Total gastrectomy versus upper pole gastrectomy for the surgical therapy of Siewert type II adenocarcinoma of the esophagus: pathology may drive the choice

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Background: Whether to adopt total or upper pole gastrectomy for the. surgical therapy of Siewert type II adenocarcinoma is controversial. We investigated patterns of greater curvature nodal metastases and cancer ascending progression into the esophagus, which are key points for the choice.

Methods: A total of 154 patients who underwent primary trans-thoracic esophageal resection, laparotomic total gastrectomy, thoracic-abdominal lymphadenectomy were categorized according to the Lauren's classification and the presence/absence of intestinal metaplasia in the esophagus and stomach. Gastric greater curvature, pyloric metastases and the esophageal resection margin status were linked with pathology categories, recurrence, cancer-specific survival.

Results: Pathological stages were IA–IIA in 11%, IIB in 12.4%, IIIA–IV in 76.6% of patients. 59% were intestinal-type, 41% were diffuse-type, 1.3% were Barrett's-type, 65% were cardiopyloric-type, and 33.7% were gastric-type adenocarcinomas. Greater gastric curvature nodal metastases were detected in 22% of stage IIIa–IV, 47% of intestinal-type and in 53% diffuse-type patients. The number of metastatic nodes at station 4 was higher in cardiopyloric-like than in gastric-like adenocarcinoma ($P<0.0001$). The 5-year cancer-specific survival of the 154 cases was 40.5%, 59.4% for intestinal-type and 0% for diffuse-type adenocarcinoma. Five-year cancer-specific survival in the absence/presence of greater gastric curvature metastases were 48.7% and 14.9%, respectively. For the intestinal type, they were 67.4% and 27.9%. Histological subtype was an independent prognostic factor.

Conclusions: Primary trans-thoracic esophageal resection + total gastrectomy + extended thoracic and abdominal lymphadenectomy is justified for intestinal type but not for diffuse type Siewert type II adenocarcinoma.

Trial Registration: ClinicalTrials.gov ID: NCT03416101.

Keywords: Esophagus; global surgery; oncology

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Introduction

The surgical treatment for Siewert type II adenocarcinoma of the esophagus (1) is still debated. Siewert, with others, indicated total gastrectomy due to the high frequency of perigastric and greater curvature nodal metastases (2-4).

On the basis of new data on the frequency of metastases at the gastric greater curvature (5-12), quite lower than those previously reported (2-4) (Table S1), it was concluded that the resection of the lower esophagus and the upper pole of the stomach could be as effective as total gastrectomy with regard to survival (7,10,11), eventually in association with neoadjuvant therapy (8,9,13). Recent papers support again the choice of total gastrectomy (14,15). The controversy may be produced by the Siewert's classification, which is not precise enough to discriminate between type II and III cases (14-17), by the different modalities of lymphadenectomy performed (18) and of the pathological specimen work-up (19-22).

In 2007 to overcome biases of the Siewert classification, we adopted a new pathologic classification based on the presence/absence of intestinal metaplasia in the esophagus and/or stomach that discriminates cases in Barrett's, cardio-pyloric and gastric types (23). Since, we started a prospective study protocol aimed to investigate biology and results of surgical therapy for esophageal adenocarcinoma. For the primary treatment of Siewert type II, we adopted the total gastrectomy associated with the esophageal resection at the azygos vein level through right thoracotomy, with an extended thoracic and abdominal (D2) lymphadenectomy; we had previously demonstrated that this technique provided a radical resection especially suited for poorly differentiated carcinoma (24). The intraoperative nodes retrieval and mapping, the pathology work-up of the surgical specimen, were aimed to investigate the oral and aboral intra mural cancer diffusion and modalities of nodal metastases spreading (24). We completed the pathology work-up with the adoption of Lauren's classification (25), which is relevant from a prognostic, epidemiological, and pathogenic perspective for esophageal adenocarcinoma (26-30).

We indicated primary surgery for tumours up to T4 (diaphragm), N1 (peritumoural stations), with the exclusion of bulky metastases. By the time we maintained this line: at periodic analysis our results (21,22,24) were similar to those reported by others (31,32) and were competitive with survivals obtained with neoadjuvant therapy followed by surgical resection (33,34).

