

Investigating the Effects of Different Lengths of Proximal Margin for Siewert Type II and Type III Adenocarcinoma of Esophagogastric Junction on Short- and Long-Term Prognosis

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Introduction: The optimal proximal margin length for Siewert type II/III adenocarcinoma of the esophagogastric junction (AEJ) remains debated. This study aimed to evaluate the effect of different proximal margin lengths on short- and long-term prognosis.

Methods: In this retrospective study, clinical data from patients undergoing surgery for Siewert type II/III AEJ between January 2019 and January 2024 were collected. Patients were stratified into three groups based on the length of the proximal margin (0.5–2 cm, 2–4 cm, and >4 cm). Short-term outcomes, including R0 resection rates and complications, along with long-term survival (OS and PFS), were evaluated. Kaplan-Meier survival analysis and Cox proportional hazards regression models were employed to assess prognostic impacts.

Results: A total of 173 patients were included (0.5–2 cm, n=57; 2–4 cm, n=60; >4 cm, n=56). The 0.5–2 cm group had significantly higher R1 resection (12.28% vs 1.67%/0%) and anastomotic recurrence rates but a lower anastomotic leak incidence compared to the other groups ($P<0.05$). The >4 cm group showed longer operative times and higher leak rates. Survival analysis revealed poorer overall survival (OS) and progression-free survival (PFS) for the 0.5–2 cm group versus other groups ($P<0.05$), with no significant difference between the 2–4 cm and >4 cm groups. Cox regression confirmed that a margin length >2 cm reduced progression risk (HR=0.793, 95% CI 0.641–0.981, $P=0.033$), particularly for tumors <4 cm, Siewert type II, and intestinal-type Lauren classification.

Conclusion: A 2–4 cm proximal margin appears to optimize the prognosis in Siewert type II/III AEJ, balancing oncologic safety and surgical outcomes. This margin length is especially beneficial for tumors <4 cm, Siewert II classification, and intestinal-type histology. A personalized surgical strategy is recommended.

Keywords: adenocarcinoma of esophagogastric junction, siewert II/III, proximal margin length, prognosis, survival analysis

Introduction

Adenocarcinoma of the esophagogastric junction (AEJ) is an adenocarcinoma originating from the gastric cardia or subcardial region that invades the esophagogastric junction (EGJ).¹ In recent years, both morbidity and mortality of AEJ have reportedly increased, posing a significant clinical challenge due to its specialized anatomical site, complex surgical maneuvers, and multiple lymphatic drainage routes.^{2,3}

The status of the surgical margin after AEJ resection is a critical prognostic factor. Achieving an R0 resection, defined as the microscopic absence of tumor cells at the resection margin, is associated with a better prognosis. Conversely, the presence of tumor cells at or near the margin (R1 resection) is linked to a higher risk of recurrence and poorer survival outcomes. The 5-year survival rate for patients with R0 resections ranges from 53% to 60%, whereas it drops significantly to 13–26% for those with R1 resections.⁴ Some studies indicate that extending the esophageal resection extent improves survival, although the primary surgical goal remains achieving an R0 resection.^{5,6} In light of this, a key question is whether lengthening the margin distance improves the prognosis for patients with locally advanced AEJ.

Currently, there are no universally recognized standards for the optimal proximal margin distance. Consequently, the chosen margin length is often based on institutional tradition or surgeon experience rather than robust evidence-based

data.⁷ It has been reported that intramural jump metastases increase significantly when esophageal invasion exceeds 4 cm, suggesting that a longer margin may be necessary. However, longer resection margins are associated with a higher risk of complications, such as anastomotic leaks.^{8,9} The tension on the esophagus during surgery can cause retraction, complicating the accurate assessment of the margin and underscoring the importance of achieving an adequate safety distance beyond the macroscopic tumor border.^{10,11} Therefore, this study aims to evaluate the impact of different proximal margin distances on the prognosis of patients with Siewert type II/III AEJ.

