Impact of proximal resection margin involvement on survival outcome in patients with proximal gastric cancer

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ABSTRACT

Aim The aim of this study was to evaluate the risk factors for proximal resection margin involvement and its impact on survival outcome in patients with proximal gastric cancer.

Methods A total of 488 patients who underwent potentially curative resection for proximal gastric cancer were retrospectively reviewed. Clinicopathological characteristics and survival differences between patients with positive and negative resection margins were compared and prognostic factors were determined by Cox multivariate analysis.

Results In this study, 7.6% (37/488) of patients with proximal gastric cancer had a positive proximal resection margin after postoperative histopathological examination. Positive resection margins were significantly associated with advanced tumour stage and more aggressive biological features including larger tumour size, serosal invasion and lymphovascular invasion. Serosal invasion (OR 4.543, 95% CI 2.201 to 9.380, p<0.001) and lymphovascular invasion (OR 2.279, 95% CI 1.129 to 4.600, p<0.05) were independent risk factors for positive proximal resection margins. In terms of survival outcome, positive resection margins had an adverse impact on the prognosis of patients with proximal gastric cancer (median DFS: 20.7 vs 30.2 months, p<0.001). The multivariate analysis indicated that positive resection margins (HR 1.494, 95% CI 1.042 to 2.142, p=0.029), T stage (T3–T4, HR 2.264, 95% CI 1.484 to 3.454, p<0.001) and N stage (N1–N2 stage, HR 1.696, 95% CI 1.279 to 2.248, p<0.001; N3 stage, HR 2.691, 95% CI 1.967 to 3.681, p<0.001) were independent prognostic factors for patients with proximal gastric cancer.

Conclusion Proximal resection margin involvement was an indicator of more aggressive tumours and an independent prognostic factor for patients with proximal gastric cancer. Aggressive efforts should be made to achieve a negative resection margin if gastric cancer was deemed to be potentially resectable.

INTRODUCTION

According to Global Cancer Statistics 2018, gastric cancer remains the common cause of cancer-related deaths worldwide in the past few years despite a declining trend in its overall incidence.[1] The optimal treatment option for patients with resectable gastric cancer remains curative resection with negative margins and adequate lymphadenectomy. However, recurrence following the curative resection is a critical problem for these patients.[2]

R0 curative resection was defined as en bloc complete resection of the primary tumour without microscopically residual tumour cells in both proximal and distal resection margins. Thus, a microscopically negative resection margin was the prerequisite for R0 resection. Although the intraoperative frozen section was used to determine the resection margin status, resection margin involvement still be detected in histopathological examination after surgery. It has been reported that the incidence of microscopically positive resection margins ranged from 2.3% to 11.2% in patients with potentially resectable gastric cancer.[3–6] To date, there remains considerable debate regarding the prognostic significance of resection margin status for patients with gastric cancer. Not surprisingly, many studies have demonstrated that microscopical resection margin involvement had a negative impact on local recurrence and survival outcomes.[3 6–8] However, other studies reported that positive resection margin was not an independent prognostic factor for patients with gastric cancer, although it was significantly associated with aggressive biological features of tumour.[9 10] In previous studies, the patients with different tumour locations or resection types or with proximal or distal resection margin involvement were analysed together, which could result in a conflicting finding. In the present study, we mainly focused on risk factors for proximal resection margin involvement and its impact on survival outcomes in patients with proximal gastric cancer.

MATERIALS AND METHODS

Patients

We retrospectively reviewed medical records and clinicopathological data of 488 patients with proximal gastric cancer who underwent subtotal or total gastrectomy with curative intent at the Department of Surgical Oncology, First Affiliated Hospital of China Medical University from January 2000 to January 2012. The patients who underwent palliative gastrectomy or with clinical and radiological evidence of peritoneal dissemination or distant metastasis were excluded from this study. Other exclusion criteria included gastro-oesophageal junction tumour (Siewert II and III type), gastric remnant carcinoma, synchronous malignancy

in other organs, neoadjuvant chemotherapy and insufficient medical data.

