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Utility of the Proximal Margin Frozen Section for Resection of Gastric Adenocarcinoma: A 7-Institution Study of the US Gastric Cancer Collaborative

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ABSTRACT

Background. The proximal gastric margin dictates the extent of resection for gastric adenocarcinoma (GAC). The value of achieving negative margins via additional gastric resection after a positive proximal margin frozen section (FS) is unknown.

Methods. The US Gastric Cancer Collaborative includes all patients who underwent resection of GAC at seven institutions from 2000–2012. Intraoperative proximal margin FS data and final permanent section (PS) data were classified as R0 or R1, respectively; positive distal margins were excluded. The primary aim was to evaluate the impact on local recurrence of converting a positive proximal FS-R1 margin to a PS-R0 final margin by additional resection. Secondary endpoints were recurrence-free survival (RFS) and overall survival (OS).

Results. Of 860 patients, 520 had a proximal margin FS and 67 were positive. Of these, 48 were converted to R0 on PS by additional resection. R0 proximal margin was achieved in 447 patients (86 %), PS-R1 in 25 (5 %), and converted FS-R1-to-PS-R0 in 48 (9 %). The median follow-up was 44 months. Local recurrence was significantly decreased in the converted FS-R1-to-PS-R0 group compared to the PS-R1 group (10 vs. 32 %; $p = 0.01$). Median RFS was similar between the FS-R1-to-PS-R0 and PS-R1 cohorts (25 vs. 20 months; $p = 0.49$), compared to 37 months for the PS-R0 group. Median OS was similar between the FS-R1-to-PS-R0 conversion and PS-R1 groups (36 vs. 26 months; $p = 0.14$) compared to 50 months for the PS-R0 group. On multivariate analysis, increasing T-stage and N-stage were associated with worse OS; the FS-R1-to-PS-R0 proximal margin conversion was not significantly associated with improved RFS ($p = 0.68$) or OS ($p = 0.44$).

Conclusion. Conversion of a positive intraoperative proximal margin frozen section during gastric cancer resection may decrease local recurrence, but it is not associated with improved RFS or OS. This may guide decisions regarding the extent of resection.

Gastric adenocarcinoma (GAC) remains the fourth most common malignancy worldwide and a leading cause of cancer-related mortality.[1] The best curative treatment option for gastric cancer remains surgical resection with negative margins and an adequate lymphadenectomy.[2]

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Multiple studies have demonstrated that a microscopically positive (R1) margin after resection may be associated with worse prognosis, although the prognostic effect of an R1 margin may differ between early and advanced stage GAC.[3–10] An extensive single-institution analysis recently demonstrated that a positive final margin was independently associated with decreased survival only in patients with T1-T2 disease or less than three positive nodes, but not in patients with more advanced stage disease.[3] Other groups have similarly found that the negative prognostic effect of an R1 margin may apply only to patients with early GAC; in patients with more advanced GAC, the influence of a positive margin appears to be outweighed by other adverse pathologic features such as increasing depth of tumor invasion or nodal involvement.[4,7,10]

The proximal gastric margin typically dictates the extent of resection for GAC and influences operative decision-making of whether to perform a distal, subtotal, or total gastrectomy, depending on tumor location. Thus, attempts to achieve a negative proximal margin affect the extent of gastrectomy and the type of reconstruction, which in turn may impact the risk of postoperative complications and subsequent quality-of-life.[11,12] Few studies have examined the prognostic value of a positive frozen section (FS) margin during GAC resection and whether conversion of an initially positive FS margin to a final negative permanent section (PS) margin is associated with improved outcomes.[5,13–15] The value of achieving negative margins by additional gastric resection after a positive proximal margin FS remains unknown. The purpose of this study was to determine the effect of converting a positive FS proximal margin to a negative PS final margin on the risk of local recurrence, recurrence-free survival, and overall survival in a large, representative multi-institutional cohort of patients undergoing GAC resection.

