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Adenocarcinoma of the oesophagogastric junction Siewert II: An oesophageal cancer better cured with total gastrectomy

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ABSTRACT

Introduction: Type II AEG is now considered as oesophageal cancer in the seventh and eighth edition of TNM classification but optimal surgical approach for these tumors remains debated. The objective of the study is to assess and compare surgical and oncological outcomes of two surgical approaches: superior polar oesogastrectomy (SPO) or total gastrectomy (TG) in patients with type II adenocarcinoma of the oesophagogastric junction (AEG).
Material and methods: 183 patients with type II AEG treated from 1997 to 2010 in 21 French centers by SPO or TG were included in a multicenter retrospective study. The surgical and oncological outcomes were compared between these two surgical approaches.
Results: A TG was performed in 64 (35%) patients whereas 119 (65%) patients were treated by SPO with transthoracic approach in 100 of them (83.2%) and transhiatal approach with cervicotomy in 19 (16.8%). Surgical outcomes were comparable between the two approaches with a postoperative mortality rate of 4.9% and a severe operative morbidity rate within 30 days of 15.3%. Median survival in patients operated on by TG was of 46 months compared to 27 months in patients treated by SPO ($p = 0.118$). At multivariate analysis, TG appears to be an independent good prognostic factor compared to SPO ($HR = 1.847$; $p = 0.008$). However, TG was also associated with a higher rate of incomplete resection, (12.5% vs 5.9%; $p = 0.120$).
Conclusion: When TG allows obtaining tumor-free resection margins, this approach should be preferred to SPO.

Introduction

While the incidence of gastric adenocarcinoma decreases in western developed countries, the incidence of lower oesophagus and oesophagogastric junction adenocarcinoma increases [1,2].

Located between the oesophagus and the stomach, the staging and treatment of adenocarcinomas of the oesophagogastric junction (AEG) remain controversial. In most prospective randomized trials assessing the efficiency of different therapeutic strategies, AEG were mixed with either oesophageal adenocarcinomas or gastric cancers [3–5].

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In order to better define the specificities of AEG and to compare various therapeutic strategies, Siewert and colleagues have proposed a classification of AEG tumors based on the distance between the tumor's epicenter and the anatomical cardia [6]. Tumors with an epicenter located 1-5 cm above the anatomical cardia were classified Type I, those located between 1 cm above and 2 cm below were named Type II and those within 2–5 cm below the gastric cardia were named type III [7]. According to this classification, AEG type I is considered as a distal oesophageal tumor requiring superior polar oesogastrectomy (SPO) via transthoracic or transhiatal approach. Conversely, AEG type III is treated as proximal gastric cancer by total gastrectomy (TG). For patients with type II AEG, also named true carcinoma of the cardia, both optimal surgical approach and perioperative oncological treatment remain debated. Many surgeons resect these tumors by oesophagectomy as for Type I, while others do perform total gastrectomy with resection of the distal oesophagus as for Type III. Literature does not provide definitive evidence of which strategy should be favored [8–20].

It is noteworthy that, since the publication of the seventh edition of the TNM classification (TNM7) [21], all AEGs have been staged as oesophageal carcinomas, regardless of their Siewert type. On the contrary, in the eighth edition of the TNM classification [22] (TNM8), AEG type III is classified as gastric cancer whereas AEG type I and II are classified as esophageal cancer, illustrating the difficulty to categorize these AEG. Thus, AEG type II is considered as an oesophageal carcinoma according to the TNM8 classification but can be treated either as a gastric cancer or an oesophageal cancer, mainly depending on the surgeon's habits rather than on scientific evidence.

Trying to clarify this important issue, this large French retrospective multicentric study aimed to compare surgical and oncological outcomes of the two main surgical strategies (SPO or TG) in patients with type II AEG.

Patients and methods

Patients

A multicentric database for oesophageal and gastric adenocarcinoma was built-up in the FREGAT program, gathering 3202 patients from 21 participating French surgical centers consecutively operated on between January 1997 and March 2010. Among them, patients classified and treated by their surgeon as AEG type II according to Siewert's classification defined on endoscopic findings, without preoperative evidence of hepatic, peritoneal or pulmonary metastasis, and considered as resectable with curative intent on preoperative assessment were selected. Only patients treated either by SPO or by TG were finally included in this study.

In each center, therapeutic strategy including the choice of perioperative chemotherapy or preoperative chemoradiotherapy, as well as the surgical approach, was elaborated in multidisciplinary weekly meetings of surgeons, oncologists, pathologists and radiologists.

