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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Frequency of Resection After Preoperative Chemotherapy or Chemoradiotherapy for Gastric Adenocarcinoma

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ABSTRACT

Objective. The purpose of this study was to determine differences in stage and resection rates for patients with gastric adenocarcinoma managed with upfront surgery, preoperative chemotherapy, or preoperative chemoradiation therapy.

Methods. The medical records of 8382 patients with gastric or gastroesophageal cancer treated from January 1995 to November 2014 were reviewed. Chi square and logistic regression analysis was used to identify differences in treatment groups and variables associated with resection.

Results. Of 533 patients evaluated for gastrectomy, 174 patients underwent upfront surgery, 90 underwent preoperative chemotherapy, and 269 underwent preoperative chemoradiation therapy. Patients treated with preoperative therapy had more advanced endoscopic ultrasound and computed tomography imaging findings. Preoperative treatment was completed in 81 % of patients administered chemotherapy and 93 % of patients administered chemoradiation. Progressive, unresectable, or metastatic disease was identified in 27 % of preoperative chemotherapy and 26 % of chemoradiation patients. Toxicity or worsening comorbidities associated with an inability to undergo resection were identified in 2 % of chemotherapy patients and 6 % of chemoradiation patients. Potentially curative resection was performed in 92, 71, and 64 % of patients treated with upfront surgery, preoperative chemotherapy, and preoperative chemoradiation, respectively. For patients treated with chemoradiation, the absence of regional lymphadenopathy on imaging was the only pretreatment variable associated with resection (odds ratio 1.77, 95 % confidence interval 1.04–3.03; $p = 0.04$).

Conclusions. Patients treated with preoperative therapy often have more advanced disease prior to treatment initiation and therefore potential for disease progression. However, toxicity that prevents resection is rare, which is an important consideration in selecting preoperative treatment.

Recent National Comprehensive Cancer Network (NCCN) guidelines for the treatment of resectable gastric cancer recommend that patients be evaluated for either preoperative therapy or upfront surgery, with consideration for postoperative therapy.[1] The established treatment options, which are based on evidence from large randomized controlled trials in Western populations, include perioperative chemotherapy or adjuvant chemoradiation.[2,3] Preoperative chemoradiation therapy is also a treatment option for tumors involving the gastroesophageal junction.[4] Surgeons must currently balance several factors when devising treatment plans, such as the risk of disease progression during preoperative treatment compared with the risk of patients poorly tolerating postoperative treatment.

Because of the difficulty in administering postoperative chemotherapy and chemoradiotherapy after major abdominal surgery, some centers have used preoperative therapy for gastric cancer, particularly in patients with more advanced disease.[5–8] Several phase II clinical trials have demonstrated the feasibility, safety, and low margin-positivity rate of this

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approach.[9–11] In addition, long-term follow-up has shown excellent survival rates in patients who complete preoperative therapy and undergo resection.[12]

However, it is not yet clear which patients benefit the most from preoperative therapy. Specifically, we do not yet understand how the demographic and clinical characteristics of patients selected for upfront surgery, preoperative chemoradiation therapy, or preoperative chemotherapy may differ from one another. In addition, the percentage of patients who initiate preoperative therapy and ultimately undergo surgery and potentially curative resection is unknown. Therefore, the purpose of this study was to compare the clinical and treatment characteristics of patients who were treated with upfront surgery, preoperative chemotherapy, or preoperative chemoradiation therapy at our institution. In addition, we sought to identify variables associated with the ability to undergo potentially curative resection.

METHODS

We retrospectively reviewed a prospectively maintained database containing the records of 8382 patients with histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction who were treated at The University of Texas MD Anderson Cancer Center from January 1995 to November 2014. Patients with gastric and gastroesophageal junction Siewert type II and III adenocarcinoma with a planned gastrectomy were included.[13] We selected (i) patients with no histologic evidence of metastatic disease at diagnosis in whom upfront gastrectomy had been performed with therapeutic intent, and (ii) patients who had been treated with preoperative chemotherapy or preoperative chemoradiation therapy before a planned gastrectomy. Patients undergoing treatment for gastroesophageal junction Siewert type I and II adenocarcinoma with planned esophagectomy were excluded.[1] The study was approved by the MD Anderson Cancer Center Institutional Review Board.

