research article

Outcomes of the surgical treatment for adenocarcinoma of the cardia - single institution experience

Stojan Potrc, Arpad Ivanecz, Bojan Krebs, Urska Marolt, Bojan Iljevec, Tomaz Jagric

Department of Abdominal Surgery, Surgical Clinic, University Medical Centre Maribor, Maribor, Slovenia

Radiol Oncol 2018; 52(1): 65-74.

Received 15 August 2017
Accepted 31 Avgust 2017

Correspondence to: Assoc. Prof. Stojan Potrč, M.D., Ph.D., Department of Abdominal Surgery, Surgical Clinic, University Medical Centre Maribor, Ljubljanska 5, Maribor, Slovenia. Phone: +386 2 321 1301; Fax: +386 2 321 1257; E-mail: potrc13@gmail.com

Disclosure: No potential conflicts of interest were disclosed.

Background. Adenocarcinomas at the cardia are biologically aggressive tumors with poor long-term survival following curative resection. For resectable adenocarcinoma of the cardia, mostly esophagus extended total gastrectomy or esophagus extended proximal gastric resection is performed; however, the surgical approach, transhiatal or transthoracic, is still under discussion. Postoperative morbidity, mortality and long-term survival were analyzed to evaluate the potential differences in clinically relevant outcomes.

Patients and methods. Of altogether 844 gastrectomies performed between January 2000 and December 2016, 166 were done for the adenocarcinoma of the gastric cardia, which we analyzed with using the Cox proportional hazards model.

Results. 136 were esophagus extended total gastrectomy and 125 esophagus extended proximal gastric resection. A D2 lymphadenectomy was performed in 88.2%, splenectomy in 47.2%, and multivisceral resections in 12.4% of patients. R0 resection rate was 95.7%. The mean proximal resection margin on the esophagus was 42.45 mm. It was less than 21 mm in 9 patients. Overall morbidity regarding Clavien-Dindo classification (> 1) was altogether 28.6%. 15.5% were noted as surgical and 21.1% as medical complications. The 30-day mortality was 2.2%. The 5-year survival for R0 resections was 33.4%. Multivisceral resection, depth of tumor infiltration, nodal stage, and curability of the resection were identified as independent prognostic factors.

Conclusions. Transhiatal approach for resection of adenocarcinoma of the cardia is a safe procedure for patients with Siewert II and III regarding the postoperative morbidity and mortality; moreover, long-term survival is comparable to transthoracic approach. The complications associated with thoracoabdominal approach can therefore be avoided with no impact on the rate of local recurrence.

Key words: proximal gastric cancer; transhiatal resection; complications; survival

Introduction

The incidence of gastric cancer sited in the proximal third and esophago-gastric junction (EGJ) was rising worldwide; however, in Europe this tendency seems to be stabilizing.[1] Adenocarcinomas of the cardia (ACC) are the most frequent type within these tumors. They are typically diagnosed at an advanced stage of disease progression.[2-5] As a result, they are difficult to treat and the patient prognosis is poor even after curative surgical resection comparing to those sited in distal two thirds of stomach. The extension of gastrectomy in the mediastinum makes the resection of ACC more demanding and burdened by higher postoperative morbidity. Consequently, the long-term survival rate after surgical resection has been reported to be lower, ranging from 16% to 40%.[6-9]

The Siewert's classification (S I–III), founded almost 20 years ago, still presents an important ba-

doi: 10.1515/raon-2017-0038

sis for decision-making in clinical praxis for EGJ tumors; however, its implication regarding strict decision for thoraco-abdominal or transhiatal approach for ACC SI and SII is still under discussions.[8,10] Different reports of meta-analyses reveal contradictory conclusions and randomized control studies are lacking. In the western world, presently the only clear recommendation stays for SIII tumors to be approached transhiatal, whereas in the eastern world also SII tumors are mostly resected transhiatal.[9-14] The tumor free segment of the esophagus to be achieved is 5 cm and the infiltration of the esophagus should not exceed 2 cm.[15]

Extent of organ resection and lymphadenectomy are the next issue of discussion without any clear evidence based on the randomized control studies; however, most ACC of S I and II are surgically managed by distal esophagectomy with proximal gastrectomy, while distal esophagectomy with total gastrectomy is often applied in S III tumors.[7] In clinical practice, the exact origin of EGJ tumors can sometimes be hard to define, which complicates the choice between distal esophagectomy with total gastrectomy and esophagectomy with proximal gastrectomy.[16]

Regarding the extent and region of lymphadenectomy needed for ACC, huge nation-wide Japanese study analyzing the records of 2807 patients having had R0 resection of EGJ carcinoma was able to confirm that the incidence of lymph node metastases correlates highly with T stage and site of the tumor. In stomach, predominant cancer (2 cm below EGJ) lymph node metastases in the middle and upper mediastinum were seldom detected even in T3/4 tumors (< 6% in T4), whereas in esophagus predominant tumors (2 cm above EGJ) metastases to the lymph nodes were detected more often (> 30% in T4).[17]

Randomized control studies have demonstrated the preoperative therapy with chemoradiotherapy or chemotherapy alone improves survival outcome for patients in stages more than T1 and/or more than N0 in which R0 resection was possible. Evidence suggests, but does not confirm, that radiation-containing regimens are more beneficial.[16,18-20]

The aim of the present study was to reveal perioperative morbidity and mortality as well as long-term survival in proximal gastric adenocarcinoma resected exclusively with transhiatal approach. We also searched for correlations of clinicopathological factors with morbidity, mortality and long-term survival.

