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SYSTEMATIC REVIEWS AND META-ANALYSES

Thoracoabdominal versus transhiatal surgical approaches for adenocarcinoma of the esophagogastric junction—a systematic review and meta-analysis

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Abstract

Purpose The aim of this systematic review and meta-analysis was to compare the oncological and perioperative outcomes of transhiatally extended gastrectomy (TEG) and thoracoabdominal esophagectomy (TAE) for therapy of adenocarcinomas of the esophagogastric junction (AEG) with focus on AEG type II, as the optimal approach for these tumors is still unclear.

Methods MEDLINE, EMBASE, and the Cochrane Library (CENTRAL) were searched until July 24, 2018. Studies comparing TAE and TEG for surgical treatment of AEG type tumors have been included. Patient's baseline and perioperative data have been extracted and meta-analyses have been conducted for the outcomes: number of dissected lymph nodes, R0-resection rate, anastomotic leak rate, postoperative morbidity, and 30-day mortality.

Results Of 6709 articles identified, 8 studies have been included for further analysis. One thousand thirty-four patients underwent TAE, and 1177 patients TEG. No differences were found between the approaches in regard to number of dissected lymph nodes (MD −0.96; 95% CI −3.07 to 1.15; $p = 0.37$), R0-resection rates (OR 0.97; 95% CI 0.57 to 1.63; $p = 0.90$), anastomotic leak rates (OR 1.13; 95% CI 0.69 to 1.86; $p = 0.63$), and 30-day mortality (OR 1.53; 95% CI 0.90 to 2.61; $p = 0.11$). However, a higher rate of postoperative morbidity was found after TAE (OR 1.55; 95% CI 1.12 to 2.14; $p = 0.008$).

Conclusions The optimal approach to surgical therapy of AEG II still remains unclear. This study identified a significantly higher rate of postoperative morbidity after TAE at comparable surgical outcomes. Due to major limitations concerning the quality of included studies, current data strongly mandates a properly designed randomized controlled trial to identify the optimal surgical approach for AEG type II tumors.

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Introduction

In the last 20 years, the incidence of adenocarcinoma of the esophagogastric junction (AEG) has been rising rapidly, especially in developed countries [1]. AEG comprise more than a third of all esophageal cancers, with a rising share [2]. Surgery in combination with or without neoadjuvant or adjuvant therapy is the treatment of choice for resectable cases with a curative intent [3–5]. AEG tumors are commonly classified according to Siewert et al. and divided into three types according to their position referring to the esophagogastric junction, AEG type I to III [6]. Even though the carcinomas of the cardia are of rising importance, they are not classified as a separate entity. While originally staged as gastric carcinomas until 2010 [7, 8], they are now mainly included in the esophageal cancers within the latest 8th edition of the TNM classification. Furthermore, the 8th edition classifies the carcinomas of the cardia depending on its epicenter rather than the upper edge of the tumor as was the case in the 7th edition [9]. Consequently, the classifications by Siewert and the UICC approach each other. It is of interest that in AEG I tumors lymph node metastases occur less frequently than in AEG II tumors [10]. Additionally, it has been suggested that AEG II tumors are mainly of gastric origin, whereas intestinal metaplasia and dysplasia occurring in Barrett's esophagus lead to AEG I tumors [11]. Based on these findings, different surgical approaches have been proposed for curative treatment including transhiatally extended gastrectomy (TEG), left or right thoracoabdominal esophagectomy (TAE) with intrathoracic anastomosis [12, 13], and transhiatal esophagectomy [14]. While no major controversies exist about the surgical strategies for AEG type I and III tumors, for AEG type II tumors the optimal treatment remains unclear, with some surgeons preferring a transhiatal abdominal approach while others favor a thoracic approach. Some studies have shown that a thoracoabdominal approach is needed to achieve sufficient mediastinal and abdominal lymphadenectomy as well as negative resection margins [15], especially in proximal AEG type I tumors. On the other hand, there are indications for higher morbidity rates after thoracoabdominal surgery and poor outcome of patients even after resection and radical lymphadenectomy [16]. Other groups have therefore advocated that TEG might be sufficient, despite its limited mediastinal lymphadenectomy in comparison to transthoracic approaches [17]. One meta-analysis in 2012 found no differences in survival or postoperative mortality and morbidity between transthoracic resection and transhiatal resection. But conclusions were limited as all junctional tumors were included and the transhiatal approach included transhiatal gastrectomies as well as transhiatal esophagectomies [18].

In summary, optimal surgical treatment for adenocarcinomas of the gastroesophageal junction is still a matter of debate which is reflected in current guidelines which fail to make clear recommendations [19, 20].