The included patients were classified into three groups: (i) patients treated with upfront surgery; (ii) patients treated with preoperative systemic chemotherapy; and (iii) patients treated with preoperative chemoradiation therapy with induction chemotherapy. The demographic and clinicopathologic variables retrieved from patient records included age, sex, primary tumor location, histologic grade, signet ring cell status, T and N stages as determined by endoscopic ultrasonography (EUS), and extent of disease as determined by computed tomography (CT). The following CT observations were used to determine the extent of disease: presence of a gastric mass or gastric thickening; presence of a locally invasive primary lesion (defined as extension into the gastrohepatic ligament or adjacent organs); regional lymphadenopathy (D1 distribution); extra-regional lymphadenopathy (D1 +/D2 distribution); distant lymphadenopathy; and findings suspicious for metastases, such as trace ascites or possible carcinomatosis. The distribution of lymphadenopathy was assessed by imaging and was defined according to Japanese gastric cancer guidelines.[14]

Preoperative chemotherapy alone included regimens of epirubicin/oxaliplatin/xeloda, 5-fluorouracil/cisplatin/taxol, 5-fluorouracil/oxaliplatin/taxol, and epirubicin/cisplatin/5-fluorouracil. Radiation therapy of 45 Gy was administered for tumors that did not involve the gastroesophageal junction and 50.4 Gy for gastroesophageal primary tumors using 6–18 MV photons.[5,12] Induction chemotherapy, prior to chemoradiation, included trial protocols of 5-fluorouracil/cisplatin, 5-fluorouracil/cisplatin/taxol, 5-fluorouracil/oxaliplatin, and off-protocol treatment with these systemic agents or 5-fluorouracil/docetaxel/oxaliplatin. Chemotherapy that was administered in association with radiation therapy included a fluoropyrimidine, with or without a taxane or platinum compound.[5,12]

Treatment outcomes included completion of planned preoperative treatment, the finding of unresectable or metastatic disease on exploratory laparotomy or laparoscopy, the ability to undergo potentially curative resection, and receipt of adjuvant chemotherapy or chemoradiotherapy. Our primary outcome measure was the achievement of a potentially curative resection. Potentially curative resection was defined as a non-palliative gastrectomy with no evidence of metastatic disease present on final pathologic analysis, independent of resection (R) status or number of examined nodes. Treatment completion was defined as completion of the planned number of chemotherapy cycles (with or without dose modification) or dose of radiation therapy.

A Chi square analysis was used to compare differences among patients who were selected for upfront surgery, preoperative chemotherapy, and preoperative induction chemotherapy with chemoradiation therapy. Univariate and logistic regression analyses were used to identify variables associated with the ability to undergo potentially curative resection. All reported p values were two-sided, and statistical significance was defined as $p < 0.05$. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Our search identified 174 patients treated with upfront surgery, 90 patients treated with preoperative chemotherapy, and 269 patients treated with preoperative chemoradiation therapy, for a total of 533 included patients. The comparison of patient characteristics drawn from our medical records

TABLE 1 Clinicopathologic and treatment characteristics of the study population, stratified by treatment group

