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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Characteristics and Survival of Gastric Cancer Patients with Pathologic Complete Response to Preoperative Therapy

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ABSTRACT

Background. Pathologic complete response of a primary tumor (ypT0) after preoperative therapy is associated with improved overall survival (OS). However, whether other variables are associated with outcome for gastric cancer patients with ypT0 status is unknown.

Methods. This study reviewed an institutional database of patients who underwent resection of gastric or gastroesophageal adenocarcinoma after preoperative therapy and identified patients with ypT0 status. Cox regression models were used to identify clinicopathologic predictors of OS.

Results. Of 77 patients with ypT0 status identified in this study, 36 (47%) had gastroesophageal junction tumors. At presentation, 62 patients (81%) had clinical T3 disease, and 7 (9%) had clinical T4 disease. The clinical nodal status was positive (cN+) for 45 patients (58%). Preoperative chemoradiation was administered to 75 patients (97%). The median follow-up duration was 3.54 years. The median OS was 10 years, and the 5-year OS rate was 61%. Univariable analysis identified age of 65 years or older at the time of diagnosis, histologic grade, and ypN status as significant predictors of OS. Multivariable analysis confirmed age of 65 years or older [hazard ratio (HR), 4.26; $p < 0.001$] and persistent nodal disease (ypN+ status; HR, 5.12; $p < 0.001$) to be independently associated with OS. Clinical stage was not associated with survival. In the subset of ypT0N0 patients, no clinicopathologic feature was predictive of survival.

Conclusion. For gastric or gastroesophageal adenocarcinoma patients with ypT0 status after preoperative therapy, ypN+ status substantially reduced survival. Pretreatment clinical stage had no impact on OS for patients with a pathologic complete response.

The American Joint Committee on Cancer's *AJCC Cancer Staging Manual,* eighth edition separated clinical tumor-node-metastasis (cTNM) from pathologic (pTNM) stage and introduced a new post-neoadjuvant therapy pathologic stage (ypTNM).[1] The latter classification is especially useful in the treatment of patients with resectable gastric and gastroesophageal adenocarcinoma, for whom preoperative chemotherapy, chemoradiation, or both have increasingly become recognized as the standard of care.[2–5]

Currently, posttreatment resected specimens are evaluated for the degree of response to therapy. Those with no viable tumor cells in the primary tumor are given ypT0 designation and considered to have a primary tumor pathologic complete response. Those with no viable tumor

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in the primary tumor or lymph nodes are regarded as having ypT0N0 status. The 8–20% of gastric and gastroesophageal cancer patients who achieve a pathologic complete response to therapy have better long-term survival outcomes than the patients who do not.[6–12] We have previously published the rate of ypT0 at our institution (16%).[6] However, despite a demonstrable survival benefit, a pathologic complete response is not synonymous with cure. A small series of gastric cancer patients with ypT0N0 status found a 15% mortality rate and a 25% recurrence rate at 5 years.[13] A larger series in a similar population demonstrated a 27% recurrence rate at 5 years.[9] Little is known about the determinants of outcome in this subpopulation of patients. We undertook the current study to determine the specific factors associated with outcome for gastric and gastroesophageal adenocarcinoma patients who undergo surgery with curative intent and are found to have a pathologic complete response to preoperative therapy in the primary tumor.

METHODS

With institutional review board approval, we reviewed data from a prospectively maintained database of patients with primary gastric and gastroesophageal adenocarcinoma who underwent surgery with curative intent at our institution between 1996 and 2016. We identified all the patients who achieved a primary tumor pathologic complete response after preoperative therapy and included them in this study. Patients with a history of gastrectomy were excluded from the analysis.

