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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Is It Time to Abandon the 5-cm Margin Rule During Resection of Distal Gastric Adenocarcinoma? A Multi-Institution Study of the U.S. Gastric Cancer Collaborative

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ABSTRACT

Background. A proximal margin distance of 5 cm is advocated for resection of gastric adenocarcinoma (GAC). We assessed the prognostic value of proximal margin (PM) distance on survival outcomes after resection of distal GAC.

Methods. All patients who underwent resection of distal GAC (antrum/body) from 2000 to 2012 at seven institutions of the U.S. Gastric Cancer Collaborative were included. Patients with positive distal margins or macroscopic residual disease were excluded. The prognostic value of PM distance (assessed in 0.5-cm increments) on overall (OS) and recurrence-free survival (RFS) was assessed by Kaplan–Meier and multivariate regression analysis.

Results. A total of 465 patients underwent resection of distal GAC. Of these, 435 had R0 resections; 30 patients had a positive PM. 143 patients had stage I, and 322 had stage II–III tumors. Median follow-up was 44 months. Average PM distance was 4.8 cm. Median OS for patients with PM of 3.1–5.0 cm ($n = 110$) was superior to patients with PM $\leq$ 3.0 cm ($n = 176$) (48.1 vs. 29.3 months; $p = 0.01$), while a margin >5.0 cm ($n = 179$) offered equivalent survival to PM 3.1–5.0 cm (50.6 months, $p = 0.72$). The prognostic value of margin distance was stage specific. On multivariate analysis of stage I patients, PM 3.1–5.0 cm remained associated with improved OS [hazard ratio (HR), 0.16; 95 % confidence interval (95 % CI), 0.04–0.60; $p = 0.01$]. In stage II–III, neither PM 3.1–5.0 cm nor PM > 5.0 cm was significantly associated with OS; OS was dictated by T stage and nodal involvement.

Conclusions. The prognostic value of proximal margin distance after resection of distal gastric cancer appears stage specific. In stage I, a 3.1- to 5.0-cm proximal margin is associated with the same improved OS as a > 5.0-cm margin. In stage II–III disease, other adverse pathologic factors more strongly impact survival than proximal margin distance.

Historically, surgical doctrine has advocated obtaining a proximal margin of at least 5 cm when performing resection of gastric adenocarcinoma (GAC). The basis for this recommendation is largely derived from several decade-old studies that reported decreased rates of local recurrence when gastric cancer was resected with a proximal margin (PM) of >5–6 cm of normal gastric tissue.[1,2] While numerous studies have demonstrated a negative prognostic

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effect of microscopically positive (R1) margins following resection of GAC, recent data suggest that the impact of R1 margin involvement on survival outcomes may differ based on tumor stage.[3–7] In addition, few studies have examined the influence of resection margin distance on rates of locoregional recurrence and survival outcomes since the initial work by Papachristou et al. and Bozzetti et al., yet both the NCCN guidelines and Japanese Gastric Cancer Treatment Guidelines continue to recommend wide proximal margins based on these data.[1,2,8–10] More recently, however, several studies have failed to demonstrate improved outcomes associated with greater PM resection distance beyond a negative (R0) margin, questioning the utility of more extensive resection.[11–13]

In clinical practice, the application of the 5-cm PM recommendation may affect the decision to perform a distal versus subtotal versus total gastrectomy for GAC, which in turn can impact the method of reconstruction and can have profound implications on postoperative morbidity and quality of life. Previous prospective randomized trials found no significant difference in survival outcomes between patients treated with subtotal and total gastrectomy, while subtotal gastrectomy has repeatedly been associated with better nutritional status and improved quality-of-life.[14–19]

Given the discrepant and historical nature of existing data, the primary aim of this study was to assess the prognostic value of PM distance on overall survival (OS) and recurrence-free survival (RFS) following resection of distal gastric cancer, in order to determine if a shorter PM distance might offer comparable oncologic outcomes to the standard recommendation of 5 cm.

METHODS

Study Population

All patients who underwent resection of GAC from January 2000 to December 2012 at each of the seven institutions of the U.S. Gastric Cancer Collaborative (GCC) were identified from the comprehensive multi-institutional database. Patients undergoing curative intent resection of distal gastric cancer, defined as tumor located within the gastric antrum or body, with a PM distance measurement recorded in the pathology report, were selected for analysis. Patients undergoing endoscopic therapy were excluded. In order to analyze the effect of PM distance on recurrence and survival outcomes in isolation, patients with a positive distal margin were excluded. Patients with known metastatic disease who underwent palliative resections and those with macroscopic residual disease present at grossly positive (R2) transection margins were also excluded from analysis. Patients with proximal tumors of the cardia or GE junction were not included in the current study.

