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Transhiatal distal esophagectomy for Siewert type II cardia cancer can be a treatment option in selected patients

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ABSTRACT

Background: While surgical treatment of Siewert I and III (S1,S3) Esophagogastric Junction (EGJ) cancer is codified, the efficay of transhiatal procedure with anastomosis in the lower mediastinum for Siewert II (S2) still remains a dibated topic.
Methods: This is a large multicenter retrospective study. The results of 598 consecutive patients submitted to resection with curative intent from January 2000 to January 2017 were reported. Clinical and oncological outcomes of different procedures performed in S2 tumor were analyzed to investigate the efficacy of transhiatal approach.
Results: The 5-year overall survival rate (OS) was poor (32%) for all Siewert types. The most performed operations in S2 cancer were proximal gastrectomy + transthoracic esophagectomy (TTE or Ivor-Lewis procedure, 60%), total gastrectomy + transhiatal distal esophagectomy with anastomosis in the chest (THE, 24%) and total gastrectomy + transthoracic esophagectomy (TGTTE, 15%). Cardiovascular and pulmonary complications were higher after TTE. On the contrary, surgical complications were significantly higher after THE. Postoperative mortality was similar. The distribution of TNM stages was different in the 3 types of procedures: patients submitted to THE had an earlier stage disease. With this bias, OS after THE was higher than after TTE but the difference was not significant (49.85% vs 28.42%, $p = 0.0587$).
Conclusions: Despite a higher rate of postoperative surgical complications, OS after total gastrectomy and transhiatal distal esophagectomy was at least comparable to that of transthoracic approach in less advanced S2 tumors. Therefore, THE with anastomosis in the chest could be a treatmen option in earlier S2 tumors.

Introduction

Cancer of the esophagogastric junction (EGJ) is located at the passage between the esophagus and the stomach; it was divided into three types (Siewert I, II and III or S1, S2 and S3) according to its

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topographic characteristics since 1987 [1]. Although recent TNM 8th revision has changed previous Siewert classification, this is still adopted to identify the proper surgical treatment which mainly depends on tumor location [2].

In the eight AJCC/UICC cancer staging manual, Adenocarcinoma Grading was divided in 4 categories (Gx, G1, G2 and G3, corresponding to unknown, well differentiated, moderately differentiated and poorly differentiated glandular aspects).

In fact there are several treatment options for EGJ tumors. For *early stages*, endoscopic-mucosal resection and submucosal dissection are therapeutic strategies of choice as their reported mortality and morbidity rates are significantly lower than those observed after surgery, with similar survival outcomes [3,4].

Early EGJ tumors excluded from endoscopic resection criteria should be submitted to surgery following the same indications adopted for advanced cancer, except from neoadjuvant treatment.

Advanced EGJ tumors should be treated with multimodal therapy. S1 and S2 cancer with tumor grading $\geq$2 should undergo preoperative treatment (chemoradiation therapy or chemotherapy alone) [5]. S3 advanced tumors should be managed like advanced gastric cancers and therefore in western countries, following recent international guidelines, they are submitted to neoadjuvant treatment, despite a lack of strong evidence of its survial benefit [6–8].

Surgical options for S1 and S3 tumors are nowadays quite codified. The most common procedures for S1 are proximal gastrectomy with *transthoracic* subtotal (Ivor Lewis procedure, TTE) or total (McKeown procedure) esophagectomy with adequate mediastinal lymph node dissection; S3 optimal treatment is total gastrectomy and *transhiatal* distal esophagectomy with lower mediastinal and abdominal (D2) node dissection (THE).

Treatment of S2 cancer still remains a debated topic. At present, there is no evidence on which is the optimal treatment of this type of tumor which has both abdominal and thoracic metastatic nodes in up to one third of patients [9]. Therefore, in several population studies, both TTE and THE are reported as procedures widely performed, with debated clinical and oncological outcomes and survival [10–12].

The aim of this retrospective observational multicentre study was to analyze a 17 years experience of eight referral centres from Piedmont (North-West Italy) in the managment of EGJ carcinoma. The objectives of the study were to assess the short-term, oncological and survival outcomes in the whole patients' population and to investigate the efficacy of THE in S2 tumors.