The variables collected were age, sex, race/ethnicity, date of diagnosis, date of surgery, date of recurrence (if any), date of death or last follow-up visit, histologic grade, signet ring cell morphology, tumor location, clinical TNM stage, preoperative radiation therapy, type of surgical resection, extent of lymph node dissection (D1 vs. D1+/D2), number of lymph nodes examined, need for concomitant organ resection, and posttreatment pathology. We have previously published our method for determining clinical TNM stage based on preoperative endoscopic ultrasonography, computed tomography, and positron emission tomography, as well as the routine performance of pretreatment staging laparoscopy.[6]

Statistical Analysis

Chi square analysis was performed to identify differences in characteristics between the ypT0N0 and ypT0N+ patients. We defined overall survival (OS) as the period between the date of diagnosis and the date of death. Those alive or lost to follow-up evaluation were censored at the time of the last known follow-up visit.

Uni- and multivariable Cox regression analyses were used to estimate hazard ratios (HRs) and 95% confidence intervals to identify clinicopathologic factors associated with an increased risk of death. We estimated 5-year OS using the Kaplan–Meier method and created survival curves stratified by TNM stage and ypN status. These were compared using the log-rank test. We performed an additional in-depth review of the medical record to further characterize patients with persistent positive nodal disease (ypT0N+ status).

We considered p values lower than 0.05 to be significant. All analyses were performed using SAS version 9.4 (SAS, Cary, NC, USA).

RESULTS

We identified 77 patients with ypT0 status after preoperative therapy. Patient and tumor characteristics are summarized in Table 1. The patients were predominantly white (67.5%) and male (72.7%). In terms of age, 31 patients were at least 65 years old (40.3%). Preoperative biopsy demonstrated that the majority of the patients had poorly differentiated (59.7%) or moderately differentiated (29.9%) tumors.

Signet ring cell morphology was present in 16 of the patients (20.1%). The most common tumor locations were the gastroesophageal junction (46.8%) and the gastric body (27.3%). The cohort included 8 patients (10.4%) with cT2 disease and 62 patients (80.5%) with cT3 disease. Notably, seven patients (9.1%) with cT4 disease also achieved ypT0 status. The majority of the patients (58.4%) had clinical evidence of nodal disease (cN+ status).

All the patients received preoperative therapy, and all but two patients received radiation therapy according to previously published techniques.[14] The most common resections performed were total gastrectomy (39%) and esophagectomy (Ivor-Lewis, 22.1%; transhiatal, 2.6%). Concomitant en bloc adjacent organ resection was necessary for removal of the primary tumor in 8 cases (10.4%), and 57 patients (74%) had an extended (i.e., D1+ or D2) lymph node dissection.

The number of nodes examined was 16 or more for 61% of the patients, and 87% of the patients had negative (ypN0) nodal status after treatment. According to Chi square analysis, the ypT0N+ patients were more likely than the ypT0N0 patients to have cM1 status, to require en bloc concomitant organ resection, and to have fewer than 16 lymph nodes examined.