Patients and methods

The medical records of 844 consecutive patients who had gastric resection for adenocarcinoma of the stomach from January 1, 2000 through December 31, 2016 at the Department of Abdominal Surgery at Surgical clinic UMC Maribor, Slovenia were retrospectively reviewed. Patients resected for gastric stump tumors and those in which entire stomach was affected were excluded from the study. 161 patients with ACC and transhiatal resected were considered for the analyses. The level of the location on the gastric cardia was determined concerning the Siewert's classification.[8,10]

Patients' preoperative physical status was expressed by the American Society of Anesthesiology score (ASA).[21]

After the diagnosis of ACC was initially confirmed by endoscopy and biopsy, computed tomography (CT) of thorax and abdomen was done to rule out dissemination of the disease and to assess the locoregional stage to gain the clinical stage as well as to judge whether the tumor would be resectable with transhiatal approach.

As all other oncological patients, they were presented to the oncological board for treatment planning. Until 2010, adjuvant radio-chemo therapy was indicated in stages pT2 and higher and/or pN+; however, since 2010, all amenable patients in stage higher than cT2 and higher and/or cN+ were submitted for neoadjuvant oncological treatment.

If there were no contraindications regarding general status, radical resection in terms distal esophagectomy with total gastrectomy or esophagectomy with proximal gastrectomy was done with strategy to provide 6–7 cm in vivo distance from the upper aspect of the tumor. The distal esophagectomy with total gastrectomy was preferred; however, in some patients with poorer general status or if the mesentery was to short, esophagectomy with proximal gastrectomy was done. A ring of hiatal part of the diaphragm was regularly excised en-block with the resected specimen. If there were no contraindications regarding general status, a D2 lymphadenectomy (stations 1, 2, 3, 4sa, 4sb, 5, 6, 7, 8a, 9, 11p, 11d) was performed including distal mediastinal lymph nodes (station 110, 111).[22] The spleen was usually preserved, unless there was macroscopic infiltration, lymph node No. 10 was clearly enlarged, or the tumor extended toward the grater curvature and was adhered to the stomach wall.[23] Additional resections of infiltrated neighbor organs were done to assure R0 resection.

TABLE 1. Clinicopathological characteristics of the patients resected for adenocarcinomas of the cardia (ACC)

Gender (n=161)	**Male**	120	74.5%	
	Female	41	25.5%	
Age *(Mean, 95% CI)* (n = 161)		64. 6 ± 10.1	Lower: 62.90	Upper: 66.31
American Society of Anesthesiology score (ASA) (n = 161)	**1**	53	32.9%	
	2	83	51.6%	
	3	25	15.5%	
Type of resection (n=161)	**Distal esophagectomy and total gastrectomy**	136	84.5%	
	Distal esophagectomy and proximal gastrectomy	25	15.5%	
Extend of lymphadenectomy (n = 161)	**D1**	19	11.8%	
	D2	142	88.2%	
Metastatic lymph nodes *(mean, 95% CI)* (n = 161)		6.11 ± 7.7	Lower: 4.91	Upper: 7.32
All harvested lymph nodes *(mean, 95% CI)* (n = 161)		23.20 ± 11.7	21.37	25.03
Splenectomy (n = 161)		76	47.2%	
Additional oncological resections		20	12.4%	
R0 resection		154	95.7%	
Proximal resection margin in mm *(mean, 95% CI)* (n = 142)		42.45 ± 20.7	Lower: 39.0	Upper: 45.80
Proximal resection margin < 20 mm (in fixed specimen + 0,9cm stapler ring) (n = 142)		9	5.6%	
Diameter of the tumor in mm *(mean, 95% CI)* (n = 161)		63.16 ± 23.1	Lower: 58.18	Upper: 68.15
Any type of oncological treatment completed		56	34.8%	

At operation, definite site of the tumor and Siewert type were determined.

Intravenous antibiotic (1.5 g cefuroxime and 0.5 g metronidazole or 0.35 g gentamycin and 0.6 g clindamycin) and subcutaneous antithrombotic (4000 IE enoxaparin or 3800 nadroparin or 5000 IE dalteparine) prophylaxis were successively used in all patients 1 hour and 12 hours prior to operation. Urine catheter and nasogastric tube were usually inserted after induction of anesthesia.

Almost all patients were admitted in the high dependency unit except if admission to the intensive care unit was indicated. Patients started to receive fluid food on the third day. To confirm and also to stimulate the peristaltic movements 50 ml of hypertonic contrast (Gastrografin) is routinely administrated on the third or fourth day after operation. Gastric tube was removed after appearance of bowel movements or the first stools.

Resected specimens were examined according to standard pathophysiologic procedure and classified according to Lauren, WHO, TNM and UICC classification as well as according to differentiation of tumor cells (gradus).[24-26] Before fixation of the specimen, the proximal tumor free distance on the specimen has been measured by the pathologists. Additional 9 mm of stapler cylinder (circular stapler 25 mm) were added to the distance measured by the pathologists.

Any complication occurring postoperatively within 90 days was considered as surgery related and noted according to Clavien-Dindo classification.[27] Additionally, surgical and medical complications were listed separately. Postoperative deaths within 30 and 90 days were considered as probable consequence of surgery and were declared as postoperative mortality (30- and 90-day mortality).

