Updates in Surgery (2019) 71:401–409
https://doi.org/10.1007/s13304-019-00665-w

REVIEW ARTICLE

Minimal length of proximal resection margin in adenocarcinoma of the esophagogastric junction: a systematic review of the literature

Nadja Niclauss[1] · Minoa K. Jung[1] · Mickael Chevallay[1] · Stefan P. Mönig[1]

Received: 10 July 2018 / Accepted: 22 June 2019 / Published online: 26 June 2019

Abstract
The minimal length of proximal margin (PM) in esophagogastric junction cancer has not been established yet and its impact on patient survival remains unclear. Pubmed, Embase and Scopus databases were searched for "adenocarcinoma of the esophagogastric junction", "adenocarcinoma of the gastroesophageal junction" and "cardia cancer", each combined with "proximal margin". English written studies that specified PM length in AEG were included. Survival data in relation to PM were extracted. 13 studies, that were all retrospective case series, with a total number of 2648 patients met inclusion criteria and were analyzed. While 93% of 230 patients with Siewert type I had esophagectomy, 69% of 1270 patients with Siewert type II and 93% of 872 patients with Siewert type III had transhiatal extended gastrectomy. Minimal PM length was treated by five studies and ranged between 2 and 6 cm. While three studies defined minimal PM by the necessary length to obtain R0 resection, two studies found minimal PM length significantly associated with survival. Multivariate analyses revealed in two studies an independent impact of PM on survival, whereas one study did not found any significant relation between PM and survival. One study showed that PM length was significantly associated with survival in T2–4N0–2 tumors, but not in T1 or N3 tumors. In conclusion, available retrospective studies did not allow a conclusion for a minimal length of PM and showed no clear evidence for an impact of PM length on survival. Taking into consideration available data and the shrinkage phenomenon, a PM > 2 cm might be necessary to obtain a sufficient PM.

Keywords Esophagogastric junction · Adenocarcinoma of the esophagogastric junction · Proximal margin · Minimal proximal margin · Systematic review

Introduction

Most countries show a decline in the incidence of gastric adenocarcinoma, partly due to the declining rates of infection with Helicobacter pylori that is the major cause of chronic active gastritis [1]. On the contrary, adenocarcinoma of the esophagus and the esophagogastric junction (EGJ) show a rising incidence in most Western countries [2–4]. Adenocarcinoma of the esophagogastric junction (AEG) are classified according to the Siewert classification [5]. This topographic anatomical classification subdivides AEG into three types according to a location in relation to the *z* line, with type I localized from 5 to 1 cm proximal, type II from 1 cm proximal to 2 cm distal and type III from 2 to 5 cm distal the *z* line. According to the eighth edition of TNM classification [6], AEG are classified and staged as esophageal cancer, as long as the tumors epicenter is within 2 cm of the *z* line, with or without invasion of the esophagus. When the epicenter of the tumor is more than 2 cm distal the *z* line, the cancer is classified and staged as stomach cancer even with invasion of the EGJ. There is no consensus about the best surgical strategy in AEG. In particular, the appropriate extent of resection in the esophagus and the stomach, the extent and the sites of lymphadenectomy and the optimal surgical approach remain uncertain [7]. Similarly, no consensus exists about the minimal length of proximal resection margin in AEG and there are only few literature regarding this issue. Proximal margin (PM) length is crucial for R0 and R1 resection status and hence for survival outcome [8, 9]. We performed, in this study, a systematic review of the literature treating minimal proximal resection margin length in AEG.

✉ Nadja Niclauss
nadja.niclauss@hcuge.ch

[1] Division of Visceral Surgery, Department of Surgery, University of Geneva, Hospitals and School of Medicine, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland

Materials and methods

We performed database searches on Pubmed, Embase and Scopus databases with the three keywords "adenocarcinoma of the esophagogastric junction", "adenocarcinoma of the gastroesophageal junction" or "cardia cancer", each combined with " proximal margin". Results obtained after the title and abstract screening and exclusion of doubles underwent a full-text screening. Inclusion criteria were published English written articles of studies treating AEG and specifying PM length. Resulting studies were classified according to the Oxford Centre for Evidence-based Medicine (CEBM) levels [10]. PM data were extracted from analyzed studies and given as range and median or mean ± SD. Recommended minimal PM lengths, if available, were extracted from studies. Given data from univariate survival analyses were extracted from texts and tables. For multivariate survival analysis, given HR and p values from regression models were extracted from texts and tables. Differences in the proportion of T-, N- or R-status were analyzed by Chi-square test. A p value < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, United States).

Results

Database search resulted in 312 articles, with 115 articles found in Pubmed, 90 in Embase and 107 in Scopus (Fig. 1). After title and abstract screening and exclusion of doubles 27 articles were left that underwent a full-text screening. Finally, 13 articles met the inclusion criteria.