For all included patients, the following demographic, clinical and pathological variables were collected from their medical records and pathological reports: age, sex, tumour diameter, Lauren classification, histology type, the presence of lymphovascular invasion, resection extent, the number of retrieved lymph nodes, tumour invasion depth (T category) and the number of lymph node metastasis (N category). Written informed consent was obtained from all patients before the surgery.

Surgical procedures and histopathological assessment

Total gastrectomy with Roux-en-Y oesophagojejunostomy usually was a preferred option for patients with proximal gastric cancer. In case of the tumour with the early clinical stage, proximal subtotal gastrectomy was selectively performed. D1$^+$ or D2 lymphadenectomy was performed by a specialised and experienced surgical team, and the extent of lymph node dissection was in accordance with the criteria described by Japanese Gastric Cancer treatment guidelines. We performed combined splenectomy if the spleen was directly invaded by local carcinomatosis or lymph nodes around the splenic artery and splenic hilum was involved.

In this study, the distance of the proximal resection margin was defined as the distance from the proximal limit of tumour lesions to the resection line of the stomach. According to the Japanese Gastric Cancer treatment guidelines,[11] the length of proximal resection margin was at least 2 cm for patients with early gastric cancer, at least 3 cm for patients with advanced gastric cancer with expansive growth pattern and >5 cm for patients with advanced gastric cancer with diffused and infiltrative growth pattern. Intraoperative frozen-section examination was selectively used to evaluate the status of proximal resection margin, especially when the minimum length of proximal resection margin could not be obtained or resection margin involvement was suspected during the operation. Proximal resection margin status was assessed based on the presence of microscopic residual cancer cells. A positive resection margin was defined as the presence of microscopic residual cancer cells at the proximal resection line. If microscopic residual cancer cells were detected in the intraoperative frozen section, additional sections parallel to the section line from the entire margin areas of lesions need to be repeatedly taken. If necessary, additional extending resection was performed to achieve a negative resection margin as possible as it can be. Histopathological examination was independently performed by two experienced pathologists using H&E staining. Histology type was documented according to the Lauren classification.[12] The pathological stage was determined by the eighth edition of tumour, node, metastases staging system of the American Joint Commission on Cancer.

Follow-up

All patients included in this study were regularly followed up with a standardised protocol. Follow-up assessment included ultrasonography, abdominal CT and tumour biomarker test at each visit.[13] In addition, upper digestive endoscopy was annually carried out during the follow-up period. If obvious clinical symptoms and signs were observed or tumour recurrence was suspected, the patients were readmitted for more systematic examinations and tests. Recurrences were classified as locoregional relapse, hematogenous metastasis and peritoneal dissemination. Locoregional recurrences included the recurrence at gastric remnant or anastomotic site and regional lymph node metastasis. The diagnosis of tumour recurrence was mainly depended on the clinical findings, radiological evaluation, endoscopic examination and/or pathological biopsy. In this patient cohort, the median follow-up period was 28 months (range 3–163 months). For the analysis of disease-free survival (DFS), the event was defined as postoperative recurrence at any site or the death owing to gastric cancer-related causes.

Statistical analysis

The clinicopathological characteristics between the two groups were compared using Pearson's χ^2 test or Fisher's exact test for categorical variables and using the Mann-Whitney U test for continuous variables. The logistic regression analysis was used to determine risk factors for positive proximal resection margins in patients with proximal gastric cancer. DFS in patients with proximal gastric cancer was analysed using Kaplan-Meier methods, the prognostic difference between the patients with positive and negative margins was compared using the log-rank test. The Cox proportional hazard model with a stepwise selection procedure, in which all covariates were adjusted simultaneously, was used to determine independent prognostic factors for patients with proximal gastric cancer. The relationships between the prognostic outcome and each clinicopathological factor were expressed as HRs and its 95% CIs. All statistical analyses were performed using the SPSS V.21.0 statistical package (IBM, New York, USA), and the statistical significance was accepted at p value <0.05.

RESULTS

Clinicopathological characteristics and risk factors for positive proximal resection margins in patients with proximal gastric cancer

This patient cohort consisted of 406 males (83.2%) and 82 females (16.8%), with a median age of 61 years (range 30–81). Of 488 patients who underwent potentially curative resection for proximal gastric cancer without clinical or radiological evidence of distant metastasis, 37 patients (7.6%) had a positive resection margin. Concerning tumour stage, 8 patients with proximal resection margin involvement were stage II and 29 patients were stage III, and none of the stage I patients had positive resection margins.