Pretreatment work-up and perioperative treatments

In all centers, the preoperative assessment included complete medical history, physical examination, upper gastro-intestinal endoscopy with biopsies and abdomino-pelvic and chest computed tomographic scans. The diagnosis of an AEG type II was done endoscopically and was confirmed on pathological examination. Patients whose endoscopic diagnosis of AEG type II was not confirmed during surgery, demonstrating a type I or type III AEG, were excluded from this study. According to Siewert's classification, the diagnosis of AEG type II was based on distance separating the upper and lower borders of the tumor from the gastro-esophageal junction defined as the proximal end of the gastric folds. Endoscopic ultrasound and positon emission tomography (PET) were performed depending on local policies and in accordance with French National Guidelines [23,24]. Since 2005, according to reported prospective trials [3,4], a perioperative chemotherapy by cisplatin and fluorouracil associated or not with epirubicin was recommended for AEG type II considered as gastric cancer greater than clinical T2N0 stage. Conversely, many AEG type II were considered as oesophageal cancers and were treated with preoperative chemoradiotherapy associating fluorouracil and cisplatin with concomitant radiotherapy delivering 45 Gy in 25 fractions over 5 weeks, when tumor was classified as stage 3 on pretreatment workup. Malnutrition was defined by a weight loss exceeding 10% in the last 6 months.

Surgical technique

The used surgical approaches were mainly based on the preferences and habits of each surgical department aiming to achieve complete macroscopic and microscopic tumor clearance. Thus some departments preferentially opted for total gastrectomy extended to the distal oesophagus while others preferred superior polar oesogastrectomy.

Three different surgical approaches were used: total gastrectomy with transhiatal resection of the distal oesophagus (TG) or superior polar oesogastrectomy (SPO) resecting the oesophagus with the proximal stomach, through either combined transhiatal and cervical approach or thoracotomy. When a total gastrectomy with transhiatal resection of the distal oesophagus was performed, lymph nodes dissection includes a D2-lymphadenectomy and a dissection of the lymph nodes of the lower mediastinum whereas a two-fields lymphadenectomy including inferior mediastinal nodes and hilar nodes was performed in SPO.

Pathological analysis

Resected specimens were examined by pathologists experienced in digestive diseases. Retrieved lymph nodes, surgical margins and mural extension of the tumor were systematically assessed. TNM stages were defined according to the seventh edition of UICC/TNM classification [21].

A curative resection (R0) was defined as macroscopically and microscopically complete. A R1 resection indicated microscopically involved margins either laterally or at oesophageal, gastric or duodenal margins. A R2 resection indicated macroscopic residual tumor left by surgery.

Postoperative outcomes and follow-up

Morbidity and mortality were recorded at 30 and 90 days after surgery and classified according to Clavien Dindo classification for surgical complications by retrospective review of each patient's chart [25]. Severe morbidity was defined as any complication classified grade 3 or more according to Clavien-Dindo's classification.

Long-term follow-up included physical examination, tumor markers measurement and either abdominal ultrasound and chest radiography or thoracic and abdomino-pelvic computed tomography scan, every 4 months for 2 years and every 6 months thereafter for 3 more years at least, according to French guidelines [23,24]. Locoregional recurrence was defined as cancer recurrence within the regional resection area or local anastomotic site. Distant recurrence was defined as peritoneal recurrence, liver metastasis or metastasis at other extra-abdominal sites as well as nodal metastasis beyond the regional nodes.

Statistical analysis

Categorical data were compared using the Chi2 test or Fisher's exact test and continuous data were compared using the independent-samples *t*-test. Overall survival (OS) and disease-free survival (DFS) were estimated with the Kaplan-Meier method and included postoperative deaths. The Log Rank test was used to compare survival curves. Univariate Cox regression was used to identify the prognostic factors of OS and DFS. Multivariate analyses were performed using a Cox proportional stepwise procedure, including non-redundant prognostic factors identified by univariate analysis on the first step of the analysis. A $p < 0.2$ was defined for systematic entry into the model. All statistical analyses were performed using SPSS version 22.0 (IBM, New-York, USA). A *p* value ≤ 0.05 was considered as significant.

The study complied with the French National Health guidelines on research involving human subjects. The database used comes from the ADCI001 study, accepted by the regional institutional review board on April 13, 2010 and registered on the clinicaltrials.gov website (record ADCI001; identifier NCT01249859)

Results

Among the 3202 patients from the FREGAT database, 260 were defined on endoscopic findings as Siewert II, without preoperative evidence of metastatic disease. One hundred and eighty-three patients were treated by SPO or by TG. These 183 patients were operated in 17 surgical centers, including 147 patients in 9 high volume centers (more than 10 esophagectomies) and 14 patients in 8 low volume centers.

Preoperative data (Table 1)

The clinical characteristics of the whole population and those of the two groups defined by the used surgical technique are reported in Table 1. The two groups did not differ for their demographic characteristics. Mean age at diagnosis was 62.0±11.3 years. Most patients (89%) were men. The American Society of Anesthesiology

Table 1
Clinical and pathological data.

