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ORIGINAL ARTICLE

Predictors and Prognostic Implications of Perioperative Chemotherapy Completion in Gastric Cancer

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Abstract

Background Perioperative chemotherapy in gastric cancer is increasingly used since the "MAGIC" trial, while clinical practice data outside of trials remain limited. We sought to evaluate the predictors and prognostic implications of perioperative chemotherapy completion in patients undergoing curative-intent gastrectomy across multiple US institutions.

Methods Patients who underwent curative-intent resection of gastric adenocarcinoma between 2000 and 2012 in eight institutions of the US Gastric Cancer Collaborative were identified. Patients who received preoperative chemotherapy were included, while those who died within 90 days or with unknown adjuvant chemotherapy status were excluded. Predictors of chemotherapy completion and survival were identified using multivariable logistic regression and Cox proportional hazards.

Results One hundred sixty three patients were included (median age 63.3, 36.8% female). The postoperative component of perioperative chemotherapy was administered in 112 (68.7%) patients. Factors independently associated with receipt of adjuvant chemotherapy were younger age (odds ratio (OR) 2.73, $P = 0.03$), T3 tumors (OR 14.3, $P = 0.04$), lymph node metastasis (OR 5.82, $P = 0.03$), and D2 lymphadenectomy (OR 4.12, $P = 0.007$), and, inversely, postoperative complications (OR 0.25, $P = 0.008$). Median overall survival (OS) was 25.1 months and 5-year OS was 36.5%. Predictors of OS were preexisting cardiac disease (hazard ratio (HR) 2.7, 95% CI 1.13–6.46), concurrent splenectomy (HR 4.11, 95% CI 1.68–10.0), tumor stage (reference stage I; stage II HR 2.62; 95% CI 0.99–6.94; stage III HR 4.86, 95% CI 1.81–13.02), and D2 lymphadenectomy (HR 0.43, 95% CI 0.19–0.95). After accounting for these factors, adjuvant chemotherapy administration was associated with improved OS (HR 0.33, 95% CI 0.14–0.82).

Conclusion Completion of perioperative chemotherapy was successful in two thirds of patients with gastric cancer and was independently associated with improved survival.

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Introduction

Gastric cancer has a major global public health impact and is the third leading cause of cancer-related mortality worldwide.[1] In 2016, there will be an estimated 26,000 new diagnoses of gastric cancer and more than 10,000 deaths in the USA alone.[2] Historically, when feasible, surgical resection has been the cornerstone of treatment and typically involves a partial or total gastrectomy with a varying extent of regional lymphadenectomy. Unfortunately, even after radical oncologic procedures, recurrence remains high and long-term prognosis is poor for many patients.[3,4]

The challenging natural history and unfavorable oncologic outcomes after resection alone have led to the current multidisciplinary approach to gastric cancer care. A variety of chemotherapy and radiotherapy regimens are currently being used both in the preoperative (neoadjuvant) and the postoperative (adjuvant) setting. The most common approaches in Western centers has been either postoperative radiotherapy (with 5-fluorouracil infusion) or perioperative (pre- and postoperative) chemotherapy, typically involving epirubicin, cisplatin, and 5-fluorouracil. Both approaches have been demonstrated to be superior to surgery alone for the treatment of gastric cancer.[5,6] Evidence assessing their comparative effectiveness is, however, limited and remains the focus of current trials.[7]

While the popularity of perioperative chemotherapy in gastric cancer has certainly increased since the "MAGIC" trial in 2006,[6] data on its benefits in actual clinical practice, outside the controlled environment of a clinical trial, remain limited. Specifically, it is uncertain how many patients who are started on a perioperative chemotherapy regimen actually receive the postoperative component of the protocol, a question made more relevant by the fact that even within the controlled environment of the "MAGIC" trial, only 103 of 208 patients (49.5%) who completed preoperative chemotherapy and surgery also received postoperative chemotherapy.[6] The purpose of this study was to assess the current clinical practice of perioperative chemotherapy for gastric cancer in a large, multi-institutional US cohort of patients undergoing curative-intent resection, evaluating the predictors and prognostic implications of perioperative chemotherapy completion.

