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Original Article

Providing Reliable Prognosis to Patients with Gastric Cancer in the Era of Neoadjuvant Therapies: Comparison of AJCC Staging Schemata

Gina Kim [1], **Patricia Friedmann** [1,2], **Ian Solsky** [1], **Peter Muscarella** [1], **John McAuliffe** [1], **Haejin In** [1,3]

[1]Department of Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA
[2]Department of Cardiothoracic and Vascular Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA
[3]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

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Correspondence to
Haejin In
Department of Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, 1300 Morris Park Ave, Block Building #112, Bronx, NY 10461, USA.
E-mail: hin@montefiore.org

ORCID iDs
Gina Kim
https://orcid.org/0000-0002-4389-8653
Ian Solsky
https://orcid.org/0000-0002-9871-5068
Peter Muscarella
https://orcid.org/0000-0003-1448-5507
Haejin In
https://orcid.org/0000-0003-3267-6585

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ABSTRACT

Purpose: Patients with gastric cancer who receive neoadjuvant therapy are staged before treatment (cStage) and after treatment (ypStage). We aimed to compare the prognostic reliability of cStage and ypStage, alone and in combination.
Materials and Methods: Data for all patients who received neoadjuvant therapy followed by surgery for gastric adenocarcinoma from 2004 to 2015 were extracted from the National Cancer Database. Kaplan-Meier (KM)curves were used to model overall survival based on cStage alone, ypStage alone, cStage stratified by ypStage, and ypStage stratified by cStage. P-values were generated to summarize the differences in KM curves. The discriminatory power of survival prediction was examined using Harrell's C-statistics.
Results: We included 8,977 patients in the analysis. As expected, increasing cStage and ypStage were associated with worse survival. The discriminatory prognostic power provided by cStage was poor (C-statistic 0.548), while that provided by ypStage was moderate (C-statistic 0.634). Within each cStage, the addition of ypStage information significantly altered the prognosis (P<0.0001 within cStages I–IV). However, for each ypStage, the addition of cStage information generally did not alter the prognosis (P=0.2874, 0.027, 0.061, 0.049, and 0.007 within ypStages 0–IV, respectively). The discriminatory prognostic power provided by the combination of cStage and ypStage was similar to that of ypStage alone (C-statistic 0.636 vs. 0.634).
Conclusions: The cStage is unreliable for prognosis, and ypStage is moderately reliable. Combining cStage and ypStage does not improve the discriminatory prognostic power provided by ypStage alone. A ypStage-based prognosis is minimally affected by the initial cStage.

Keywords: Gastric cancer; Stomach; Prognosis; Survival; Outcomes research

INTRODUCTION

There are approximately 25,000 new cases of gastric cancer annually in the United States, resulting in over 10,000 deaths [1]. Management and prognosis vary widely based on the

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Author Contributions

Conceptualization: K.G., I.H.; Data curation: K.G., F.P.; Formal analysis: F.P.; Funding acquisition: K.G., I.H.; Writing - original draft: K.G., F.P., I.H.; Writing - review & editing: K.G., F.P., I.S., M.P., M.J., I.H.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

stage of the disease. While upfront resection is possible for patients with early stage disease, perioperative chemotherapy is recommended for patients with T2 or higher tumors or those with nodal involvement [2]. The American Joint Committee on Cancer (AJCC) defines staging guidelines for gastric cancer based on the status of the tumor, nodes, and metastasis (TNM). The eighth edition of the staging manual, published in 2017, introduced 2 new staging systems: the clinical stage (cStage) and the post-neoadjuvant therapy pathologic stage (ypStage) [3].

Introduction of these 2 new staging systems is beneficial since prognoses determined based on pathologic stage may be more accurate for patients who undergo surgery up front than for those who receive neoadjuvant therapy prior to surgery. This change introduces a new dilemma: patients who undergo neoadjuvant therapy are assigned a cStage at the time of diagnosis and a ypStage after surgery, resulting in 2 different predictors for each patient.