Comprehensive review of each patient's medical record identified all pertinent demographic, preoperative, intraoperative, and pathologic data. In addition, data regarding neoadjuvant and adjuvant therapies, postoperative outcomes, recurrence patterns, and overall survival were collected. Peritoneal cytology was not routinely performed at all member institutions during the study period; thus these data were not available for analysis. Pathologic staging was designated per the AJCC seventh edition guidelines for gastric cancer.[20] The Social Security Death Index was used to verify survival data. Each university's Institutional Review Board approved the research protocol.

Margin Analysis

Proximal margin distance, as measured from the resection specimen by the surgical pathologist, was analyzed in 0.5-cm increments. The primary objective was to evaluate the prognostic value of PM distance on OS and RFS after resection of distal GAC. Recurrence was classified as local (anastomotic or gastric remnant), regional (regional lymph nodes), or distant (peritoneal, hepatic, pulmonary, or other sites of metastatic disease). For analysis of RFS, the event was defined as recurrence at any site. Analysis of PM distance in 0.5-cm increments (i.e., 2.5 cm vs. 2.0 cm vs. 1.5 cm, etc.) was performed to determine the PM distance at which an asymptotic plateau in survival outcomes occurred, beyond which no apparent further increase in OS or RFS was observed. This PM distance value was then compared with the historical standard recommendation of PM $>$ 5.0 cm.

Statistical Analysis

Survival analyses were conducted by Kaplan–Meier methodology. Categorical and continuous variables were analyzed by Chi square analysis and t test, respectively. Univariate and multivariate Cox regression analyses were performed to assess the impact of PM distance on OS and RFS within the context of other adverse clinicopathologic variables. Variables with p value ≤ 0.05 on univariate analysis were included in the multivariate models for OS and RFS. Statistical significance was defined as a p value <0.05. Statistical analyses were performed with SPSS 19.0 software (IBM Inc., Armonk, NY).

RESULTS

Of 965 patients in the U.S. GCC database, 465 patients underwent resection of distal GAC with curative intent. Basic demographics and clinicopathologic features for the

TABLE 1 Overall demographics and clinicopathologic features of all patients undergoing resection of distal gastric adenocarcinoma ($n = 465$)

Variable	*N* (%) or mean ± SD
Age (years)	65.4 ± 12.7
Male gender	264 (57 %)
ASA class	
1	4 (1 %)
2	148 (32 %)
3	286 (62 %)
4	14 (3 %)
BMI (kg/m^2)	26.1 ± 13.4
Albumin <3.0 gm/dL	49 (12 %)
Gastrectomy extent	
Distal	105 (23 %)
Subtotal	244 (52 %)
Total	116 (25 %)
EBL, mL	260 ± 222
Lymphadenectomy extent	
D0–D1	168 (36 %)
D2–D3	297 (64 %)
Perioperative transfusion	98 (21 %)
Diffuse-type histology	98 (21 %)
Linitis plastica	22 (5 %)
Tumor size, cm	4.8 ± 3.5
Proximal margin distance (cm)	5.0 ± 3.9
Tumor grade, poor	325 (70 %)
Signet ring	198 (43 %)
LVI	187 (40 %)
PNI	114 (25 %)
T stage	
T1	130 (28 %)
T2	54 (12 %)
T3	155 (33 %)
T4	126 (27 %)
N stage	
N0	189 (41 %)
N1	86 (19 %)
N2	79 (17 %)
N3	110 (24 %)
TNM stage	
I	143 (31 %)
II	119 (25 %)
III	203 (44 %)
Neoadjuvant chemotherapy	80 (17 %)
Any adjuvant therapy (chemo and/or XRT)	245 (53 %)

cohort are summarized in Table 1. A total of 116 patients (25 %) underwent total gastrectomy, 244 (52 %) underwent subtotal gastrectomy, and 105 (23 %) underwent distal gastrectomy. Mean PM distance was 4.8 ± 3.5 cm;