METHODS

Study Population

The US Gastric Cancer Collaborative (GCC) represents a consortium of seven high-volume, academic institutions: Emory University, The Johns Hopkins University, Ohio State University, Stanford University, Wake Forest University, Washington University in St. Louis, and the University of Wisconsin. All patients who underwent resection of GAC via a transabdominal approach between January 2000 and December 2012 at each of the seven institutions were identified. Pertinent demographic, preoperative, intraoperative, and pathologic data were identified from each patient's medical record; pathology staging was assigned according to the American Joint Committee on

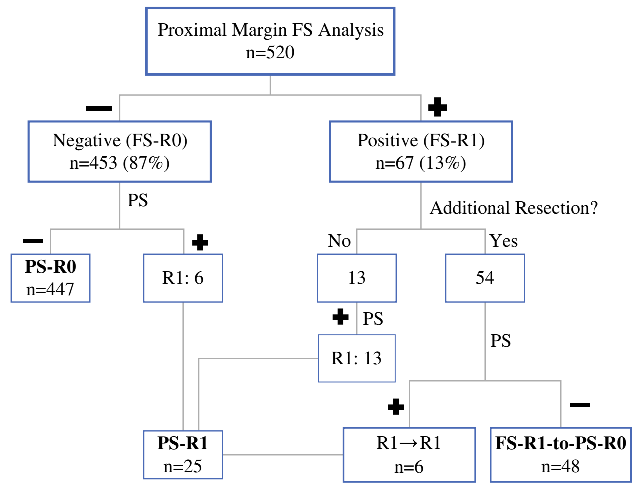


FIG. 1 Division of patient cohorts based on proximal margin frozen section (FS) and permanent section (PS) status. *R0* microscopically negative, *R1* microscopically positive

Cancer Staging Manual, 7th edition.[16] In addition, data regarding neoadjuvant and adjuvant therapies, postoperative outcomes, and recurrence and overall survival were collected. Survival data were verified with the Social Security Death Index. Institutional review board approval was obtained at each respective institution.

Only patients undergoing curative intent resection of GAC who had intraoperative proximal margin frozen section (FS) analysis performed were included; patients undergoing palliative resection, those with known metastatic disease, and 30-day perioperative mortalities were excluded from the analysis. Patients with grossly positive (R2) margins were excluded, and in order to independently evaluate the benefit of converting a positive proximal FS margin to a negative (R0) margin on final permanent section (PS), patients with a positive distal margin on PS were excluded.

Proximal margin status on intraoperative FS analysis was classified as positive (FS-R1) or negative (FS-R0) based on the presence or absence of microscopic residual disease, respectively. The decision of whether to proceed with additional gastric resection in the case of an FS-R1 was at the discretion of the attending surgeon. Final permanent section (PS) proximal margin status was similarly classified as positive (PS-R1) or negative (PS-R0). To assess the utility of converting an FS-R1 to a PS-R0 via additional gastric resection, three subsets were created for analysis based on a similar prior model [17]: PS-R0 patients; PS-R1 patients, encompassing all patients with a positive final PS margin, regardless of FS status and whether or not additional resection was attempted; and FS-R1-to-PS-R0 patients who underwent successful conversion of a positive FS margin (Fig. 1).

The primary objective was to evaluate the effect on local recurrence rates of converting an initial FS-R1 to a final PS-R0 by additional resection. Recurrence was classified as local (anastomotic or gastric remnant), regional (regional lymph nodes), or distant (peritoneal, hepatic, pulmonary, or other sites of metastatic disease). Secondary endpoints included recurrence-free survival (RFS), using the endpoint of any recurrence at any site, and overall survival (OS).

Statistical Analysis

All statistical analysis was conducted with SPSS 19.0 software (IBM Inc., Armonk, NY). Perioperative clinicopathologic factors were compared using χ^2 analysis for categorical variables and Student's t test or one-way analysis of variance for continuous variables, as indicated. Logistic regression analysis was used to determine the association of pathologic variables with the risk of local recurrence. Kaplan–Meier survival plots were calculated for RFS and OS. Univariate and multivariate Cox log-rank regression analyses were performed to assess the effect of proximal margin conversion on RFS and OS in the context of other adverse pathologic features. Statistical significance and the threshold for inclusion of variables in the multivariate model for each endpoint were predefined as $p < 0.05$.

