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Influence of the surgical technique on survival in the treatment of carcinomas of the true cardia (Siewert Type II) - Right thoracoabdominal vs. transhiatal-abdominal approach☆

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A R T I C L E I N F O

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A B S T R A C T

Introduction: It is still a matter of debate whether subtotal esophagectomy via a right thoracoabdominal approach (RTA) or extended gastrectomy using a transhiatal-abdominal approach (TH) is the favorable technique in the treatment of Siewert type II esophago-gastric junction adenocarcinoma (EJA).
Materials and methods: Patients undergoing RTA or TH for EJA at our institution between 2000 and 2013 were extracted from a prospective database. Of 270 patients 91 (33.7%) underwent RTA and 179 (66.3%) were treated by TH.
Differences in baseline characteristics, 30d mortality and complications were investigated using the $\chi 2$-test or exact testing. Survival analysis was performed using the Kaplan-Meier method and log rank testing. Median survival and hazard ratios were calculated and multivariable analysis of predictors was performed using a Cox model. Confounders were balanced using propensity score matching (PSM).
Results: No significant difference between the two procedures was detected regarding overall-survival (OS) and disease-free survival (DFS). 30d mortality rates were 1.1% in the RTA group and 4.5% in the TH group ($p = 0.134$). Morbidity was 34.1% in the RTA and 24.6% in the TH group ($p = 0.006$). Cox regression analysis identified age, ASA class and UICC stage as independent prognostic factors for OS. After PSM survival curves (OS + PFS) showed no significant difference.
Conclusion: The present study could not detect a difference between RTA and TH from the oncologic point of view; RTA was not associated with higher 30d mortality. RTA for Siewert Type II EJA is justified whenever the oral tumor margin cannot be safely reached via a transhiatal approach.

Introduction

The nature of adenocarcinomas of the esophago-gastric junction (EJA) is not yet defined. In fact EJA has been handled both as a gastric tumor or an esophageal tumor, without reaching a univocal classification and a treatment gold standard.

Before 2010 EJA type II had been unequivocally classified as gastric cancers by the UICC [1]. According to the UICC-2010 classification system EJA were classified as esophageal tumors when they were invading the esophago-gastric junction (EGJ), and had an epicenter within 5 cm of the EGJ, which is the case in Siewert Type II EJA [2]. In the present UICC 8th edition cancers involving the EGJ whose epicenter is within the proximal 2 cm of the cardia (Siewert types I/II) are staged as esophageal cancers, while cancers whose epicenter is more than 2 cm distal from the EGJ are classified as stomach cancers even if the EGJ is involved [3].

Siewert's group concluded that EJA I should be considered as esophageal cancer, while EJA II and III as gastric cancer [4,5]. Huang and Hasegawa held the same view [6,7].

Gertler et al. was of the opinion that neither gastric nor

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esophageal cancer classification properly suited EJA II/III [8].

True cardia carcinomas are in fact characterized by a higher frequency of differentiated types, greater depth of invasion, higher incidence of metastasis and poorer prognosis [9,10].

The incidence of EJA is significantly increasing in the western countries, being the 2nd most common cause of cancer-related death [11].

These tumors show a poor response to chemo-radiotherapy and the best curative option is surgical resection [12,13].

Nowadays a platinum-based chemotherapy or chemo-radiotherapy followed by surgery is the standard of care for locally advanced tumors in Western countries [14, 15 16]. The two most frequently used surgical approaches are an esophageal resection with proximal gastrectomy and gastric-tube reconstruction via a right (Ivor-Lewis) or left thoraco-abdominal approach (RTA/LTA) [16,17] or an extended gastrectomy through an abdominal-transhiatal approach (TH) [11–21].

Arguments in favor of RTA are the possibility of achieving greater oral margins and a more extended mediastinal lymph node dissection. TH is a less invasive procedure, allowing for a more extended intra-abdominal lymphadenectomy along the greater curvature. The anastomosis in TH is more challenging, due to the extension into the mediastinum.

The aim of this study was to evaluate morbidity and survival data of patients with type II EJA undergoing either RTA or TH in a German tertiary referral-center between 2000 and 2013 in order to define the best possible approach regarding oncological outcome, R0 resection rate, morbidity, and survival.

Patients and methods

Tumor- and patient-related data of patients undergoing curative RTA or TH for type II EJA at the Klinikum Rechts der Isar, Munich, Germany, between 2000 and 2013 were extracted from a prospectively documented gastric-cancer data base. Patients with a secondary malignancy, systemic metastases or R2 resection were excluded.

