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Thoracoabdominal gastrectomy and distal 2/3 esophageal resection with wide lymph node dissection for type II and III adenocarcinoma at the gastro-esophageal junction

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ABSTRACT

Background: For locally advanced Siewert type II and III tumors we have performed total gastrectomy including resection of the distal 2/3 of the esophagus, through separate abdominal and right chest incisions (THX-ABD). The procedure involves wide lymphadenectomy in the abdomen/chest and a Roux-en-Y jejunostomy to the level of the azygos vein or above. The aim of the study was to investigate short- and long-term results for this rarely used procedure.
Methods: Retrospective study of 83 radio-chemotherapy naïve patients with adenocarcinoma at the gastro-esophageal junction (Siewert type II n = 65 and type III n = 18) operated upon 1986–2011.
Results: 2/83 (2.4%) patients died in hospital. 70/83 (84%) patients had R0-resections. 82/83 (99%) patients had free longitudinal resection margins. Overall 5-year survival was 22/83 (27%).
Conclusion: THX-ABD can be performed with high rates of R0 resections and with low in-hospital mortality. Long-term survival rate was not better compared with less extensive surgical procedures.

Introduction

The optimal surgical strategy for tumors of the GEJ varies depending on their epicenter as classified by Siewert.[1] For Siewert type I tumors, transhiatal esophagectomy (THE) with neck anastomosis or transthoracic esophagectomy (TTE) are widely accepted surgical procedures.[2] Siewert type III tumors are preferably removed according to the principles of abdominal gastrectomy and through a widened hiatus, also the distal esophagus with lymph nodes in the lower mediastinum.[3,4]

Surgery for locally advanced Siewert type II and III tumors is often a challenging procedure and there are technical considerations that needs to be clarified before surgical resection can commence. Tumor growth into the distal esophagus might result in too short proximal resection margin with the abdominal approach without additional esophageal resection. A left combined thoracoabdominal approach (LTA) is of no help because the aortic arch prevents further esophageal resection.[5] Thus, a right thoracic approach or a THE with neck anastomosis is necessary to reach the azygos vein or above. Tumor growth in the upper part of the stomach might preclude the formation of a gastric tube as a substitute. The colon interposition is seldom an alternative as primary esophageal replacement because of concerns of postoperative problems such as graft necrosis and mortality.[6] Remaining for reconstruction is a long Roux-loop, a more reflux resistant reconstruction, though surgically demanding when it is about to reach the level of the azygos vein or above for the anastomosis. When neither TTE with gastric pull-up, nor a traditional abdominal gastrectomy is an option due to concerns of free resection margins (≥5 cm) for Siewert II and III tumors of the GEJ, we have performed total gastrectomy with resection of the distal 2/3 of the esophagus, lymph node dissection on both sides of the diaphragm, and a long Roux loop reconstruction (THX-ABD). The procedure is performed through separate abdominal and thoracic incisions to achieve adequate length of proximal and distal resection margins. The addition of a right thoracotomy to the surgical procedure carries the potential for better tumor and lymph node clearance as compared to the above described approaches. As described by Sasako and co-workers, an estimation of the therapeutic benefit of

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the additional lymph node clearance can be performed by using the index of estimated benefit from lymph node dissection (IEBLD).[7]

Based on our previous results,[8] we hypothesize that the extensive thoraco-abdominal esophagogastrectomy procedure including wide lymphadenectomy on both sides of the diaphragm and a loop-Roux loop (THX-ABD) improves the prognosis without adding postoperative morbidity/mortality. The aim of this study was to evaluate morbidity, mortality, the distribution of tumor positive lymph nodes, and the potential survival benefit of the THX-ABD concept for patients with chemo- and radiotherapy naïve Siewert II and III tumors at the GEJ. The aim was also to compare the outcome to other surgical procedures described in the literature, performed for tumors within this area.

Material and methods

From a prospectively maintained database, a retrospective single center study was conducted from 1986 to 2011. After 2011 almost all patients received neoadjuvant treatment for their tumors, and hence were no longer eligible for this study.

Based on the diagnostic work up of an upper GI endoscopy and a thoracoabdominal CT scan, an operative strategy was created. A palliative approach was chosen, including a less extensive lymph node dissection, if the surgeons unexpectedly found signs of disseminated disease during surgery. To minimize anastomotic recurrences, we always tried to achieve safe proximal and distal resection margins even in patients who had palliative resections.

