Prognostic Value of Nodal Response After Preoperative Treatment of Gastric Adenocarcinoma

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ABSTRACT

Background: Pathologically positive lymph nodes (ypN+) after preoperative chemotherapy are associated with poor survival in patients with gastric cancer. Little is known about the association between response to preoperative therapy and the benefit of postoperative therapy. **Methods:** This retrospective cohort study of the National Cancer Database included patients with clinically node-positive (cN+) gastric cancer treated with preoperative therapy followed by surgery (2006–2014). Preoperative treatment modality was categorized as the inclusion of radiation therapy (RT) or chemotherapy alone. Pretreatment clinical and pathologic stages were used to determine pathologic treatment response rates. The association between overall risk of death and preoperative treatment, disease response, and adjuvant therapy use was evaluated using multivariable Cox regression. **Results:** Preoperative RT was used in 53.6% of 1,976 patients with cN+ gastric cancer, (74.3% cardia and 10.1% noncardia). The nodal response rate was 38.9% and was higher with RT than with chemotherapy alone (cardia, 46.0% vs 29.1%; $P<.001$; noncardia, 43.8% vs 31.9%; $P=.06$). Preoperative RT was associated with an approximate 2-fold increase in the odds of pathologic response compared with chemotherapy. Overall, use of adjuvant therapy was not associated with a decreased risk of death. A primary tumor response with residual nodal disease was not associated with survival (hazard ratio [HR], 1.03; 95% CI, 0.66–1.60). However, a nodal response with residual primary disease was significantly associated with survival (HR, 0.54; 95% CI, 0.44–0.65). **Conclusions:** More than one-third of node-positive gastric cancers showed pathologic nodal response with preoperative treatment. RT is associated with a higher response than chemotherapy. Patients with ypN+ disease have worse survival, regardless of whether they receive postoperative therapy. Future gastric cancer trials should evaluate the role of preoperative RT and individualize postoperative therapy use.

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Background

Gastric cancer is the fifth most common cancer and second leading cause of cancer-related death globally.[1] Despite improved survival outcomes with multimodality treatment (MMT) compared with surgery alone, nearly half of patients who undergo surgical resection will experience relapse.[2–7] Given that pathologically positive lymph nodes (ypN+) are independently associated with poor survival, more effective preoperative MMT strategies are critical for improving oncologic outcomes.[8]

Challenges to a single MMT approach for lymph node–positive gastric cancer include limitations in clinical staging, patient performance status, and variable response to preoperative treatment.[4–6] Preoperative staging modalities have poor negative predictive value, resulting in the understaging of nearly 40% of patients with clinically node-negative disease.[9] Patients whose disease is understaged may undergo upfront surgery and require postoperative therapy once lymph node metastases are identified in the resection specimen. However, reported rates of postoperative therapy completion are 22.9% to 41.6% due to postoperative complications, poor nutritional status, functional decline, and residual toxicity from preoperative therapy.[4–6,10]

Although perioperative chemotherapy and postoperative chemoradiation are the 2 evidence-based options for gastric cancer,[4,6] ongoing multicenter trials are investigating whether strategies that move most or all of the adjuvant therapy to the preoperative setting will increase the likelihood of MMT completion and, in doing so, improve cancer-related outcomes (ClinicalTrials.gov identifiers: NCT02931890, NCT01924819). Pending the results of these trials, 2 important questions remain. First, whether disease response rates are different after preoperative radiation therapy (RT) compared with chemotherapy is unclear—in other gastrointestinal malignancies, the use of preoperative RT is associated with higher pathologic response rates relative to chemotherapy alone.[11,12] Second, how the conversion of clinically node-positive (cN+) disease to pathologically node-negative (ypN0) might affect the need for postoperative

therapy is unknown. Therefore, the objectives of this study were to characterize disease response rates after preoperative chemotherapy either alone or with RT, and to examine whether a pathologic lymph node response to preoperative treatment affected the need for postoperative (ie, adjuvant) therapy. Our hypotheses were that preoperative RT is associated with an increased rate of nodal response and that adjuvant therapy is associated with improved survival among patients with persistent ypN+ gastric cancer.