In the present study we considered cases classified type II according to Siewert's, who were primarily operated upon between 2007 and 2017. We investigated the frequency of chest/abdominal nodal metastases with a particular focus on gastric greater curvature stations, the recurrence patterns, the submucosal orad cancer diffusion into the esophagus, 5-year survival according to these data and the Lauren's classification. We present the following article in accordance with the STROBE reporting checklist (available at: http://dx.doi.org/10.21037/aoe-2020-13).

Methods

Preoperative diagnosis and clinical staging

The preoperative work-up included upper gastrointestinal tract endoscopy with multiple tumours' and surrounding mucosa biopsies, barium swallow, thoracic and abdominal CT, PET or CT-PET. Tumours were staged according to the AJCC/UICC TNM 8th edition (35).

Surgical technique

The surgical technique we adopted (21,22,24) is extensively described in Supplementary 1 and Figure S1. Briefly, a midline or transverse laparotomy and a muscle-sparing lateral-anterior right thoracotomy were performed. The esophagus was resected at the level of the azygos vein arch, and a frozen section of the resection margin was routinely performed to achieve a proximal clean resection margin (24). The surgical specimen was comprehensive of distal esophagus, stomach and omentum. The digestive tract continuity was established with Roux-en-Y esophagojejunostomy.

Lymphadenectomy was extended to the thoracic stations R 2–4, 7–8–9, numbered according to Mountain's classification (36) (Supplementary 2 and Figure S2), to the abdominal stations 1–12, numbered according to the Japanese Research Society for Gastric Cancer (JRSGC) 1998 classification (37) (Supplementary 2 and Figure S2).

Nodes were removed en bloc with the adjacent fat/connective tissue to achieve total lymphadenectomy (22). The surgical team labelled each lymph node when it was removed from the peripheral stations; lymph node fragments were excluded to avoid N over-count.

Mortality at 90 days and morbidity were extracted from the database.

Pathology

The pathologic work-up of the surgical specimen (21,22,24) is illustrated in detail in Supplementary 3 and Figure S3. Based on the presence (+) or absence (−) of Barrett's intestinal metaplasia (BIM) and intestinal metaplasia in the stomach (GIM), cases were categorized as Barrett's-like type (BIM+/GIM−), cardiopyloric-like type (BIM−/GIM−), or gastric-like type (BIM−/GIM+) (21,23).

Adenocarcinoma was classified according to Lauren as intestinal, mixed, or diffuse type (25). Lymphovascular invasion was defined as absent or present (35), perineural diffusion and the ratio of the number of metastatic lymph nodes to the total number of nodes yielded (LNR) (22) were determined. Tumour grade (G) was grouped as 1+2 and 3+4.

Follow-up and survival

After surgery, patients were followed up twice per year (clinical assessment, serum oncologic markers, at each follow-up, upper gastrointestinal tract endoscopy, chest/abdominal CT, PET, or CT-PET, once per year). Site(s), relapse modalities, and date and cause of death were registered. Cancer-specific survival (in months), calculated from the date of surgery to the date of death due to documented recurrent disease, was adopted instead of overall survival, as it may better indicate the course of a specific disease and the effects of therapy (38).

Adjuvant therapy

In the absence of general contraindications, adjuvant chemotherapy and radiation therapy were administered according to guidelines (39,40) in cases of pN+, R1 surgery, lympho-vascular invasion or after documented recurrence.

Ethics committee approval

The local institutional review board of the IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (CEAV/IRST) approved the use of the database maintained by the Division of Thoracic Surgery for research purposes (No L3P1223). The study was conducted in accordance with the Declaration of Helsinki (as revised in Edinburgh 2000).

Statistical analysis

Data are represented as median and interquartile range (IQR) for continuous variables and as n (%) for categorical variables. The χ^2 test or Fisher's test (expected number less than 5) and the Mann-Whitney test were used to analyse categorical and continuous variables. Cancer-specific survival analyses were performed using the Kaplan-Meier method and the log-rank test. Univariable and multivariable (forward stepwise conditional method) Cox regression analyses were performed to estimate the effects of clinical and pathological parameters on cancer-specific survival. Multivariable logistic regression analysis was performed to identify the predictors of lymph node metastases in the greater gastric curvature. P values <0.05 were considered significant. Data were analysed using SPSS (version 15.0) (SPSS Inc., Chicago, IL, USA).