AEJ is most commonly classified using the Siewert classification based on the tumor's epicentral location relative to the EGJ: type I (1–5 cm above the EGJ), type II (1 cm above to 2 cm below the EGJ), and type III (2–5 cm below the EGJ).¹² While subtotal esophagectomy is standard for type I tumors, the optimal surgical strategy for type II and III remains controversial.¹³ The extent of lymph node metastasis (LNM) in type II AEG correlates with the degree of esophageal and gastric infiltration, leading to differing preferences for transthoracic esophagectomy (TTE) by thoracic surgeons and transhiatal total gastrectomy (THTG) by gastrointestinal surgeons.¹⁴

This study focuses exclusively on Siewert type II/III AEJ patients treated via a transabdominal approach to analyze the impact of proximal margin distance on short- and long-term outcomes and to identify the optimal margin length to inform clinical practice. Recent overviews of gastric cancer highlight the evolving therapeutic landscape, emphasizing the need for refining surgical standards to improve patient outcomes.^{15–17}

Patients and Methods

Patient Selection

A total of 173 patients with Siewert type II/III adenocarcinoma of the esophagogastric junction who were treated at Bethune International Peace Hospital in Shijiazhuang, Hebei, China, from January 2019 to January 2024 were included in this retrospective study. Inclusion criteria were: (1) pathologically confirmed Siewert type II/III AEJ; (2) no neoadjuvant therapy received before surgery; (3) clear histopathological determination of the proximal margin status; (4) pathological staging of T1-4aN0-3M0. Exclusion criteria included: (1) Siewert type I AEJ; (2) multifocal gastric cancer; (3) synchronous tumors in other organs; (4) invasion of adjacent organs or distant metastasis; (5) receipt of perioperative immunotherapy, chemotherapy, or radiotherapy (Figure 1).

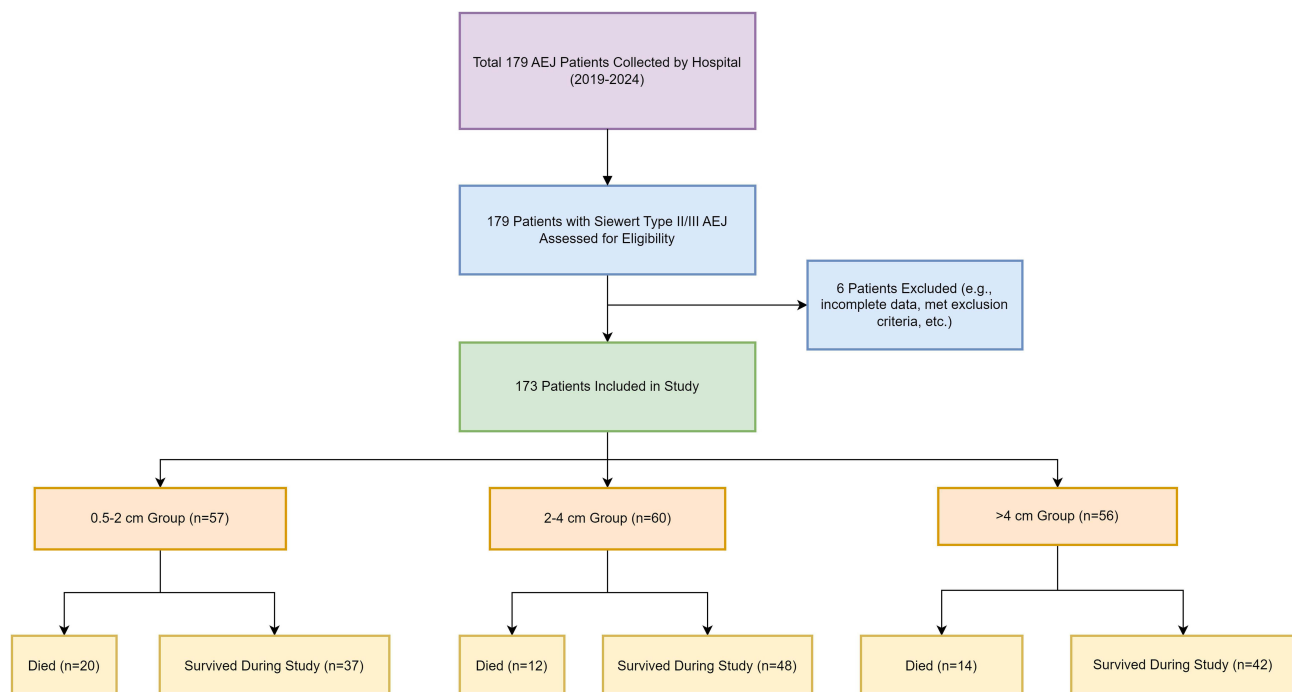


Figure 1 Flow chart of patient selection.

