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1 **Adenocarcinoma of the Oesophagogastric Junction Siewert II: an oesophageal cancer**
2 **better cured with total gastrectomy**

3
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41 **ABSTRACT**

42 **Introduction:** Type II AEG is now considered as oesophageal cancer in the seventh edition
43 of TNM classification but optimal surgical approach for these tumors remains debated. The
44 objective of the study is to assess and compare surgical and oncological outcomes of two
45 surgical approaches: superior polar oesogastrectomy (SPO) or total gastrectomy (TG) in
46 patients with type II adenocarcinoma of the oesophagogastric junction (AEG).

47 **Material and Methods:** 183 patients with type II AEG treated from 1997 to 2010 in 21 French
48 centers by SPO or TG were included in a multicenter retrospective study. The surgical and
49 oncological outcomes were compared between these two surgical approaches.

50 **Results:** A TG was performed in 64 (35%) patients whereas 119 (65%) patients were treated
51 by SPO with transthoracic approach in 100 of them (83.2%) and transhiatal approach with
52 cervicotomy in 19 (16.8%). Surgical outcomes were comparable between the two approaches
53 with a postoperative mortality rate of 4.9% and a severe operative morbidity rate within 30
54 days of 15.3%. Median survival in patients operated on by TG was of 46 months compared to
55 27 months in patients treated by SPO ($p=0.118$). At multivariate analysis, TG appears to be
56 an independent good prognostic factor compared to SPO ($HR=1.847$; $p=0.008$). However, TG
57 was also associated with a higher rate of incomplete resection, (12.5% vs 5.9%; $p=0.120$).

58 **Conclusion:** When TG allows obtaining tumor-free resection margins, this approach should
59 be preferred to SPO.

60

61 **Keys words:** Oesophago-gastric junction; true cardia adenocarcinoma; total gastrectomy;
62 superior polar oesogastrectomy; Siewert classification

63

64 **INTRODUCTION**

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

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

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

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

94 Trying to clarify this important issue, this large French retrospective multicentric study aimed
95 to compare surgical and oncological outcomes of the two main surgical strategies (SPO or
96 TG) in patients with type II AEG.
97

98 PATIENTS AND METHODS

99

100 Patients

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

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

112

113 Pretreatment work-up and perioperative treatments

114 In all centers, the preoperative assessment included complete medical history, physical
115 examination, upper gastro-intestinal endoscopy with biopsies and abdomino-pelvic and chest
116 computed tomographic scans. The diagnosis of an AEG type II was done endoscopically and
117 was confirmed on pathological examination. Patients whose endoscopic diagnosis of AEG
118 type II was not confirmed during surgery, demonstrating a type I or type III AEG, were
119 excluded from this study. According to Siewert's classification, the diagnosis of AEG type II
120 was based on distance separating the upper and lower borders of the tumor from the gastro-
121 esophageal junction defined as the proximal end of the gastric folds. Endoscopic ultrasound
122 and positon emission tomography (PET) were performed depending on local policies and in
123 accordance with French National Guidelines[23,24]. Since 2005, according to reported
124 prospective trials[3,4], a perioperative chemotherapy by cisplatin and fluorouracil associated
125 or not with epirubicin was recommended for AEG type II considered as gastric cancer **greater**
126 **than clinical T2N0 stage** . Conversely, many AEG type II were considered as oesophageal
127 cancers and were treated with preoperative chemoradiotherapy associating fluorouracil and

128 cisplatin with concomitant radiotherapy delivering 45 Gy in 25 fractions over 5 weeks, when
129 tumor was classified as stage 3 on pretreatment workup. Malnutrition was defined by a weight
130 loss exceeding 10% in the last 6 months.