RESULTS

Of 860 patients who underwent curative intent resection, 520 had proximal margin FS analysis performed. Of this cohort, 453 patients (87 %) had a negative FS (FS-R0) and 67 patients (13 %) had a positive FS (FS-R1) (Fig. 1). Fifty-four of these 67 patients underwent additional resection, with 48 who were successfully converted to negative PS proximal margin; these 48 patients (9 %) were designated FS-R1-to-PS-R0. Despite additional gastric resection, the other six patients with FS-R1 remained positive (PS-R1), as did the 13 patients in whom additional resection was not attempted. Of the 453 patients with FS-R0, 447 (86 % of total cohort) were also negative on PS (PS-R0 cohort); the remaining six patients had a false negative FS and were positive on PS (PS-R1). In total, 25 patients (5 %) had a positive proximal margin on PS (PS-R1 cohort) (Fig. 1).

Demographics and clinicopathologic features of the 520 patients are summarized in Table 1. The majority of patients presented with tumors of the gastric antrum or body ($n = 354$; 68 %); most patients were diagnosed with locally advanced GAC, defined as T3-T4 disease ($n = 315$; 61 %) and/or lymph node involvement ($n = 310$; 59 %). Nearly equal number of patients underwent total (44 %) versus subtotal (41 %) gastrectomy, and the majority of patients (72 %) underwent D2 lymph node dissection. The average proximal margin resection distance for all patients, as measured on the pathologic specimen, was 4.6 cm. Median follow-up was 44 months (range 0.3–132.7 months).

Pathologic features stratified by proximal margin FS status are presented in Table 2. A positive proximal margin FS was associated with larger average tumor size (6.9 vs. 4.6 cm; $p < 0.001$), increasing N-stage ($p = 0.003$), a greater frequency of proximal tumors (43 vs. 29 %; $p = 0.02$), diffuse Lauren type histology (36 vs. 19 %; $p = 0.03$), linitis plastica (19 vs. 4 %; $p < 0.001$), and signet ring histology (63 vs. 39 %; $p = 0.001$). A positive FS was associated with more aggressive disease. On multivariate regression analysis, increasing tumor size, proximal location, and signet ring histology remained significantly associated with a positive proximal margin FS (Table 3).

The distribution of pathologic features among the PS-R0, PS-R1, and converted FS-R1-to-PS-R0 cohorts is summarized in Table 1. Patients who underwent PS-R1 and FS-R1-to-PS-R0 resections demonstrated larger tumors, more diffuse type histology, greater T-stage and N-stage, more poorly differentiated tumors, more linitis plastica and signet ring pathology, and were more likely to undergo total gastrectomy as compared to those who underwent PS-R0 resections (Table 1). Compared to the PS-R0 cohort, patients in the PS-R1 and FS-R1-to-PS-R0 cohorts were significantly more likely to develop postoperative complications ($p = 0.01$), major (Clavien grade III–V)[18] complications ($p = 0.02$), and anastomotic leaks ($p < 0.001$).

Local Recurrence

A significantly greater proportion of patients in the PS-R1 cohort experienced local recurrence (32 %) as compared to the PS-R0 or converted FS-R1-to-PS-R0 cohorts (9 % and 10 %, respectively; $p = 0.01$) (Table 1). Overall rates of recurrence at any site did not differ significantly among the three groups ($p = 0.64$) (Table 1), with similar rates of distant recurrence observed across the three cohorts ($p = 0.96$).

Compared to patients in the PS-R1 cohort, the risk of local recurrence on univariate analysis was significantly decreased in both the PS-R0 cohort (hazard ratio [HR] 0.22, 95 % CI 0.09–0.54; $p = 0.001$) and the FS-R1-to-PS-R0 cohort who underwent conversion (HR 0.25, 95 % CI 0.07–0.86; $p = 0.03$). On multivariate analysis, accounting for other adverse pathologic factors (Table 4), a PS-R0 resection displayed a trend toward decreased risk of local recurrence (HR 0.38, 95 % CI 0.13–1.09; $p = 0.07$)

TABLE 1 Clinicopathologic features of all patients with proximal margin frozen section analysis ($n = 520$) – stratified by PS-R0, PS-R1, and converted FS-R1-to-PS-R0 cohorts