Previous studies have shown that ypStage provides a more accurate prognosis than to cStage [4,5]. This may be attributed to the inherent inaccuracies of preoperative staging modalities and tumor response to neoadjuvant therapy [5]. The purpose of this study was to compare the reliabilities of cStage and ypStage, alone and in combination, for determining prognoses in patients undergoing surgery following neoadjuvant therapy for gastric cancer.

MATERIALS AND METHODS

Patient selection

This study was conducted using the National Cancer Database (NCDB). The NCDB is a clinical oncology database sourced from hospital registry data collected from facilities accredited by the Commission on Cancer and sponsored by the American College of Surgeons and the American Cancer Society. The database covers over 70% of newly diagnosed cancers in the U.S. [6].

Data for all patients aged 18 years or older who underwent surgery (including local excision) following neoadjuvant therapy for gastric cancer from to 2004–2015 were included in the analysis. Information on age, sex, race, tumor location, grade, histology, Charlson-Deyo comorbidity score, and type of preoperative therapy were collected. TNM data available in the NCDB were used to standardize stage according to criteria defined by the seventh edition of the AJCC. Patients with a prior history of other cancer diagnoses, those who were treated or diagnosed at a non-reporting facility, those who had cStage 0 disease, and those who could not be staged due to missing TNM data were excluded from analysis.

Statistical analyses

Descriptive statistics were used to examine patients and tumor characteristics. The primary endpoint was overall survival. Survival was determined using NCDB variables "Last Contact or Death, Months from Dx" and "Participant User File (PUF) Vital Status." Survival distributions were estimated using the Kaplan-Meier (KM) method. KM curves were generated for cStages I–IV and ypStages 0–IV. Additionally, within each cStage, KM curves were generated for ypStages 0–IV–IV to determine the effect of adding ypStage to the survival predicted by cStage alone. Similarly, within each ypStage, KM curves were generated for cStage I–IV to determine the effect of adding cStage to the survival predicted by ypStage alone. The discriminatory power of the models was estimated using Harrell's C-statistics.

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Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The research project was approved by the Institutional Review Board (##2017-8074).

RESULTS

Patient characteristics

Data for 8,977 patients who met the inclusion and exclusion criteria were evaluated (**Fig. 1**). The median age at the time of diagnosis was 62. The majority of patients in our cohort were male (76%), Caucasian (77%), and with few comorbidities (94% with Charlson-Deyo score 0 or 1). Tumors were more commonly located in the cardia (67%); most were adenocarcinomas (79%) and poorly differentiated (57%). Approximately half of the patients (54%) received both neoadjuvant chemotherapy and radiation, while 43% of patients received chemotherapy alone and 1% of patients received only radiation (**Table 1**).

Response to neoadjuvant therapy

Fig. 2A displays the number of patients in each cStage and ypStage. Each panel in **Fig. 2B** displays cStage data and the final ypStage distribution. First, 33% of patients had a lower ypStage than cStage (downstaged), suggesting a favorable tumor response to neoadjuvant therapy. Conversely, 23% of patients had a higher ypStage than cStage (upstaging), suggesting progression of the disease. The final ypStage was the same as the initial cStage in 44% of patients, suggesting minimal response to preoperative treatment. Among patients in whom the stage changed following neoadjuvant therapy, the majority (70%) of patients revealed a change by one stage, while the rest 30% showed changes by 2 or more stages.