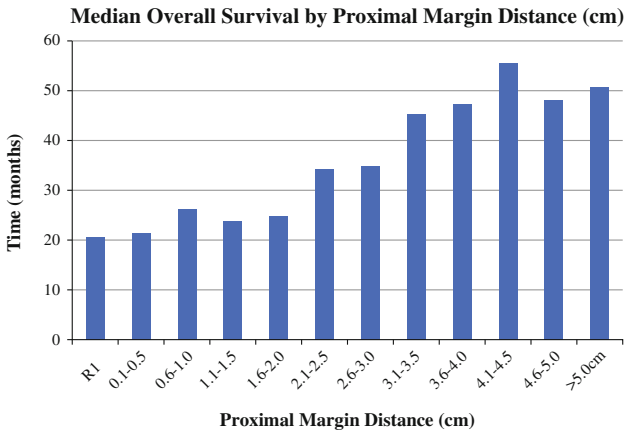


FIG. 1 Median overall survival stratified by proximal margin distance increments

median PM was 4.0 cm [interquartile ratio (IQR), 2.0–7.0 cm]. Thirty patients had microscopically positive (R1) proximal margins. A minority of patients presented with early-stage, TNM stage I disease ($n = 143$; 31 %), compared with 322 patients (69 %) presenting with more advanced TNM stage II and III disease. Median follow-up for survivors was 44 months (range 0.3–137.9 months).

On initial analysis of PM distance by .5-cm increments, a PM > 3.0 cm appeared to be associated with the optimal OS and RFS. Significantly greater survival was associated with increasing PM distance up to 3.0 cm (e.g., outcomes for PM > 2.5 cm were improved vs. PM ≤ 2.5 cm, and for PM > 3.0 vs. ≤ 3.0 cm); further increases in PM distance beyond a 3.0-cm cutoff, however, were not associated with further improvements in outcomes (Fig. 1). In order to assess outcomes compared with the historical standard recommendation of PM > 5 cm, clinicopathologic features of patients with PM distance 3.1–5.0 cm were compared with those with PM > 5.0 cm (Table 2). Demographic, operative, and pathologic features were similar between the 2 cohorts. Patients with PM > 5.0 cm had a higher incidence of diffuse-type histology (20 vs. 10 %; $p = 0.05$), but tumor size, tumor grade, presence of lymphovascular invasion (LVI) and perineural invasion (PNI), T stage, and N stage did not differ significantly between the two groups. The use of neoadjuvant chemotherapy and adjuvant chemotherapy and/or radiation therapy was also similar. In addition, patients with PM of 3.1–5.0 cm demonstrated an equivalent incidence of locoregional recurrence compared with those with PM > 5.0 cm (11 vs. 12 %; $p = 0.91$).

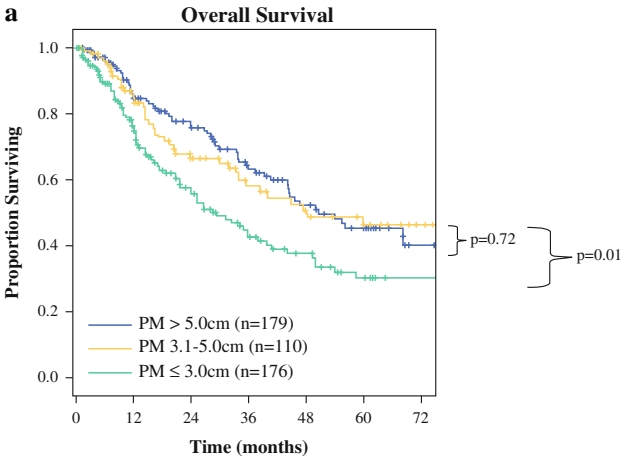
Survival Analysis

For survival analysis, cohorts of patients with a PM ≤ 3.0 cm ($n = 176$), PM of 3.1–5.0 cm ($n = 110$), and PM > 5.0 cm ($n = 179$) were assessed. On Kaplan–

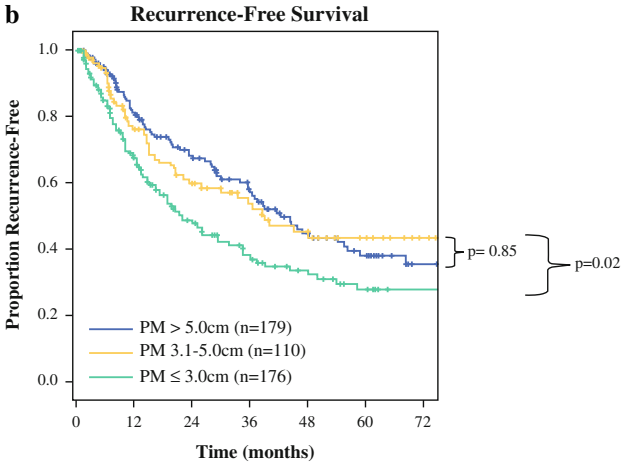
TABLE 2 Comparison of clinicopathologic features between cohorts of patients with proximal margin (PM) distance 3.1–5.0 cm ($n = 110$) versus margin distance >5.0 cm ($n = 179$)