Data Collection

Patient clinical information, including baseline characteristics, surgical details, short-term outcomes, and follow-up data, was collected from electronic medical records and telephone follow-ups. Baseline characteristics included age, gender, body mass index (BMI), tumor size, T stage, N stage, number of lymph node metastases, differentiation grade, presence of lymphovascular or perineural invasion, length of esophageal invasion, Siewert type, Lauren classification, and Borrmann type. Short-term outcomes included R0/R1 resection rate, operative time, blood loss, postoperative complications (eg, anastomotic leak), and length of hospital stay. Long-term outcomes were PFS and OS.

Surgical Procedures

All patients underwent curative-intent surgery via a transabdominal approach, consisting of either proximal or total gastrectomy with D2 lymph node dissection. The type of anastomosis (esophagogastric or esophagojejunal Roux-en-Y) was performed based on tumor location and extent. Intraoperatively, if the proximal margin was deemed potentially insufficient, a frozen section analysis was performed. If positive, an additional 1–2 cm of the esophagus was resected. All surgical procedures adhered to the Japanese Gastric Cancer Treatment Guidelines.⁶ The proximal margin length was measured on the fresh, unstretched surgical specimen immediately after resection by the operating surgeon and confirmed by a pathologist (Figure 2).

Follow-up

All patients were followed up until January 2024. Tumor recurrence and metastasis were assessed by enhanced chest and abdominal CT scans every 3–6 months for the first two years and annually thereafter. Overall survival (OS) was defined as the time from surgery to death from any cause. Progression-free survival (PFS), also referred to as disease-free survival (DFS) in this context, was defined as the time from surgery to the first instance of tumor recurrence, metastasis, or death from any cause.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, USA). Categorical variables were compared using the chi-square test or Fisher's exact test, while continuous variables were compared using ANOVA or the



Figure 2 Representative pictures of margin distance of fresh tumor samples.

Kruskal–Wallis test. Survival curves were generated using the Kaplan–Meier method and compared with the Log rank test. Univariate and multivariate Cox proportional hazards models were used to identify independent prognostic factors and calculate hazard ratios (HRs) with 95% confidence intervals (CIs). A two-sided P-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 173 patients were included. The baseline patient and tumor characteristics are summarized in [Table 1](#). The mean age was 66.05 ± 9.64 years, and 108 (62.4%) patients were male. The cohort was divided into three groups based on proximal margin length: 0.5–2 cm (n=57, 32.9%), 2–4 cm (n=60, 34.7%), and >4 cm (n=56, 32.4%). There were no significant differences in baseline characteristics among the three groups, indicating they were comparable for analysis. Regarding the location of lymph node metastasis, data was available for 73 patients with positive nodes. In the 0.5–2 cm group (n=24 positive), 8 (33.3%) had mediastinal involvement. In the 2–4 cm group (n=28 positive), 7 (25.0%) had mediastinal involvement. In the >4 cm group (n=21 positive), 5 (23.8%) had mediastinal involvement. The difference was not statistically significant (P=0.671), though this analysis is limited by sample size ([Supplementary Table 1](#)).

