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Management of the Positive Proximal Margin during Total Gastrectomy: Dose Re-Excision Benefit all the Time? Findings of a Small-Sample Retrospective Study

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Abstract

Background and Objectives: Positive proximal margin during total gastrectomy suggest non-curative resection, but benefits and risks of extended resection remains controversial. We aim to assess the necessity of re-excision intraoperatively in case of a positive proximal margin.

Methods: 1,115 consecutive gastric cancer patients undergoing total gastrectomy were reviewed retrospectively between August 2014 and March 2017. Thirty-four patients with positive proximal margins were divided into two groups according to whether intraoperative re-excision was performed. The clinicopathologic and prognostic data were analyzed.

Results: Sixteen patients (52.9%) with intraoperative re-excision belonged to re-excision group. There was no significant difference regarding to overall morbidity, mortality and length of stay in hospital between groups. But more frequent occurrence of anastomotic leakage was found in re-excision group (p=0.016). Higher position of anastomosis was found in re-excision group and associated with more anastomotic leakage. Overall survival and progression free survival showed no difference after a short follow-up between groups, although patients in re-excision group had more R0 resections.

Conclusion: During total gastrectomy when negative margin was not achieved at the first attempt, extended resection might result in higher risk of anastomotic leakage instead of better prognosis due to advanced tumor stage.

Keywords: Adenocarcinoma of the esophagogastric junction; Total gastrectomy; Proximal margin; Frozen section

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Introduction

Adenocarcinoma of the Esophagogastric Junction (AEG) is an important clinical issue with growing incidence [1] and poor prognosis [2-4], whose biological behavior is not entirely consistent with gastric cancer. Siewert type I AEG is very rare in China, while for Siewert type I and II AEG which are more common in China, curative total gastrectomy is often regarded as the mainstay therapy [5]. An adequate tumor-free margin was often recommended for gastric cancer including AEG, because positive distal or proximal resection margin was considered related to the diminished survival in a majority of series [6-8]. The involvement of resection margin is affected by various risk factors including margin distances, tumor locations, tumor sizes and lymphatic infiltration and so on [9], nevertheless, the management of a positive frozen section was still debated sometimes during total gastrectomy. Some researchers showed that it might not be necessary in every patient with advanced tumor to achieve R0 resection when taking the surgical challenges and risks into consideration and the prognostic value of resection margin status could be reduced in advanced gastric cancer cases. As a matter of fact, positive proximal resection margin did not always relate to poorer survival in the curative resection [10,11] and more frequently found in palliative resections [12]. According to a study conducted recently, margin status can only be considered as an independent index of survival in patients with the disease of T1 or T2 or those with less than three disease-positive nodes [13]. Frozen sections of esophageal margin are often recommended so as to achieve a tumor-free proximal margin [14]. However, a positive intraoperative proximal resection margin usually poses a management dilemma for surgeons – would more extended resection always benefit patients when

anastomotic complications get higher? Neither randomized trials nor meta-analyses had been published on the subject. It looks reasonable to conduct re-excision only in the groups where R0 resections would benefit survival. Kim et al. [11] found that patients could achieve survival benefits from re-excision based on frozen section results only when there were less than 5 positive lymph nodes. Here, our research was intended to evaluate advantages and disadvantages of re-excision following a positive esophageal frozen section in total gastrectomy, and to assess the influence of an extended resection on patients' prognosis.

