2 Staging of Gastric Cancer: Current Revision and Future Proposal

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Gastric cancer (GC) is the fourth most common malignancy and ranks the third as cause of death (990,000 cases, 738,000 deaths) worldwide (ref. [1] WHO). Due to the lack of cost-effective screening test and the lack of specific symptoms, most gastric cancer cases were diagnosed at the advanced stages. It is very important to appropriately stage GC patients since it is associated with the choice of treatment modalities and patients' prognosis. The current staging modalities include endoscopy, CT, PET/CT, and laparoscopy. The primary goals of the staging are to evaluate whether a patient has regional or distant metastasis (M), whether the tumor involves local/regional lymph nodes (N), and whether the depth of tumor invasion into the different histology layers between mucosa and serosa (T). Combining the three components, Union for International Control Cancer (UICC)/American Joint Committee on Cancer (AJCC) has defined the most commonly used GC staging system, tumor-node-metastasis (TNM) staging system [1]. As the improvement in cancer awareness, methods in cancer screening, advancement in chemotherapy and target therapy, and patients' disease characteristics are constantly changing and so does the prognosis. Hence, the UICC/AJCC TNM staging system has been revised accordingly every few years since its induction into clinical practice since 1977. The seventh edition UICC/AJCC TNM classification for GC was modified after the Buffalo Meeting 2008 as the result of the consensus between the Eastern (Japanese and Korean) and Western GC classification. In 2010, the seventh edition (7th ed.) TNM classification for GC, comprising of the data from Japan and Korean, was published with minor revisions in T stage and major revisions in N stage compared to the previous editions of TNM classification [2].

The seventh edition UICC/AJCC TNM classification for GC

T1a	Tumor invades lamina propria
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades subserosa
T4a	Tumor penetrates serosa without invasion of adjacent structures
T4b	Tumor invades adjacent structures
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in more than 15 regional lymph nodes
M0	No distant metastasis
M1	Distant metastasis
pM1	Distant metastasis microscopically confirmed

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Stage grouping of GC in accordance with the seventh edition UICC/AJCC TNM classification

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIIB	T4b	N0 or N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4a	N3	M0
	T4b	N2 or N3	M0
Stage IV	Any T	Any N	M1

Revisions on the Current Edition TNM Classification for Gastric Cancer

Explicit Staging in Esophagogastric Junction Carcinoma

Carcinoma of the esophagogastric junction (EGJ) is defined by the WHO as "tumors cross the EGJ regardless of where the bulk of the tumors lies" [3]. The classification carcinoma of EGJ, defined by Siewert and Stein, was approved at the second International Gastric Cancer Congress in Munich in April 1997 [4]. In accordance with the anatomic cardia, EGJ cancer can be divided into three subtypes: type I, adenocarcinoma of the distal esophagus with the tumor center located between 1 and 5 cm above the anatomic EGJ; type II, true carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below the EGJ; and type III, subcardial carcinoma with the tumor center between 2 and 5 cm below EGJ. This classification was approved at the consensus conference of the International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE) and has been accepted and used worldwide before the seventh edition TNM classification was published [5].

According to the sixth edition TNM classification, EGJ carcinoma may classify into either esophageal cancer or GC on the basis of the judgment of the physicians. However, many investigators found that adenocarcinoma of the proximal stomach was similar, or even identical, to Barrett's esophagus-associated distal esophageal adenocarcinoma on the basis of comparable characteristics in epidemiology [6], clinical presentations [7], molecular pathobiology [8], and histopathology [9]. Subsequently, AJCC adopted the notion that all EGJ cancer should be required to comply with the rule for esophageal adenocarcinoma, which has been published in the seventh edition of the cancer staging manual [10]. The seventh edition TNM classification included the meticulous classification of EGJ carcinoma. However, an obvious issue of major concern was the following rule: "A tumor with the epicenter of within 2 to 5 cm below the EGJ and also extends into the esophagus is classified and staged using the esophageal scheme. Tumors with an epicenter in the stomach greater than 5 cm from the EGJ or those within 5 cm of the EGJ without extension in the esophagus are classified and staged using the gastric carcinoma scheme." In another word, EGJ carcinoma included in the esophageal chapter on the basis of the new TNM staging system according to the anatomical criteria "5 cm rule" proposed by Siewert was based on an obscure concept of the tumor epicenter. Some of the gastric fundus tumor might be considered as esophageal cancer [11]. As the result, the current revision did not resolve the well-known controversial issue: Should type III tumors be treated as GC invading the EGJ, considering the origin of the tumors? Some literatures have shown that esophagectomy has not improved the survival rate compared to an extensive gastrectomy for type II tumors arising from the same origin as type III tumors [5]. In fact, more and more clinicians think that the optimal treatment modalities should be selected based on the distance

of tumor invasion to the stomach or esophagus rather than the location of the central region of the tumor [12].