Interestingly, the proportion of patients in each cStage who remained at the same ypStage was similar for each stage I–III (41%, 44%, and 43%, respectively) and was slightly higher for cStage IV (50%). The proportion of patients who were upstaged to ypStage IV was also similar for each stage I–III (approximately 3% for each cStage). It should be noted that although only

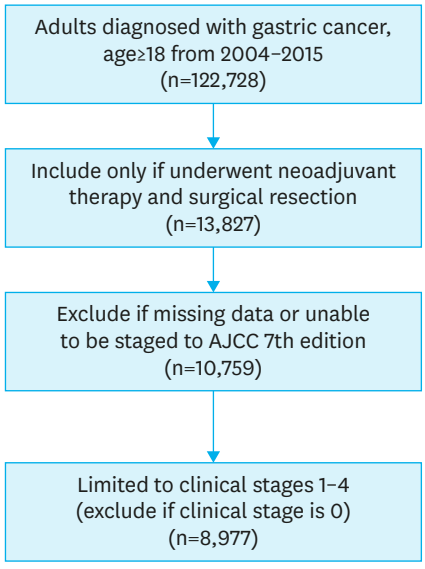

Fig. 1. Patient selection.
AJCC = American Joint Committee on Cancer.

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Table 1. Patient characteristics

Characteristic	Number of patients (n=8,977)
Age (median)	62
Male	6,799 (75.7)
Race	
White	6,910 (77.0)
Black	773 (8.6)
Hispanic	739 (8.2)
Asian	403 (4.5)
Other/unknown	152 (1.7)
Tumor location	
Cardia	5,994 (66.8)
Fundus	191 (2.1)
Body	394 (4.4)
Antrum	805 (9.0)
Pylorus	87 (1.0)
Lesser curvature NOS	462 (5.2)
Greater curvature NOS	168 (1.9)
Other/unknown	876 (9.8)
Grade	
Well-differentiated	290 (3.2)
Moderately differentiated	2,566 (28.6)
Poorly differentiated	5,098 (56.8)
Undifferentiated/anaplastic	109 (1.2)
Unknown	914 (10.2)
Histology	
Adenocarcinoma	7,059 (78.6)
Linitis plastica	31 (0.4)
Carcinoma (e.g. acinar, signet ring cell)	1,887 (21.0)
Charlson-Deyo score	
0	6,530 (72.7)
1	1,931 (21.5)
2	396 (4.4)
>3	120 (1.3)
Pre-operative therapy type	
Chemotherapy only	4,817 (53.7)
Chemo and radiation therapy	3,852 (42.9)
Radiation therapy only	99 (1.1)
Unspecified	209 (2.3)

Values are presented as number (%).
NOS = not otherwise specified.

patients who underwent surgery were included, 6% of the patients had ypStage IV disease, suggesting that resection for these patients may have been palliative.

Survival estimates

As expected, increasing cStage and ypStage were associated with a worse survival (log-rank test, P<0.0001) (**Fig. 3**). The 5-year survival rates for cStages I–IV were 48%, 37%, 31%, and 22%, respectively, while those for ypStages 0–IV were 60%, 59%, 35%, 17%, and 11%, respectively.

When patients in each cStage were further stratified by their final ypStage, their prognoses varied widely from the prognoses provided by cStage alone (log-rank test, P<0.0001 for cStages I–IV). The 5-year survival rates for each cStage when stratified by ypStages 0–IV were cStage I: 65%, 62%, 37%, 12%, and 0%; cStage II: 59%, 57%, 35%, 17%, and 5%; cStage III: 58%, 55%, 33%, 19%, and 0%; cStage IV: 52%, 36%, 23%, 8%, and 17% (**Fig. 4**). Conversely, when patients in each ypStage were further stratified by their initial cStage, their prognoses varied minimally from the prognoses provided by ypStage alone (log-rank test, P<0.287,