Patients and Methods

A total of 1,115 patients suffering from gastric adenocarcinoma including AEG who underwent total gastrectomy between August 2014 and March 2017 were recorded at the Department of General Surgery, Zhongshan Hospital, Fudan University. Patients with any history of other cancers or pre-operative therapy for gastric cancer were excluded. Informed consent from patients was approved by the hospital *Clinical Research Ethics Committee*. A macroscopically tumor-free proximal resection margin was achieved on all patients. D2 lymph node dissection was routinely performed according to the Japanese Gastric Cancer Treatment Guidelines (version 3) [15]. Spleen-preserving No. 10 lymph node dissections were performed if necessary according to the guidelines. Roux-en-Y esophagojejunostomy was selected for all the patients in reconstruction. 530 cases performed intraoperative frozen section to clarify the proximal margin status. There was no formalized standard to identify which patients or samples should be assessed by frozen section since this was a retrospective research. Basically, the decision to conduct a frozen section was based on the preoperative histology, the tumor's macroscopic appearance, as well as the proximal distance to the resection margins. A standard cryostat section followed by hematoxylin and eosin staining was utilized to conduct frozen-section margin analysis. We defined a positive intraoperative frozen section as the presence of tumor cells or severe dysplasia within 1 mm from the resection margin. Thirty-four patients showed a positive intraoperative proximal margin amongst the 530 patients (Figure 1A). The permanent section was used as the "gold standard" to assess the intraoperative frozen section's accuracy. Twenty-one patients didn't undergo extended gastric resection (non-re-excision group) after a microscopically positive frozen section in consideration of surgical difficulties (a long section of esophagus has been removed), advanced tumor stage (extensive lymph node metastasis, obvious tumor invasion and so on) and/or patients' physical conditions (elderly, severe hypertension, heart disease and other complications). The reasons were listed in Figure 1B why these patients didn't undergo re-excision. The clinicopathological features of the other 18 patients without re-excisions were used for comparison.

The proximal resection distance was defined as the distance between the lesion's proximal edge and the cutting line. Due to the esophageal elasticity, there are often biases in the length of resected esophagus measured intraoperatively or after resection. The length of resected esophagus was not easy to measure correctly due to shrinkage of esophagus after resection especially when re-resection performed. The location of anastomosis was a reliable indication which was consistent with the length of resected esophagus. The location of anastomosis was finally examined by abdominal CT scan within 12 to 14 weeks after operation. A-T distance is defined as the distance between the anastomosis and lower margin of 12th thoracic vertebra. Patients' demographics and clinicopathologic characteristics as well as survivals were collected. Based on the seventh version of AJCC/UICC guidelines, TNM stage was reported. Follow-up was carried out by means of outpatient clinic or telephone interview. Survival time was measured from the operation date to the last follow-up date of March 30th, 2018 or to death. In addition, to identify whether R0 resections are critical to advanced gastric cancer patients, we collected a consecutive series of non-metastatic gastric cancer patients with TNM III stage from January 2003 to December 2013 (n=1156). Survival analyses were performed for patients undergoing gastrectomy and lymphadenectomy with no less than 15 lymph nodes resected. The research's flow diagram is shown in Figure 1A. Statistical analyses were performed using SPSS version 10.0 (SPSS, Chicago, IL, USA), GraphPad Prism version 6. Univariate analysis was done using two-tailed chi-square test or unpaired Student's t-test. Survival probability was estimated using the Kaplan-Meier method. The survival curves were compared using the log-rank test. $P<0.05$ was considered statistically significant.

Results

The clinicopathological and surgical related characteristics of the 34 patients were summarized in Table 1. Thirty-two patients (94.1%) were males and 2 patients were females. Total gastrectomy was performed in all 34 patients through transhiatal approach, and