Variable	Patients with PM 3.1–5.0 cm ($n = 110$)	Patients with PM > 5.0 cm ($n = 179$)	p value
Age (years)	65.5 ± 12.5	64.8 ± 12.6	0.66
Male gender	74 (67 %)	101 (56 %)	0.09
ASA			0.42
1	0	3 (2 %)	
2	32 (30 %)	61 (35 %)	
3	71 (67 %)	105 (61 %)	
4	3 (3 %)	4 (2 %)	
BMI (kg/m^2)	25.6 ± 5.7	26.6 ± 6.4	0.19
Albumin < 3.0 gm/dL	10 (10 %)	22 (14 %)	0.49
Op type			0.06
Distal	27 (25 %)	42 (24 %)	
Subtotal	54 (49 %)	109 (61 %)	
Total	29 (26 %)	28 (16 %)	
EBL (mL)	243 ± 198	256 ± 249	0.66
LN dissection			0.61
D0–D1	40 (36 %)	55 (31 %)	
D2–D3	70 (64 %)	124 (69 %)	
Perioperative transfusion	26 (24 %)	34 (19 %)	0.43
Diffuse-type histology	11 (10 %)	35 (20 %)	0.047
Linitis plastica	2 (2 %)	3 (2 %)	1.00
Tumor size (cm)	4.7 ± 3.3	4.0 ± 2.8	0.09
Tumor grade, poor	75 (69 %)	126 (72 %)	0.75
Signet ring	41 (37 %)	73 (41 %)	0.42
LVI	43 (39 %)	70 (42 %)	0.92
PNI	28 (33 %)	34 (26 %)	0.31
T stage			0.25
T1	29 (26 %)	64 (36 %)	
T2	15 (14 %)	22 (12 %)	
T3	42 (38 %)	50 (28 %)	
T4	24 (22 %)	43 (24 %)	
N stage			0.80
N0	50 (45 %)	79 (44 %)	
N1	24 (22 %)	31 (17 %)	
N2	14 (13 %)	30 (17 %)	
N3	22 (20 %)	39 (22 %)	
TNM stage			0.09
I	35 (32 %)	66 (37 %)	
II	39 (35 %)	42 (23 %)	
III	36 (33 %)	71 (40 %)	
Neoadjuvant chemotherapy	22 (20 %)	26 (15 %)	0.29
Adjuvant therapy (chemotherapy or XRT)	54 (49 %)	99 (55 %)	0.37
Locoregional recurrence	12 (11 %)	22 (12 %)	0.91

PM proximal margin, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *EBL* estimated blood loss, *LN* lymph node, *LVI* lymphovascular invasion, *PNI* perineural invasion, *XRT* radiation therapy

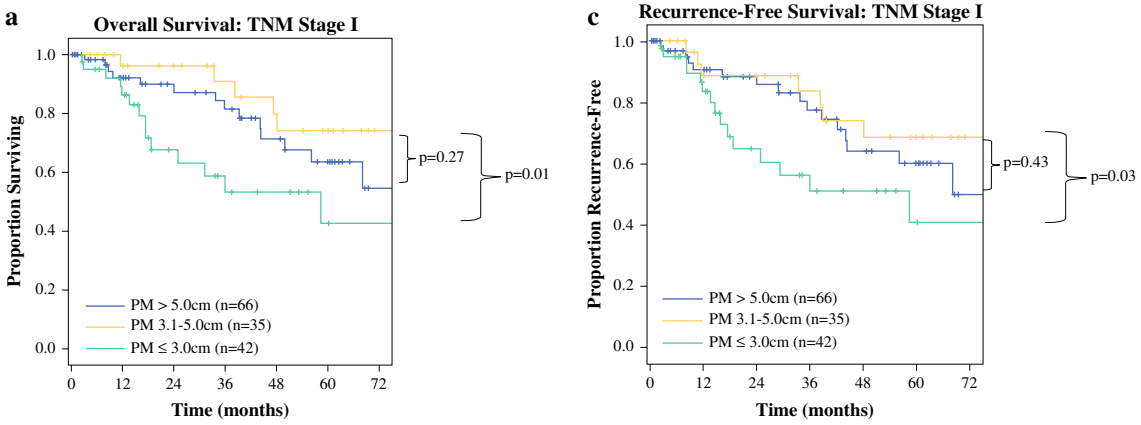


Proximal Margin Distance	Median OS (mos)	3-yr OS (%)	5-yr OS (%)
≤ 3.0cm (n=176)	29.3	42%	30%
3.1-5.0cm (n=110)	48.1	58%	46%
>5.0cm (n=179)	50.6	63%	45%