Variable	Upfront surgery ($n = 174$)		Preoperative chemotherapy ($n = 90$)		Preoperative chemoradiation ($n = 269$)		p value
	N	%	*N*	%	*N*	%	
Median age, years (range)	66.2 (24.9–88.0)		64.4 (32.5–86.7)		60.3 (20–84.09)		
Age (years)							**<0.01**
<55	44	25.3	23	25.6	87	32.3	
55 to <65	39	22.4	23	25.6	86	32.0	
≥65	91	52.3	44	48.9	96	35.7	
Sex							0.21
Female	77	44.3	39	43.3	98	36.4	
Male	97	55.7	51	56.7	171	63.6	
Location							**<0.01**
Body/antrum	145	83.3	69	76.7	150	55.8	
GEJ/cardia	29	16.7	21	23.3	119	44.2	
Histologic grade							0.09
Well/moderately differentiated	43	24.7	21	23.3	48	17.8	
Poorly differentiated	116	66.7	67	74.4	205	76.2	
Not recorded	15	8.6	2	2.2	16	6.0	
Signet ring cells							0.65
Absent	93	53.5	49	54.4	134	49.8	
Present	81	46.5	41	45.6	135	50.2	
EUS T stage							**<0.01**
1	56	32.2	1	1.1	1	0.4	
2	28	16.1	8	8.9	22	8.2	
3	43	24.7	54	60.0	191	71.0	
4	1	0.6	8	8.9	22	8.2	
Not performed/not recorded	46	26.4	19	21.1	33	12.3	
EUS N stage							**<0.01**
0	115	66.1	31	34.4	95	35.3	
1	22	12.6	31	34.4	115	42.8	
≥2	0	0.0	8	8.9	22	8.2	
Not performed/not recorded	37	21.3	20	22.2	37	13.8	
CT imaging							
Gastric mass	83	47.7	73	81.1	227	84.4	**<0.01**
Locally invasive primary lesion	4	2.3	8	8.9	21	7.8	**0.03**
Regional lymphadenopathy	25	14.4	38	42.2	132	49.1	**<0.01**
Extra-regional lymphadenopathy (D1 +/D2)	2	1.2	9	10.0	37	13.8	**<0.01**
Distant lymphadenopathy	3	1.7	5	5.6	27	10.0	**<0.01**
Findings suspicious for metastases	3	1.7	11	12.2	14	5.2	**<0.01**
Completion of preoperative treatment							**<0.01**
No	0	0.0	17	18.9	18	6.7	
Yes	0	0.0	73	81.1	251	93.3	
NA	174	100.0	0	0.0	0	0.0	
Potentially curative resection							**<0.01**
No	14	8.1	26	28.9	98	36.4	
Yes	160	92.0	64	71.1	171	63.6	
Exploratory surgery with unresectable or metastatic disease							**<0.01**
No	168	96.6	87	96.7	236	87.7	
Yes	6	3.5	3	3.3	33	12.3	

TABLE 1 continued

Variable	Upfront surgery ($n = 174$)		Preoperative chemotherapy ($n = 90$)		Preoperative chemoradiation ($n = 269$)		p value
	N	%	*N*	%	*N*	%	
Adjuvant chemotherapy							**<0.01**
No	155	89.1	60	66.7	267	99.3	
Yes	19	10.9	30	33.3	2	0.7	
Adjuvant chemoradiotherapy							**<0.01**
No	149	85.6	79	87.8	269	100.0	
Yes	25	14.4	11	12.2	0	0.0	

Bold values indicate $p < 0.05$

GEJ gastroesophageal junction, *EUS* endoscopic ultrasonography, *CT* computed tomography, *NA* not applicable

indicated that patients in the three treatment groups differed significantly across many variables (Table 1). Records showed that patients treated with upfront surgery were significantly older and more frequently had distally located tumors (in the body or antrum) than those treated with preoperative therapy. Patients treated with preoperative chemotherapy or chemoradiation therapy had more advanced tumors according to pretreatment EUS T and N staging and CT imaging characteristics. Preoperative treatment was completed in 81 % of patients who received preoperative chemotherapy and 93 % of patients who received preoperative chemoradiation therapy. A potentially curative resection was performed in 92, 71, and 64 % of patients treated with upfront surgery, preoperative chemotherapy, and preoperative chemoradiation therapy, respectively. Only 101 patients treated with preoperative surgery had recommendations for adjuvant treatment, of which 44 received chemotherapy ($n = 19$) or chemoradiotherapy ($n = 25$). Of patients treated with preoperative chemotherapy, 33 % also received postoperative chemotherapy and 12 % received postoperative chemoradiotherapy.

Figure 1 illustrates the treatment patterns and pathways to potentially curative resection in the study cohort. Unresectable or metastatic disease was identified at surgery in 14 (8 %) patients treated with upfront surgery, 7 (8 %) patients treated with preoperative chemotherapy, and 38 (14 %) patients treated with preoperative chemoradiation therapy. The unresectable or metastatic disease noted at surgery was primarily metastatic, with 5 of 7 (71 %) patients treated with preoperative chemotherapy and 36 of 38 (95 %) patients treated with preoperative chemoradiation having distant disease. Progressive disease was noted on imaging in 17 (19 %) and 32 (12 %) patients treated with preoperative chemotherapy and preoperative chemoradiation therapy, respectively. The progressive disease on imaging was also primarily metastatic, rather than locally advanced, with 16 of 17 (94 %) patients treated with chemotherapy and 31 of 32 (97 %) patients treated with chemoradiation demonstrating distant disease. Toxicity or worsening comorbidities prevented 2 (2 %) patients treated with preoperative chemotherapy and 15 (6 %) patients treated with preoperative chemoradiation therapy from undergoing resection.