Patients were staged according to the 2010 UICC TNM staging system by CT of the thorax/abdomen/pelvis and esophago-gastro-duodenoscopy (EGD) with endoscopic ultrasonography. The oral tumor margin was routinely documented. All cases were re-reviewed in a multidisciplinary team conference and presence of Siewert type II cancers was confirmed. Carcinoma of the true cardia was present when the tumor epicenter (or main tumor mass) was located in the transition zone of 1 cm above to 2 cm below the anatomic cardia (oral end of the longitudinal gastric mucosal folds on endoscopic examination). The decision for multimodal therapy ahead of surgery was based on the clinical tumor stage. Patients with locally advanced tumor stages (cT3/cT4/cN0/cM0 or cTany/cN+/cM0) underwent neoadjuvant chemotherapy according to local guidelines. All other patients (cT1/cT2 cN0 cM0) were scheduled for primary resection. The choice of procedure was left to the surgeon's discretion without prior determination of the procedure. The surgical procedure was scheduled four weeks after the end of chemotherapy.

RTA: Abdominothoracic en bloc esophagectomy (Ivor-Lewis) via a right transthoracic approach was performed as detailed elsewhere [22]. The intraabdominal lymphadenectomy consisted of a modified D2-procedure, sparing the parapyloric and perigastric lymphnodes along the greater curvature.

TH:A total gastrectomy with a standard D2 lymphadenectomy was performed via laparotomy. Distal esophagectomy and removal of mediastinal lymph-nodes was performed through the hiatus. Reconstruction was performed according to the Roux-en-Y technique.

R0-resection was defined when no residual tumor cells were detected at the margin. The >1 mm definition was not applied for this cohort. Frozen sections from the oral margins were routinely examined intraoperatively.

Patients with 30 day mortality were included in the survival analysis. 30d mortality was compared using the χ^2-test. Survival analysis was performed using the Kaplan-Meier method for estimating survival probabilities and the log rank test for comparisons between patient groups. Median survival and hazard ratios were calculated and multivariate analysis of predictors was performed using a Cox proportional hazards model. Variables with a $p < 0.1$ in univariable Cox regression analysis were entered into the multivariable model.

To correct for the observational bias in receiving either an Ivor Lewis procedure or a transhiatal gastrectomy, a propensity score analysis adjusting for prognostic variables and variables that could potentially influence the choice of the procedure was performed for the association of the selected procedure and overall and relapse-free survival following recommended statistical practice. Hereby 1:1 matching with a caliper of 0.2 using the nearest-neighbor method as matching algorithm and logistic regression as estimation algorithm was employed.

The statistical analysis was performed using SPSS Statistics V. 23 (IBM Corp, Ehningen, Germany) with a R plugin and R version 2.1.3 (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). SPSS was fitted with a custom dialog for propensity score matching [24].

Results

Baseline characteristics (Table 1)

270 patients were eligible (228 male and 42 female); 91 (33.7%) underwent RTA and 179 (66.3%) TH. The average age was 58.8 ± 10.3 and 63.3 ± 11 years respectively. RTA was performed more often in males than in females (35.96% vs. 18.42%, $p = 0.067$). Neoadjuvant chemotherapy was administered in 83 (91.2%) patients undergoing RTA and in 108 (60.3%) patients undergoing TH ($p = 0.001$). An R0 resection was achieved in 69 (75.8%) and 139 (77.7%), respectively ($p = 0.735$). An extraluminal extension of the resection was necessary in 11 (12.1%) patients undergoing RTA and 68 (38%) undergoing TH ($p < 0.001$). The mean esophageal extension of the tumor was 4.8 cm and 2.7 cm in the RTA and TH group, respectively ($p = 0.001$). No significant difference in the number of resected lymph nodes was detected (RTA vs. TH: 27.9 vs. 26.4; $p = 0.244$).

Morbidity and mortality (Table 2)

The RTA group showed a higher complication rate (34.1% vs. 24.6%; $p = 0.006$). Hereby anastomotic leaks (4.4% vs. 2.8%) and wound infections (12.1% vs. 1.7%) were more common in the RTA subgroup. There was no significant difference regarding pulmonary ($p = 0.08$) and cardiac ($p = 0.43$) complications between the two surgical approaches. Severe complications (CD $\geq$ IIIA) occurred in 6.6% of the patients in the RTA-group and in 13.3% of the patients in the TH-group without statistical significance ($p = 0.21$).

However, this did not translate into a higher 30 day mortality rate, which was 1/91 (1.1%) in the RTA group and 8/179 (4.5%) in the TH group ($p = 0.134$). In-hospital mortality was 6.7% (7.8% in the TH group and 4.4% in the RTA group, $p = 0.286$) and 90 day mortality was 7.4% (8.4% in the TH group vs. 5.5% in the RTA group, $p = 0.392$).

Table 1
Baseline characteristics: 270 patients with AEGII were surgically resected. Of these, 91 patients (33.7%) received right thoraco-abdominal resections (RTA) and 179 patients (66.3%) underwent transhiatal abdominal resection (TH).