Methods

Data Collection

This study analyzed outcomes from the US Gastric Cancer Collaborative, a database of patients who underwent resection for gastric adenocarcinoma in one of 8 academic medical centers (New York University, Emory University, Johns Hopkins University, Stanford University, The Ohio State University, University of Wisconsin, Wake Forest University, and Washington University in St Louis). Each participating institution obtained institutional review board approval for this multicenter study. All patients who received preoperative chemotherapy between 2000 and 2012, in addition to curative-intent resection, were identified. The decision to offer preoperative chemotherapy was at the treating physicians' discretion after a multidisciplinary discussion. Patients with perioperative mortality (death from any cause at 90 days) or unknown postoperative chemotherapy status were excluded. Major complications were defined as Clavien-Dindo grade III or IV and minor complications as Clavien-Dindo grade I or II. Demographic and clinicopathologic characteristics, perioperative, recurrence, and survival outcomes were collected. The seventh edition of the *American Joint Committee on Cancer (AJCC) Staging Manual* was used to determine disease stage.

Statistical Analyses

Discrete variables were described as medians with interquartile range (IQR). Categorical variables were described as totals and frequencies. Age was dichotomized at the cohort median age of 63.3 years. Univariable comparisons were assessed using the Chi-square or Fisher's exact test, as appropriate. Univariable and multivariable logistic regression models were constructed to determine the association of relevant clinicopathologic factors with receipt or completion of perioperative chemotherapy. Overall survival (OS) for the study population was estimated from the time of surgery using the Kaplan-Meier method and differences were assessed using the log-rank test. Multivariable Cox proportional hazards regression was used to identify factors associated with disease recurrence and overall survival, excluding perioperative deaths (mortality within 90 days). Variables were initially entered into the model based on statistical ($P < 0.10$) or clinical (age, resection margin, postoperative radiotherapy, and postoperative chemotherapy) significance and a backward stepwise elimination with a threshold of $P = 0.20$ was used to select variables in the final model. All analyses were carried out with Stata version 12.0 (StataCorp, College Station, TX) and a two-tailed P value of less than 0.05 was considered statistically significant.

Results

Clinicopathologic Characteristics of the Cohort

Two hundred patients with gastric adenocarcinoma who received preoperative chemotherapy prior to curative-intent

resection were identified. Among these patients, there were eight (4%) patients with 90-day mortality who were excluded. Data on the receipt of adjuvant chemotherapy was unavailable in additional 29 patients (14.5%), who were therefore also excluded, leading to our final cohort of 163 patients (Fig. 1, Table 1). The median patient age in the final cohort was 63.3 years (IQR, 56.1–69.6 years). The majority of patients were male (n = 103; 63.2%) and of white race (n = 110; 67.5%). Ninety-four patients (57.7%) had Epirubicin-based preoperative chemotherapy regimen similar to that of the "MAGIC" trial, while the remainder had variations of this protocol, most commonly capecitabine/5-FU plus carboplatin/cisplatin/oxaliplatin (n = 35, 21.5%). Most patients underwent partial gastrectomy (n = 100; 61.3%), while a subset underwent total gastrectomy (n = 63; 38.7%). A minimally invasive approach was used in 36 patients (22.1%). On final pathology, the median tumor size was of 3.6 cm (IQR, 2.0–6.0 cm), and lymph node metastasis was noted in 54.0% (n = 88) of patients. The majority of patients presented with locally advanced disease, with 27.9% (n = 43) and 44.8% (n = 69) having stage II and III disease on final pathology.

Predictors of Perioperative Chemotherapy Completion

Among the 163 patients included in the final cohort, 112 (68.7%) received the postoperative component of the perioperative chemotherapy regimen while the remaining 51 (31.3%) did not. There was no difference in the receipt of postoperative chemotherapy among the participating institutions (range 50–86%, P = 0.15). The association between the completion of perioperative chemotherapy and several clinicopathologic and operative characteristics was evaluated (Table 2). Gender, race, type of resection, surgical approach, tumor size, and histologic grade were not associated with receipt of the postoperative component of perioperative chemotherapy. However, in both univariable and multivariable regression models, younger age (< 63.3 years, odds ratio (OR) 2.73, 95% confidence interval (CI) 1.1–6.8), D2 lymph node dissection (OR 4.12, 95% CI 1.5–11.6), and lymph node metastasis (OR 5.82, 95% CI 1.2–28.4) were all associated with increased likelihood of receiving adjuvant chemotherapy, while the occurrence of postoperative complications (OR 0.25, 95% CI 0.1–0.7) was associated with a decreased likelihood of receiving adjuvant chemotherapy.