131

132

133 **Surgical technique**

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

138

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

147

148 **Pathological analysis**

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

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

156 **Postoperative outcomes and follow-up**

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

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

168

169 **Statistical analysis**

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

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

184

185 **RESULTS**

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

191

192 **Preoperative data (Table 1).**

193 The clinical characteristics of the whole population and those of the two groups defined by the
194 used surgical technique are reported in Table 1. The two groups did not differ for their
195 demographic characteristics. Mean age at diagnosis was 62.0 +/- 11.3 years. Most patients
196 (89%) were men. The American Society of Anesthesiology (ASA) score was 1 or 2 in 83% of
197 patients and 17% of patients exhibited malnutrition at diagnosis. There was no significant
198 difference in the distribution of pretherapeutic clinical stages (pretherapeutic cTNM) between
199 the two surgical approaches.

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

206

207 **Surgical management and Postoperative outcomes (Table 1)**

208 Among the 183 AEG type II included in this study, 64 (35%) were treated by TG and 119
209 (65%) were treated by SPO with a transthoracic approach in 100 patients (83.2%), a
210 transhiatal approach combined with cervicotomy in 19 patients (16.8%). Nine patients (4.9%)
211 died in the first postoperative month and three in the next two months, accounting for an
212 operative mortality rate at 90 days of 6.6%. The mortality rate was comparable between TG
213 group (7.8%) and SPO group (5.9%; p=0.755). Postoperative complications in the 90 first
214 postoperative days, either surgical or medical, were reported in 102 patients (55.7%), with no

215 difference between patients treated by TG or SPO (59.4% vs 53.8%; $p=0.468$). In 30 patients
216 (16.4%), these complications were graded III or IV (severe complications), according to
217 Clavien Dindo classification, with no difference between patients treated by TG or SPO
218 (18.8% vs 15.1%; $p=0.528$). List of postoperative complications is detailed in supplemental
219 data (**Table 1 suppl.**). Interestingly, distribution of early complications was different between
220 the 2 surgical approaches ($p=0.001$). Thus, early respiratory complications were more
221 frequently observed in SPO group (21.8%) than in TG group (7.8%). On the contrary,
222 abdominal collection were more frequent in patients who underwent TG (12.5%) than in
223 patients undergoing SPO (0%)

224

225 **Histological data (Table 1)**

226 Tumors resected by SPO were significantly more frequently pT3-T4 than tumors resected by
227 TG (54% vs 36%, $p=0.021$), but the rate of incomplete resection was higher in TG group
228 (12.5%) than in SPO (5.9%), without reaching significance ($p=0.12$). As expected, upper
229 (oesophageal) margin was more frequently microscopically invaded after TG than SPO
230 (10.9% vs 4.2%) but without reaching significance ($p=0.115$).

231

232 Nodal metastases were observed in about 60% of patients in both TG and SPO groups, but
233 the median number of retrieved lymph nodes was higher in TG (21.5 [7 - 48]) than in SPO
234 (17.5 [4 - 47]; $p=0.016$). However the median number of retrieved lymph nodes was
235 comparable between patients who underwent SPO without neoadjuvant chemotherapy (20 [4-
236 47]) and patients who underwent TG (21.5 [7-48]; $p=0.331$)

237

238 **Prognostic factors of survival**

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

242 In univariate analysis (**Table 2**), 8 variables were associated with poor OS: preoperative
243 malnutrition ($p=0.017$), severe postoperative morbidity within the first postoperative month
244 ($p<0.001$), the nodal status (pN stage) ($p<0.001$), histological pTNM stage ($p=0.003$), vertical

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

251

252 During the follow-up, recurrence was observed in 72 patients (39.3%) including 21 patients
253 (32.8%) in the TG group and 51 patients (42.8%) in SPO group. Local recurrence was
254 observed in 3 patients (4.7%) who were operated on by TG and in 8 patients operated on by
255 SPO (6.7%). Distant metastasis were observed in 12 patients (18.7%) in TG group and 23
256 patients (19.3%) in SPO group. Both local and systemic recurrence was observed in 6
257 patients (9.4%) with TG and in 30 patients (26.3%) with SPO. The median length of disease-
258 free survival (DFS) was 22.5 months (95%CI: 17-28 months) with a 5-years disease-free
259 survival rate of 37%. In univariate analysis (Table 3), the 8 variables previously associated
260 with poorer OS, as well as pT stage were associated with a poorer DFS. A higher median
261 DFS was observed for patients treated by TG compared to SPO (24.0 ± 26.1 months vs. 20.0
262 ± 4.2 months; $p=0.201$) (Figure 2). In multivariate analysis, five factors were independently
263 associated with poor DFS, including male sex, postoperative severe morbidity within the first
264 month, nodal status (pN stage), incomplete resection and resection by SPO (Table 3).

