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# Impact of ypT, ypN, and Adjuvant Therapy on Survival in Gastric Cancer Patients Treated with Perioperative Chemotherapy and Radical Surgery

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## ABSTRACT

**Background.** Perioperative chemotherapy and surgery is the standard of care in advanced gastroesophageal cancer patients, but its impact among those treated with radical surgery still needs further assessment. We present the results of this multimodality treatment approach in a gastric cancer patients cohort treated with D2 lymphadenectomy. We aimed to identify prognostic factors associated with improved survival.

**Patients and Methods.** This retrospective cohort study enrolled patients treated with perioperative chemotherapy and resection in a single cancer center in Brazil between 2006 and 2016. Subjects presenting tumors of the gastric stump, esophageal tumors, or treated with intraperitoneal chemotherapy were excluded. Intention-to-treat survival analysis was performed for all subjects who started neoadjuvant chemotherapy, and prognostic factors were determined among those who had R0 resection.

**Results.** This study included 239 patients, of whom 198 had R0 resection. The mean age was 59.9 years, and most

had clinical stage IIB or III disease (88%). Among the 239 patients who started neoadjuvant chemotherapy, 207 (86.6%) completed all neoadjuvant treatment cycles, and surgical resection was performed in 225 subjects (94.1%). Overall 60-day morbidity and mortality rates were 35.6% and 4.4%, respectively. For the entire cohort, median survival was 78 months and the 5-year survival rate was 55.3%. Factors associated with worse survival were ypT3–4 stage, ypN + stage, extended resection, and no adjuvant chemotherapy.

**Conclusions.** Perioperative chemotherapy resulted in very good outcomes for patients treated with radical surgery, and downstaging after chemotherapy was shown to be a major determinant of prognosis.

In many Western countries, surgery with perioperative chemotherapy is the standard of care for treatment of patients with stage II–III gastric cancer. This multimodality treatment approach has been associated not only with a survival improvement compared with surgery alone, but also with an increase in complete (R0) resection rate and tumor downstaging.[1,2] However, surgical quality control in these studies remains controversial, as a significant number of subjects did not receive an appropriate lymphadenectomy and the same survival improvement was not shown in a similar German trial in which over 90% of patients had D2 lymphadenectomy.[3]

Multicenter retrospective studies have also demonstrated good survival results and identified significant prognostic factors. Nonetheless, some issues remain

unsolved, such as the predominance of esophageal tumors in some cohorts[4] and the heterogeneity of surgical treatments, with over 30% of incomplete resections (R1/R2 resections) in one study.[5] Thus, perioperative chemotherapy in gastric cancer patients treated with radical R0 resection and D2 lymphadenectomy remains a matter of debate, with several groups questioning the role of the neoadjuvant component, especially for those with factors associated with poor response to chemotherapy.[6]

We present herein the results of perioperative chemotherapy and radical surgery of gastric cancer patients treated in a single institution, with the aim of identifying prognostic factors of improved survival.

## PATIENTS AND METHODS

This is a retrospective cohort study of patients who were treated in a large cancer center in Brazil. Data were obtained from a prospectively collected database that has included all resected gastric cancer individuals since 1988 and from electronic charts of those with biopsy-confirmed gastric adenocarcinoma who started neoadjuvant chemotherapy but received no resection afterwards. This study was approved by the institutional Ethics Review Board.

### Study Population

This cohort included subjects with advanced non-metastatic gastric adenocarcinoma who were treated with perioperative chemotherapy and resection between January 2006 and December 2016. Patients who started neoadjuvant chemotherapy but had no resection were also included.

We excluded patients with the following characteristics: gastric stump tumors, esophagectomy as the main surgical procedure, treatment with radiotherapy or any form of intraperitoneal chemotherapy (IPC).

### Staging

Patients' staging routinely included multidetector computer tomography (MD-CT) with a stomach dedicated protocol (S-MDCT), based on meticulous methods for gastric distension with gas or water.[7] The technique we have most recently used has been described elsewhere.[8]

Lesions characterized as cT3 or cT4 had gastric wall thickening with contrast enhancement, and those that were cN+ had enlarged lymph nodes over 8 mm in larger axis or necrosis inside. Magnetic resonance imaging (MRI) was obtained when patients were allergic to iodine contrast or MD-CT was not conclusive about liver lesions. Endoscopic ultrasound (EUS) staging was not routinely performed due to budget restrictions during the study time frame. Staging laparoscopy prior to preoperative chemotherapy was recommended for all patients after 2013. Before that, it was performed only in cases with suspected metastases.