For patients surviving longer than 90 days after operation, recurrence of the disease was determined by image procedures (CT, PET CT), cytological analyses of abdominal and pleural effusions as well as by autopsy reports.

Clinical and pathological data were prospectively stored in a computerized database. Data from the follow-up were obtained by our own outpatient follow-up and by the National cancer register of Slovenia. Complete follow-up was obtained as of June 1, 2017.

We obtained informed consent from all patients and performed all procedures according to the guidelines of the Helsinki Declaration.

Clinicopathological factors involved in correlation analyses were: gender, age, ASA, type of resection, extent of lymphadenectomy, additional

oncological resections, length of the proximal tumor free segment of esophagus, (mean and group < 2.1 cm), TNM classification, Lauren classification, perineural invasion, any completed oncological treatment, perioperative morbidity and mortality as well as long term survival.

For the calculation of long-term survival, only patients who survived 90 days after operation were included.

Continuous data are expressed as mean ± standard deviation and categorical variables are given as percentages. Continuous variables were compared with Student's t-tests for parametric data and Mann-Whitney U tests for nonparametric data. Chi-square tests were used for comparisons of discrete variables. Survival analysis was performed with the Kaplan-Meier method. The differences between groups were compared with the log-rank test. All of the predictors that were significant on univariate analysis were included in the multivariate analysis (Cox regression model). P values < 0.05 were defined as the limit of significance. For statistical analysis, SPSS version 22 for Windows 7 (IBM Analytics, Armonk, NY) was used.

TABLE 2. Type of additional oncological resections (n = 161)

	n	%
Left pancreatectomy	9	5.6
Liver resection	1	0.6
Local peritonectomy	6	3.7
Segmental resection of the jejunum	1	0.6
Resection of left suprarenal gland	2	1.2
Segmental colon resection	1	0.6
Total	**20**	

TABLE 3. Pathological classifications: depth of tumor infiltration (T), lymph node metastases (N), Lauren type, perinevral (n = 161)

		n	%
T0		1	0.6
T1		20	12.4
T2		21	13.0
T3		87	54.0
T4a		22	13.7
T4b		10	6.2
N0		48	29.8
N1		21	13.0
N2		41	25.5
N3a		33	15.6
N3b		18	11.2
Lauren type	Intestinal	97	67.8
	Diffuse	26	18.2
	mixed	20	14.0
Presence of perineural invasion		82	54.2

Results

Of altogether 844 patients resected for gastric adenocarcinoma, 161 (120 males, 41 females, mean age 64.6 ± 10.9 years) had resection for adenocarcinoma of the gastric cardia.

Demographic data of all patients are given in Table 1. There were 136 distal esophagectomies with total gastrectomies and 125 distal esophagectomies with proximal gastrectomies. The former was more often done in older patients (esophagectomy with proximal gastrectomy *vs.* distal esophagectomy with total gastrectomy: 72.52 ± 8.5 *vs.* 63.15 ± 10.7 years; p < 0.0001) and in some cases for technical reasons (short mesentery of the Roux loop). Distal esophagectomy with total gastrectomy was found to correlate with higher N stages (N > 0: 73.5% *vs.* 52.0%; p = 0.03); however, there was no difference regarding T stage.

Tumors were classified regarding the Siewert classification (6 type I, 29 type II, 126 type III). In all 6 patients with S I type ACC, a distal esophagectomy with total gastrectomy was done; in S II type, 25 (86.2%) patients had distal esophagectomy with total gastrectomy and 4 (13.8%) esophagectomy with proximal gastrectomy; whereas in S III type, 105 (83.3%) patients had distal esophagectomy with total gastrectomy and 21 (16.7%) esophagectomy with proximal gastrectomy. Regarding this, there were no significant correlations.

A D2 lymphadenectomy was performed in 88.2% (Table 1). In comparison to D1 lymphadenectomy, a significantly higher number of lymph nodes was harvested in D2 lymphadenectomy (mean, 24.07 ± 11.5 *vs.* 16.31 ± 11.3; p = 0.01). It was less extensive in esophagectomy with proximal gastrectomy than in distal esophagectomy with total gastrectomy by declarative way (D2 in esophagectomy with proximal gastrectomy *vs.* D2 in distal esophagectomy with total gastrectomy: 68.0% *vs.* 91.9%; p = 0.003) as well as regarding the mean count of all harvested lymph nodes (esophagectomy with proximal gastrectomy *vs.* distal esophagectomy with total gastrectomy: 17.60 ± 10.48 *vs.* 24.18 ± 11.65; p = 0.027).

Splenectomy was part of a resection in 47.2% patients, more often significant in distal esophagecto-

TABLE 4. List of surgical **(A)** and general complications **(B)** occurring within 90 days after resection (n = 161)

A

	n	%
No complications	136	84.5
Intraabdominal abscess	6	3.7
Intraabdominal bleeding (within 48h)	4	2.5
Acute gangrenous cholecystitis	2	1.2
Leak from the esophagojejuno anastomosis	3	1.9
Enteric fistula	1	0.6
Disruption of laparotomy	1	0.6
Ileus	2	2.5
Ischemic colitis	1	0.6
Pancreatitis	4	2.5
Late rupture of pseudoaneurysm of splenic a.	1	0.6
Total complications	25	15.5

B

	n	%
No complications	127	78.9
Heard failure	9	5.5
Bronchopneumonia	11	6.8
Pneumo/ fluidothorax	3	1.9
Pulmonary embolia	2	1.2
Brain stroke	3	1.9
Febrile state of unknown origin	5	3.1
Decompensation of liver cirrhosis	1	0.6
Total complications	33	21.1

my with total gastrectomy than in esophagectomy with proximal gastrectomy (50.7% *vs.* 28.0%; p = 0.029), in higher T (T > 2 stages: 55.1% *vs*. 33.3%; p= 0.027) and N stages (N > 0 stages: 52.2% *vs*. 35.4%; p = 0.037).