Comparison of Short-Term Outcomes

Short-term postoperative outcomes differed significantly among the three groups ([Table 2](#)). The 0.5–2 cm group had a significantly higher R1 resection rate (12.3%) compared to the 2–4 cm (1.7%) and >4 cm (0%) groups (P=0.003). Similarly, the anastomotic recurrence rate was highest in the 0.5–2 cm group (8.8%, P=0.021). Conversely, the incidence of anastomotic leak was significantly lower in the 0.5–2 cm group (1.8%) compared to the 2–4 cm (10.0%) and >4 cm (14.3%) groups (P=0.041). The 0.5–2 cm group also had shorter operative times, less intraoperative bleeding, and shorter hospital stays. The >4 cm group had the longest operative times and the highest rates of anastomotic leak. Notably, the mean length of esophageal resection was progressively longer across the groups: 3.3 ± 0.8 cm for the 0.5–2 cm margin group, 5.1 ± 1.0 cm for the 2–4 cm group, and 6.8 ± 1.1 cm for the >4 cm group (P<0.001).

Table 1 Baseline Patient and Tumor Characteristics Overall and by Proximal Margin Group

Variable	Total (n=173)	0.5–2 cm (n=57)	2–4 cm (n=60)	>4 cm (n=56)	P-value
Age (years), mean±SD	66.05±9.64	66.51±9.82	65.23±9.01	66.57±10.23	0.735
Sex, n (%)					0.986
Male	108 (62.4)	36 (63.2)	37 (61.7)	35 (62.5)	
Female	65 (37.6)	21 (36.8)	23 (38.3)	21 (37.5)	
Tumor size >4cm, n (%)	37 (21.4)	15 (26.3)	14 (23.3)	8 (14.3)	0.278
T stage, n (%)					0.934
T1-T2	34 (19.7)	12 (21.1)	11 (18.3)	11 (19.6)	
T3-T4	139 (80.3)	45 (78.9)	49 (81.7)	45 (80.4)	
N stage, n (%)					0.607
N0-N1	100 (57.8)	33 (57.9)	32 (53.3)	35 (62.5)	
N2-N3	73 (42.2)	24 (42.1)	28 (46.7)	21 (37.5)	
Differentiation, n (%)					0.598
High/moderate	102 (59.0)	28 (49.1)	35 (58.3)	32 (57.1)	
Poor	71 (41.0)	29 (50.9)	25 (41.7)	25 (42.9)	
Siewert type, n (%)					0.572
II	96 (55.5)	34 (59.6)	34 (56.7)	28 (50.0)	
III	77 (44.5)	23 (40.4)	26 (43.3)	28 (50.0)	
Lauren pattern, n (%)					0.991
Intestinal	59 (34.1)	19 (33.3)	20 (33.3)	20 (35.7)	
Diffuse/mixed	114 (65.9)	38 (66.7)	40 (66.7)	36 (64.3)	

Table 2 Short-Term Postoperative Outcomes in the Three Groups

Variable	0.5–2 cm (n=57)	2–4 cm (n=60)	>4 cm (n=56)	P-value
R1 resection rate, n (%)	7 (12.3)	1 (1.7)	0 (0)	0.003
Anastomotic leak, n (%)	1 (1.8)	6 (10.0)	8 (14.3)	0.041
Anastomotic recurrence, n (%)	5 (8.8)	1 (1.7)	0 (0)	0.021
Total operative time (min), median (IQR)	170 (155–190)	187 (170–205)	195 (180–215)	<0.001
Intraoperative bleeding (mL), median (IQR)	100 (80–150)	100 (80–160)	120 (100–200)	0.021
Postoperative hospital stay (days), median (IQR)	11 (9–14)	11 (10–15)	12 (10–18)	0.032
Length of esophageal resection (cm), mean±SD	3.3 ± 0.8	5.1 ± 1.0	6.8 ± 1.1	<0.001

Survival Analysis

Kaplan-Meier survival analysis (Figure 3A and B) showed that patients in the 0.5–2 cm group had significantly poorer OS and PFS compared to those in the 2–4 cm and >4 cm groups ($P<0.05$ for both). There was no significant difference in OS or PFS between the 2–4 cm and >4 cm groups ($P>0.05$).