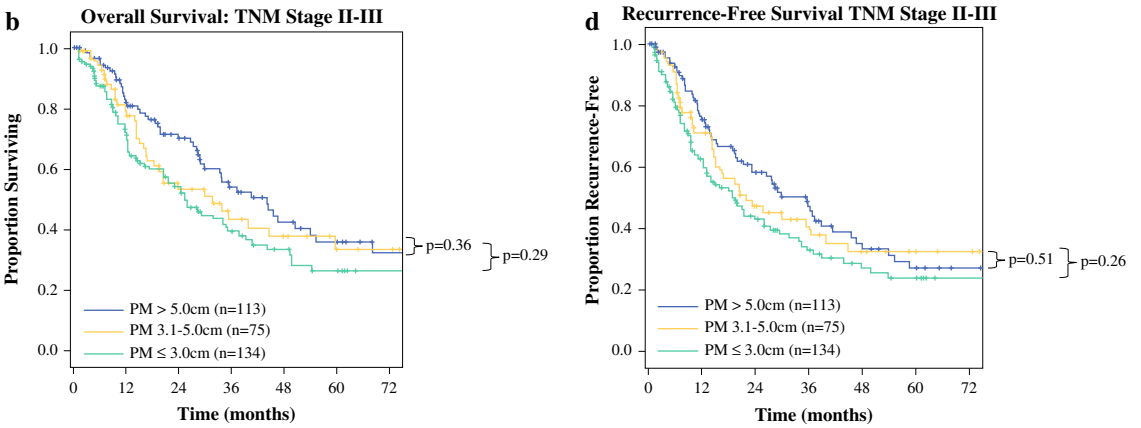
Proximal Margin Distance	Median RFS (mos)	3-yr RFS (%)	5-yr RFS (%)
≤ 3.0cm (n=176)	21.2	38%	28%
3.1-5.0cm (n=110)	38.9	54%	44%
>5.0cm (n=179)	42.2	67%	38%

FIG. 2 **a** Kaplan–Meier survival analysis of overall survival (OS) for all patients ($n = 465$), by proximal margin (PM) distance. **b** Kaplan–Meier survival analysis of recurrence-free survival (RFS) for all patients ($n = 465$), by proximal margin (PM) distance



Proximal Margin Distance	Median OS (mos)	3-yr OS (%)	5-yr OS (%)
≤ 3.0cm	58.4	55%	43%
3.1-5.0cm	MNR	91%	74%
>5.0cm	MNR	82%	64%

Proximal Margin Distance	Median RFS (mos)	3-yr RFS (%)	5-yr RFS (%)
≤ 3.0cm	58.4	53%	41%
3.1-5.0cm	MNR	84%	69%
>5.0cm	68.2	77%	60%



Proximal Margin Distance	Median OS (mos)	3-yr OS (%)	5-yr OS (%)
≤ 3.0cm	25.2	41%	24%
3.1-5.0cm	31.8	43%	32%
>5.0cm	44.2	54%	37%

Proximal Margin Distance	Median RFS (mos)	3-yr RFS (%)	5-yr RFS (%)
≤ 3.0cm	19.5	33%	24%
3.1-5.0cm	21.9	40%	32%
>5.0cm	35.5	47%	27%

FIG. 3 **a** Kaplan–Meier analysis of overall survival stratified by TNM stage: stage I. **b** Kaplan–Meier analysis of overall survival stratified by TNM stage: stage II–III. **c** Kaplan–Meier analysis of recurrence-free survival stratified by TNM stage: stage I. **d** Kaplan–Meier analysis of recurrence-free survival stratified by TNM stage: stage II–III

Meier analysis, patients with a PM of 3.1–5.0 cm demonstrated significantly longer median OS compared with patients with PM $\leq$ 3.0 cm (48.1 vs. 29.3 months; $p = 0.01$), while a PM $>$ 5.0 cm was not associated with any further improvement in OS versus PM 3.1–5.0 cm (50.6 vs. 48.1 months; $p = 0.72$; Fig. 2a). Similarly, patients with a PM of 3.1–5.0 cm demonstrated significantly longer median RFS compared with patients with PM $\leq$ 3.0 cm (38.9 vs. 21.1 months; $p = 0.02$), while a PM $>$ 5.0 cm was not associated with any further improvement in RFS versus PM 3.1–5.0 cm (42.2 vs. 38.9 months; $p = 0.85$; Fig. 2b).