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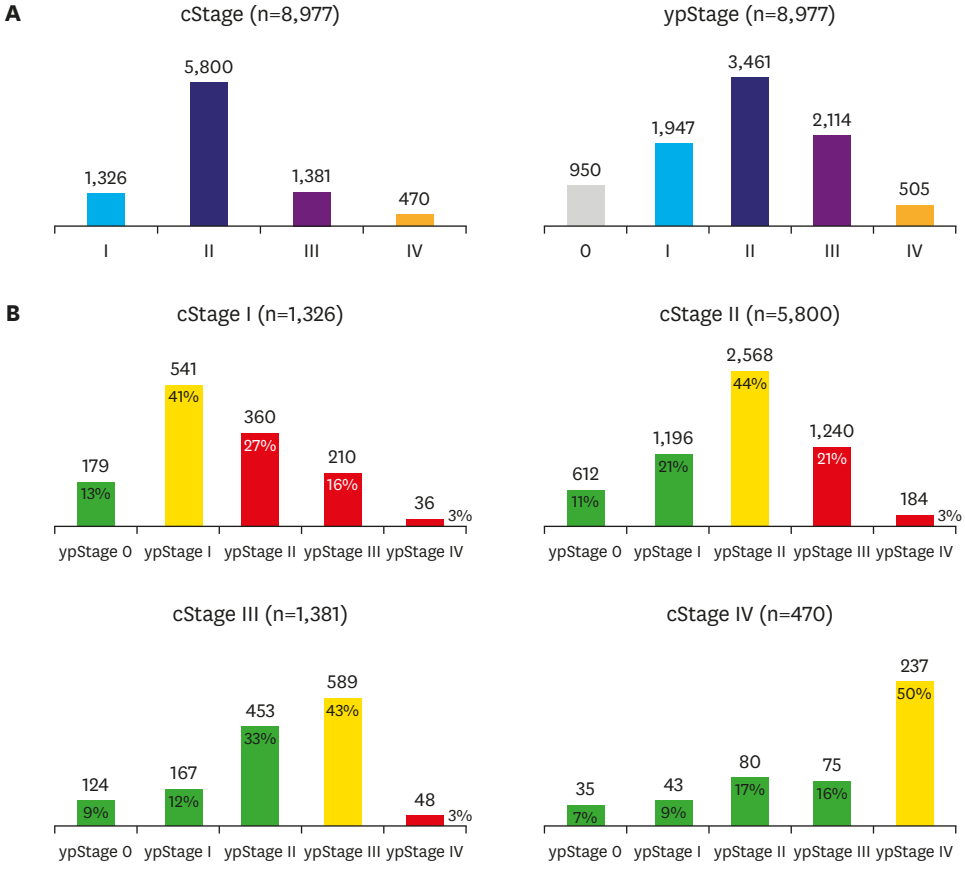

Fig. 2. Distribution of patients. (A) The distribution of patients within each cStage and ypStage. (B) The distribution of patients in each cStage and their final ypStage. Each panel represents a distinct cStage. The bars represent their final ypStages. Green bars indicate patients who were downstaged from the initial cStage. Yellow bars indicate patients who remained at the same stage. Red bars indicate patients who were upstaged from the initial cStage.
cStage = clinical stage; ypStage = post-neoadjuvant therapy pathologic stage.

0.027, 0.061, 0.049, and 0.007 for ypStages 0–IV, respectively). For example, among patients who were found to ultimately have ypStage 0 or ypStage II disease, the overall survival was not significantly different whether they started with cStage I or cStage IV disease. Although there was a statistically significant association between cStage and survival within ypStages

