

IMPACT OF SURGICAL APPROACH ON IMMEDIATE AND LONGTERM RESULTS FOR PATIENTS WITH ADVANCED LOCAL ESOPHAGOGASTRIC JUNCTION ADENOCARCINOMA

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Abstract

Due to the localization of these tumors at the border between the stomach and the esophagus, the optimal surgical strategy for patients with adenocarcinoma of the esophagus junction is controversial. Evaluation of the influence of surgical approach on immediate and longterm results for patients with adenocarcinoma of esophagogastric junction. Between 2010-2017, 62 patients with locally advanced gastroesophageal junction adenocarcinomas were treated at St. Mary Hospital. The surgical approach was: abdominal in 40 patients – mainly for patients with Siewert type III - 72.5%. Other types of surgical approach: abdominocervical in 4 patients, abdominothoracic - 5 patients, triple approach in 5 patients were mainly used for patients with Siewert type I (11 patients). Patients with Siewert type II had either abdominal (11 patients) or combined (7 patients). Postoperative morbidity was 46.77%. Anastomotic fistula occurred in 17 patients as follow: after abdominal approach in 10 patients, 2 patients after abdomino cervical approach, 2 patients after abdominothoracic approach, and 3 patients after triple approach. Postoperative mortality was 4.8%. The late complications were anastomotic stenosis in 14 patients. Anastomotic tumor recurrence was diagnosed in 7 patients. Survival analysis shows different survival curves in the way that the abdominocervical approach led to a reduced survival rate: 0% at 24 months, while the triple approach recorded a superior survival, 50% at 5 years. Intermediate curves I noticed after abdominal approach with 52.56% survival rate and 46.2% for abdominothoracic approach. Patients operated using abdominal approach had a significantly different mortality compared to patients operated by combined approach. The surgical approach did not influence the occurrence of postoperative complications - anastomotic fistula, fistula severity or pulmonary complications.

Keywords: esophagogastric junction, adenocarcinoma, surgical approach

Introduction

Locally advanced esophago-gastric junction adenocarcinomas (AEG) require a complex multimodal strategy that associates

surgical treatment with preoperative or postoperative radiotherapy and chemotherapy. Due to the localization of these tumors at the limit between the stomach and the esophagus, the optimal surgical strategy for patients with AEG

is controversial. Regardless of the surgical approach, complete removal of the primary tumor and lymph nodes must be the primary objective of the surgical treatment for tumors [1].

According to the classification proposed by Siewert and Stein, adenocarcinoma of the gastroesophageal junction can be classified topographically into three types: distal esophagus carcinomas (type I), cardia carcinomas (type II) and subcardial carcinomas (type III). This surgical classification has been proved to be useful for planning the extension of resection and for comparing epidemiological data and therapeutic results from different series. The preoperative assessment is performed by barium meal and endoscopic examination and it allows the surgeon to plan the type of esophageal and gastric resection as well as the surgical approach in preoperative stage. Type I adenocarcinoma is treated by esophageal resection as a trans hiatal or transthoracic esophagectomy with resection of the lesser gastric curvature. Type II and type III adenocarcinomas are treated by a gastrectomy and a distal esophageal resection with D2 lymphadenectomy by an abdominal-transhiatal or abdominal-transthoracic approach [2].

The prognosis of AEG is significantly related to the degree of lymph nodes involvement [3]. These tumors have the potential to metastasize into perigastric and abdominal aorta lymph nodes. Lymphatic flow is primarily directed towards the abdomen, so the majority of patients present involvement of the cardia and lesser curvature nodes (1,2,3,7) [4]. Other gastric nodes (4, 4sb, 4d, 5, 6) have a very low incidence of metastases. Metastasis into the abdominal para-aortic area (16a2) is noticed in about 15% of AEG patients, representing the most common site of node recurrence [5].

Considering the high proportion of metastasis in lower mediastinal lymph nodes [6], dissection of this area is required for the treatment of AEG tumors of any type. On the contrary, lymph node metastasis in the upper or middle mediastinum in Siewert type II or III tumors is relatively rare [7]; therefore, there is no need for extended dissection of this area by thoracotomy for the specified types of tumors.

