be
“clinically overt,” and this is based mainly on physical examination, with imaging only serving as supporting evidence. HPV+ OPC staging is an exception because it does not include ENE at all. This decision was based mainly on a multi-institutional retrospective study by Haughey et al of 704 patients treated with primary resection, in which the number of involved nodes, but not pathologic ENE (pENE), was a statistically significant predictor of overall survival. However, the data on low value of ENE for prognostication of HPV+ OPC is quite controversial. In the paper by Haughey et al, though not statistically significant, pENE had a hazard ratio of 1.61 for survival ($P = .06$), and a more recent, much larger study using the National Cancer Data Base found that pENE was a strong predictor of survival. It should also be noted that pENE, but not nodal count, has been a strong indication for adding concurrent chemotherapy to postoperative radiation therapy; therefore, the observed effect of pENE on survival may be reduced by the more intensive treatment given to patients with this factor.

The extent of ENE may also be important for prognosis, and rENE is likely a better predictor of extensive pENE than minimal pENE. Radiographic ENE has low sensitivity but high specificity for presence of pENE, and there is a high prevalence of pENE among HPV+ OPC patients; thus, if rENE is observed, pENE is likely present. Patients with OPC with rENE may not be ideal candidates for primary surgical therapy because if they are found to have pENE they are likely to receive trimodality therapy with chemotherapy, with potential for increased toxicity compared with definitive chemoradiation.

Some issues should be taken into consideration before using rENE in future staging systems or for trial eligibility. Presently, there is no consensus definition of rENE, and its prevalence likely varies between radiologists and imaging types (computed tomography vs magnetic resonance imaging). Artificial intelligence methods may be useful in the future to help standardize rENE grading but are still investigational at this time and can be sensitive to imaging parameters such as slice thickness and magnetic resonance imaging field strength.

In summary, it is plausible that rENE is a true independent risk factor for disease recurrence in HPV+ OPC, and we hope that other centers will try to validate these findings with their own data. We also hope that centers will collaborate to standardize the reporting of rENE for prospective testing and validation.

**References**