



Influence of the Proximal Margin Length on Local Anastomotic Recurrence in Adenocarcinoma of the Gastroesophageal Junction: A Single-center Experience

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Abstract

Introduction: Curative resection with adequate margins is a treatment principle in gastroesophageal junction cancers. There is still no comprehensive agreement on the length of the negative proximal margin after total gastrectomy in Siewert II and III tumors. Extending the proximal negative margin in this anatomical region is very difficult in some cases and can cause more complications for the patients.

Methods: In a prospective cross-sectional study, 35 patients with GEJ Siewert II and III adenocarcinomas who underwent total radical gastrectomy from 2017 to 2020 were included. Proximal margin length was measured immediately after resection in the operation room. Then, patients were evaluated for local recurrence at the anastomosis site after two years by endoscopic examination. The relationship between negative proximal margin length, local recurrence rate, and overall survival was evaluated.

Results: About 35 patients were included in the study. Twenty-nine (82.9%) cases had negative proximal margins, and 6 (17.1%) cases had positive proximal margins. The least negative proximal margin length was 0.1 cm, and the most were 5 cm. The mean margin was 2±1.6 cm. Based on the endoscopic and pathologic findings, the local recurrence at the anastomosis site was 20% in two years of follow-up. The incidence of local tumor recurrence was higher in patients with positive margins versus patients with negative ones (11.4% vs. 8.6%, P=0.007). There was no significant relationship between the negative proximal margin length and the incidence of local anastomotic recurrence.

Conclusion: According to our findings, in total gastrectomy for Siewert II and III gastric cardia tumors, it is necessary to reach the negative proximal margin in all tumor stages; however, the length of the negative proximal margin has no effect on the rate of local recurrence at the anastomosis site.

Keywords: Gastric adenocarcinoma, Siewert II and III, Proximal margin length

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Introduction

Gastroesophageal junction adenocarcinoma is one of the most prevalent gastrointestinal

cancers, and its incidence has increased dramatically worldwide (1-4). Siewert classification divided the tumors of this region into three types. According to this classification, tumors 1 cm proximal to the

gastroesophageal junction (GEJ) are type I, from 1 cm proximal to 2 cm distal to the GEJ are type II, and distal to 2–5 cm below the GEJ are type III (5). In the case of Siewert type I tumors, the treatment of choice is like esophageal cancers, and esophagectomy is required. In contrast, in the case of type II or III tumors, total gastrectomy is a more appropriate choice (6-8).

Despite many studies, no comprehensive agreement exists on the length of the proximal negative margin after total gastrectomy in such tumors (9-20). Some guidelines suggest 4-6 cm as the negative proximal margin length (21, 22). On the other hand, many studies show that it is enough to reach the negative margin, and a further negative margin length has no effect on the survival of the patients or recurrence rate (23-27). Some studies have shown that the positive proximal margin (R1 resection) does not influence the survival rate in cases of >3 involved lymph nodes and T3,4 tumors (14). Creating further negative proximal margin requires more complicated operations, such as esophageal resection and anastomosis in the thorax, which could impose more complications on patients, especially in cases of unfavorable patients' general conditions and high-risk surgeries.

There are few studies on the effect of negative margin and its length on the local recurrence rate at the anastomosis site. This study aimed to investigate the influence of the negative proximal margin length on the local anastomotic recurrence in GEJ adenocarcinoma in a referral cancer center in Iran.

Material and Methods

Study Design

We designed a cross-sectional prospective study on the new patients diagnosed with gastroesophageal junction tumors. We included patients with tumors 1 cm above to 5 cm below the GEJ (Siewert II and III). All of the included patients underwent total gastrectomy in Shahid Modarres Hospital, Tehran, Iran, from 2017 to 2020. The patients with comorbidities such as diabetes, ischemic heart disease, and a history of prior cancer were excluded from the study. Other exclusion criteria were stage IV tumors, Siewert I tumors, subtotal gastrectomy surgeries, non-adenocarcinoma tumors, and thoracotomy for more resection, intra-thoracic anastomosis. We used the census method and included all patients who fulfilled our criteria. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (ethical code: IR.SBMU.MSP.REC.1398.471).