To achieve an R0 resection, additional organs resections were needed in 20 patients (12.4%) (Table 2). Multivisceral resections were typically more often done in higher T (16.0% *vs*. 2.4%; p = 0.014) and N stage (15.9% *vs*. 4.2%; p = 0.029).

R0 resection rate was 95.7%. The mean proximal resection margin on the esophagus was 42.45 mm. It was less than 21 mm in 9 patients (6 in Siewert III, 3 in Siewert II, 0 in Siewert I); however, only one of those patients had R1 resection because of tumor infiltration in proximal resection margin. In remaining 8 patients, the resection was declared as R2 resections because of nonresectable liver metastases (3 patients), metastasis in the mesentery (1patient), retroperitoneal spread (1 patient) and peritoneal carcinosis (1 patient).

Pathological features regarding TNM classification, Lauren classification and perineural infiltration of the tumors are given in Table 3.

According to the Clavien-Dindo classification (> 1) in altogether 28.6% of patient's complications occurred within 90 days in the postoperative course. 15.5% were noted as surgical and 21.1% were medical complications. The list of surgical and general complications is presented in Tables 4A and 4B. In 7.5% of patients, surgical and medical complications overlapped. Off all clinicopathological characteristics, only shorter mean proximal tumor free margin correlated significantly with onset of surgical complications (34.35 mm ± 21.2 *vs:* 43.78 mm ± 9.8; p = 0.024), whereas there were no significant correlations with medical complications.

Twenty-six (16.1%) patients needed reoperation, 7 (4.3%) were treated by percutaneous or endoscopic intervention (no general anesthesia); however, the rest of 13 patients could be treated conservatively.

Four (2.2%) patients died within 30 days from operation; however, additional 8 (7.5%) patients died within 90 days from operation. Both mortalities were significantly increased in surgical (30-day mortality: 12.5% *vs*. 0.7%; p = 0.011, 90-day mortality: 29.2% *vs*. 3.6%; p < 0.0001) and medical complications (30-day mortality: 9.1% *vs*. 0.8%; p = 0.027, 90-day mortality: 18.2% *vs*. 4.7%; p = 0.018) or if surgical treatment was indicated for complications (30-day mortality: surgical treatment *vs.* intervention *vs.* conservative *vs*. no treatment = 15.4% *vs.* 0% *vs.* 7.7% *vs.* 0%; p = 0.02, 90-day mortality: surgical treatment *vs.* intervention *vs.* conservative *vs.* no treatment = 38.5% *vs*. 0% *vs.* 11.5% *vs*. 0%, p < 0.0001).

In 54 (36.2%) of 149 patients (no 90-day mortality) recurrence of the disease could be confirmed. The patterns regarding the region (supradiaphragmatic, infradiaphragmatic) and type of recurrence are given in Table 5. No clinicopathological factor (type of resection, extent of the lymphadenectomy, splenectomy, T stage, N stage, Siewert type, Lauren classification, gradus of the tumor, length of tumor free resection margin) revealed any correlation to recurrence except if additional resection was needed to assure R0 resection (p = 0.011)

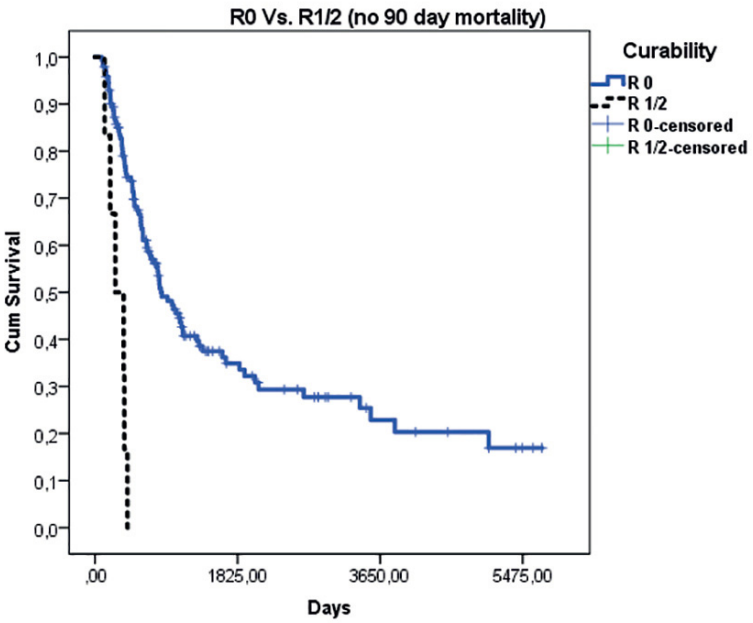

FIGURE 1. Long-term survival after resection for adenocarcinoma of the cardia in regard to curability of the resection (R0 vs. R1/2) (n = 149, median survival in days: 846 ± 118 vs. 260 ± 107; HR = 0,223, Log Rank: p < 0001).

revealing higher incidence of intraabdominal than mediastinal and systemic recurrence.