On subset analysis stratified by TNM stage, among patients with TNM stage I disease, a PM of 3.1–5.0 cm remained associated with significantly longer median OS versus PM $\leq$ 3.0 cm [median not reached (MNR) vs. 58.4 months; $p = 0.02$], while a PM $>$ 5.0 cm offered no further improvement in OS versus PM 3.1–5.0 cm (MNR vs. MNR; $p = 0.27$; Fig. 3a). On subset analysis of TNM stage II–III disease, no statistically significant differences in median OS or 5-year OS were observed between patients with PM of 3.1–5.0 cm and PM $\leq$ 3.0 cm (31.8 vs. 25.2 months; $p = 0.36$), or between patients with PM $>$ 5.0 cm and PM of 3.1–5.0 cm (44.2 vs. 31.8 months; $p = 0.29$; Fig. 3b).

Similarly, for patients with TNM stage I disease, a PM of 3.1–5.0 cm was associated with significantly longer median RFS versus PM $\leq$ 3.0 cm (MNR vs. 58.4 months; $p = 0.03$), while a PM $>$ 5.0 cm offered no further improvement in RFS versus PM 3.1–5.0 cm (68.2 months

TABLE 3 Multivariate Cox regression analysis of risk factors associated with overall survival, stratified by TNM stage

Variable	Stage I tumors ($n = 143$)		Stage II and III tumors ($n = 322$)	
	HR (95 % CI)	p value	HR (95 % CI)	p value
ASA class	2.34 (1.16–4.72)	0.02	1.19 (0.83–1.73)	0.36
Albumin < 3.0 gm/dL	1.55 (0.22–10.87)	0.66	1.05 (0.62–1.77)	0.86
T stage				
T1	Ref	Ref	Ref	Ref
T2	1.84 (0.47–7.24)	0.38	2.69 (0.60–12.06)	0.19
T3	–	–	2.95 (0.71–12.32)	0.14
T4	–	–	4.33 (1.03–18.26)	0.04
N stage				
N0	Ref	Ref	Ref	Ref
N1	2.05 (0.54–7.77)	0.29	1.03 (0.58–1.89)	0.92
N2	–	–	1.40 (0.80–2.44)	0.24
N3a	–	–	1.92 (1.09–3.41)	0.03
N3b	–	–	2.80 (1.41–5.57)	0.003
Tumor size	1.01 (0.80–1.27)	0.93	1.04 (0.99–1.09)	0.16
Diffuse-type histology	1.26 (0.27–5.83)	0.77	1.40 (0.92–2.14)	0.12
Perioperative transfusion	3.21 (1.29–7.96)	0.01	1.07 (0.69–1.72)	0.76
Proximal margin				
0–3.0 cm	Ref	Ref	Ref	Ref
3.1–5.0 cm	0.16 (0.04–0.60)	0.01	0.98 (0.63–1.57)	0.98
> 5.0 cm	0.43 (0.17–1.06)	0.07	0.94 (0.62–1.42)	0.75
Any adjuvant therapy	0.42 (0.13–1.36)	0.15	0.46 (0.31–0.67)	<0.001

vs. MNR; $p = 0.43$; Fig. 3**c**). Among patients with TNM stage II–III disease, no statistically significant differences in median RFS were observed between patients with PM of 3.1–5.0 cm and PM $\leq$ 3.0 cm (21.9 vs. 19.5 months; $p = 0.26$) or between patients with PM > 5.0 cm and PM of 3.1–5.0 cm (35.5 vs. 21.9 months; $p = 0.51$; Fig. 3d).

Multivariate Analysis

On MV regression analysis for OS among patients with TNM stage I disease, achieving a PM distance of 3.1–5.0 cm remained significantly associated with improved OS compared with patients with PM $\leq$ 3.0 cm [hazard ratio (HR), 0.16; 95 % confidence interval (95 % CI), 0.04–0.60; $p = 0.01$], while PM > 5.0 cm offered no additional survival advantage (Table 3). On MV regression analysis among patients with TNM stage II–III disease, neither PM of 3.1–5.0 cm ($p = 0.98$) nor PM > 5.0 cm ($p = 0.75$) was significantly associated with OS in the context of other adverse pathologic factors; in these patients with advanced stage disease, OS was impacted by increasing T stage and N stage and the delivery of adjuvant therapy after resection (Table 3).