Results

All 154 Siewert type II cases operated upon primarily in the considered period were suitable for the study. Six patients died within 90 postoperative days (6/154, 3.8%) for mediastinitis due to anastomotic fistula in 5 patients and peritonitis after dehiscence of the Roux jejunal anastomosis in 1 patient. Major morbidity included intrathoracic anastomotic leakage in 3 patients, necrosis of the jejunal loop in 2 patients, and torsion of the jejunal loop in 1 patient (6/154 patients, 3.8%). The R0 resection rate was 97.4% (150/154). Four cases showed submucosal microscopic involvement of the esophageal resection margin (R1, 2.6%). Two were of the diffuse type and two of the signet ring cells type; two patients were younger than 40 years. Sex, age, histology, grading and pathologic (p) staging data are displayed in *Table 1*.

A total of 4,825 nodes were yielded (median 30.5, interquartile range per patient 22–38; minimum, 8 nodes; maximum, 61 nodes).

The clinical N staging parameter was under-estimated in 47% of cases with respect to pathological N stage, which was 2 or 3 instead of 0 or 1. Overall, 91 (59%) were adenocarcinomas of the intestinal type, 10 were mixed type (6.5%) and 53 (34.5%) were diffuse type. Mixed type cases were included in the diffuse type (diffuse + mixed 41%) for analysis. Statistically significant differences between the intestinal and diffuse histological subtypes pNodes (P<0.0001), p staging (P<0.0001) and LNR (P<0.0001) were calculated. Of 154 cases, 120 (78%) were negative for metastases at the greater curvature/pyloric lymphatic nodes, while 34 cases (22%) were positive. Of 34 cases, 24 had metastases at station 4sa (15.6%), 9 at station 4sb (5.8%), and 1 at station 4d (0.6 %). Nineteen of 34 patients were positive also at station 6 (12.3%). In *Table 2*, cases that were negative

Table 1 Distribution of demographic parameters and pTNM staging (AJCC 8th edition) in 154 Siewert type II adenocarcinomas according to Lauren's histological classification

Parameters	Total	Intestinal type	Diffuse type	P
Total	154	91 (59%)	63 (41%)	
Gender				0.303
Male	124 (80.5%)	76 (83.5%)	48 (76.2%)	
Female	30 (19.5%)	15 (16.5%)	15 (23.8%)	
Age median (IQR)	65.5 (58–71)	66 (59–71)	65 (57–69)	0.143
Grade				<0.0001
1–2	65 (42.2%)	65 (71.4%)	–	
3–4	89 (57.8%)	26 (28.6%)	63 (100%)	
p tumour				0.110
1	5 (3.2%)	5 (5.5%)	–	
2	21 (13.6%)	15 (16.5%)	6 (9.5%)	
3	109 (70.8%)	59 (64.8%)	50 (79.4%)	
4	19 (12.4%)	12 (13.2%)	7 (11.1%)	
P nodes				
0	43 (27.9%)	36 (39.6%)	7 (11.1%)	
1	38 (24.7%)	23 (25.3%)	15 (23.8%)	<0.0001
2	27 (17.5%)	18 (19.8%)	9 (14.3%)	
3	46 (29.9%)	14 (15.3%)	32 (50.8%)	
p metastases				
0	150 (97.4%)	88 (96.7%)	62 (98.4%)	0.645
1	4 (2.6%)	3 (3.3%)	1 (1.6%)	
p stage				<0.0001
1a	4 (2.6%)	4 (4.4%)	–	
1b	–	–	–	
1c	13 (8.4%)	10 (11%)	3 (4.8%)	
2a	–	–	–	
2b	19 (12.3%)	15 (16.4%)	4 (6.3%)	
3a	7 (4.6%)	5 (5.5%)	2 (3.2%)	
3b	59 (38.3%)	36 (39.6%)	23 (36.5%)	
3c	–	–	–	
4a	52 (33.8%)	21 (23.1%)	31 (49.2%)	
Lymph node ratio median (IQR)	0.10 (0.00–1)	0.06 (0.00–0.14)	0.28 (0.06–0.42)	<0.0001

Table 2 Distribution of Group 1 patients (120 cases) and Group 2 patients (34 cases) that were positive for gastric curvature and pyloric lymph nodes metastases according to histological subtype (Lauren's classification). The distribution of lymph node metastases in the thoracic and abdominal lymphatic stations is shown at the bottom of the table