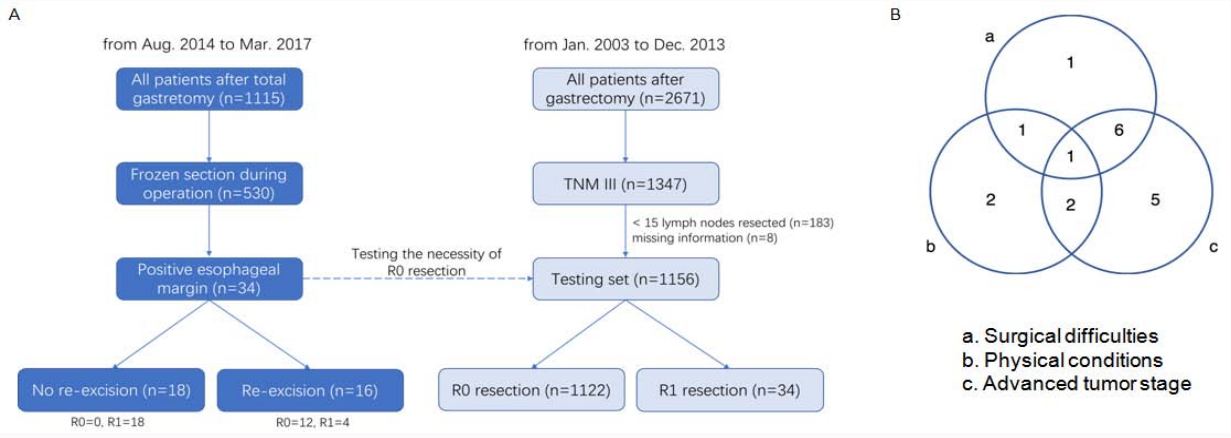


Figure 1: Patients and methods involved in this study. A. The flow diagram of the study. B. Reasons for the patients without undergoing re-excisions in this study (n=18).