Variables	Whole population N = 183	Total gastrectomy N = 64	Superior Polar Oesogastrectomy N = 119	p-value
Age (mean±SD)	62.0 ± 11.3	63.5 ± 12.4	61.3 ± 10.7	0.214
Sexe				0.621
Male	163 (89.1)	58 (90.6)	105 (88.2)	
Female	20 (10.9)	6 (9.4)	14 (11.8)	
ASA score				0.372
1-2	152 (83.1)	51 (79.7)	101 (84.9)	
3-4	31 (16.9)	13 (20.3)	18 (15.1)	
Malnutrition	31 (16.9)	8 (12.5)	23 (19.3)	0.240
High volume center	147 (80.3%)	48 (75%)	99 (83.2%)	0.184
Pretherapeutic clinical staging (cTNM)				0.071
Stage 1	33 (18)	17 (26.6)	16 (13.4)	
Stage 2	44 (24)	12 (18.8)	32 (26.9)	
Stage 3	106 (57.9)	35 (54.7)	71 (59.7)	
Neoadjuvant Therapy				0.072
None	100 (54.6)	39 (60.9)	61 (51.3)	
Chemotherapy alone	46 (25.1)	18 (28.1)	28 (23.5)	0.494
Radiochemotherapy	37 (20.2)	7 (10.9)	30 (25.2)	0.022
Operative mortality	9 (4.9)	4 (6.3)	5 (4.2)	0.722
Operative Morbidity (30 days)	91 (49.7)	35 (54.7)	56 (47.1)	0.325
Severe operative morbidity (30 days)	28 (15.3)	12 (18.8)	16 (13.4)	0.342
Operative Morbidity D30 - D90	32 (17.5)	11 (17.2)	21 (17.6)	0.938
pT Stage				0.034
pT0,pTis,pT1	43 (23.5)	19 (29.7)	24 (20.2)	
pT2	53 (29)	22 (34.4)	31 (26.1)	
pT3	66 (36.1)	14 (21.9)	52 (43.7)	
pT4	21 (11.5)	9 (14.1)	12 (10.1)	
pN stage				0.104
pN0	70 (38.3)	27 (42.2)	43 (36.1)	
pN1	61 (33.3)	15 (23.4)	46 (38.7)	
pN2, pN3	52 (28.4)	22 (34.4)	30 (25.2)	
Number of retrieved LN (Median [Min-Max])	19 [4 - 48]	21.5 [7 - 48]	17.5 [4 - 47]	0.016*
Number of positive LN (Median [Min-Max])	2 [0 - 31]	2 [0 - 31]	2 [0 - 23]	0.776*
pTNM stage				0.075
Stage I	61 (33.3)	28 (43.8)	33 (27.7)	
Stage II	32 (17.5)	8 (12.5)	24 (20.2)	
Stage III	90 (49.2)	28 (43.8)	62 (52.1)	
Vertical margin involvement	12 (6.6)	7 (10.9)	5 (4.2)	0.115
Lateral margin involvement	7 (3.8)	4 (6.3)	3 (2.5)	0.241
Incomplete resection (R1/R2)	15 (8.2)	8 (12.5)	7 (5.9)	0.120
Adjuvant Therapy				0.441
None	115 (62.8)	44 (68.8)	71 (59.7)	
Chemotherapy	50 (27.3)	14 (21.9)	36 (30.3)	
Radiochemotherapy	18 (9.8)	6 (9.4)	12 (10.1)	

ASA score: American Society of Anaesthesiologists; R1: microscopic incomplete resection; R2: macroscopic incomplete resection.
* Mann-Whitney test.

(ASA) score was 1 or 2 in 83% of patients and 17% of patients exhibited malnutrition at diagnosis. There was no significant difference in the distribution of pretherapeutic clinical stages (pretherapeutic cTNM) between the two surgical approaches.

Neoadjuvant chemotherapy was used in 46 patients (25%) and neoadjuvant radiochemotherapy in 37 patients (20%). The latter was more frequently used in patients operated on by SPO (25% vs 11%, p = 0.022). Moreover, neoadjuvant therapy was statistically associated with pretherapeutic clinical stages. Thus, only 6.1% of patients classified cTNM stage 1 received neoadjuvant therapy, whereas they were 38.6% in stage 2 and 60.4% in stage 3 (p < 0.001).

Surgical management and postoperative outcomes (Table 1)

Among the 183 AEG type II included in this study, 64 (35%) were treated by TG and 119 (65%) were treated by SPO with a transthoracic approach in 100 patients (83.2%), a transhiatal approach combined with cervicotomy in 19 patients (16.8%). Nine patients (4.9%) died in the first postoperative month and three in the next two months, accounting for an operative mortality rate at 90 days of 6.6%. The mortality rate was comparable between TG group (7.8%) and SPO group (5.9%; p = 0.755). Postoperative complications in the 90 first postoperative days, either surgical or medical, were reported in 102 patients (55.7%), with no difference between patients treated by TG or SPO (59.4% vs 53.8%; p = 0.468). In 30 patients (16.4%), these complications were graded III or IV (severe complications), according to Clavien Dindo classification, with no difference between patients treated by TG or SPO (18.8% vs 15.1%; p = 0.528). List of postoperative complications is detailed in supplemental data (Supplemental Table 1). Interestingly, distribution of early complications was different between the 2 surgical approaches (p = 0.001). Thus, early respiratory complications were more frequently observed in SPO group (21.8%) than in TG group (7.8%). On the contrary, abdominal collection were more frequent in patients who underwent TG (12.5%) than in patients undergoing SPO (0%)

Histological data (Table 1)

Tumors resected by SPO were significantly more frequently pT3-T4 than tumors resected by TG (54% vs 36%, p = 0.021), but the rate of incomplete resection was higher in TG group (12.5%) than in SPO (5.9%%), without reaching significance (p = 0.12). As expected, upper (oesophageal) margin was more frequently microscopically invaded after GT than SPO (10.9% vs 4.2%) but without reaching significance (p = 0.115).