Our analysis then identified several variables that were significantly associated with the ability to undergo potentially curative resection in the entire study cohort. As expected, univariate analysis of the entire cohort (patients who received upfront surgery and those who received preoperative therapy) demonstrated that tumors located in the body or antrum and EUS T stage I or II disease, EUS N stage 0 disease, and a lack of CT imaging findings indicative of metastasis at pretreatment assessment were significantly associated with the achievement of potentially curative resection (Table 2). Multivariate analysis of the entire cohort also demonstrated that EUS T stage I or II disease, lack of regional lymphadenopathy on CT imaging, and lack of CT findings suspicious for metastatic disease at diagnosis were significantly associated with potentially curative resection (Table 3). Patients treated with upfront surgery were more likely to undergo resection when compared with patients treated with preoperative chemoradiation therapy.

Fewer significant variables were found when the analysis was limited to patients who underwent preoperative treatment with either preoperative chemotherapy or preoperative chemoradiation therapy (Table 2). In patients who received either kind of preoperative treatment, absence of regional lymphadenopathy and lack of CT findings suspicious for metastatic disease were associated with achievement of potentially curative resection. On multivariate analysis of the entire cohort, we found that patients who were treated with preoperative chemotherapy were no more likely to undergo potentially curative resection than were patients in the preoperative chemoradiation therapy group (Table 3). On multivariate analysis of patients treated with either type of preoperative therapy (preoperative chemotherapy or preoperative chemoradiation therapy), younger age, absence of