Parameter		RTA	%	TH	%	p
pts.		91	*33.7*	179	*66.3*	
age (mean ± SEM)		58.8 ± 10.3		63.6 ± 11.0		*0.001[*]*
Sex	Male	82	*90.1*	146	*81.6*	*0.067[§]*
	Female	9	*9.9*	33	*18.4*	
ASA	1	73	*80.2*	107	*59.8*	***0.003**[§]*
	2	12	*13.2*	52	*29.1*	
	3	6	*6.6*	20	*11.2*	
neoadj. CTx	No	8	*8.8*	71	*39.7*	***<0.001**[§]*
	yes	83	*91.2*	108	*60.3*	
UICC 2010	0	6	*6.6*	5	*2.8*	*0.114[§]*
	I	14	*15.4*	51	*28.5*	
	II	29	*31.9*	55	*30.7*	
	III	34	*37.4*	55	*30.7*	
	IV	8	*8.8*	13	*7.3*	
R-status	0	69	*75.8*	139	*77.7*	*0.735[§]*
	1	22	*24.2*	40	*22.3*	
R-status oral margin	0	87	*96.7*	166	*92.7*	*0.277[+]*
	1	1	*1.1*	7	*3.9*	
	x	2	*2.2*	6	*3.4*	
Grading	1	1	*1.1*	2	*1.1*	*0.358[+]*
	2	20	*22.0*	55	*30.7*	
	3	62	*68.1*	115	*64.2*	
	4	6	*6.6*	5	*4.1*	
	x	2	*2.2*	2	*1.1*	
extralum. ext.	no	80	*87.9*	111	*62*	***<0.001**[§]*
	yes	11	*12.1*	68	*38*	
esophageal ext. [cm] mean (min-max)		4.8 (0–11)		2.7 (0–8)		***<0.001**[#]*
resected LN mean (min-max)		27.9 (10–63)		26.4 (5–71)		*0.244[#]*

[*]T-test, [§]X^2-test, [#]Mann-Whitney *U* test, [+]Monte-Carlo significance.

Table 2
Clinical outcomes: 30-day mortality and postoperative complications.

Parameter		RTA	%	TH	%	p
pts.		91	*33.7*	179	*66.3*	
30d mortality	No	90	*98.9*	171	*95.5*	0.134[#]
	Yes	1	*1.1*	8	*4.5*	
complications	None	60	*65.9*	135	*75.4*	***0.006**[+]*
	anast. Leak	4	*4.4*	5	*2.8*	
	wound inf.	11	*12.1*	3	*1.7*	
	intraabd. abscess/peritonitis	1	*1.1*	8	*4.5*	
	other postoperative	8	*8.8*	15	*8.4*	
	Medical	7	*7.7*	13	*7.3*	

§X^2-test, #Fisher's exact test, +Monte-Carlo significance.

Table 3
Recurrence: Localizations.

Parameter		RTA	%	TH	%	p
pts.		91	*33.7*	179	*66.3*	
recurrence	None	61	*67.0*	137	*76.5*	***0.025**[a]*
	R1/progression	4	*4.4*	13	*7.3*	
	local	3	*3.3*	11	*6.1*	
	LYM	7	*7.7*	5	*2.8*	
	HEP	4	*4.4*	2	*1.1*	
	PER	2	*2.2*	5	*2.8*	
	OTH	3	*3.3*	3	*1.1*	
	Multiple	7	*7.7*	3	*1.1*	

[a] Monte-Carlo significance.

Recurrence (Table 3)

The recurrence rate was higher in the RTA group (33%), with recurrences mostly occurring systemically. Recurrence in the TH group was observed in 23.5% of cases, which mostly occurred locally ($p = 0.025$).

Survival

Patients undergoing TH showed a statistically insignificant better outcome in terms of overall-survival (OS) ($p = 0.448$). Median OS was 34.4 ± 6.2 months for patients undergoing RTA and 48.6 ± 10.7 months for the TH group (Fig. 1a).

Disease free survival (DFS) was longer in the TH group, not reaching significance-level (Median DFS for RTA vs. TH: 22.0 ± 3.6 months vs. 43.0 ± 7.2 months, $p = 0.085$) (Fig. 1b).

Conversely, OS in patients with a tumor extending less than 3 cm into the thoracic esophagus was better when treated by TH than with RTA. This difference did not reach significance-level either (esophageal extension ≤3 cm: median OS TH vs. RTA: 58.3 ± 1.6 months vs. 25.7 ± 3.4 months, $p = 0.064$; esophageal extension >3 cm: median OS TH vs. RTA: 35.9 ± 9.4 months vs. 37.5 ± 11.9 months, $p = 0.592$) (Fig. 2a and b).