Study design, CEBM level of evidence and PM measurement are specified in Table 1. Resulting articles were all retrospective case series with a total of 2648 patients with AEG. Classification according to CEBM levels of evidence resulted in a level of evidence of 4 for all 13 studies. Because of the shrinkage phenomenon [11], Mariette et al. multiplied all PM lengths in their study by two [9]. To render PM length comparable to the other studies, we converted all PM lengths indicated in the study of Mariette et al. back to half-length. In 7 out of 12 studies, PM was measured macroscopically on the resection specimen before fixation. In two out these seven studies specimen were stretched before measurement [12, 13]. Barbour et al. measured PM length after stretching and fixation [14]. Kinoshita et al. measured PM microscopically on frozen section [15].

Siewert type and type of operation are shown in Table 2. Of a total of 2648 patients, 230 had Siewert type I, 1270 had Siewert type II and 872 had Siewert type III adenocarcinoma. All 276 patients in the studies of Papachristou

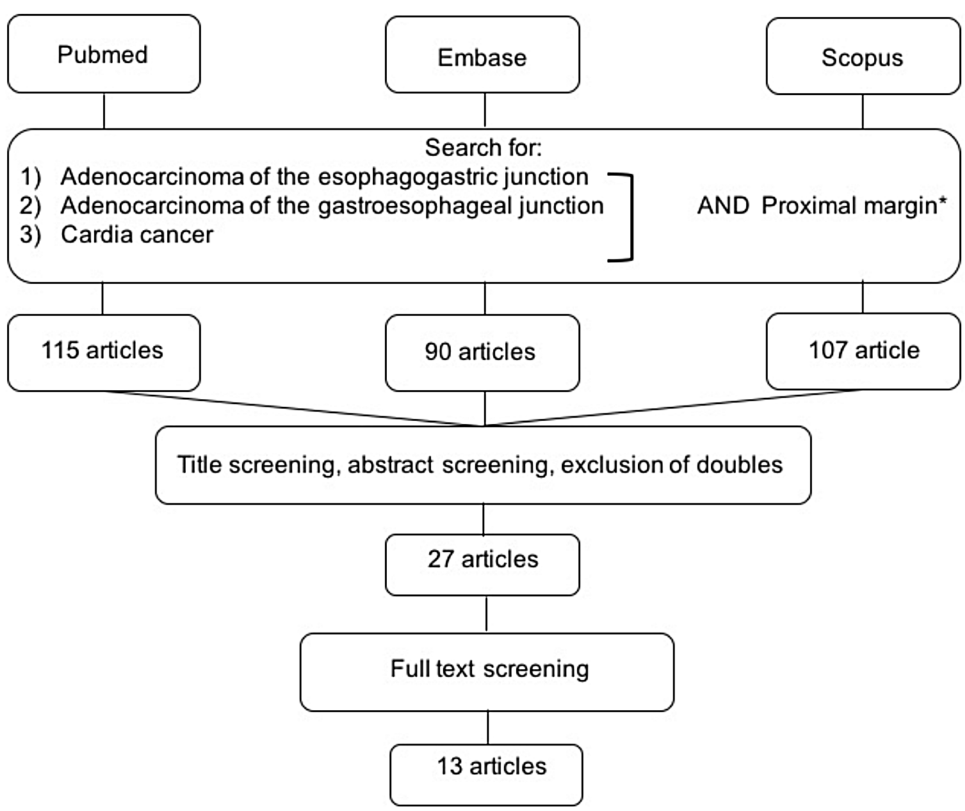

Fig. 1 Flowchart of systematic database search

Table 1 Study design, CEBM level of evidence and proximal margin measurement

Study	*N*	Study design	CEBM level of evidence	Proximal margin measurement
Papachristou et al. [16]	101	Retrospective, case series	4	Macroscopic, before fixation
Tsujitani et al. [17]	175	Retrospective, case series	4	Macroscopic, before fixation
Mariette et al. [9]	94	Retrospective, case series	4	Macroscopic, before fixation (multiplied by 2)
Ito et al. [18]	82	Retrospective, case series	4	Macroscopic, before fixation
Shen et al. [19]	191	Retrospective, case series	4	Macroscopic, before fixation
Barbour et al. [14]	505	Retrospective, case series	4	Macroscopic, before fixation
Johansson et al. [23]	133	Retrospective, case series	4	ND
Kinoshita et al. [15]	10	Retrospective, case series	4	Microscopic, on frozen section
Mine et al. [12]	140	Retrospective, case series	4	Macroscopic, after stretching and before fixation
Feng et al. [13]	693	Retrospective, case series	4	Macroscopic, after stretching and before fixation
Lee et al. [20]	301	Retrospective, case series	4	ND
Duan et al. [21]	136	Retrospective, case series	4	ND
Sugita et al. [22]	87	Retrospective, case series	4	ND

Technique of proximal margin measurement, if available, is indicated

ND no data available

et al. and Tsujitani et al. had transhiatal extended gastrectomy without specifying Siewert type [16, 17]. While five studies treated only Siewert type II and III [12, 13, 18–20], three studies treated type I–III [9, 14, 23] and 3 studies only type II [15, 21, 22] adenocarcinoma.