Materials and methods

Between January 2010 and December 2017, in the Center of Excellence in Esophageal Surgery, from St Mary`s Clinical Hospital in Bucharest, were surgically treated 62 patients with locally advanced AEG. These patients constituted a study group analyzed retrospectively. The age of patients varied between 42 and 86 years, with an average of 64 years. Patients were diagnosed with upper gastro intestinal endoscopy and biopsy, barium swallow, ultrasound scan, endoscopic ultrasonography (EUS) and computer tomography. The preoperative classification into Siewert type is based mainly on the correlation of the endoscopy with the radiological aspect (figures 1 and 2).



Figure 1 - Vegetative tumor of gastroesophageal junction, Siewert I type- UGI endoscopy view (Image database Center of Excellence in Esophageal Surgery)

According to Siewert classification, the group comprised of type I - 11 patients, type II - 18 patients and type III - 33 patients. Neoadjuvant radio chemotherapy was performed by 17 patients. After the preoperative treatment, the patients included were reassessed with: UGI endoscopy, barium swallow, abdominothoracic CT and esophageal eco-endoscopy (EUS) for the assessment of the clinical and imaging response to the treatment (Figure 3).



Figure 2 - Stenosis of the distal esophagus – barium swallow (Image database Center of Excellence in Esophageal Surgery)



Figure 3 - Gastroesophageal junction and distal esophagus narrowed after neoadjuvant radiochemotherapy (Image database Center of Excellence in Esophageal Surgery).

Results

The surgical approach was abdominal in 40 patients - mainly in Siewert III type patients - 72.5%. The other types of surgical approaches: abdomino-cervical in 4 patients, abdomino-

thoracic - 5 patients, triple approach McKeown in 5 patients; were mainly used for patients with Siewert I type (11 patients). Patients with type Siewert II had either an abdominal approach and that was the case for 11 patients either combined for 7 patients (Figure 4).

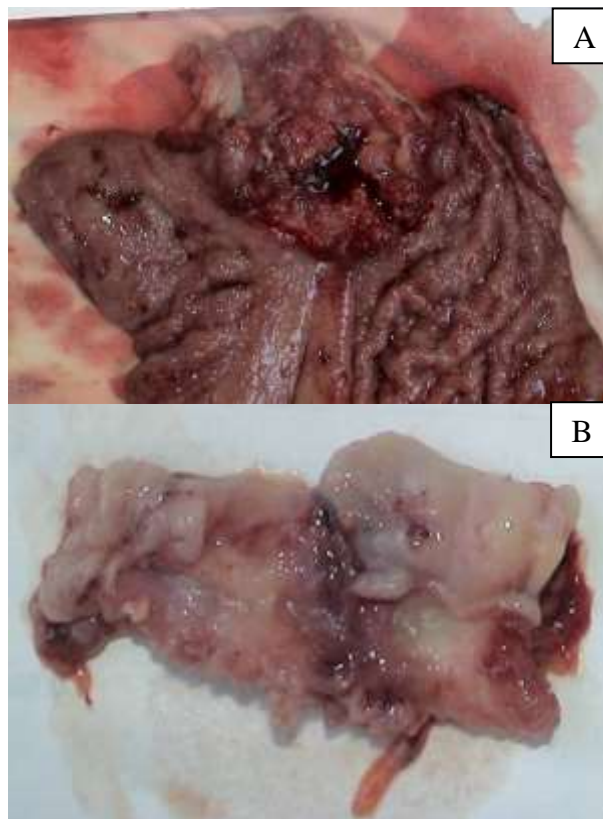


Figure 4 - Total gastrectomy with distal esophagectomy specimen, abdominal approach, intraoperative pathology with esophageal margin positive (A), trans thoracic extended esophageal resection (B) (Image database Center of Excellence in Esophageal Surgery).