Prognostic factors

Age ($p = 0.047$), ASA score ($p = 0.025$), R-status ($p < 0.001$) and UICC stage ($p < 0.001$) were prognostic factors in univariable Cox regression analysis, while grading (G) marginally failed to reach significance-level ($p = 0.057$).

After these factors were entered into the multivariable Cox model, age ($p = 0.017$; HR 1.020, 95%CI 1.005–1.036), ASA-class ($p = 0.021$; ASA I: Ref.; ASA II: HR 0.555, 95%CI 0.367–0.840; ASA III: HR 0.835, 95%CI 0.466–1.494) and higher UICC stage ($p < 0.001$; Stage 0: Ref.; Stage I: HR 3.334, 95%CI 0.447–24.855; Stage II: HR 7.283, 95%CI 1.000–53.043; Stage III: HR 15.471, 95%CI 2.141–111.777; Stage IV: HR 60.513, 95%CI 7.936–461.438) were identified as independent negative prognostic factors for OS.

After propensity score matching (PSM) for ASA, age, UICC stage, R-status, grading, extent of esophageal involvement, neoadjuvant chemotherapy and postoperative complications, potential confounders were evenly balanced (Suppl.-Fig. 1). In the matched patients no difference in OS (RTA: 37.5 ± 13.6 months TH: 35.7 ± 6.5 months, $p = 0.669$) and DFS (RTA: 27.0 ± 7.9 months TH: 24.0 ± 6.5 months, $p = 0.535$) could be detected (Fig. 3a and b).

Discussion

In accordance with our results and with the recent literature, it appears that both surgical techniques are yielding satisfactory surgical outcomes in a high volume center.

Regarding oncologic outcome, we could not detect a significant difference between both techniques (neither OS nor DFS). OS in unmatched patients with a tumor extending no more than than 3 cm into the esophagus was better when treated by TH. This result might be influenced by a selection bias: the choice of performing TH rather than RTA could be influenced by an impaired physical condition of the respective patient that may not be adequately mirrored by the ASA-class. A study including EJA I, II and III obtained similar results [25]. Among others, main predictors for poor survival were advanced tumor stage and residual tumor. Thoracotomy was identified as a negative prognostic factor.

Kurokawa et al. compared 10 year follow-up data of 85 patients undergoing LTA vs. 82 undergoing TH for EJA type II and III, showing no advantage in terms of OS or recurrence rate for LTA, while morbidity and mortality were significantly worse after LTA [26]. Carboni et al. [27] reached the same conclusion. Omloo et al. conversely detected a survival benefit after performing RTH, but only for EJA I [28].

The low rate of R0 resections achieved in our study has to be noticed (75.8% vs. 77.7%, RTA vs. TH). This could be explained by the advanced stages in our cohort and the fact that margin-positivity predominantly occurred in the third dimension, where radicality is limited at the aorta and no frozen sections can be obtained during surgery. The oral margin was routinely checked using frozen sections during surgery. In the case of a positive oral margin surgery was extended until a clear margin could be obtained. In fact, the R0 rate at the oral margin exceeded 90% in both groups. A paramount question for the choice of the resection in EJA is whether it is technically possible to obtain a safe oral margin using a transhiatal approach, and if there is an intrathoracic extension beyond which an R0 resection is less likely. The studies of Mine et al. [29] and of Kurokawa et al. [26] proposed a cutoff of 2 cm for esophageal invasion. Other studies show that a reasonable cut-off could be 3 cm, both in terms of survival and the achievement of a R0 resection [21,29]. Our findings are in line with these results: patients with an intra-thoracic extension of the tumor of more than 3 cm definitely did not have a survival benefit from TH compared to RTA (Fig. 2). When different cutoffs for the esophageal tumor extension were tested (data not shown), patients in the unmatched group had a (insignificant) survival benefit up to an extension of 3 cm, when the transhiatal approach was used. This advantage was lost with higher extensions into the distal esophagus (data not shown). This emphasizes the importance of the esophageal extension for the choice of the operative approach in EJA.