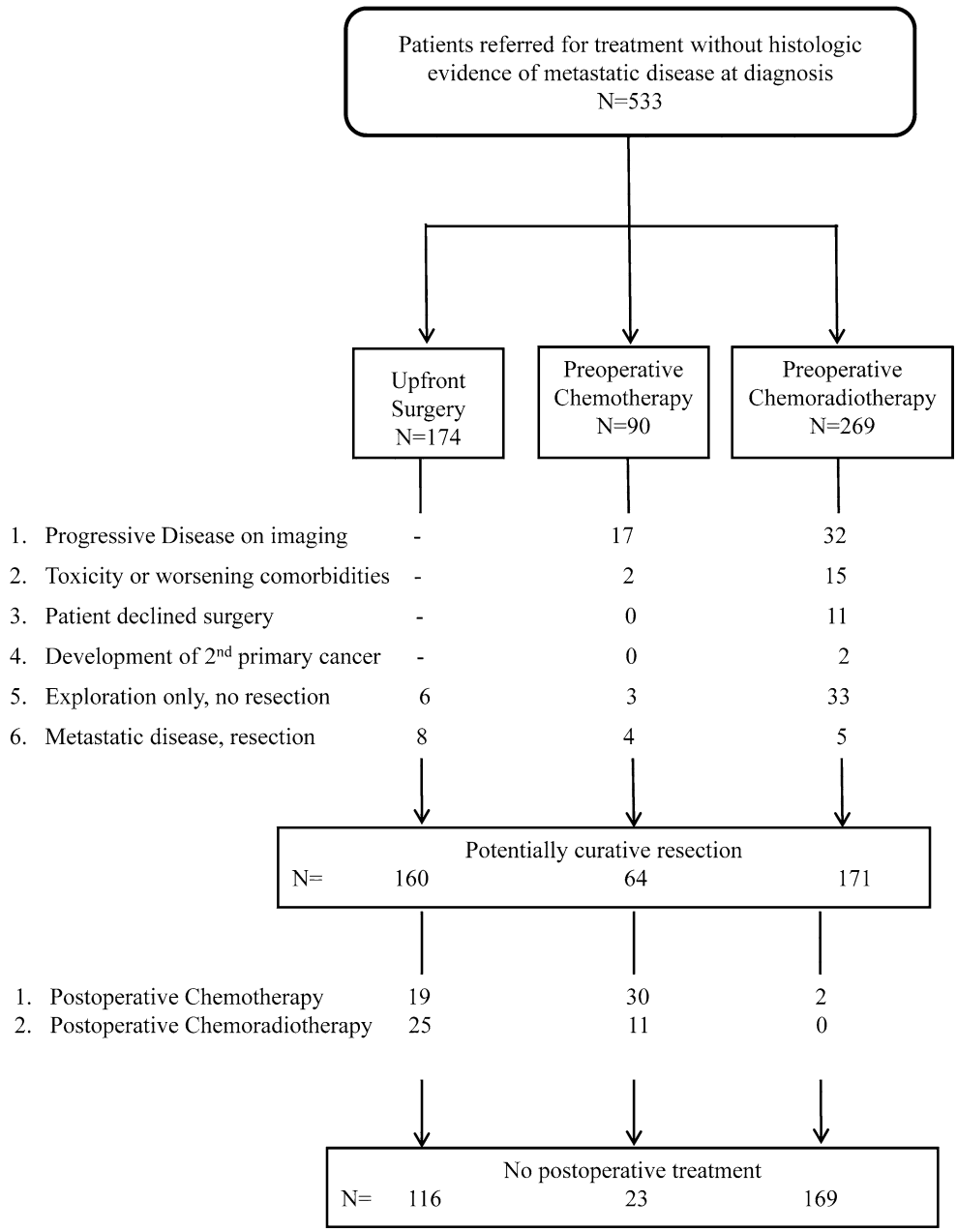

FIG. 1 Resection and treatment patterns for patients with gastric and gastroesophageal adenocarcinoma managed with upfront surgery, preoperative chemotherapy, or preoperative chemoradiotherapy

regional lymphadenopathy, and lack of CT findings suspicious for metastatic disease were associated with potentially curative resection. When we limited the multivariate analysis to the group treated with preoperative chemoradiation therapy, only the absence of regional lymphadenopathy was associated with achievement of potentially curative resection.

DISCUSSION

In this retrospective study of patients with gastric and gastroesophageal cancer who underwent evaluation for treatment and gastrectomy, we identified several significant differences among patients who were selected for upfront surgery, preoperative chemotherapy, and preoperative chemoradiation therapy. The potential for finding metastatic disease at attempted resection, preoperative treatment completion rates, and frequency of adjuvant therapy administration have been provided for the three main approaches to the treatment of gastric cancer. We focused on the outcome measure of potentially curative resection because it is the most important surgical variable affecting long-term survival rates.

NCCN guidelines propose three main treatment options for medically fit patients with potentially resectable gastric cancer: upfront surgery, preoperative chemotherapy, or preoperative chemoradiation therapy.[1] The NCCN

TABLE 2 Univariate analysis of factors associated with the ability to undergo potentially curative resection

Variable	All patients			Preoperative chemotherapy or preoperative chemoradiation			Preoperative chemoradiation		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value	OR	95 % CI	*p* value
Age, years (ref. <55 years)			**0.02**			**0.04**			0.29
55 to <65	0.56	0.34–0.93		0.50	0.28–0.87		0.62	0.33–1.17	
≥65	1.01	0.62–1.65		0.74	0.43–1.28		0.68	0.37–1.26	
Sex (ref. male)			**0.02**			0.15			0.13
Female				1.40	0.89–2.21		1.50	0.88–2.54	
Location (ref. GEJ/cardia)			**<0.01**			**<0.01**			**0.01**
Body/antrum	2.29	1.53–3.42		2.01	1.29–3.14		1.87	1.13–3.10	
Grade (ref. poorly differentiated)			0.35			0.71			0.71
Well/moderately differentiated	1.40	0.84–2.31		1.27	0.72–2.24		1.32	0.68–2.59	
Not recorded	1.41	0.60–3.36		1.11	0.40–3.05		1.00	0.35–2.87	
Signet ring cells (ref. absent)			0.20			0.08			0.29
Present	1.29	0.88–1.91		1.47	0.95–2.28		1.31	0.80–2.15	
EUS T stage (ref. III/IV)			**<0.01**			0.06			0.16
I/II	8.62	3.67–20.25		2.99	1.12–8.01		2.92	0.96–8.87	
Not performed/not recorded	1.07	0.65–1.74		0.82	0.45–1.50		0.94	0.45–2.00	
EUS N stage (ref. N+)			**<0.01**			0.16			0.59
N0	2.73	1.73–4.31		1.43	0.87–2.34		1.13	0.65–1.96	
Not performed/not recorded	0.95	0.56–1.58		0.79	0.43–1.44		0.75	0.36–1.58	
CT imaging (ref. findings present)									
No gastric mass	2.53	1.53–4.18	**<0.01**	0.87	0.49–1.55	0.63	0.82	0.42–1.60	0.55
No locally invasive primary lesion	2.91	1.43–5.94	**<0.01**	1.60	0.75–3.45	0.23	0.86	0.34–2.22	0.76
No regional lymphadenopathy (D1)	3.22	2.16–4.81	**<0.01**	2.04	1.31–3.17	**<0.01**	1.78	1.08–2.94	**0.02**
No extra-regional lymphadenopathy (D1 +/D2)	2.02	1.09–3.73	**0.03**	1.39	0.74–2.62	0.30	1.22	0.60–2.49	0.58
No distant lymphadenopathy	2.01	0.99–4.07	0.05	1.53	0.74–3.20	0.25	1.03	0.45–2.35	0.94
No findings suspicious for metastases	4.90	2.24–10.76	**<0.01**	3.10	1.35–7.12	**<0.01**	2.44	0.82–7.26	0.11
Treatment (ref. preoperative chemoradiation therapy)			**<0.01**			0.19			
Upfront surgery	6.55	3.59–11.94							
Preoperative chemotherapy	1.41	0.84–2.37		1.41	0.84–2.37				