TABLE 1 Patient and tumor characteristics

Variable	All patients (n = 77) n (%)	ypT0N0 (n = 67) n (%)	ypT0N+ (n = 10) n (%)	p value
Age (years)				0.299
≥ 65	31 (40.3)	29 (43.3)	2 (20.0)	
Sex				0.447
Female	21 (27.3)	17 (25.4)	4 (40.0)	
Male	56 (72.7)	50 (74.6)	6 (60.0)	
Race/ethnicity				0.591
White	52 (67.5)	46 (71.6)	6 (60.0)	
Black	5 (6.5)	4 (6.0)	1 (10.0)	
Asian	5 (6.5)	4 (6.0)	1 (10.0)	
Hispanic/Latino	15 (19.5)	13 (19.4)	2 (20.0)	
Tumor location				0.808
GEJ	36 (46.8)	30 (44.8)	6 (60.0)	
(Siewart 2)	19 (24.7)	17 (25.4)	2 (20.0)	
(Siewart 3)	17 (22.1)	13 (19.4)	4 (20.0)	
Cardia	6 (7.8)	6 (9.0)		
Body	21 (27.3)	18 (26.9)	3 (30.0)	
Antrum	14 (18.2)	13 (19.4)	1 (10.0)	
Histologic grade				0.416
Well-differentiated	1 (1.3)	1 (1.5)		
Moderately differentiated	23 (29.9)	18 (26.9)	5 (50.0)	
Poorly differentiated	46 (59.7)	39 (58.2)	5 (50.0)	
Unknown	7 (9.1)	7 (10.4)		
Signet ring cell morphology	16 (20.1)	14 (20.9)	2 (20.0)	0.999
cT category				0.827
1				
2	8 (10.4)	7 (10.4)	1 (10.0)	
3	62 (80.5)	53 (79.1)	9 (90.0)	
4	7 (9.1)	7 (10.4)		
cN status				0.181
Negative	32 (41.6)	30 (44.8)	2 (20.0)	
Positive	45 (58.4)	37 (55.2)	8 (80.0)	
cM category				0.025
0	72 (93.5)	64 (95.5)	8 (80.0)	
1 (cytology-positive)	2 (2.6)	2 (3.0)		
1 (paraaortic lymph node)	3 (3.9)	1 (1.5)	2 (20.0)	
Preoperative radiation therapy				0.999
Yes	75 (93.4)	65 (97.0)	10 (100.0)	
No	2 (2.6)	2 (3.0)		
Type of resection				0.213
Total gastrectomy	30 (39.0)	26 (38.8)	4 (40.0)	
Subtotal gastrectomy	23 (30.0)	22 (32.8)	1 (10.0)	
Proximal gastrectomy	5 (6.5)	3 (4.5)	2 (20.0)	
Ivor-Lewis esophagectomy	17 (22.1)	14 (20.9)	3 (30.0)	
Transhiatal esophagectomy	2 (2.6)	2 (3.0)		
Concomitant organ resection				0.044
Yes	8 (10.4)	4 (6.0)	4 (40.0)	
Pancreatectomy	3 (3.9)	2 (3.0)	1 (10.0)	
Splenectomy	3 (3.9)	2 (3.0)	1 (10.0)	

TABLE 1 continued

Variable	All patients (n = 77) n (%)	ypT0N0 (n = 67) n (%)	ypT0N+ (n = 10) n (%)	p value
Hepatectomy	3 (2.6)	1 (1.5)	2 (20.0)	
Colon/small bowel	1 (1.3)	1 (1.5)		
Extent of LN dissection				0.275
D1	20 (26.0)	16 (23.9)	4 (40.0)	
D1+/D2	57 (74.0)	51 (76.1)	6 (60.0)	
No. of LNs examined				0.041
< 16	30 (39.0)	23 (34.3)	7 (70.0)	
≥ 16	47 (61.0)	44 (65.7)	3 (30.0)	
ypN status				–
Negative	67 (87.0)	67 (100.0)		
Positive	10 (13.0)		10 (100.0)	

GEJ gastroesophageal junction, *LN* lymph node

The median follow-up period for the entire cohort was 3.5 years. The median OS was 10.0 years, and the 5-year OS rate was 61.2%. For the patients with ypT0N0 status, the median OS was 10.2 years, and the 5-year OS rate was 68.8%. In contrast, the patients with ypT0N+ status had a median OS of 2.56 years and a 5-year OS rate of 22.9%.

Survival estimates for the ypT0 patients via the Kaplan–Meier method are shown in Fig. 1. Stratification by preoperative clinical *T*, *N*, and *M* categories demonstrated no differences in OS. In contrast, stratification by posttreatment nodal status showed that the ypT0N0 patients experienced significantly longer survival than the ypT0N+ patients (p = 0.019).

Uni- and multivariable Cox regression analyses for OS are shown in Table 2. Among other variables, clinical stage was not associated with OS. Whereas age, histologic grade, and ypN category were associated with OS in the univariable analysis, only age (HR, 4.26; p <0.001) and ypN category (HR, 5.12; p <0.001) were independently associated with OS in the multivariable analysis. In the cohort of patients with ypT0N0 disease, no preoperative clinicopathologic variable other than age was associated with OS in the univariable Cox regression analysis (Table S1).