Proposal of Positive Cytology as Distant Metastasis

Peritoneal washing cytology, as a preoperative staging tool, has been gradually adapted into clinical practice. Leake et al. [13] recently demonstrated that recurrence rates for patients positive for peritoneal cytology ranged from 11.1% to 100%, while those negative for intraperitoneal free cancer cells (IFCCs) had recurrence rates of 0–51%. Overall survival was significantly decreased for patients with positive peritoneal cytology by using a systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Other reports in the literature indicate that a positive peritoneal cytology is an independent predictor of poor prognosis following curative surgery, with median survival of as poor as distant metastasis [14–16]. In addition, Yamamoto et al. [17] also validated that GC with peritoneal cytology (+) had a poor prognosis because it is associated with non-curative factors, peritoneal dissemination, and liver or LNs metastases. Mezhir et al. [16] recommended to abandon gastrectomy for patients with positive peritoneal cytology even in the absence of gross peritoneal disease due to the poor outcomes. Thus, both the Japanese Gastric Cancer Association (JGCA) and the seventh edition TNM classification classify positive peritoneal cytology as stage IV disease [18]. Conversely, few authors reported that peritoneal washing cytology using samples harvested in the abdominal cavity was not able to predict peritoneal recurrence or survival in GC patients [19]. Depending on the various methods for performing a peritoneal washing cytology, there is a large discrepancy in the frequency of a positive peritoneal cytology. The rate of positive cases was found more than 20% on a routine cytology, 35% on immunohistochemistry, and 50% on RT-PCR in cases of a serosa invasion-positive GC [20]. Inevitably, there is a large discrepancy in the positive rates and median survival time of the positive cases among different institutions. Therefore, the prognosis and treatment of patients with no macroscopic peritoneal metastases but with peritoneal cytology-positive diseases remain as controversial issues. Further rigorous definition of the methods in detecting peritoneal washing tumor cell and studies in the staging and the appropriate comprehensive treatment of this group of patients are needed.

Minimum Number of Examined Lymph Nodes

The recommended minimum number of examined (dissected) LNs required for proper staging remains controversial, because this number varies considerably between institutions and countries. Before 1997, all staging systems (UICC, AJCC, and Japanese Committee on Cancer) used for this disease defined N stage by the location of LN metastases relative to the primary tumor (I do not understand this sentence). Subsequently, many studies revealed that the number of positive nodes best defined the prognostic influence of metastatic LNs in GC. In 1997, the UICC and AJCC redefined the pathologic nodal status based on the number of involved nodes rather than their location. In an effort to improve staging accuracy, it was recommended that a minimum of 15 lymph nodes should be examined to guarantee the accuracy of prognostic prediction of N stage, especially in the definition of N0 [21]. Karpeh et al. [22] demonstrated that the overall distribution of patients staged by the fifth edition AJCC classification did not change significantly if 15 or more LNs were examined, but median survival for N1, N2, and N3 by the fifth edition AJCC classification increased significantly when 15 or more LNs were examined. It must be emphasized that the extent of LN dissection and the thoroughness of the pathologist's examination of the specimen together determine the number of LNs ultimately retrieved [23]. It is clear that techniques such as fat clearing can increase the number of nodes and that an increase in the number of examined lymph nodes will increase the number of positive nodes, which will alter the stages [24]. Recently,

Smith et al. [25] reported that survival would improve by 7.6% (T1/2N0), 5.7% (T1/2N1), 11% (T3 N0), or 7% (T3 N1) if every 10 extra LNs were dissected in the Surveillance, Epidemiology, and End Results database between 1973 and 1999. Furthermore, they demonstrated that a cut-point analysis yielded the greatest survival difference at 10 LNs examined but continued to detect significantly superior survival differences for cut points at up to 40 LNs, always in favor of more LNs examined [25]. Son et al. [26] analyzed the survival rates of 10,010 patients who underwent curative gastrectomy from 1987 to 2007 and then showed that patients who had T1 tumor classification, N0 LN status, and stage I disease with an insufficient number of examined LNs (≤15 nodes) after curative gastrectomy had a significantly worse prognosis than patients who had ≥16 examined LNs. In accordance with the fifth/sixth edition TNM classification, Nio et al. [27] analyzed 223 pN0 patients with GC and then found that patients with pN0 in pT1 stage should be required for a minimum of six examined nodes. Jiao et al. [28] reported that the number of examined LNs was the independent predictors of overall survival of patients with node-negative GC, and patients with ≤15 examined LNs were more likely to experience locoregional and peritoneal recurrence than those with no less than 16 examined LNs.