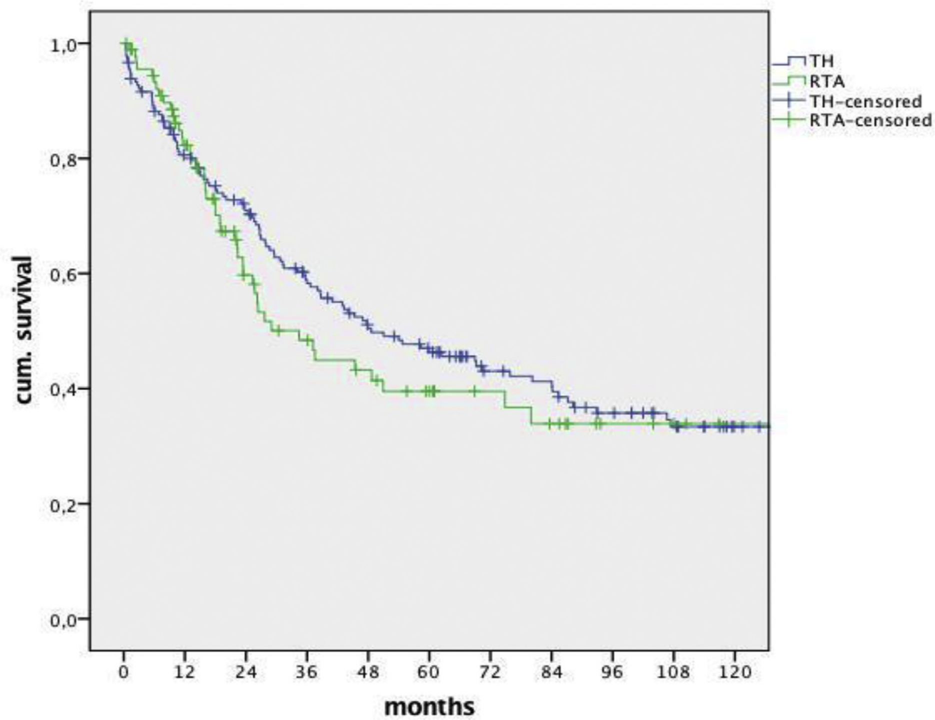
As expected, the RTA group showed a higher complication rate in our study (34.1% vs. 24.6%; $p = 0.006$), anastomotic leaks (4.4% vs. 2.8%) and wound infections (12.1% vs. 1.7%) being the most frequent surgical complications. However, the higher complication rate did not translate into a higher 30 day mortality rate, which was 1/91 (1.1%) in the RTA group and 8/179 (4.5%) in the TH group ($p = 0.134$).

Our results showed no significant difference in the number of resected lymph nodes (LN). This could be explained by the fact that a (modified) D2-lymphadenectomy was routinely performed in both groups. Nevertheless, the role of the exact extent of lymphadenectomy in EJA is still unclear. A study by Okholm et al. stated that local lymphadenectomy offers a significant therapeutic benefit, whereas the survival decreases as the metastases become more distant [30]. Another study by Yamashita et al. [17] suggested that the paracardial and the lesser curvature lymphnodes (LN) must be dissected. Hasegawa et al. [31] reached the same conclusion, stating that the involvement of further LN-stations implicates the existence of micro-metastases beyond the limitations of the surgical field, which could be better controlled by chemotherapy.

Goto et al. [32] detected a higher N-stage in Siewert type II rather than type III, probably due to more advanced pT-stages, underlining the importance of the intra-abdominal lymphadenectomy, especially of the lower perigastric LN. The impact of lower mediastinal lymphadenectomy could not be properly investigated.

The minimal number of LNs to be dissected is still elusive. A retrospective, exploratory study by Sisic et al. [33] showed a high prognostic relevance of the number of dissected LNs. RTA ensures a better lymphadenectomy of the lower mediastinum, but no resection of the LNs at the greater curvature and the pylorus. Conversely the standard lymphadenectomy in TH is a D2 lymphadenectomy including the LN stations #19, #20, #110 and #111 [34], which allows for a more radical intraabdominal lymphadenectomy, but with limited radicality in the mediastinum.

Yamashita et al. [17] compared the extent and location of lymphadenectomy to assess its survival benefit. A low incidence of LN-metastasis at the greater curvature was detected, and the index of