Parameters	Group 1 (n=120)			Group 2 (n=34)		
	Intestinal type histology	Diffuse type histology	P	Intestinal type histology	Diffuse type histology	P
Total	75 (62.5%)	45 (37.5%)		16 (47%)	18 (53%)	
Barrett's-like type (BIM+/GIM–)	2 (2.6%)	–	0.189	–	–	1.00
Cardiopyloric-like type (BIM–/GIM–)	44 (58.7%)	33 (73.3%)		11 (68.8%)	12 (66.7%)	
Gastric-like type (BIM–/GIM+)	29 (38.7%)	12 (26.7%)		5 (31.2%)	6 (33.3%)	
Grade						
1–2	56 (74.7%)	–	<0.0001	9 (56.3%)	–	<0.0001
3–4	19 (25.3%)	45 (100%)		7 (43.7%)	18 (100%)	
pTumour						
1	4 (5.3%)	–	.094	1 (6.2%)	–	0.490
2	15 (20%)	6 (13.3%)		–	–	
3	47 (62.7%)	37 (82.3%)		12 (75%)	13 (72.2%)	
4	9 (12%)	2 (4.4%)		3 (18.8%)	5 (27.8%)	
pNodes						
0	36 (48%)	7 (15.6%)	0.001	–	–	0.001
1	16 (21.3%)	14 (31.1%)		7 (43.8%)	1 (5.6%)	
2	14 (18.7%)	9 (20%)		4 (25%)	–	
3	9 (12%)	15 (33.3%)		5 (31.2%)	17 (94.4%)	
pStage			0.012			0.001
1a	4 (5.4%)	–		–	–	
1b	–	–		–	–	
1c	10 (13.3%)	3 (6.7%)		–	–	
2a	–	–		–	–	
2b	15 (20%)	4 (8.8%)				
3a	3 (4%)	2 (4.5%)		2 (12.5%)	–	
3b	26 (34.6%)	20 (44.5%)		10 (62.5%)	3 (16.6%)	
3c	–	–		–	–	
4a	17 (22.7%)	16 (35.5%)		4 (25%)	15 (83.4%)	
Lymph node ratio median (IQR)	0.04 (0-0.11)	0.12 (0.06–0.43)	<0.0001	0.20 (0.10–0.33)	0.33 (0.29–0.39)	0.060
Lymphovascular invasion			<0.0001			0.323
Absent	38 (50.7%)	2 (4.4%)		3 (18.8%)	1 (5.6%)	
Present	37 (49.3%)	43 (95.6%)		13 (81.2%)	17 (94.4%)	

Table 2 (*continued*)

Table 2 (*continued*)

Parameters	Group 1 (n=120)			Group 2 (n=34)		
	Intestinal type histology	Diffuse type histology	P	Intestinal type histology	Diffuse type histology	P
Perineural invasion			<0.0001			0.323
Absent	36 (48%)	4 (8.9%)		3 (18.8%)	1 (5.6%)	
Present	39 (52%)	41 (91.1%)		13 (81.2%)	17 (94.4%)	
Lymph node metastases stations 2–4 R	5 (6.6%)	–		–	–	
Lymph node metastases station 7	4 (5.3%)	2 (4.4%)		–	–	
Lymph node metastases stations 8–9	21 (28 %)	16 (35.5%)		1 (6.2%)	2 (11.1%)	
Lymph node metastases celiac trunk	2 (2.6%)	2 (4.4%)		-	1 (6.2%)	
Lymph node metastases hepatic artery	1 (1.3%)	2 (4.4%)		1 (6.2%)	2 (11.1%)	
Lymph node metastases lesser curvature	26 (34.6%)*	22 (48.8%)°		16 (100%)*	18 (100%)°	
Lymph node metastases greater curvature	–	–		16 (100%)	18(100%)	
Lymph node metastases splenic artery	1 (1.3%)	–		–	1 (6.2%)	
Lymph node metastases pancreatic and pyloric	–	–		3 (18.8%)	16 (88.8%)	

*P<0.0001 lymph node metastases at the lesser curvature in intestinal type Group 1 *vs.* Group 2. °P<0.0001 lymph node metastases at the lesser curvature in diffuse type Group 1 *vs.* Group 2.