Overall 5-year survival was 33.4%. Any long-term survival could only be expected if resection was R0 (n = 149, median survival for R0 *vs.* R1/2 in days: 846 ± 118 *vs.* 260 ± 107; HR = 0.223, Log Rank: p < 0.0001) (Figure 1). Patients who survived surgical or medical complications in the postoperative course, irrelevant of its treatment modality, could expect comparable long-term survival to those without any complications (surgical complications: p = 0.317, medical complications: p = 0.986, type of treatment of complications: p = 0.888). In univariate analysis (Log Rank) for long-term survival splenectomy (yes *vs.* no), multivisceral resection (yes *vs.* no), gradus of the tumor (G 1–3), perineural invasion (yes *vs.* no), T stage (T < 3 *vs.* T >2), N stage (N0 *vs.* N > 0) and curability of the procedure (R0 *vs.* R1/2) proved as significant factors for long-term survival (Table 6).

The multivariate survival analysis (Cox regression analysis) multivisceral resection, depth of tumor infiltration (T < 3 *vs.* T > 2), nodal stage (N 0 *vs.* N > 0), and curability of the resection (R) proved as independent prognostic factors for long-term survival (Table 7).

TABLE 5. Pattern of recurrence after resection of the cardia for adenocarcinoma (n = 149, 90-day mortality excluded)

	n	%
No recurrence	**95**	**63.8**
Infradiaphragmal local recurrence	24	16.1
Supradiaphragmal local recurrence	2	1.3
Liver metastases	8	5.4
Liver metastases and infradiaphragmal recurrence	8	5.4
Lung metastases	1	0.7
Lung metastases and infradiaphragmal recurrence	1	0.7
Lung metastases and supradiaphragmal recurrence	3	2.0
Liver and lung metastases	5	3.4
Dissemination – other (bones, neck)	2	1.3
Total	149	

Discussion

The question which procedure is the best for patients with ACC has sparked a debate raging for more than a decade, but the final verdict is still a matter of debate.[5-13] To promote an easier stratification of patients for surgery, Siewert and colleges have proposed a classification of EGJ cancer patients based on the tumor location in their benchmark paper.[8] There are many who share their opinion that the tumors arising in the distal esophagus (S I) behave like esophageal tumors and are best treated with thoraco-abdominal approach, whereas S III tumors are treated like gastric tumors with the transhiatal approach.[9,10,12,16,18,19,28] However, there is much less agreement regarding the extent of resection and approach in S II tumors.[5,7,29-31] At our institution, most of the patients with S II tumors, as well as those with S III tumors, were treated transhiatal with distal esophagectomy with total gastrectomy, esophagectomy with proximal gastrectomy being done only in short mesentery or if patients were in suboptimal general condition. To determine whether this approach is safe for patients with S II and S III, we performed a retrospective study where we analyzed the results of a 16-year period of trans-abdominally operated patients with ACC.

In ACC, the resection margin has to be extended on the thoracic part of the distal esophagus in order to obtain free resection margins. There are two ways to obtain such a margin. The surgeon can choose a thoraco-abdominal approach and easily access even the carinal part of the esophagus, exposing the patients to a potentially harmful thoracotomy. The other method is the transhiatal approach to the distal part of the esophagus with en-bloc excision of a cylinder of the diaphragm

TABLE 6. Correlation for long-term survival in univariate analysis (Log Rank) for different clinicopathological characteristics. (n = 149, 90-day mortality excluded)

		Median survival (days)	HR	95% CI		p
				Lower	Upper	
Splenectomy	**No** **Yes**	1004 ± 148 616 ± 168	1.502	0.998	2.260	0.049
Multivisceral resection	**No** **Yes**	929 ± 132 324 ± 158	3.045	1.709	5.425	< 0.0001
Gradus of the tumor	**1** **2** **3**	1377 ± 504 855 ± 180 613 ± 97	1.478	1.095	1.994	0.011
Perineural invasion	**No** **yes**	1308 ± 466 660 ± 65	2.118	1.377	3.260	0.001
T stage	**T1 and 2** **T3 and 4**	3839 ±* 611 ± 79	4,147	2.297	7.488	< 0.0001
N stage	**N0** **> N0**	1915 ± 424 540 ± 70	3.037	1.810	5.096	< 0.0001
Curability of the procedure (R)	**R 0** **R 1/2**	846 ± 118 260 ± 107	2.110	1.359	3.276	< 0.0001

* less than 50% of patients censored

which obviates the need to perform a thoracotomy; however, the access to the more proximal part of the esophagus is obscured due to technical limitations of the technique.[6-9]