92.6% ($N=213$) of all patients with Siewert type I adenocarcinoma had an esophagectomy while 7.4% ($N=17$) had a transhiatal extended gastrectomy. 69.1% ($N=877$) of all patients with Siewert type II adenocarcinoma had a transhiatal extended gastrectomy, while 30.9% ($N=393$) had an esophagectomy. Of all Siewert type III patients, 93.1% ($N=812$) had a transhiatal extended gastrectomy and 6.9% ($N=60$) had an esophagectomy.

T-status, N-status, R-status and PM lengths of all study populations are shown in Table 3. R0 and R1 resection rates varied between 64.4–100% and 0–35.6%, respectively. PM lengths varied between 0 and 16 cm, whereas in two studies PM lengths were given as interval (Tsujitani et al.: <1, 1–2, >2 cm, Ito et al.: <2, 2–3.9, 4–5.9, ≥ 6 cm) without indicating exact values [17, 18]. 5 studies defined minimal PM length [9, 12, 14, 17, 18]. Minimal PM ranged between 2 and 6 cm. Three studies defined minimal PM by the length necessary to obtain a free proximal resection margin [9, 17, 18]. Correspondingly, minimal PM in the study of Mariette et al. corresponded to the length of PM in R0 resection. Tsujitani et al. defined two different minimal PM of 2 or 4 cm depending on a well- or ill-defined type of esophageal invasion, respectively [17].

Analysis of all studies defining minimal PM revealed a much higher proportion of T4 carcinoma in the study of Tsujitani et al. compared to the other studies (81.7% (Tsujitani et al.) vs. 3.2% (Mariette et al.), 4.9% (Ito et al.) and 1.4% (Barbour et al.); $p<0.001$) [17]. Mine et al. did only indicate the number of T3 and T4 carcinoma together [12].

When analyzing R-status in the five studies defining minimal PM, Ito et al. had a significantly higher ratio of R1 resections compared to the other four studies (25.6% (Ito et al.) vs. 13.7% (Tsujitani et al.), 8.5% (Mariette et al.), 2.8% (Barbour et al.) and 1.4% (Mine et al.); $p<0.001$). Furthermore, 9.8% of all patients in the study of Ito et al. had R2-resections in contrast to 0% R2-resections in the other four studies [18].

Out of five studies defining minimal PM, two studies defined minimal PM by univariate survival analysis (Table 4) [12, 14]. Barbour et al. determined by changepoint analysis a PM of more than 3.8 cm as most predictive for overall survival. They found a 5-year overall survival of 29% for a PM ≤ 3.8 cm and 47% for a PM >3.8 cm ($p=0.0004$) [14]. Mine et al. observed for the subgroup of 100 patients with carcinoma categorized as pT2–4 N0–3 M0 the most significant difference in survival at a cutoff of 2 cm. Kaplan–Meier analysis revealed a 5-year overall survival of 59% for a PM ≤ 2 cm compared to 83% for a PM >2 cm ($p=0.027$) [12].

To determine the impact of PM on survival, three studies performed multivariate analyses. Data are shown in Table 5. Barbour et al. performed multivariate analysis on a subgroup of 275 patients with R0 resection with at least 15 lymph nodes examined. They found a PM longer than 3.8 cm independently associated with better survival (HR 0.69, $p=0.03$ for PM >3.8 vs. ≤ 3.8 cm). Subgroup analysis of early-stage carcinoma (T1) revealed that PM was not a prognostic factor (HR 2, $p=0.25$ for PM >3.8 vs. ≤ 3.8 cm). In T2–T4 tumors, PM was