Nodal metastases were observed in about 60% of patients in both TG and SPO groups, but the median number of retrieved lymph nodes was higher in TG (21.5 [7 - 48]) than in SPO (17.5 [4 - 47]; p = 0.016). However the median number of retrieved lymph nodes was comparable between patients who underwent SPO without neoadjuvant chemotherapy (20 [4-47]) and patients who underwent TG (21.5 [7-48]; p = 0.331)

Prognostic factors of survival

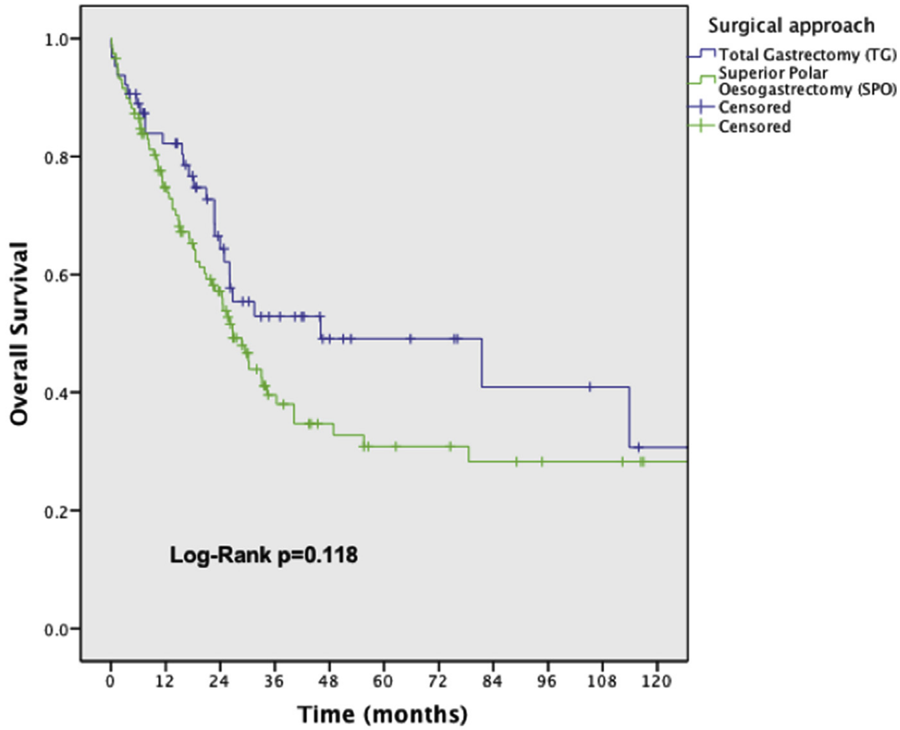
Follow-up data were available for all 183 patients with a median length of follow-up in surviving patients of 41.9 months (95%CI: 32.6–51.2 months). The median overall survival (OS) was 29.4 months (95%CI: 23.4–35.4 months) with a 5-years OS rate of 37%.

In univariate analysis (Table 2), 8 variables were associated with poor OS: preoperative malnutrition (p = 0.017), severe

Table 2
Prognostic factors of overall survival (univariate and multivariate analysis).

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Sexe Female	0.480	0.210–1.097	0.082	0.426	0.185–0.982	0.045
Age>60	1.264	0.833–1.917	0.270	-	-	-
ASA score 3-4	1.485	0.904–2.438	0.118	-	-	-
Malnutrition	1.855	1.117–3.083	0.017	-	-	-
High volume center	0.816	0.498–1.339	0.421			
Neoadjuvant Therapy	1.035	0.685–1.563	0.870			
Neoadjuvant RadioChemotherapy	1.229	0.757–1.997	0.404	-	-	-
Neoadjuvant Chemotherapy exclusive	0.852	0.508–1.430	0.545	-	-	-
SPO (vs TG)	1.418	0.913–2.203	0.120	1.847	1.172–2.908	0.008
Operative morbidity (30d)	1.321	0.883–1.978	0.176			
Severe operative morbidity (30d)	3.354	2.029–5.544	<0.001	4.649	2.704–7.994	<0.001
Operative morbidity (90d)	1.184	0.691–2.027	0.539			
Ajduvant Therapy	0.728	0.469–1.129	0.156			
Adjuvant RadioChemotherapy	0.686	0.332–1.415	0.307	-	-	-
Adjuvant Chemotherapy exclusive	0.815	0.500–1.330	0.414	-	-	-
pT stage			0.148	-	-	-
pT2	1.581	0.849–2.944	0.148	-	-	-
pT3	1.757	0.961–3.210	0.067	-	-	-
pT4	2.287	1.099–4.757	0.027	-	-	-
pN			0.001			0.041
pN1	1.212	0.726–2.024	0.462	1.412	0.835–2.388	0.198
pN2/pN3	2.382	1.443–3.932	0.001	1.993	1.167–3.403	0.012
pTNM stage			0.011			
Stage II	1.626	0.861–3.073	0.134			
Stage III	2.142	1.301–3.526	0.003			
Vertical margin involvement	3.160	1.632–6.119	0.001			
Circumferential margin involvement	2.759	1.203–6.331	0.017			
Incomplete resection (R1/R2)	2.439	1.328–4.478	0.004	3.019	1.613–5.651	0.001
Signet-ring cell histotype	1.648	1.092–2.485	0.017	-	-	-