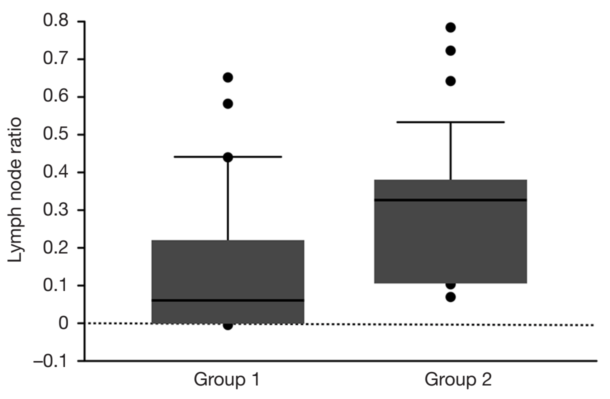

Figure 1 Box-plot representation of the values of the lymph node ratios (the ratio of the number of metastatic lymph nodes to the total number of nodes yielded) in Group 1 (median .06; IQR: 0–0.22) and Group 2 (median 0.30; IQR: 0.10–0.38) patients (P<0.0001).

(group 1) and positive (group 2) for greater gastric curvature and pyloric lymph node metastases are distributed according to histological intestinal/diffuse subtype, grading (G), staging parameters, LNR, lymph-vascular invasion, perineural invasion, the percentage of metastases at the thoracic and abdominal lymphatic stations and the categorization of cases according to the presence/absence of BIM and GIM.

Statistically significant differences were found between groups 1 and 2 for grading (P=0.048), pT (P=0.015), pN (P<0.0001), p staging (P<0.0001), and LNR (P<0.0001) (*Table 2*). The median LNR (*Figure 1*) was higher in group 2 because both the number of positive lymph nodes (numerator) and the number of yielded lymph nodes (denominator) were greater than in group 1 (P<0.0001 and P=0.001, respectively). Logistic regression analysis identified the LNR as the only predictor of lymph node metastases in the greater curvature of the stomach (P=0.003; OR =1.045, 95% CI: 1.016–1.078). Within both groups, statistically significant differences between the intestinal and diffuse histological subtypes were found for pN, p staging, and LNR (*Table 2*). Siewert type II category was cardiopyloric-type in 100/154, 65% (BIM–/GIM–); gastric-type in 52/154, 33.7% (BIM–/GIM+); and Barrett's-type in 2/154, 1.3% (BIM+/GIM–). Statistically significant differences with regards to age between gastric-like (median 67.5, IQR: 60.5–72.2 years) and cardiopyloric-like (median 63, IQR: 57.2–69 years) types were found (P=0.023). No significant differences between two types with regards to sex, histology (intestinal and diffuse type), grading, pT, pN, pM, p staging, and LNR were detected. In *Table 3*, cases

Table 3 Gastric greater curvature lymph nodes metastases (station 4 sa, sb, d, see text)

Lauren's classification	Case series (No. Pts)	BIM-/GIM-cardiopyloric pattern						BIM-/GIM+ gastric pattern						BIM+/GIM-Barrett's pattern			
		No. Pts	Pts+	%	# NH	#NH+	%	No Pts	Pts+	%	# NH	#NH+	%	No Pts	#NH	# NH+	%
Intestinal	91	55	16	29.1	240**	35°°	14.5	34	5	12.5	221**	8°°	3.6	2	17	–	–
Diffuse	63	45	18	40	181***	51°°°§§§	28.1	18	6	33.3	129***	9°°°§§§	6.9	–	–	–	–
Total	154	100	24	24	421*	86°§	20.4	52	11	21.1	350*	17°§	4.8	2	17	–	–

The case series (154 patients) is distributed according to the presence or absence of Barrett's (BIM) and gastric (GIM) intestinal metaplasia (see text) and histological subtype (Lauren's classification). For each sub-group, the number of patients, the percentage of patients positive for metastases, the number of lymph nodes harvested and the number of lymph nodes positive for metastases at station 4 are reported. No Pts, Number of patients; Pts +, Number of patients with lymph nodes positive for metastases; # NH, Number of lymph nodes harvested; # NH+, Number of lymph nodes positive for metastases. Number of lymph nodes harvested: *, gastric-like (median 6, 4-8 IQR) versus cardiopyloric-like types (median 4, IQR 0–6) P<0.0001; **, intestinal subtype: gastric-like (median 6, IQR 4-8) versus cardiopyloric-like types (median 3, IQR 0–7) P=0.002; ***, diffuse subtype: gastric-like (median 7, IQR 5.7–8.5) versus cardiopyloric-like types (median 4, IQR 0–5.5) P=0.001. Number lymph nodes positive for metastasis at the gastric greater curvature and pyloric stations (# 4 sa, sb, d, # 6). §, gastric-like (median 2, IQR 1-2) versus cardiopyloric-like type (median 3, IQR 3-4) P<0.0001; intestinal subtype: gastric-like (median 2, IQR 1.2–2.7) versus cardiopyloric-like type (median 3, IQR 2–4) P=0.066; §§§, diffuse subtype: gastric-like (median 1.5, IQR 1–2) versus cardiopyloric-like type (median 3.5, IQR 3–5.5) P=0.001. Frequency of lymph nodes positive for metastasis at the gastric greater curvature station (nominal distribution: positive/negative) (# 4 sa, sb, d): °, gastric-like versus cardiopyloric-like type P<0.0001; °°, intestinal subtype: gastric-like versus cardiopyloric-like type P<0.0001; °°°, diffuse subtype: gastric-like versus cardiopyloric-like type P<0.0001.