Residual carcinoma was identified in the regional lymph nodes of 10 patients despite achievement of a complete pathologic response in the primary tumor. Additional characteristics of these ypT0N+ patients are shown in Table 3. Among these 10 patients, 8 had cN+ disease, 6 had gastroesophageal junction tumors, and 6 had poorly differentiated tumors. Those who underwent surgery before 2000 received preoperative chemoradiation alone, whereas those after 2000 received chemotherapy followed by chemoradiation. Seven patients, showed clear evidence of a treatment effect in the examined nodes. All but two of the ypT0N+ patients experienced distant recurrence, with the time to recurrence ranging from 0.4 to 3.3 years. The OS for the patients with disant recurrence ranged from 1.4 to 4.7 years, whereas those without recurrence showed survival longer than 8 years at the time of the last follow-up evaluation.

DISCUSSION

In this single-institution study we performed a focused investigation into the determinants of OS in the specific subgroup of gastric and gastroesophageal cancer patients with compete pathologic response in the primary tumor. We found only age and ypN status to be predictors of OS. The pretreatment/preoperative characteristics of our ypT0 patient population were similar to those in other published series of patients with pathologic complete response.[9]

The clinical stage of the ypT0 patients varied widely. Our cohort included patients with clinical T4 disease as well as those who required concomitant en bloc organ resection at the time of surgery. Most of the patients (58.4%) were clinically staged with cN+ disease, yet only 13% had persistent nodal disease after neoadjuvant therapy (ypN+ status).

Our data highlight the overall excellent prognosis of the ypT0 patients. The median OS for the patents with pathologic complete response was 10 years. This is markedly better than that seen for all patients with resectable disease who undergo preoperative chemoradiation followed by surgery (median OS, 5.8 years).[12] We found that no preoperative clinicopathologic factor other than age was associated with OS, including clinical nodal status and other components of clinical stage.

Conversely, ypN status had a significant and sizeable effect on OS (HR, 5.12). The patients with ypT0N+ status had a median OS of 2.56 years, compared with a median