Methods

Data Source

A retrospective cohort study was performed of patients with cN+ gastric cancer identified in the National Cancer Database (NCDB)—a prospective, hospital-based cancer registry maintained by the American Cancer Society and the American College of Surgeons' Commission on Cancer (CoC). The database includes >70% of incident cancer cases diagnosed at >1,500 CoC-accredited centers. This study was approved by the Baylor College of Medicine Institutional Review Board and the Michael E. DeBakey Veterans Affairs Medical Center Research and Development Committee.

Study Cohort

Sequential exclusions to define the analytic cohort are presented in Figure 1. The analytic cohort included 1,976 patients with cN+ adenocarcinoma treated with preoperative therapy followed by gastric resection. Patients not treated at the reporting facility were excluded to improve the accuracy of treatment ascertainment. The cohort was restricted to patients with cN+ disease to focus on nodal response.

Variables

The NCDB provides patient sociodemographic information derived from the 2008–2012 American Community Survey. Degree of comorbidity is provided using the Charlson/Deyo Comorbidity Index. Clinical data regarding the primary tumor, treatment administered, and sequence of MMT are also provided. These data were used to categorize all patients based on type of preoperative therapy received. All patients in the cohort received preoperative chemotherapy. However, because the NCDB does not specify whether a patient received concurrent chemoradiation or sequential chemotherapy followed by concurrent chemoradiation, as is typical with the use of NCDB data, patients were categorized by whether RT was used during preoperative treatment (ie, patients received either chemotherapy alone or RT and chemotherapy). Treatment data were used to categorize patients as having received adjuvant therapy.

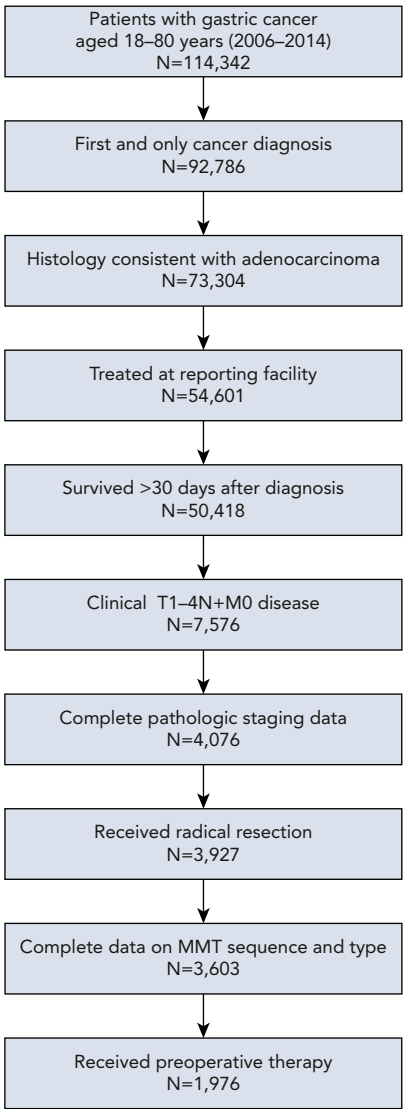

Figure 1. Study cohort selection.
Abbreviation: MMT, multimodality treatment.

Statistical Analysis

Standard descriptive statistics were used to examine the distribution of categorical and continuous variables. Information on clinical stage (prior to any treatment) and subsequent pathologic stage after preoperative treatment and resection were used to gauge disease response. Disease response was evaluated based on (1) pathologic complete response (pCR), defined as ypT0N0 or any residual disease; (2) primary tumor response, defined as ypT0 or ypT+ regardless of nodal response; and (3) nodal response, defined as ypN0 or ypN+ regardless of primary response. The primary outcome of interest was overall survival (OS). The Kaplan-Meier method and log-rank test were used to compare OS distributions.

Multivariable logistic regression was used to evaluate the association between pathologic response and type of preoperative treatment administered. Model covariates included age, sex, race, insurance status, income level, education level, region, Charlson/Deyo Comorbidity Index, treatment facility type, primary tumor site, and tumor grade. Multivariable Cox regression was used to evaluate the association between pathologic response, receipt of adjuvant therapy, and risk of death. In addition to the model covariates, margin status and an interaction term between adjuvant therapy and disease response were included. The assumption of proportional hazards was assessed using Schoenfeld residuals. To delineate the relative effect of disease becoming ypT0 or ypN0, 2 subgroups were also evaluated: patients whose disease became ypT0 but remained ypN+ and those whose disease became ypN0 but remained ypT+. To address survivor treatment bias, a 90-day landmark was used in survival models (resulting in 1,867 patients evaluated in survival analyses).[13] Sensitivity survival analyses were conducted among patients with cardia tumors and among those treated with neoadjuvant RT.