Therefore, the latest edition TNM classification specifies that "histological examination of a regional lymphadenectomy specimen should ordinarily include 16 or more LNs" to avoid understaging. However, only 1/3 of the gastric cancer patients have more than 15 lymph nodes examined (my Annals of Surgery paper). In fact, the new UICC/AJCC system confirmed the following sentence (added in previous editions) as regards the pN0 definition: "If the LNs are negative, but the number ordinarily examined is not met, classify as pN0." Therefore, this appears to mean that the figure of 16 is a recommendation, but no longer a requirement, for pN0 staging [11]. At the meantime, Wang et al. [29] clearly showed that for patients who have N0 disease and <16 LN examined, their survival is the same for patients who had N1 disease with >15 examined LN. All those evidence indicated two paradox problems that the seventh edition system is facing: It is well known that inadequate (<16) examined lymph nodes will cause stage migration. On the other hand, most American patients have <16 LN examined.

Bilici et al. [30] recently reported that the superiority of classification based on the ratio between metastatic and examined nodes to determine N stage for prediction of overall survival of patients with radically resected GC could not be proved, even in patients with <16 examined LNs. This numeric change seems to arise from the figure of 16 introduced for N3b in the seventh edition TNM classification more than from the "numeric controversies" of literature.

Has the latest UICC TNM stipulated that GC should be staged independent of the number of examined LNs? As we know, the main reasons for examination of an insufficient number of LN s after curative gastrectomy are inaccurate LN dissection or retrieval. Besides, harvesting of a number of nodes "small" to differentiate N subcategories is not a guarantee for enough extent of lymphadenectomy. Therefore, it is worthwhile to discuss whether the requirement of appropriate threshold of examined LNs for accurate evaluation N stage of GC.

Proposed Lymph Node Ratio to Be Included in the Staging System

The ratio between metastatic and dissected (examined) LNs has been proposed as a simple, convenient, and reproducible system that can be used to better identify the subgroup of gastric, breast, pancreatic, and colon cancer patients with similar prognosis, thus minimizing the stage migration phenomenon that can be observed using the TNM classification [31–33]. Owing to decrease the stage migration, many investigators emphasized that ratio between metastatic and dissected LNs is a convenient, repeatable, and creditable variable for accurate prediction of the prognosis of GC patients, regardless of the number of dissected LNs and extent of lymphadenectomy [34, 35]. It is still controversial whether the ratio

between metastatic and dissected LNs is superior to the number of metastatic LNs for predication of the overall survival of GC patients. Wang et al. [29] demonstrated that AJCC staging misclassified 57% of patients and TNrM staging misclassified only 12% when misclassification was defined as any subgroup in which median survival fell outside the 95% confidence interval of the GC patient group's overall median survival.

On the other hand, several authors reported the negative results of the ratio between metastatic and dissected LNs for prediction the prognosis of patients with adequate dissected nodes, especially in the group of patients with 15 or more dissected nodes [36, 37]. Actually, it is absolutely incorrect that the number of the examined nodes can instead be use as an indicator of the extent of node dissection. In addition, how to accurately define the cutoffs of ratio between metastatic and dissected LNs is unclear else. However, we demonstrated that the ratio between metastatic and dissected LNs was an important variable which was capable of the improvement of the survival discrimination of GC patients with positive LNs [37]. Therefore, the clinical values of the ratio between metastatic and dissected LNs need to be further discussed in elaborate analysis.