Study Process

After obtaining informed consent from patients and routine preoperative preparations, patients underwent total radical gastrectomy and modified D2 lymphadenectomy. In addition, 2 cm of the distal

esophagus and 2 cm of the post-pyloric duodenum were resected. The proximal margin was sent for the frozen section during the operation, and after being sure about negative margins, the reconstruction was performed with the Roux-en-Y esophagojejunostomy technique. The anastomosis was done either by hand-sewing or using a circular stapler. If positive margins were reported on the frozen section, the proximal margin was re-excised with a margin of 1 cm, and then the anastomosis was performed. After the specimen excision, the gastroesophageal junction was opened longitudinally, and the distance from the tumor to the cut end of the esophagus was measured and recorded.

Patients were followed up postoperatively after 1, 6, 12, 18 and 24 months. We evaluated them regarding dysphagia and local recurrence symptoms. In the case of positive symptoms, an upper endoscopy was done, and a biopsy was taken from the site of anastomosis. Eventually, all symptom-free patients underwent upper endoscopy at the end of two years.

Statistical Analysis

Demographic and clinicopathological information were collected and analyzed using SPSS-22. The data distribution was evaluated by checking the skewness, kurtosis, and standard deviation (SD). Parametric, non-parametric, and qualitative data are presented as mean±standard deviation (SD), median (range), and number (percentages) as appropriate. The Kolmogorov-Smirnov test assessed the data distribution and showed that the distribution was asymmetric. We used Pearson's chi-squared, Mann-Whitney, and Fisher's Exact test for data analysis, and a P-value less than 0.05 was considered statistically significant.

Results

Forty-four patients were included in the study. Nine patients did not complete the follow-up period, from whom seven cases died in the postoperative period or two years follow-up, and two of them had SCC in the permanent pathology. Of the remaining 35 patients, 21 (60%) were males, and 14 (40%) were females. Regarding age, 57.1% of patients were 65 or younger, and 42.9% were older than 65. According to the Siewert classification, 57.1% of cases were in the Siewert II class, and 42.9% were in Siewert III. All of the patients underwent total gastrectomy with d2 lymph node dissection and reconstruction with Roux-en-Y esophagojejunostomy. Patients' demographic and clinicopathologic data are shown in Table 1.

On permanent microscopic evaluation, 29 patients (82.9%) had a negative, and six (17.1%) had a positive proximal margin. The least negative proximal margin length was 0.1 cm, and the most was 5 cm. The average margin was 2±1.6 cm. Based on the endoscopic evaluation after two years of follow-up

Table 1: Clinicopathological and surgical-related characteristics for all patients (N=35)

Characteristic	Parameter
Age (Year)	
Mean (mean±SD)	64.7 (61.6)
Age (n, %)	
≤65	20 (57.1%)
>65	15 (42.9%)
Gender (n, %)	
Male	21 (60%)
Female	14 (40%)
Siewert type (n, %)	
II	20 (57.1%)
III	15 (42.9%)
Tumor size, mm, (n, %)	
≤3	9 (25.7%)
>3	26 (74.3%)
Tumor size, mm, (n, %)	
≤6	20 (57.1%)
>6	15 (42.9%)
Tumor size, mm, (n, %)	
≤10	30 (86.7%)
>10	5 (14.3%)
Differentiation status (n, %)	
Well	3 (8.6%)
Moderately	13 (37.1%)
Poor	19 (54.3%)
N Stage (n, %)	
N0	18 (51.4%)
N1	8 (22.9%)
N2	3 (8.6%)
N3	6 (17.1%)
Lymph node invasion (n, %)	
No	21 (60%)
Yes	14 (40%)
Margin type (n, %)	
Negative	29 (82.9%)
Positive	6 (17.1%)
T Stage (n, %)	
T1	16 (45.7%)
T2	10 (28.6%)
T3	3 (8.6%)
T4	6 (17.1%)
Proximal frozen section (n, %)	
Negative	23 (65.7%)
Positive	12 (34.3%)
Length of proximal margin (cm) (mean±SD)	2.1±1.6 (cm)
Operation time (min) (mean±SD)	218.62±81.36 (min)