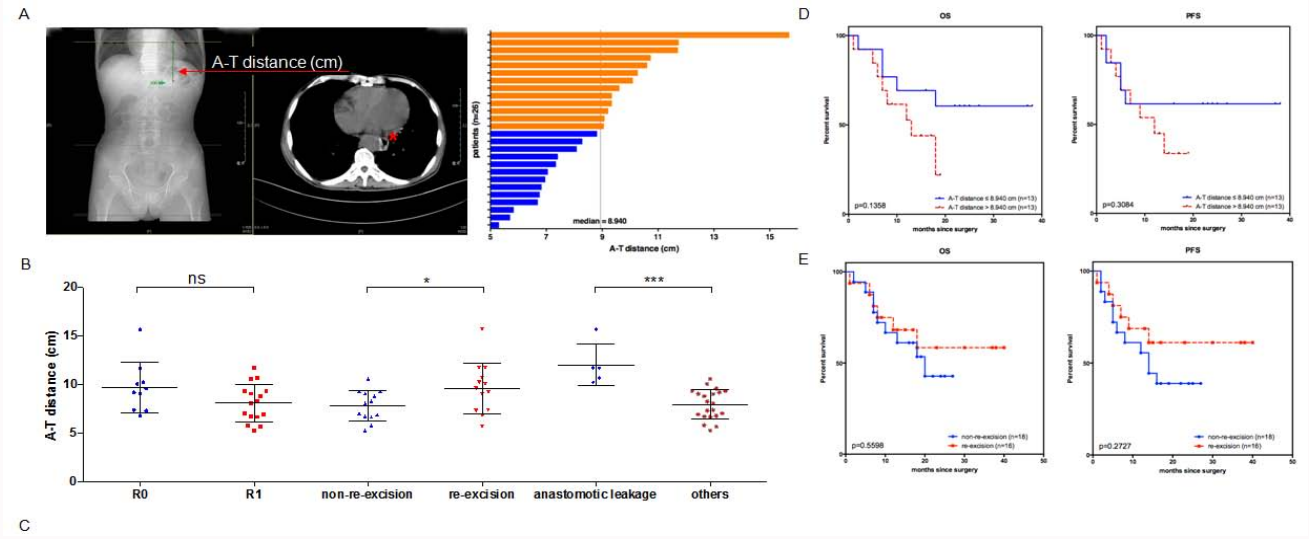
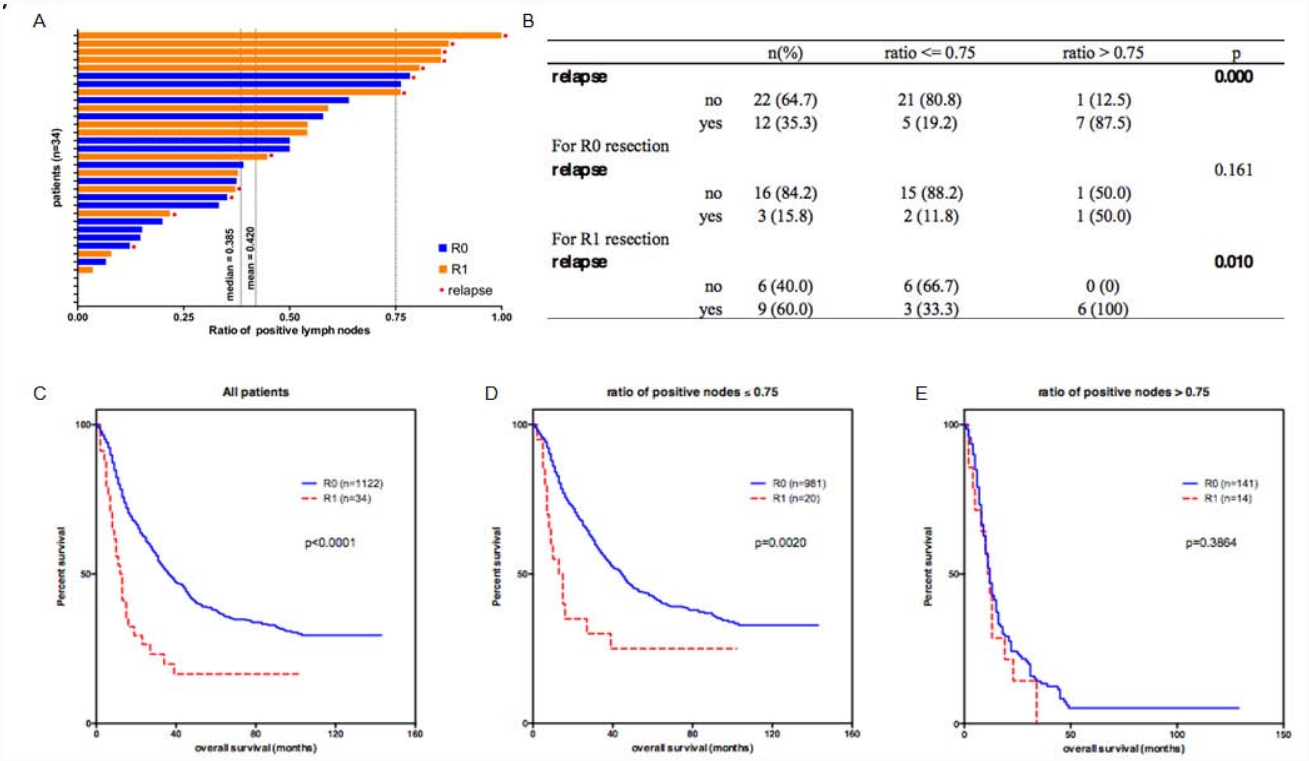


Figure 2: Re-excision was associated with more anastomotic leakage rather than a better prognosis. A. A-T distance was measured by postoperative CT scan in 26 out of 34 patients (mean =8.757 cm, median =8.940 cm). The location of anastomosis was marked with yellow line (left) and red star (right); B. A-T distance was significantly higher in re-excision group and patients with anastomotic leakage (n = 5), compared to their counterparts. However, there was no difference on A-T distance between R0 and R1 resection group; C. Greater A-T distance was associated with higher risk of anastomotic leakage (p=0.013); D. KM curves showed that larger A-T distance was not significantly associated with better overall survival (OS, p=0.1358) or progression free survival (PFS, p=0.3084); E. Re-excision was not associated with better OS (p=0.5598) or PFS (p=0.2727).