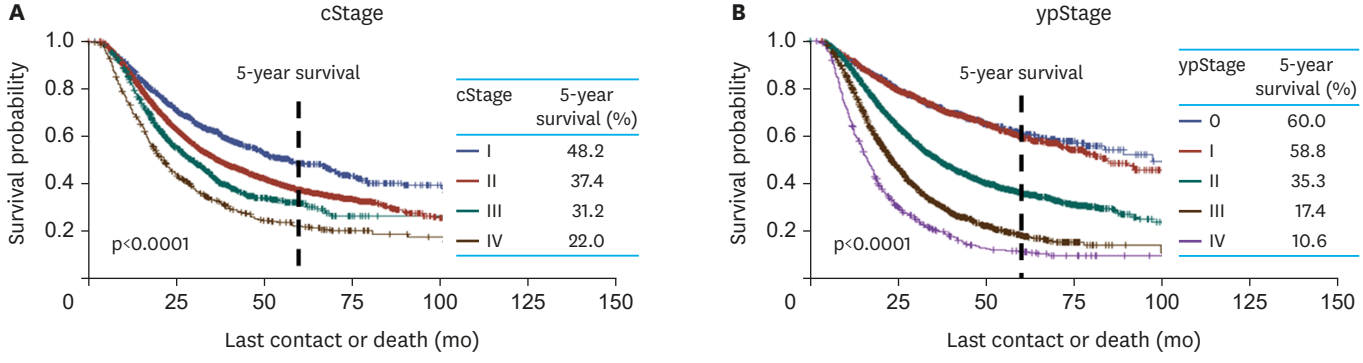

Fig. 3. Kaplan-Meier curves modeling survival. (A) Survival curve for cStages. (B) Survival curve for ypStages.
cStage = clinical stage; ypStage = post-neoadjuvant therapy pathologic stage.

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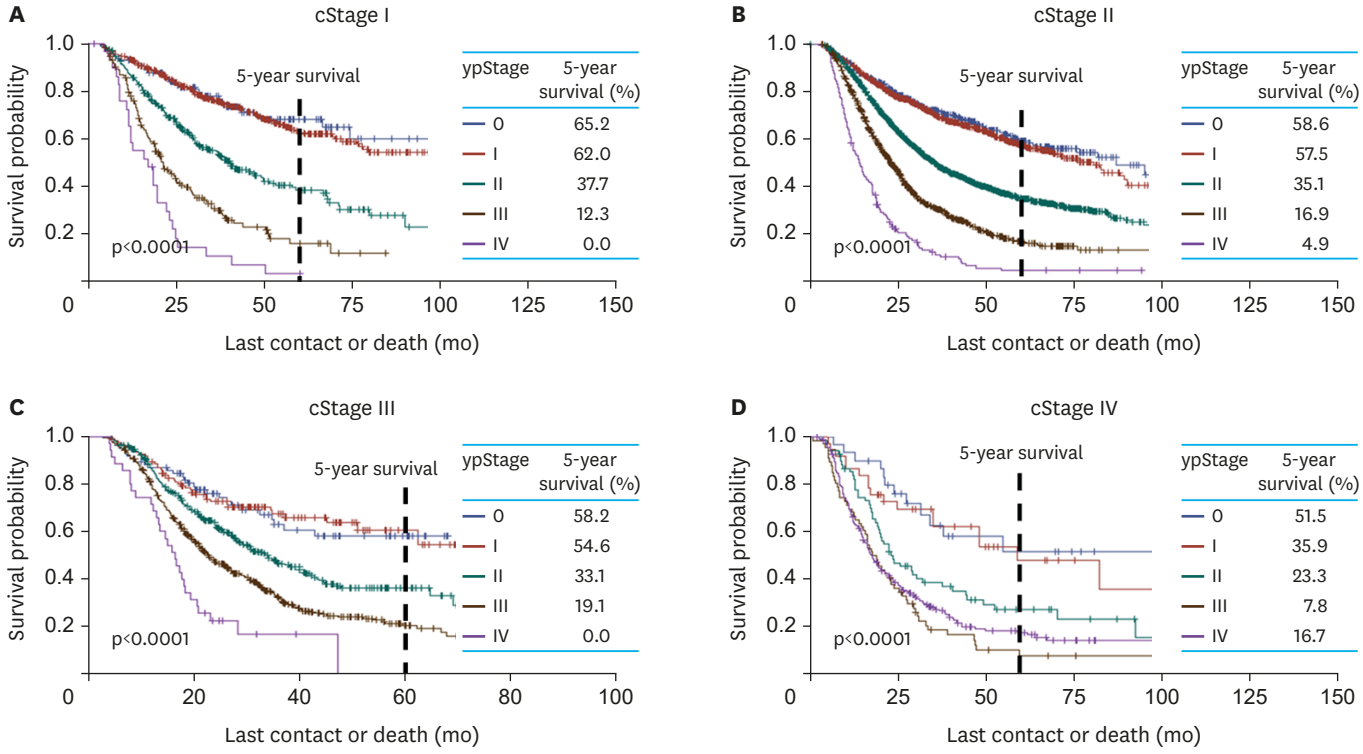