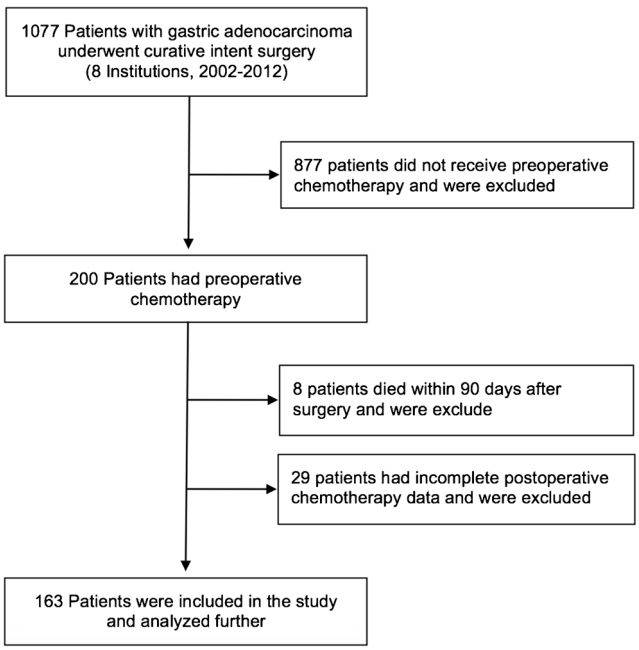

Fig. 1 Study population

Predictors of Survival in Patients Who Received Preoperative Chemotherapy

The median overall survival was 25.1 months after a median follow-up of 20 months. The 1-, 3-, and 5-year overall survival was 71.6, 40.1, and 36.5%, respectively. The factors that were associated with worse overall survival in the univariable analysis are detailed in Table 3. In the multivariable proportional hazards model, the independent predictors of poor survival included a history of cardiac disease (hazard ratio (HR) 2.7, 95% CI 1.13–6.46), the need for splenectomy at the time of gastrectomy (HR 4.11, 95% CI 1.68–10.0), and the AJCC tumor stage (reference stage I; stage II: HR 2.62; 95% CI 0.99–6.94; stage III: HR 4.86, 95% CI 1.81–13.02). In contrast, a D2 lymphadenectomy (HR 0.43, 95% CI 0.19–0.95) and the administration of adjuvant chemotherapy (HR 0.33, 95% CI 0.14–0.82) were independently associated with improved survival.

During follow-up, 70 patients (43.5%) developed disease recurrence. The impact of individual factors on recurrence was assessed. In the multivariable proportional hazards model, higher AJCC tumor stage was independently associated with recurrence (reference stage I; stage III: HR 3.77; 95% CI 1.44–9.9), while the administration of adjuvant chemotherapy was independently associated with lower recurrence rates (HR 0.52, 95% CI 0.27–0.96). With regard to disease recurrence, patients with stage II tumors benefited the most from the administration of adjuvant chemotherapy (20 vs. 64.7% recurrence for those who did and did not receive adjuvant chemotherapy, respectively; P = 0.003); for patients with stage III disease, the benefit was less pronounced (52.6 vs. 63.6%, recurrence for those who did and did not receive adjuvant chemotherapy, respectively; P = 0.50).

Discussion

The current study demonstrated that in a large, modern North American patient cohort, a significant number of patients with