Material and methods

Between January 2000 and January 2017, 598 consecutive patients with histological diagnosis of EGJ cancer were resected with curative intent in eight reference centers from Piedmont.

After preoperative staging (endoscopy with biopsy, chest and abdomen CT scan and EUS in 78% of cases), tumors were classified in S1, S2 and S3 following Siewert classification [1]. Surgical strategy was chosen in accordance with the location of cancer epicenter and on the basis of the lenght of invasion of the esophagus as well as of surgeons' and centers' habits. Intraoperative frozen section was done routinely only in 5 centers (444 patients).

Surgical procedures

Patients were submitted to different resections and reconstructions mainly based on cancer location and centers' habits. Proximal gastrectomy and right transthoracic subtotal esophagectomy with anastomosis in the middle chest (Ivor Lewis procedure, TTE); total gastrectomy and transhiatal distal esophagectomy with esophagojejunal anastomosis in the lower mediastinum (THE) and total gastrectomy and right transthoracic subtotalesophagectomy with anastomosis in the middle chest (TGTTE) were performed more frequently. Transhiatal or transthoracic total esophagectomy with anastomosis in the neck, explorative laparoscopy and explorative laparotomy were performed in a few cases. Details on lymph node dissection are available as supplemetary material *(lymph node dissection sheet)*.

During transthoracic procedures the continuity of the digestive tract was restored with the gastric tube after proximal gastrectomy or with a jejunal loop after total gastrectomy.

Tumor stages were recorded following TNM classification 7th edition of malignant cancers, but Stage IA and IB have been grouped in Stage I, stage IIA and IIB have been grouped in Stage II, and Stage IIIA, IIIB and IIIC have been grouped in Stage III [13]. Therefore 4 main stages were taken in consideration (Table 4).

Each case was analyzed from pathologysts using both World Health Organization classification [14] and Lauren criteria [15].

Four hundred and eighty-one patients were submitted to a curative resection with pathologic confirmation (no tumor residual, R0); residual tumor was found in 61 cases, 44 of them with microscopic (R1) and 17 with macroscopic tumor residual (R2). We don't have informations about curativity for the remaining 57 cases.

Statistics

Continuous variables are reported as mean and SD for normally distributed variables and as median and interquartile range (IQR) for non-normal distributions, whereas categorical variables are reported as frequencies and percentages. Normality distribution has been tested with the Shapiro-Wilk normality test.

Univariate analysis of the difference between groups was performed with the Student *t*-test or, when appropriate, the nonparametric Mann-Whitney test for continuous variables and with the chi-squared test for categorical data (with Fisher correction when needed).

Survival curves were estimated with the Kaplan-Meier method and compared by Cox regression model.

Adjusted Effects of Siewert type and type of procedure on Overall Survival in the whole population and in S2 alone were estimated by including age at surgery, gender, stage and resection status as covariates in Cox models.

For all the used test, statistical significance level was set at the conventional $p < 0.05$.

The results were analyzed using the StataSE 15 statistical software (Stata Corp., College Station, TX).

Results

One hundred thirty-three patients underwent neoadjuvant treatment (119 chemoterapy alone and 14 chemoradiation therapy); 247 patients were submitted to adjuvant treatment.

The percentage of males was higher than that of females (82,77% vs 17,23% respectively). The male/female ratio was 8:2. The median age of patients' population was 67,3 years (ranging from 24 to 89); more than 50% of patients were 69–89 year old (Table 1).

Among the 598 patients, 164 (27,4%) had a S1, 237 (39,6%) had a S2 and 197 (32,94%) had a S3 tumor. The main demographic characteristics according to Siewert classification are detailed in Table 1.

About ninety per cent of S1 patients underwent TTE while 119 (60.4) S3 were treated with THE. In S2 cancers, the type of surgical resection and of approach were different among participating centres and sometimes also among patients of the same centre. Both TTE and THE were performed. Also TGTTE was performed in several cases.

Three hundred and ten patients were submitted to TTE (51,8%),

Table 1
Demographic Characteristics, type of procedure and of reconstruction performed in the whole patients' population.