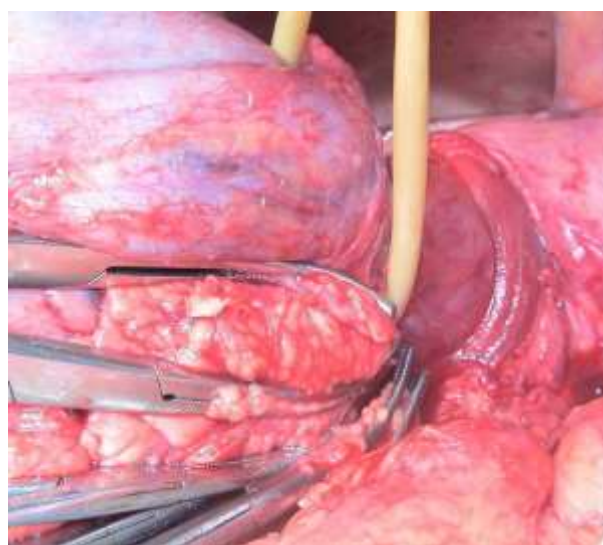


Figure 5 - Dissection of the lymph nodes around left gastric artery.

Approach	Abdominal (N=40)	Abdomino- cervical (N=4)	Abdomino- thoracic (N=13)	Triple approach (N=5)	p_value (test)
Siewert_Type					0.000001
I	0/40 (0.0%)	2/4 (50.0%)	5/13 (38.5%)	4/5 (80.0%)	(Likelihood Ratio)
II	11/40 (27.5%)	2/4 (50.0%)	4/13 (30.8%)	1/5 (20.0%)	
III	29/40 (72.5%)	0/4 (0.0%)	4/13 (30.8%)	0/5 (0.0%)	

Table 1. Correlation of types of surgical approach with tumor Siewert type - statistical data processing

The significant difference between the approach percentage ($p_{\text{value}} = 0.000001$, Likelihood Ratio) for the different types of Siewert classification (table 1), as follow: abdominal approach was used for patients with Siewert type III (Figure 5), double or triple combined approach was performed for patients with Siewert type I.

Esophageal anastomoses were performed with the jejunum in 41 patients and the stomach in 21 patients. The location of the anastomosis was cervical in 9 patients, mediastinal in 11 patients and for 42 patients was the abdomen (Figures 6-9).



Figure 6 - Diaphragmatic level eso-jejunal anastomosis - intraoperative aspect.

Postoperative morbidity was 46.77%. Anastomotic fistula occurred in 17 cases, after abdominal approach 10 patients, 2 patients after abdominal cervical approach, 2 patients after abdominal transthoracic approach, and 3 patients after triple approach.

With regard to the severity of the fistula according to the classification of the Consensus Group of Esophagectomy Complications (2015), most fistulas were grade 2 in 10 patients

and required endoscopic treatment, surgical treatment has been required for 5 patients with grade 3 fistulas, 3 patients following abdominal approach, one patient following thoracic approach and another one following the triple approach

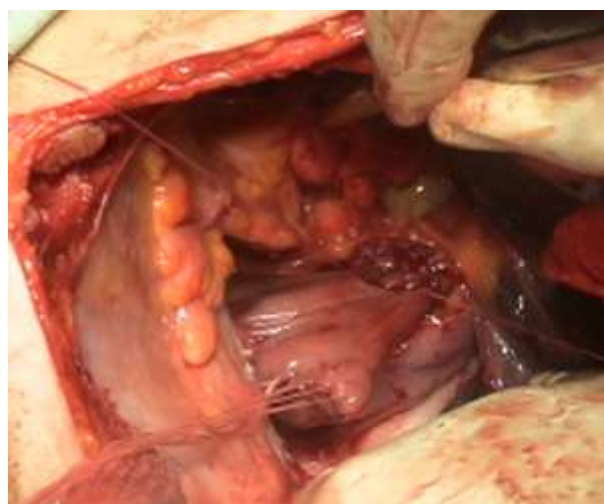


Figure 7 - Intrathoracic eso-jejunal anastomosis, transthoracic and abdominal approach- intraoperative aspect.



Figure 8 - Tubulized stomach passed through - intraoperative aspect.