The THX ABD is an extensive procedure described in detail elsewhere.[8] The first phase of the procedure followed the principles of an abdominal gastrectomy with a D1+ or D2 lymph node dissection in the abdomen including splenectomy and distal pancreatic resection when indicated. Extensive dissection in the hiatal region always included at least 1 cm of the diaphragm surrounding the large tumors to ensure a wide circumferential resection margin and division of the diaphragmatic vein to gain maximum access to the lower mediastinum from the abdomen. The esophagus was preliminarily divided a couple of cm marginal proximal to the tumor and the stomach was removed. The challenge of preparing a long and straight Roux loop, at least 60 cm long, was started as close as possible to the ligament of Treitz. We endeavored to acquire an intact network of vessels in the mesentery at the very end of the Roux loop. The prepared Roux loop was often denuded from its serosa and fat to achieve enough length.

The second phase continued with a separate right posterolateral thoracotomy in the fifth or sixth intercostal space. Esophageal dissection and lymph node harvesting were continued up to the azygos vein or beyond where a stapled circular esophago-jejunal anastomosis end-to-side was constructed. We returned to the abdomen during the third phase of the procedure to straighten the Roux loop, secure it to the crus of the diaphragm, to make sure no rotation was present, and to reduce the hiatal opening. This was to facilitate the emptying of food and to avoid herniation of the Roux loop. The final phase of the procedure also included a stapled entero-enteroanastomosis 60 cm below the hiatus and a feeding jejunostomy.

The in-hospital regimen always included a postoperative radiograph of the anastomosis with water-soluble contrast medium on the 5th to the 7th post-operative day. The patients had scheduled follow-ups 1, 3, 6, 9 and 12 months after discharge from the hospital, the second year two follow-ups and then annually during the years 2–5. If there was a suspicion of tumor recurrence, endoscopy and radiological examination were performed generously.

The classification of the individual tumor as either a Siewert type II or III was made by the operating surgeon based on per-operative judgement as well as the post-operative pathology report. Pathological tumor staging was performed according to the seventh edition of the International Union Against Cancer tumour node metastasis (TNM) classification.[9] The exact numbers of all dissected lymph nodes as well as the number of positive lymph nodes were only reported in the latter part of the study period. To estimate tumor stage, all patients with a note in the pathology report of 'a positive lymph node' in a specific position were judged to have one positive lymph node in that position. All patients with pathology reports including a passage of 'positive lymph nodes' in a specific location were interpreted as having only two positive nodes in that position.

The index of estimated benefit from lymph node dissection (IEBLD) was calculated by multiplying the incidence of metastasis by the percentage of 5-year survival rate of patients with positive lymph nodes at that station.[7] The overall cumulative 5-year survival rate of patients with metastasis at each nodal station was calculated irrespective of the presence/absence of metastases at other nodal stations.

Statistical analyses were performed using the SPSS® version 23 (SPSS, Inc., Chicago, IL). Values were expressed as median values and range. Survival status of the patients was determined by follow up date (February 16th, 2016) or the date of death according to the Population Register of Sweden. Survival rates were shown graphically as Kaplan-Meier plots and compared using the log rank test. A multivariable Cox regression model was performed using all significant univariate impact factors. A p-value of <0.05 was regarded as significant.

The study was approved by the Regional Ethics Committee, Lund University, Sweden (Dnr 2013/587).

Results

Our database search generated 83 patients (70 men and 13 women) with Siewert type II ($n = 65$) and III ($n = 18$) tumors of the GEJ. Of these, four patients had *ad hoc* palliative resections. Baseline patient characteristics, duration of surgery, hospital stay and tumor data are presented in Table 1.

Morbidity and mortality

In 18/83 patients (22%) we found complications Clavien Dindo 3b-5. The Roux-loop of one patient showed signs of ischemia during the primary operation and had to be removed immediately. Gastrointestinal continuity was never re-established and the patient died on post-operative day 69 due to hemorrhagic pancreatitis. The other in-hospital death resulted from sudden circulatory collapse on post-operative day 23. Anastomotic leakages were observed in eight patients: five of them required operative intervention including one patient in whom the Roux-loop had to be removed due to complete necrosis. In this patient, gastrointestinal continuity was re-established 3 months later by means of a new Roux-loop. The other three patients with anastomotic leakages were treated conservatively. All anastomotic leakages were confirmed radiologically. Pulmonary complications were observed in 21 patients. The in-hospital mortality was 2/83 (2.4%) (Table 2). No in-hospital deaths were recorded after 2001.