Siewert type					
	1	2	3	Total	p
Number of patients. nr (%)	164 (27.4)	237 (39.6)	197 (32.9)	598 (100)	
Sex M/F. nr (%)	145/19	191/46	159/38	495 (82.8)/103 (17.2)	0.080
Age. mean (range)	65.5 ± 11.4 (23–86)	66.8 ± 11.3 (32–88)	68.4 ± 10.7 (39–90)	67.0 ± 11.2 (23–90)	0.053
***AJCC/UICC Grading nr (%)**					0.961
Gx	7(4.3)	10 (4.2)	11 (5.6)	28 (4.7)	
G1	4 (2.4)	8 (3.4)	9 (4.6)	21 (3.5)	
G2	51 (31.1)	79(33.3)	51 (25.9)	181 (30.3)	
G3	102 (62,2)	140 (59.1)	126(63.9)	368 (61.5)	
ASA Score					1
missing	8 (4.8)	13 (5.5)	11 (5.6)	32 (5.3)	
2	32 (19.6)	43 (18.1)	35 (17.8)	110 (18.4)	
3	124 (75.6)	181 (76.4)	151 (76.6)	456 (76.3)	
Type of resections. nr (%)					
TTE	147 (89.6)	140 (59.1)	23 (11.7)	310 (51.8)	<0.001
THE	1 (0.6)	60 (25.3)	119 (60.4)	180 (30.1)	
TGTTE	11 (6.7)	35 (14.8)	54 (27.4)	100 (16.7)	
Others	5 (3.1)	2 (0.8)	1 (0.5)	8 (1.3)	
Type of Reconstructions (%)					
Esophago-Gastric tube anastomosis	149 (91.4)	140 (59.6)	23 (11.7)	312 (52.5)	<0.001
Esophago-jejunostomy	10 (6.1)	95 (40.4)	173 (88.3)	278 (46.8)	
Esophago-colostomy	2 (1.2)	0	0	2 (0.3)	
Others	2 (1.2)	0	0	2 (0.3)	

TTE = Proximal gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest.
THE = Total gastrectomy + transhiatal distal esophagectomy and anastomosis in the lower mediastinum.
TGTTE = Total gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest.

180 patients underwent THE (30,1%) and 100 patients were submitted to TGTTE (16,7%). Six patients did not undergo surgical resection because of substantial peritoneal seeding, unresectable local tumor or distant metastases detected during the procedure.

The type of resection and of reconstruction performed according to the different Siewert types are reported in Table 1.

Mainly, transhiatal approach was associated with less general (mainly cardiocirculatory and pulmonary) post operative complications ($p = 0.018$), a shorter duration of mechanical ventilation, and a significant reduced lenght of stay (LOS) in Intensive Care Unit and in the hospital compared to transthoracic resections ($p = 0.009$) (Table 2).

Surgical postoperative complications were observed in 112 patients (18.7%); the type and the number of the events stratified according to the procedure performed are detailed in Table 2.

The mean/median overall LOS were 19.34/15 days. The shortest median LOS occurred in THE group (14 days) followed by TTE (15 days) and by TGTTE group (16 days) (Table 2).

Overall postoperative mortality rate was 1.70% and 3.20% at 30 and 60 days after operation. It was higher after THE as compared both to TTE and to TGTTE (3.9/5.5% versus 0.6/2.2% and 1.0/2.2% respectively) (Table 2).The differerences among the procedures were not statistically significant ($p = 0.052$ and 0.243).

After pathological examination tumors were classified as stage I, II, III and IV in 14.7, 20.0, 53.7 and 11.5% respectively.

Follow-up was complete for 520 patients (85,61%). Median follow-up time was 16 months. The estimated rate of overall survival (OS) in the whole population was 73.07% at 12 months (95% confidence interval,CI, 68.57–77.03%), 54.99% at 24 months (95% CI, 49.82–59.86%) and 31.97 (95% CI, 26.39–37.67%) at 60 months.

We proceeded to analyze OS by Siewert type and by the type of procedure performed.

OS rates stratified by Siewert type with a follow-up of at least 24 months was 58.52% for S1 (95% CI, 48.33–67.38%), 59.96% for S2 (95% CI, 51.60–67.34%) and 46.39% for S3 (95% CI, 37.48–54.82%). Five-year OS rate was 37.71%, 31.96 and 26.54 in S1, S2 and S3 respectively (95% CIs, 27.13 to 48.24, 22.55 to 41.74 and 17.87–35.99% respectively). The difference of OS between S1 and S3 was significant ($p = 0.015$).