Bold values indicate $p < 0.05$

OR odds ratio, *CI* confidence interval, *GEJ* gastroesophageal junction, *EUS* endoscopic ultrasonography, *CT* computed tomography

recommendation for upfront surgery with consideration for postoperative chemoradiation therapy is based on Intergroup Study 0116, a randomized clinical trial that demonstrated a 9 % benefit in 3-year overall survival rates in patients treated with adjuvant chemoradiation.[2] Upfront D2 gastrectomy with adjuvant chemotherapy is also an accepted treatment modality in the NCCN guidelines, based on the results of a trial conducted in South Korea, China, and Taiwan.[15] Alternatively, preoperative chemotherapy, as part of a perioperative chemotherapy approach, has been shown (by the Medical Research Council Adjuvant Gastric Infusional Chemotherapy [MAGIC] Trial) to provide a 13 % improvement in 5-year overall survival rates.[3] The usefulness of preoperative chemoradiation in treating gastroesophageal junction cancers has been established by the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS)0.[4] Smaller phase II clinical trials have also provided evidence in support of the use of preoperative chemoradiation in the treatment of gastric cancer.[9] Because all the available studies of preoperative and postoperative treatments have their own limitations, there is currently no single accepted standard of treatment for gastric cancer. When choosing an initial treatment, physicians must balance the risk of disease progression and treatment resistance during preoperative treatment against the risk of patients poorly tolerating postoperative treatment after upfront surgery.

Several studies have shown that patients often have difficulty tolerating adjuvant therapy after gastrectomy. Only 64 % of patients in Intergroup Study 0116 completed treatment as planned, even after meeting the study's inclusion criteria—confirmation of recovery from surgery and adequate nutritional intake.[2] In the MAGIC trial, 103 of 208 (50 %) patients who completed preoperative

TABLE 3 Multivariate analysis of factors associated with the ability to undergo potentially curative resection

Variable	All patients			Preoperative chemotherapy or preoperative chemoradiation			Preoperative chemoradiation		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value	OR	95 % CI	*p* value
Age, years (ref. <55 years)			**0.02**			**0.02**			0.15
55 to <65	0.46	0.26–0.81		0.42	0.23–0.77		0.54	0.28–1.05	
≥65	0.76	0.44–1.32		0.62	0.35–1.12		0.59	0.31–1.13	
Sex (ref. male)			0.09			0.33			0.23
Female	1.48	0.94–2.32		1.27	0.78–2.06		1.40	0.81–2.42	
EUS T stage (ref. III/IV)			**<0.01**			0.17			0.38
I/II	2.66	1.04–6.80		1.74	0.62–4.90		2.10	0.66–6.70	
Not performed/not recorded	0.52	0.29–0.93		0.63	0.33–1.20		0.83	0.38–1.80	
CT imaging (ref. findings present)									
No regional lymphadenopathy	2.10	1.34–3.31	**<0.01**	2.03	1.26–3.28	**<0.01**	1.77	1.04–3.03	**0.04**
No findings suspicious for metastases	3.82	1.66–8.78	**<0.01**	3.35	1.40–7.98	**0.01**	2.58	0.84–7.84	0.09
Treatment (ref. preoperative chemoradiation)			**<0.01**			0.10			–
Upfront surgery	4.36	2.18–8.69		–	–		–	–	
Preoperative chemotherapy	1.61	0.91–2.84		1.60	0.91–2.80		–	–	