Table 1 Clinicopathologic and operative characteristics

	All patients (n = 163)	Perioperative chemotherapy (n = 112)	Preoperative chemotherapy alone (n = 51)	P value
Age, year, median (IQR)	63.3 (56.1–69.6)	60.5 (55.4–68.5)	66.1 (59.0–69.6)	**0.03**
Female gender	60 (36.8)	44 (39.3)	16 (31.4)	0.33
Race				
White	110 (67.5)	73 (65.2)	37 (72.5)	0.17
Black	30 (18.4)	20 (17.9)	10 (19.6)	
Asian	10 (6.1)	10 (8.9)	0 (0)	
BMI > 30	39 (23.9)	27 (24.1)	12 (23.5)	0.94
Preoperative albumin				0.83
≥ 4 g/dL	62 (38.0)	42 (37.5)	20 (39.2)	
< 4 g/dl	101 (62.0)	70 (62.5)	31 (60.8)	
Extent of resection				0.55
Total gastrectomy	63 (38.7)	45 (40.5)	18 (35.3)	
Partial gastrectomy	100 (61.3)	67 (59.5)	33 (64.7)	
Splenectomy	23 (14.1)	18 (16.1)	5 (9.8)	0.29
Lymphadenectomy				**0.006**
D1	33 (20.2)	15 (13.4)	18 (35.3)	
D2	130 (79.8)	97 (86.6)	33 (64.7)	
Resection margin				0.056
R0	150 (92.0)	100 (89.3)	50 (98.0)	
R1	13 (8.0)	12 (10.7)	1 (2.0)	
Tumor location				0.47
Antrum	45 (27.6)	30 (26.8)	15 (29.4)	
Body	55 (33.7)	42 (37.5)	13 (25.5)	
Fundus	20 (12.3)	15 (13.4)	5 (9.8)	
Cardia	15 (9.8)	9 (8.0)	6 (11.8)	
GE junction	21 (12.9)	13 (11.6)	8 (15.7)	
Size, cm, median (IQR)	3.6 (2–6)	3.6 (2.1–6)	3.35 (1.9–5.5)	0.86
T classification				**0.020**
T1	21 (14.1)	10 (9.4)	11 (25.6)	
T2	27 (18.1)	21 (19.8)	6 (13.9)	
T3	52 (34.9)	37 (34.9)	15 (34.9)	
T4	49 (32.9)	38 (35.9)	11 (25.6)	
Lymph node metastasis	88 (54.0)	73 (65.2)	15 (27.5)	**< 0.001**
Lymph nodes harvested, median (IQR)	18 (12–26)	20 (12–28)	15 (12–22)	0.12
AJCC Stage				**0.006**
I	35 (22.7)	19 (17.6)	16 (34.8)	
II	43 (27.9)	26 (24.1)	17 (37.0)	
III	69 (44.8)	58 (53.7)	11 (23.9)	
IV	7 (4.6)	5 (4.6)	2 (4.3)	
Histological grade				0.87
Well	5 (3.4)	3 (2.9)	2 (4.7)	
Moderate	38 (25.9)	27 (26.0)	11 (25.6)	
Poor	104 (70.7)	74 (71.1)	30 (69.7)	
Signet ring	62 (38.0)	42 (37.5)	20 (39.2)	0.96
Lymphovascular invasion	63 (40.5)	48 (42.9)	15 (29.4)	0.17

Table 1 (continued)

	All patients (n = 163)	Perioperative chemotherapy (n = 112)	Preoperative chemotherapy alone (n = 51)	P value
Perineural invasion	30 (18.4)	19 (17.0)	11 (21.6)	0.38
Linitis plastica	14 (8.6)	11 (9.8)	3 (5.9)	0.41
Postoperative complications				
Major complications	24 (14.7)	14 (12.5)	10 (19.6)	0.24
Minor complications	37 (22.7)	24 (21.4)	13 (25.5)	0.57
Any complications	61 (37.4)	38 (33.9)	23 (45.1)	0.17

Major complications: Clavien-Dindo grade III and IV; minor complications: Clavien-Dindo grade I and II; data are n (%) unless otherwise noted. Bold face indicates $P < 0.05$

IQR interquartile range, *GE* gastroesophageal, *AJCC* American Joint Committee on Cancer

gastric cancer who received preoperative chemotherapy and underwent curative-intent surgery did not receive adjuvant chemotherapy and, therefore, did not complete their perioperative regimen. Younger patients with more advanced disease, as reflected by the lymph node involvement and tumor T classification, and those who underwent more aggressive surgical resection, as reflected by the degree of lymphadenectomy, were more likely to receive adjuvant chemotherapy. In addition, patients who experienced postoperative complications, after adjusting for other clinical factors, were four times less likely to receive their adjuvant chemotherapy treatment. Importantly, perioperative chemotherapy completion may have long-term implications for the patient's outcome; in our series, those who did not receive the postoperative component had approximately double the risk for disease recurrence and faced shorter survival.

Our findings should be interpreted in the context of the "MAGIC" trial, the hallmark randomized controlled trial of perioperative chemotherapy in the management of gastric cancer,[6] as well as the French FNCLCC and FFCD multicenter study of perioperative chemotherapy for lower esophageal and gastric cancer.[8] Similar to these studies, we found that a significant number of patients who receive preoperative chemotherapy and undergo curative-intent resection will not receive the postoperative chemotherapy component of their protocol. In our cohort, 31.5% of patients did not complete perioperative chemotherapy, a lower rate compared to the approximately 50% reported in both aforementioned trials. This discrepancy could be explained by the retrospective design of our study and our exclusion criteria. Patients with early postoperative death (within 90-days) and unknown postoperative chemotherapy status comprised approximately 20% of the original cohort in our study and were excluded to avoid any undue confounding effects on survival and to more accurately delineate predictors of perioperative chemotherapy completion, respectively. However, it is likely that most of these patients never received postoperative chemotherapy, shifting our perioperative chemotherapy completion rates closer to the "MAGIC" and the FNCLCC/FFCD trials. Furthermore, while predictors of perioperative chemotherapy completion were not analyzed in the "MAGIC" trial, the reported reasons for not starting postoperative chemotherapy are consistent with our findings: the most common ones were early death or disease progression, postoperative complications, and patient choice. Unfortunately, despite the fact that over a decade has elapsed since Cunningham et al. published their results, with the exception of the FNCLCC/FFCD trial, data regarding the use and benefit of perioperative chemotherapy as an adjunct to surgery remain limited, and to our knowledge, there is no other large series of patients, prospective or retrospective, focusing on this topic.