Therefore, this systematic review and meta-analysis was conducted to retrieve all studies comparing thoracoabdominal esophageal resection with mediastinal lymphadenectomy and intrathoracic anastomosis with the transhiatal abdominal surgical approach in patients with AEG type tumors. The aim of this systematic review was to compare both surgical approaches in regard to their oncologic outcome (rates of negative resection margins, extent of lymphadenectomy), overall survival, and postoperative morbidity and mortality, with focus on AEG II tumors.

Methods

This systematic review is reported in line with current PRISMA guidelines [21]. The study was preformed according to a prespecified protocol, which is available from the authors upon request. The study was registered (Prospero CRD42016036476).

Literature search

We conducted searches of the electronic databases MEDLINE (via Pubmed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) on July 24, 2018. The references of the included articles were hand-searched to identify additional relevant studies. We used the patient-intervention-comparison-outcome (PICO) scheme to build our search strategy using search terms describing the patient and intervention. An example of the search strategy for the MEDLINE database via Pubmed can be found in supplement 1. The search strategies for the other databases were adapted to the specific vocabulary of each database. No language restrictions were applied.

Study selection, data collection, data items

Two authors (PH and SB) independently reviewed the title and abstract of all records as well as the full-texts of all articles assessed for eligibility. In case of disagreement, a third reviewer (ALM) was consulted and the decision of inclusion was made after discussion of the article. We included all randomized controlled trials (RCT), controlled clinical trials (CCT), case-control studies, and retrospective analyses of databases comparing TAE and TEG for surgical treatment of AEG type tumors. Case reports were excluded. Two authors (PH and SB) independently conducted data extraction of the oncologic and perioperative parameters in a prespecified data extraction form. Data forms with all extracted items are listed as supplementary material (supplement 2). Outcomes were the number of dissected lymph nodes, the R0-resection rate, postoperative morbidity, rate of anastomotic leakage, and postoperative mortality and all forms of survival (overall, disease-free, progression-free, etc.). If studies included tumors other than adenocarcinomas of the esophagogastric junction (e.g., squamous cell carcinomas), results were included only when the studies allowed for a subgroup analysis of AEG tumors. Similarly, if surgical techniques other than TAE and TEG were included, results were included only if outcomes for the different techniques were reported.

Summary measures and synthesis of results

Principal summary measures were mean and standard deviation (SD) for continuous parameters where the mean difference was measured. For dichotomous outcomes, the number of events and total numbers were extracted and the odds ratio was measured. Where necessary due to reported median and range, the calculation of mean and standard deviation described by Hozo et al. was performed [22]. For analysis of survival outcomes, if survival was not reported directly, hazard ratios were extracted from Kaplan-Meier curves whenever possible. Statistical analysis and meta-analysis was performed using the Mantel-Haenszel random effects method (Review Manager, Version 5.3 Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Between trials and within each study heterogeneity was evaluated using I^2 and results of over 60% were considered as substantial heterogeneity.

Risk of bias across studies

Bias was judged using the Cochrane tool for risk of bias for included RCTs and as recommended by the Cochrane Collaboration the ROBINS-I tool to evaluate the risk of bias in non-randomized studies of interventions [23]. Publication bias was assessed using a funnel plot (Review Manager, Version 5.3 Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

Results

Of 6709 studies identified by the database search, 5128 remained after removing duplicates. Of these, 118 were included after screening title and abstracts. Of those, 110 were excluded for the following reasons after retrieving the full-texts: 103 as they did not compare TAE or TEG or reported no surgical details, 3 studies because they contained no data on the prespecified endpoints of this systematic review, 2 others were found to be duplicates, and one was a double publication. One of the excluded studies was the 10-year follow-up of an included RCT and additional data was extracted in this case. Finally, eight manuscripts were included in the qualitative and quantitative analyses (PRISMA flowchart, see Fig. 1). These eight studies included one multicenter RCT [12] and its 10-year follow-up results [24] as well as seven retrospective single-center analyses of prospectively kept databases [25–30]. One of these single-center studies reported our own data regarding this patient collective [30]. Characteristics of the studies and perioperative data are described in Table 1 and Table 2.

Number of dissected lymph nodes

Four of the eight included studies reported the number of dissected lymph nodes after pathological examination [12, 25, 30, 31] ($n = 825$ patients). Meta-analysis including the data of these three studies (Fig. 2) showed no significant differences between the surgical approaches in respect to the number of retrieved lymph nodes (MD −0.96; 95% CI −3.07 to 1.15; $p = 0.37$; $I^2 = 50\%$).