A D2 lymphadenectomy comprising dissection of perigastric, suprapancreatic and the lower mediastinal lymph nodes was routinely done along with EETG (in 88%).[22] Spleen was usually preserved, unless there was macroscopic adherence of the tumor to the spleen, suspicious lymph nodes in station 10, the tumor extended toward the greater curvature and penetrated the muscularis layer of the stomach, or if the spleen was unintentionally injured at the resection. Many studies supported this approach for tumors types S II and S III.[17,23,32-34] Yamashita analyzed the pattern of lymph nodes involvement in patients of tumors extending in the region of the EGJ. They found that in gastric predominant EGJ tumors suprapancreatic lymph nodes had the highest metastases rate. The incidence of upper and middle mediastinal lymph node metastases were negligible and their dissection offered no survival benefit.[17] Furthermore, an interesting fact was that even in esophagus predominating EGJ tumors, the rate of upper and middle mediastinal tumors was less relevant in adenocarcinoma than in squamous cell carcinoma of the esophagus predominating EGJ tumors. Similar results were obtained by other authors.[32-34] Moreover, the most prevalent site of lymph node recurrence was abdominal para-aortic.[17] This fact matches with the results of our study regarding the site of the recurrence. The most frequent metastatic lymph nodes are the proximal gastric lymph nodes, nodes at the esophageal hiatus, lower mediastinum and suprapancreatic lymph nodes.[33] Regarding this results and regarding the patterns of recurrence, many authors share the opinion that an extensive mediastinal lymph node dissection is unnecessary.[17,32-34] It therefore seems reasonable that the mediastinal lymphadenectomy *via* thoraco-abdominal approach is not mandatory.

The concern about the sufficient proximal resection margin is reason why some institutions recommend a thoraco-abdominal approach. Some authors argue that a sufficient proximal margin can only be obtained with a thoracic approach.[32] The R0 resection rate at our institution where the transhiatal approach with excision of the hiatal part of the diaphragm is practiced for S II and S III patients was obtained in 95.7%. This rate compares favorably to other papers that report a R0 rate from 80% to 95%.[35-38] With the transhiatal approach, we obtained a mean proximal resection margin of 42.4 mm, which is similar to margins obtained by other authors with the thoraco-abdominal approach.[32,35-38]

TABLE 7. Multivariate analysis (Cox regression) for long-term survival after resection for adenocarcinoma of the cardia (n = 149, 90-day mortality excluded)

	B	HR	95,0% CI		p
			Lower	Upper	
Multivisceral resection	-0.716	0.489	0.273	0.876	0.016
T < 3 *vs.* **T > 2**	-1.065	0.345	0.181	0.655	0.001
N 0 *vs.* **N > 0**	-0.620	0.538	0.307	0.942	0.030
Curability of resection (R)	0.747	2.110	1.359	3.276	0.001

Duan reported a 38 mm margin with right thoraco-abdominal approach in their patients' population, which corresponds to the results obtained in our study.[32] Studies have demonstrated that in patients with type S II and S III only in a dismal number of patients the tumor invaded more than 25 mm beyond the proximal margin.[37,38] A proximal margin of 38 mm in these patients was associated with a survival benefit.[16] Hence most authors agree that a proximal margin of more than 2 cm is sufficient to obtain an R0 resection and prevent an esophageal recurrence in SII and SIII patients.[16,37,38] The resection margin obtained on our institution was longer than suggested by these authors, but what is even more, it is comparable to reports from papers evaluating the thoraco-abdominal approach.[32]

Since it is evident that with the thoraco-abdominal approach free proximal margins and adequate lymphadenectomy can be obtained, it is only feasible to choose a procedure that offers a potentially less invasive and less morbid approach to patients with SII and SIII tumors. Although we did not perform a comparison of transhiatal and thoraco-abdominal approach, we did, however, analyzed the perioperative morbidity and mortality of the transhiatal extended total gastrectomy in order to see whether the transhiatal approach would have a lover complication rate than reported by others for the thoraco-abdominal approach. The 90-day intrahospital morbidity was 28.6% in our patients' cohort. The transhiatal approach has been shown by many authors to carry significantly less morbidity compared to thoraco-abdominal approach.[12,37,39] The complication rates for the transhiatal approach were reported to be from 25% to 28% and were similar to those in our institution.[12,13,36,37,39] In a meta-analysis done by Wei *et al.*, a significantly higher morbidity of the thoraco-abdominal approach has been found and was attributed to pulmonary complications.[12] The rate of pulmonary complications was only 9.2% in our cohort compared to 28.2% reported by Blank *et al*.[13] However, the 30-days mortality was reported to be similar no matter what approach was chosen for EGJ cancer patients.[13,36,37] The reported mortality rates from 1.1 to 3.8% compare favorably to our hospital where the 30-day mortality was 2.2%.[12,13,36,37] We also found a significant association between general and surgical complications and 30-day mortality. This correlation between complications and 30-day mortality is an important fact to consider when planning an operation for patients with S II and S III tumors; surgeons should offer their patients a curative approach with a smaller probability of complications.

The overall 5-year survivals for S II and S III patients were reported to be from 16% to 58%.[6-9,13,33,35,39] Although the Eastern authors consistently reported 5-year survival rates above 40%, most of Western authors report survivals over 30%.[13,33] Many studies also confirmed that the overall 5-year survival did not depend on the surgical approach as long as R0 resection could be obtained.[13,33,35,37,39] The patients in our cohort had a 5-year OS of 33.4%. The independent predictors for long-term survival were T and N stage, multivisceral resection and microscopic free surgical margins. Although, it is difficult to compare our 5-year overall survival to other results published, since the stages, general condition of patients, perioperative treatment and tumor location differ between studies; however, these results show that the type of approach does not influence the long-term survival.[37] The proximal extension of the resection margin did therefore not improve the survival of S II and S III patients. Moreover, the rate of local recurrences in the thoracic cavity seems not to be affected by the type of approach. In most of our patients, an infradiaphragmatic recurrence in the form of peritoneal carcinosis (16.1%) followed by hematological dissemination was noted. Only a minor portion of parents had a recurrence in the thoracic cavity (3.3% of patients). No correlation was found between clinicopathological characteristics and the type of recurrence, which supports the statement that the type of resection does not influence on the survival as long as an R0 resection is performed.