Prefix "y" for TNM Classification After Neoadjuvantly Treated Tumor

For locally advanced lesion, the standard treatment is perioperative chemotherapy in Europe [38–42]. So far, R0 resection is aimed for by gastrectomy with standard D2 lymphadenectomy [41]. However, even with D2 gastrectomy and adjuvant chemotherapy with S-1, the prognosis of tumor is not satisfactory [43]. Neoadjuvant chemotherapy, which is an exception to improve the radical resection condition, is under heated discussion about its definite role in improving cure rate for GC patients [44, 45]. Authors reported that only about 21% GC patients had complete or subtotal tumor regression, which may provide objective and highly valuable prognostic information in addition to posttherapeutic lymph node status [46]. In addition, response of the primary tumor does not guarantee recurrence-free long-term survival, but histopathological complete responders have better prognosis compared to partial responders [47]. Although the percentage of major responder tumors after perioperative chemotherapy is low in GC [48], the pathological assessment may be affected by possible tumor regression. In the seventh edition TNM classification, a clinical TNM classification recorded following the neoadjuvant therapy should be identified by the prefix "y," as "ycTcNcM." Actually, the ypTNM classification is used to reflect the extent variation of tumor after neoadjuvant therapy. In analyzing the results, it can be differentiated between patients treated with primary surgery (cTNM, pTNM) and those treated by surgery following neoadjuvant treatment (ycTNM, ypTNM) [49].

Proposal of the Next Edition TNM Classification for Gastric Cancer

Amendment Both Extent and Number of Dissected Lymph Nodes as the Prerequisites for Staging the Lymph Node Metastasis

As compared with the sixth edition TNM classification system involving N stage, the seventh edition more reliably and accurately categorized the number of metastatic LNs for the purpose of predicting the overall survival of patients after curative surgery, regardless of the extent of lymphadenectomy or the number of examined LNs. However, the only treatment known to offer cure for GC is adequate surgery for potentially exhaustive removal of the primary tumor and the metastatic LNs. It is undoubtedly that the stage migration may be brought out by using the seventh edition TNM classification in GC patients who have undergone D1 lymphadenectomy or presented with less than 16 examined LNs, which can result in lower N stage classifications and falsely higher survival rate. The patients with the extragastric LN metastasis had the obviously lower 5-year survival rate

than patients with the perigastric LN metastasis or without any LN metastasis [50]. It is worth noting that limited lymphadenectomy cannot provide the accurate extent of LN metastasis owing to the lack of dissection and examination of extragastric LNs, which is the key causation for the bias of prognosis evaluation. D2 lymphadenectomy and no less than 16 examined/dissected LNs, as the requisite guarantees for adequate quality of the surgery, can provide sufficient information concerning nodal metastases to allow the prediction of prognosis using the seventh edition of the TNM classification system involving N staging [51].

Occult Tumor Cells in Lymph Nodes as a Novel Subcategory of N Stage

Although many researchers demonstrated that the postoperative prognosis of node-negative GC patients was significantly better than that of node-positive GC patients, minority of node-negative GC patients had recurrence and poor survival [52–54]. Multivariate analysis showed that D1 lymphadenectomy, few dissected nodes, and serosal involvement were the risk factors of postoperative recurrence of node-negative GC patients [54]. Biffi et al. [55] reported that more extended LN resection offers protection, as node-negative GC patients who had ≤15 nodes removed had significantly worse disease-free survival and overall survival at multivariate analysis than patients in whom >15 nodes were removed. In addition, authors also demonstrated that the sufficient number of negative LNs harvested might improve the overall survival rate of GC patients after curative gastrectomy [56, 57].

Occult tumor cells in LN may result in the inaccuracy of pathological N category [58]. Latest research revealed that the majority of the retrieved studies (75%) evaluating the predictive role of occult tumor cells concluded that its presence was associated with a worse prognosis of GC patients by using the systematic analysis [59]. Therefore, increasing the number of examined LNs during surgery could reduce the chance of residual malignancy and improve the prognosis of GC, even in negative-node patients [60]. Occult tumor cells that comprised micrometastases (MM; >0.2 mm and < or = 2.0 mm) and isolated tumor cells (ITC; < or = 0.2 mm) are the original hematoxylin and eosin-stained sections of all LNs from patients that are previously considered as tumor-negative by the local pathologist. The number of examined LNs and the percentage of occult tumor cell in positive LNs were identified to be independent risk factors for locoregional disease recurrence and distant disease recurrence, respectively [58]. Yonemura et al. [61] demonstrated that 5 of the 37 negative-node patients with isolated tumor cells (pN0(i+)) versus 1 of the 271 negative-node patients with no evidence of isolated tumor cells (pN0(i−)) died from recurrence by using immunohistochemical detection ($P = 0.014$). Lee et al. [62] found that LN micrometastases were identified by cytokeratin immunostaining in 196 GC patients classified as pN1, consisting of 20 cases with micrometastases (pN1mi(i+)), 34 cases with only micrometastases (pN1mi), and 142 cases with pN1 with one or more macrometastases (pN1). Although the association between occult tumor cells and patients' overall survival is still controversial, the high recurrence rate for patients has been detected by using immunohistochemical method with micrometastases [63].