R0-resection rate

Regarding the rate of negative resection margins as another important oncological outcome, five of the included studies reported the rate of R0-resections in their study collective ($n = 958$ patients) [12, 25, 29–31]. Parry et al. reported a higher R0-resection rate after TAE compared to TEG, Sasako et al. and Johansson et al. had a slightly higher rate in the TEG group without differentiating between types of AEG. In the study by Kauppila et al. as well as in our own single-center study, the R0-resection rate was comparable between the groups. Consequently, meta-analysis (Fig. 3) showed no statistically significant differences between the two surgical approaches regarding the rate of R0-resection (OR 0.97; 95% CI 0.57 to 1.63; $p = 0.90$; $I^2 = 38\%$).

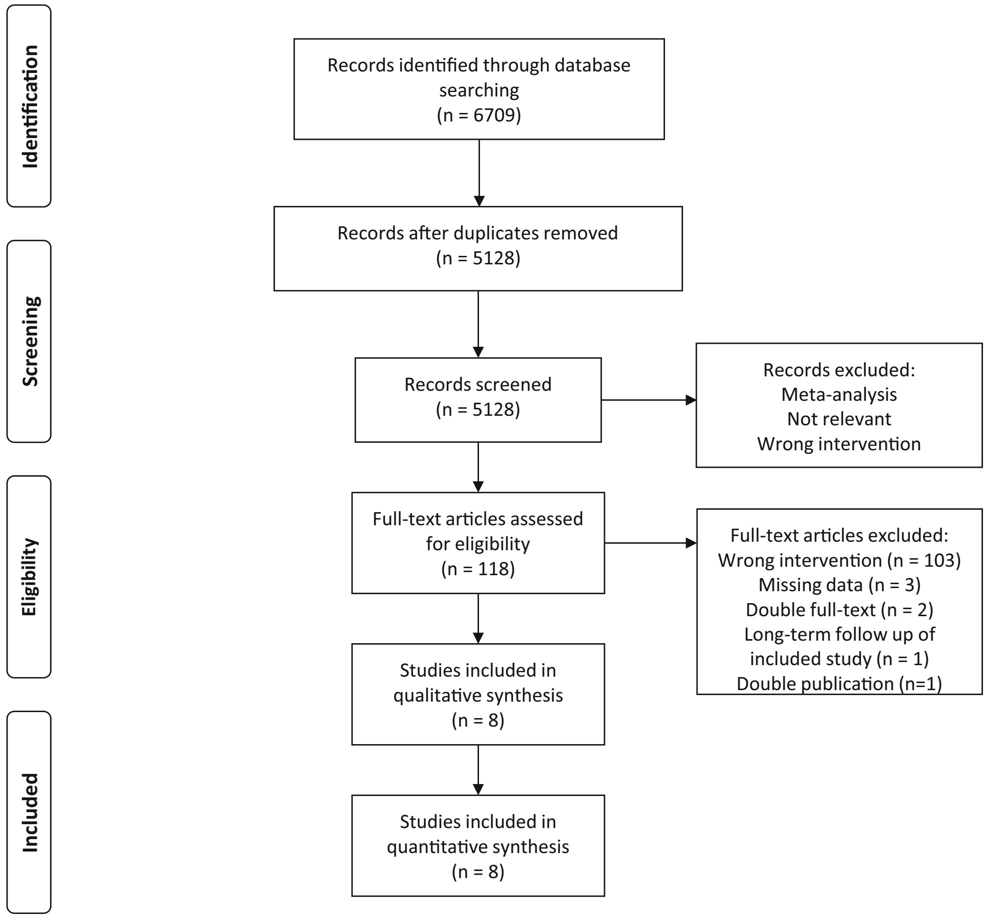

Fig. 1 PRISMA flowchart of identification and inclusion process

Postoperative morbidity

Six studies included an analysis of the postoperative morbidity of their patients ($n = 398$ complications in $n = 836$ patients) [12, 25, 27–30]. None of the individual studies showed any significant differences between TAE and TEG. Meta-analysis of the six included studies (Fig. 4), however, resulted in a significantly higher morbidity rate after TAE compared to the TEG (OR 1.55; 95% CI 1.12 to 2.14; $p = 0.008$; $I^2 = 0\%$). However, the method of assessing postoperative morbidity differed widely between the studies. In the analyses of our own patient cohort, we used the well-established classification of postoperative morbidity described by Dindo et al. [32]. Johansson et al. and Schumacher et al. reported in detail serious adverse events, others listed numbers of morbidities without further definition.