Table 2: Effect of margin status on recurrence (Mann-Whitney test)

Recurrence	Margin status		P value
	Negative	Positive	
No (28 (80.0%))	26 (74.3%)	2 (5.7%)	0.008
Yes (7 (20.0%))	3 (8.6%)	4 (11.4%)	
Total	29 (82.9%)	6 (17.1%)	

and pathologic findings, the local recurrence at the anastomosis site was 20%. The prevalence of local tumor recurrence was significantly higher in patients with positive margins versus patients with negative ones in permanent section pathologic examination (11.4% versus 8.6%, $P=0.007$).

Although there is a lower local recurrence at the site of anastomosis in patients with a microscopic

negative margin, there was no significant relationship between the length of the negative proximal margin and the prevalence of local recurrence.

We divided the variable of negative proximal margin into three groups, <0.5, 0.5–3, and >3, yet found no relationship between negative proximal margin and local recurrence at the anastomosis site ($P>0.05$ for all).

There was no significant relationship between margin status and the differentiation and T-stage of the tumor ($P>0.05$).

Also, there was no significant relationship between proximal negative margin length and local recurrence based on the T-stage and tumor differentiation ($P>0.05$).

A negative proximal margin was in reverse relation with lymphatic metastasis. In patients with less lymph node involvement (lower N status), the prevalence of a proximal negative margin was higher ($P>0.028$). However, there was no relationship between negative margin length and the N status of the tumor. Also, there was no statistically significant relationship between the length of the negative proximal margin and the rate of local recurrence based on the N status of the tumor. Table 2 shows the results of the relationship between proximal negative margin length and local recurrence rate.

Discussion

Adenocarcinoma of the gastroesophageal junction (GEJ) is among the most invasive tumors whose incidence is increasing, especially in some specific regions such as Iran (28). Despite significant improvement in diagnosis, management, and surgical techniques, gastric cardia adenocarcinoma accounts for a high mortality and morbidity rate (29). In addition to TNM staging of the tumors, the proximal margin status is one of the most important prognostic factors, especially in Siewert II and III tumors. According to guidelines, reaching the negative proximal margin in total gastrectomy surgery is necessary; traditionally, the negative proximal margin length is 2 to 3 cm in the early stage and 5 to 6 cm in advanced-stage tumors (24). Despite many recent studies, there is still disagreement about the length of the negative proximal margin (17, 23, 24, 26, 27, 30, 31).

Another issue in gastric cardia tumors is the limitation in the length of the negative proximal margin, which is challenging due to its anatomical position. Suppose we want to do a larger distal esophageal resection and give more margins. In that case, we need higher anastomosis in the posterior mediastinum, which increases the risk of anastomosis leak or need for thoracoabdominal incision or left thoracotomy for intrathoracic anastomosis, imposing more complications on the patients (32). There are many studies concerning the effect of negative margin on the overall survival; most of them state that the negative margin length does not affect the overall survival. However, there are few studies on the effect of negative margin length on the local recurrence rate at the site of anastomosis, which was the purpose of this research.

Mine et al., in their study in 2013, found that a minimum negative proximal margin length of 2 cm is necessary and sufficient for Siewert II and III

tumors (33). In another study by Kim et al., published in 2014, a positive proximal margin was associated with a poor prognosis. Further negative proximal margin lengths were not recommended and did not affect the overall survival and local recurrence (24). In another study by Feng et al. in 2016, the negative proximal margin length had no effect on the survival rate of patients undergoing total gastrectomy, and only reaching a negative microscopic margin was sufficient for the treatment (23). Schoenfeld et al. conducted a study on 91 patients in 2016, and they showed that a positive margin increased recurrence and decreased survival even in the case of postoperative aggressive adjuvant therapy (34).