Variable	All patients ($n = 520$)	PS-R0 ($n = 447$)	PS-R1 ($n = 25$)	FS-R1-to-PS-R0 ($n = 48$)	p value
Male gender	306 (59 %)	265 (59 %)	13 (52 %)	28 (58 %)	0.77
Age, years	64 ± 13	65 ± 13	63 ± 13	63 ± 13	0.52
ASA class					0.69
1	11 (2 %)	11 (3 %)	0	0	
2	163 (32 %)	139 (32 %)	8 (32 %)	16 (34 %)	
3	307 (61 %)	261 (60 %)	16 (64 %)	30 (64 %)	
4	24 (5 %)	22 (5 %)	1 (4 %)	1 (2 %)	
BMI	25.7 ± 5.6	25.7 ± 5.6	26.4 ± 6.0	25.7 ± 5.6	0.61
Operation type					<0.001
Distal	77 (15 %)	75 (17 %)	2 (8 %)	0	
Subtotal	215 (41 %)	198 (44 %)	7 (28 %)	10 (21 %)	
Total	228 (44 %)	174 (39 %)	16 (64 %)	38 (79 %)	
EBL (mL)	280 ± 256	280 ± 272	334 ± 177	300 ± 232	0.56
Lymphadenectomy					
<D2 dissection	143 (28 %)	119 (27 %)	12 (48 %)	12 (25 %)	0.12
≥D2 dissection	377 (72 %)	328 (73 %)	13 (52 %)	36 (75 %)	
Tumor size, cm	4.9 ± 3.6	4.6 ± 3.1	7.0 ± 5.0	6.9 ± 5.2	<0.001
Histologic type					0.002
Diffuse	112 (22 %)	83 (19 %)	8 (32 %)	21 (44 %)	
Intestinal	249 (48 %)	225 (50 %)	7 (28 %)	17 (35 %)	
Mixed	13 (3 %)	12 (3 %)	0	1 (2 %)	
Not reported	146 (28 %)	127 (28 %)	10 (40 %)	9 (19 %)	
Linitis plastica	30 (6 %)	15 (3 %)	4 (16 %)	11 (23 %)	<0.001
Tumor location					0.03
Antrum	167 (32 %)	154 (35 %)	4 (16 %)	9 (19 %)	
Body	187 (36 %)	159 (36 %)	10 (40 %)	18 (38 %)	
Cardia	54 (10 %)	42 (9 %)	1 (4 %)	11 (23 %)	
Fundus	50 (10 %)	44 (10 %)	3 (12 %)	3 (6 %)	
GE junction	51 (10 %)	39 (9 %)	6 (24 %)	6 (13 %)	
T stage					0.01
Pathologic CR	6 (1 %)	6 (1 %)	0	0	
T1	123 (24 %)	113 (26 %)	1 (4 %)	9 (19 %)	
T2	69 (13 %)	65 (15 %)	1 (4 %)	3 (6 %)	
T3	161 (31 %)	135 (31 %)	7 (28 %)	19 (40 %)	
T4a	122 (24 %)	95 (22 %)	12 (48 %)	15 (31 %)	
T4b	32 (6 %)	26 (6 %)	4 (16 %)	2 (4 %)	
Tumor grade					0.04
Well	32 (6 %)	28 (6 %)	1 (4 %)	3 (6 %)	
Moderate	132 (25 %)	122 (29 %)	2 (8 %)	8 (17 %)	
Poor	333 (64 %)	274 (65 %)	22 (88 %)	37 (77 %)	
Signet ring	217 (42 %)	169 (38 %)	20 (80 %)	28 (58 %)	<0.001
LVI	194 (37 %)	158 (35 %)	15 (60 %)	21 (44 %)	0.03
PNI	98 (19 %)	76 (17 %)	10 (40 %)	12 (25 %)	0.08
N stage					<0.001
N0	210 (40 %)	192 (43 %)	2 (8 %)	15 (31 %)	
N1	85 (16 %)	76 (17 %)	3 (12 %)	6 (12 %)	
N2	90 (17 %)	80 (18 %)	3 (12 %)	7 (15 %)	
N3	135 (26 %)	98 (22 %)	17 (68 %)	20 (42 %)	