Anastomotic leakage

The number of patients suffering from anastomotic leakage was reported separately by six of the eight included studies [12, 25, 27–30]. Overall, 112 anastomotic leaks were reported in 969 patients. Diagnosis of the anastomotic leakage was performed using endoscopy or CT scan. The overall anastomotic leak rate was 13.8% after TAE and 9.2% after TEG. However, meta-analysis of all data (Fig. 5) showed no statistically significant difference between the two approaches (OR 1.13; 95% CI 0.69 to 1.86; $p = 0.63$; $I^2 = 0\%$).

Survival and mortality

Most of the included trials compared long-term overall survival between TAE and TEG. Unfortunately, only a systematic review but no meta-analysis of long-term survival data was possible either due to the differences in reporting of survival data, lack of reporting or the inferior quality of Kaplan-Meier curves which impeded extraction of hazard ratio data. Parry et al. [25] found no significant differences in 5-year survival between the groups but a trend towards higher survival rates after TAE ($p = 0.05$). Furthermore, they found no difference in 5-year disease-free survival ($p = 0.25$) between TAE and TEG in the AEG type II subgroup. The RCT of Sasako et al. [12] and its 10-year follow-up data published by Kurokawa et al. [24] could also not detect any statistically significant difference in overall survival between the two groups, neither at 5 year

Table 1 Characteristics of included studies

Trial	Year of publication	Type of study	Operative procedures	Lymphadenectomy	AEG type	Subgroup analysis for AEG II	Number of centers	Number of patients	Neoadjuvant therapy	Follow-up period	Survival analysis
Blank et al.	2017	Retrospective analysis of prospective database	Right TAE and TEG	D2 and 2-field lymphadenectomy	II	Yes	Monocenter (Germany)	242	Yes	Median 42.4 months	Yes
Johansson et al.	2008	Retrospective analysis of prospective database	Right TAE and TEG with thoracotomy for anastomosis	D2 and 2-field lymphadenectomy	I-III	Yes (without data)	Monocenter (Sweden)	133	Yes	5 years	No
Kauppila et al.	2017	Prospective cohort study	TAE and TEG	"Moderately extensive lymphadenectomy," but no consensus between centers	II-III	No	Multicenter (n = n.a.) (Sweden)	240	Rarely used	5 years	Yes
Nakamura et al.	2008	Retrospective analysis of prospective database	TAE and TEG	Not stated	I-III	No	Monocenter (Japan)	155	Not stated	Mean 47 months (11–146)	No data
Parry et al.	2015	Retrospective analysis of prospective database	TAE (AEG I) and TEG (AEG II, III)	D2 lymphadenectomy	II	Yes	Monocenter (Netherlands)	176	Yes	5 years	Yes
Sasako et al.	2006	RCT	Left TEA and TEG	D2 and 2-field lymphadenectomy	II-III	No	Multicenter (n = 27) (Japan)	167	Not stated	10 years	Yes
Schumacher et al.	2009	Retrospective analysis of prospective database	TAE (AEG I) and TEG (AEG II, III)	D2 and 2-field lymphadenectomy	I-III	No	Monocenter (Germany)	96	Not stated	Mean 16 months (1–57)	Disease-free survival
Siewert et al.	2000	Retrospective analysis of prospective database	Right TAE (AEG I) and TEG (AEG II, III)	D2 and 2-field lymphadenectomy	I-III	Yes (without data)	Monocenter (Germany)	1002	Yes	Mean 68 months (1–193)	Yes

Table 2 Perioperative outcomes of included studies

Trial	Total patients	Patients per group		Number of dissected lymph nodes (mean)		R0-resection rate (%)		Postoperative morbidity (%)		Anastomotic leakage (%)		30-day mortality (%)		5-year survival (%)	
		TAE	TEG	TAE	TEG	TAE	TEG	TAE	TEG	TAE	TEG	TAE	TEG	TAE	TEG
Blank et al.	242	56	186	24	24	83.9	85.9	57.1	47.3	14.3	11.8	5.4	2.7	57.5	38.8
Johansson et al.	133	96	37	n.a.	n.a.	71.9	83.8	n.a.	n.a.	3.1	5.4	5.2	2.9	n.a.	n.a.
Kauppila et al.	240	155	85	14.2	14.2	86.5	84.7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	24.0	23.0
Nakamura et al.	155	71	84	n.a.	n.a.	n.a.	n.a.	31.0	25.0	7.0	6.0	0.0	1.2	n.a.	n.a.
Parry et al.	176	155	21	19	22	87.1	71.4	76.8	66.7	2.8	23.8	1.9	4.8	n.a.	n.a.
Sasako et al.	167	85	82	60	68	88.2	92.7	49.4	34.1	8.2	6.1	3.5	0.0	37.9	52.3
Schumacher et al.	96	29	67	n.a.s	n.a.	n.a.	n.a.	38.0	31.3	3.4	7.5	3.4	4.5	n.a.	n.a.
Siewert et al.	1002	387	615	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	5.2	2.9	n.a.	n.a.