		n(%)	ratio <= 0.75	ratio > 0.75	p
relapse					**0.000**
	no	22 (64.7)	21 (80.8)	1 (12.5)	
	yes	12 (35.3)	5 (19.2)	7 (87.5)	
For R0 resection					
relapse					0.161
	no	16 (84.2)	15 (88.2)	1 (50.0)	
	yes	3 (15.8)	2 (11.8)	1 (50.0)	
For R1 resection					
relapse					**0.010**
	no	6 (40.0)	6 (66.7)	0 (0)	
	yes	9 (60.0)	3 (33.3)	6 (100)	

Figure 3: R0 resection might not be the most important prognostic factor in patients suffering from advanced gastric cancer with serious lymph nodes metastasis. Among these 34 patients, average of lymphatic metastatic ratio was 0.420, with the median of 0.385. Higher lymph node ratio (LNR, more than 0.75) was associated with higher risk of relapse (Fig 3A), and the details were shown in Fig 3B. In the retrospective analysis of 1156 gastric cancer patients, we found that R0 resection was not associated with a better prognosis compared to R1 resection among those with higher LNR (more than 0.75; Fig 3C).

16 patients (47.1%) had re-excision operations (re-excision group) including two patients through additional transthoracic approach. The others who didn't have an extended resection belong to the non-re-excision group (n=18). The median age was 65 years ranging from 53 to 84 years. The average tumor size was 6.39 cm ranging from 2.0 cm to 16.0 cm. It was 6.96 cm (range 2.0 cm to 16.0 cm) in the non-re-excision group as compared with 5.75 cm (range 2.0 cm to 13.0 cm) in the re-excision group. The two groups showed no significant difference regarding age, gender, and tumor size, depth of invasion, lymph node metastasis, distant metastasis, TNM stage

Table 1: Clinicopathologic Variables for AEG Patients with positive intraoperative frozen sections (with or without re-excision.

	n (%)	no re-excision	re-excision	p
Gender				0.487
male	32 (94.1)	16 (88.9)	16 (100)	
female	2 (5.9)	2 (11.1)	0 (0)	
Age (years)				
median	65	65	63	
range	53-84	53-79	53-84	
Length of proximal margin				**0.002**
<=5 cm	18 (52.9)	14 (77.8)	4 (25.0)	
>5 cm	16 (47.1)	4 (22.2)	12 (75.0)	
Permanent pathology				**<0.001**
R0	12 (35.3)	0 (0)	12 (75.0)	
R1	22 (64.7)	18 (100)	4 (25.0)	
Pathological type				0.729
differentiated	12 (35.3)	7 (38.9)	5 (31.3)	
undifferentiated	22 (64.7)	11 (61.1)	11 (68.8)	
Lauren type				0.681
intestinal	7 (20.6)	3 (16.7)	4 (25.0)	
diffuse	27 (79.4)	15 (83.3)	12 (75.0)	
nerve involved				0.250
no	9 (26.5)	3 (16.7)	6 (37.5)	
yes	25 (73.5)	15 (83.3)	10 (62.5)	
vessels involved				0.052
no	9 (26.5)	2 (11.1)	7 (43.8)	
yes	25 (73.5)	16 (88.9)	9 (56.3)	
Depth of invasion				0.151
T1	3 (8.8)	0 (0)	3 (18.8)	
T2	1 (2.9)	0 (0)	1 (6.3)	
T3	11 (32.4)	6 (33.3)	5 (31.3)	
T4	19 (55.9)	12 (66.7)	7 (43.8)	
N stage				0.222
N0	4 (11.8)	1 (5.6)	3 (18.8)	
N1	2 (5.9)	0 (0)	2 (12.5)	
N2	4 (11.8)	2 (11.1)	2 (12.5)	
N3	24 (70.6)	15 (83.3)	9 (56.3)	
Distant metastasis				0.230
M0	31 (91.2)	15 (83.3)	16 (100)	
M1	3 (8.8)	3 (16.7)	0 (0)	
TNM stage				0.065
I	3 (8.8)	0 (0)	3 (18.8)	
II	1 (2.9)	0 (0)	1 (6.3)	
III	27 (79.4)	15 (83.3)	12 (75.0)	
IV	3 (8.8)	3 (16.7)	0 (0)	
Length of stay after operation				1.000
<=11 days	17 (50.0)	11 (52.4)	6 (46.2)	
>11 days	17 (50.0)	10 (47.6)	7 (53.8)	
Combined cardiovascular diseases				0.303
no	17 (50.0)	11 (61.1)	6 (37.5)	
yes	17 (50.0)	7 (38.9)	10 (62.5)	
Perioperative morbidity				0.303
no	17 (50.0)	11 (61.1)	6 (37.5)	
yes	17 (50.0)	7 (38.9)	10 (62.5)	
Anastomotic leakage				**0.016**
no	29 (85.3)	18 (100)	11 (68.8)	
yes	5 (14.7)	0 (0)	5 (38.5)	
Hospitalization expenses (RMB)				0.250
<=100,000	25 (73.5)	15 (83.3)	10 (62.5)	
>100,000	9 (26.5)	3 (16.7)	6 (37.5)	