Within the study cohort, 19.3% of patients were missing data for at least 1 model covariate. However, no statistically significant difference in OS was seen between those with and without missing covariate data (log-rank P=.14). As such, analyses were conducted using a case-complete approach and using 5 sets of imputed data obtained through multiple imputations by chained equations to address missing values. Because similar results were obtained using both approaches, imputed findings are presented. A 2-sided P value of <.05 was considered statistically significant. Analyses were conducted using STATA, version 14 (StataCorp LP).

Results

The study cohort included 1,976 patients. Cardia tumors were present in 67.8% of patients. Chemotherapy alone was used as preoperative treatment in 25.7% of those with cardia primaries compared with 90.0% of patients with noncardia primaries. Preoperative RT was used in 74.3% of patients with cardia primaries compared with 10.1% of those with noncardia primaries. Demographic and clinical characteristics stratified by type of preoperative treatment are summarized in Table 1. Among patients treated with preoperative chemotherapy, 43.8% of patients received adjuvant therapy (among whom 67.7% received only adjuvant chemotherapy, 18.4% received adjuvant chemotherapy and RT, and 13.9% received only adjuvant RT), whereas 12.8% of those treated with preoperative RT received adjuvant therapy (all of whom received only adjuvant chemotherapy).

Table 1. Demographic and Clinical Characteristics Stratified by Tumor Location

Characteristics	Noncardia (%)	Cardia (%)
Patients, n	637	1,339
Demographic		
Mean age ± SD, y	60.1 ± 11.6	60.2 ± 10.2
Age		
<50 y	19.5	14.3
50–59 y	23.1	28.6
60–69 y	33.6	38.3
≥70 y	23.9	18.8
Sex, male	61.9	85.3
Race		
White	60.6	94.5
Black	22.0	3.2
Other	15.9	1.9
Missing	1.6	0.5
Insurance status		
Insured	44.7	56.1
Medicare/Medicaid	46.2	40.0
Uninsured	7.4	1.8
Other	0.9	1.4
Missing	0.8	0.8
Income[a]		
≥$63,000	34.7	36.6
Missing	1.3	1.1
Education[b]		
<7%	22.3	27.3
Missing	1.1	1.0
Region		
Metropolitan	69.9	51.8
Urban	19.3	28.1
Rural	8.2	16.6
Missing	2.7	3.6
Charlson/Deyo Comorbidity Index		
0	72.7	74.7
1	21.8	20.2
≥2	5.5	5.2
Treatment facility type		
Academic/Research	67.4	62.8
Comprehensive cancer center	17.7	22.6
Community cancer center	3.3	1.9
Other	6.4	8.8
Missing	5.2	3.8

(continued on next page)

[a]Based on 2008–2012 American Community Survey data (https://www.census.gov/programs-surveys/acs/). The percentage of patients whose area of residence (based on ZIP code) had a median household income ≥$63,000 (adjusted for 2012 inflation) is presented.

[b]Based on 2008–2012 American Community Survey data (https://www.census.gov/programs-surveys/acs/). The percentage of patients whose area of residence (based on ZIP code) had <7% adults who did not attain a high school education is presented.

Table 1. Demographic and Clinical Characteristics Stratified by Tumor Location (cont.)

Characteristics	Noncardia (%)	Cardia (%)
Clinical		
Grade, differentiation		
Well/Moderate	19.9	32.6
Poor/Undifferentiated	73.9	55.8
Missing	6.1	11.6
Clinical T stage		
1	5.0	3.7
2	19.3	15.8
3	62.3	77.2
4	13.3	3.4
Pathologic T stage		
0/In situ	7.2	14.3
1	8.8	12.9
2	21.0	22.9
3	44.6	48.0
4	18.4	1.9
Pathologic N+ stage		
Positive	66.9	58.3
Lymph nodes examined		
≥15	68.3	51.1
Missing	0.9	1.6
Treatment sequence		
Perioperative therapy	43.8	19.3
Preoperative therapy only	56.2	80.7
Neoadjuvant treatment		
Chemotherapy only	90.0	25.7
Chemotherapy + radiation	10.1	74.3
Multiagent chemotherapy	92.5	89.7
Margin		
Positive	12.7	9.3
Missing	1.9	1.1