In the study of Koumariou et al. in 2019, the rate of microscopic margin involvement was reported at 18.9%, which worsened the prognosis of patients, and the importance of achieving a negative proximal margin was shown (35). Niclauss et al., in 2019, systematically reviewed the results of 13 articles. They recommended the length of the negative proximal margin between 2 and 6 cm but did not consider the effect of neoadjuvant therapy on the proximal margin. This study investigated the effect of margin on the overall survival rate, not just local recurrence at the anastomotic site (36).

In the study by Kim et al. 2020, the average margin length in advanced gastric cancers after total gastrectomy was 3.5 cm. They examined the proximal margin length in ≤ 1.0 cm, 1.1-3.0 cm, 3.1-5.0 cm, and >5.0 cm groups. The researchers concluded that the negative proximal margin length was not a prognostic factor in gastric cancers and did not affect patients' local recurrence and recurrence-free survival (37). A meta-analysis and systematic review study by Jiang et al. in 2021 showed that a positive margin (R1 resection) is associated with lower five-year survival and overall survival, and surgeons should try to perform an R0 resection with a negative proximal margin (20).

The results of our prospective study on the patients with gastric cardia cancer undergoing neoadjuvant chemoradiotherapy indicate that a positive proximal margin is associated with a very high local recurrence rate at the anastomotic site, and surgeons must always try to reach the negative proximal margin. On the other hand, our experience, similar to the results of most recent studies and other similar studies in this field, shows that achieving the negative proximal margin in Siewert II and III gastric cardia tumors is enough, regardless of the size and stage of the tumor, and trying to reach to more negative margin length does not affect the local recurrence. On the other hand, creating proximal negative margins can impose more complications on the patients (25-27).

In contrast to the studies that investigated the prognostic effect of the positive proximal margin only in stages I and II of gastric cancer and did not consider any effect of the positive proximal margin in stages III and IV (38), in our study, we showed that

the positive proximal margin in all stages of gastric cardia cancer increases local recurrence at the site of anastomosis, and re-excision to achieve a clear margin is strongly recommended for all patients.

To improve the results, it may be better that the re-excised specimen be sent again for a frozen section during the operation to ensure the negative margin and then do the anastomosis. However, in a few cases, permanent pathology reported proximal margin involvement, opposite to the frozen section results (39, 40).

The advantages of this study include its prospective nature, consideration of the effect of preoperative chemo-radiotherapy, evaluation of local recurrence at the anastomosis site by endoscopy and biopsy, measurement of proximal margin by the surgeon before fixing the specimen in formalin, and evaluation of the relationship between the negative margin and its length and the tumor stage.

The disadvantages of the present study include the small number of cases, the short duration of patients' follow-up, not increasing the margin length in the case of esophagojejunostomy with circular stapling, not evaluating the overall survival rate, not considering the effect of adjuvant chemotherapy regimen, and performing the re-excision and anastomosis without a second pathology report if the first frozen section was positive.

Conclusion

In total gastrectomy for Siewert II and III gastric

cardia tumors, reaching a negative proximal margin in all tumor stages is necessary. However, the length of the negative proximal margin does not affect the local recurrence rate at the anastomosis site. According to the results of this study, performing a total gastrectomy with a negative proximal margin is sufficient for these tumors, and there is no need for a thoracoabdominal incision or left thoracotomy for more proximal incision or esophagectomy. However, creating a maximum negative proximal margin in the abdomen may be reasonable depending on the patient's condition before and during surgery and the likelihood of complications.

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Authors' Contribution

Study conception and design: Adel Zeinalpour, Nasser Malekpour Alamdari, Barmak Gholizadeh; drafting of the manuscript and acquisition of data: Saeidreza Ghaderi, Hamed Ebrahimibagha; critical revision: Barmak Gholizadeh. All authors revised successive versions of the manuscript and approved the final version for publication.

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