Clinicopathological characteristics of patients with gastric cancer with and without resection margin involvement are summarised in table 1. In comparison to the patients without resection margin involvement, positive resection margins were significantly associated with larger tumour size (8.01±3.14 vs 5.67±2.38 cm, p<0.001), more frequent serosal invasion (67.6% vs 29.5%, p<0.001), lymphovascular invasion (45.9% vs 23.7%, p=0.003) and lymph node metastasis (86.5% vs 63.0%, p=0.004) as well as more advanced tumour stage (stage III 78.4% vs 50.3%, p=0.001). We next investigated the risk factors for proximal resection margin involvement in patients with proximal gastric cancer. The results indicated that serosal invasion (OR 4.543, 95% CI 2.201 to 9.380, p<0.001) and lymphovascular invasion (OR 2.279, 95% CI 1.129 to 4.600, p<0.05) were independently associated with increased risk of positive resection margins (table 2).

Impact of proximal resection margin status on survival outcome in patients with proximal gastric cancer

As shown in figure 1, the median DFS was 20.7 months in the patients with positive resection margins and 30.2 months in the patients with negative resection margins, respectively. There was a significant survival difference between the two patient groups

Table 1 Comparison of baseline characteristics between the patients with positive and negative resection margins

Factor	Patients (%)	Resection margin		P value
		Positive margin (n=37)	Negative margin (n=451)	
Age (years)				0.1
<60	194 (39.8%)	10 (27.0%)	184 (40.8%)	
≥60	294 (60.2%)	27 (73.0%)	268 (59.2%)	
Mean±SD (years)	60.5±10.2	62.6±8.9	60.4±10.3	0.199
Gender				0.203
Female	82 (16.8%)	9 (24.3%)	73 (16.2%)	
Male	406 (83.2%)	28 (75.7%)	378 (83.8%)	
Tumour size (cm)				0.012
<5	141 (28.9%)	4 (10.8%)	137 (30.4%)	
≥5	347 (71.1%)	33 (89.2%)	314 (69.6%)	
Mean±SD (cm)	5.85±2.51	8.01±3.14	8.62±3.57	<0.001
Lauren classification				0.155
Intestinal	199 (40.8%)	11 (29.7%)	188 (41.7%)	
Diffuse	289 (59.2%)	26 (70.3%)	263 (58.3%)	
Lymphovascular invasion				0.007
No	364 (74.6%)	20 (54.1%)	344 (76.3%)	
Yes	124 (25.4%)	17 (45.9%)	107 (23.7%)	
Serosal invasion				<0.001
No	330 (67.6%)	12 (32.4%)	318 (70.5%)	
Yes	158 (32.4%)	25 (67.6%)	133 (29.5%)	
T stage				0.007
T1–T2	76 (15.6%)	0 (0%)	76 (16.9%)	
T3–T4	412 (84.4%)	37 (100%)	375 (83.1%)	
Lymph node metastasis				0.004
No	172 (35.2%)	5 (13.5%)	167 (37.0%)	
Yes	316 (64.8%)	32 (86.5%)	284 (63.0%)	
Resection extent				0.83
Subtotal	206 (42.2%)	15 (40.5%)	191 (42.4%)	
Total	282 (57.8%)	22 (59.5%)	260 (57.6%)	
Retrieved lymph nodes				0.01
Mean±SD	20.6±11.4	16.3±10.8	20.9±11.4	
TNM stage				0.001
I–II	237 (47.6%)	8 (21.6%)	229 (49.7%)	
III	251 (52.4%)	29 (78.4%)	222 (50.3%)	

TNM, tumour, node, metastases.

(p<0.001). According to the univariate analysis, resection margins status (p<0.001), resection extent (p<0.05), tumour size (p<0.001), lymphovascular invasion (p<0.001), the depth of tumour invasion (T stage, p<0.001) and the number of lymph node metastasis (N stage, p<0.001) were found to be significantly associated with poor survival outcome in patients with proximal gastric cancer. Using Cox multivariate analysis, we found that positive resection margins (HR 1.494, 95% CI 1.042 to 2.142, p=0.029), T stage (T3–T4, HR 2.264, 95% CI 1.484 to 3.454, p<0.001) and N stage (N1–N2 stage, HR 1.696, 95% CI 1.279 to 2.248, p<0.001; N3 stage, HR 2.691, 95% CI 1.967 to 3.681, p<0.001) were independent prognostic factors for patients with proximal gastric cancer (table 3).