[a]Based on 2008–2012 American Community Survey data (https://www.census.gov/programs-surveys/acs/). The percentage of patients whose area of residence (based on ZIP code) had a median household income ≥$63,000 (adjusted for 2012 inflation) is presented.
[b]Based on 2008–2012 American Community Survey data (https://www.census.gov/programs-surveys/acs/). The percentage of patients whose area of residence (based on ZIP code) had <7% adults who did not attain a high school education is presented.

Figure 2A presents pathologic response rates stratified by type of preoperative treatment. Relative to those treated with preoperative chemotherapy, patients treated with RT had higher rates of disease response (pCR) regardless of whether their primary was in the cardia (13.6% vs 7.0% for chemotherapy; P=.001; primary response, 16.6% vs 7.9%, respectively; P<.001; nodal response, 46.0% vs 29.1%, respectively; P<.001) or was a noncardia primary (15.6% vs 4.4% for chemotherapy; P<.001; primary response, 17.2% vs 6.1%, respectively; P=.001; nodal response, 43.8% vs 31.9%, respectively; P=.06). Use of adjuvant therapy (Figure 2B) was generally lower when any type of disease response was found in patients with cardia primaries (pCR, 7.6% vs no pCR, 20.9%; P<.001; ypT0, 9.9% vs ypT+, 20.8%; P<.001; ypN0, 11.1% vs ypN+, 25.1%; P<.001) and noncardia primaries (pCR, 31.4% vs no pCR, 44.5%; P=.13; ypT0, 41.3% vs ypT+, 44.0%; P=.72; ypN0, 32.7% vs ypN+, 49.3%; P<.001). RT use was associated with an approximately 2-fold increase in the odds of all forms of disease response (Table 2).

Relative to patients with nonresponsive disease, those with gastric cancer who achieved a pCR had significantly higher rates of OS at 5 years (42.7% vs 67.0%; log-rank P=.003), complete primary response (42.9% vs 58.2%; log-rank P=.003), and complete nodal response (32.3% vs 67.7%; log-rank P<.001). Rates of OS at 5 years in patients with cardia primaries were also higher after a pCR (30.0% vs 59.6%; log-rank P<.001), complete primary response (30.1% vs 53.5%; log-rank P<.001), and complete nodal response (23.0% vs 48.7%; log-rank P<.001). No significant difference in OS based on use of adjuvant therapy was seen among patients with cardia (no adjuvant, 35.8% vs adjuvant, 34.3%; log-rank P=.94) and noncardia primaries (no adjuvant, 47.8% vs adjuvant, 43.8%; log-rank P=.16).

Regardless of the presence of a disease response, use of adjuvant therapy was not associated with a decreased risk of death (Table 3). By comparison, all forms of disease response were associated with a significantly decreased risk of death (pCR: hazard ratio [HR], 0.47; 95% CI, 0.34–0.63; primary response: HR, 0.55; 95% CI, 0.42–0.72; nodal response: HR, 0.49; 95% CI, 0.41–0.59). Among patients who experienced a complete primary tumor response but residual nodal disease, the benefit associated with the primary response was attenuated and became nonsignificant (HR, 1.03; 95% CI, 0.66–1.60). However, even in the presence of residual primary disease, a nodal response remained significantly associated with a decreased risk of death, and the magnitude of this effect was essentially unchanged (HR, 0.54; 95% CI, 0.44–0.65). All findings were similar when patients with cardia tumors and those treated with neoadjuvant RT were evaluated separately.

