Editorial Commentary

Comparison between 7th and 8th edition of AJCC TNM staging system for gastric cancer: old problems and new perspectives

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Gastric cancer (GC) represents one of the most common causes of cancer mortality worldwide (1). Although considerable progress in diagnostic and therapeutic tools can improve the outcome of GC patients, surgery remains the only curative therapy. Actually, surgical resection with lymphadenectomy is considered the only curative therapeutic approach for resectable GC, while preoperative and adjuvant chemotherapies, as well as chemoradiation, can improve the outcomes aiming at the reduction of recurrence and extension of survival. However, lymphadenectomy for surgical treatment of GC has remained an open issue between the European and Japanese surgical schools for several years. At present, on the basis of scientific and practical outcomes, the Western perspective regarding the lymphadenectomy in GC surgery has been overturned. As a result, the majority of national as well as several supranational scientific societies are converging on the D2 lymphadenectomy as the standard of care with curative intent (2). The main goal of GC surgery is to preserve the post-operative functionality as well as the quality of life and maximize long-term oncological outcomes by means of proper surgical approach with a tailored lymphadenectomy (3,4). To this address, precise classification of the tumor stage, incorporating the lesion depth (T parameter), lymph node involvement (N parameter) and the presence of distant metastases (M parameter), is of paramount importance for prognostic assessment and stage-specific therapeutic strategy (5). The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) staging system has been extensively used for clinical research and practice in defining GC stage, representing the most relevant tumor-related prognostic factor (6). Over the past 30 years there is been a succession of several versions of this classification system and, since 2017, the 8th edition of TNM staging system has been introduced, resulting in several changes from the previous version (7). First of all, the anatomic landmark between the esophagus and the stomach has been redesigned: esophagogastric junction (EGJ) cancers with the center of lesion confined to the first two centimeters of the proximal stomach are defined as esophageal cancers. EGJ cancers extending over two centimeters of the upper stomach are defined as gastric neoplasms. Additionally, although the division of pN3 in pN3a (7–15 positive lymph nodes) and pN3b (more than 15 positive lymph nodes) was already introduced in the 7th edition, no change in final pathologic TNM staging was implicated. The prognostic difference between N3a and N3b was previously demonstrated in an Italian Research Group for Gastric Cancer (IRGGC) multicentric study, and this separation for stage grouping was suggested to improve the prognostic accuracy (8). Sano *et al.* (9) suggested a new categorization on the basis of results from 25,411 patients collected from 59 institutions in 15 countries. Indeed, both groups were defined as the pathologic setting in the 8th edition. This leads to changes in pathological staging. In fact, T1N3bM0 and T2N3bM0 from stage IIB and IIIA, respectively, in the 7th edition, were reclassified as stage IIIB in the newest edition. Similarly, T3N3bM0 was reclassified from stage IIIB as stage IIIC, as well as T4bN0M0 and T4aN2M0 are

down-staged from IIIB to IIIA. In addition, T4aN3aM0 and T4bN2M0 tumors from IIIC were reclassified as IIIB. Yu *et al.* (10) retrospectively reviewed 1,633 resectable GC patients with lymph node metastasis who had received D2 gastrectomy with curative intent followed by adjuvant chemotherapy alone (CA) or concomitant chemo-radiotherapy (CCRT), to compare the 7th and 8th edition of AJCC staging system. Six of 371 stage IIB patients (1.6%) and 40 of 360 stage IIIA patients (11.1%) according to the 7th edition of AJCC staging system were redistributed to IIIB stage according to the 8th edition. Of 298 stage IIIB patients, 75 (25.2%) were restaged as IIIC while 60 (20.1%) as IIIA. Moreover, 67 of 115 patients (58.3%) with above stage IIIC were reclassified as stage IIIB according to the new TNM. Analysis of recurrence-free survival highlighted better discrimination of 8th edition as regard the stages from IIIA to IIIC, independently from adjuvant CA or CCRT treatment. Interestingly, even if there was no statistical difference, the OS curves were better specified in advanced stages according to 8th edition, with the same trend despite to adjuvant regimen. As the authors emphasized, on the other hand, the retrospective nature and the possibility of selection/referral bias could restrict the generalizability of the study.