It is difficult to draw definitive conclusions from our study since the best way to determine the superiority of an approach would be a prospective randomized controlled trial. Our study is biased by the retrospective nature of the study design. Moreover, patients from different treating periods were included. During that time, the perioperative neoadjuvant treatment has changed and became more efficient, and this might have had an impact on overall survival. Also, the development of interventional radiological techniques has enabled us to resolve many complications non-operatively that would have otherwise been treated with surgical procedures and increased the perioperative morbidity. And finally, because of the long study period, we did not take into account the impact of modern minimally invasive techniques that have emerged recently.

This study supports the conclusion that the transhiatal approach is a safe procedure for S II and S III patients and that the morbidity and mortality associated with the surgery are low. The compli-

cations associated with transthoracic approach can therefore be altogether avoided with no impact on the rate of local recurrence. Our results confirm that the resection of ACC with transhiatal approach provides comparable proximal resection margins to thoraco-abdominal approach. The number of thoracic recurrences is negligible with the transhiatal approach and the long-term survival is comparable to other institutions irrelevant on approach. Based on these results, we feel that the transhiatal EETG, or in selected patients EEPG, is the procedure of choice for patients with ACC of type S II and S III.

References

1. Dubecz A, Solymosi N, Stadlhuber RJ, Schweigert M, Stein HJ, Peters JH. Does the incidence of adenocarcinoma of the esophagus and gastric cardia continue to rise in the twenty-first century?-a SEER database analysis. *J Gastrointest Surg* 2013; Epub 2013/11/16. doi:10.1007/s11605-013-2345-8
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; **97:** 142-6. doi:10.1093/jnci/dji024
3. Kusano C, Gotoda T, Khor CJ, Katai H, Kato H, Taniguchi H, et al. Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center in Japan. *J Gastroenterol Hepatol* 2008; **23:** 1662-5. doi:10.1111/j.1440-1746.2008.05572.x
4. Blaser MJ, Saito D. Trends in reported adenocarcinomas of the oesophagus and gastric cardia in Japan. *Eur J Gastroenterol Hepatol* 2002; **14:** 107-13.
5. Yamashita K, Sakuramoto S, Nemoto M, Shibata T, Mieno H, Katada N, et al. Trend in gastric cancer: 35 years of surgical experience in Japan. *World J Gastroenterol* 2011; **17:** 3390-7. doi:10.3748/wjg.v17.i29.3390
6. Mariette C, Castel B, Toursel H, Fabre S, Balon JM, Triboulet JP. Surgical management of and long-term survival after adenocarcinoma of the cardia. *Br J Surg* 2002; **89:** 1156-63. doi:10.1046/j.1365-2168.2002.02185.x
7. Haverkamp L, Ruurda JP, van Leeuwen MS, Siersema PD, van Hillegersberg R. Systematic review of the surgical strategies of adenocarcinomas of the gastroesophageal junction. *Surg Oncol* 2014; **23:** 222-8. doi:10.1016/j.suronc.2014.10.004
8. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1998; **85:** 1457-9. doi:10.1046/j.1365-2168.1998.00940.x
9. Kauppila JH, Lagergren J. The surgical management of esophago-gastric junctional cancer. *Surg Oncol* 2016; **25:** 394-400. doi:10.1016/j.suronc.2016.09.004
10. Kulig P, Sierzega M, Pach R, Kolodziejczyk P, Kulig J, Group PGCS. Differences in prognosis of Siewert II and III oesophagogastric junction cancers are determined by the baseline tumour staging but not its anatomical location. *Eur J Surg Oncol* 2016; **42:** 1215-21. doi:10.1016/j.ejso.2016.04.061
11. Mine S, Sano T, Hiki N, Yamada K, Kosuga T, Nunobe S, et al. Proximal margin length with transhiatal gastrectomy for Siewert type II and III adenocarcinomas of the oesophagogastric junction. *Br J Surg* 2013; **100:** 1050-4. doi:10.1002/bjs.9170
12. Wei MT, Zhang YC, Deng XB, Yang TH, He YZ, Wang ZQ. Transthoracic vs transhiatal surgery for cancer of the esophagogastric junction: a meta-analysis. *World J Gastroenterol* 2014; **20:** 10183-92. doi:10.3748/wjg.v20.i29.10183
13. Blank S, Schmidt T, Heger P, Strowitzki MJ, Sisic L, Heger U, et al. Surgical strategies in true adenocarcinoma of the esophagogastric junction (AEG II): thoracoabdominal or abdominal approach? *Gastric Cancer* 2017. Epub 2017/07/06. doi:10.1007/s10120-017-0746-1
14. Uzunoglu FG, Reeh M, Kutup A, Izbicki JR. Surgery of esophageal cancer. Langenbecks *Arch Surg* 2013; **398:** 189-93. doi:10.1007/s00423-013-1052-y