The OS at two years was 60% (95% CI, 53–67%) after TTE, 53% (95% CI, 43–62%) after THE and 44% (95% CI, 31–55%) after TGTTE.

Cox regression analysis showed that Siewert type 1, age, male gender and UICC stage were significant predictors of OS. (Table 6, supplementary material).

Then we analyzed the early outcome and the oncological and survival data related to the type of surgical procedure performed in patients with S2 tumor to investigate the efficay of THE in this subsite of EGJ tumor.

Sixty per cent of patients with S2 were submitted to TTE while THE was performed in 24% and TGTTE in the remaining 15% of patients.

Table 3 shows postoperative general and surgical complications, reoperation, LOS and mortality. We observed 36.7% of postoperative surgical complication after THE, 15.7% after TTE and 11.4% after TGTTE. The differences were statistically significant ($p = 0.004$).

Anastomotic leaks occurred more frequently after THE (13.3%) than after TTE (3.6%) or TGTTE (5.7%). The differences were not significant (p 0,081).

In contrast, TTE showed the highest rate (35.7%) of general complications (mainly pulmonary and cardiovascular), although the difference among the three subgroups of patients was not statistically significant ($p = 0.411$).

Postoperative mortality was similar in the 3 subgroups.

The distribution of tumor stages was different in the three arms. Stage III/IV tumors were more frequent in patients with transthoracic approach (61.3/7.3% in TTE and 50.0/20.6% in TGTTE group respectively) while patients submitted to THE had a stage I/II tumor in 15.5/36.2% of cases respectively ($p < 0.001$) (Table 4).

The mean number of nodes yelded/positive was 23.75/5.08 after THE, 25.89/5.05 after TTE and 22.6/6.77 after TGTTE ($p = 0.6414$/ $p = 0.6428$).

The proximal margin was involved by the tumor in 3 patients, 2 after THE (4.08%) and 1 after TGTTE (3.22%).

Table 2
General complications, surgical complication, reoperation, lenght of stay and mortality in the whole patients' population.

	TTE Nr (%)	THE Nr (%)	TGTTE Nr (%)	Others Nr (%)	P value	Combined Nr (%)
Total number patients	310	180	100	8		598
General						
Cardiovascular Complications	29 (9.4)	9 (5.0)	14 (14.0)	0 (0.0)	0.064	52 (8.7)
pulmonary Complications	60 (19.4)	25 (13.9)	18 (18.0)	0 (0.0)	0.297	103 (17.2)
Renal Complications	4 (1.3)	0 (0.0)	1 (1.0)	0 (0.0)	0.360	5 (0.8)
DIC	1 (0.3)	0 (0)	0 (0)	0 (0)	1.000	1 (0.2)
Deep Venous Thrombosis	3 (1.0)	2 (1.1)	1 (1.0)	0 (0)	1.000	6 (1.0)
Infection of Central venous catheter	9 (2.9)	5 (2.8)	1 (1.0)	0 (0)	0.741	15 (2.5)
Total General Complications	106 (34.1)	41 (22.7)	35 (35.0)	0 (0)	**0.018**	182 (30.4)
Surgical						
Anastomosis leakage	15 (4.8)	16 (8.9)	5 (5.0)	1 (12.5)	0.190	37 (6.2)
Pneumothorax	17 (5.5)	2 (1.1)	1 (1.0)	0 (0)	**0.035**	20 (3.3)
Abnominal collection	1 (0.3)	4 (2.2)	2 (2)	0 (0)	0.165	7 (1.2)
Jejunal stump leakage	0 (0)	2 (1.1)	0 (0)	0 (0)	0.145	2 (0.3)
Duodenal stump leakage	0 (0.3)	4 (2.2)	0 (0)	0 (0)	**0.045**	4 (0.7)
Wound failure	1 (0.3)	2 (1.1)	0 (0)	0 (0)	0.600	3 (0.5)
Esophago-brochial fistula	1 (0.3)	1 (0.6)	0 (0)	0 (0)	1.000	2 (0.3)
Gastric tube perforation	4 (1.3)	0 (0)	0 (0)	0 (0)	0.335	4 (0.7)
gastric tube necrosis	1 (0.3)	0 (0)	0 (0)	0 (0)	1.000	1 (0.2)
Pancreatic fistula	0 (0)	3 (1.7)	0 (0)	0 (0)	0.096	3 (0.5)
bleeding	7 (2.3)	9 (5)	2 (2)	0 (0)	0.379	18 (3.0)
Trouble of swallowing	2 (0.7)	1 (0.6)	0 (0)	0 (0)	1.000	3 (0.5)
Dysphonia	1 (0.3)	0 (0)	0 (0)	0 (0)	1.000	1 (0.2)
others	4 (1.3)	2 (1.1)	1 (1.0)	0 (0)	1.000	7 (1.2)
Total surgical complications	54 (17.4)	46 (25.5)	11 (11)	1 (12.5)	**0.019**	112 (18.7)
Reoperation Nr	20 (6.5)	17 (9.4)	6 (6)	1 (12.5)	0.412	44 (7.4)
LOS median(IQR)	15 (12; 20)	14 (11; 18.5)	16(12.5; 25.5)	11.5(6; 26)	**0.009**	15 (12; 21)
30-days mortality	2 (0.7)	7 (3.9)	1 (1)	0 (0)	0.052	10 (1.7)
60-days mortality	7 (2.3)	10 (5.6)	2 (2)	0 (0)	0.243	19 (3.2)