Table 2 Siewert type and type of surgery

Study	Patient number (*N*)	Siewert (*N*)	Esophagectomy (*N*)	Esophagectomy (*N*/%)/Siewert type	Gastrectomy (*N*)	Gastrectomy (*N*/%)/Siewert type
Papachristou et al. [16]	101	ND	0		0 101	ND
Tsujitani et al. [17]	175	ND	0		0 175	ND
Mariette et al. [9]	94	46 (I) 34 (II) 14 (III)	55	46/100% (I) 9/26.5% (II) 0 (III)	39	0 (I) 25/73.5% (II) 14/100% (III)
Ito et al. [18]	82	0 (I) 59 (II) 23 (III)	27	0 (I) 23/39% (II) 4/17.4% (III)	55	0 (I) 36/61% (II) 19/82.6% (III)
Shen et al. [19]	191	0 (I) 30 (II) 161 (III)	0		0 191	0 (I) 30/100% (II) 161/100% (III)
Barbour et al. [14]	505	112 (I) 276 (II) 117 (III)	352	100/89.3% (I) 199/72.1% (II) 53/45.3% (III)	153	12/10.7% (I) 77/27.9% (II) 64/54.7% (III)
Johansson et al. [23]	133	72 (I) 52 (II) 9 (III)	96	67/93.1% (I) 26/50% (II) 3/33.3% (III)	37	5/6.9% (I) 26/50% (II) 6/66.7% (III)
Kinoshita et al. [15]	10	0 (I) 10 (II) 0 (III)	0		0 10	0 (I) 10/100% (II) 0 (III)
Mine et al. [12]	140	0 (I) 92 (II) 48 (III)	0		0 140	0 (I) 92/100% (II) 48/100% (III)
Feng et al. [13]	693	0 (I) 404 (II) 289 (III)	0		0 693	0 (I) 404/100% (II) 289/100% (III)
Lee et al. [20]	301	0 (I) 90 (II) 211 (III)	0		0 301	0 (I) 90/100% (II) 211/100% (III)
Duan et al. [21]	136	0 (I) 136 (II) 0 (III)	136	0 (I) 136/100% (II) 0 (III)	0	0
Sugita et al. [22]	87	0 (I) 87 (II) 0 (III)	0		0 87	0 (I) 87/100% (II) 0 (III)
Total	2648	230 (I) 1270 (II) 872 (III)	666	213/92.6% (I) 393/30.9% (II) 60/6.9% (III)	1982	17/7.4% (I) 877/69.1% (II) 812/93.1% (III)

Total numbers (*n*) of Siewert type and type of surgery are shown for each study. In the early studies of Papachristou et al. and Tsujitani et al. Siewert types are not yet specified. Type of surgery is either esophagectomy or transhiatal extended gastrectomy. Given ratios are in relation to numbers of patients per Siewert type

ND no data available

a significant prognostic factor (HR 0.67, $p = 0.03$ for PM > 3.8 vs. ≤ 3.8 cm). For T2–T4 carcinoma with N0–N2 status, PM was a more significant prognostic factor (HR 0.45, $p < 0.01$ for PM > 3.8 vs. ≤ 3.8 cm). PM was not predictive for survival in T2–T4 carcinoma with N3 status ($p = 0.48$) [14].

Mine et al. identified in a subgroup of 100 patients with carcinoma categorized as pT2–4 N0–3 M0 a proximal margin of 2 cm or less independently associated with worse survival (HR 3.56, $p = 0.008$ for PM ≤ 2 vs. > 2 cm) [12].

Feng et al. did not define a minimal PM length as their survival analysis did not result in a significant relation between PM length and survival for both Siewert type II (HR 0.965, $p = 0.764$) and Siewert type III (HR 0.97, $p = 0.831$) carcinoma. In contrast to the other two studies that performed survival analyses, the authors reported a higher proportion of carcinoma with N3 status (29.9% (Feng et al.) vs. 5% (Barbour et al.) and 17% (Mine et al.); $p < 0.001$) [13].

3 out of 13 studies included patients who received neoadjuvant therapy. 24% of all patients in the study of Ito et al.

Table 3 pT-, pN-, R-status and proximal margin length

Study	pT-status (%)	pN-status (%)	R-status (%)	PM (cm)—range (median/mean*)	Minimal PM (cm)
Papachristou et al. [16]	ND	ND	64.4 (R0) 35.6 (R1)	0–6 (2.3)	ND
Tsujitani et al. [17]	18.3 (T1–3) 81.7 (T4)	85.7 (N0) 14.3 (N1–3)	86.3 (R0) 13.7 (R1)	ND (1.16*)	> 2 (well-defined) > 4 (ill-defined)
Mariette et al. [9]	17 (T1) 33 (T2) 46.8 (T3) 3.2 (T4)	31.9 (N0) 68.1 (N1)	91.5 (R0) 8.5 (R1)	0–10 (4(R0), 1.75(R1))	≥ 4
Ito et al. [18]	12.2 (T1) 36.6 (T2) 46.3 (T3) 4.9 (T4)	40.2 (N0) 39 (N1) 22 (N2–3)	64.6 (R0) 25.6 (R1) 9.8 (R2)	ND	≥ 4 (T1/T2) ≥ 6 (T3/T4)
Shen et al. [19]	15.2 (T1) 45 (T2) 34.6 (T3) 5.2 (T4)	36.6 (N0) 32.5 (N1) 14.7 (N2) 16.2 (N3)	91.6 (R0) 8.4 (R1)	0.8–7 (2.5*)	ND
Barbour et al. [14]	21.8 (T1) 21.6 (T2) 55.2 (T3) 1.4 (T4)	39 (N0) 40 (N1) 16 (N2) 5 (N3)	97.2 (R0) 2.8 (R1)	0–16 (3.5)	>3.8
Johansson et al. [23]	ND	ND	75.2 (R0) 15 (R1) 9.8 (R2)	ND (9.5-esophagectomy, 7.8-gastrectomy)	ND
Kinoshita et al. [15]	ND	ND	100 (R0)	1–2.3 (1.45)	ND
Mine et al. [12]	28.6 (T1) 15 (T2) 56.4 (T3–4)	57 (N1) 26 (N2) 17 (N3)	98.6 (R0) 1.4 (R1)	0–5 (2)	>2
Feng et al. [13]	13.3 (T2) 50.9 (T3) 35.8 (T4)	27.3 (N0) 22.2 (N1) 20.6 (N2) 29.9 (N3)	100 (R0)	0.1–5 (2.4)	ND
Lee et al. [20]	33.9 (T1) 17.9 (T2) 32.9 (T3) 15.3 (T4)	ND	ND	ND (1.18*)	ND
Duan et al. [21]	12.5 (T1–2) 86.8 (T3–4)	32.4 (N0) 47.1 (N1) 15.4 (N2) 5.1 (N3)	ND	ND (2.74*)	ND
Sugita et al. [22]	42.5 (T1) 17.2 (T2) 27.6 (T3) 12.6 (T4)	55.2 (N0) 19.5 (N1 11.5 (N2) 13.8 (N3)	100 (R0)	0.3–2.6 (0.95*)	ND