### Treatment

Fluoropyrimidine/platinum-based chemotherapy regimens were divided into three categories: (I) platinum-based doublets (carboplatin + paclitaxel, carboplatin + 5-FU, CDDP + 5-FU, FOLFOX, XELOX, FLOX), (II) epirubicin-based triplets (ECF, ECX, EOX), or (III) taxane-based triplets (DCF, DCX). We considered patients to have completed neoadjuvant or adjuvant treatments when all planned cycles of that treatment phase were administered. Toxicity information was collected according to the Common Terminology Criteria for Adverse Events (CTCAE 4.03).[9]

### Variables

Clinical variables included age, gender, and American Society of Anesthesiologists (ASA) preoperative score[10] Clinical staging was also reported.

Surgical data included the extent of resection and lymphadenectomy, in accordance with the guidelines of the Japanese Gastric Cancer Association,[11] multivisceral resections, and blood transfusion.

Morbidity and mortality analyses comprised all 60-day postoperative events, even after hospital discharge. Details on chemotherapy regimens and their respective compliance were also collected.

Anatomopathological variables examined were tumor location, Lauren histological type, margin status, depth of invasion (T stage), and number of positive lymph nodes (N stage), complying with the tumor–node–metastasis (TNM) manual of the American Joint Committee on Cancer 8th edition.[12]

### Survival

Overall survival was defined as the interval in months between the date of the start of neoadjuvant chemotherapy and the date of death from any cause or last hospital visit. Loss to follow-up was defined as patient's absence in two consecutive visits, with no outcome information after this period.

### Statistical Analysis

Quantitative variables are expressed by a measure of central tendency (mean or median) along with their

appropriate measure of dispersion: standard deviation (sd) or interquartile range (IQR).

Overall survival analysis included the Kaplan–Meier product-limit estimator for all 239 patients who started neoadjuvant chemotherapy. Median follow-up was determined through the reverse Kaplan–Meier method. Cox regression analysis was performed to obtain crude and adjusted hazard ratios (HR) for these patients. Model building was done through forward selection, and confounding was assessed for every covariate in the final model. The proportional hazards assumption was checked with log–log plots of survival functions. We also performed sensitivity analysis excluding all cases who died up to the 60th postoperative day, in order to evaluate whether the predictore day, in order to evaluate cludi.

$p$ value $< 0.05$ (two-tailed) was considered statistically significant. Statistical analyses were performed using the SPSS software package (released 2011, IBM SPSS Statistics for Windows, version 20.0, IBM Corp., Armonk, NY).

## RESULTS

### Clinicopathological Characteristics

During the study time frame, 336 individuals with nonmetastatic gastroesophageal tumors started treatment with perioperative chemotherapy. Among them, 42 had an esophagectomy, 41 received IPC, 8 had tumors of the gastric stump, and 6 received preoperative radiotherapy. These patients were excluded from further analysis, and the final study sample included 239 patients. Their treatment sequence and associated events are presented in Fig. 1.

Patients' mean age was 59.7 years, and 70% were classified as ASA 1 or 2. Staging was performed with MD-CT in all but two subjects, and 58% had a laparoscopy before the start of chemotherapy. Among subjects treated until 2013 ($n = 122$), only 33% had a staging laparoscopy; that number increased to 83% among patients treated in 2014 and beyond. Also, among the 97 patients who did not have the procedure, 18 had M1 disease at resection time and 21 had disease relapse. Overall, 88% of the study population had clinical stage IIB or III.

Surgical resection was performed in 225 patients. Half of them had total gastrectomy, and extended resection was needed for 31 individuals. All patients treated with R0 resection ($n = 198$) had D2 lymphadenectomy, with a median of 31 dissected nodes (IQR 23–43).

