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Review

Revisiting the 8th AJCC system for gastric cancer: A review on validations, nomograms, lymph nodes impact, and proposed modifications

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ABSTRACT

Gastric cancer is the fifth most frequently diagnosed cancer worldwide, behind breast, lung, colorectal, and prostate cancers. In gastric cancer, multimodality treatment shows prospective benefits and also improves survival. Surgery, however, is the mainstay of curative treatment. The staging of gastric cancer patients is critical for harmonization of care. Accurate stages assure that informed clinical decisions are timely made. The American Joint Committee on Cancer (AJCC) staging system is the most widely applied system in to determine the disease's prognosis and survival prediction. The recently adopted 8th AJCC TNM staging system has been revised to enhance its survival predictive power. Subsequent studies have established the validity of the current edition, demonstrating improved stage stratification, discriminatory power, and survival prediction. However, other studies have cast doubt on the superiority of the new edition. Innovations aimed at further improving its prognosis have resulted in developing of novel models. Advances in our understanding of the tumor microenvironment and molecular categorization of cancer have resulted in proposals for their inclusion in TNM staging as potential complementary factors that enhance survival prediction and prognostic assessment ability. The purpose of this study is to conduct a review of the published literature regarding the validity of the 8th AJCC TNM staging system, proposed modifications, and nomograms.

1. Introduction

After breast cancer, lung cancer, colorectal cancer, and prostate cancer, gastric cancer is the fifth most frequently diagnosed type of cancer worldwide. It is the fourth leading cause of cancer-related mortality globally [1]. Staging is a critical component of care and treatment, and its accuracy and consistency enable caregivers to make informed decisions regarding their patients' care [2,3]. It also simplifies the process of evaluating therapy response. Accordingly, the International Union for Cancer Control/American Joint Committee on Cancer (UICC/AJCC) has the broadest global adoption for assessing the prognosis and management of gastric cancer patients [4]. The staging manual is based on the Tumor-Node-Metastasis staging system. This tool has undergone several changes in the past decades to improve its prognostic performance [4,5].

The 8th edition of the AJCC TNM staging manual came as a modification of the 7th edition [6]. Following its publication in 2010, the 7th edition of the manual drew criticism for its stratification ability, lack of uniformity within subclasses of the same stage, and questionable reproducibility [7–10]. Consequently, modifications were made in the 8th edition to mitigate shortcomings of the 7th edition, which included dividing the pN3 stage into pN3a and pN3b and adjusting subgroup staging [4]. Subsequent studies affirmed the improved prognostic prediction and stratification of the 8th edition over the 7th [2,6]. Others, however, failed to replicate these findings and concluded that the two systems performed similarly in terms of prognostic performance [11]. Regional disparities in surgical practice significantly impact the necessity of subgroup adjustments. In the Eastern countries, the common standard practice is D2 lymphadenectomy, whereas the Western countries adopt a much more limited lymph node dissection [12–14].

Furthermore, the 8th AJCC TNM staging system introduced staging for patients who received neoadjuvant therapy (ypTNM), and clinical TNM staging abbreviated as cTNM. Before the 8th edition, there was no official clinical staging system, and the pathologic staging was used

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instead without ascertained validity [15]. Additionally, the eighth edition clearly defined the esophagogastric junction and cardia cancer staging systems and redefined the tumor grading system. Analysis of a sizeable cohort of patients inferred these changes [16]. Despite improved accuracy, the work to further enhance the predictive power of the tool and its stratification has continued. The advances in molecular science and genomics have similarly led to the identification of specific markers that have a chance of enhancing the 8th edition's predictive power [17,18]. This study aims to review articles published on validations, modification on the TNM and ypTNM staging, and proposed tumor markers and molecular markers of cancer on the 8th AJCC TNM staging system. Concurrently, we aim to review publications on proposed nomograms, the impact of retrieved lymph node numbers as suggested by the manual, and the significance of lymph node ratio in prognostic separation and survival prediction since its first publication.

2. Validation of the 8th AJCC TNM staging system

Since its publication in 2016 and official inception in 2018, the 8th AJCC gastric cancer staging system has been validated for its prognostic applicability using parameters such as discriminatory ability and model fitness, monotonicity, and homogeneity. Accordingly, tests including the linear trend chi-square, likelihood ratio chi-square, Harrell's concordance index, Akaike information criterion (AIC), time-dependent receiver operating characteristics (t-ROC) curves, and the Bayesian information criterion (BIC) have been employed. A higher Harrell's C-index value, log-rank test, or linear trend chi-square test defined a better discriminative ability and monotonicity. In contrast, smaller AIC values were preferred for improved prognostic separation [19–21].