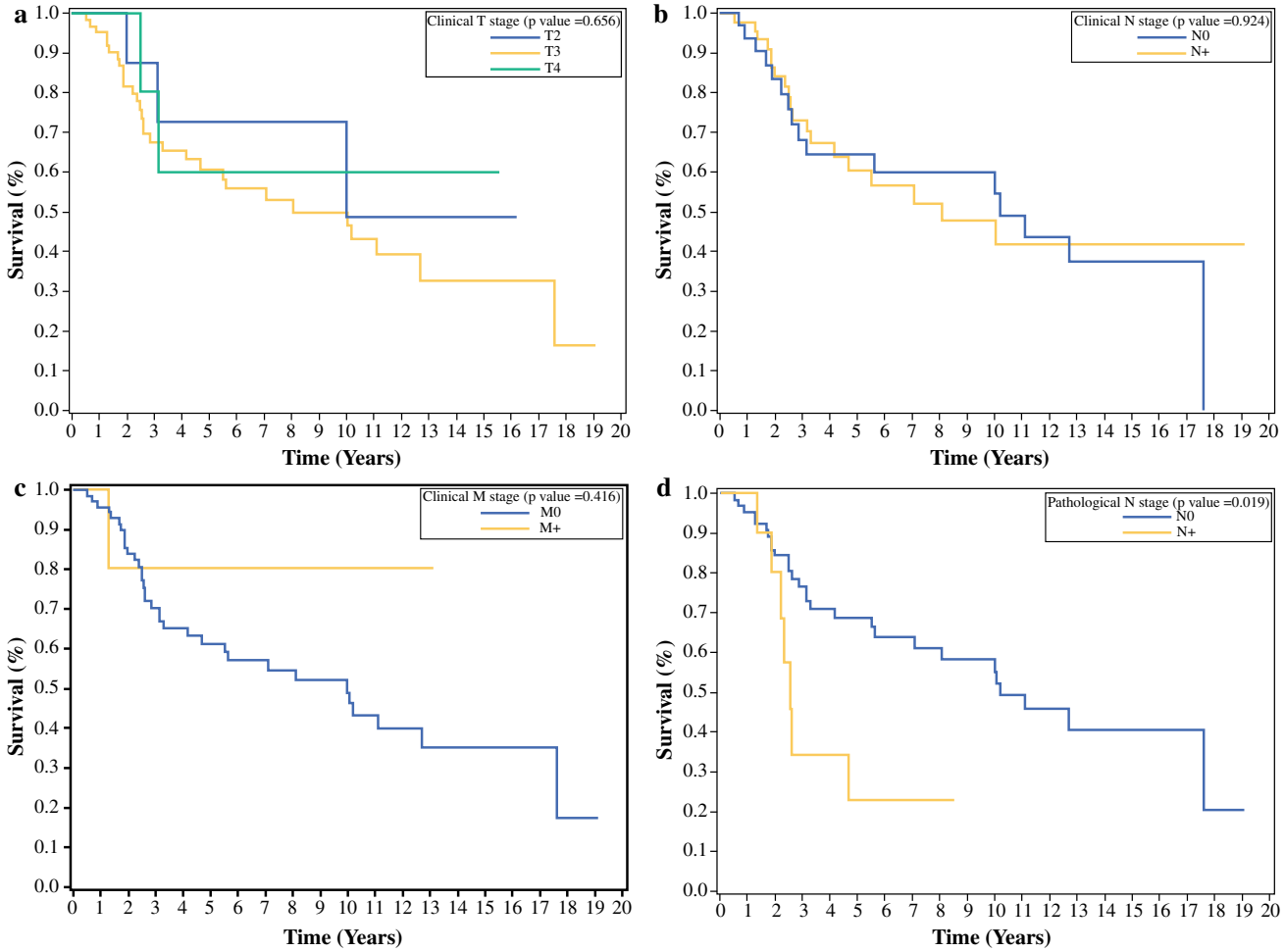

FIG. 1 Kaplan-Meier overall survival curves for patients with ypT0 status. The curves are stratified by clinical **a** *T*, **b** *N*, and **c** *M* categories and **d** posttreatment nodal stage (ypN)

OS of 10.2 years for those with ypT0N0 status. Among the ypT0N0 patients, none of the clinicopathologic factors studied were independently associated with OS except age, which is likely the main determinant of OS in this cohort with excellent oncologic outcome.

We have previously demonstrated that the presence or absence of viable tumor in the primary lesion (ypT0–T3) has no impact on OS as long as the treated nodes are negative (ypN0).[15] Furthermore, we also have shown that patients with nodal downstaging [i.e., patients with clinically positive but pathologically negative nodes after preoperative therapy (cN+/ypN0 status)] have survival outcomes similar to those of patients with clinically and pathologically negative nodes (cN0/ypN0 status).[16] These studies and the current study add to a growing body of literature that emphasizes the critical importance of ypN status in determining the prognosis for patients with gastric and gastroesophageal cancer. A post hoc analysis in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial demonstrated an apparent increase in OS associated with increasing primary tumor response to chemotherapy (analyzed as tumor regression grades 1–5 based on the degree of response). However, this effect was dependent on lymph node status, which was a much stronger and independent predictor of survival in that cohort.[17]

A large National Cancer Database series of 5058 gastric and gastroesophageal cancer patients demonstrated a survival advantage for patients who received preoperative chemotherapy compared with those who received postoperative chemoradiation therapy alone. This survival advantage was associated with a statistically significant difference in the number of patients with clearance or downstaging of lymph node disease.[18] Achieving a response to therapy in nodal disease may therefore be the factor that ultimately determines prognosis.