Discussion

Randomized controlled trials have shown that MMT for gastric cancer yields superior cancer-related outcomes compared with surgery alone.[4,6] However, the reported rate of MMT completion, especially postoperative therapy, may be compromised by postoperative complications and toxicity from preoperative chemotherapy and RT.[4–6] Therefore, alternative strategies using more or all MMT before surgery are being evaluated (ClinicalTrials.gov

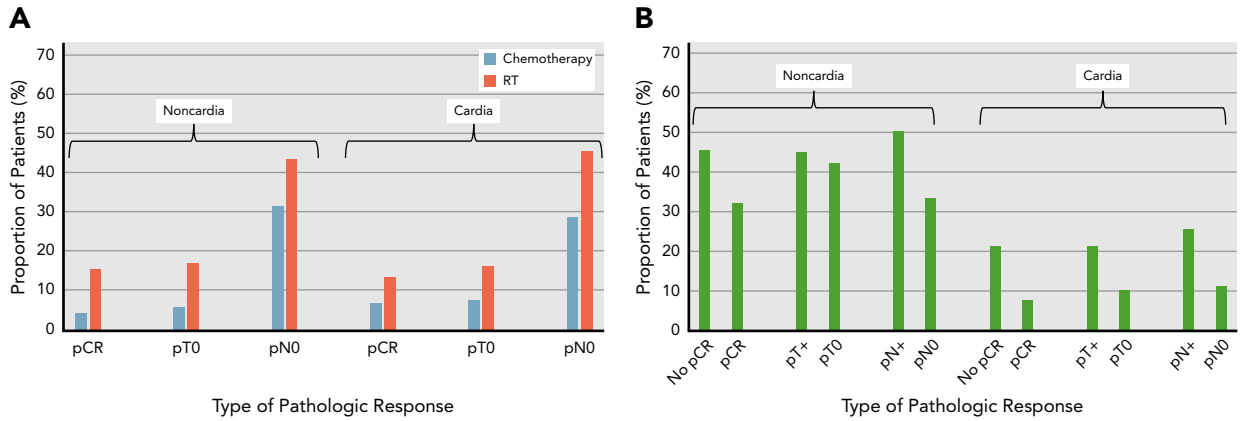

Figure 2. (A) Pathologic response rates stratified by type of preoperative treatment. (B) Adjuvant therapy use stratified by pathologic response. Abbreviations: pCR, pathologic complete response; RT, radiation therapy.

identifiers: NCT02931890, NCT01924819). Our large national cohort study of patients with cN+ gastric cancer supports several important conclusions that can help inform the multimodal management of locally advanced gastric cancer as long-term results from clinical trials are anticipated. First, preoperative RT is associated with higher response rates compared with chemotherapy alone. Second, adjuvant therapy after preoperative treatment and resection is not clearly associated with a survival benefit, even among patients who have residual nodal disease. Finally, although disease response is associated with a significantly decreased risk of death, this effect seems to be primarily driven by a nodal response after preoperative treatment rather than response of the primary tumor.

Although 2 randomized studies have demonstrated benefit from postoperative chemoradiation in gastric cancer, there may be a role for preoperative chemoradiation, similar to the current approach for treating rectal and esophageal cancers.[4,5,14,15] Multiple studies have shown that preoperative chemoradiation may increase response rates in gastric and esophageal cancers. For example, previous phase I and II studies have reported pathologic complete or partial response rates of 20% to 83% after preoperative radiation for gastric cancer.[16–21] Similarly, the randomized phase III POET study examined the role of preoperative chemotherapy compared with preoperative chemotherapy and chemoradiation among patients with gastroesophageal junction (GEJ) adenocarcinoma.[22] Although the study was underpowered because of poor accrual, patients who received preoperative chemoradiation had significantly better local progression-free survival and a trend toward improved OS compared with those who received only preoperative chemotherapy. Although the pCR rate after preoperative RT in our cohort was lower than that reported in these trials, our data suggest that the addition of preoperative RT yields a higher response rate than chemotherapy alone. Ongoing multicenter trials such as TOPGEAR and CRITICS-II will answer this question more definitively. TOPGEAR is a phase III trial comparing perioperative epirubicin/cisplatin/5-fluorouracil (ECF) chemotherapy versus perioperative ECF plus preoperative 5-fluorouracil–based chemoradiation.[23] A recently reported interim safety analysis showed no significant difference in surgical complications or treatment-related toxicity. CRITICS-II is a phase II study comparing 3 preoperative MMT approaches: (1) docetaxel/oxaliplatin/capecitabine (DOC) alone, (2) induction DOC followed by chemoradiation (weekly carboplatin/paclitaxel), and (3) concurrent chemoradiation (weekly carboplatin/paclitaxel) alone (NCT02931890). Although long-term results will not be reported for several years, preliminary data from these trials and our data from the NCDB suggest that preoperative RT may be an effective strategy for achieving a disease response before proceeding with surgical resection.