Evidently, the new staging system was deemed more accurate in prognostication and uniform in segmentation of subgroups with the maintenance of group order [22,23]. A comparative study to the seventh edition revealed that the eighth edition was superior in predicting the overall survival of gastric cancer patients. Hence, it guides decision-making during the management of gastric cancer patients [24]. Other investigators observed similar findings [25,26]. The separation of pN3 provided stage III changes that minimized stage migration tendency.

Interestingly, the latest edition seems valid and applicable in predicting prognosis among patients with residual gastric cancer [27]. Furthermore, Fang et al. reported a better homogeneity in the eighth version and noticed comparable prognostic performance between it and the seventh edition. The t-ROC curves in their study appeared to overlap during overall and disease-free survival assessment [28]. Moreover, a comparison of stage IIIB and IIIC in assessing the 5-year overall survival using the restaging system appeared to ameliorate survival rate discrimination [29,30]. However, the new edition isn't entirely superior, as other studies indicating comparable c-index values and similar long-term prognostic performance to previous editions [31,32].

Several modifications in the pTNM have been suggested to improve its discriminatory ability and prognostic stratification [33–35]. These propositions followed a wide variation in the median overall survival of patients at the same stage between different sub-classes, especially in stage III, and similar survival rates between stages IIIC and IV. The modified systems demonstrated good comparative values. For instance, Lin and colleagues noted that while assessing gastric cancer patients' 10-year overall survival rate, merging stage IB and IIA produced an excellent prognostic staging tool over its counterpart [36]. Furthermore, Cao et al. recommended the incorporation of T4aN3bM0/T4bN3bM0 into stage IV as it led to a better separation of stages [37]. Additionally, Chen and colleagues suggested the incorporation of pT4aN0M0 into stage IIIA of the eighth AJCC staging system for a better prognostic stratification than when categorized as stage IIB [38].

2.1. Proposed modifications on the ypTNM stage of the 8th AJCC TNM staging

There are several perceived limitations in the predictive accuracy of the ypTNM stage, which include a lack of elaborated discrimination in its stages, a small number of patients and a short follow-up duration during its formulation, and the absence of a difference between the 8th edition ypTNM and the 7th edition AJCC system. Additionally, the absence of some categories in the ypTNM staging system has also been identified as a constraint that may limit its predictive accuracy in gastric cancer patients. Moreover, under-staging of gastric cancer has been ascribed to limited lymphadenectomy; thus, with extensive lymph node dissection (D2), the current ypTNM staging may not be accurate. Lastly, the staging system only divides non-metastatic gastric cancer patients' post-neoadjuvant therapy into three stages (i.e., I-III) [25,39–41].

Lin and colleagues utilized the eighth staging system (I-III) to group their patients and classified complete pathological response as ypT0N0 or ypT0N + not included in the AJCC system. Patients included were those who received neoadjuvant chemotherapy. The modified ypTNM system (I, II, IIIA&IIIB) had superior prognostic prediction than the eighth edition. Otherwise, their study appreciated the significance of the number of lymph nodes harvested [42]. These results were consistent with the observations from Li et al. during their assessment of overall survival rates of 1 and 3-years [43].

In a multicentre study by Zhong et al., a modified ypT stage (IA, IB, II, IIIA &IIIB) had a better discriminatory ability and predictive homogeneity when compared to the AJCC's ypTNM [40]. Additionally, Li et al. developed a modified ypTNM system that was superior to the original ypTNM with a higher c-index value. However, they recommended further detailed analysis, allowing subgroupings of each stage with better prognostic accuracy [44]. Nonetheless, the clinical utility of ypT stage remains questionable among node-negative gastric cancer patients as no improvement in survival was observed (ypT0-3N0M0) [45].

2.2. Proposed tumor markers and molecular markers for inclusion in the 8th AJCC edition or future revisions

Combining carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) has improved sensitivity without compromising specificity [46,47]. Accordingly, Lin and colleagues proposed incorporating CEA/CA19-9 levels into the AJCC TNM staging system following improved prognostic prediction outcomes among stage III gastric cancer patients at 1, 3, and 5-years. Multivariate analysis also identified it as an independent predictor of survival in AJCC stage III gastric cancer [48].