Approach	Abdominal (N=40)	Abdomino- cervical (N=4)	Abdomino- thoracic (N=13)	Triple approach (N=5)	p_value (test)
Fistula=Yes	10/40 (25.0%)	2/4 (50.0%)	2/13 (15.4%)	3/5 (60.0%)	0.220342
Fistula_grade					
1	1/10 (10.0%)	0/2 (0.0%)	0/2 (0.0%)	1/3 (33.3%)	0.664849
2	6/10 (60.0%)	2/2 (100%)	1/2 (50.0%)	1/3 (33.3%)	
3	3/10 (30.0%)	0/2 (0.0%)	1/2 (50.0%)	1/3 (33.3%)	
Pulmonary Complication	5/40 (12.5%)	1/4 (25.0%)	4/13 (30.8%)	1/5 (20.0%)	0.517877

Table 2 - Correlation of the type of surgical approach with immediate postoperative complications - statistical data processing.

Approach	Abdominal (N=40)	Abdomino- cervical (N=4)	Abdomino- thoracic (N=13)	Triple approach (N=5)	p_value (test)
Deaths	0/40 (0.0%)	2/4 (50.0%)	1/13 (7.7%)	0/5 (0.0%)	0.009625

Table 3- Correlation of type of surgical approach with postoperative mortality - statistical data processing

Approach	Abdominal (N=40)	Abdomino- cervical (N=4)	Abdomino- thoracic (N=13)	Triple approach (N=5)	p_value (test)
Stenosis=Yes	7/40 (17.5%)	1/4 (25.0%)	4/13 (30.8%)	2/5 (40.0%)	0.601845
Recurrence	5/5 (100%)	0/1 (0.0%)	1/1 (100%)	1/2 (50.0%)	0.079879

Table 4 - Correlation of surgical approach with long term complications - statistical data processing

Approach	Abdominal (N=40)	Abdomino-cervical (N=4)	Abdomino- thoracic (N=13)	Triple approach (N=5)	p_value (test)
Deaths	17/40 (42.5%)	4/4 (100%)	7/13 (53.8%)	1/5 (20.0%)	0.042153

Table 5 - Correlation of the type of surgical approach with mortality (not postoperative) - statistical data processing

Approach	Total N	N of Events	Censored	
			N	Percent
A	40	17	23	57.5%
AC	4	4	0	0.0%
AT	13	7	6	46.2%
ATC	5	1	4	80.0%
Overall	62	29	33	53.2%

Table 6 - Survival analysis – influence of surgical approach on overall survival-statistical data analyzing processing



Figure 9 - Cervical esophago-gastric anastomosis, intraoperative aspect.

I have not noticed statistically significant differences by comparing postoperative complications - anastomotic fistula, fistula grade and pulmonary complications to the type of surgical approach (Table 2).

Postoperative mortality was 4.8% - 2 patients died from the abdominal cervical group - one

I have not noticed statistically significant differences comparing long term complications like anastomotic stenosis and anastomotic relapse to the type of surgical approach.

Survival analysis shows different survival curves in the sense that the abdominal cervical approach led to a reduced survival rate: 0% at 24 months, while the triple approach recorded a superior net survival of 50% at 5 years (Table 5-7). Intermediate curves were noticed after abdominal approach with 52.56% survival rate and 46.2% for abdominal transthoracic approach (Figure 10).

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	15.752	3	0.001
Breslow (Generalized Wilcoxon)	14.834	3	0.002

Table 7 - Test of equality of survival distributions for the different levels of Approach.

patient with pulmonary complications and another one by decompensated liver cirrhosis, in the 3rd postoperative day and a patient from the abdominal transthoracic approach by sepsis due to a grade 3 fistula

Significant difference between type of approach (p_value = 0.009625, Likelihood Ratio) for postoperative mortality (Table 3), as follow: between abdominal approach (0.0%) and abdominal cervical approach (50.0%).

Patients operated using abdominal approach had significantly low mortality compared to patients operated by combined approach.

Long term complications were: anastomotic stenosis in 14 patients, especially those who had anastomotic fistula. These occurred in the first months postoperatively and were treated by multiple sessions of endoscopic balloon dilations mainly. Anastomotic tumor recurrence was diagnosed in 7 patients (table 4).

Patients enrolled in the study lot were followed up for an average of 35.4 months. On January 1, 2018, 33 patients enrolled in the study group were alive.