DIC = diseminated intravascular coagulation; **LOS**: lenght of stay; **TTE** = Proximal gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest; **THE** = Total gastrectomy + transhiatal distal esophagectomy and anastomosis in the lower mediastinum; **TGTTE** = Total gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest.

The median follow-up time was 16 months.

The OS rates at two years was 63.27% (95% CI, 45.12–76.84%) after THE, 64.79% (95% CI, 53.86–73.76%) after TTE and 40.86% (95% CI, 21.68–59.21%) after TGTTE. Overall 5-year survival rate was 49.85%, 28.42% and 19.15% after THE, TTE and TGTTE respectively (95% CIs, 30.48 to 66.49, 15.86 to 42.35 and 5.64–38.68%, respectively) (Fig. 1). There was no difference in OS between THE and TTE ($p = 0.587$) while OS of TGTTE was significantly lower (p 0.035).

Multivariate Cox regression analysis showed that in Siewert type 2 patients only male gender (HR 2.55, 95% CI 1.24–5.25, $p = 0.011$) and Stage III and IV (HR 4.85 and 12.38, 95%CIs 1.84–12.77 and 4.17–36.72, $p = 0.001$ and $p = 0.000$) were indipendent predictors of OS. (Table 7, supplementary material).

Discussion

[16–18] [17]. [16,17,19].
[20–22] [20–22].

Cancers at the EGJ or intra-abdominal esophagus have been traditionally managed surgically with either subtotal/distal esophagectomy with partial gastrectomy or with extended gastrectomy with or without thoracotomy. Regardless of the approach, R0 resection, a 4 cm distal (gastric) margin, a 5-cm proximal (esophageal) margin and resection of at least 15 nodes in regional stations according to the primary tumor location are mandatory [16,17].

In literature long-term survival rates of patients resected with curative intent have been reported as ranging between 22% and 38% [18–21]. Consistent with these figures, the 5-year OS rate of R0 patients was 32% in this series as well.

Surgical treatment of S1 and S3 tumors is nowadays quite codified while the optimal treatment of S2 cancer still remains a debated topic worldwide. For S1 tumor a transthoracic approach is requested to obtain a complete mediastinal LN yeld and to improve oncological outcome and survival, despite the extent of esophagectomy (subtotal vs total) and consequently the site of the anastomosis (neck vs upper/middle chest) [11,22].

Transthoracic approach was reported as the optimal choice in S1 patients in several western trials, with anastomosis either in the chest [9] or in the neck [23,24]. In fact. the transthoracic approach enables lymph node dissection of the upper and middle mediastinum. which is not accessible through the esophageal hiatus.