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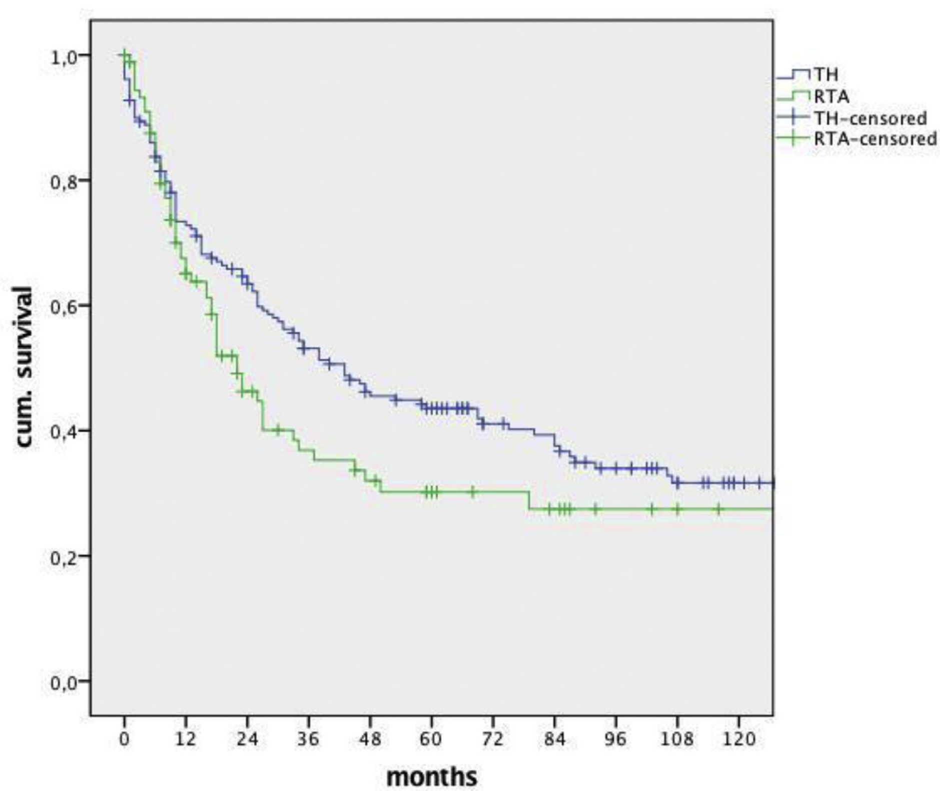
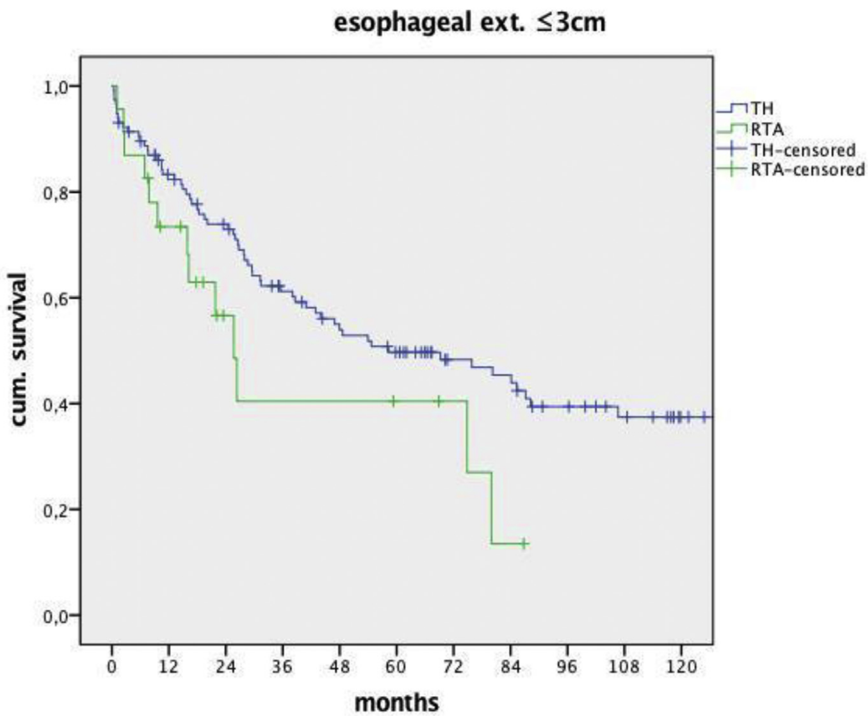


b

Fig. 1. a Overall Survival (Median OS: RTA: 34.4 ± 6.2 months; TH: 48.6 ± 10.7 months), $p = 0.448$. b Disease free survival (Median DFS: RTA: 22.0 ± 3.6 months; TH: 43.0 ± 7.2 months), $p = 0.085$.