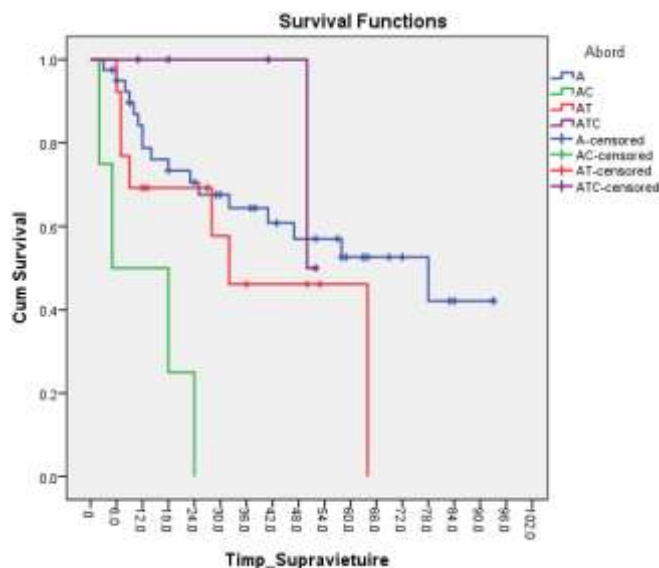


Figure 10 - Survival curves.

Means and Medians for Survival Time

Approach	Mean ^a				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
A	58.334	6.172	46.236	70.432	78.000	24.648	29.690	126.310
AC	12.250	5.234	1.991	22.509	5.000	8.000	.000	20.680
AT	38.692	7.971	23.070	54.315	32.000	9.873	12.649	51.351
ATC	51.000	.707	49.614	52.386	50.000	.	.	.
Overall	53.143	5.067	43.213	63.074	58.000	12.128	34.229	81.771

a. Estimation is limited to the largest survival time if it is censored.

Survival	6 mths	12 mths	18 mths	24 mths	36 mths	48 mths	60 mths
Approach=A	94.9%	78.8%	73.4%	70.5%	64.4%	57.0%	52.6%
Approach=AC	50.0%	50.0%	25.0%	0.0%	0.0%	0.0%	0.0%
Approach=AT	92.3%	69.2%	69.2%	69.2%	46.2%	46.2%	46.2%
Approach=ATC	100%	100%	100%	100%	100%	100%	50.0%

Table 8 - Survival analysis and data processing for different types of approaches.

Discussions

For adenocarcinoma of the gastro esophageal junction (AEG), the Siewert classification with its three subtypes is well established as a practical approach for surgical treatment. Transthoracic esophagectomy with resection of the lesser gastric curvature followed by the gastric tube pull up is generally accepted as the surgical standard for type I AEG. Intrathoracic esophago gastro stomy has become the most commonly used anastomotic technique (Ivor Lewis esophagectomy) [8]. The same approach was used for patients in the study group who presented Siewert type I tumors.

For Siewert III type tumors, extended total gastrectomy is the best surgical approach [8]. In our study group we used the abdominal approach for 29/33 patients with this type of tumor, and for 4 patients the abdominal thoracic approach was used.

For true cardia carcinomas (Siewert type II), it has not yet been decided which of the aforementioned surgical procedures offers the best long-term survival. If it is technically possible with regard to a complete resection, extended gastrectomy should be preferred because of a better postoperative comfort [8]. In the studied group for Siewert II tumors we have

used for 11/17 an abdominal approach and a combined approach for other 7 patients.

Due to localization, pathogenesis and biological behavior, most authors agree that Siewert type I junction adenocarcinoma tumors are best treated as distal esophageal cancer and that Siewert type III tumors are best treated as gastric cancer. Siewert type II tumors are actually best treated surgically as gastric cancer [9]. For patients in the lot we noticed a similar approach with these authors.

Some authors consider that using Ivor-Lewis procedure can perform a thoracic and an abdominal dissection of lymph nodes and does not lead to more postoperative complications than left thoracotomy in patients with Siewert type I tumors [10]. In the studied lot Ivor Lewis approach was preferred for patients with Siewert type I tumors.

In patients with Siewert type I tumors, the transthoracic approach does not provide any survival benefit to the abdominal-cervical approach but is associated with higher morbidity. In patients with Type II or Type III tumors, an abdominal approach results in equal or superior survival and lower postoperative mortality than a combined approach [1]. In patients in the study group, we found a higher mortality following abdominal- cervical approach. Morbidity through the anastomotic

fistula was higher when the anastomosis fistula was located at the cervical level and several pulmonary complications met after the abdominal-thoracic approach.