Singly, the impact of an immune factor on tumors diminishes due to the complex nature of the antitumor immune response. Correspondingly, Xing and colleagues using a novel protein-based prognostic classifier and five immune features, noted remarkable differences in the overall survival rate of high and low-risk groups. When this classifier was merged with age and pTNM staging, it had a more substantial prognostic value than pTNM alone. Thus, the authors concluded that the nomogram might be applicable in selecting patients who will gain from adjuvant chemotherapy [49]. Furthermore, Wen et al. proved a prognostic model using four Immunoscores (PD-L1^{+} immune cells (IC), PD-L1^{+} tumor cells (TC), PD-1^{hi}, and CD8^{More}) incorporated into TNM staging had better prognostic power than TNM alone and had potential among operable gastric cancer patients. These scores divided gastric cancer patients with similar stages into low, medium, and high-risk groups [50].

Similarly, Jiang and colleagues demonstrated that merging Immunoscores (CD3invasive margin (IM), CD3center of tumor (CT), CD8IM, CD45ROCT, and CD66bIM) and TNM staging produced an improved predictive tool than TNM alone. They suggested that the model may help identify stage II and III gastric cancer patients who benefit from adjuvant chemotherapy. Investigators viewed the two systems as complementing the predictive ability of the TNM system [51]. Koh et al. established the

association between PD-L1/CD8-based immune types and EBV+, MSI-H GCs, and illustrated their prognostic impact in stage II/III gastric cancer [52].

Recently, Yin and colleagues identified the CD144 gene as a useful prognostic indicator in assessing the risk of disease progression among stage III gastric cancer patients. In their study, the expression of CD144 led to expanded sub-classification of stage III into IIIa, IIIb, and IIIc. Further analysis revealed CD144 expression level was an independent predictor for disease-free survival, whereas Borrmann type and the level of CD144 expression were independent predictors of overall survival [53]. The 8th AJCC TNM suggests sapient inclusion of these markers in the staging [4].

2.3. Proposed nomograms

Some of the eighth AJCC's limitations during formulation include less number of lymph nodes dissected (limiting the applicability of the system in extended lymphadenectomies), absence of prognostic factors linked to individual survival such as age, tumor size, body mass index, and so on, and lack of markers of systemic inflammatory response [54,55]. Thus, several authors developed new tools or nomograms to mitigate the perceived constraints. A nomogram based on body mass index category, tumor location, T and N stages was reported to have a more refined prognostic accuracy when compared to the eighth AJCC [43]. Additionally, another nomogram based on log odds of positive lymph nodes (LODDS) was more predictive of overall and cancer-specific survival for signet ring cell carcinoma than TNM staging alone [56]. Bando and colleagues devised a novel pre-treatment model that accurately predicted the overall survival in gastric cancer patients than AJCC TNM and recommended its use in patient counseling [57].

Furthermore, Wang et al. created an integrated nomogram that includes inflammatory markers, tumor markers (CEA&CA19-9), tumor characteristics, and certain proteins such as albumin. Their model had better predictive power and discriminatory ability than the AJCC TNM system [58]. Tumorigenesis initiates a complex cascade of immune and inflammatory reactions critical for tumor formation, invasion, growth, and progression [59]. Numerous reports on the significance of some indexes developed from these cells in determining prognosis exist in different fields [59,60]. Correspondingly, a nomogram based on systemic immune-inflammation index to predict survival among gastric cancer patients was reckoned superior to the available systems. Consequently, the authors recommended the model as authentic in predicting post-gastrectomy survival among gastric cancer patients [61].

Zheng and colleagues model's based clinicopathological data and independent prognostic risk factors affecting gastric (MA) NEC cancer had a remarkable predictive ability for 1, 3, and 5-year disease-free survival and recurrence patterns [62]. Furthermore, Lin and colleagues conceptualized the application of recursive partition analysis in the prognostic prediction of node-negative gastric cancer. The tool produced superior outcomes than the AJCC [63]. A nomogram based on T stage, N stage, comprehensive treatment, age at diagnosis, grade, and tumor size performs better in the individualized prediction of survival among patients with resectable disease, including stage III/IV patients [64].

3. Impact of retrieved lymph node number and lymph-node ratio in 8th AJCC staging

The 8th AJCC recommends examining at least 16 retrieved nodes for better staging, but when possible, ≥30 lymph nodes are preferred for accurate staging and prognosis determination. Correspondingly, examining ≥15 lymph nodes improved the prognostic power of the eighth AJCC in non-cardia gastric cancer patients [65]. Similarly, equipping the eighth AJCC with ≥15 examined lymph nodes while using the recursive partition analysis improved survival prediction ability [66]. Thus, it can be considered anything below 15 examined lymph nodes represents inadequacy of lymphadenectomy likely to reduce the quality of postoperative care. Nonetheless, a tumor-mode-ratio-metastasis system predicted survival more accurately than the eighth AJCC [67].