Lymph nodes

A median of 22 (4–76) lymph nodes were harvested in patients ($n = 40$) whose pathology reports included the exact number of examined lymph nodes (Table 3). The right (No.1) and left (No.2) paracardial lymph node stations were the most common sites of metastatic nodes, being present in 29/83 and 27/83 of the patients,

Table 1
Patient characteristics, data on surgery and hospital stay.

Gender		**Splenectomy**	
Male	70	Yes (planned)	65
Female	13	Due to injury	1
		No (planned)	15
Median age (range)	66 (27–89)	Previously resected	2
ASA score		**Distal pancreatic resection**	
1	25	Yes	13
2	43	No	70
3	15		
		Median (range) hospital stay (days)	16 (9–73)
Median (range) duration of surgery (h)	11.5 (7.8–15.6)		
Median (range) blood loss during surgery (ml)	1100 (250–3800)		
Surgeons post-op opinion of radicality			
Radical	77		
Borderline radical	2		
Palliative	4		

Table 2
Mortality and morbidity.

Mortality (%)		**Complications managed without surgery**	
In hospital	2/83 (2.4)	Focal ischemic necrosis in the conduit or anastomotic leakage	4[a]
90-day	5/83 (6.0)	New onset of atrial fibrillation or cardiac failure	9
		Pulmonary complications total	21[b]
In hospital mortality	2	Respiratory insufficiency	5
		Aspiration	3
Hemorrhagic pancreatitis	1	Pneumonia	8
Persistent cardiac failure	1	Pneumothorax	3
		Pleural effusion	4
Reoperations	12	Abdominal abscess	3
		Deep vein thrombosis	1
Focal ischemic necrosis in the conduit or anastomotic leakage	5	Others	6
Ileus	2		
Necrotic/hemorrhagic pancreatitis	2		
Abscess with intact anastomosis	1		
Chylothorax	1		
Infectious pleural effusion	1		

[a] The only patient with an ischemic Roux-limb resected during the index operation never had the gastrointestinal continuity re-established.
[b] Number of patients. Some patients had more than one pulmonary complication.

Table 3
Tumor and lymph node data.

Tumor site		**Depth of tumor invasion (pT)**	
Cardia (type II)	65	1	4
Subcardia (type III)	18	2	8
		3	63
Tumor type		4	8
Adenocarcinoma with Barrett	11		
Adenocarcinoma without Barrett	72	**N-stage**	
		N0	24
Extent of dissection		N+	59
R0	70	N1	27[c]
R1	13	N2	20[c]
		N3	12[c]
Tumor free upper margin			
yes	82	**Median (range) number of harvested lymph nodes**	22 (4–76)[d]
no	1		
		Tumor stage	
Tumor free lower margin		I	6
yes	82	II	22
no	1	III	43
		IV	12
Tumor free circumferential margin			
yes	71		
no	12		
Median (range) resection margin measured from upper end of the tumor (cm)	7.6 (0–16)[a]		
Median (range) of the maximum tumor size (cm)	6.0 (1–17)[b]		

[a] Calculated on those patients with a denotation of the exact distance of the free proximal resection margin (n = 66).
[b] Calculated on those patients with a denotation of the exact number of maximum tumor size (n = 79).
[c] Estimation due to lack of the exact number of pathological lymph nodes in the pathology report.
[d] Calculated on those patients with an exact number of dissected lymph nodes in the pathology report (n = 40).

respectively (Supplement 1). They were followed in order of frequency by nodes located in lower mediastinum (No.110), at the celiac trunk (No.9), at the left gastric artery (No.7) and along the lesser curvature (No.3). Nine patients had positive lymph nodes retrieved via right thoracotomy whom all had Stage IIIC or IV disease with zero 5-year survival.

Therapeutic lymph node index

The calculation showed the highest index for nodal station No 7 (7.2), followed by No 1 (4.8), Nos 2 and 3 (3.6), No 11 (2.4) and Nos 9 and 110 (1.2) (Supplement 1). The index was 0 for all nodal stations dissected via right thoracotomy, not resectable through abdominal only approach.

Patterns of tumor recurrence

Some 3/50 patients with R0 resections who later died because of relapse in their cancer had an anastomotic recurrence. The rest of the cancer recurrences were either within (n = 16) the field of dissection or the patient had systemic disease (n = 31).

Survival analysis

Overall five-year survival for the cohort was 22/83 (27%) and 22/79 (28%) with *ad hoc* palliative resections excluded. Long-term survival in the univariate analysis was best determined by tumor stage ($p < 0.005$), N0 vs. N+ ($p < 0.005$), R-status ($p = 0.04$) and T-stage (T1-T2 vs. T3-T4 ($p = 0.04$)). In the multivariable model including only significant impact factors from the univariable Cox regression model, tumor stage (p=<0.005) was the only factor with a significant impact on long-term survival (Table 4 and Fig. 1).