The overall 60-day morbidity rate was 35.6%, and the 60-day mortality rate was 4.4%. The most common clinical complications were arrhythmia (19 cases) and pneumonia (nine cases), while the surgical ones were abdominal abscess (27 cases) and pancreatic fistulae (15 cases).
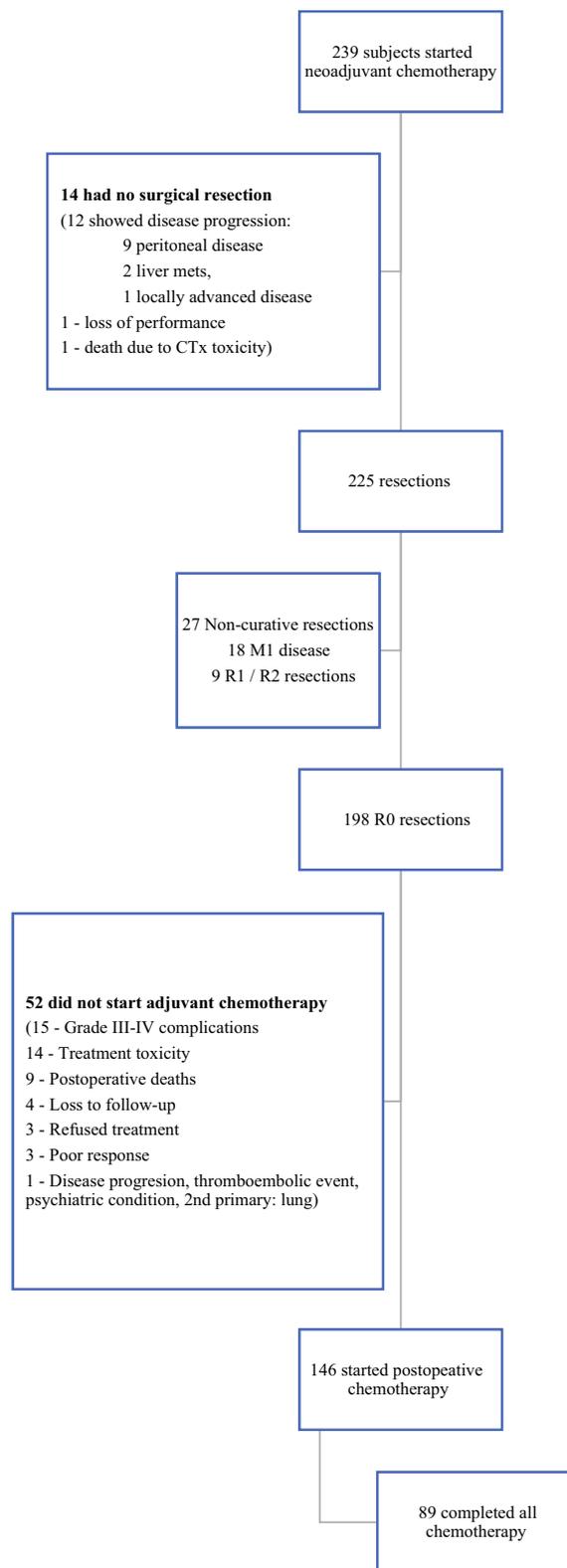


FIG. 1 Flowchart of all 239 gastric cancer patients who started neoadjuvant chemotherapy

**TABLE 1** Clinical, surgical, and pathological data of 239 patients with gastric cancer who started neoadjuvant chemotherapy