For S3 tumors. total gastrectomy with transhiatal resection of the distal esophagus is recommended. The JCOG 9502 trial compared transhiatal approach (THE) with anastomosis in the lower mediastinum versus extended esophagectomy using a left thoracoabdominal approach (LTA) for patients with S2 or S3 tumors [12]. This trial was prematurely closed when a planned interim analysis concluded that it was unlikely that LTA would be significantly better than THE. This study showed that LTA does not provide a survival advantage as compared to THE in the treatment of curable gastric cancers with an esophageal invasion of 3 cm or less. which corresponds mainly to tumors classified as Siewert type 2 or 3. Authors concluded that LTA could be avoided for type II or III tumors. The thoracotomy-sparing transhiatal approach is less invasive and associated with lower morbidity and mortality.

On the contrary. no standard surgical treatment has been defined for S2 tumors. Several reports are in favour to TH procedure because of its lower rate of cardiopulmonary complications and shorter LOS [10]. A large sample-size clinicopathological study [18] concluded that type II tumors should be treated in the same way as type III tumors. with a transhiatal limited procedure. In another

Table 3
General complications, surgical complications, reoperation, lenght of stay and mortality by the type of procedure performed in Siewert type II EGJ tumors.

	TTE Nr (%)	THE Nr (%)	TGTTE Nr (%)	P value	Combined Nr (%)
Total number patients	140	60	35		237[a]
General complications					
Cardiovascular Complications	13 (9.3)	5 (8.3)	3 (8.6)	1.000	21 (8.9)
pulmonary Complications	26 (18.6)	8 (13.3)	7 (20)	0.749	41 (17.3)
Renal Complications	2 (1.4)	0 (0)	0 (0)	1.000	2 (0.8)
DIC	0 (0)	0 (0)	0 (0)	–	0 (0)
Deep Venous Thrombosis	2 (1.4)	1 (1.7)	1 (2.9)	0.790	4 (1.7)
Infection of Central venous catheter	7 (5)	1 (1.7)	0 (0)	0.426	8 (3.4
Total	**50 (35.7)**	**15 (25.0)**	**11 (31.4.)**	0.411	**76 (32.1)**
Surgical complications					
Anastomosis leakage	5 (3.6)	8 (13.3)	2 (5.7)	0.081	15 (6.3)
Pneumothorax	6 (4.3)	0 (0)	0 (0)	0.221	6 (2.5)
Abnominal collection	0 (0)	2 (3.3)	1 (2.9)	0.088	3 (1.3)
Jejunal stump leakage	0 (0)	1 (1.7)	0 (0)	0.409	1 (0.4)
Duodenum stump leakage	0 (0)	3 (5)	0 (0)	**0.044**	3 (1.3)
Wound rupture	0 (0)	1 (1.7)	0 (0)	0.409	1 (0.4)
Esophago-brochial fistula	0 (0)	1 (1.7)	0 (0)	0.409	1 (0.4)
Gastric tube perforation	4 (2.9)	0 (0)	0 (0)	0.374	4 (1.7)
Necrosis of gastric tube	1 (0.7)	0 (0)	0 (0)	1.000	1 (0.4)
Pancreatic fistula	0 (0)	2 (3.3)	0 (0)	0.101	2 (0.8)
bleeding	3 (2.1)	3 (5)	0 (0)	0.445	6 (2.5)
Trouble of swallowing	0 (0)	0 (0)	0 (0)	–	0 (0)
Dysphonia	0 (0)	0 (0)	0 (0)	–	0 (0)
others	3 (2.1)	1 (1.7)	1 (2.9)	1.000	5 (2.1)
Total	**22 (15.7)**	**22 (36.7)**	**4 (11.4)**	**0.004**	**48 (20.3)**
Reoperation Nr	11 (7.9)	8 (13.3)	3 (8.6)	0.575	22 (9.3)
30 days mortality	0 (0)	0 (0)	0 (0)	–	0 (0)
60 days mortality	3 (2.1)	1 (1.7)	0 (0)	1.000	4 (1.7)
LOS median(IQR)	15 (12; 19)	16 (13; 29)	15 (12; 22)	0.295	15 (12; 21)

LOS: length of stay; **TTE** = Proximal gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest; **THE** = Total gastrectomy + transhiatal distal esophagectomy and anastomosis in the lower mediastinum; **TGTTE** = Total gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest.
[a] 2 "others procedures" have been added for calculation of combined percentages.