are distributed according to BIM/GIM and the Lauren's classification classes. The number of cases for each sub-group, with and without gastric greater curvature and pyloric nodal metastases, the number of lymph nodes harvested and the number of lymph nodes positive for metastases at the greater curvature stations are reported.

Of 148 patients who survived surgery, cancer recurred in 87 (58.7%) [27/88 (30.6%) intestinal type; 60/60 (100%) diffuse type]. Recurrence occurred at one site in 67 patients (liver, 21; lumbar-aortic nodes, 14; anastomotic level, 10; mediastinum, 10; lung, 6; brain, 5; cervical nodes, 1) and at multiple sites in 9 patients (liver and lumbar-aortic nodes, 4; bones and peritoneal area, 2; bones and anastomotic level, 2, anastomotic level and lumbar-aortic nodes, 1); peritoneal or pleura carcinosis was observed in 11 patients. The sites and modalities of recurrence were equal between the histological subtypes. Kaplan-Meier cancer-specific survival curves for the whole series and according to histology are shown in *Figure 2* (5-year survival for all cases: 40.5%; for intestinal and diffuse type cases: 59.4% and 0%, respectively; P<0.0001). Univariable Cox regression analysis showed that G (P<0.0001), pT (P=0.005), pN (P<0.0001), p staging (P<0.0001), lymphovascular invasion (P<0.0001), perineural diffusion (P<0.0001), Lauren's histology (P<0.0001), and LNR (P=0.001) significantly correlated with cancer-specific survival. Multivariable Cox regression analysis identified Lauren's histology (P<0.0001; HR 2.9, 95% CI: 1.6–5.4) and lymphovascular invasion (P=0.028; HR 2.7, 95% CI: 1.1–6.6) as independent prognostic factors that significantly influenced cancer-specific survival.

Figure 3 shows cancer-specific survival curves for the intestinal and diffuse histological types in patients without (Group 1) and with (Group 2) greater gastric curvature/pyloric metastases (intestinal type Group 1 *vs.* Group 2, P=0.038; diffuse type Group 1 *vs.* Group 2, P=0.158). Patients without greater gastric curvature/pyloric metastases had significantly longer cancer-specific survival regardless of histological subtype.

Discussion

In the past, it was generally presumed that station 4 metastases were more frequent in Siewert type III than in type II (1,2,10,11); station 4 high metastases rates were related to the higher percentage of cases of type III erroneously classified as type II (2,41,42).

In this series, in cardiopyloric-like type cases, metastases at the greater curvature region were detected in 20.4% of lymph nodes harvested, while in the gastric-like type, they occurred in 4.8% (P<0.0001); according to Lauren (25), cases were 59% intestinal type and 41% diffuse + mixed type. Histology, pTNM, and LNR parameters showed that