Interestingly, another study involving a more limited number of examined lymph nodes commended the accuracy of an adjusted 8th AJCC staging system based on examined lymph nodes (eLNs) which had a better prognostic separation. However, the investigators insisted on the significance of a higher number of lymph nodes required in assessing the 5-year overall survival among node-negative gastric cancer patients [68]. Otherwise, a re-classified N and TNM system predicted the 5-year survival more accurately than the eighth AJCC; thus, the model is deemed prognostically feasible in both a limited and adequate number of examined lymph nodes [69].

Many investigators recommend an increased number of lymph nodes during surgery to improve prognostic accuracy and minimize stage migration [70–72]. Consequently, investigators proposed that for accurate prognostic assessment, ≥16 examined lymph nodes for node-negative patients and >30 examined lymph nodes in node-positive patients were require [73]. Moreover, equipping the eighth AJCC with ≥30 eLNs improved prognostic accuracy among stage III gastric cancer patients after R0 resection. However, investigators of the latter study recommended an external validation of their results [6]. Likewise, the incorporation of 30eLNs into the eighth AJCC improved prognostic stratification [74]. For a selected group of gastric cancer patients (such as those aged>60 years, male in gender, who underwent total gastrectomy and had stage IIB gastric cancer disease), retrieval of ≥30 lymph nodes is associated with a better 5-year overall survival rate [75]. Otherwise, a tumor-ratio-metastasis system comprising 5 lymph node ratio categories had a more homogenous prognosis prediction than the eighth AJCC system [76].

Many researchers believe the anatomical location definition of lymph provides an optimal prognosis prediction. Accordingly, topographic localization of metastatic lymph nodes predicted the 5-year overall and disease-free survival better than the eighth AJCC [77]. Similarly, anatomic location-based node stations produce better prognostic stratification than the AJCC and Japanese Gastric Cancer Association system [78]. Otherwise, if retrieving ≥16 is deemed challenging, retrieval of >13 and > 9 lymph nodes at Group 1 and 2, respectively, provides a more accurate prognosis prediction and minimizes staging migration [79].

3.1. Other proposed modifications and inclusions in the 8th AJCC TNM staging system

Several potential additional factors can be adopted into the AJCC staging to enhance its prognostic performance. Correspondingly, splitting tumor stage pT2 according to the depth of infiltration of muscularis propria layer (i.e., pT2a & pT2b) yields more accurate prognostic evaluation for pT2 gastric cancer patients [80]. Shang et al. recommended judicious provision of adjuvant chemotherapy for stage I gastric cancer patients as lymphovascular invasion was not an independent prognostic factor for stage I disease [81]. Interestingly, a study based on N0 patients with a much larger accrual and follow-up time revealed the association between lymphovascular invasion and prognosis determination. The inclusion of Lymphovascular invasion improved the accuracy of the eighth edition prognostic prediction. Thus, adjuvant chemotherapy among pT3N0M0 patients is commendable. However, the investigators recommend more research and external validation of their findings [82].

Blood indices and other blood markers have been associated with prognosis prediction in gastric cancer. Accordingly, the inclusion of preoperative fibrinogen level ≥4.0 g/l into eighth AJCC outperformed AJCC alone prognostically. Thus, adjuvant chemotherapy is a commendable consideration for patients with preoperative fibrinogen ≥4.0 g/l as it was associated with a poor prognosis [83]. Similarly, the presence of tumor deposits has been associated with poor overall

survival. Thus, including tumor deposits into the eighth AJCC improves AJCC's prognostic accuracy among patients with tumor deposits [84]. The survival comparability of T4bN3a, N3b, and Cytology only stage IV and unified into stage IVa implied N3b patients are eligible to receive more intensive chemotherapy regimens [85]. Jeong et al. noted the efficacy of the clinical TNM staging schemata in survival discrimination among gastric cancer patients. Still, it had no benefits in prognostic performance over the pTNM [86]. However, the current edition doesn't improve the predictive accuracy of endoscopic ultrasound [87].

4. Conclusion

The eighth AJCC staging system is potentially crucial in predicting the prognosis of gastric cancer patients. However, future editions should consider disparities in surgical practices, particularly lymph nodes dissection and location, molecular characterization, and individual factors that are likely to influence the prognosis of the patients.

Provenance and peer review

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Declaration of competing interest

The authors declare no conflict of interest.

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