Table 2. Association Between Type of Preoperative Therapy and Disease Response

	Odds Ratio (95% CI)		
Preoperative Treatment	**pCR**	**Primary Response**	**Nodal Response**
Noncardia			
Chemotherapy	Ref	Ref	Ref
RT	2.37 (1.32–4.25)	2.27 (1.40–3.68)	2.01 (1.56–2.60)
Cardia			
Chemotherapy	Ref	Ref	Ref
RT	2.10 (1.19–3.69)	2.25 (1.34–3.78)	2.08 (1.54–2.81)

Models adjusted for age, sex, race, insurance status, income level, education level, region, Charlson/Deyo Comorbidity Index, treatment facility type, and primary tumor grade (and tumor location in the overall models).
Abbreviations: pCR, pathologic complete response; RT, radiation therapy.

Table 3. Associations Between Pathologic Response, Adjuvant Therapy, and Overall Risk of Death

	Hazard Ratio (95% CI)		
	pCR	Primary Response	Nodal Response
No response, no adjuvant	Ref	Ref	Ref
Response, no adjuvant	0.47 (0.34–0.63)	0.55 (0.42–0.72)	0.49 (0.41–0.59)
No response, adjuvant	1.02 (0.86–1.20)	1.03 (0.87–1.21)	0.94 (0.79–1.13)
Adjuvant in responders	0.62 (0.23–1.65)	0.85 (0.48–1.53)	0.83 (0.58–1.19)
Cardia			
No response, no adjuvant	Ref	Ref	Ref
Response, no adjuvant	0.46 (0.32–0.64)	0.55 (0.41–0.75)	0.48 (0.39–0.59)
No response, adjuvant	1.00 (0.80–1.23)	1.02 (0.82–1.27)	0.91 (0.72–1.14)
Adjuvant in responders	0.48 (0.11–2.05)	0.72 (0.34–1.52)	0.83 (0.55–1.27)
Neoadjuvant radiation			
No response, no adjuvant	Ref	Ref	Ref
Response, no adjuvant	0.48 (0.34–0.68)	0.57 (0.42–0.78)	0.49 (0.39–0.62)
No response, adjuvant	1.04 (0.79–1.38)	1.05 (0.78–1.42)	0.88 (0.66–1.17)
Adjuvant in responders[a]	—	0.65 (0.25–1.73)	0.90 (0.46–1.76)

Models adjusted for type of neoadjuvant treatment, age, sex, race, insurance status, income level, education level, region, Charlson/Deyo Comorbidity Index, treatment facility type, tumor grade, margin status, and interaction between adjuvant and response (and tumor location in the overall models).
Abbreviation: pCR, pathologic complete response.
[a]Hazard ratio estimate for adjuvant use among complete responders could not be obtained because only 5 patients met the 90-day landmark, were treated with neoadjuvant radiotherapy, and received adjuvant therapy.

Use of adjuvant therapy has been a mainstay of MMT in patients with gastric cancer. However, our data suggest there may not be a benefit associated with adjuvant therapy after preoperative treatment followed by resection. In reality, data reported from the seminal MMT trials in gastric cancer do not clearly support the use of adjuvant therapy after preoperative treatment and resection. For example, patients included in the INT-0116 and CLASSIC trials were not treated with preoperative therapy.[4,7] In the MAGIC trial, patients were randomly selected to surgery alone or perioperative chemotherapy, but only two-thirds of patients who completed preoperative treatment went on to receive additional chemotherapy postoperatively, and only 22.9% completed their course of adjuvant chemotherapy.[6] Therefore, it is unclear whether the observed benefit of MMT arises from preoperative treatment alone, or whether there is additional benefit from postoperative treatment. This issue has been evaluated in patients with rectal cancer, in which MMT is also commonly used. The randomized phase II Spanish GSR-3 trial demonstrated that total preoperative therapy yielded similar oncologic outcomes but lower adverse events and higher compliance rates compared with traditional preoperative RT and postoperative chemotherapy.[24] Because pathologic nodal status has been established as an important prognostic indicator, our data suggest that adjuvant therapy may not be a good postoperative salvage option in patients found to be persistently node-positive on final pathologic review after preoperative therapy.[8] Instead, because administration of adjuvant therapies in the postoperative setting is challenging and postoperative MMT completion rates are low, more novel approaches that can optimize the receipt of preoperative treatment and are effective at eliciting a disease response are likely needed to improve oncologic outcomes.[4,6,10]