Discussion

From a patient's perspective, long-term survival, or at least prolonged life without too many advanced side-effects, is a prerequisite for accepting major surgery. From a tumor-spreading perspective, patients with tumors located in between the abdomen and chest may potentially benefit from a wide resection in both body compartments. From a surgical perspective, we have shown that THX-ABD, can be performed with high rates of tumor free resection margins and low short-term mortality in chemo- and radiotherapy naïve patients with type II and III tumors of the GEJ. However, even though the procedure may be associated with fewer local recurrences, it does not cure more no of patients.

Tumors of the GEJ may be operated on with less extensive procedures[3,4] if a free proximal resection margin is achieved. All patients in this study had wide resection of the tumor area offering generous access to the lower mediastinum through a widened hiatus. Still, the median size of Siewert type III tumors in our study was 6 cm meaning, from our viewpoint, performing a safe anastomosis from the abdomen without jeopardizing the proximal resection margin was never an option. In addition, achieving a long free proximal resection margin, a known prognostic factor for improved survival,[10] is seldom a problem with the THX-ABD, even for larger tumors of the GEJ. Using a long Roux-loop we agree with Ninomiya et al.[11] that returning to the abdomen during the third phase is crucial to succeed with the procedure. Extended proximal esophageal resection is also an option when using the colonic interposition as primary esophageal replacement. Some investigators argue the advantages of the colon as an esophageal substitute,[12,13] while others argue the contrary.[6,14]

The THX-ABD implies extensive lymph node dissection which is known to improve staging, contribute to more accurate survival estimates and might also have the potential of improved survival.[15–18] Claiming the opposite, another study showed no survival benefit for those patients having more lymph nodes removed during surgery for esophageal cancer.[19] In addition, a survival benefit was shown for patients with more dissected lymph nodes who received treatment with surgery alone, but not for patients who received neoadjuvant chemoradiotherapy plus surgery.[20]

The extent of proximal tumor growth into the esophagus and distal into the stomach of tumors of the GEJ have both been correlated with the risk of metastatic lymph node spread to the thoracic and the lymph nodes along the greater curvature/antrum, respectively.[21,22] The THX-ABD incorporates all the lymph nodes in the middle/lower mediastinum as well as the nodes along the greater curvature/antrum within the field of dissection. Hence it can be argued that the THX-ABD should be the method of choice for selected patients with large tumors at the GEJ.

In line with other investigators who used the therapeutic value index,[7] we found the paracardial nodes, the nodes along the lesser curve and the nodes at the root of the left gastric artery to have the highest therapeutic benefit to dissect.[23,24] Only 9/83 (11%) patients in our cohort had positive lymph nodes retrieved from the right thoracotomy. Like previous reports,[25] this was associated with poor long-term outcome in our study. Consequently, in terms of potential therapeutic benefit extensive lymph node dissection of the

Table 4
Impact factors for survival (uni-and multivariate Cox regression).

	Univariate analysis	Multivariate analysis		
	p-value	p-value	Hazard ratio	95% CI
Extent of dissection (R0 vs. R1)	0.04	0.60	1.19	0.63–2.24
T1-2 vs. T3-4	0.04	0.07	0.26	0.06–1.13
N0 vs. N+	<0.005	0.18	0.29	0.05–1.83
Tumor stage	<0.005	0.002		
I			reference	
II			6.43	1.12–37.01
III			50.73	1.96–1313.65
IV			155.43	5.42–4458.52
N+ harvested from right thoracotomy	0.12			
Anastomotic insufficiency	0.28			
Reoperation	0.91			
Cardia type (II vs. III)	0.67			
Duration of surgery	0.29			
ASA-score	0.84			
Age	0.33			