265

266 Considering that incomplete tumor resection was an independent prognostic factor for OS
267 and DFS but could result from erroneous preoperative assessment and wrong choice of
268 surgical approach, an analysis was conducted in the 168 patients with complete tumorous
269 resection (R0 resection). In univariate analysis, median overall survival was better for patients
270 treated by TG (81.47 ± 35.9 months) than patients treated by SPO (28.70 ± 4.1 months;
271 $p=0.049$) (Figure 3). In the same way, disease-free survival was better for patients treated by
272 TG (74.90 ± 38.3 months) than patients treated by SPO (22.53 ± 4.7 months) without
273 reaching significance ($p=0.062$) (Supplemental Figure 1).

274

275 In multivariate analysis in this group of patients, SPO remained an independent predictor of
276 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;
277 p=0.017) (Supplemental tables 2 and 3).
278

279 **DISCUSSION**

280

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

283 This study included only patients with true cardia adenocarcinoma (AEG Siewert's type II). In
284 addition to the well-known prognostic factors of overall and disease-free survivals — such as
285 sex, age, malnutrition, preoperative treatment, postoperative morbidity, adjuvant treatment,
286 pT stage, pN stage, completeness of resection (R0 resection vs R1 resection) — the type of
287 resection (SPO or TG) was an independent prognostic factor for both overall (HR: 1.847;
288 95%CI: 1.172 - 2.908; p=0.008) and disease-free survivals (HR: 1.630; 95%CI: 1.062 - 2.501;
289 p=0.025). Thus, overall survival was better after TG with modified D2 lymphadenectomy than
290 after SPO with mediastinal/upper abdominal lymphadenectomy (3- and 5-years overall
291 survivals: 52.9% vs 39.6% and 49.1% vs 30.8% respectively; p=0.118) and this difference
292 became statistically significant when we considered other prognostic factors such as
293 complete resection, severe postoperative morbidity and pTNM stage.

294

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

307 Two main objectives dictate the choice between these two surgical approaches (TG or SPO).

308 The first one is to achieve a complete tumor resection with free resection margins (R0

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

325

326 The second main objective to be achieved during AEG type II surgery and dictating the
327 choice of the surgical approach, is to obtain an optimal lymphadenectomy in order to achieve
328 optimal tumor's staging and harvesting of all metastatic lymph nodes. The better OS and
329 DFS observed in TG group could result from the different lymphadenectomies in the two
330 surgical approaches. Thus, during TG with D2 lymphadenectomy, lymph nodes localized
331 along the greater curvature (lymph node station 4 according to Japanese Gastric Cancer
332 Association[38]) and those located in infra pyloric area (station 6) are systematically removed
333 while they are preserved by SPO. Siewert and al. showed that 16% of patients with AEG type
334 II had lymph node metastases along the greater curvature, and 6.5% had metastatic infra
335 pyloric lymph nodes[19]. Conversely, only SPO is able to provide middle and upper
336 mediastinal lymphadenectomy that can harvest invaded lymph nodes present in 11% of type
337 II AEG[18].

338 This lymphatic spread depends on the distance between the oesogastric junction (EGJ) and
339 the proximal and distal tumor's edges respectively for mediastinal and abdominal lymph
340 nodes. Kurokawa et al.[39] has indeed recently demonstrated that a distance between EGJ
341 and the proximal edge of the tumor greater than 3 cm was the only independent prognostic
342 factor for middle mediastinal metastatic lymph nodes for patients with AEG type II. In this
343 subgroup of patients, a transthoracic approach may therefore provide a therapeutic benefit.
344 Conversely, in patients with a distance from the EGJ to the distal edge of the tumor inferior to
345 3cm, the incidence of metastatic lymph nodes in the greater curvature area or in the infra
346 pyloric region was only 2.2% [30]. Thus, the contradictory results observed in the different
347 study comparing TG and SPO for the treatment of AEG type II are probably related to
348 variations of tumoral extension toward the esophagus or the stomach which are not
349 mentioned in most retrospective studies as well as in ours[18,28,40,41].