ASA score: American Society of Anaesthesiologists; SPO: Superior Polar Oesogastrectomy; TG: Total Gastrectomy; R1: microscopic incomplete resection; R2:macroscopic incomplete resection; 30d: 30 days after surgery; 90d: 90 days after surgery.
Variables grayed out in multivariate analysis were not included in the first step of the multivariate analysis.
Variables marked with "-" in multivariate analysis were included in the first step of anaylsis but removed during the stepwise process.



No at risk											
TG	64	48	30	19	11	9	8	5	5	4	2
SPO	119	79	52	25	18	14	13	11	9	9	6

Fig. 1. Overall survival curves for patients who underwent total gastrectomy (TG) or superior polar oesogastrectomy (SPO).

postoperative morbidity within the first postoperative month ($p < 0.001$), the nodal status (pN stage) ($p < 0.001$), histological pTNM stage ($p = 0.003$), vertical margin involvement ($p = 0.001$), Circumferential margin involvement ($p = 0.017$), incomplete resection ($p = 0.004$) and signet ring cell histological type ($p = 0.017$). The better median overall survival of patients treated by TG (46.01 ± 28.5 months vs. 26.8 ± 2.4 months) did not reach significance ($p = 0.118$) (Fig. 1). In multivariate analysis, five factors were independently associated with poor OS, including male sex, postoperative severe morbidity within the first month, nodal involvement (pN stage), incomplete resection and resection by SPO (Table 2).

During the follow-up, recurrence was observed in 72 patients (39.3%) including 21 patients (32.8%) in the TG group and 51 patients (42.8%) in SPO group. Local recurrence was observed in 3 patients (4.7%) who were operated on by TG and in 8 patients operated on by SPO (6.7%). Distant metastasis were observed in 12 patients (18.7%) in TG group and 23 patients (19.3%) in SPO group. Both local and systemic recurrence was observed in 6 patients (9.4%) with TG and in 30 patients (26.3%) with SPO. The median length of disease-free survival (DFS) was 22.5 months (95%CI: 17-28 months) with a 5-years disease-free survival rate of 37%. In univariate analysis (Table 3), the 8 variables previously associated with poorer OS, as well as pT stage were associated with a poorer DFS. A higher median DFS was observed for patients treated by TG compared to SPO (24.0 ± 26.1 months vs. 20.0 ± 4.2 months; $p = 0.201$) (Fig. 2). In multivariate analysis, five factors were independently associated with poor DFS, including male sex, postoperative severe morbidity within the first month, nodal status (pN stage), incomplete resection and resection by SPO (Table 3).

Considering that incomplete tumor resection was an independent prognostic factor for OS and DFS but could result from erroneous preoperative assessment and wrong choice of surgical approach, an analysis was conducted in the 168 patients with complete tumorous resection (R0 resection). In univariate analysis, median overall survival was better for patients treated by TG (81.47 ± 35.9 months) than patients treated by SPO (28.70 ± 4.1 months; $p = 0.049$) (Fig. 3). In the same way, disease-free survival was better for patients treated by TG (74.90 ± 38.3 months) than patients treated by SPO (22.53 ± 4.7 months) without reaching significance ($p = 0.062$) (Supplemental Fig. 1).

In multivariate analysis in this group of patients, SPO remained an independent predictor of poor OS (HR = 1.90, 95%CI:1.16–3.13; $p = 0.011$) and DFS (HR = 1.78, 95%CI:1.11–2.85; $p = 0.017$) (Supplemental Tables 2 and 3).

Discussion

The optimal surgical approach for AEG type II remains controversial and varies according to the habits of surgical teams and surgeons [8,14–16,18,19,26,27].

This study included only patients with true cardia adenocarcinoma (AEG Siewert's type II). In addition to the well-known prognostic factors of overall and disease-free survivals — such as sex, age, malnutrition, preoperative treatment, postoperative morbidity, adjuvant treatment, pT stage, pN stage, completeness of resection (R0 resection vs R1 resection) — the type of resection (SPO or TG) was an independent prognostic factor for both overall (HR: 1.847; 95%CI: 1.172–2.908; $p = 0.008$) and disease-free survivals (HR: 1.630; 95%CI: 1.062–2.501; $p = 0.025$). Thus, overall

Table 3
Prognostic factors of disease-free survival (univariate and multivariate analysis).

