



Editorial: Cancer Staging in Squamous Cell Carcinoma of the Vermilion Lip

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The eighth edition of the AJCC Cancer Staging Manual implemented several major changes to improve and refine the prognostic value of head and neck cancer staging. With each iteration the AJCC Cancer Staging Manual becomes more detailed, and this latest edition, adopted in 2018, reflects our progressively greater understanding of the biology of head and neck cancer. The goals of staging are to provide a reliable standard of classifying tumors based on tumor-node-metastasis (TNM) status and location and help better direct therapy to improve patient outcomes. The classification system also provides a mechanism for standardizing communication about prognosis and treatment outcomes across different institutions, regions, and countries. One change in the eighth edition, for example, is the introduction of a new staging system for high-risk human papillomavirus (HPV)-associated oropharyngeal cancers, recognizing the fact that these tumors have a biology and prognosis distinct from non-HPV associated cancers in the same anatomic location. Although early versions of TNM staging were based on anatomic involvement, we can anticipate that future revisions to the TNM staging system will incorporate our greater understanding of the molecular underpinnings of head and neck cancer.¹

Despite this greater, more refined understanding of carcinogenesis, in this issue of the *Annals of Surgical Oncology*, Yung et al. show that the complex anatomy of the head and neck harbors locations with cancers that defy

clean categorization and staging by virtue of their unique structure and site.² The past seventh edition of the AJCC included squamous cell cancers of the vermilion lip (vISCC) with cancers of the oral cavity (oSCC), but the eighth edition recognizes that the exterior location of the vermilion relative to the oral cavity implies exposure to ultraviolet (UV) light, evidenced by UV damage mutation signatures in vISCC.³ As a transition zone between cutaneous hair bearing skin and the oral cavity, vISCC is thought to have a clinical course between the generally more aggressive tobacco and alcohol abuse associated oSCC, and cutaneous squamous cell cancers (cSCC) with a more favorable prognosis.⁴ Despite this reclassification grouping vISCC with cutaneous cancers, the unique anatomy of the vermilion lip still makes it distinct from both oSCC and cSCC.

The vermilion lip is neither a part of the nonkeratinizing oral mucosa in the adjacent oral cavity, nor a part of the hair-bearing keratinizing skin. The epithelium of the vermilion lip is thin, highly vascular, and overlies the orbicularis muscle, which is richly and superficially innervated.⁵ This network of blood vessels and nerves in close proximity to the surface epithelial layer provides less of a barrier to lymphovascular and perineural invasion relative to other cutaneous sites. Since deep invasion beyond the subcutaneous fat and perineural invasion both upstage cSCC to pT3, the less than 2 mm average thickness of the epithelium, dermis, and subcutaneous fat in the vermilion lip imply that classifying vISCC with oSCC risks inappropriately upstaging cancers in this location.

In their retrospective analysis, Yung et al. suggest that this may indeed be the case with AJCC8 staging for vISCC.² They study 297 patients who presented with vISCC over a 15-year period in the Sydney Local Health District and found that the changes in the pT AJCC

classification resulted in 24% of patients being upstaged with no patients being downstaged, and with respect to overall staging, 21% of patients were upstaged while none were downstaged. Overall, this resulted in a significant number of patients being upstaged to stage III disease. These pT3 patients did well with respect to locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) compared with stage II patients, which affected the predictive power of overall staging based on AJCC8; DFS and OS at 5 years was similar or better in the stage III group compared with the stage II group. Factors such as perineural invasion (PNI), and the need for post-operative radiation therapy (PORT) were associated with worsened LRC and nodal metastases was associated with worse OS. Overall upstaging did not change the LRC, DFS, or OS of patients compared with patients that remained in the original stage, suggesting the new system did not offer any additional prognostic information compared with AJCC7.

The authors conclude that the unique anatomy of the vermilion lip made upstaging due to depth of invasion (DOI) or PNI far more likely. While the AJCC7 system classified a majority of vLSCC patients as pT1 and stage I, AJCC8 appears to push a lot of these patients into stage III without offering new prognostic information. The authors also compare their OS data with past published series and show that their series of vLSCC patients had better OS than oSCC at 5 years and cSCC at 10 years, also hinting that AJCC8 may be upstaging patients with vLSCC inappropriately relative to other cSCC. Overall, for the patients in this retrospective study, the new AJCC8 classification system was unable to stratify pT2–3 patients with respect to clinical course and prognosis. Limitations of the study include its retrospective nature and the fact that there were very few patients with nodal disease or T4 lesions. Therefore, the ability of AJCC8 in predicting prognosis for these patients remains unknown.

The vermilion lip represents a relatively small area of the head and neck and is a transition zone between cutaneous skin and the oral cavity. As such, it intrinsically has

features that are unique and intermediate between the two larger subsites it borders. The head and neck contains many other areas that are distinctive, such as the ear canal, making it impractical to have separate staging for each specialized area. Given low rates of nodal metastases and similarities in risk factors (UV light), it is logical for vLSCC to be classified with cSCC. Clinicians must be aware that, except for very superficial in situ lesions with minimal invasion, there is a risk of upstaging and thus overtreatment for vLSCC with AJCC8. It may be appropriate to consider the absolute depth of invasion and perineural invasion only rather than including invasion of subcutaneous fat as a criterion for upstaging T1 lesions, especially since the vermilion lip is a relatively easy anatomic location to visualize and monitor for recurrence.

DISCLOSURES Baran Sumer, M.D., OncoNano Medicine Inc., Co-Founder, Consultant, Co-Inventor.

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