TABLE 2 Uni- and multivariable Cox analyses of overall survival for ypT0 patients (n = 77)

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis (≥ 65 vs. < 65 years)	2.98 (1.49–5.97)	**0.002**	4.26 (1.99–9.13)	< **0.001**
Sex (female vs. male)	0.82 (0.39–1.73)	0.606		NS
Race/ethnicity (ref. white)		0.854		NS
Black	0.89 (0.12–6.62)	0.907		NS
Asian	0.72 (0.28–1.90)	0.512		NS
Hispanic/Latino	0.62 (0.15–2.62)	0.526		NS
Tumor location (GEJ vs. other)	1.15 (0.59–2.24)	0.679		NS
Histologic grade (ref. moderately differentiated)		**0.016**		NS
Poorly vs. well-/moderately differentiated	0.39 (0.19–0.81)	0.011		NS
Unknown vs. well-/moderately differentiated	0.24 (0.07–0.87)	0.030		NS
Signet ring cells (present vs. absent)	0.44 (0.18–1.08)	0.075		NS
Clinical T category (ref. T2)		0.612		NS
T3	1.65 (0.50–5.43)	0.409		NS
T4	1.06 (0.18–6.33)	0.953		NS
Clinical N category (positive vs. negative)	0.97 (0.49–1.90)	0.924		NS
ypN category ((N+ vs. N0)	2.69 (1.14–6.33)	**0.024**	5.12 (1.97–13.32)	< **0.001**
Concomitant organ resection (yes vs. no)	1.93 (0.89–4.17)	0.095		NS
Type of resection (esophagectomy vs. gastrectomy)	0.87 (0.40–1.87)	0.720		NS
No.of lymph nodes examined (≥ 16 vs. < 16)	0.60 (0.31–1.17)	0.135		NS

p values < 0.05 are given in bold

HR hazard ratio, *CI* confidence interval, *NS* not significant, *GEJ* gastroesophageal junction

All but 2 patients received neoadjuvant chemoradiation, so this variable was removed from the model

In light of the aforementioned findings, gastric and gastroesophageal cancer patients with ypT0N+ disease represent an intriguing population. These patients have manifested a dramatic response to preoperative chemotherapy, as evidenced by the primary tumor, yet have retained nodal disease. In our cohort, it appears that the ypT0N+ patients also largely demonstrated some response to treatment in the regional lymph nodes (7 of 10 confirmed) but lacked a complete response. This residual, viable nodal disease is associated with and may ultimately drive early distant recurrence and poor outcome. Little is understood about the difference in tumor biology that accounts for resistance to therapy in nodal disease, particularly in cases of primary tumors that have a pathologic complete response.

In the current series, none of the ypT0N+ patients received adjuvant therapy. Some data suggest that gastroesophageal cancer patients who receive neoadjuvant therapy followed by resection benefit from adjuvant chemotherapy,[19] but no general consensus exists regarding the benefit of and indications for adjuvant chemotherapy in such patients. Furthermore, efforts to develop models predicting response to adjuvant chemotherapy have excluded patients who have received preoperative therapy.[20,21]

Our group has previously demonstrated that preoperative therapy does not increase the risk of minor or major perioperative complication (Clavien-Dindo 3-5), anastomotic leak, or symptomatic intraabdominal fluid collection for patients undergoing resection of gastric cancer.[14,22,23] And whereas patients that experience a major perioperative complication after upfront surgery suffer decreased survival relative to those without a complication, those that experience a major perioperative complication after preoperative therapy do not.[23] These data, together with the important prognostic information provided by the treated nodal basin, add further support to the increasingly used strategy of preoperative therapy for patients with potentially resectable disease.[14,22,24]