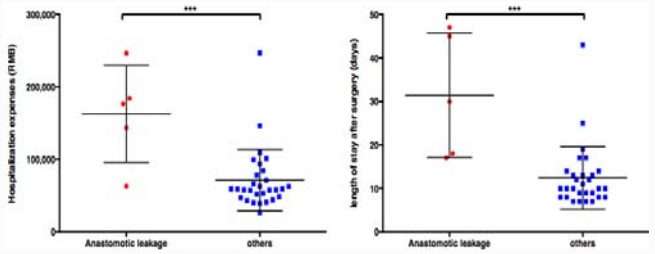


Figure S1: Perioperative anastomotic leakage indicated longer stay and enhanced cost of hospitalization.

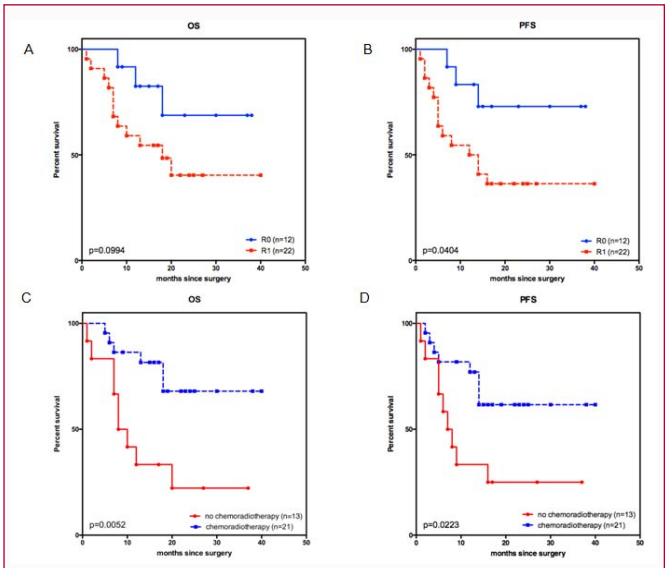


Figure S2: For these 34 patients with positive intraoperative frozen sections, on-time scheduled adjuvant chemotherapy was a key prognostic factor indicating better OS and PFS.

and pathological type. Although there was a higher incidence of perioperative morbidity in re-excision group, no statistical difference was found (62.5% *vs.* 38.9%, p=0.303). However, as shown in Table 1, re-excision was significantly associated with more anastomotic leakage (38.5% *vs.* 0%, p=0.016), and one patient (6.3%) in re-excision group died of anastomotic leakage and severe infection. The length of resected esophagus was significantly different between two groups. A-T distances were assessed using postoperative CT scan (Figure 2A), which can reflect the extent of resected esophagus. Twenty-six out of 34 patients took CT scans in our hospital after surgery within 3