| Variable | No. of patients (N = 239) | % |
|---|---|---|
| Age (years) | | |
| Mean (SD) | 59.7 (12.2) | |
| Gender | | |
| Male | 143 | 59.8 |
| Female | 96 | 40.2 |
| ASA (n = 234) | | |
| 1–2 | 167 | 69.8 |
| 3–4 | 67 | 31.2 |
| Staging | | |
| MDCT | 237 | 99.2 |
| MRI | 13 | 5.8 |
| EUS | 23 | 9.6 |
| Laparoscopy | 138 | 57.7 |
| Clinical stage | | |
| cT1–2 cN0 | 5 | 2.1 |
| cT1–2 cN+ | 23 | 9.6 |
| cT3–4 cN0 | 87 | 36.4 |
| cT3–4 cN+ | 124 | 51.9 |
| Surgical resection (n = 225) | | |
| Total gastrectomy | 110 | 48.9 |
| Subtotal gastrectomy | 115 | 51.1 |
| Multivisceral resections (n = 225) | 31 | 13.8 |
| Blood transfusion (n = 225) | 53 | 23.6 |
| R0 resection (n = 225) | 198 | 88.0 |
| Overall morbidity (n = 225) | 80 | 35.6 |
| Major morbidity (n = 225) | 44 | 19.5 |
| Mortality (n = 225) | 10 | 4.4 |
| Histology (n = 225) | | |
| Diffuse | 91 | 40.4 |
| Intestinal | 103 | 45.8 |
| Mixed | 23 | 10.2 |
| Undetermined | 8 | 3.6 |
| Tumor site | | |
| Upper third | 48 | 20.1 |
| Middle third | 67 | 28.0 |
| Distal third | 124 | 51.9 |
| Pathological complete response (PCR) (n = 225) | 28 | 12.4 |
| yp T stage (n = 225) | | |
| yp T0 | 28 | 12.4 |
| yp T1 | 41 | 18.2 |
| yp T2 | 34 | 15.1 |
| yp T3 | 41 | 18.2 |
| yp T4a | 73 | 32.4 |
| yp T4b | 8 | 3.6 |
| yp N stage (n = 225) | | |
| yp N0 | 118 | 52.4 |
| yp N1 | 30 | 13.3 |
| yp N2 | 37 | 16.4 |
| yp N3a | 29 | 12.9 |
| yp N3b | 11 | 4.9 |
| M stage (n = 225) | | |
| M0 | 207 | 92 |
| M1 | 18 | 8 |

Pathology reports identified a similar frequency of intestinal- and diffuse-type tumors, and lesions more often arose in the body and antrum of the stomach (around 80%). Pathologic complete response occurred in 12.4% of cases, and another 33% had ypT1/T2 tumors. Patients' clinico-pathological data are presented in Table 1.

### Perioperative Chemotherapy

Among the 239 patients who started neoadjuvant chemotherapy, 207 (86.6%) completed all neoadjuvant treatment cycles. Over 90% had either platinum-based doublet or epirubicin-based triplet regimens. Table 2 presents the treatment toxicity profile. There was one chemotherapy-related death in this phase in a patient who developed grade IV neutropenia and sepsis.

Regarding postoperative chemotherapy, 146 subjects started treatment, but only 89 completed all cycles (37.2% of all patients who started neoadjuvant chemotherapy). Also, the use of the platinum-based doublet increased from 59 to 70% in the adjuvant treatment setting.

### Survival Outcomes

Median follow-up was 45 months (95% confidence interval 39.5, 50.2), and 13 subjects (5.4%) were lost to follow-up. Median overall survival of all 239 patients was 78 months, and their estimated 5-year overall survival rate was 55.3%. Survival probabilities for patients who had pathologic complete response (pCR), stage I, II, III, and IV disease were 88.9%, 95.2%, 67.2%, 33.6%, and 4.4%, respectively (Fig. 2). When only subjects who had R0 resection were analyzed ($n = 198$), median survival was not achieved, and 5-year survival rate was 65.9%.

The following prognostic factors were independently associated with worse survival: ypT3–4 stage, ypN+ stage, extended resection, and no adjuvant chemotherapy (Table 3). When patients experiencing postoperative death were removed, adjuvant treatment did not remain as an independent predictor of survival (data not shown). However, in this subset analysis, the 5-year overall survival rate was 59.9% among those who did not receive postoperative chemotherapy, versus 70.3% for those who had it.

### DISCUSSION

This study encompasses a large cohort of gastric cancer patients treated with neoadjuvant chemotherapy and resection in a single cancer center, with acceptable morbidity and mortality rates and very good survival outcomes, particularly among those who achieved tumor downstaging. Patients' staging included at least a high-quality MD-CT, and about half had a staging laparoscopy, which became our standard of care protocol after 2013.

The early clinical outcomes observed in this cohort resemble the ones observed in large perioperative chemotherapy trials. Almost 90% of our patients completed the planned neoadjuvant treatment, as observed in the Magic Trial[1] and in the ACCORD-07[2] study populations. Postoperative mortality up to the 30th postoperative day in our series was similar to that achieved in the recent Critics Trial[13] (3.5% versus 3.0%) and lower than earlier European studies.[1,2] Regarding the adjuvant component of therapy, 25% of our cases did not start postoperative chemotherapy and less than half of them completed all planned cycles.