Ratios (%) of pT-status (T1–T4), pN-status (N0–N3) and R-status (R0–R2) from each study population are shown. Available proximal margin (PM) lengths from each study are indicated in cm as a range with median () or mean (*) value. Minimal proximal margin lengths (minimal PM), if available, are indicated in cm

PM proximal margin, *ND* no data available

received neoadjuvant chemoradiotherapy, corresponding to 32% of patients with Siewert type II and 4% of patients with Siewert type III carcinoma [18]. In the study of Johansson et al., 3% of all patients were treated with neoadjuvant chemotherapy and 1.5% with neoadjuvant radiotherapy [23]. 19.3% of all patients treated by Mine et al. received neoadjuvant chemotherapy [12].

Discussion

We performed a systematic review of the literature treating proximal resection margin of AEG. Data are scarce and we found 13 studies specifying PM length, whereupon only 5 studies defined minimal PM length.

Table 4 Proximal margin length and univariate survival analysis

Study	Patient number (*N*)	Minimal PM (cm)	Determination of minimal PM	5-year OS (%) <> minimal PM	*p* value
Barbour et al. [14]	505	> 3.8	Change-point analysis	29 (≤ 3.8 cm) 47 (> 3.8 cm)	0.0004
Mine et al. [12]	100	> 2	Kaplan–Meier analysis	59 (≤ 2 cm) 83 (> 2 cm)	0.027

Univariate analyses from two studies to determine minimal proximal margin (minimal PM) are shown. Ratios (%) of 5-year overall survival (5-year OS) are shown for patients with resections shorter and greater than minimal proximal margin length. *p* values were determined by log-rank test

PM proximal margin

Table 5 Proximal margin length and multivariate survival analysis

Study	N-status (%)	Subgroup analysis	Multivariate analysis		
			Variable	HR	*p* value
Barbour et al. [14]	39 (N0) 40 (N1) 16 (N2) 5 (N3)	All	PM > 3.8 cm vs. ≤ 3.8 cm	0.69	0.03
		T1 (R0 resection, ≥ 15 lymph nodes)	PM > 3.8 cm vs. ≤ 3.8 cm	2	0.25
		T2–4 N0–3 (R0 resection, ≥ 15 lymph nodes)	PM > 3.8 cm vs. ≤ 3.8 cm	0.67	0.03
		T2–4 N0–2 (R0 resection, ≥ 15 lymph nodes)	PM > 3.8 cm vs. ≤ 3.8 cm	0.45	<0.01
Mine et al. [12]	57 (N0–1) 26 (N2) 17 N3)	T2–4 N0–3, R0 resection	PM ≤ 2 cm vs. > 2 cm	3.56	0.008
Feng et al. [13]	27.3 (N0) 22.2 (N1) 20.6 (N2) 29.9 (N3)	T2–4 N0–3, R0 resection	PM	0.965 (Siewert II) 0.97 (Siewert III)	0.764 0.831

Multivariate analyses from three studies to investigate the impact of proximal margin (PM) on survival are shown. Subgroup analysis was performed by Barbour et al. for all T1 tumors, all T2–T4 tumors and T2–T4 tumors with different N-status (N0–3, N0–2). Barbour et al. and Mine et al. used Cox proportional hazard regression model, Feng et al. used logistic regression analysis to determine Hazard ratios (HR) and *p* values

PM proximal margin, *ND* no data available

Whenever treating proximal resection margin, the shrinkage phenomenon described in 1986 by Siu et al. has to be considered [11]. Siu and colleagues showed that the esophagus specimen shrinks to about half the size after resection. The authors observed even a greater shrinkage of the upper margin compared to the lower margin (44 vs. 54% of in situ length, respectively) after resection and before fixation. Therefore, cited minimal PM ranging between 2 and 6 cm would be between about 4 and 12 cm in situ. In all five studies defining minimal PM, margins were measured macroscopically after resection and before fixation. Additionally, Mine and colleagues performed stretching on a board before measurement.