Bold values indicate $p < 0.05$

OR odds ratio, *CI* confidence interval, *EUS* endoscopic ultrasonography, *CT* computed tomography

chemotherapy and surgery also completed postoperative chemotherapy.[3] The CROSS trial showed that 161 (94 %) of 171 patients who received preoperative chemoradiotherapy underwent resection. However, it should be noted that these results may not be generalizable to patients undergoing gastrectomy as the majority of patients in the CROSS trial underwent transhiatal or transthoracic esophagectomy with gastric tube reconstruction and a cervical anastomosis.[4]

High-quality population-based and multi-institutional studies also provide information regarding therapy completion rates after gastrectomy. Such studies are critical for incorporating the results of randomized clinical trials into clinical practice. A study of patients with gastric cancer from the National Cancer Data Base found that 34 % of patients with stage III gastric cancer received surgery alone during the years 2005–2007.[16] In a study of 271 Danish patients referred for evaluation for preoperative chemotherapy for lower esophageal, gastroesophageal junction, and gastric cancer, 87 % completed preoperative chemotherapy, 86 % underwent surgery, and 49 % initiated postoperative chemotherapy.[17] A notable finding in the Danish study was that only 33 % of the intent-to-treat population completed the full perioperative treatment, including surgery.[17]

Although the difficulties that may arise in postoperative therapy administration have been clearly established, the risk of disease progression during preoperative therapy must be more thoroughly assessed.[18] In the MAGIC trial, 37 of the 250 (15 %) patients assigned to perioperative chemotherapy did not receive postoperative chemotherapy owing to disease progression or early death.[3] However, in the CROSS trial of preoperative chemoradiation therapy, only 7 of 180 (4 %) patients did not undergo surgery because their disease progressed during preoperative treatment.[4] Population-based studies suggest that the disease progression rate is on the order of 13 %.[17]

One of the most important findings in our study is that we provide further information regarding patients' tolerance of preoperative therapy. We found low rates of intolerance of preoperative chemotherapy and inability to proceed with resection: only 2 of 90 (2 %) patients did not undergo resection because of toxicity or worsening comorbidities. However, compared with those who underwent preoperative chemotherapy, patients who were treated with preoperative chemoradiation showed a higher rate of toxicity or worsening comorbidities that precluded attempted resection (6 %). Our study also contributes to the body of research on the perioperative treatment of gastric cancer by assessing the frequency of progressive disease associated with initial disease staging. In our study, patients treated with upfront surgery had significantly earlier disease stage, as determined by EUS and CT imaging, than those treated with preoperative therapy. As we expected, this cohort had a relatively low rate (8 %) of unresectable or metastatic disease that prevented potentially curative resection. However, patients treated with preoperative chemotherapy—who typically had more advanced-stage disease—had a 27 % rate of progressive, unresectable, or metastatic disease. Patients treated with preoperative chemoradiation also had a high rate of progressive, unresectable, or metastatic disease (26 %), although,

as for patients treated with preoperative chemotherapy alone, this may reflect the more advanced disease stage typical of these patients in addition to the potential for treatment resistance. Clearly, better predictors of which tumors will respond to preoperative treatment are needed to more accurately identify those patients who should be treated with upfront surgery. Our data on toxicity and progressive disease rates can help inform future comparisons of treatment approaches and address the inherent selection bias in comparing survival outcomes.

CONCLUSIONS

Patients treated with preoperative chemotherapy or chemoradiation therapy may be at risk for disease progression, even though resection is rarely precluded because of toxicity. Because these patients often initiate therapy with more advanced disease, initial imaging findings are the most important factors to consider in identifying patients who are unlikely to undergo potentially curative resection. Future studies are needed to identify variables associated with resistance to preoperative chemotherapy and chemoradiation therapy to improve upon the current high rates of progressive disease. Efforts to minimize toxicity will likely have many benefits but may not have a significant impact on resection rates.

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