Editorial Commentary

Staging systems for gastric cancer: more complex than TNM

Aslam Ejaz, Timothy M. Pawlik

Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Cancer Hospital and Solove Research Institute, Columbus, OH, USA

Correspondence to: Aslam Ejaz, MD, MPH. Assistant Professor of Surgery, Division of Surgical Oncology, The Ohio State University Comprehensive Cancer Center, 320 W. 10th Avenue, M-260 Starling Loving Hall, Columbus, OH 43210, USA. Email: aslam.ejaz@osumc.edu.

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Gastric cancer is an aggressive malignancy with varying incidences worldwide. Accurate staging systems are necessary in order to help determine prognosis and guide treatment. Given the rapidly evolving role of multimodal systemic (chemotherapy, targeted therapy) and regional (chemoradiation) therapy in both the neoadjuvant and adjuvant setting, there is an even greater need for comprehensive and accurate prognostic staging systems. As such, we read with great interest the current study by Ye and colleagues in *Surgical Oncology* that externally validated the 8th American Joint Commission on Cancer (AJCC) and the modified 8th AJCC system for advanced gastric cancer. The authors utilized a large cohort of 684 patients from a single institution in Southern China. Compared with the AJCC 7th edition, the authors noted that stage migration occurred in 23.2% of patients. Utilizing a cutoff of 30 lymph nodes (LN) retrieved, the authors reported that stage migration occurred in 15.8% of patients from the AJCC 8th edition to the modified 8th AJCC edition. These data add a new perspective to the literature on the staging of advanced gastric cancer. However, as with any large retrospective database study, a number of important factors need to be considered.

Among the patients who experienced stage migration, approximately three-quarters of these individuals were downstaged (n=101), whereas the remaining 58 patients were upstaged. However, when the modified staging system was applied, the majority of patients were upstaged (n=87) rather than downstaged (n=21). These findings were largely due to a significant number of patients not having at least 30 lymph nodes examined (46%). These data highlight the fact that the number of lymph nodes retrieved may be multifactorial. First, the approach to lymphadenectomy among gastric cancer patients has not been universally accepted. To date, 8 randomized trials have evaluated this topic: 3 comparing a D3 with D2 lymphadenectomy, and 5 comparing D2 with D1 lymphadenectomy. Initial reports of trials evaluating a D2 versus D1 lymphadenectomy reported similar long-term oncologic outcomes, though recent long-term results of the Dutch Gastric Cancer Trial (DGCT) reported a significantly improved disease-specific survival among patients who underwent a D2 lymphadenectomy (1). The optimal number of lymph node retrieval, however, has not been universally accepted and current US National Cancer Comprehensive Network guidelines recommend a minimum retrieval of 15 lymph nodes versus the 30 proposed in the modified staging system. Second, lymph node retrieval has been demonstrated to be a quality indicator of not only the surgeon, but also multiple modifiable and non-modifiable factors (2). These factors include both patient (e.g., body mass index/obesity) and provider (e.g., experience/technique of pathologist) factors. As such, aside from surgical technique, low lymph node retrieval and subsequent differing patient outcomes may be multi-factorial.

Of note, the data reported by Ye and colleagues were in contrast to the findings reported by In *et al.* (3). In the study by In *et al.*, the authors noted good concordance of the 8th AJCC staging system with overall survival based on data from the United States (3). One possible explanation for the discrepancy may be the fact that prognosis is not simply based on tumor stage and nodal involvement.

In recent years, there have been several developments in the molecular pathogenesis of gastric cancer. The Cancer Genome Atlas Network published the results of a comprehensive molecular evaluation of 295 primary gastric adenocarcinomas in 2014 (4). Gastric cancer was divided into four subtypes: tumors positive for EBV (19%), microsatellite unstable tumors (22%), genomically stable tumors (20%), and tumors with chromosomal instability (50%) (4). It is likely that this heterogeneity in molecular pathogenesis among patients with gastric cancer may be responsible for the differences in prognostic performance of the various validation studies, which have examined varied patient populations. As such, further studies are needed to evaluate the incorporation of genetic and molecular information into future staging systems.

There are several additional considerations when interpreting the data by Ye and colleagues. For example, patients who received neoadjuvant chemotherapy were excluded from the analysis. This point is important as neoadjuvant chemotherapy may impact lymph node yield and thus impact the prognostic capability of the modified staging system. Additionally, data on type of and completion of adjuvant chemotherapy was not included in the study, which also may have influenced the results. Finally, there was a large number of patients who had missing data that were excluded, which may introduce bias (e.g., missing not at random).

In conclusion, determining prognosis for patients with gastric cancer remains a challenge. Changing systemic and regional therapies, differing qualities of surgical care, and potential heterogeneity in the molecular and genetic pathogenesis of the disease remain barriers to a single ideal staging system. As such, readers should interpret the data from the current study somewhat cautiously as the ability to estimate prognosis for patients with gastric cancer continues to evolve.

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Footnote

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