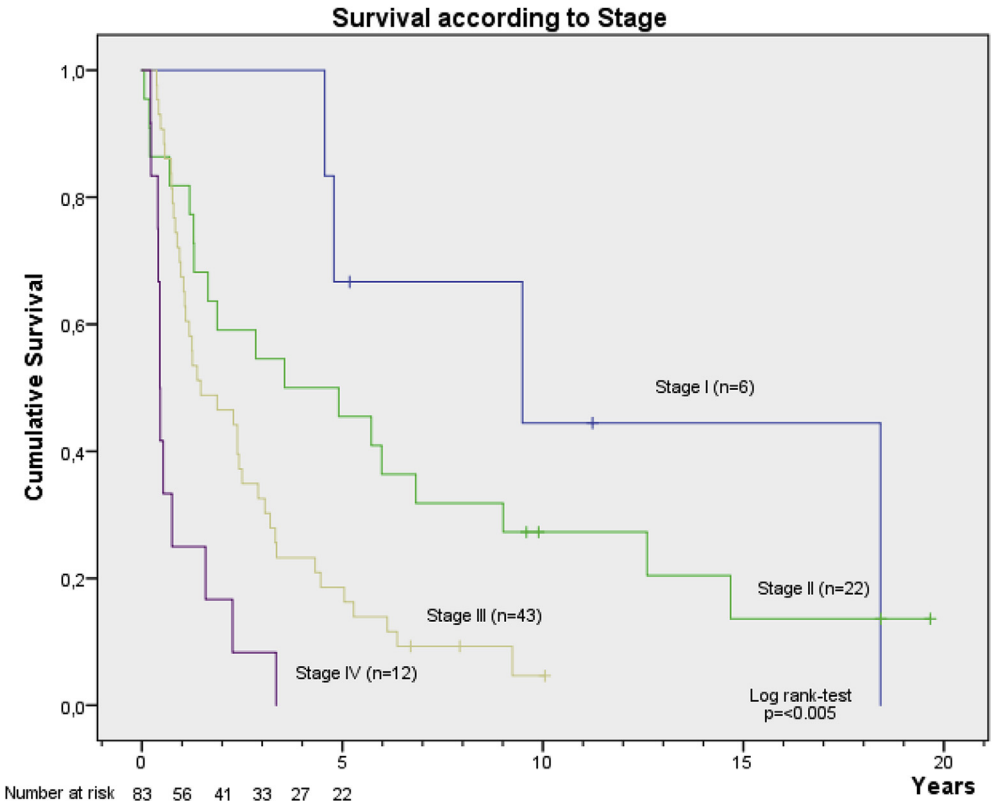

Fig. 1. Survival according to Stage.

middle and lower posterior mediastinum via a right thoracotomy is not indicated for these tumors.

A limitation of this study is the lack of denotations on the exact number of positive lymph nodes in each specific position of the pathology report during the first half of the study period. This probably led to an underestimation of the N-status and hence an underestimation in staging of these patients.

Even though patients with ASA 3 were included in our study, only 2/83 patients (2.4%) died in hospital post-operatively. In comparison to other studies with a thoracoabdominal approach,[2] 32/83 (39%) patients had an uneventful post-operative recovery. This rate was lower than other reports of less extensive surgery for the same type of tumors.[3,26] In addition, 21/83 (25%) patients experienced pulmonary complications in our study. This was higher than reports of the abdominal only approach.[26]

The overall five-year survival rate of 27%, best explained by tumor stage, following the THX-ABD procedure is not superior to the results of less extensive surgical procedures[2,26] (Supplement 2). The THX-ABD procedure may well eradicate the local tumor, in our study manifested by an R0 resection rate of 70/83 (84%). Although a proximal resection margin of approximately 8 cm and wide lymph node dissection was achieved by this surgery alone strategy, we failed to prevent later systemic disease in the 50/83 patients who died of recurrent disease. These facts indicate the need for alternative or additional treatment strategies to improve both long-term outcome and palliation. The benefit of pre-operative oncological treatment was clearly evident in the CROSS study.[27] On the other hand, in a Swedish nationwide cohort study of patients with adenocarcinoma of the GEJ, neither neoadjuvant chemotherapy nor chemoradiotherapy compared to surgery alone significantly improved survival.[28]

Conclusion

Although a complex and time-consuming procedure, the THX-ABD can be performed with low rates of post-operative mortality. Based on the absent benefit in terms of survival due to the extended thoracic dissection and the added morbidity due to the right thoracotomy in this study, the use of this procedure can be questioned for routine use in Siewert II and III tumors of the GEJ. In our view, it should be reserved for selected patients with large tumors in this region, as an alternative instead of utilizing a colonic interposition, when neither the TTE nor the abdominal only approach is an option to achieve R0. The role of this procedure in the era of neoadjuvant oncological treatment remains investigational.

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Disclosures

All contributing authors declares no conflicts of interest.

Authors'contributions

MJ, BW and JJ all contributed to the conception and design as well as the acquisition of data for this article. MJ, BW, PD, CSvH, TZ, MH, DF and JJ all contributed to the analysis and interpretation of the data, drafting and revising of the work and gave their final approval for the work to be published.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.11.049.

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