Fig. 4. Kaplan-Meier curves modeling survival for cStage stratified by ypStage. (A) cStage I stratified by ypStage. (B) cStage II stratified by ypStage. (C) cStage III stratified by ypStage. (D) cStage IV stratified by ypStage.
cStage = clinical stage; ypStage = post-neoadjuvant therapy pathologic stage.

I, III, and IV, these differences were small and unlikely to be clinically relevant. The 5-year overall survival rates for each ypStage when stratified by cStages I–IV were ypStage 0: 65%, 59%, 58%, and 52%; ypStage I: 62%, 58%, 55%, and 36%; ypStage II: 38%, 35%, 33%, and 23%; ypStage III: 12%, 17%, 19%, and 8%; ypStage IV: 0%, 5%, 0%, and 17% (**Fig. 5**).

Discriminatory performance of survival models

Harrell's C-statistics for survival models based on cStage alone, ypStage alone, and combined were calculated to compare the discriminatory performance of each model. Harrell's C-statistic for cStage alone was 0.548, for ypStage alone was 0.634, and for combined cStage and ypStage was 0.636. In summary, the addition of ypStage to cStage yielded a 16% increase in Harrell's C-statistic (0.548 vs. 0.636), whereas the addition of cStage to a model that only includes ypStage yielded minimal change (0.634 vs. 0.636). These findings support that ypStage provides a better prognosis than cStage. Interestingly, the addition of the initial cStage does not impact the prognostic accuracy provided by ypStage. In other words, the response to neoadjuvant therapy (whether patients were up- or down-staged) itself does not appear to impact prognosis, other than to determine the ultimate pathologic stage.

DISCUSSION

The findings of this study confirm that up- and down-staging are common following neoadjuvant therapy. In our cohort, 56% of patients were up- or down-staged. As expected, ypStage provided a more accurate prognosis than cStage. Interestingly, when both cStage