We analyzed the patterns of first recurrence in patients with disease progression (Supplementary Table 2). In the 0.5–2 cm group, 10 of 20 recurrences (50.0%) were locoregional (anastomotic or regional nodes). In contrast, the 2–4 cm group had 4 of 12 (33.3%) and the >4 cm group had 3 of 14 (21.4%) locoregional recurrences. While the higher rate of locoregional recurrence in the shortest margin group did not reach statistical significance ($P=0.211$), likely due to the small number of events, it aligns with the higher rates of R1 resection and anastomotic recurrence observed in this group.

Cox Regression Analysis of Prognostic Factors

Univariate Cox regression analysis showed that a proximal margin length of <2 cm was associated with worse PFS. In the multivariate analysis (Table 3), after adjusting for confounding factors, a proximal margin length >2 cm (combining the 2–4 cm and >4 cm groups) was an independent predictor of improved PFS (HR=0.793, 95% CI 0.641–0.981, $P=0.033$) compared to a margin <2 cm. However, this association was not statistically significant for OS (HR=0.819, 95% CI 0.661–1.015, $P=0.068$).

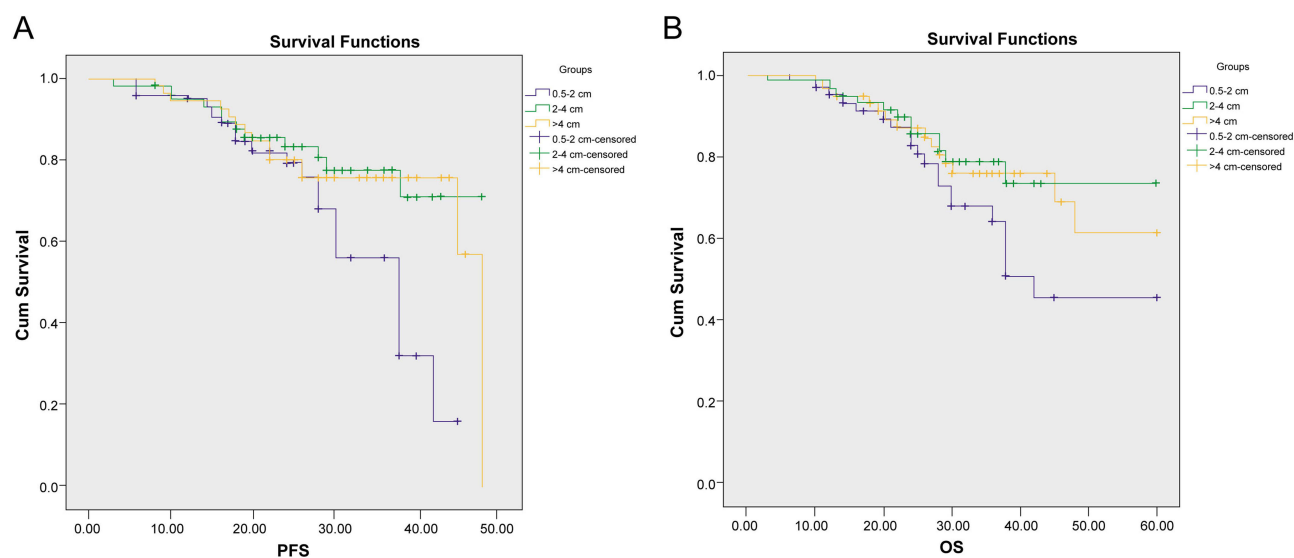


Figure 3 Kaplan-Meier survival curves for the impact of the lengths of proximal margin on PFS (A) and OS (B).

Table 3 Multivariate Cox Proportional Hazards Analysis for Survival

Variable	Hazard Ratio (95% CI)	P-value
Progression-Free Survival (PFS)		
Proximal margin <2 cm vs ≥2 cm	0.793 (0.641–0.981)	0.033
T stage (T3-T4 vs T1-T2)	2.150 (1.102–4.195)	0.025
N stage (N2-N3 vs N0-N1)	2.581 (1.459–4.568)	0.001
Overall Survival (OS)		
Proximal margin <2 cm vs ≥2 cm	0.819 (0.661–1.015)	0.068
T stage (T3-T4 vs T1-T2)	2.011 (0.988–4.092)	0.054
N stage (N2-N3 vs N0-N1)	2.890 (1.599–5.221)	<0.001

Subgroup Analysis for Progression-Free Survival

The subgroup analysis for PFS endpoints (Figure 4) revealed that a proximal margin of 2–4 cm was particularly beneficial for patients with tumors <4 cm in diameter, Siewert Type II classification, and an intestinal Lauren pattern. Conversely, for tumors >4 cm or Siewert Type III, a margin >4 cm showed a trend toward better prognosis. For patients with T4 or N3 stage disease, a margin >4 cm also demonstrated a significant improvement in PFS.