On MV regression analysis of risk factors for RFS among TNM stage I patients, a PM distance of 3.1–5.0 cm remained significantly associated with improved RFS compared with patients with PM $\leq$ 3.0 cm (HR, .30; 95 % CI, .10–.88; $p = 0.03$), while PM > 5.0 cm conferred no additional advantage (Table 4). On MV analysis of patients with TNM stage II–III disease, neither PM of 3.1–5.0 cm ($p = 0.51$) nor PM > 5.0 cm ($p = 0.46$) was significantly associated with RFS in the context of other adverse pathologic factors; in patients with advanced stage disease, significant risk factors associated with RFS included increasing T stage and N stage and the delivery of adjuvant therapy after resection (Table 4).

DISCUSSION

In this large, multi-institutional analysis of the U.S. Gastric Cancer Collaborative, the prognostic value of proximal margin distance for survival outcomes after resection of distal GAC of the antrum and body was stage specific. Among patients with stage I GAC, a proximal resection margin of 3.1–5.0 cm was associated with similarly improved OS and RFS as margin distance >5.0 cm. In more advanced stage II and III disease, PM distance, regardless of the extent of resection, has little effect on survival outcomes in the context of other adverse pathologic factors. Thus, a PM > 3.0 cm appears adequate for resection of all distal GAC.

TABLE 4 Multivariate Cox regression analysis of risk factors for recurrence-free survival, stratified by TNM stage

Variable	Stage I tumors ($n = 143$)		Stage II and III tumors ($n = 322$)	
	HR (95 % CI)	p value	HR (95 % CI)	p value
ASA class	2.11 (1.11–3.98)	0.02	1.14 (0.82–1.57)	0.44
Albumin < 3.0 gm/dL	1.06 (0.19–6.04)	0.95	1.10 (0.70–1.73)	0.68
T stage				
T1	Ref	Ref	Ref	Ref
T2	1.03 (0.31–3.49)	0.96	3.07 (0.69–13.65)	0.14
T3	–	–	3.58 (0.86–14.88)	0.08
T4	–	–	5.41 (1.29–22.66)	0.02
N stage				
N0	Ref	Ref	Ref	Ref
N1	1.90 (0.47–7.75)	0.37	1.24 (0.71–2.17)	0.45
N2	–	–	1.43 (0.84–2.43)	0.19
N3a	–	–	2.02 (1.17–3.50)	0.01
N3b	–	–	2.99 (1.58–5.64)	0.001
Tumor size	1.01 (0.82–1.22)	0.99	1.01 (0.97–1.07)	0.58
Diffuse-type histology	1.46 (0.32–6.65)	0.62	1.38 (0.93–2.04)	0.11
Perioperative transfusion	3.00 (1.31–6.87)	0.01	1.19 (0.80–1.76)	0.39
Proximal margin				
0–3.0 cm	Ref	Ref	Ref	Ref
3.1–5.0 cm	0.30 (0.10–0.88)	0.03	0.87 (0.57–1.33)	0.51
>5.0 cm	0.54 (0.23–1.26)	0.15	0.87 (0.59–1.27)	0.46
Any adjuvant therapy	0.98 (0.41–2.48)	0.98	0.57 (0.40–0.81)	0.002

HR hazard ratio, *95 % CI* 95 % confidence interval, *ASA* American Society of Anesthesiologists

On analysis of the entire cohort, patients with PM distance of 3.1–5.0 cm demonstrated significantly greater OS and RFS compared with patients with PM $\leq$ 3.0 cm, while PM distance >5.0 cm was not associated with any further improvement in OS or RFS. On subset analysis of stage I disease, even after accounting for the potential influence of diffuse-type histology and other adverse pathologic features, PM distance of 3.1–5.0 cm offered comparable survival outcomes to PM distances >5.0 cm. On analysis of patients with stage II–III disease, while patients with PM >5.0 cm had slightly, but nonsignificantly, improved median RFS compared with those with PM 3.1–5.0 cm (35.5 vs. 21.9 months; $p = 0.51$), the 5-year OS rates were no different between these 2 cohorts (27 vs. 32 %). Similarly, while patients with PM > 5.0 cm had slightly improved median OS compared with those with PM 3.1–5.0 cm (44.2 vs. 31.8 months), this difference was not statistically significant and the difference in 5-year OS rates was minimal (37 vs. 32 %). Among patients with more advanced stage GAC, survival outcomes appear to be influenced by T stage and N stage and the delivery of adjuvant therapy, whereas margin distance is not significantly associated with RFS or OS.