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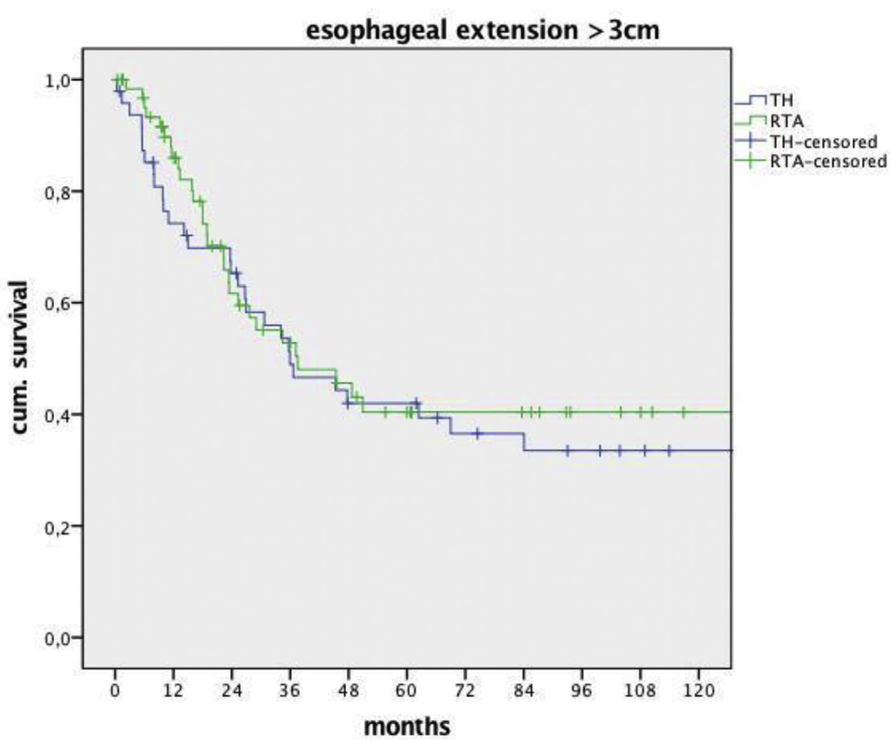
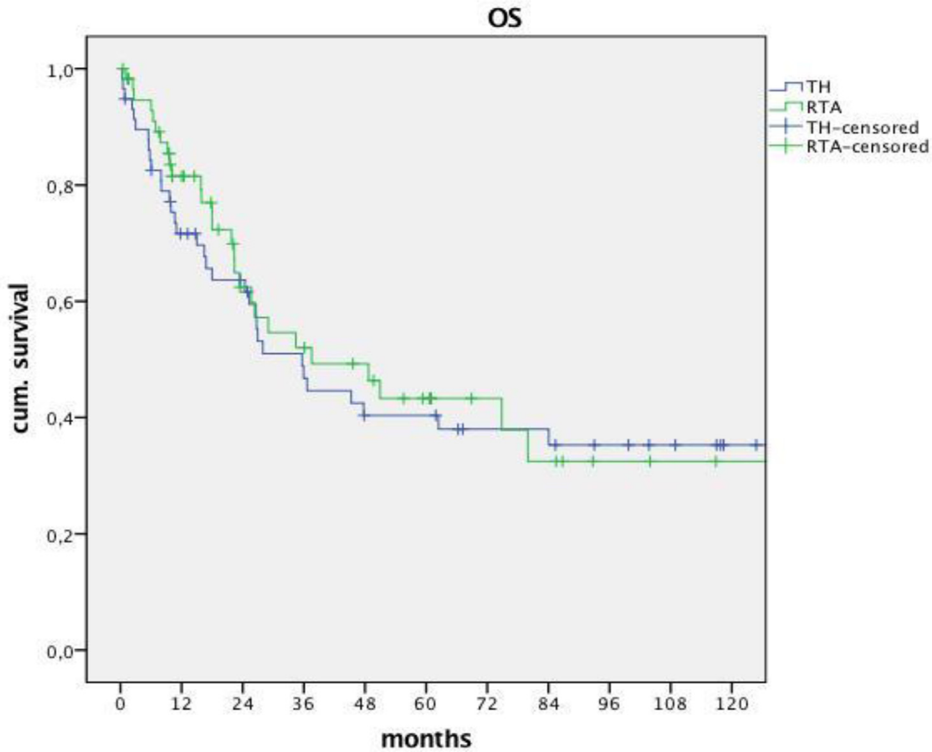


b

Fig. 2. a: Esophageal extension ≤3 cm: median OS RTA vs. TH: 58.3 ± 16.6 months vs. 25.7 ± 3.4 months, $p = 0.064$; b: esophageal extension >3 cm: median OS RTA vs. TH: 35.9 ± 9.4 months vs. 37.5 ± 1.9 months, $p = 0.592$.