Subgroup Analysis for Overall Survival

To further explore the impact of proximal margin length on OS, we performed a parallel subgroup analysis (Supplementary Figure 1 and Supplementary Table 3). While the overall analysis did not show a statistically significant OS benefit for margins >2 cm, subgroup analysis revealed some trends. For patients with tumors <4 cm and Siewert Type II classification, a 2–4 cm margin showed a tendency toward better OS, though it did not reach statistical significance (HR=0.89, 95% CI: 0.358–2.214, P=0.803; HR=1.355, 95% CI: 0.501–3.664, P=0.550, respectively). These findings suggest that while PFS benefits are clear, the impact on OS is more nuanced and may require larger cohorts to detect significant differences within specific subgroups.

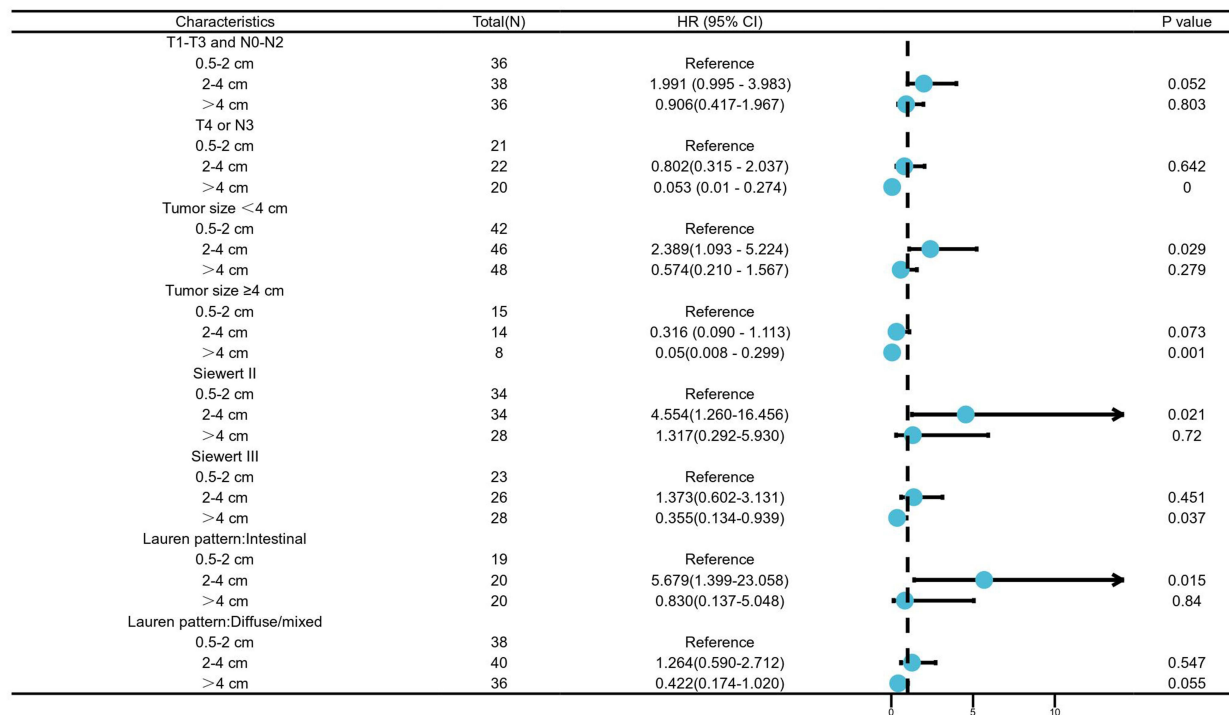


Figure 4 Forest plot of subgroup analysis for Progression-Free Survival (PFS).