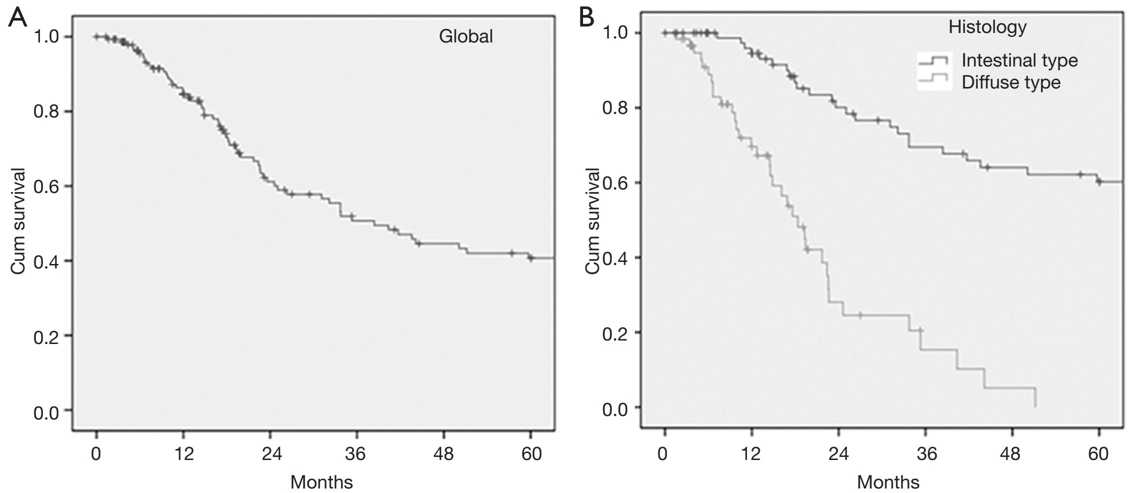

Figure 2 Kaplan-Meier cancer-specific survival curves for the whole series (A) and for the patients with the intestinal and diffuse histological types (P<0.0001) (B).

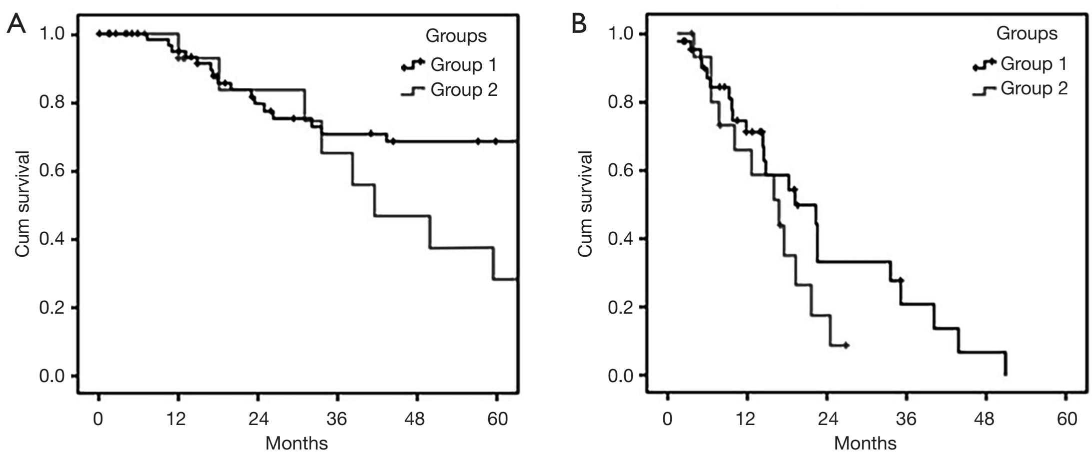

Figure 3 Patients positive (Group 1) and negative (Group 2) for greater gastric curvature metastases. (A) Kaplan-Meier cancer-specific survival curves for patients with the intestinal histological type in Group 1 and Group 2 (P=0.038). (B) Kaplan-Meier cancer-specific survival curves for patients with the diffuse histological type in Group 1 and Group 2 (P=0.158).

the diffuse type is clearly more aggressive than the intestinal type. Lauren's histological subtype was an independent prognostic factor.

Greater curvature and pyloric lymph node metastases were detected in 34 of 154 cases (22%), in stage IIIa–IV only, 47% in intestinal-type and 53% in diffuse-type. Four of 154 cases (2.59%) had positive esophageal resection margins at the azygos vein level. Two cases were of the diffuse type, and 2 were of the signet ring cell type (a 37-year-old man "*a posteriori*" resulted to have a CDH1 hereditary disease).

In 154 cases, the 5-year cancer-specific survival was 40.5%, with 59.4% for intestinal type and 0% for diffuse type. According to the absence/presence of gastric greater curvature metastases, the 5-year cancer-specific survival rates were 48.7% *vs.* 14.9%, respectively; for intestinal type, they were 67.4% *vs.* 27.9%, and for diffuse type, it was 0% independently from the nodal status.

For "esophageal adenocarcinoma", pathology may: (I) discriminate cases originated from Barrett's, cardio-pyloric and gastric mucosa, which have different patterns of nodal metastases and aggressiveness (21,22); (II) offer interesting biological/prognostic indications.