Extracapsular Lymph Node Involvement in Gastric Cancer

Tumor penetration of the LN capsule in metastatic LNs is called as extracapsular LN involvement. For several nongastrointestinal malignancies, like breast, prostate, pharynx, larynx, and bladder cancer, the prognostic value of extracapsular LN involvement has already been demonstrated to be negatively associated with overall and disease-free survival of patients [64–70]. Recent systematic review showed that extracapsular LN involvement was a common phenomenon in patients with gastrointestinal malignancies and could identify a subgroup of patients with a significantly worse survival [71]. Tanaka and colleagues concluded that extracapsular LN involvement was a significant risk factor for peri-

toneal dissemination and liver metastasis in GC patients [72, 73], which was similar to the research results reported by Alakus in 2010 [74]. With the multivariate analysis, extracapsular LN involvement also was identified to be an independent risk factor influencing the outcome of patients with GC [75]. The further study showed that the presence of extracapsular LN involvement could affect the survival of GC patients with only single LN metastasis [75]. Additionally, Nakamura reported that extracapsular LN involvement was also identified to be useful in combination with N stage of the TNM classification, representing a promising indicator to refine the LN metastatic category in GC [76].

Other Variables' Assessment for Enhancement of the Efficiency of Stage of Gastric Cancer

Recent researchers showed some variables might be potential targets for improvement of the efficiency of the stage of GC, which need to be assessed in the future large-scale. Owing to peritoneal dissemination and distal metastases occurring in the comparatively late stages of disease, accurate diagnosis is critical for successful design of the therapeutic strategy of GC and for greatly enhancement of the efficacy of medical intervention [77]. To date, many potential biomarkers have been elucidated in GC by detecting serum protein antigens, oncogenic genes, or gene families through improving molecular biological technologies [78]. DNA methylation plays a significant role in the oncogenesis and the progress of human carcinogenesis. It has been validated the significant relationship between specific gene methylation and clinicopathological features in GC. The ability to detect small amounts of methylated DNA among tissues allows researchers to use DNA methylation as a molecular biomarker in GC in a variety of samples, including serum, plasma, and GC [79]. Gene amplification and protein overexpression of human epidermal growth factor receptor 2 (HER2) play an important role in the proliferation, apoptosis, adhesion, angiogenesis, and aggressiveness of many solid tumors, including GC [80]. More recent studies released that HER2 is a poor prognostic factor in GC patients [81–83], especially those with liver metastases and/or LN metastasis [84, 85].

Yamaguchi et al. [86] proposed that tumor size, given as the maximum diameter of tumor, could provide important information useful for evaluating the potential impact of GC double time screening programs in terms of the degree of improvement in prognosis. Surgeons usually pay more attention to tumor size than depth of tumor invasion because tumor size might have a direct impact upon patients' surgical management and outcome. Researchers demonstrated that there were obvious correlations between tumor size and other tumor-relative clinicopathological variables such as LN metastasis, depth of tumor invasion, and type of Lauren classification, which might result in the poor prognosis of GC patients [87–90].

In view of the impact of occult tumor cells on prognostic evaluation, the negative LNs, identified by the conventionally pathological examination, should be reconsidered for the reality of the negative results of these LNS. Recently, several results were reported to demonstrate that the number of negative LNs was a potential predictor of prognosis of GC. Deng et al. [91, 92] showed the detailed contents of researches of negative LNs in gastric cancer as follows: (1) negative lymph node count was significantly associated with the overall survival of patients, which could enhance the prognostic prediction accuracy of the ratio between positive and dissected LNs for the GC patients; (2) negative lymph node count is a key factor for improvement of the prognosis of GC patients who underwent the D2 lymphadenectomy; (3) ratio between negative and positive LNs was identified to be the optimal lymph node category for evaluation of the overall survival of gastric cancer, rather than N stage or ratio between positive and dissected LNs.

Lastly, a complete harmonization between the TNM classification of stomach tumors proposed by UICC/AJCC and JGCA would be of great importance. Does the No.14v really need to be excluded from the local lymph nodes in advanced GC?

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