Pathologic results were also similar. Complete R0 resections were more frequent than in the Magic Trial,[1] whereas in other randomized trials they were accomplished more than 80% of the time.[2,3,13] Downstaging was similar to what was observed in the Dutch study,[13] albeit with slightly more ypT3–4 cases in our series. Also, the proportion of pCR cases was close to that obtained with the new FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) regimen.[14]

Our study population showed very good survival outcomes. Median and 5-year overall survival rates, for either patients who started neoadjuvant chemotherapy or those who were resected with curative intent, were higher than in the larger trials,[1,2,13] but similar to a European Organisation for Research and Treatment of Cancer (EORTC) trial[3] and a recent American cohort.[15] This disparity could be explained by the heterogeneity in hospital volume in multicenter studies, which affected survival and recurrence in the Critics Trial,[16] and could also be related to the extent of lymph node dissection. It has been shown before that survival in Western trials in which D2 lymphadenectomy is routinely performed[17] becomes closer to the surgery-only arms of Asian studies.[18] Moreover, aspects associated with pharmacoethnicity and the ethnical/admixture components of our population should be considered,[19,20] and may contribute to the understanding of distinct response rates.

The main survival prognostic factors in our study were the pathologic T and N stages after neoadjuvant treatment. The impact of node-negative disease (ypN0) has been demonstrated in earlier perioperative treatment series,[21] while the role of the ypT category is not as clear. Some series have not shown ypT to be an independent prognostic factor,[5,15,22] whereas others have identified a prognostic impact of both ypT and ypN stages.[4] A European multicenter study of esophageal and gastroesophageal (GE) junction tumors identified survival numbers among patients with a ypT stage that were correspondent to the same pT stage in subjects who were treated with upfront surgery.[23] In our series, 5-year survival among individuals with pCR