This study is the first to report on the actual current clinical practice in referral US surgical oncology centers with regard to perioperative chemotherapy in gastric cancer. With a paucity of data regarding the outcomes of patients receiving perioperative chemotherapy and the factors that predict treatment completion outside of clinical trials, our results offer further evidence that disease severity and postoperative complications are the primary determinants of postoperative chemotherapy administration in this population. Additionally, the multi-institutional nature of our study design reduces the potential for isolated personal or institutional treatment preferences being over-represented in the final cohort and significantly influencing the analyses. Finally, unlike analyses based on the Surveillance Epidemiology and End Results (SEER) database or other national cohorts, this study leverages the detailed patient, operative, treatment, and follow-up data of the US Gastric Cancer Collaborative, allowing for a more accurate assessment of predictors of perioperative chemotherapy completion and survival.

Several limitations need to be considered when interpreting our data. As a retrospective study, there is always the possibility of selection bias, while the multicenter nature of our cohort leads to considerable variability in the therapeutic regimens administered. However, this geographically diverse population reflects the current clinical practice in the USA

Table 2 Factors associated with completion of perioperative chemotherapy

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age < 63.3 years	2.44	1.23–4.85	**0.011**	2.73	1.10–6.80	**0.03**
Female gender	1.41	0.70–2.86	0.33			
Race						
Other race	Ref	–				
White	0.71	0.34–1.47	0.35			
Extent of resection						
Partial gastrectomy	Ref	–				
Total gastrectomy	1.23	0.62–2.45	0.55			
Splenectomy	1.76	0.62–5.04	0.29			
Lymphadenectomy						
D1	Ref	–		Ref	–	
D2	2.67	1.27–5.60	**0.009**	4.12	1.47–11.58	**0.007**
Resection margin						
R0	Ref	–		Ref	–	
R1	6.00	0.76–47.5	0.09	6.47	0.66–62.04	0.11
Tumor size ≥ 3.6 cm	1.05	0.54–2.05	0.89			
T classification						
T1	Ref	–		Ref	–	
T2	3.85	1.11–13.4	**0.034**	6.38	0.93–43.62	0.06
T3	2.71	0.95–7.72	0.06	14.27	1.1–184.65	**0.04**
T4	3.8	1.28–11.28	**0.016**	4.80	0.32–71.5	0.36
Lymph node metastasis	4.48	2.18–9.22	**< 0.001**	5.82	1.20–28.36	**0.03**
AJCC Stage						
I	Ref	–		Ref	–	
II	1.29	0.52–3.18	0.58	0.15	0.02–1.47	0.10
III	4.44	1.76–11.21	**0.002**	0.73	0.04–13.0	0.83
IV	2.11	0.36–12.35	0.41	0.20	0.01–7.6	0.38
Histological grade						
Well	Ref	–				
Moderate	1.64	0.24–11.18	0.62			
Poor	1.64	0.26–10.34	0.60			
Signet ring	0.98	0.49–1.96	0.96			
Lymphovascular invasion	1.65	0.80–3.43	0.18	0.40	0.13–1.30	0.13
Perineural invasion	0.68	0.28–1.62	0.39			
Linitis plastica	1.74	0.46–6.53	0.41			
Postoperative complications	0.63	0.32–1.23	0.17	0.25	0.09–0.70	**0.008**

Bold face indicates $P < 0.05$

OR odds ratio, *AJCC* American Joint Committee on Cancer

and, therefore, offers actual practice data that complement and validate the findings of the randomized controlled trials. In addition, even though our results indicate that perioperative chemotherapy completion is associated with reduced recurrence rates and improved survival, establishing causality was not the objective of this study and cannot be achieved with this design. The reader should be aware that while postoperative chemotherapy in patients who already received preoperative chemotherapy for gastric cancer has not been specifically studied in the past, studies have reported mixed results when evaluating the benefit from postoperative chemotherapy compared to surgery alone.[9–12] Finally, tumor regression grade after preoperative chemotherapy was not readily available for the tumors included in the study and, therefore, could not be included in the multivariable survival models.