Table 4
7th edition-TNM stage distribution, lymph node yeld and lymph node involvement in Siewert type II patients' population.

	TTE Nr (%)	THE Nr (%)	TGTTE Nr (%)	P Value
Total number patients	140	60	34	
Missing	3	2	1	
Stage I (IA + IB)	13 (9.5)	9 (15,5)	4 (11.8)	**<0.001**
Stage II (IIA + IIB)	30 (21.9)	21 (36.2)	6 (17.7)	
Stage III (IIIA + IIIB + IIIC)	84 (61.3)	17 (29.3)	17 (50.0)	
Stage IV	10 (7.3)	11 (19.0)	7 (20.6)	
LN yeld				
Nr LN mean (range)	25.89 (3; 71)	23.75 (6; 92)	22.6 (7; 82)	0.6414
Nr pos LN mean (range)	5.05 (0; 35)	5.08 (0; 36)	6.77 (0; 37)	1.000
Rate pos LN (%)	19.5	21.4	29.9	0.6428

TTE = Proximal gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest; **THE** = Total gastrectomy + transhiatal distal esophagectomy and anastomosis in the lower mediastinum; **TGTTE** = Total gastrectomy + transthoracic subtotal esophagectomy and anastomosis in the middle chest; **LN** = lymph nodes; **pos** = positive.

recent trial. 44 patients with R0 resection of a S2 tumor had a 5-year OS of 25.7%. which did not significantly differ according to the type of surgical approach adopted as well ($p = 0.53$) [25]. Finally. no long-term survival advantage for either TTE or THE procedure was found in a multivariate analysis of a subgroup of 52 patients with a S2 tumor [26]. Neverthleless. the need for clear longitudinal and circumferential resection margins and for the adequacy of lymphadenectomy makes several authors prefer the transhiatal approach [25–27].

Tosolini et Al recently reported a prospective analysis of 270 partients undergoing either TTE or THE for siewert type II cancer. They could not detect a difference between TTE and THE from the oncologic point of view and Cox regression analysis identified only Age, ASA class and UICC stage as indipendent predictors of OS [28].

Although the sample size seems large, the present series has a long inclusion time and an apparent low patients' recruitment per center/per year (mean, 4 cases). Several aspects should be considered when analyzing this case volume. First, 3 out of these 8 centers (teams) were working in the same main hospital and in strict collaboration for several years. Second, only 2 of these centers have been registering patients since 2000. The remaining 6 centers started their recruitment from 2008 (2 centers) or 2010 (4 centers). Therefore, the final case volume per center/per year was 10.5 cases. Third, this overall low recruitment certainly reflected the problem of centralization of surgical oncology in our Region and, more generally, in Italy. This process of centralization is ongoing at the moment. As a results, since 2018 in our Region only 6 centers are registering and operating cardia cancer, and only 4 centers are treating esophageal cancer. Due to the lack of centralization policy and the consequent low recruitment the inclusion period of this