months, and A-T distances ranged from 5.31 cm to 15.79 cm (median =8.940 cm, mean =8.757 cm). We found that both re-excision and anastomotic leakage were significantly associated with larger A-T distances (Figure 2B and 2C). Moreover, anastomotic leakage was significantly associated with more hospitalization expenses and length of stay (Figure S1). The median follow-up time after surgery was17 months (ranging from 1 to 40 months). Although re-excision was found indicating higher rate of R0 resections (75% *vs.* 0%, p<0.001), neither performing re-excision nor A-T distance was associated with Overall Survival (OS) or Progression-Free Survival (PFS) as were shown in Figure 2D and 2E. However, R0 resection confirmed by paraffin pathology and appropriate postoperative chemotherapy both indicate a better prognosis compared with their counterparts (Figure S2). Further analysis showed that most of the patients with short-term recurrence and metastasis had a relatively advanced N stage. The probability of postoperative recurrence and metastasis increased significantly in patients with Lymph Node Ratio (LNR) more than 0.75 (87.5% *vs.* 19.2%, P<0.001). Oncological relapse and permanent pathological R1 resections usually occurred in those with LNR over 0.75 (Figure 3A and 3B), which may indicate a more severe tumor aggressiveness and malignant biological behavior. In order to find out whether patients with LRN>0.75 would benefit from R0 resections or not, especially in case of positive frozen sections, we retrospectively collected and analyzed the survival data of 1,156 gastric cancer patients undergoing gastrectomy from January 2003 to December 2013 (Figure 1), and results showed that histologically positive margins were not associated with worse outcomes if LNR was more than 0.75 (Figures 3C-3E).