Ivor Lewis's minimally invasive esophagectomy for adenocarcinomas of the gastroesophageal junction is a future approach to reducing morbidity caused by laparotomy and thoracotomy. One study showed that the rate of anastomotic fistula after this approach is still high, possibly due to the diversity of anastomotic techniques and the percentage of patients treated with neoadjuvant chemoradiation. An aggressive approach to complications leads to a low mortality of 2.1%. Improvement and standardization of anastomotic techniques are required to perform a safe intrathoracic anastomosis [11]. In the studied group, patients were not operated by the minimally invasive approach due to the technical difficulties posed by intrathoracic anastomosis.

Another study in the literature showed that the results for the Ivor Lewis classic approach and minimally invasive way were comparable for the anastomotic fistula rate, the resection edges (R0), the excised lymph nodes and the length of the hospitalization [12].

The laparoscopic assisted approach for total gastrectomy is associated with better short-term outcomes for patients with Siewert type II and III tumors. In addition, it may lead to an increased number of excised lymph nodes and longer survival, especially for patients with Siewert II type tumors [13].

Other authors support this opinion, compared to open surgery, laparoscopic approach was associated with a significantly lower intraoperative blood loss and a prolonged operating time, with no significant differences in postoperative hospitalization duration, morbidity percent, proximal margins length and total number of lymph node excised, but the number of mediastinal lymph nodes excised was higher using laparoscopic approach. The transhiatal laparoscopic resection for Siewert type II tumors is a technical challenge but seems feasible and safe in regards of oncological, technical or short-term aspects when performed by an experienced surgical team [14].

In terms of survival rates at 5 years, one study showed that for patients with Siewert type

II tumors, these were comparable for the transthoracic and transabdominal approach, while for patients with Siewert III tumors the survival rate at 5 years was significantly lower in the transthoracic group compared to transabdominal group [15].

We also noticed differences in survival for other patients in the study group, the triple approach led to a statistically significantly different survival rate compared to the abdominal cervical approach. Intermediate curves I noticed for the abdominal and abdominal thoracic approach (Table 8).

Other authors showed that noticeable differences were found between the clinical-pathological characteristics of the three tumor types, but there was no significant difference in survival rate at 5 years among the three types of curative resection.

The results of a study regarding the need for routine splenectomy revealed that survival without ganglion recurrence in the splenic hilum was not significantly different in patients with gastrectomy, gastrectomy and splenectomy and gastrectomy and distal pancreatectomy, therefore routine splenectomy is not required for AEG II or III. For patients in the study we did not use routine splenectomy but performed it only when we detected adenopathy in the splenic hilum [17].

Conclusions

Patients operated using abdominal approach had a significantly lower mortality compared to patients operated by combined approach.

The surgical approach did not influence the occurrence of postoperative complications like anastomotic fistula, fistula severity or pulmonary complications.

Morbidity due to anastomotic fistula was higher when the anastomosis was located at the cervical level and more lung complications occurred after transthoracic approach.

Long term survival is high for triple approach patients and significantly low in transhiatal resections.