Table 2 The multivariate analysis of risk factors for positive resection margins

Factor	OR	95% CI of OR	P value
Age (≥60 years)	1.837	0.833 to 4.055	0.205
Sex (male)	0.572	0.244 to 1.341	0.291
Tumour size (≥5 cm)	2.205	0.731 to 6.650	0.090
Lauren type (diffuse type)	1.362	0.629 to 2.953	0.351
Serosal invasion (yes)	4.543	2.201 to 9.380	<0.001
Lymphovascular invasion (yes)	2.279	1.129 to 4.600	0.022
TNM stage (stage III)	1.973	0.876 to 4.443	0.064

TNM, tumour, node, metastases.

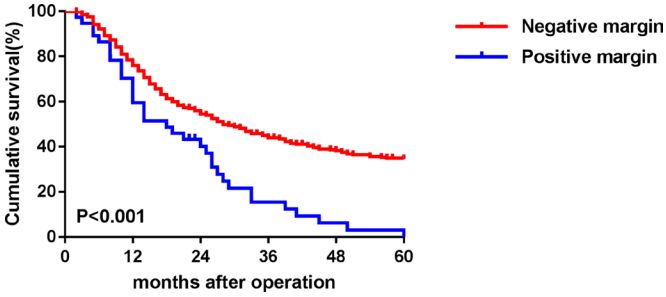

Figure 1 Comparison of survival outcome between patients with proximal gastric cancer with positive and negative resection margins.

DISCUSSION

In case of total gastrectomy for proximal gastric cancer, it is important for surgeons to evaluate the status of proximal resection margin because it could determine the extent of oesophagogastrectomy and surgical method (if thoracotomy needs to be performed). According to the previous reports, the incidence of proximal resection margin involvement was 5.0%–8.2%,[9 10 14] which was higher than distal resection margin involvement.[4 7] In the present study, 7.6% of patients with proximal gastric cancer had a positive proximal resection margin after postoperative histopathological examination. In addition, the result of intraoperative frozen-section biopsy was not always consistent with the final permanent sections at times. In this series of patients, about 3.7% of patients (18/488) had a positive resection margin on final permanent sections, but not on the intraoperative frozen section. Our results demonstrated that patients with positive resection margins had more aggressive biological features and a more advanced tumour stage than those with negative resection margins. Serosal invasion and lymphovascular invasion were independent risk factors for proximal resection margin involvement.

Similarly, some studies reported that the incidence of positive resection margins significantly increased with the depth of tumour invasion and advanced tumour stage.[6 15 16] Bozzetti *et al* reported that the risk of proximal resection margin involvement was significantly higher when the tumour infiltrated into serosal surface or beyond it.[17] Also, Rhome *et al* showed that lymphovascular invasion, advanced tumour stage and larger tumour size were independent risk factors for resection margin involvement in patients with gastric adenocarcinoma.[5] In addition to these factors, it has been reported that Borrmann IV type, poorly differentiated type and diffuse-type gastric cancer were significantly associated with increased risk of resection margin involvement.[4 6 14 18] Therefore, resection margin involvement may be an indicator of more advanced or aggressive tumours. Although the adequacy of resection margin length need be judged by the surgeons, macroscopic normal resection margin determined by intraoperative inspection was usually insufficient to ensure the pathological clearance due to the intramural spread of gastric cancer.[19] Due to the excellent sensitivity, specificity and diagnostic accuracy for resection margin involvement,[20] intraoperative frozen-section examination could help us to reduce the risk

Table 3 Univariate and multivariate analysis of prognostic factors for patients with proximal gastric cancer