This study was limited first and foremost by its retrospective design. As such, it was susceptible to both selection and treatment bias, among other types of inherent bias. The small study size may have affected our ability to identify true determinants of outcome and may explain why traditionally important factors such as histologic grade fell out of the multivariable analysis. Our data are missing important pieces that might prove useful for future research, most notably mutational analyses of both the primary tumor and nodal disease. Such future analyses

TABLE 3 Description of patients with ypT0N+ status

Patient number	Tumor location	Clinical stage[I]	Histology	Preoperative therapy regimen		Date of surgery	Resection	Residual LN disease		Adjuvant therapy	Outcome		
				Chemotherapy	Chemoradiation			No. positive LNs/ no. LNs removed	Treatment effect present		Recurrence-free survival(years)	Site of recurrence	Overall survival(years)
1	GEJ	cT3N1M0	Poorly differentiated		5-FU/45 Gy	8/29/ 1996	Proximal gastrectomy	1/3	Yes	No	0.4	Bone, brain	2.4
2	Gastric body	cT3N0M0	Poorly differentiated		5-FU/45 Gy	5/29/ 1998	Total gastrectomy	2/12	Yes	No	0.6	Peritoneum	2.2
3	GEJ	cT3N1M0	Poorly differentiated		Irinotecan/ 45 Gy	11/16/ 1998	Proximal gastrectomy	1/14	NA	No	1.1	Lung	1.9
4	GEJ	cT3N0M0	Moderately differentiated		5-FU, paclitaxel/ 45 Gy	4/9/1999	Ivor-Lewis	1/15	NA	No	–	–	8.5
5	Antrum	cT3N1M0	Poorly differentiated		5-FU/45 Gy	9/13/ 1999	Subtotal gastrectomy	1/14	NA	No	0.6	Liver	1.4
6	Gastric body	cT3N1M0	Moderately differentiated	Etoposide, leucovorin, 5-FU	Paclitaxel, carboplatin/ 45 Gy	7/31/ 2000	Total gastrectomy	2/10	Yes	No	0.9	Liver	2.6
7	GEJ	cT3N1M0	Moderately differentiated	Irinotecan, 5-FU, docetaxel	50.4 Gy	2/6/2003	Ivor-Lewis	1/7	Yes	No	3.3	Bone	4.7
8	Gastric body	cT2N1M1	Poorly differentiated	Cisplatin, 5-FU, docetaxel	5-FU/45 Gy	7/25/ 2007	Total gastrectomy	2/39	Yes	No	–	–	8.2
9	GEJ	cT3N1M1	Poorly differentiated	Docetaxel, oxaliplatin, capecitabine	Capecitabine/ 50.4 Gy	10/31/ 2012	Ivor = Lewis	5/19	Yes	No	0.7	Brain	2.0
10	GEJ	cT3N1M0	Moderately differentiated	Oxaliplatin, capecitabine	Capecitabine/ 45 Gy	7/8/2014	Total gastrectomy	1/20	Yes	No	0.6	Liver	2.6

LN lymph node, *GEJ* gastroesophageal junction, *5-FU* fluorouracil, *NA* not available

[I]Pretreatment clinical stage

could provide insight into the genetic basis of persistent nodal disease in patients with primary tumor pathologic complete response.

CONCLUSION

We performed a focused survival analysis of gastric and gastroesophageal cancer patients who achieved pathologic complete response after preoperative therapy. Preoperative clinicopathologic factors including American Joint Committeeon Cancer (AJCC) clinical stage did not predict outcome for patients with ypT0 and ypT0N0 disease. Although ypT0 patients may expect excellent OS, this study again highlights the critical role that ypN status plays in determining the ultimate outcome. Patients with pathologic complete response in the primary tumor but persistent nodal disease represent a unique patient population for which further study not only may elicit information necessary to improve outcomes, but also may advance overall understanding regarding the progression of disease and development of treatment resistance in patients with gastric and gastroesophageal adenocarcinoma.

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DISCLOSURE There are no conflicts of interest.

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