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EDITORIAL – THORACIC ONCOLOGY

Setting the Stage for Esophageal Cancer: Bulk versus Breadth

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Nodal staging of esophageal cancers has undergone some evolution in recent American Joint Committee on Cancer (AJCC) editions, with each iteration being incrementally more discriminative than the last with respect to clinical outcomes. However, these attempts at stratification have remained imperfect and ultimately fail to take into account the complexity of the nodal drainage patterns of the cervical, thoracic, and abdominal segments of the esophagus.[1,2] Many groups have demonstrated the poor ability of the current AJCC nodal staging system to differentiate outcomes among patients with advanced nodal disease. The determination of nodal status is of critical importance as pathologic nodal status is among the most important independent prognosticators of disease-specific survival.[3–5] This metric is sometimes challenging to reliably achieve as matted nodes may appear to be a single enlarged node, or enlarged nodes may be fractured during backtable dissection or gross examination and appear to be multiple distinct nodes. These seemingly minor details can effect drastic downstaging or upstaging of a patient's nodal status.

It stands to reason that the *breadth* of a tumor's nodal metastasis could be more informative than the *bulk* of its nodal metastasis in characterizing its behavior. Consider the following two patients with otherwise similar features: the first patient has two metastatic nodes immediately adjacent to the primary tumor; the second patient has a metastatic node immediately adjacent to the primary tumor and an additional metastatic node in a more distant nodal station. It would seem that the first patient's nodal spread has a certain bulk, while the second patient's nodal spread has some bulk *and* some breadth. Although their nodal stage is identical, should we conceptualize these patients' cancers differently?

In this issue of *Annals of Surgical Oncology*, Yuan and colleagues have reported on the performance of a station-based (S), rather than number-based (N), nodal staging system for esophageal cancer.[6] This S system accounts for the number of lymph node stations harboring metastatic lymph nodes—defined here as S0 (no metastatic nodes), S1 (1 station with metastatic nodes), S2 (2–3 stations with metastatic nodes), and S3 ($\geq$ 4 stations with metastatic nodes)—while the traditional number-based system accounts for the overall number of metastatic nodes without regard for location.

While this is among the earliest and largest studies to assess the performance of this competing S system, and the first to do so in a multi-institutional cohort, the concept itself is not a novel idea. A similar system was proposed by Xu et al.[7] in 2011 involving the station-distance of lymph node metastases from the primary tumor and the number of operative fields harboring metastatic lymph nodes in a small retrospective cohort. Chen et al.[8] examined a related system based on the number of fields involved by lymph node metastasis but failed to successfully demonstrate any discriminative performance. An S system performed essentially equally as well as the N staging system in a 2015 study by Ning et al.[9] Peng et al.[10] suggested that the number of resected lymph node stations, independent of the overall number of resected lymph nodes, could be used as a predictor of improved overall survival, including in patients with unfavorable preoperative clinicopathologic features. In a contemporaneous report, an overlapping group found that the application of an S system could discriminate overall survival differences among patients with advanced pathologic nodal stages, while the N system failed to identify such differences within their cohort.[11]

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Each of these studies was conducted retrospectively by Chinese groups involving patients from single centers with esophageal squamous cell carcinoma (SCC).

The present group retrospectively analyzed a cohort of nearly 2300 patients with esophageal SCC who underwent esophagectomy at three Chinese hospitals over a 4-year period. The authors found that application of the S system to these patients was at least as discriminative as the current N system. While increasing N and S stages were each independently associated with poorer overall survival, they performed essentially identically well as predictors of survival. They posit that the S system provides a potentially more simple framework for stratifying the degree of nodal involvement in light of established logistical challenges with the N system.

Any praise garnered for this concept by the present study is not without recognition of some obvious barriers to the wide acceptance of such a system. First, these data, like their predecessors, were derived from a cohort of patients with SCC, which may not be applicable to patients with adenocarcinoma and therefore may not be generalizable in Western populations. Second, the authors report a relatively short median follow-up time of 44 months, despite the study period ending in 2012, and 5-year survival of 44.3%, which may imply that many patients were lost to follow-up. Third, patients were excluded from this study if they received any neoadjuvant therapy. The predominant practice in the care of locally advanced esophageal cancer currently involves induction chemoradiation, which may therefore confound the potential application of these data to many patients in this population. Finally, there is little evidence presented here that the S system confers any substantial superiority over the existing N system based solely on their discriminative capability.

Further study is needed to clarify any potential benefit that can be gained by employing the S system rather than the N system in the staging of esophageal cancer. This effort should involve prospective evaluation of more heterogeneous groups of patients across multiple institutions whose management more closely resembles real-world practices in the treatment of esophageal SCC as well as adenocarcinoma. Only then will we be able to determine whether any meaningful significance exists between the nodal bulk and the nodal breadth of esophageal cancer.

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