	Univariate analysis		Multivariate analysis	
Factor	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age (years)		0.153	–	–
<60	1			
≥60	1.180 (0.940 to 1.481)			
Gender		0.277	–	–
Female	1			
Male	0.849 (0.632 to 1.141)			
Tumour size (cm)		<0.001		0.479
<5	1		1	
≥5	1.663 (1.281 to 2.160)		1.105 (0.838 to 1.457)	
Lauren classification		0.090		0.404
Intestinal	1		1	
Diffuse	1.218 (0.970 to 1.529)		1.064 (0.845 to 1.339)	
Lymphovascular invasion		<0.001		0.119
No	1		1	
Yes	1.783 (1.400 to 2.272)		1.221 (0.944 to 1.578)	
T stage		<0.001		<0.001
T1–T2	1		1	
T3–T4	3.096 (2.056 to 4.661)		2.264 (1.484 to 3.454)	
N stage		<0.001		<0.001
N0	1		1	
N1–N2	1.997 (1.516 to 2.630)	<0.001	1.696 (1.279 to 2.248)	<0.001
N3	3.399 (2.514 to 4.595)	<0.001	2.691 (1.967 to 3.681)	<0.001
Resection extent		0.0270		0.290
Subtotal	1		1	
Total	1.287 (1.029 to 1.608)		1.099 (0.872 to 1.384)	
Resection margins		<0.001		0.029
Negative	1		1	
Positive	2.110 (1.481 to 3.007)		1.494 (1.042 to 2.142)	
Retrieved lymph nodes		0.155	–	–
<16	1			
≥16	0.848 (0.677 to 1.064)			

of positive resection margin and need for reoperation and to determine the extent of surgical resection. To achieve a negative resection margin and better surgical outcome, intraoperative frozen-section examination should be routinely performed in patients with gastric cancer, especially for those with above-mentioned high-risk factors.

The impact of positive resection margins on prognostic outcome in patients with gastric cancer remains controversial. Many studies have demonstrated that resection margin involvement had a negative impact on local recurrence and survival outcomes.[3 6–8] Woo *et al* showed that the median DFS of patients with gastric cancer with positive resection margins was only 11.6 months, which was worse than that of 27.1 months in those with negative resection margins.[3] The data from two Chinese, high-volume research institutions indicated that the 5-year overall survival (OS) of the patients with positive and negative resection margins were 24.2% and 36.8%, respectively; a significant survival difference between two patient groups was observed.[7] However, other studies reported that positive resection margin was not independently associated with recurrence or poor survival outcome in patients with gastric cancer.[9 10] In a retrospective analysis including 191 patients who underwent total gastrectomy for gastric cardia adenocarcinoma, Shen *et al* reported a significant relationship between positive resection margins and advanced disease, but resection margin involvement was not an independent prognostic factor for these patients.[9] On the other hand, the prognostic impact of resection margin involvement may differ for patients with early and advanced gastric cancer. Several studies reported that there was a significant survival difference between patients with positive and negative margins for early gastric cancer or node-negative gastric cancer, but not for patients with advanced gastric cancer.[6 21 22] The adverse effect of positive resection margins in patients with advanced gastric cancer might be overwhelmed by more important prognostic factors such as the depth of tumour invasion and lymph node metastasis.[8] Additionally, frequent peritoneal dissemination and distant recurrence may partially explain why the presence of positive resection margins had no prognostic significance for the patients with advanced tumour stage.[14]

In general, the proximal resection margin of >2 cm should be guaranteed in patients with early gastric cancer, and >5 cm length should be done in patients with advanced gastric cancer. However, it is often very difficult to achieve the recommended length of proximal resection margin due to tumour stage, tumour location, histological type and individual condition. Recently, some related studies have reported that the distance of proximal resection margin does not affect the local recurrence and long-term survival outcome in patients with gastric cancer when a negative resection margin was obtained.[23 24] Therefore, there may not be an absolute

criterion for the optimum distance of proximal resection margin to ensure a negative resection margin. To achieve R0 resection, the safest way was still to determine no microscopic residual cancer cells at resection margins via intraoperative frozen-section biopsy. It may not be necessary to obtain an excessive length of proximal resection margin, especially for those with a negative resection margin.