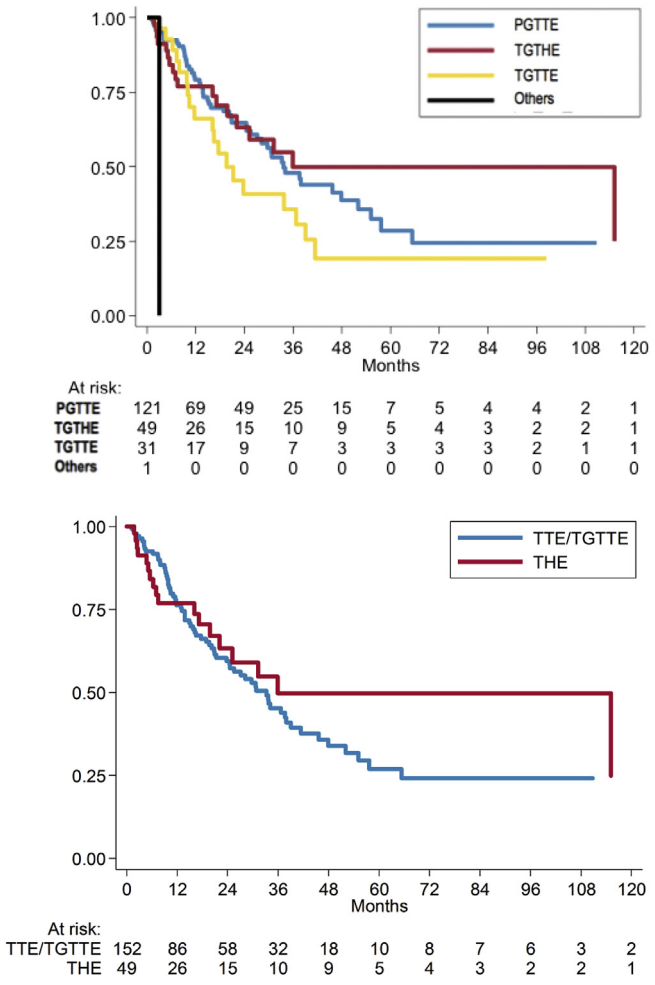

Fig. 1. Overall survival by the type of procedure performed in Siewert type II patients' population (a), and by putting together TTE with TGTTE (b).

rectrospective study was very long and therefore several biases related to changes in indication to preoperative treatment and types of regimens administered can have affected some treatment results. Anyway this reflects the policy of treating cardia cancer during the recruitment period. In the present Series, S2 cancers represented the 40% of patients' population. The most performed procedure in this subgroup of patients was TTE (60%); THE and TGTTE were performed in the remaining 24% and 15% of patients. In the whole population, earlier (30-days) mortality, although in line with literature data, was slightly higher after THE than after TTE (probably due to higher incidence of surgical complications ($p = 0.004$)) but this difference was not statistically significant ($p = 0.052$). Furthermore, 60-days mortality was absolutely comparable ($p = 0.243$). In particular, 3 patients had troubles of swallowing after their surgery, which were investigated with swallow- and upper GI- contast X-ray; in all of these cases an abnormal upper GI motility was observed; two patients were submitted to endoscopic examination which showed edema of the anastomotic area. All patients were treated conservatively. A case of dysphonia was observed after a TTE procedure. The patient was examined by an Otholaryngologist and a transient vocal cordal paralysis was confirmed by laringoscopy; the patient was followed up and treated without any invasive procedures.

In S2 population, cardiovascular and pulmonary complications were higher after transthoracic access, while surgical complications and anastomotic leaks were higher after transhiatal procedure, but 30 and 60 days mortality rates were not different in TTE and THE ($p = 1$). However, the distribution of tumor stages in S2 patients' population was different in the 3 types of procedures performed. While about 70% of patients with TTE procedures had a tumor at TNM stage 3 or 4, about 50% of THE patients had a TNM stage 1 or 2 disease.

The number of LN retrieved was not statistically different among the three arms of treatment and this could certainly contribute to explain the absence of *significant* difference in oncologic and survival outcomes between TT and TH procedures.

Our results seem to confirm data coming from other studies that have compared TT and TH approach for S2 tumor. These studies reported no significant differences in oncologic and survival outcomes and often observed improved clinical outcomes (complications and lenght of hospital stay) after TH procedures. However, in these previous reports the distribution of TNM stages in the subtypes of procedure performed was rather not detailed.

In the present series. despite a higher surgical morbidity rate, without a related higher need of reoperation, patients submitted to TH approach had less pulmonary and cardiovascular complications and, as a result, postoperative mortality was very low and similar in both groups. Oncologic outcomes (mainly the number of LN retrieved) were comparable in TT and in TH patients. A description of the distribution of TNM stages in patients from the three groups of procedure was performed; mainly, TH group included patients with less advanced disease as compared to TT groups. Overall survival after THE was comparable to that after Ivor Lewis procedure.

In conclusion, in selected Siewert type II tumors with less advanced disease (stage I and II), when adequacy of free distal margins and LN yeld is obtained, the transhiatal approach can be a treatment option with the same oncological outcomes as transthoracic procedure but with reduced cardiopulmonary complications.

Declarations of interest

None.

Disclosure statement

All Authors state that they do not have any conflicts of interest do declare (see enclosed disclosure statement form signed by all authors).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.04.001.

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