Decade-old studies by Papachristou and Bozzetti and colleagues, demonstrating decreased rates of microscopic residual disease and local recurrence with greater resection margins, formed the basis for the classic 5–6 cm margin recommendations for resection of GAC.[1, 2, 8] Ito et al. similarly reported that a gross PM distance of $\geq$4 cm for T1–T2 tumors and $\geq$6 cm for T3–T4 tumors was necessary to consistently achieve microscopically negative margins for GAC of the gastric cardia; these results have been extrapolated to other tumor locations within the stomach and are also cited in the NCCN management guidelines for GAC.[21]

More recently, several studies have questioned the need for such wide proximal resection margins. Jang et al. reported on a series of 402 patients with advanced GAC located in the middle third of the stomach.[11] They found no significant difference in stage-stratified 5-year OS between patients who underwent total versus subtotal gastrectomy and found no significant improvements in 5-year OS rates associated with increasing proximal resection margin distances (1 vs. 2 vs. 3 vs. 4 vs. 5 cm). This lack of association between 5-year OS rates and greater proximal margin distance beyond a simple R0 margin was true even for diffuse-type or infiltrative histology tumors.

A similar analysis of 125 patients with GAC located in the middle third of the stomach treated with subtotal or total gastrectomy found no significant difference in local

recurrence rates or stage-stratified 5-year OS based on the extent of resection.[12] In addition, no significant differences in 5-year OS were demonstrated for increasing proximal margin distance (1 vs. 2 vs. 3 vs. 4 vs. 5 cm), as long as an R0 resection was obtained. Stage-specific analyses of survival outcomes according to proximal margin distance were not performed, limiting comparison to the current study.

Based on a large, single-institutional analysis of 2081 patients with early gastric carcinoma, including 1306 patients with distal gastric tumors, Kim et al. proposed that proximal resection margins of >1 mm may be adequate for early-stage GAC.[13] They reported the rate of microscopically positive margins was <0.1 % when the gross resection margin was >1 mm and found no significant differences in the rates of local recurrence or 10-year OS with increasing proximal margin distance (>1 vs. 10 vs. 30 mm). Most patients in this cohort (88 %) presented with stage IA disease, compared with only 19 % in the current study.

In a large single-institution series of 1,472 patients, Ha and Kwon reported no significant differences in rates of recurrence or 5-year OS for patients with "early" GAC with PM distance <2 versus ≥ 2 cm.[22] Among patients with advanced GAC, improved 5-year OS was observed for patients with PM distance ≥3 cm versus those with PM distance <3 cm, particularly in the setting of diffuse-type histology and tumors located within the distal third of the stomach.

The 2010 guidelines of the Japanese Gastric Cancer Association recommended gross proximal resection margins of ≥2 cm for T1 tumors, ≥3 cm for T2–T4 tumors with more "expansive growth pattern" or intestinal-type histology, and ≥5 cm for T2–T4 tumors with diffuse-type histology.[9] The results of the current study suggest a PM distance of >3 cm may be uniformly adequate for the resection of distal GAC and that a more extensive proximal resection is not associated with significantly improved survival outcomes. Whether these findings hold true for more proximal gastric cancer warrants further analysis.

The conclusions of this analysis are limited by the retrospective design of the study. Prospective, randomized data would more conclusively address these findings. In addition, while the multi-institutional nature of the dataset strengthens the statistical analysis, potential differences in pathologic processing and margin measurements of GAC specimens by multiple pathologists across the seven institutions may have occurred. A key limitation of this analysis, and many previous studies, is that all PM distances were pathology gross specimen measurements, not intraoperative measurements. One study examining surgical margins found that upon resection of gastric cancer, the gastric specimen demonstrates immediate contraction of 14 % of its measured length on average and then continues to contract for 12–24 h after formalin fixation.[23] Thus the PM distance measured on the resected specimen by the surgical pathologist, although an adequate approximation, does not exactly reflect the intraoperative measurement on which the surgeon must base the decision of where to transect the stomach.

In conclusion, the prognostic value of proximal margin distance following distal gastric cancer resection appears to be stage specific. In stage I disease, a proximal resection margin of 3.1–5.0 cm is associated with similarly improved OS and RFS as a greater margin distance of >5.0 cm. In more advanced stage II and III disease, proximal margin distance, whether >3 or >5 cm, has little effect on survival outcomes in the context of other adverse pathologic factors. Thus, a proximal margin >3.0 cm appears adequate for resection of distal GAC. This in turn may affect intraoperative decisions regarding the extent of resection.

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