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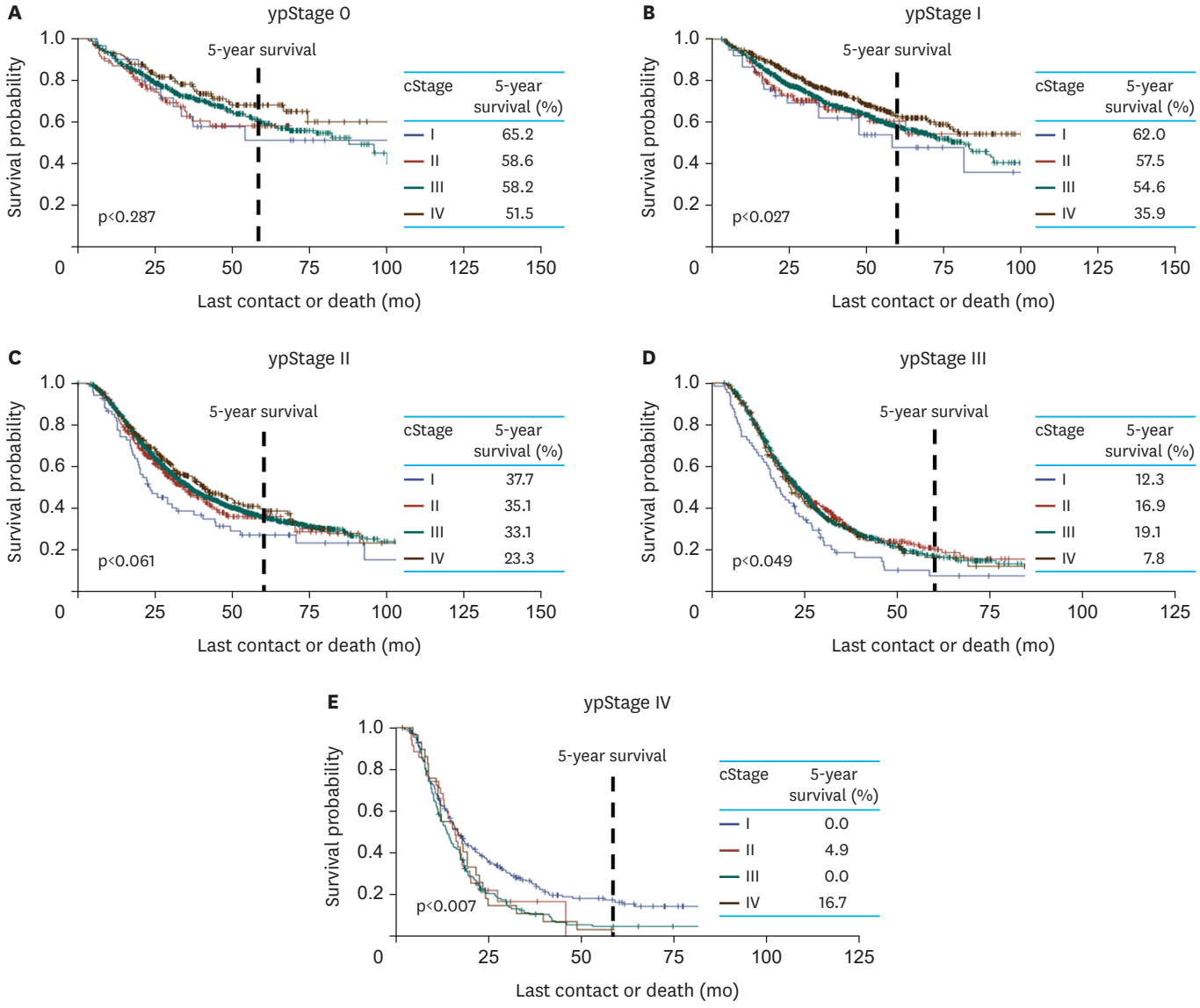

Fig. 5. Kaplan-Meier curves modeling survival for ypStage stratified by cStage. (A) ypStage 0 stratified by cStage. (B) ypStage I stratified by cStage. (C) ypStage II stratified by cStage. (D) ypStage III stratified by cStage. (E) ypStage IV stratified by cStage.
cStage = clinical stage; ypStage = post-neoadjuvant therapy pathologic stage.

and ypStage were considered together, the addition of cStage had a minimal influence on the prognosis based on ypStage alone. Regardless of whether patients started with initial cStage I or IV disease, they had a similar overall survival if they were found to have the same ypStage. This observation is confirmed by a similar Harrell's C-statistics for the Cox regression model based on ypStage alone (0.634) and ypStage plus cStage (0.636).

Our findings are consistent with prior studies demonstrating that pathological stage is a better predictor of survival than the cStage. Rohatgi et al. [7] showed in prospectively collected data that pathologic stage and R0 resection were independently related to survival, while none of the pretreatment parameters correlated with survival. Similarly, Ajani et al. [8] showed that no pretreatment parameters predicted survival, while the degree of pathologic response, pathologic stage, and R0 resection correlated with overall and disease-free survival.