References

- [1]Stein HJ, Feith M, Siewert JR. Individualized surgical strategies for cancer of the esophagogastric junction. *Ann Chir Gynaecol.* 2000;89(3):191-8.
- [2]Mönig SP, Schröder W, Beckurts KT, Hölscher AH. Classification, diagnosis and surgical treatment of carcinomas of the gastroesophageal junction. *Hepatogastroenterology.* 2001 Sep-Oct;48(41):1231-7.
- [3]Dresner SM, Lamb PJ, Bennett MK, Hayes N, Griffin SM: The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogastric junction. *Surgery* 2001;129:103-109.
- [4]Pedrazzani C, de Manzoni G, Marrelli D, Giacomuzzi S, Corso G, Minicozzi AM, Rampone B, Roviello F: Lymph node involvement in advanced gastroesophageal junction adenocarcinoma. *J Thorac Cardiovasc Surg* 2007;134:378-385.
- [5]Hosokawa Y, Kinoshita T, Konishi M, Takahashi S, Gotohda N, Kato Y, Daiko H, Nishimura M, Katsumata K, Sugiyama Y, Kinoshita T: Clinicopathological features and prognostic factors of adenocarcinoma of the esophagogastric junction according to Siewert classification: experiences at a single institution in Japan. *Ann Surg Oncol* 2012;19:677-683.
- [6]Leers JM, DeMeester SR, Chan N, Ayazi S, Oezcelik A, Abate E, Banki F, Lipham JC, Hagen JA, DeMeester TR: Clinical characteristics, biologic behavior, and survival after esophagectomy are similar for adenocarcinoma of the gastroesophageal junction and the distal esophagus. *J Thorac Cardiovasc Surg* 2009;138:594-602.
- [7]Siewert JR, Stein HJ, Feith M: Adenocarcinoma of the esophago-gastric junction. *Scand J Surg* 2006;95:260-269
- [8]Schröder W, Lambertz R, van Hillegesberger R, Bruns C. Differentiated surgical approach for adenocarcinoma of the gastroesophageal junction. *Chirurg.* 2017 Dec;88(12):1010-1016.
- [9]Mullen JT, Kwak EL, Hong TS What's the Best Way to Treat GE Junction Tumors? Approach Like Gastric Cancer. *Ann Surg Oncol.* 2016 Nov;23(12):3780-3785.
- [10]Duan XF, Gong L, Ma MQ, Yue J, Tang P, Shang XB, Jiang HJ, Yu ZT Comparison of the effect of lymph node dissection performed by Ivor-Lewis or left-sided thoracic esophagogastric resection for Siewert type II adenocarcinoma of the esophagogastric junction *Zhonghua Zhong Liu Za Zhi.* 2017 Mar 23;39(3):190-194.
- [11]Straatman J, van der Wielen N, Nieuwenhuijzen GA, Rosman C, Roig J, Scheepers JJ, Cuesta MA, Luyer MD, van Berge Henegouwen MI, van Workum F, Gisbertz SS, van der Peet DL. Techniques and short-term outcomes for total minimally invasive Ivor Lewis esophageal resection in distal esophageal and gastroesophageal junction cancers: pooled data from six European centers. *Surg Endosc.* 2017 Jan;31(1):119-126.
- [12]Noble F, Kelly JJ, Bailey IS, Byrne JP, Underwood TJ. A prospective comparison of totally minimally invasive versus open Ivor Lewis esophagectomy. *Dis Esophagus.* 2013 Apr;26(3):263-71
- [13]Huang CM, Lv CB, Lin JX, Chen QY, Zheng CH, Li P, Xie JW, Wang JB, Lu J, Cao LL, Lin M, Tu RH. Laparoscopic-assisted versus open total gastrectomy for Siewert type II and III esophagogastric junction carcinoma: a propensity score-matched case-control study. *Surg Endosc.* 2017 Sep;31(9):3495-3503.
- [14]Sugita S, Kinoshita T, Kaito A, Watanabe M, Sunagawa H Short-term outcomes after laparoscopic versus open transhiatal resection of Siewert type II adenocarcinoma of the esophagogastric junction. *Surg Endosc.* 2018 Jan;32(1):383-390.
- [15]Zhang W, Chen X, Liu K, Yang K, Chen X, Zhao Y, Zhao Y, Chen J, Chen L, Hu J. Comparison of survival outcomes between transthoracic and transabdominal surgical approaches in patients with Siewert-II/III esophagogastric junction adenocarcinoma: a single-institution retrospective cohort study. *Chin J Cancer Res.* 2016 Aug;28(4):413-22.
- [16]Bai JG, Lv Y, Dang CX. Adenocarcinoma of the Esophagogastric Junction in China according to Siewert's classification. *Jpn J Clin Oncol.* 2006 Jun;36(6):364-7.
- [17]Suh YS, Lee KG, Oh SY, Kong SH, Lee HJ, Kim WH, Yang HK Recurrence Pattern and Lymph Node Metastasis of Adenocarcinoma at the Esophagogastric Junction. *Ann Surg Oncol.* 2017 Nov;24(12):3631-3639.