TABLE 1 continued

Variable	All patients ($n = 520$)	PS-R0 ($n = 447$)	PS-R1 ($n = 25$)	FS-R1-to-PS-R0 ($n = 48$)	p value
TNM stage					<0.001
I	162 (31 %)	142 (33 %)	0	10 (21 %)	
II	118 (23 %)	106 (24 %)	4 (16 %)	8 (17 %)	
III	240 (46 %)	189 (43 %)	21 (84 %)	30 (62 %)	
Neoadjuvant therapy	129 (25 %)	110 (25 %)	8 (32 %)	11 (23 %)	0.67
Adjuvant chemo.	278 (54 %)	233 (52 %)	18 (72 %)	27 (56 %)	0.40
Adjuvant XRT	174 (34 %)	141 (32 %)	14 (56 %)	19 (40 %)	0.12
Any complication	210 (40 %)	168 (38 %)	13 (52 %)	29 (60 %)	0.01
Major complication	85 (16 %)	65 (15 %)	7 (28 %)	13 (27 %)	0.02
Anastomotic leak	26 (5 %)	15 (4 %)	3 (15 %)	8 (18 %)	<0.001
Any recurrence	155 (30 %)	128 (29 %)	9 (36 %)	18 (38 %)	0.64
Local recurrence	55 (11 %)	42 (9 %)	8 (32 %)	5 (10 %)	0.01
Distant recurrence	111 (21 %)	95 (21 %)	5 (20 %)	11 (23 %)	0.96
RFS, months	35.6 (28–43)	37.2 (23–51)	20.1 (14–26)	25.4 (11–40)	0.08
OS, months	44.2 (35–54)	49.9 (37–64)	25.6 (25–27)	35.7 (20–52)	0.07

ASA American Society of Anesthesiologists, *BMI* body mass index, *chemo.* chemotherapy, *CR* complete response, *EBL* estimated blood loss, *FS* frozen section, *GE* gastroesophageal, *LVI* lymphovascular invasion, *OS* overall survival, *PNI* perineural invasion, *PS* permanent section, *RFS* recurrence-free survival, *XRT* radiation therapy

compared to PS-R1, but the benefit of margin conversion among the FS-R1-to-PS-R0 cohort was absent ($p = 0.26$).

Survival Analysis

On Kaplan–Meier analysis, patients in the PS-R0 cohort demonstrated significantly greater median RFS compared to the PS-R1 cohort (37.2 vs. 20.1 months, $p = 0.05$) (Fig. 2a); the converted FS-R1-to-PS-R0 cohort, however, showed no improvement in RFS compared to the PS-R1 cohort (25.4 vs. 20.1 months; $p = 0.49$). Similarly, the PS-R0 cohort was associated with significantly improved OS compared to the PS-R1 cohort (median 49.9 vs. 25.6 months; $p = 0.02$) (Fig. 2b), whereas the converted FS-R1-to-PS-R0 cohort failed to show a significant difference in OS compared to the PS-R1 cohort (35.7 vs. 25.6 months; $p = 0.14$).

On multivariate regression analysis for RFS (Table 5), increasing T-stage ($p < 0.001$) and increasing N-stage ($p < 0.001$) were the only significant risk factors associated with decreased RFS. Margin status was not significantly associated with RFS. On multivariate analysis for OS (Table 6), increasing T-stage ($p < 0.001$), increasing N-stage ($p = 0.001$), and linitis plastica pathology ($p = 0.03$) remained the only significant risk factors associated with decreased OS. Obtaining a negative proximal margin was not significantly associated with OS in the context of other adverse pathologic factors. Subset analyses stratifying patients by overall TNM stage did not reveal FS-R1-to-PS-R0 conversion to be associated with either RFS or OS on multivariate analysis, even in early stage disease (data not shown).

DISCUSSION

This study represents one of the largest multi-institutional surgical series of patients with resected gastric cancer to date, and serves as a valuable cross-sectional representation of the severity of disease treated at US academic centers. The frequency of proximal margin involvement on frozen section was 13 % ($n = 67$), and the false-negative rate for FS analysis was 1.3 %, similar to previous series.[19] After 48 of the 67 patients with positive FS margins were successfully converted to PS-R0 by additional resection, the final rate of positive proximal margin involvement was 4.8 % ($n = 25$), comparable to other studies.[3,8]

A positive proximal FS was associated with more locally advanced disease and more adverse tumor features. Compared to the PS-R0 cohort, patients in both the PS-R1 and converted FS-R1-to-PS-R0 cohorts demonstrated larger tumor size, higher T-stage and N-stage, more diffuse-type histology, and more poorly differentiated tumors, suggesting that a positive proximal margin FS may simply be a marker of more aggressive disease. Although the rate of local recurrence was significantly decreased in the successfully converted FS-R1-to-PS-R0 patients compared to patients with a positive final PS-R1 margin, patients in the