**TABLE 2** Perioperative chemotherapy (CTx) regimens and toxicity outcomes in gastric cancer patients

| Event | No. | % |
|---|---|---|
| *Neoadjuvant treatment* | 239 | |
| Completed proposed neoadjuvant CTx | 207 | 86.6 |
| Dose reduction | 5 | 2.1 |
| CTx regimen | | |
| Platinum-based doublet | 142 | 59.4 |
| Epirubicin-based triplet | 71 | 29.7 |
| Taxane-based triplet | 26 | 10.9 |
| Grade III/IV toxicity | 51 | 21.3 |
| Neutropenia | 20 | 8.4 |
| Diarrhea | 14 | 5.9 |
| Mucositis | 11 | 4.6 |
| Vomiting | 7 | 2.9 |
| Nausea | 6 | 2.5 |
| Neuropathy | 4 | 1.7 |
| Thromboembolic events | 3 | 1.3 |
| Renal failure | 2 | 0.8 |
| Asthenia | 1 | 0.4 |
| Reasons for not completing treatment | | |
| Gastrointestinal toxicity | 7 | 2.9 |
| Hematologic toxicity | 7 | 2.9 |
| Cardiac toxicity | 2 | 0.8 |
| Mucositis | 2 | 0.8 |
| Disease progression | 2 | 0.8 |
| Loss of performance | 2 | 0.8 |
| Thromboembolic event | 1 | 0.4 |
| Liver failure | 1 | 0.4 |
| Death | 1 | 0.4 |
| Not reported | 2 | 0.8 |
| *Adjuvant chemotherapy* | 146 | |
| Started adjuvant chemotherapy | 146 | 61.1 |
| Completed proposed adjuvant CTx | 89 | 37.2 |
| CTx regimen | | |
| Platinum-based doublet | 102 | 69.9 |
| Epirubicin-based triplet | 28 | 19.2 |
| Taxane-based triplet | 6 | 4.1 |
| Other regimens | 5 | 3.4 |
| Not reported | 5 | 3.4 |
| Grade III/IV toxicity | 31 | 21.2 |
| Nausea | 12 | 8.2 |
| Neutropenia | 11 | 7.5 |
| Diarrhea | 7 | 4.8 |
| Asthenia | 5 | 3.4 |
| Vomiting | 2 | 1.4 |
| Mucositis | 1 | 0.7 |
| Neuropathy | 1 | 0.7 |
| Reasons for not completing treatment | | |
| Loss of performance | 14 | 9.6 |
| Gastrointestinal toxicity | 8 | 5.5 |
| Asthenia | 5 | 3.4 |
| Disease progression | 4 | 2.7 |
| Hematologic toxicity | 4 | 2.7 |
| Refused treatment | 3 | 2.1 |
| Thromboembolic event | 1 | 0.7 |
| Neuropathy | 1 | 0.7 |
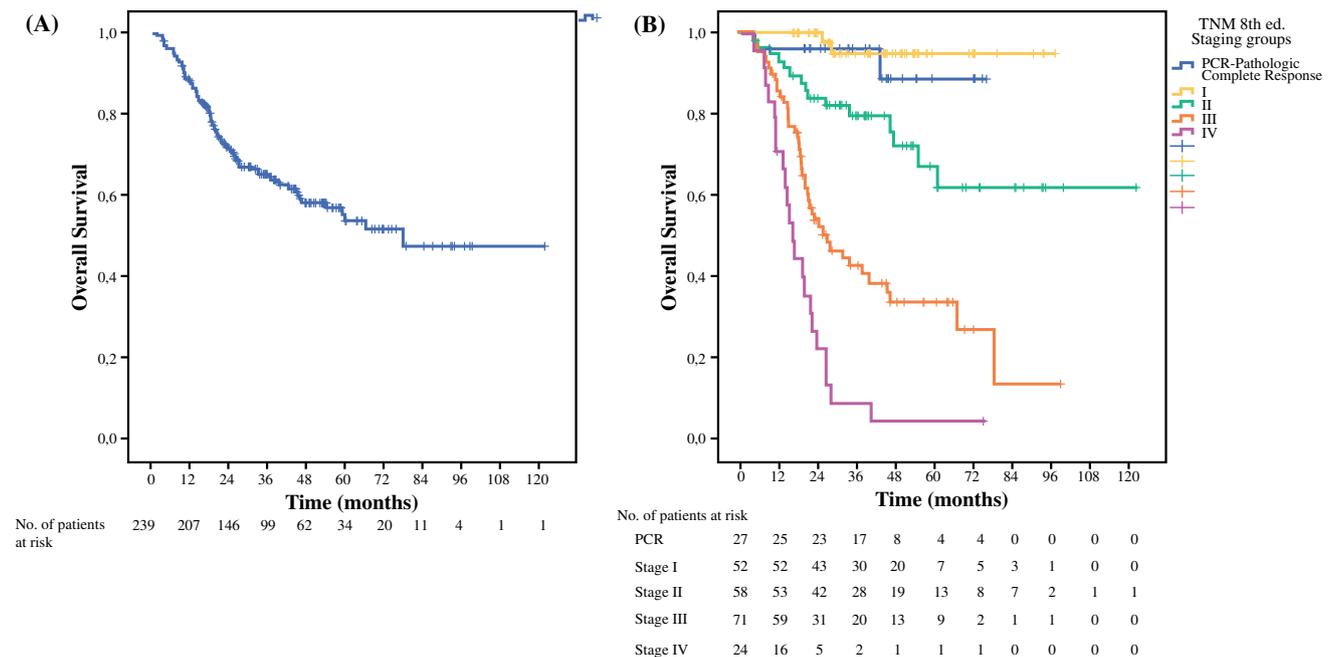
FIG. 2 Overall survival and overall survival by TNM stage with complete response group curves

and stage I disease was 90%, and among those with stage II and III disease was 59.7% and 38.7%, respectively. These outcomes neighbor those reported by our group in a series of patients who had upfront surgery.[24]

It has been shown by multiple studies that chemotherapy improves survival in gastric cancer patients treated with resection and D2 lymphadenectomy.[18,25] The use of the perioperative strategy has been favored in our institution since 2007, not only due to better treatment compliance and the potential negative impact of postoperative complications in survival outcomes,[26] but also because tumor downstaging is a very important prognostic factor.[4,5,21–23] Nevertheless, a remaining challenge is still the early identification of patients who will not respond to chemotherapy. In our series, those with stage III disease had significantly worse survival. It may be argued that some of these subjects had metastatic disease that went undetected in preoperative staging, as laparoscopy was only performed in a little more than half of the patients, but pathologic stage was not associated with having a laparoscopy. A German series identified tumor site, degree of differentiation, and Lauren histology as prognostic factors associated with worse pathologic response and prognosis,[27] but these clinicopathological characteristics were not predictors of survival in our series.