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Sexe Female	0.497	0.231–1.072	0.075	0.443	0.203–0.966	0.041
Age>60	1.291	0.863–1.931	0.214	1.454	0.962–2.199	0.076
ASA score 3-4	1.388	0.858–2.246	0.182	-	-	-
Malnutrition	1.869	1.152–3.032	0.011	-	-	-
High volume center	0.883	0.546–1.427	0.610			
Neoadjuvant Therapy	1.112	0.752–1.645	0.595			
Neoadjuvant RadioChemotherapy	1.206	0.752–1.932	0.437	-	-	-
Neoadjuvant Chemotherapy exclusive	0.977	0.612–1.558	0.921	-	-	-
SPO (vs. TG)	1.311	0.864–1.990	0.200	1.630	1.062–2.501	0.025
Operative morbidity (30d)	1.442	0.977–2.127	0.065			
Severe Operative morbidity (30d)	3.056	1.880–4.968	<0.001	4.054	2.416–6.802	<0.001
Operative morbidity (90d)	1.523	1.023–2.268	0.038			
Ajduvant Therapy	0.825	0.548–1.243	0.358			
Adjuvant RadioChemotherapy	0.816	0.425–1.568	0.542	-	-	-
Adjuvant Chemotherapy exclusive	0.877	0.557–1.380	0.570	-	-	-
pT stage			0.008	-	-	-
pT2	1.721	0.928–3.192	0.085	-	-	-
pT3	2.037	1.125–3.691	0.019	-	-	-
pT4	3.325	1.651–6.694	0.001	-	-	-
pN			<0.001			0.022
pN1	1.181	0.717–1.947	0.514	1.190	0.712–1.991	0.506
pN2/pN3	2.619	1.624–4.222	<0.001	1.976	1.196–3.266	0.008
pTNM stage			0.002			
Stage II	1.599	0.852–2.999	0.144			
Stage III	2.393	1.478–3.875	<0.001			
Vertical margin involvement	3.626	1.922–6.842	<0.001			
Lateral margin involvement	2.776	1.213–6.353	0.016			
Incomplete resection (R1 or R2)	2.847	1.663–4.876	<0.001	3.138	1.711–5.758	<0.001
Signet-ring cell histotype	1.788	1.205–2.653	0.004	-	-	-

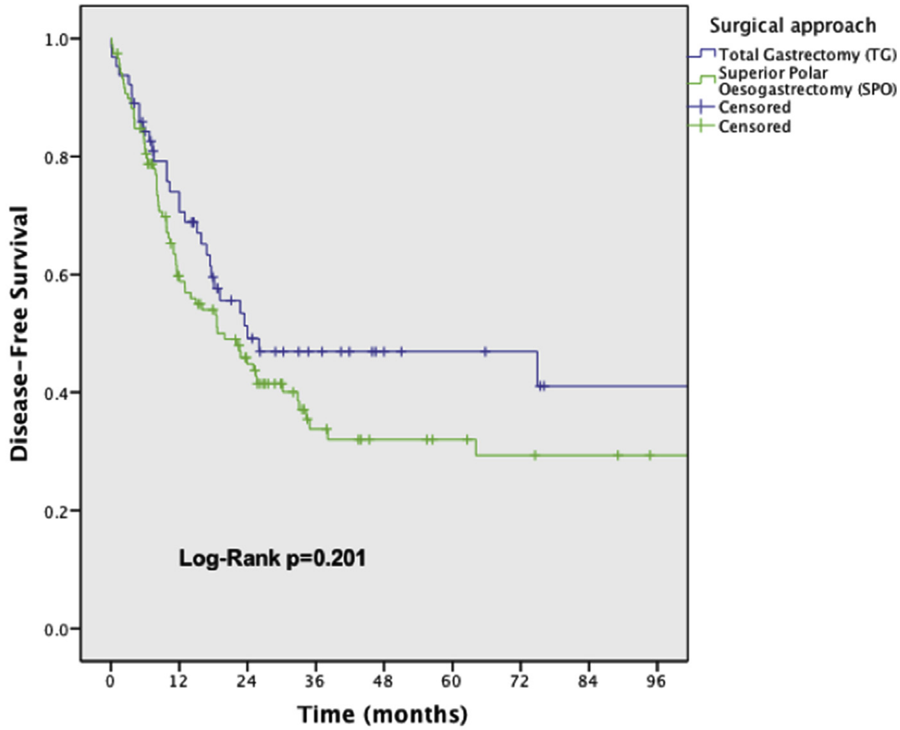
ASA score: American Society of Anaesthesiologists; SPO: Superior Polar Oesogastrectomy; TG: Total Gastrectomy; R1: microscopic incomplete resection; R2: macroscopic incomplete resection; 30d: 30 days after surgery; 90d: 90 days after surgery.
Variables grayed out in multivariate analysis were not included in the first step of the multivariate analysis.
Variables marked with "-" in multivariate analysis were included in the first step of anaylsis but removed during the stepwise process.

survival was better after TG with modified D2 lymphadenectomy than after SPO with mediastinal/upper abdominal lymphadenectomy (3- and 5-years overall survivals: 52.9% vs 39.6% and 49.1% vs 30.8% respectively; $p = 0.118$) and this difference became statistically significant when we considered other prognostic factors such as complete resection, severe postoperative morbidity and pTNM stage.