TABLE 2 Pathologic features associated with proximal margin FS status

Variable	FS-negative ($n = 453$)	FS-positive ($n = 67$)	p value
Tumor size (cm)	4.6 +/−3.2	6.9 +/−5.2	<0.001
Lauren class			0.03
Diffuse	88 (19 %)	24 (36 %)	
Intestinal	225 (50 %)	24 (36 %)	
Mixed	12 (2 %)	1 (2 %)	
Not reported	128 (29 %)	18 (26 %)	
Linitis plastica	17 (4 %)	13 (19 %)	<0.001
Location			0.02
Antrum	154 (34 %)	13 (19 %)	
Body	163 (36 %)	24 (36 %)	
Cardia	42 (9 %)	12 (18 %)	
Fundus	46 (10 %)	4 (6 %)	
GE junction	39 (9 %)	12 (18 %)	
T stage			0.09
Pathologic CR	6 (1 %)	0	
T1	111 (25 %)	12 (18 %)	
T2	63 (14 %)	6 (9 %)	
T3	140 (31 %)	21 (31 %)	
T4a	99 (22 %)	23 (34 %)	
T4b	27 (6 %)	5 (8 %)	
Pathologic grade			0.11
Well	27 (6 %)	5 (8 %)	
Moderate	121 (28 %)	11 (16 %)	
Poor	282 (66 %)	51 (76 %)	
Signet ring	175 (39 %)	42 (63 %)	0.001
LVI	165 (36 %)	29 (43 %)	0.40
PNI	82 (18 %)	16 (24 %)	0.35
N stage			0.003
N0	190 (42 %)	19 (28 %)	
N1	77 (17 %)	8 (12 %)	
N2	80 (18 %)	10 (15 %)	
N3	105 (23 %)	30 (45 %)	
TNM stage			0.01
I	139 (31 %)	13 (20 %)	
II	107 (24 %)	11 (16 %)	
III	197 (45 %)	43 (64 %)	

CR complete response, *FS* frozen section, *GE* gastroesophageal, *LVI* lymphovascular invasion, *PNI* perineural invasion

FS-R1-to-PS-R0 cohort failed to demonstrate significantly improved RFS or OS as compared to the PS-R1 cohort. On multivariate analysis for RFS and OS, increasing T-stage and N-stage remained the most significant determinants of patient outcomes, whereas margin status was not significantly associated with RFS or OS after accounting for other adverse pathologic features.

TABLE 3 Multivariate regression analysis of pathologic factors associated with positive proximal margin frozen section status

Variable	HR	95 % CI	p value
Tumor size, cm	1.19	1.07–1.32	0.001
Lauren class: diffuse	1.23	0.50–3.05	0.65
Linitis plastica	2.34	0.33–16.65	0.40
Location: proximal	2.32	1.02–5.29	0.046
Signet ring	3.26	1.30–8.14	0.012
T stage	1.44	0.95–2.17	0.09
N stage	1.05	0.74–1.48	0.80

CI confidence interval, *HR* hazard ratio

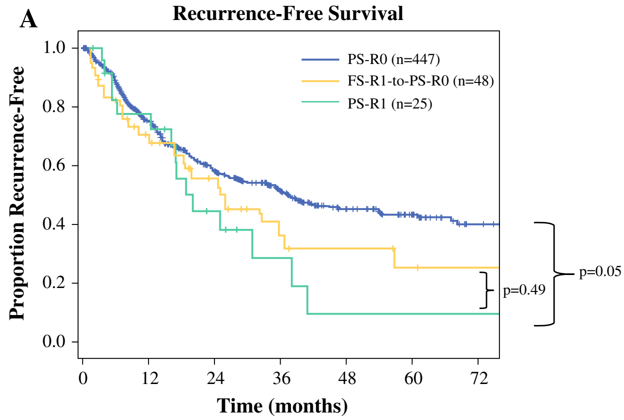
TABLE 4 Multivariate logistic regression analysis of factors associated with increased risk of local recurrence