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

358 Moreover, the great number of lymph nodes retrieved in TG compared to SPO that was
359 observed in our study could be explained by many factors. Firstly, patients who underwent
360 SPO received more frequently preoperative radiochemotherapy, which was associated with a
361 reduction in the number of lymph nodes retrieved, as observed in a study from the Dutch
362 Upper Gastrointestinal Cancer Audit, as well as in a post-hoc analysis of a randomized
363 controlled trial[44,45]. Thus, in patients who underwent SPO, a mean number of 13,26 lymph
364 nodes were retrieved in preoperative radiochemotherapy subgroup compared to 21.48 lymph
365 nodes retrieved in no preoperative radiochemotherapy subgroup ($p<0.001$). Patients with no
366 preoperative radiochemotherapy and SPO had comparable number of lymph nodes retrieved
367 than patients with TG (21.48 vs. 21.5). Secondly, TG is anatomically frequently associated

368 with a greater number of lymph nodes retrieved than SPO, according to the study published
369 by Reeh et al[42]. Nevertheless, it can not be ruled out that insufficient lymph node dissection
370 in the SPO group may have contributed to lower survival in this group.

371

372

373

374 Because of its retrospective design, our study has some limitations. First, some confounding
375 factors that led to prefer one surgical approach over another were not available in the
376 database. Thus, the precise magnitude of the extension of tumors toward the esophagus or
377 the stomach was not available. Similarly, the length of the abdominal esophagus and the
378 presence of a hiatal hernia were not specified. These missing data, that can guide the choice
379 of the surgical approach, make it impossible to achieve a propensity score based analysis in
380 our study. However, due to its multicentric nature, these confounding factors were potentially
381 distributed similarly in both groups (TG and SPO), limiting these distribution biases. Indeed,
382 some participating departments favor TG for the treatment of AEG type II while others prefer
383 SPO to treat these patients. Other potential limitations of our study are the absence of
384 systematic intraoperative frozen section that could increase the rate of incomplete resections
385 (R1 resection) and the exclusion of patients with section invaded by tumor in whom a total
386 esogastrectomy was performed. However patients with AEG type II treated by total
387 esogastrectomy were excluded in order to exclude patients for whom the choice of surgical
388 approach between TG and SPO was not possible.

389

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

396

397

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582

583 **FIGURE LEGENDS**

584 **Figure 1** : Overall survival curves for patients who underwent total gastrectomy (TG) or
585 superior polar oesogastrectomy (SPO)

586

587 **Figure 2**: Disease-free survival curves for patients who underwent total gastrectomy (TG) or
588 superior polar oesogastrectomy (SPO)

589

590 **Figure 3** : Overall survival curves for patients who underwent total gastrectomy (TG) or
591 superior polar oesogastrectomy (SPO) with complete resection (R0 resection)

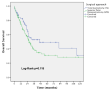
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593 **Supplemental figure 1**: Disease-free survival curves for patients who underwent total
594 gastrectomy (TG) or superior polar oesogastrectomy (SPO) with complete resection (R0
595 resection)

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10 of 100

100 200 300 400 500 600 700 800 900 1000

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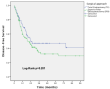
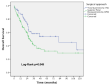


Fig. 10. 100

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By group

Time	0	25	50	75	100	125	150	175	200	225	250
Survival	100	85	70	55	45	40	38	35	35	35	35

Table1 : 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

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			
Adjuvant 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 analysis but removed during the stepwise process.

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			
Adjuvant 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 analysis but removed during the stepwise process