(TEG 52% vs. TAE 38%, $p = 0.93$) nor at 10 year follow-up (TEG 36% vs. TAE 26%, $p = 0.22$). Similarly, the study by Siewert et al. [26] including the largest cohort of patients failed to show a statistically significant difference in cumulative survival between the two approaches at a mean follow-up of 68 months. Schumacher et al. [27] described a 3-year disease-free survival of about 40% without any significant difference between the approaches ($p = 0.40$). Kauppila et al. [31] found no differences between the two surgical strategies regarding the long-term survival with 24% of the patients living 5 years after TAE and 23% after TEG. In our own patient cohort [30] with a median overall survival of 38.4 months, we found significantly higher 5-year survival rates after TAE compared to TEG (57.5 vs. 38.8%; $p = 0.02$). Also, disease-free survival was significantly higher at 5 years after TAE compared to TEG (79.1 vs. 44.8%; $p = 0.002$).

Whereas most of the included studies failed to report raw data of long-term survival and diversity between reported outcomes and time points was too variable to perform meta-analyses of long-term survival, all included studies reported the 30-day mortality following surgery. Overall mortality within 30 days after surgery was 3.5% in the TAE group and 2.7% in the TEG group. The meta-analysis (Fig. 6) resulted in no significant differences dependent on the surgical approach (OR 1.53; 95% CI 0.90 to 2.61; $p = 0.11$; $I^2 = 0\%$).

Current evidence for AEG II subgroup

As Table 1 shows, the studies conducted by Parry et al. [25] as well as our own data are the only studies that provide specific data of the AEG II subgroup. Subgroup analyses of the data of these two studies resulted in no significant differences between the patient groups due to a very limited number of patients. Parry et al. found no significant differences in the number of dissected lymph nodes ($p = 0.52$), postoperative morbidity ($p = 0.31$), anastomotic leakage ($p = 0.66$), or the 30-day mortality ($p = 0.40$) between the TAE and TEG group. The only significant difference found in this study was a significantly higher rate of positive circumferential resection margins in the TEG group, whereas the overall rates of R0-resections did not differ ($p = 0.06$). Our own data showed higher 5-year overall survival rates ($p = 0.02$) as well as higher disease-free survival rates after 5 years ($p = 0.002$) for patients that have been treated by the TAE approach compared to TEG. The other perioperative outcomes also showed comparable results between the groups.

Risk of bias

Risk of bias across studies was assessed as described. The study by Sasako et al. [12] was the only included RCT and showed overall low risk of bias using the Cochrane tool for

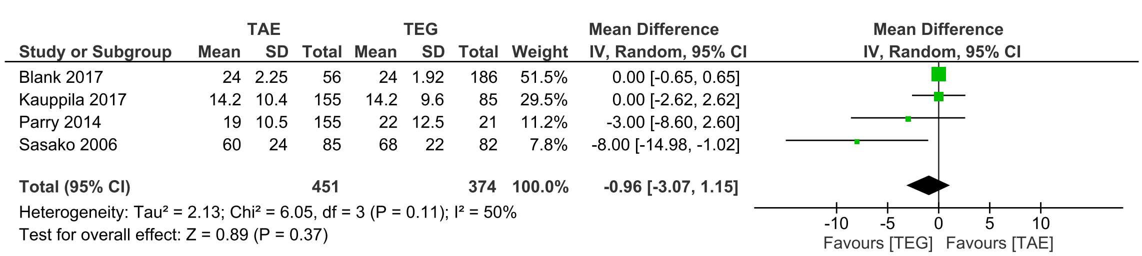

Fig. 2 Forest plot of meta-analysis of total number of dissected lymph nodes

Study or Subgroup	TAE Events	TAE Total	TEG Events	TEG Total	Weight	Odds Ratio M-H, Random, 95% CI
Blank 2017	47	56	158	186	23.0%	0.93 [0.41, 2.10]
Johansson 2008	69	96	31	37	18.4%	0.49 [0.19, 1.32]
Kauppila 2017	134	155	72	85	25.3%	1.15 [0.54, 2.44]
Parry 2014	135	155	15	21	16.7%	2.70 [0.94, 7.77]
Sasako 2006	75	85	76	82	16.6%	0.59 [0.20, 1.71]
Total (95% CI)		**547**		**411**	**100.0%**	**0.97 [0.57, 1.63]**
Total events	460		352			