Surprisingly, the majority of patients with Siewert type II adenocarcinoma in the analyzed studies had a transhiatal extended gastrectomy, and only about a third had an esophagectomy. The studies of Barbour et al. and Mine et al. treated both predominantly Siewert type II carcinoma (Table 2) [12, 14]. While Barbour et al. performed mainly (69.7%) esophagectomy, Mine et al. performed exclusively transhiatal extended gastrectomy. As pointed out by Mine and colleagues, PM length depends on necessity from surgical strategy [12]. That might explain why minimal PM is shorter in the study of Mine et al. than in the study of Barbour et al. Survival data reported by Mine et al. are better than those reported by Barbour et al. (Table 4), even though both studies are comparable in terms of R0 and R1 resection rates (Table 3). One explanation might be differences in multimodal treatment. While 19% of patients in the study of Mine et al. had neoadjuvant chemotherapy before surgery, all patients in the study of Barbour et al. were treated by surgery alone. Correspondingly, several studies have shown that perioperative chemotherapy improves survival in patients with AEG compared to surgery alone [24, 25]. Furthermore, Mine et al. performed their study on a highly selected patient population that was suitable for a transhiatal approach with involvement of the esophagus of no more than 3 cm [12]. That could be an explanation for better survival data and for the discordance of optimal PM results between Mine et al. and the other 4 studies that recommended longer minimal PM (Table 3). Interestingly, Tsujitani et al. observed that a PM of 2 cm was sufficient to obtain R0 resection in carcinoma with a well-defined type of esophageal invasion, whereas a PM of 4 cm was recommended in carcinoma with an ill-defined type of esophageal invasion [17]. Duan et al. compared three different surgical techniques of esophagectomy in type II AEG and revealed a mean PM length of 3.8 cm in Ivor-Lewis esophagectomy compared to 2.4 and 1.9 cm in left transthoracic and left thoracoabdominal approach, respectively. They concluded that only the Ivor-Lewis approach could obtain a satisfactory length of PM [21]. Lee and colleagues who performed transhiatal extended gastrectomy in all their patients observed a higher recurrence rate in type II and III AEG compared to cancers of the upper third of the stomach that might be due to insufficient proximal resection margins. The authors proposed a greater length of PM with the removal of mediastinal lymph nodes in advanced AEG [20].

Indeed, there is an ongoing debate about surgical strategy in AEG that is either subtotal esophagectomy with proximal gastrectomy or transhiatal extended gastrectomy. A broad consensus exists that AEG type I should be treated as esophageal cancer and an esophagectomy be performed, while AEG type III should be treated as gastric cancer with transhiatal extended gastrectomy [7]. Still, the origin of AEG type II, either esophagus or stomach, and its best surgical strategy remain unclear [7, 26]. In Eastern countries, AEG type II and III show no differences in clinicopathologic features and display similar oncologic outcomes. Therefore, both AEG type II and III should be considered as gastric cancer [27]. Similarly, studies from Western countries report inferior survival for patients with AEG type II and III compared to AEG type I [28]. However, it has been postulated that AEG type II in Western countries might rather arise from Barrett's mucosa of the esophagus due to a higher prevalence of reflux disease. Hence subtotal esophagectomy with proximal gastrectomy might be the optimal surgical approach in Western countries [26]. After all, there might be arguments for both surgical strategies in AEG type II.

As resection margins should be shorter in patients treated with transhiatal extended gastrectomy compared to subtotal esophagectomy, survival analyses comparing both procedures in AEG are of interest for our study. Haverkamp and colleagues performed a meta-analysis of ten cohort studies comparing transhiatal extended gastrectomy and esophagectomy in AEG. No survival benefit of either surgical approach, no difference in R0 resection rate nor lymph node yield were observed. Same results were obtained in the subgroup analysis of AEG type II tumors [29]. The study of Barbour and colleagues was the only study in the meta-analysis from Haverkamp et al. that observed significantly better overall survival in patients treated with esophagectomy compared to gastrectomy [14]. A recent study from Scandinavia is in line with previous studies and showed no difference in 5-year mortality between gastrectomy and esophagectomy [30]. Similarly, Parry et al. did not find a significant influence of surgical strategy on overall survival in multivariate analysis, but a higher rate of positive circumferential resection margin at the site of the esophagus in patients treated with gastrectomy [31]. An analysis of two large-volume databases from the United States reported a higher overall survival for esophagectomy compared to gastrectomy of 26 versus 21 months ($p = 0.025$), but in multivariate analysis surgical approach was not an independent predictor of survival [32]. In contrast, Blank et al. reported in a single-center study a significantly longer survival after esophagectomy and confirmed type of surgery as an independent prognostic factor in locally advanced AEG type II [33]. In conclusion, some literature shows a survival advantage in patients treated with esophagectomy, but there is no clear evidence for an impact of surgical approach on survival. Additionally, data of a randomized trial are lacking.