The results of this study offer useful information to clinicians managing patients with gastric cancer. Our data highlight the deleterious effects of postoperative complications on

Table 3 Factors associated with overall survival after gastrectomy in patients who received preoperative chemotherapy

Variable			Survival analysis (Cox)		
	Median survival (months)	*P* value	HR	95% CI	*P* value
Age		0.67			
≥ 63.3 years	24.4				
< 63.3 years	34.0				
Race		0.06			
Other race	Not reached		Ref		
White	22.2		2.42	0.97–6.04	**0.06**
History of cardiac disease		0.07			
Absent	28.4		Ref		
Present	13.1		2.7	1.13–6.46	**0.03**
Splenectomy		**< 0.001**			
Not performed	28.4		Ref		
Performed	7.4		4.11	1.68–10.0	**0.002**
Lymphadenectomy		0.09			
D1	17.3		Ref		
D2	35.3		0.43	0.19–0.95	**0.04**
Resection margin		0.86			
R0	25.6				
R1	25.1				
T classification		**0.002**			
T1	84.9				
T2	Not reached				
T3	17.3				
T4	16.4				
Lymph node status		**< 0.001**			
No lymph node metastasis	84.8				
Lymph node metastasis	14.0				
AJCC Stage		**< 0.001**			
I	84.8		Ref		
II	29.2		2.62	0.99–6.94	0.053
III	15.6		4.86	1.81–13.02	**0.002**
IV	6.8		28.02	6.75–116.4	**< 0.001**
Histological grade					
Well	Not reached	**0.045**			
Moderate	47.5				
Poor	16.8				
Lymphovascular invasion		**< 0.001**			
Absent	84.8				
Present	13.3				
Perineural invasion		**0.03**			
Absent	35.3				
Present	16.4				
Linitis plastica		**0.003**			
Absent	25.8		Ref		
Present	8		2.53	0.77–8.33	0.13
Postoperative complication					
Not occurred	25.6	0.87			
Occurred	17.4				
Postoperative radiotherapy		0.89			

Table 3 (continued)

Variable			Survival analysis (Cox)		
	Median survival (months)	*P* value	HR	95% CI	*P* value
Not received	23.8				
Received	25.1				
Postoperative chemotherapy		0.98			
Not received	25.8		Ref		
Received	25.1		0.33	0.14–0.82	**0.01**

Bold face indicates $P < 0.05$

HR hazard ratio, *NS* not significant, *AJCC* American Joint Committee on Cancer

the completion of adjuvant treatments, which has been previously demonstrated by our group and others in the context of gastric cancer and other malignancies.[13–16] In addition, pending prospective validation, our results indicate that adjuvant chemotherapy in the context of a perioperative chemotherapy regimen confers survival and recurrence benefits and should be offered when possible. Particular consideration should be given to patients with stage II disease, since they seem to derive the most benefit from perioperative chemotherapy completion. Finally, our study underscores the necessity for prospective trials to assess the benefit of adjuvant chemotherapy and/or radiotherapy among patients who received preoperative chemotherapy for gastric cancer, particularly in the current era of surgical technique where D2 lymphadenectomies are more prevalent.

Conclusion

This study demonstrates that in actual clinical practice, at least one third of patients who receive preoperative chemotherapy and undergo curative-intent resection for gastric cancer will not receive the postoperative component of their regimen. As patients with more aggressive disease seemed to be more likely to complete the treatment, while those with postoperative complications were not, our results suggest that, ultimately, the management decisions with regard to the completion of perioperative chemotherapy reflect the risk-benefit calculations of the multidisciplinary treatment team. The fact that adjuvant chemotherapy administration was independently associated with reduced risk of recurrence and improved postoperative survival offers more data to help guide these decisions in the future.

Authors' Contributions Study conception and design: Karagkounis, Squires, Melis, Poultsides, Worhunsky, Jin, Fields, Spolverato, Pawlik, Votanopoulos, Levine, Schmidt, Bloomston, Cho, Weber, Berman, Pachter, Newman, Staley, Maithel, Hatzaras.

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Analysis and interpretation of data: Karagkounis, Maithel, Hatzaras.

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