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Unfortunately, the difference between cStage and ypStage may reflect the inherent inaccuracy of clinical staging rather than the biological response to neoadjuvant therapy. The reported accuracy of computed tomography (CT) and endoscopic ultrasound (EUS) for identifying T and N stages is low. The accuracy of EUS for distinguishing T0–1a disease from more advanced disease is estimated to be around 75%–82%. The reported accuracies of EUS and CT for identifying individual N stage are 43%–66% and 56%–65%, respectively [9,10]. However, Patel et al. [11] showed that when patients were re-staged using EUS and laparoscopy after neoadjuvant therapy, the new cStage did correlate with survival (P=0.16 pre-treatment vs. P=0.01 post-treatment), suggesting that clinical staging can predict prognosis reliably despite the inherent limitations.

A retrospective study comparing pathologic node negative (ypN0) vs. node positive (ypN+) status showed that patients with ypN0 had a significantly longer overall survival. This remained true even for patients who had clinical node positive (cN+) disease who were down-staged to ypN0. Furthermore, patients with cN+/ypN0 disease had similar 5-year survival rates as patients with cN0/yp0 disease (hazard ratio, 0.90 [95% CI, 0.54–1.48]) [12]. Another study reviewed pathologic specimens from the MAGIC trial and compared tumor regression vs. nodal status as predictors of survival. It was found that tumor regression grade and nodal status were both negatively related to survival on univariate analysis; however, on multivariate analysis, only lymph node status was independently predictive of survival [13]. These studies support our results showing that response to neoadjuvant therapy influences overall survival and that post-treatment lymphatic spread plays an important role in determining a prognosis.

Patients with low cStage who were found to have ypStage IV may have had occult or subclinical distant metastatic disease at the time of diagnosis, which were missed on imaging. Even with modern CT imaging modalities, sensitivity for peritoneal metastasis has been shown to be as low as 28% [14]. Mizrak et al. [15] found that 13% of patients with negative peritoneal cytology at initial staging developed evidence of metastatic disease following neoadjuvant therapy, with 6% of them being noted to have metastatic disease at the time of surgery. In this study, 5.6% of the patients had ypStage IV or metastatic disease at the time of surgery.

Interestingly, there was a small minority of patients initially classified with cStage III or IV disease who were found to have ypStage 0 following neoadjuvant therapy. This may represent a group of patients who are excellent responders to neoadjuvant therapy. Notably, these patients had an excellent prognosis of over 50% 5-year survival. Prior studies have shown that within ypStage 0, nodal status is a strong predictor of survival and that achieving ypN0 is associated with a significant survival advantage regardless of ypT [5,12]. Therefore, studying patients who achieve ypStage 0, especially ypN0, may elucidate tumor- or patient-specific factors that can predict excellent responses and prognoses.

The limitations of this study were related to the use of a cancer registry database. The cancer registry does not collect information on the tests performed to determine the cStage. Hence, we are unable to comment on the accuracy of diagnostic modalities, such as EUS, CT, and diagnostic laparoscopy. Additionally, many patients were excluded due to incomplete database information, and there was no way to verify the accuracy of the data entered by the registrars. Furthermore, the types of surgical procedures and preoperative therapy could not be controlled for due to the limitations on data available through the NCDB. Lastly, patients who were upstaged to having metastatic disease during their clinical staging work-up and did not undergo surgery are underrepresented because our analysis was limited to surgical patients.

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Despite these limitations, this study was conducted using one of the largest databases in the world and included almost 9,000 patients with gastric cancer who underwent surgical resection following neoadjuvant therapy. The findings of our analysis appear to be valid since the data used in this study represent the real-world population. Regardless of the diagnostic methods used, patients were assigned a cStage according to the medical practitioner's best judgment and choice of treatment must be presumed to have been based on cStage.

In conclusion, for patients with gastric cancer undergoing neoadjuvant therapy, cStage is unreliable for prognosis and ypStage is moderately reliable. The combination of cStage and ypStage does not improve the discriminatory prognostic power provided by ypStage alone. A prognosis determined on the basis of ypStage is minimally affected by the initial cStage, and may be confidently provided to patients regardless of whether they were up- or down-staged following neoadjuvant therapy.

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