We have shown in our study that there is only scarce evidence for an impact of PM length on survival. Available data treating PM, and specifically PM in relation to patient survival, are very limited. Results of Barbour et al. are very interesting as they show that PM length might be associated with patient survival in T2–T4 carcinoma, but not in early stage carcinoma (T1) nor in carcinoma with disseminated lymph node metastases (N3) [14]. From three studies performing multivariate analysis, two could demonstrate an independent impact of PM on survival [12, 14]. One study could not confirm these results but treated a different patient population with a higher ratio of N3 tumors [13].

In conclusion, available data from the 13 analyzed studies do not allow to draw a conclusion for a minimal length of proximal resection margin nor to recommend a surgical strategy. Taken together, available data recommend a minimal resection margin between 2 and 6 cm. Therefore, a margin of 2 cm, as proposed by Mine et al., might be insufficient.

A clear drawback of our study is the limitation of available data treating PM, particularly in relation to survival data. Another drawback is the poor quality of available studies with a low level of evidence. Furthermore, analyzed studies are very heterogeneous and hardly comparable with each other.

Analyzed studies in this review did not treat the impact of neoadjuvant therapy on the proximal resection margin. Nevertheless, while most studies excluded patients with neoadjuvant therapy, three studies partially included patients who received neoadjuvant therapy. Two of them included approximately 20% of patients with neoadjuvant therapy and recommended proximal resection margin lengths of 2 cm (Mine et al.) and 4 cm for T1/2 or 6 cm for T3/4, respectively (Ito et al.). As recommended margin lengths of all analyzed studies varied between 2 and 6 cm as well, no conclusion about the impact of neoadjuvant therapy on proximal resection margin length can be drawn from these data. To our knowledge, there is no literature available treating the impact of neoadjuvant therapy on proximal resection margin and future studies might highlight this issue.

Compliance with ethical standards

Conflict of interest Minoa Jung received a fellowship grant from Johnson & Johnson and Intuitive Surgical. The other authors declare that they have no conflicts of interest.

Human rights and animal participants Research of this article does not involve human participants or animals.

Informed consent For this kind of study, formal consent is not required.

References

1. Correa P, Chen VW (1994) Gastric cancer. Cancer Surv 19–20:55–76
2. Devesa SS, Blot WJ, Fraumeni JF (1998) Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 83:2049–2053
3. Bollschweiler E, Wolfgarten E, Gutschow C, Hölscher AH (2001) Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 92:549–555
4. Steevens J, Botterweck AA, Dirx MJ, van der Brandt PA, Schouten LJ (2010) Trends in incidence of oesophageal and stomach cancer subtypes in Europe. Eur J Gastroenterol Hepatol 22:669–678. https://doi.org/10.1097/MEG.0b013e32832ca091
5. Siewert JR, Hölscher AH, Becker K, Gössner W (1987) Cardia cancer: attempt at a therapeutically relevant classification. Chirurg 58:25–32
6. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P (2017) Cancer of the esophagus and esophagogastric junction: an eigth edition staging primer. J Thorac Oncol 12:36–42
7. Mariette C, Piessen G, Briez N, Gronnier C, Triboulet JP (2011) Oesophagogastric junction adenocarcinoma: which therapeutic approach? Lancet Oncol 12:296–305. https://doi.org/10.1016/S1470-2045(10)70125-X
8. Mattioli S, Di Simone MP, Ferruzzi L, D'Ovidio F, Pilotti V, Carella R et al (2001) Surgical therapy for adenocarcinoma of the cardia: modalities of recurrence and extension of resection. Dis Esophagus 14:104–109
9. Mariette C, Castel B, Balon JM, Van Seuningen I, Triboulet JP (2003) Extent of oesophageal resection for adenocarcinoma of the oesophagogastric junction. Eur J Surg Oncol 29:588–593. https://doi.org/10.1016/S0748-7983(03)00109-4
10. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed 24 June 2019
11. Siu KF, Cheung HC, Wong J (1986) Shrinkage of the esophagus after resection for carcinoma. Ann Surg 203:173–176
12. Mine S, Sano T, Hiki N, Yamada K, Kosuga T, Nunobe S et al (2013) Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the oesophagogastric junction. Br J Surg 100:1050–1054. https://doi.org/10.1002/bjs.9170
13. Feng F, Tian Y, Xu G, Liu S, Liu Z, Zheng G et al (2016) The length of proximal margin does not influence the prognosis of Siewert type II/III adenocarcinoma of esophagogastric junction after transhiatal curative gastrectomy. Springerplus 5:588–593. https://doi.org/10.1186/s40064-016-2240-3
14. Barbour AP, Rizk NP, Gonen M, Tang L, Bains MS, Rusch VW et al (2007) Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. Ann Surg 246:1–8. https://doi.org/10.1097/01.sla.0000255563.65157.d2
15. Kinoshita T, Gotohda N, Kato Y, Takahashi S, Konishi M, Okazumi S et al (2012) Laparoscopic transhiatal resection for Siewert type II adenocarcinoma of the esophagogastric junction: operative technique and initial results. Surg Laparosc Endosc Percut Tech 22:e199–e203. https://doi.org/10.1097/SLE.0b013e31825a72e2
16. Papachristou DN, Fortner JG (1980) Adenocarcinoma of the gastric cardia. The choice of gastrectomy. Ann Surg 192:58–64
17. Tsujitani S, Okuyama T, Orita H, Kakeji Y, Maehara Y, Sugimachi K et al (1995) Margins of resection of the esophagus for gastric cancer with esophageal invasion. Hepatogastroenterology 42:873–877
18. Ito H, Clancy TE, Osteen RT, Swanson RS, Bueno R, Sugarbaker DJ et al (2004) Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg 199:880–886. https://doi.org/10.1016/j.jamcollsurg.2004.08.015
19. Shen JG, Cheong JH, Hyung WJ, Kim J, Choi SH, Noh SH (2006) Influence of a microscopic positive proximal margin in the treatment of gastric adenocarcinoma of the cardia. World J Gastroenterol 12:3883–3886
20. Lee IS, Ahn JY, Yook JH, Kim BS (2017) Mediastinal lymph node dissection and distal esophagectomy is not essential in early esophagogastric junction adenocarcinoma. World J Surg Oncol 15:28–35. https://doi.org/10.1186/s12957-016-1088-x
21. Duan XF, Yue J, Tang P, Shang XB, Jiang HJ, Yu ZT (2017) Lymph node dissection for Siewert II esophagogastric junction adenocarcinoma: a retrospective study of 3 surgical procedures. Medicine (Baltimore) 96:7–12. https://doi.org/10.1097/MD.0000000000006120
22. Sugita S, Kinoshita T, Kaito A, Watanabe M, Sunagawa H (2018) Short-term outcomes after laparoscopic versus open transhiatal resection of Siewert type II adenocarcinoma of the esophagogastric junction. Surg Endosc 32:383–390. https://doi.org/10.1007/s00464-017-5687-6
23. Johansson J, Djerf P, Oberg S, Zilling T, von Holstein CS, Johnsson F et al (2008) Two different surgical approaches in the treatment of adenocarcinoma at the gastroesophageal junction. World J Surg 32:1013–1020. https://doi.org/10.1007/s00268-008-9470-7
24. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M et al (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. NEJM 355:11–20. https://doi.org/10.1056/NEJMoa055531
25. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G et al (2011) Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 29:1715–1721. https://doi.org/10.1200/JCO.2010.33.0597