Such a finding is in line with previous studies of Siewert and al. [28,29], suggesting to treat AEG type II as AEG type III by total gastrectomy and D2 lymphadenectomy, rather than by superior polar oesophagogastrectomy because of their common epidemiological and histological characteristics. Nevertheless, Siewert et al. did not demonstrate any significant difference in overall survival between the two surgical approaches [19] [28,30–34]. On the contrary, the monocentric retrospective study recently published by Blank et al., suggested better overall and disease-free survival in patients with AEG type II treated by SPO rather than TG. These discrepancies could result from the use of different, criteria to choose the surgical approach for each patient, inducing potential distribution biases in these two monocentric studies. Because of its multicentric design, our study limits these distribution biases by comparing patients with equivalent tumors but treated in various departments in which criteria for choosing the surgical approach are likely to vary.

Two main objectives dictate the choice between these two surgical approaches (TG or SPO). The first one is to achieve a complete tumor resection with free resection margins (R0 resection), which is a major prognostic factor in most studies [26,35,36]. In our study, the rate of incomplete resection did not differ significantly between TG and SPO although the observed higher R1 resection rate after TG (12.5% vs 5.9%; $p = 0.120$) was due to more frequent upper margin involvement (10.9% vs 4.2%; $p = 0.115$). This has been previously reported in another French study and was considered as in favor of SPO for Siewert II AEG [14]. Indeed, the combined thoracic and abdominal approach performed during SPO yields larger proximal safety margins than TG performed by abdominal approach only. Barbour et al. reported gross proximal margin length as a significant predictor of overall survival and that patients with gross proximal margin length greater than 3,8 cm experienced significantly improved survival. This gross proximal margin length was more frequently obtained after SPO than after TG. However, Mine et al. showed that a gross proximal margin length greater than 2 cm in resected specimen (i.e. approximately 2,8 cm in vivo) appeared sufficient to obtained microscopically complete resection (R0 resection) in patients with AEG type II when there was less than 3 cm of oesophagus involved on preoperative investigations [37]. In these cases, a TG seems then sufficient without requiring additional thoracotomy.

The second main objective to be achieved during AEG type II surgery and dictating the choice of the surgical approach, is to obtain an optimal lymphadenectomy in order to achieve optimal tumor's staging and harvesting of all metastatic lymph nodes. The better OS and DFS observed in TG group could result from the different lymphadenectomies in the two surgical approaches. Thus, during TG with D2 lymphadenectomy, lymph nodes localized along the greater curvature (lymph node station 4 according to Japanese Gastric Cancer Association [38]) and those located in infra pyloric area (station 6) are systematically removed while they are preserved by SPO. Siewert and al. showed that 16% of patients with AEG type II had lymph node metastases along the greater curvature, and 6.5% had metastatic infra pyloric lymph nodes [19]. Conversely, only SPO is able to provide middle and upper



No at risk									
TG	64	41	23	16	10	9	8	5	5
SPO	119	62	41	20	15	13	11	10	8

Fig. 2. Disease-free survival curves for patients who underwent total gastrectomy (TG) or superior polar oesogastrectomy (SPO).

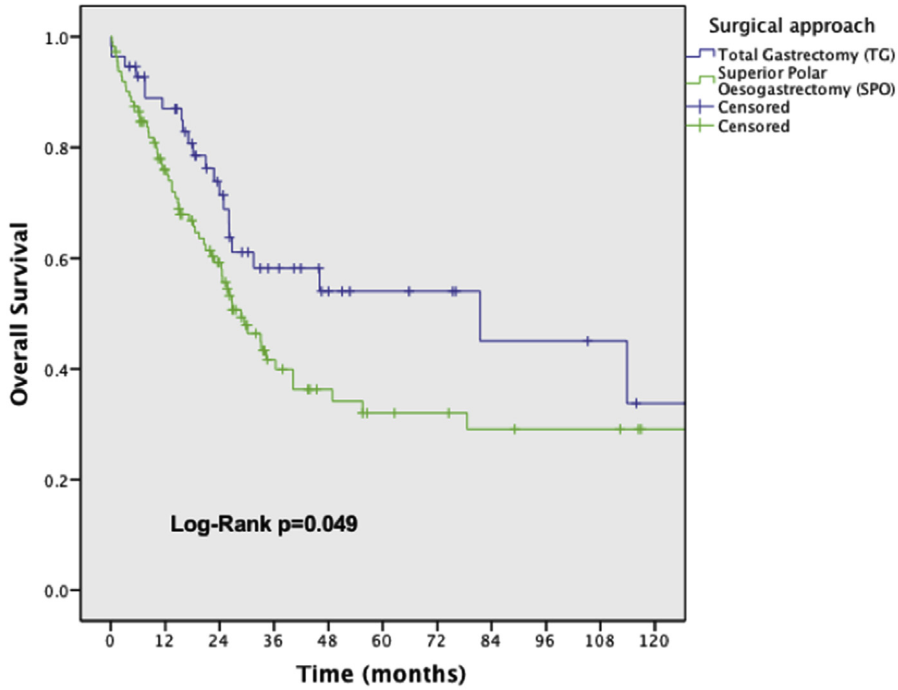
mediastinal lymphadenectomy that can harvest invaded lymph nodes present in 11% of type II AEG [18].