Variable	HR	95 % CI	p value
Tumor size	1.03	0.93–1.14	0.63
T stage	1.28	0.94–1.76	0.12
N stage	1.39	1.02–1.90	0.03
Histology type (Lauren)			
Intestinal	Ref	–	–
Diffuse	1.41	0.65–3.04	0.39
Tumor grade			
Well to moderate	Ref	–	–
Poor	1.74	0.71–4.27	0.23
Final proximal margin status			
PS-R1	Ref	–	–
PS-R0	0.38	0.13–1.09	0.07
FS-R1-to-PS-R0	0.45	0.12–1.79	0.26

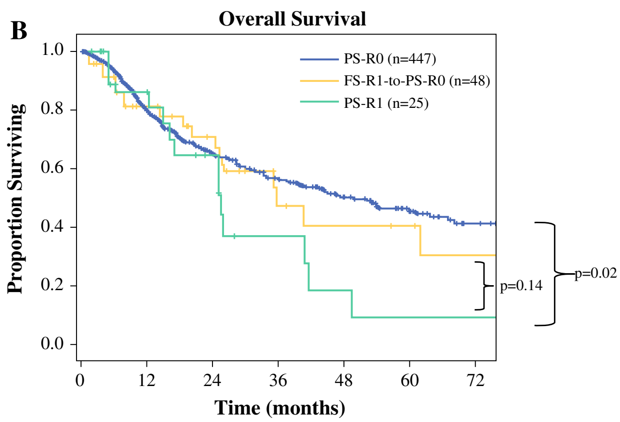
CI confidence interval, *HR* hazard ratio, *Ref*

Given the association of a positive FS with other adverse pathologic factors likely affecting outcomes, extending the gastric resection to achieve negative margins after a positive proximal FS may not significantly improve RFS or OS. This limited improvement in survival gained by additional resection and conversion of a positive FS margin must be weighed against the significantly increased risk of postoperative complications, particularly anastomotic leaks, observed among converted FS-R1-to-PS-R0 patients when making the intraoperative decision of whether to extend the resection.

The overall local recurrence rate of 11 % in the present study is in accordance with prior studies reporting locoregional recurrence rates after GAC resection of 12–25 %.[3,4,8,20–22] The majority of patients who experienced recurrent disease in the present study developed distant metastases, and the frequency of distant recurrence was strikingly similar across all patients, regardless of margin



	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
PS-R0	447	249	153	107	75	55
FS-R1-to-PS-R0	48	26	16	8	6	4
PS-R1	25	15	7	3	1	1



	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
PS-R0	447	271	167	116	83	58
FS-R1-to-PS-R0	48	27	18	8	6	5
PS-R1	25	17	10	4	2	1

FIG. 2 **a** Kaplan–Meier survival analysis of recurrence-free survival by proximal margin status. **b** Kaplan–Meier survival analysis of overall survival by proximal margin status. *FS* frozen section, *PS* permanent section

status. Given that locoregional disease is the most likely site of recurrence affected by a positive margin, the similar frequency of distant recurrence among the three cohorts may explain why the FS-R1-to-PS-R0 cohort failed to demonstrate significant improvements in RFS or OS.

We recently examined the impact of a positive FS margin during pancreaticoduodenectomy for pancreatic adenocarcinoma and found that conversion of a positive FS margin similarly failed to improve survival, as converted patients demonstrated equally poor OS as those with R1 final margins.[17] One of the few studies in gastric cancer examining the association of FS margin status with recurrence rates found that conversion of a positive FS margin by additional resection was associated with a comparable risk of locoregional recurrence as patients with an initial R0 resection,[15] similar to the results of our current study. Another previous study of GAC found that conversion of a positive FS margin by additional resection offered no survival advantage compared to patients with an R1 resection.[5] On subset analysis, only patients with ≤5 positive lymph nodes demonstrated improved survival with margin conversion.[5] In a recent matched case-control analysis, Kim et al.[13] found that patients with an initially positive FS who required additional resection to achieve a margin-negative resection had significantly worse survival than comparable patients with an initial R0 resection, similar to the findings observed in our study. In another report comparing patients with a positive FS who underwent successful conversion to a negative final margin to patients with an R1 final margin, Chen et al.[14] reported that the converted group had significantly greater OS (23 vs.