In the medical literature, there are considerable Eastern population studies describing that the 7th TNM does not appropriately classify the biologic behavior of cancer as well as the prognosis of patients. Kikuchi *et al.* (11) described no significant differences from IIB to IV stages. Furthermore, they stated that the IIB and IIIC stages survival curves appeared to be similar with those of stages IIIA and IV, respectively. Kim *et al.* (12) demonstrated comparable conclusions between stages IB and IIA and stages IIIB and IIIC. On the other hand, GC in Western countries may represent a distinct disease on the basis of presentation pattern and pathophysiology. Furthermore, western studies investigating the validity of the new staging system with a focus on the advanced stages are scarce, and the prognostic capability of this new classification remains as ambiguous.

In a retrospective analysis of a single western center, the 5-year OS rates of stage IIIB and IIIC patients (8th edition) demonstrated a significant difference (40.8% *vs.* 20.2%, P<0.001) whereas no divergence in the 5-year OS was observed according to the 7th edition criteria (37.6% *vs.* 33.2%, P=0.381), configuring the 8th TNM as a valid pathological classification system (13). There is overwhelming evidence that staging is a key factor of cancer treatment, revealing the advance of a disease, the relapse risk as well as global survival. These factors significantly affect the therapeutic strategy and stimulate the comparisons between patient cohorts across institutions and countries. The 8th edition of the TNM staging system tries to show relevant differences in stage III disease survival rates using a more elaborate structure than 7th edition. However, the newest TNM is not more accurate in predicting prognosis than the older editions. It is supposed that nodal statuses are strongly influenced by the number of lymph nodes removed and that the N category increases proportionally to the total number of harvested nodes (14). To this address, it is of note that when the number of removed lymph nodes is insufficient, stage migration will be observed in 10% to 15% of cases (15). Nevertheless, even if N3b cannot be assigned when fewer than 16 lymph nodes are harvested, the current AJCC staging system still establishes no strict minimum number of total resected lymph nodes for adequate staging, with an intrinsic recommendation that almost 15 LNs should be resected for radical gastrectomy. So, it would appear conceivable to increase the cutoff point of total resected lymph nodes to improve the discriminatory ability and the predictive accuracy of the staging system. In light of such evidence, new and modified staging systems have been proposed to overcome some of the drawbacks. Jung *et al.* (16) suggested an integrated staging system consisting of a combination of the 7th edition "T parameter" and the 6th edition "N classification". Moreover, Warneke *et al.* (17) supported the proposed of Kiel as regard the stage grouping for GC. In addition, another important point is represented by the fact that before data collection for the staging of GC has focused on data of patients after surgery, while patients undergoing neoadjuvant treatment (NT) were not included in the analyses (18,19). Even though, as the majority of patients are diagnosed with advanced tumors, mainly in the West, the distribution of patients receiving NT before surgery has increased significantly over the past decade, at the present time representing the majority of GC patients in Europe (20) reporting several studies addressing the staging systems comparison a considerable bias.

Interestingly, in recent years many novel GC classifications were also suggested and rapidly developing research is now ongoing, aiming at finding clinical as well as prognostic applications to these new findings. They are based on tumor location, histopathology, gene expression, gene amplification, DNA methylation, several cancer-relevant aberrations and also on the oncogenic pathways (21-24). Recently, two molecular classifications by The Cancer Genome Atlas (TCGA) and Asian Cancer Research

Group (ACRG) (21,22) proposed a simple division of GCs tracing new ways to treat the disease with a more tailored approach. The TCGA classification suggested four categories: Epstein-Barr virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN) and genomically stable (GS) (21). The ACRG partitioned the GC into MSI and microsatellite stable (MSS) types. The latter was further divided into epithelial-mesenchymal transition (EMT), TP53+ and TP53– groups (22). Several studies (21,22,25) reported peculiar clinical-pathological characteristics (such as age, tumor location, invasion, and stage) as well as different prognosis shown by distinct molecular subgroups. In the near future, it would be advisable to combine the TNM classification system with histopathologic and molecular tools, in order to improve both accuracy and effectiveness of the tailored approach in a scientific context of precision medicine.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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