Heterogeneity: Tau² = 0.14; Chi² = 6.50, df = 4 (P = 0.16); I² = 38%
Test for overall effect: Z = 0.12 (P = 0.90)

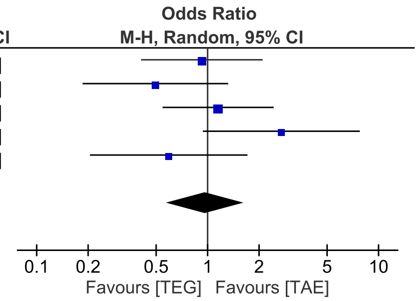

Fig. 3 Forest plot of meta-analysis of R0-resection rates

risk of bias. The only aspect in which bias cannot be excluded in this study is performance and detection bias, as there is no description of blinding attempts of the patients or outcome assessors. All non-RCTs showed a moderate or serious risk of bias (supplement 3.) as evaluated by the ROBINS-I tool [23]. The main reason for judging a serious risk of overall bias was a relevant risk for confounders. Especially confounders like different tumor extension, tumor size but also significantly differing patients' age or sex among others lead to the high risk of bias described in the manuscript. In three of the studies [29–31], there were significant differences in patient's baseline characteristics, and in three other studies [25, 26, 28], the reporting of relevant confounders was lacking.

Discussion

This systematic review and meta-analysis demonstrates the currently available data comparing the thoracoabdominal approach and the abdominal transhiatal approach for surgical therapy of AEG.

Although we identified numerous studies in our search, eventually only eight trials could be included as most studies failed to report specific outcomes for AEG type tumors, did compare other approaches than TAE and TEG, did not differentiate between the different surgical approaches, or failed to provide data on peri- and postoperative outcomes (Fig. 1). Therefore, exact reporting in accordance with current reporting guidelines seems necessary in the future to gain reliable data [33, 34]. For the same reason, subgroup analysis of AEG II tumors was poor and showed no convincing results in meta-analyses due to a limited number of selectively reported AEG II patients. This is a relevant limitation to this systematic review as the AEG II subgroup is the most relevant for which TEG and TAE are controversially debated [35].

In our meta-analyses, we did not detect a statistically significant difference in surrogate oncologic outcomes between TAE and TEG for AEG type tumors like the number of dissected lymph nodes or the rate of R0-resections (Figs. 2 and 3). However, we identified a statistically significant lower rate of postoperative morbidity following TEG compared to TAE (39 vs. 57%; $p = 0.008$; Fig. 4). No difference was found with regard to the rates of anastomotic leakage as one of the most severe postoperative complications. Similarly, this study did not show a difference in survival or 30-day mortality between the two approaches. Whereas short-term mortality was reported in all of the included studies, reporting of long-term survival rates was poor and diverse. The RCT by Sasako et al. using the left-sided TAE reported a non-significant advantage of TEG over left TAE. However, left TAE is not performed frequently in some countries as most surgeons prefer a right-sided approach to thoracic esophageal resection (Ivor-Lewis procedure) due to its better anastomotic exposure and lymph node clearance [36]. Additionally, in the study by Sasako et al., most patients in the TAE group had total gastrectomy and reconstruction by Roux en Y anastomosis. Thus, results of this study have to be treated with caution due to the variety of gastric resections in the TAE group. Parry et al. reported a non-significant trend towards a higher long-term survival after TAE compared to TEG. The side of the thoracic approach for

Study or Subgroup	TAE Events	TAE Total	TEG Events	TEG Total	Weight	Odds Ratio M-H, Random, 95% CI
Blank 2017	32	56	88	186	28.8%	1.48 [0.81, 2.71]
Johansson 2008	0	0	0	0		Not estimable
Nakamura 2008	22	71	21	84	21.0%	1.35 [0.67, 2.73]
Parry 2014	119	155	14	21	10.8%	1.65 [0.62, 4.41]
Sasako 2006	42	85	28	82	26.8%	1.88 [1.01, 3.52]
Schumacher 2009	11	29	21	67	12.6%	1.34 [0.54, 3.33]
Total (95% CI)		**396**		**440**	**100.0%**	**1.55 [1.12, 2.14]**
Total events	226		172			

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 4 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)