Because residual nodal disease after preoperative therapy suggests resistance to current chemotherapy and RT approaches, expanding the arsenal of systemic agents is critical. Ongoing studies using agents such as immunotherapy, HER2-targeted therapy, and taxanes in the preoperative setting may diversify systemic therapy options beyond the MAGIC protocol (NCT03221426, NCT02205047, NCT02730546, NCT02661971, NCT03064490).[6] In addition, because our data suggest that in patients with cN+ disease who receive preoperative therapy, a pathologic disease response (in particular a pathologic nodal response) rather than use of adjuvant therapy is associated with improved survival, one potential approach that merits further investigation is using pathologic response to preoperative treatment to guide the type and amount of therapy patients receive. For example, if no radiographic response is observed in a patient with cN+ gastric cancer treated with preoperative chemotherapy, perhaps the patient should receive a different

chemotherapy regimen or chemoradiation rather than proceeding with resection.

A pilot study of patients with resectable gastric and GEJ cancers used PET scan to evaluate response to preoperative chemotherapy.[25] Patients with <35% reduction in FDG-avidity after one cycle of chemotherapy were classified as nonresponders and changed to a different chemotherapy regimen, whereas responders continued with the original chemotherapy. Similarly, among patients with esophageal cancer, preliminary results from CALGB 80803 showed that changing preoperative chemotherapy regimens with concurrent RT in PET nonresponders is associated with improved pCR rates.[26] One important limitation to this approach is the current accuracy of clinical staging, which has poor negative predictive value for lymph node metastases.[9] Although metabolic response on PET scan is predictive of histopathologic response, approximately 30% of gastric cancers are not FDG-avid, and the sensitivity of PET scan for identifying nodal and peritoneal metastases is poor.[27,28] Although the application of this approach in patients identified as cN– may not be possible using contemporary imaging modalities, in patients identified as having cN+ disease, this type of treatment paradigm may have merit.

Our findings need to be interpreted in the context of several limitations. The NCDB does not provide specific information regarding the type of chemotherapy regimens used or the amount of preoperative and postoperative chemotherapy that patients received. However, the fact that approximately 90% of patients in both the chemotherapy and RT groups received multiagent chemotherapy suggests that patients were being treated with MAGIC or CROSS trial–type regimens. The reason patients were treated with preoperative RT rather than chemotherapy is not available in the data. Given that >90% of the patients in the RT group had proximal gastric tumors, this could indicate either that practice patterns in the general community favor treatment of proximal gastric tumors such as esophageal cancer or that difficulty exists in establishing whether a proximal tumor is gastric or esophageal in origin.[15] Similarly, the NCDB does not provide information regarding provider decision-making or treatment intent, and therefore we could not ascertain the reasons why patients did or did not receive adjuvant therapy. Furthermore, information on disease progression, disease recurrence, and quality of life was not available, and data regarding the types of clinical staging modalities used to identify patients with cN+ disease were not provided. Finally, the NCDB only contains data from CoC-accredited hospitals, which may not be entirely representative of practice patterns and outcomes at non-CoC institutions.[29,30]

Conclusions

Our findings suggest that the goal of preoperative therapy in patients with cN+ gastric adenocarcinoma should be to achieve a complete nodal response. Furthermore, given the lack of data regarding the benefit of adjuvant therapy in existing MMT trials, future work will be needed to better delineate whether patients treated in the preoperative setting derive benefit from additional adjuvant treatment. The treatment paradigm for patients with cN+ gastric cancer who undergo preoperative therapy merits careful evaluation and should perhaps shift away from adjuvant therapy and toward more selective, personalized approaches based on the degree to which each patient's disease responds to therapy. Although the ongoing TOPGEAR and CRITICS-II trials will offer further insight into the value of preoperative RT and total upfront MMT, additional studies are warranted to investigate how disease response might be used to guide the amount of preoperative treatment each patient requires before proceeding with resection.

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