Discussion

The optimal proximal margin length for Siewert type II/III AEJ is a critical surgical issue that remains unresolved. Our study demonstrates that a proximal margin of 0.5–2 cm is associated with inferior oncologic outcomes, specifically higher R1 resection rates, increased anastomotic recurrence, and poorer PFS and OS. While this shorter margin was associated with better short-term surgical metrics like lower anastomotic leak rates and shorter operative times, these benefits are overshadowed by the long-term survival disadvantage. This trade-off between short-term safety and long-term oncologic control is a central theme in our findings.

Our results suggest that a proximal margin of at least 2 cm is necessary to ensure oncologic safety. The 2–4 cm and >4 cm margin groups had comparable and significantly better survival outcomes than the <2 cm group. This aligns with findings from Mine et al, who recommended a margin of >2 cm.¹⁸ However, extending the margin beyond 4 cm did not confer an additional survival benefit in our overall analysis but was associated with increased surgical morbidity, including higher rates of anastomotic leak and longer operative times. This suggests a point of diminishing returns, where the risks of a more extensive resection may outweigh the oncologic benefits. This is consistent with other reports suggesting that overly extensive resections increase complications.⁸

A key consideration is whether the proximal margin length is an independent surgical choice or a consequence of tumor characteristics and technical difficulty. We found that the actual length of esophageal resection was significantly shorter in the 0.5–2 cm margin group compared to the other groups (3.3±0.8 cm vs 5.1±1.0 cm and 6.8±1.1 cm, respectively; $P<0.001$). This suggests that shorter margins may correlate with more technically challenging resections, potentially due to factors like higher tumor location or greater adhesion, which could themselves be confounding prognostic factors. This highlights a critical limitation of retrospective studies and reinforces the need for careful patient selection when interpreting these results.

The subgroup analysis provides a more granular perspective, suggesting that the “optimal” margin may vary based on tumor characteristics. A 2–4 cm margin appears to be sufficient and optimal for smaller tumors (<4 cm), Siewert II, and intestinal-type adenocarcinomas. For larger, more advanced tumors (eg, >4 cm diameter, Siewert III, T4/N3), a more aggressive margin of >4 cm might be necessary to achieve better local control and PFS. This supports a personalized approach to surgery for AEJ, moving away from a single standard margin for all patients. This personalized approach is increasingly important in the modern management of gastrointestinal cancers.¹⁹

This study has several limitations. First, its retrospective nature is susceptible to selection bias, although the baseline characteristics of the three groups were well-balanced. Second, the sample size, particularly for subgroup analyses, is limited, which may have prevented some trends from reaching statistical significance. Third, we did not collect data on the use of intraoperative frozen section analysis for every case, which could influence the final margin status. Finally, the exclusion of patients who received neoadjuvant therapy limits the generalizability of our findings to that patient population, which is an increasingly common treatment paradigm.

Conclusion

For patients with Siewert type II/III AEJ undergoing upfront surgery, a proximal resection margin of 2–4 cm appears to provide the best balance between oncological safety and postoperative morbidity. Margins less than 2 cm are associated with a significantly higher risk of positive margins, recurrence, and poorer survival. While margins greater than 4 cm do not offer additional survival benefits in the overall cohort, they may be warranted in specific high-risk subgroups, such as patients with large or advanced-stage tumors. However, it should be noted that subgroup analyses based on individual differences are required for Siewert type II/III patients to select the appropriate surgical approach and a suitable margin length. This underscores the importance of a personalized surgical strategy, where the final decision on margin length is tailored to individual patient and tumor characteristics rather than a one-size-fits-all approach.

Ethical Approval and Consent to Participate

The studies involving humans were approved by the Ethics Committee of Bethune International Peace Hospital (2022-KY-78). The study was conducted in accordance with the Declaration of Helsinki. The participants provided their written informed consent to participate in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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