This lymphatic spread depends on the distance between the oesogastric junction (EGJ) and the proximal and distal tumor's edges respectively for mediastinal and abdominal lymph nodes. Kurokawa et al. [39] has indeed recently demonstrated that a distance between EGJ and the proximal edge of the tumor greater than 3 cm was the only independent prognostic factor for middle mediastinal metastatic lymph nodes for patients with AEG type II. In this subgroup of patients, a transthoracic approach may therefore provide a therapeutic benefit. Conversely, in patients with a distance from the EGJ to the distal edge of the tumor inferior to 3 cm, the incidence of metastatic lymph nodes in the greater curvature area or in the infra pyloric region was only 2.2% [30]. Thus, the contradictory results observed in the different study comparing TG and SPO for the treatment of AEG type II are probably related to variations of tumoral extension toward the esophagus or the stomach which are not mentioned in most retrospective studies as well as in ours [18,28,40,41].

In a recent retrospective study, AEG staged as Siewert type I before surgery were reclassified as AEG type II after surgery in more than half of patients [42]. These patients treated as AEG type I by SPO rather than as AEG type II by TG had poorer outcomes with significantly shorter recurrence-free survival. In multivariate analysis, surgical approach was the strongest independent predictor of recurrence-free survival, indicating a benefit for TG in patients with AEG type II. This conclusion is consistent with the results of our study as well as with the surgical approach chosen by the majority of Asian and South American surgeons from high-volume centers described in a recent international audit [43].

Moreover, the great number of lymph nodes retrieved in TG compared to SPO that was observed in our study could be explained by many factors. Firstly, patients who underwent SPO received more frequently preoperative radiochemotherapy, which was associated with a reduction in the number of lymph nodes retrieved, as observed in a study from the Dutch Upper Gastrointestinal Cancer Audit, as well as in a post-hoc analysis of a randomized controlled trial [44,45]. Thus, in patients who underwent SPO, a mean number of 13,26 lymph nodes were retrieved in preoperative radiochemotherapy subgroup compared to 21.48 lymph nodes retrieved in no preoperative radiochemotherapy subgroup ($p < 0.001$). Patients with no preoperative radiochemotherapy and SPO had comparable number of lymph nodes retrieved than patients with TG (21.48 vs. 21.5). Secondly, TG is anatomically frequently associated with a greater number of lymph nodes retrieved than SPO, according to the study published by Reeh et al. [42]. Nevertheless, it can not be ruled out that insufficient lymph node dissection in the SPO group may have contributed to lower survival in this group.

Because of its retrospective design, our study has some limitations. First, some confounding factors that led to prefer one surgical approach over another were not available in the database. Thus, the precise magnitude of the extension of tumors toward the esophagus or the stomach was not available. Similarly, the length of the abdominal esophagus and the presence of a hiatal hernia were not specified. These missing data, that can guide the choice of the surgical approach, make it impossible to achieve a propensity score based analysis in our study. However, due to its multicentric nature,



No at risk											
TG	56	45	29	18	11	9	8	5	5	4	2
SPO	112	75	50	24	17	13	12	10	9	9	6

Fig. 3. Overall survival curves for patients who underwent total gastrectomy (TG) or superior polar oesogastrectomy (SPO) with complete resection (R0 resection).

these confounding factors were potentially distributed similarly in both groups (TG and SPO), limiting these distribution biases. Indeed, some participating departments favor TG for the treatment of AEG type II while others prefer SPO to treat these patients. Other potential limitations of our study are the absence of systematic intraoperative frozen section that could increase the rate of incomplete resections (R1 resection) and the exclusion of patients with section invaded by tumor in whom a total esogastrectomy was performed. However patients with AEG type II treated by total esogastrectomy were excluded in order to exclude patients for whom the choice of surgical approach between TG and SPO was not possible.

True cardia carcinoma appears in this multicentric retrospective study to be better cured by total gastrectomy than by superior polar esogastrectomy, only when this resection appears likely to yield tumor-free resection margins. A randomized trial including patients with AEG type II whose complete tumor resection appears possible by these two surgical approaches, using standardized localization criteria based on the edges of the tumors rather on their epicenter is warranted.

Conflict of interest and source of funding

The authors declare that they have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.07.022.

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