TABLE 5 Multivariate Cox regression analysis for factors associated with decreased recurrence-free survival

Variable	HR	95 % CI	*p* value
Tumor size	1.01	0.97–1.06	0.54
T stage	1.39	1.20–1.60	<0.001
N stage	1.33	1.16–1.53	<0.001
Tumor grade, poor	1.01	0.70–1.46	0.96
Signet ring	1.03	0.74–1.43	0.86
Linitis plastica	1.54	0.78–3.02	0.21
Histology type, diffuse	1.43	0.93–2.21	0.11
Final proximal margin status			
PS-R1	Ref	–	–
PS-R0	0.74	0.40–1.39	0.35
FS-R1-to-PS-R0	0.85	0.41–1.79	0.68

CI confidence interval, *HR* hazard ratio, *PS* permanent section, *FS* frozen section

TABLE 6 Multivariate regression analysis for factors associated with decreased overall survival

Variable	HR	95 % CI	*p* value
Tumor size	1.02	0.98–1.07	0.37
T stage	1.38	1.18–1.62	<0.001
N stage	1.28	1.10–1.48	0.001
Tumor grade, poor	1.08	0.73–1.60	0.69
Signet ring	1.91	0.70–1.42	0.99
Linitis plastica	2.18	1.10–4.33	0.03
Histology type, diffuse	1.28	0.80–2.05	0.30
Final proximal margin status			
PS-R1	Ref	–	–
PS-R0	0.68	0.37–1.22	0.20
FS-R1-to-PS-R0	0.78	0.42–1.47	0.44

CI confidence interval, *FS* frozen section, *HR* hazard ratio, *PS* permanent section

18 months), although on subset analysis this improved survival persisted only in patients with limited nodal involvement.

Many previous studies have been limited by the inclusion of any R1 margin, including the distal margin, in analyses of the effect of positive margin status on recurrence and survival outcomes. In practice, the FS status of the proximal margin primarily impacts intraoperative decision-making and the extent of gastric resection, as the distal margin cannot typically be extended if an appropriate initial resection 2–3 cm beyond the pylorus has been performed.[2] Consequently, patients with distal margin involvement were excluded from the present study in order to focus on the proximal margin status.

Previous studies have suggested that margin status plays a more significant prognostic role among patients with T1-T2 disease and limited nodal involvement.[3,4,7,10,23] Although stratifying by preoperative clinical stage, T-stage, N-stage, or overall TNM stage failed to demonstrate any association between converted margin status and RFS or OS, the small number of patients within the PS-R1 and FS-R1-to-PS-R0 cohorts with T1-T2 or N0-N1 disease limited the conclusions that could be drawn from these subset analyses. While stage I tumors accounted for only 20 % of all positive FS margins, an attempt at margin conversion may be warranted in this subset of patients with early-stage disease due to its association with decreased local recurrence and the reduced likelihood that patients with stage I tumors will develop distant disease. Conversely, the vast majority of positive FS margins were observed in stage II–III disease, where extending the gastric resection to attempt margin conversion had little impact on survival outcomes. Given the relatively small number of patients in the converted FS-R1-to-PS-R0 cohort, this analysis needs to be repeated in a larger data set to validate these results. The retrospective, observational nature of this study limits the definitive conclusions that can be drawn, and prospective, randomized data might help further address this question. In addition, within the converted FS-R1-to-PS-R0 cohort, only 56 % of patients received adjuvant chemotherapy and 40 % of patients received adjuvant radiation therapy. Although there were no significant differences in the rate of adjuvant therapies across the three subsets, outcomes for the converted FS-R1-to-PS-R0 patients, in particular, may potentially be improved with greater utilization of adjuvant therapies.

CONCLUSION

Although converting patients with a positive FS proximal margin by additional resection may decrease the risk of local recurrence, conversion was not associated with significantly improved RFS and OS, as most patients failed due to distant disease recurrence. Although a negative PS-R0 proximal margin was associated with significantly greater RFS and OS, as compared to a positive R1 margin, these improved results were not observed in patients who underwent conversion of an initially positive frozen section to a negative final margin (FS-R1-to-PS-R0). In the context of other adverse pathologic features, T-stage and N-stage, but not margin status, were the significant factors affecting RFS and OS on multivariate analysis. Before considering additional gastric resection to attempt conversion of a positive proximal FS, given its association with advanced T-stage and nodal involvement, the limited utility of margin conversion should be weighed against the potential increased morbidity of greater extent of resection.

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DISCLOSURE None

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