Is It Time to Add Tumor Regression Grade into the ypN Category?

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Esophageal cancer is characterized by aggressive biological behavior and generally portends an unfavorable clinical course and outcomes.¹ Nodal metastases are commonly recognized as the main predictor of disease recurrence.² In addition to the number of metastatic nodes, interest in identifying other lymph-node-related pathological characteristics that could further refine prognostic stratification is mounting. These variables include the anatomic location of nodal metastases, the presence of extra- or intracapsular spread, and the lymph node ratio.^{3–5} While the available evidence is largely derived from patients who had undergone primary esophagectomy, candidates for upfront surgery are less frequently seen in current surgical practice.^{3–5}

The use of neoadjuvant chemotherapy or chemoradiotherapy for patients with esophageal cancer has increased dramatically following the publication of the CROSS trial in 2012.⁶ On analyzing survival figures, the results of this landmark study indicated that patients with regionally advanced disease who received neoadjuvant therapy had a clear survival advantage over those who were treated with primary esophagectomy alone, especially in presence of esophageal squamous cell carcinoma (ESCC).^{6,7} However, the amount of pathological information that can be extracted from surgical specimens has been significantly affected by the introduction of neoadjuvant therapy. Specifically, the extent of tumor response to neoadjuvant

therapy—as expressed by the tumor regression grade (TRG) of the primary tumor (TRG-tumor) and/or metastatic lymph nodes (TRG-LN)—came into play.^{8–10} While it is generally accepted that a more pronounced TRG-tumor after neoadjuvant therapy portends favorable outcomes, the prognostic significance of TRG-LN is a matter of ongoing debate.^{11,12} In this issue of the *Annals of Surgical Oncology*, Hsu et al. investigate whether TRG-LN may predict survival outcomes in patients with ESCC who had been treated with neoadjuvant chemoradiotherapy followed by surgery.¹³ In their study, TRG-LN was scored as follows: 0, negative nodes without evidence of tumor involvement or regression [cN0 → ypN0]; 1, complete regression of nodal involvement [cN + → ypN0]; 2, partial regression of nodal involvement with < 50% of viable tumor; and 3, no significant regression of nodal involvement with ≥ 50% of viable tumor. The results showed favorable overall and disease-free survival figures for patients with TRG-LN scores of 0–1 (without significant intergroup differences). Conversely, poor survival outcomes were observed for those with scores of 2–3, again without intergroup differences. On multivariate analysis, TRG-LN scores of 2–3 were retained in the model as the only independent adverse predictor of OS. Thus, TRG-LN was found to outweigh the prognostic value of TRG-tumor, ypT stage, and the R0 category. Nevertheless, there are numerous factors that could have had an effect on study findings that could mitigate the prognostic value of TRG-LN for survival outcomes.

First, once there was evidence of persistent nodal involvement after neoadjuvant therapy, it is surprising that no survival differences were observed for patients with < 50% versus ≥ 50% of viable tumor (i.e., score 2 vs. score 3). Because 5-year overall survival rates were equally dismal (only 8%!) regardless of regression extent, the use

of TRG-LN would add limited prognostic information over the current ypN stage category. In this scenario, the authors should be encouraged to conduct additional subgroup analyses in patients with minimal residual nodal disease (i.e., < 10% of viable tumor) to investigate whether their survival figures are similar to those observed in patients with complete regression of nodal involvement.¹⁴ Second, the lack of survival differences in patients with TRG-LN scores of 0–1 does not imply that TRG-LN is without prognostic value in the ypN0 group. In this regard, the adverse significance of tumor-regressed nodal numbers for survival outcomes has been repeatedly reported—possibly as the result of a significant tumor burden.^{15,16} However, it is not possible to determine from the study by Hsu et al. how many nodes had signs of preexisting tumor involvement. Third, and even more importantly, a key prerequisite for accurate TRG-LN assessment is the systematic evaluation of the entire nodal structure. Theoretically, an en bloc lymph node resection (i.e., complete removal of lymph nodes with the surrounding adipose tissue as a lump following anatomical landmarks surrounding the nodes) would be ideal to achieve this goal. Because mediastinal nodes and their surrounding sheaths are more fragile and prone to tear upon dissection compared with abdominal nodes, significant variations in the thoroughness of their assessment across different institutions, surgeons, and pathologists can be expected. Undoubtedly, the presence of fragmented nodes may lead to erroneous TRG-LN estimations. Although the study by Hsu et al. does not provide information on their handling and does not mention a potential interobserver bias among different pathologists, the authors should be commended for their attempt to address an interesting research question for patients with ESCC who receive neoadjuvant therapy. The incorporation of TRG-LN assessment into the current staging system for esophageal cancer will ultimately depend on the results of large multicenter international research efforts. Similarly, the prognostic significance of TRG-LN in esophageal malignancies is to be confirmed by following a larger cohort for a longer period of time.

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