The role of postoperative chemotherapy as an independent prognostic factor should also be vetted. The main reason why patients do not receive adjuvant treatment is related to postoperative morbidity,[28] and the same was observed in this study. Although adjuvant chemotherapy did not remain as an independent prognostic factor after sensitivity analysis, a marked difference remained. It may be the case that our study was underpowered to identify adjuvant chemotherapy as an independent prognostic factor for overall survival. Therefore, the putative impact of adjuvant treatment on survival[28,29] reinforces the need for preventing postoperative complications and allowing patients to receive the complete treatment.

Limitations of this study are related to its retrospective nature, such as the heterogeneity of chemotherapy regimens and the range of staging tools used. First, we found no impact of the number of drugs in the chemotherapy regimen on survival in our cohort. One can argue that no patients in this cohort were treated with the FLOT regimen, but our rate of subjects with pCR, T- and N-category downstaging was very similar to what was found in the FLOT4-AIO study.[14]

Regarding the staging tools used in our series, the lack of a laparoscopy would mainly fail to detect patients with peritoneal disease prior to chemotherapy, which would lead to incorrect staging-centered outcomes. Concerning MDCT gastroscopy, it has been shown to have similar accuracy overall to endoscopic ultrasound, with more precise results for detecting cT3/T4 tumors.[30] Regarding the N stage, Ahn et al. reported predictive values and overall accuracy of MDCT for N– of 90.1% and 83.6%, respectively, compared with 92.6% and 90.1% for EUS.[7]

**TABLE 3** Univariable and multivariable analysis of survival prognostic factors in gastric cancer patients treated with neoadjuvant chemotherapy and R0 resection

| Variable | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| Male gender | 1.01 | (0.66, 1.54) | 0.969 | – | – | – |
| Age | 1.01 | (0.99, 1.03) | 0.319 | – | – | – |
| ASA classification | | | | | | |
|   ASA 1–2 | 1.0 | | | 1.0 | | |
|   ASA 3–4 | 1.76 | (1.14, 2.70) | 0.010 | 1.37 | (0.85, 2.23) | 0.201 |
| Tumor site | | | | | | |
|   Upper third | 1.64 | (0.98, 2.76) | 0.062 | 1.13 | (0.59, 2.17) | 0.709 |
|   Middle third | 1.63 | (1.01, 2.62) | 0.047 | 1.27 | (0.71, 2.29) | 0.422 |
|   Distal third | 1.0 | | | 1.0 | | |
| Clinical stage | | | | | | |
|   I/II | 1.0 | | | | | |
|   III (cT3–4 cN+) | 1.33 | (0.88, 2.01) | 0.181 | – | – | – |
| Resection | | | | | | |
|   Total gastrectomy | 1.30 | (0.83, 2.03) | 0.253 | – | – | – |
|   Distal gastrectomy | 1.0 | | | | | |
|   Extended resection | 3.04 | (1.80, 5.12) | < 0.001 | 1.99 | (1.08, 3.67) | 0.027 |
|   Blood transfusion | 1.42 | (0.87, 2.32) | 0.158 | – | – | – |
| Histology | | | | | | |
|   Diffuse | 1.0 | | | 1.0 | | |
|   Intestinal | 0.58 | (0.36, 0.95) | 0.030 | 0.63 | (0.37, 1.07) | 0.090 |
|   Mixed | 0.64 | (0.28, 1.44) | 0.283 | 0.78 | (0.34, 1.80) | 0.556 |
|   Adjuvant chemotherapy (at least one cycle) | 0.54 | (0.35, 0.83) | 0.005 | 0.55 | (0.33, 0.91) | 0.019 |
| ypT stage | | | | | | |
|   ypT0–1–2 | 1.0 | | | | | |
|   ypT3–4 | 6.09 | (3.29, 11.30) | < 0.001 | 3.31 | (1.68, 6.52) | 0.001 |
| ypN stage | | | | | | |
|   ypN0 | 1.0 | | | | | |
|   ypN+ | 3.90 | (2.36, 6.45) | < 0.001 | 2.41 | (1.36, 4.29) | 0.003 |

In conclusion, perioperative chemotherapy and radical surgery were associated with great outcomes in this cohort. Downstaging after chemotherapy was shown to be a significant determinant of prognosis, with patient outcomes resembling those obtained in subjects with early disease.

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