Discussion

The topic of margin clearance and prognosis value has been controversial owing to the diversity in the tumor stage, definition of margin positivity and surgical process. Kim demonstrated theater-excision in case of a positive frozen section was recommended for patients with fewer than five positive nodes [11]. According to Chen, only those with N2-stage tumor could benefit from re-excision due to a positive margin. Thus, it was proposed that when a positive margin was shown in a frozen section, the greatest efforts should be conducted to gain a negative margin in no more than N2-stage patients. Oppositely, N3 disease patients should be closely observed [16]. Similarly, Sun [17] and Cho [18] proposed that R1 resections may have adverse effects only in low-stage cancer patients. Consistent with above researches, our research suggested that the intraoperative strategy for patients with positive frozen sections should be established on the nodal status that can be assessed preliminarily in the course of operation. According to our study, patients suffering from higher rate of lymphatic metastasis (more than 0.75) would not benefit from re-excision, which is consistent to some extend with these former studies. Our study showed that R1 resection confirmed by permanent pathology did indicate worse PFS, but re-excision in case of positive frozen sections didn't, which were not fully consistent with former researches possibly because of the small sample size and limited statistical power of the study. Chan et al. [19] found that a positive esophageal margin is an independent poor prognostic factor for overall survival. Mariette et al. [6], who had reviewed 94 esophagogastric junction adenocarcinomas, reported a similar result. The following reasons might be able to explain the discrepancy. Firstly, it was a retrospective research according to the few patients suffering from positive margins in a single institution. Secondly, a positive frozen section was usually related to the advanced disease. According to Kim et al. [11] and Gall et al. [12], a positive margin might lose the predicting value for survival in the advanced-stage patients. Lastly, intraoperative re-excision was associated with higher rate of perioperative morbidity and anastomotic leakage, which delayed scheduled postoperative chemotherapy for those late-stage cancer patients, and several reports have shown that postoperative inflammation due to leakage may have a negative impact on long-term survival in patients with advanced gastric cancer [20]. The occurrence of anastomotic leakage is considered to be related with local factors (anastomotic position, tension of anastomosis, local blood supply, fluid accumulation around anastomosis, etc.) as well as systemic factors (age, cardiovascular diseases, diabetes mellitus, nutritional status, blood flow infection, etc.). Song [20] reported that higher tumor location may independently increase the risk of anastomotic leakage. Based on above findings, using CT scan after gastrectomy, we define the position of anastomosis with relatively objective criteria (A-T Distance) instead of lengths of resected esophagus in order to precisely describe anastomotic locations. Our results showed that the incidence of anastomotic leakage was significantly higher in re-excision group in case of a positive frozen section during total gastrectomy, and A-T distances in re-excision group or in patients with anastomotic leakage are significantly higher than their counterparts, which mean more extent of esophagus was resected in the re-excision group. Therefore, we recommend a one-time full resection as far as possible to achieve a negative margin. Otherwise, there could be a series of problems in case of re-excision, including esophageal retraction (inevitably too much resection of esophagus), higher anastomotic positions, greater surgical difficulties, and more esophageal injury, which may finally result in more anastomotic leakage. The increased operative morbidity and mortality of re-excision should be balanced with the benefits of re-excision, particularly amongst the advanced-stage patients as the re-excision of a positive margin may be demanding technically and need specialized surgeons with rich experience. Here a new concept of A-T distance is introduced to describe anastomotic location. We can assess the relative location of diaphragm and anastomosis from the postoperative CT scan image. A larger A-T distance shows a higher ratio of morbidity, particularly longer hospitalization stays and anastomotic leakage that may delay the beginning of scheduled adjuvant chemotherapy. Usually, the survival of this group of late-staged patients is more determined by the effect of chemotherapy rather than R0 resection. Thus, the advantages of extended resection from an oncologic standpoint should be weighed against the potential enhanced morbidity, according to patients' premorbid status and their ability to withstand more radical resections or extra incisions. Nevertheless, it seems rational to take intraoperative frozen section as the method to recognize positive margins and to achieve a negative margin with intraoperative re-excision amongst patients at relatively early stage. When intraoperative frozen section reveals a positive margin, a surgical re-excision may be taken into consideration for patients with fewer positive nodes, because, in such cases, survival tents to be controlled by the positive margin rather than the nodal status. In most situations, transhiatal approach is enough for re-excision. Transthoracic approach was recommended when complete tumor resection couldn't be achieved through transhiatal approach and proximal margin status truly had a critical impact on prognosis. In our study, intraoperative additional transthoracic approach was used in two patients who finally achieved pathological R0 resection (both are pT4aN3M0, A-T distances are 15.70 cm and 9.617 cm respectively), and he suffered from a slight anastomotic leakage with

a sufficient draining through a transthoracic drainage tube placed intraoperatively (discharged on the 18th day after surgery). How to make a clinical choice when the frozen section is positive depends on several factors including patients' physical condition (especially cardiopulmonary function), tumor staging, surgical techniques, etc. Due to the limited sample size, short median follow-up time and retrospective nature of this research, this study is not enough to draw a definitive conclusion and in-depth study and prolonged follow-up were required to comment on the potential survival strengths or weaknesses of additional resections guided by frozen section analysis. However, it can be seen from the existing results that the patients with wide range of esophageal involvement should avoid cutting of omental vessels and retain the possibility of proximal gastrectomy, so as to facilitate reconstruction of esophageal anastomosis, transthoracic approach is a potential choice if necessary. Furthermore, in some specific cases, such as young gastric cancer patients with extensive lymph nodes metastasis, neoadjuvant chemotherapy shall be considered as a way to reduce the tumor size or stage in order to achieve R0 resection more easily. To our knowledge, our study is the first to study the surgical strategy and management of positive proximal frozen sections in total gastrectomy, and more in-depth researches may be needed.

Conclusion

Re-excision was usually related to higher risk of anastomotic leakage, prolonged length of stay, increased hospitalization costs, and delayed postoperative chemotherapy rather than significant survival benefit while intraoperative frozen section indicated positive proximal margin in total gastrectomy, especially under the circumstances that patients are expected to have extensive lymph node metastasis. Therefore, surgeons were expected to determine the necessity of re-excision cautiously.

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