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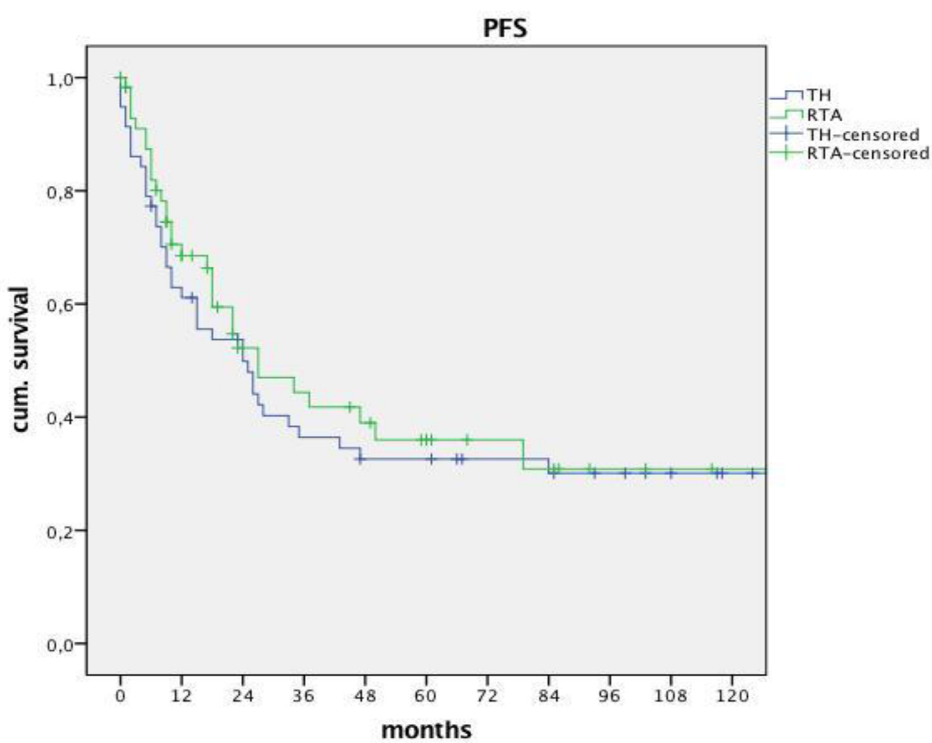

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Fig. 3. a: OS – matched patients (n = 62 vs.62). Median OS: RTA: 37.5 ± 13.6 months; TH: 35.7 ± 6.5 months, p = 0.669. b: DFS after matching DFS – matched patients (n = 62 vs.62). Median DFS: RTA: 27.0 ± 7.9 months; TH: 24.0 ± 6.5 months, p = 0.535.

estimated survival benefits from the dissection of stations #4d, #4sb and #6 in AEG II tumors was zero.

Hosokawa et al. reviewed the recurrence pattern of EJA after radical resection [35]. The most frequent route of tumor cell dissemination in EJA II was hematogenous. Multivariable analysis revealed that mediastinal LN-metastases were an independent prognostic indicator of poor recurrence-free survival. The recurrence rate in patients with mediastinal LN-metastases at the time of surgery was 100%. These data suggest that mediastinal lymphadenectomy may be effective for local control, without improving prognosis.

Although the survival outcomes did not differ significantly in the primary analysis, the result may have been substantially confounded by either selection bias or potential confounders inherent to the patient cohorts. The baseline characteristics revealed that there were substantial differences in ASA class, age and application frequency of neoadjuvant chemotherapy related to the selected procedure. This may have influenced the surgeons' choice of resection modality. Further, intra- and postoperative factors such as extended surgery, positive oral margins complication rates and differences in true tumor stage distributions may have confounded the primary outcome. In order to achieve the best comparability in the two patients' cohorts and to better define the impact of the surgical technique on survival PSM was performed. This statistical method reduces possible selection-bias in observational/non-randomized studies, eliminating potential differences between the groups. As demonstrated the baseline characteristics and postoperative factors with potential impact on survival were evenly balanced after the matching and therefore substantially improved potential biases. After PSM, the baseline characteristics were evenly balanced. The subsequent survival analyses demonstrated that still, there was no significant difference in the oncologic outcome in relation to the procedure chosen. OS and DFS were almost the same for both groups. Conclusively, survival analysis after PSM revealed that there was no difference in OS after balancing the cohorts for possible confounders. Nonetheless, the following limitations have to be taken in account: Propensity score matching is not able to balance for unmeasured factors such as surgical quality and inter-individual biologic or genetic differences. Further, unmeasured factors such as surgical quality, influence of surgical trauma, the influence of improved postoperative intensive care and general improvements in a time period over thirteen years could not be assessed in this analysis.

This analysis has further limitations: it is a single center analysis and possible selection bias could have been present that could not be controlled by PSM. Further, improvements in the efficacy of neoadjuvant treatments could not be accounted for due to the large time period of thirteen years. Another limitation is the fact that there was only limited data on lymph node retrieval related to the respective procedures. There were no records on the number of patients in the RTA group with positive mediastinal nodes above the tumor and on the number of patients in the TH group with positive nodes along the greater curvature or in the omentum. This was related to the fact that unlike Eastern Asia there was no dissection of the specific lymph node stations but an en-bloc workup of the resected specimen focusing on lymph node numbers.

Conclusion

Conclusively, this study could not detect a significant survival difference between RTA and TH from an oncologic point of view. RTA was not associated with higher morbidity and mortality compared to TH. RTA for Siewert Type II EJA appears to be preferable, whenever the oral tumor margin cannot be safely achieved by the transhiatal approach. Hereby an esophageal tumor extension of more than three cm seems to be a reasonable cutoff value.

Conflict of interest

The authors disclose no potential conflicts of interest.

Human rights statement and informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Declaration of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.09.017.

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