26. Giacopuzzi S, Bencivenga M, Weindelmayer J, Verlato G, de Manzoni G (2017) Western strategy for EGJ carcinoma. Gastric Cancer 20:S60–S68. https://doi.org/10.1007/s10120-016-0685-2
27. Suh YS, Han DS, Kong SH, Lee HJ, Kim YT, Kim WH et al (2012) Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. Ann Surg 255:908–915. https://doi.org/10.1097/SLA.0b013e31824beb95
28. Reynolds JV, Ravi N, Muldoon C, Larkin JO, Rowley S, O'Byrne K et al (2010) Differential pathologic variables and outcomes across the spectrum of adenocarcinoma of the esophagogastric junction. World J Surg 34:2821–2829. https://doi.org/10.1007/s00268-010-0738-y
29. Haverkamp L, Ruurda JP, van Leeuwen MS, Siersema PD, van Hillegersberg R (2014) Systematic review of the surgical strategies of adenocarcinomas of the gastroesophageal junction. Surg Oncol 23:222–228. https://doi.org/10.1016/j.suronc.2014.10.004
30. Kauppila JH, Wahlin K, Lagergren J (2017) Gastrectomy compared to oesophagectomy for Siewert II and III gastro-oesophageal junctional cancer in relation to resection margins, lymphadenectomy and survival. Sci Rep 7:17783–17788. https://doi.org/10.1038/s41598-017-18005-6
31. Parry J, Haverkamp L, Bruijnen RC, Siersema PD, Ruurda JP, van Hillegersberg R (2015) Surgical treatment of adenocarcinomas of the gastro-esophageal junction. Ann Surg Oncol 22:597–603. https://doi.org/10.1245/s10434-014-4047-1
32. Martin JT, Mahan A, Zwischenberger JB, McGrath PC, Tzeng CW (2015) Should gastric cardia cancers be treated with esophagectomy or total gastrectomy? A comprehensive analysis of 4,996 NSQIP/SEER patients. J Am Coll Surg 220:510–520. https://doi.org/10.1016/j.jamcollsurg.2014.12.024
33. Blank S, Schmidt T, Heger P, Strowitzki MJ, Sisic L, Heger U et al (2018) Surgical strategies in true adenocarcinoma of the esophagogastric junction (AEG II): thoracoabdominal or abdominal approach? Gastric Cancer 21:303–314. https://doi.org/10.1007/s10120-017-0746-1