15. Al-Haddad S, Chang AC, De Hertogh G, Grin A, Langer R, Sagaert X, et al. Adenocarcinoma at the gastroesophageal junction. *Ann N Y Acad Sci* 2014; **1325:** 211-25. doi:10.1111/nyas.12535
16. Di Leo A, Zanoni A. Siewert III adenocarcinoma: treatment update. *Updates Surg* 2017. Epub 2017/03/16. doi:10.1007/s13304-017-0429-9
17. Yamashita H, Seto Y, Sano T, Makuuchi H, Ando N, Sasako M. Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. *Gastric Cancer* 2017; **20(Suppl 1):** 69-83. doi:10.1007/s10120-016-0663-8
18. Kleinberg L, Brock M, Gibson M. Management of locally advanced adenocarcinoma of the esophagus and gastroesophageal junction: Finally a consensus. *Curr Treat Options Oncol* 2015; **16:** 35. doi:10.1007/s11864-015-0352-6
19. Cohen DJ, Leichman L. Controversies in the treatment of local and locally advanced gastric and esophageal cancers. *J Clin Oncol* 2015; **33:** 1754-9. doi:10.1200/jco.2014.59.7765
20. Roder JD, Bottcher K, Busch R, Wittekind C, Hermanek P, Siewert JR. Classification of regional lymph node metastasis from gastric carcinoma. German Gastric Cancer Study Group. *Cancer* 1998; **82:** 621-31.
21. Doyle DJ, Garmon E. American Society of Anesthesiologists Classification (ASA Class). StatPearls. Treasure Island (FL): StatPearls PublishingStatPearls Publishing LLC.; 2017.
22. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer* 1998; **1:** 10-24. doi:10.1007/s101209800016
23. Goto H, Tokunaga M, Sugisawa N, Tanizawa Y, Bando E, Kawamura T, et al. Value of splenectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction. *Gastric Cancer* 2013; **16:** 590-5. doi:10.1007/s10120-012-0214-x
24. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt to a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64:** 31-49.
25. *TNM classification of malignant tumours*. Eighth edition. Brierley J, Gospodarowicz MK, Wittekind C, editors. Chichester, West Sussex: John Wiley & Sons, Inc; 2017.
26. Wittekind C. [Patology of gastric carcinoma: typing, grading and staging]. [German]. *Chir Gastroenterol* 1999; **15:** 216-22. doi:10.1159/000012560.
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205-13. doi:org/10.1097/01.sla.0000133083.54934.ae.
28. Fox MP, van Berkel V. Management of gastroesophageal junction tumors. *Surg Clin North Am* 2012; **92:** 1199-212. doi:10.1016/j.suc.2012.07.011
29. Mullen JT, Kwak EL, Hong TS. What's the best way to treat GE junction tumors? Approach like gastric cancer. *Ann Surg Oncol* 2016; **23:** 3780-5. doi:10.1245/s10434-016-5426-6
30. Rizk N. Gastroesophageal junction tumors. *Ann Surg Oncol* 2016; **23:** 3798-800. doi:10.1245/s10434-016-5427-5
31. Giacopuzzi S, Bencivenga M, Weindelmayer J, Verlato G, de Manzoni G. Western strategy for EGJ carcinoma. *Gastric Cancer* 2017; **20(Suppl 1):** 60-8. doi:10.1007/s10120-016-0685-2
32. Duan F, Cui S, Song C, Zhao X, Dai L, Shen Y. Esophageal squamous cell carcinoma and gastric cardia adenocarcinoma shared susceptibility locus in C20orf54: Evidence from published studies. *Sci Rep* 2015; **5:** 11961. doi:10.1038/srep11961
33. Hosoda K, Yamashita K, Moriya H, Mieno H, Watanabe M. Optimal treatment for Siewert type II and III adenocarcinoma of the esophagogastric junction: a retrospective cohort study with long-term follow-up. *World J Gastroenterol* 2017; **23:** 2723-30. doi:10.3748/wjg.v23.i15.2723
34. Lee IS, Ahn JY, Yook JH, Kim BS. Mediastinal lymph node dissection and distal esophagectomy is not essential in early esophagogastric junction adenocarcinoma. *World J Surg Oncol* 2017; **15:** 28. doi:10.1186/s12957-016-1088-x
35. Lochowski M, Lochowska B, Kozak J. Transthoracic versus transhiatal esophagectomy - influence on patient survival. *Prz Gastroenterol* 2017; **12:** 118-21. doi:10.5114/pg.2016.64609

36. Fontana MG, La Pinta M, Moneghini D, Villanacci V, Donato F, Rindi G, et al. Prognostic value of Goseki histological classification in adenocarcinoma of the cardia. *Br J Cancer* 2003; **88:** 401-5. doi:10.1038/sj.bjc.6600663

37. Kurokawa Y, Sasako M, Sano T, Yoshikawa T, Iwasaki Y, Nashimoto A, et al. Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. *Br J Surg* 2015; **102:** 341-8. doi:10.1002/bjs.9764

38. Mine S, Watanabe M. A commentary on "Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia". *Transl Gastroenterol Hepatol* 2016; **1:** 12. doi:10.21037/tgh.2016.03.08

39. Kim KT, Jeong O, Jung MR, Ryu SY, Park YK. Outcomes of abdominal total gastrectomy for type II and III gastroesophageal junction tumors: Single center's experience in Korea. *J Gastric Cancer* 2012; **12:** 36-42. doi:10.5230/jgc.2012.12.1.36