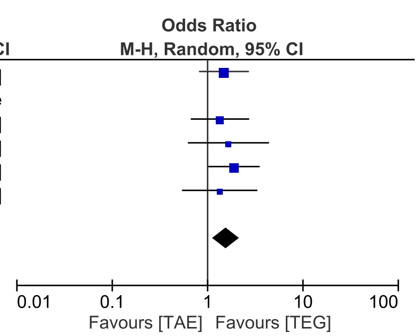

Fig. 4 Forest plot of meta-analysis of postoperative morbidity

Study or Subgroup	TAE Events	TAE Total	TEG Events	TEG Total	Weight	Odds Ratio M-H, Random, 95% CI
Blank 2017	8	56	22	186	32.8%	1.24 [0.52, 2.97]
Johansson 2008	3	96	2	37	7.4%	0.56 [0.09, 3.52]
Nakamura 2008	5	71	5	84	15.1%	1.20 [0.33, 4.31]
Parry 2014	44	155	5	21	22.0%	1.27 [0.44, 3.67]
Sasako 2006	7	85	5	82	17.5%	1.38 [0.42, 4.54]
Schumacher 2009	1	29	5	67	5.2%	0.44 [0.05, 3.97]
Total (95% CI)		**492**		**477**	**100.0%**	**1.13 [0.69, 1.86]**
Total events	68		44			

Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 5 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

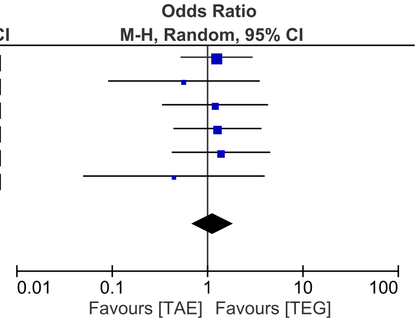

Fig. 5 Forest plot of meta-analysis of anastomotic leakage rates

patients undergoing TAE was not clearly defined in this study. In the included study of the patient cohort of our own department (Blank et al.), we found significantly higher survival rates in the TAE group compared to TEG. All TAE patients had a right-sided approach for the thoracic part of the operation. Therefore, in summary, it could be possible that the right-sided thoracic approach in TAE offers long-term advantages over the left-sided one or even TEG. Further analyses regarding this question were not possible as only sparse and limited data were available in the included studies.

There are several limitations to our analyses. First, outcome parameters have not been standardized between studies. Therefore, outcomes like postoperative morbidity are difficult to compare between studies, as clear definitions were not applied. Furthermore, diagnostic approaches were not standardized (observation bias). Thus, outcome parameters like anastomotic leak rate are difficult to compare between studies. Similarly, the diagnostic work-up for classification of AEG was not always described in detail [25, 27, 28, 31] and surgical techniques were either not clearly described or not standardized. This might not have influenced results in single-center studies, but might lead to a high risk of bias in multicenter trials.

Almost 50% percent of the included patients come from one study [26]. The only RCT by Sasako et al. [12] that compared the approaches that have been of relevance for this systematic review used a left-sided approach for TAE, which is not common in western countries and furthermore used different resection methods in the TAE group often including total gastrectomy, that largely deviates from the question of this systematic review. In addition, some studies did not clearly report the side of thoracotomy (left vs. right) [25, 27] and reconstruction methods differed between included trials. In the RCT by Sasako et al., a majority of the patients with TAE underwent an esophagogastrectomy with reconstruction as a Roux en Y esophagojejunostomy. Because of these two aspects of the Sasako trial, a sensitivity analysis without the data of this RCT has been performed and resulted in no differences in outcomes of the meta-analyses. Follow-up data was scarce with a median follow-up period of 5 years or more in only five of the seven included studies [12, 25, 26, 29, 31]. Only one trial reported the long-term outcome after 10 years [24]. Other relevant outcome measures like patient-reported outcomes (quality of life, dysphagia, a.o.) were lacking altogether in the included studies and almost all trials exhibit substantial methodological flaws (Tables 1 and 2). There was one study by Fuchs et al. [37] identified through the screening process that included quality life data but had to be excluded from further analyses as it offered no other clinical data. They found a significantly improved physical function and lower rates of dyspnea and reflux after TEG compared to TAE but no differences in overall quality of life. Four of the seven included studies [12, 27, 28, 31] did not report details about neoadjuvant therapy, which makes interpretation of oncological outcomes difficult. As another major limitation, the extent of the lymph node dissection is reported by only three of the included trials [12, 25, 30], whereas the

Study or Subgroup	TAE Events	TAE Total	TEG Events	TEG Total	Weight	Odds Ratio M-H, Random, 95% CI
Blank 2017	3	56	5	186	13.2%	2.05 [0.47, 8.86]
Johansson 2008	1	96	1	37	3.6%	0.38 [0.02, 6.22]
Nakamura 2008	0	71	1	84	2.7%	0.39 [0.02, 9.71]
Parry 2014	3	155	1	21	5.3%	0.39 [0.04, 3.98]
Sasako 2006	3	85	0	82	3.2%	7.00 [0.36, 137.66]
Schumacher 2009	1	29	3	67	5.3%	0.76 [0.08, 7.65]
Sievert 2000	20	387	18	615	66.8%	1.81 [0.94, 3.46]
Total (95% CI)		**879**		**1092**	**100.0%**	**1.53 [0.90, 2.61]**
Total events	31		29			

Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 6 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.58 (P = 0.11)

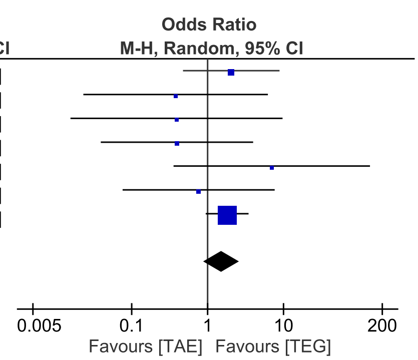

Fig. 6 Forest plot of meta-analysis of 30-day mortality

quality of lymphadenectomy represents one of the most important oncological surrogate parameters in AEG -type surgery.

The most striking limitation of this meta-analysis is the lack of data concerning the specific treatment of AEG II tumors as this was the main objective of this study. As AEG II tumors are the "true" carcinomas of the cardia at the intersection of the esophagus with the stomach, their surgical treatment remains a matter of debate for more than two decades [24]. Since the focus of this analysis was aimed at AEG II, it needs to be pointed out that only two studies provide data for the subgroup of patients with AEG II tumors [25, 30]. Parry et al. could not show a survival benefit for one of the surgical strategies but suggest a thoracoabdominal approach for patients with AEG II tumors as significantly more positive circumferential resection margins were observed after gastrectomy. The included study of our own patients cohort shows significantly higher overall long-term survival rates as well as disease-free survival after TAE compared to TEG at similar perioperative outcomes.

Another study in which AEG II tumors were selectively analyzed could not be included, as it remained unclear how the patients were treated in the different subgroups [38]. In this study, the authors claimed that patients with an AEG II tumor, who underwent an esophagectomy with gastric pull-up reconstruction, had worse outcomes than patients with an extended gastrectomy. However, it was impossible to include their data in our meta-analysis as esophagectomies were performed with a mixture of transhiatal (65%) and thoracoabdominal approaches (35%) and no separate analyses of the TAE cases was provided. Similarly, another RCT comparing a transhiatal approach with a transthoracic approach in AEG I and II tumors [39] could not be included as the transhiatal approach included transhiatal esophagectomies, as well. The authors did not find a survival benefit for any of the two procedures in the study population as a whole, but described a survival benefit and lower local recurrence rates for patients with AEG I tumors. Similarly, the RCT by Hulscher et al. [40] could not be included in this systematic review because a transthoracic esophagectomy was compared to transhiatal esophagectomy. Again, they did not find a significant difference in oncological outcomes or survival between the two approaches.

In summary, the optimal surgical treatment for the AEG, especially AEG type II, remains unclear despite the inclusion of more than 2200 patients in this systematic review.

Conclusion

This systematic review and meta-analysis shows that the optimal surgical approach to therapy of AEG II remains unclear as it was unable to show a statistical or oncologic difference between both, TAE and TEG. Consequently, optimal treatment for AEG subtypes remains elusive. This study identified a significantly lower rate of postoperative morbidity for the transhiatally extended approach at comparable oncological and surgical outcomes and postoperative short-term mortality. On the other hand, the few subgroup data of AEG II patients suggest in the individual studies higher survival rates after thoracoabdominal resection at comparable perioperative outcomes. There are some major limitations to this systematic review, as the quality of the included studies is limited and the use of standardized evaluation tools was poor in single studies. More high-quality evidence is needed especially for the correct surgical treatment for AEG II tumors and for surgery following modern multimodal neoadjuvant treatment concepts. Future trials need to be rigorous in their methodological approach and clearly define outcome parameters. In summary, current data strongly mandates a more properly designed and methodologically sound randomized controlled trial to identify the optimal surgical approach for AEG type II tumors.

Author contributions PH, SB, HN, ALM, and TS are responsible for conception and design of the study. PH, SB, KG, ALM, and TS performed the acquisition and analysis of the data, and drafted the manuscript. HN, MKD, and AU offered substantial contributions to interpretation of the data and critically revised the manuscript. All authors gave their final approval of this version of the manuscript and are accountable for all aspects of the work.

Compliance with ethical standards

No funding source is available for this study. However, the resources and facilities of the University of Heidelberg were used in conducting this study.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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