Resection margin involvement still exists in some cases despite adequate length of proximal resection margin and a negative margin on the intraoperative frozen section. In clinical practice, the management of the patients with resection margin involvement remains a dilemma for surgeons. Whether re-operation or more extensive primary resection should be performed to secure a clear resection margin for the patients with proximal resection margin remains unclear. Theoretically, the presence of microscopic residual cancer cells at the resection line may become the source of local recurrence after surgery. Therefore, surgical retreatment or extending resection aimed to achieve a negative resection margin was usually considered to improve the survival outcome of patients.[21] However, several studies consistently reported that the patients with positive resection margins could not gain a survival benefit from additional extending resection even after successful conversion to a negative resection margin.[4 14 25 26] In addition, local recurrence is not always the most common pattern of tumour relapse in patients with positive resection margins. It has been reported that peritoneal dissemination or distant recurrence in these patients was more frequent than local recurrence in terms of tumour recurrence pattern.[6 15] These findings seem to indicate that the role of additional extending resection for the patients with positive resection margins was limited. Although a recent report revealed that the prognosis of these patients could be improved by re-excision for positive resection margins,[27] high risks of postoperative complications and increased surgical trauma should be prudently weighted.

Another alternative treatment strategy was the administration of adjuvant chemoradiotherapy. To date, increasing evidence has shown that adjuvant chemotherapy could provide the potential survival benefit for patients with stage II–III gastric cancer who underwent curative resection.[28 29] In East Asian countries, capecitabine plus oxaliplatin for 6 months or S-1 monotherapy for 1 year after curative gastrectomy has become the standard treatment regimens, with a promising result. However, it is unclear whether the addition of radiotherapy could provide further benefit for patients with gastric cancer. A recent study reported a significant survival benefit in the patients with positive resection margins who received adjuvant chemoradiotherapy compared with chemotherapy alone,[5] suggesting that multidisciplinary treatment modality was warranted in the setting of incomplete resection. Similarly, Stiekema *et al* showed that 3-year and 5-year recurrence-free survival or OS of the patients with positive resection margins was not significantly different from those with negative resection margins in the setting of adjuvant chemoradiotherapy.[30] Minimal residual cancer cells could be overcome by adjuvant chemoradiotherapy following the operation and patients' own immune system. For the patients with R1 resection, adjuvant chemotherapy and radiotherapy may be considered as an alternative method, especially if a reoperation was technically challenging. These findings provided more evidence for how to manage the patients with positive resection margins. In the future, multiple-centre clinical trials with large sample size and strict eligibility criteria need to be further performed to determine appropriate clinical management for these patients.

Several limitations of the present study require further discussion. First, our study was a retrospective cohort analysis in a single institution with a small sample size. Second, intraoperative frozen-section evaluation was not performed in all included patients, which could increase the incidence of positive resection margins. Besides, diagnostic margins measured on the resection specimen by pathologists were not equivalent to the true surgical margins due to specimen shrinkage and wide use of stapler instruments for organ excisions and digestive reconstruction.[31] In most of the institutions, the resection margin status was mainly determined by the pathologists. To further improve the diagnostic accuracy, the surgeons should be encouraged to involve in the assessment of resection margin status and its length. Third, no sufficient data on the length of proximal resection margins were provided in our electronic database. Therefore, we could not further evaluate its impact on survival outcome in patients with gastric cancer.

In conclusion, the patients with positive proximal resection margins were more likely to suffer from tumour with aggressive biological features and advanced stage. Serosal invasion and lymphovascular invasion were independent risk factors for positive resection margins in patients with proximal gastric cancer. In terms of survival outcome, positive resection margins had an adverse impact on the prognosis of these patients. Aggressive efforts should be made to achieve R0 curative resection, if gastric cancer was deemed to be potentially resectable. Intraoperative frozen-section examination should be recommended in patients with gastric cancer, especially for those with advanced tumour stage, to ensure a negative resection margin.

Take home messages

- The patients with proximal resection margin involvement were more likely to suffer from tumours with aggressive biological features and advanced stage.
- Serosal invasion and lymphovascular invasion were independent risk factors for positive resection margins in patients with proximal gastric cancer.
- Proximal resection margin involvement was an independent prognostic factor for patients with proximal gastric cancer.
- For the surgeons, aggressive efforts should be made to achieve R0 curative resection if gastric cancer was deemed to be potentially resectable.

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Patient consent for publication Not required.

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