With total gastrectomy, D2 abdominal lymphadenectomy, transthoracic resection of the esophagus and of mediastinal nodal stations, we achieved 5-year cancer specific survival in 59.4% for intestinal type adenocarcinomas, of whom 64.8% were 3a–4 stage. With the same operation, none of the diffuse type cases survived over 3 years.

Greater curvature lymph nodes metastases were present in p stages III and IV only, mostly close to short gastric vessels (station 4a): these metastases possibly occurred in aggressive tumours (cardiopyloric and diffuse types), or in intestinal type cases that were diagnosed late. These data suggest that the resection of gastric greater curvature nodal stations is effective in cases of intestinal type adenocarcinoma, but not for the diffuse type.

For diffuse type adenocarcinoma, which includes signet ring cell carcinoma, in our opinion neoadjuvant therapy should be mandatory, eventually with new drug combinations (43). The same concept, to trim the extension of the surgical resection according to the aggressiveness of cancer, is probably valid for sizing the esophageal resection.

In case of intestinal type adenocarcinoma, it is not necessary to resect the esophagus at the azygos vein level; the higher the level of the esophageal-jejunal anastomosis, the higher the risk of jejunal loop ischemia-dependent complications, as demonstrated by the mortality-morbidity data displayed in this series.

In conclusion, the present study indicates that total gastrectomy associated with extended abdominal and thoracic station lymphadenectomy, with resection of the esophagus 5 centimetres above the tumour's macroscopic upper margin (44,45), may be the right choice for intestinal type adenocarcinoma as an alternative to neoadjuvant therapy followed by the Ivor Lewis operation.

This proposal needs to be verified and confirmed by retrospective pathology analyses of data collected with cooperative studies comparing the efficacies of different surgery/chemo-radiotherapy sequences (15,39) and with new research protocols. The treatment's modalities for diffuse type adenocarcinoma are also worth extensive investigation.

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Supplementary 1 Surgical technique

Total gastrectomy with omentectomy, partial esophageal resection and radical lymphadenectomy were performed. The surgery was performed through midline or transverse laparotomy and lateral-anterior right thoracotomy at the fifth intercostal space. The esophagus was resected at the arch level of the azygos vein en bloc with the entire stomach and omentum. Digestive tract continuity was established with Roux-en-Y esophagojejunostomy. In the current study, cases were included only where the concordance between Siewert's definition and the tumour's position within the E-G junction was confirmed by measurements performed on the fresh surgical specimen after the stomach was opened along the greater curvature.

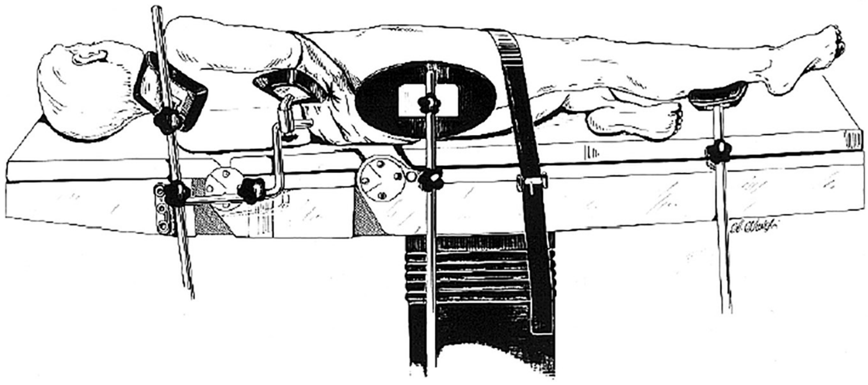
We propose a modification of the Nanson's patient position to optimize sequential or simultaneous left cervicotomy, laparotomy, and eventual right thoracotomy with one or two surgical teams. This technique permits better control of the operative field for each phase of the procedure with coordinated operating of two surgical teams on the neck, abdomen, and chest.

The patient is positioned on the bed with a 30-degree tilt of the body on the left side. The legs are positioned as for a right thoracotomic procedure. The right hand and forearm are gloved with a soft padding and the hand is tucked under the right loin. All fingers must be well extended. The trunk is kept in position by a right buttock ovalor rubber padded support and by a square swiveling rubber padded body support placed at the level of the right scapula. The right elbow is rested on a square swiveling rubber padded arm support to avoid tension on the right shoulder joint and on the brachial plexus. On the left side the body is framed by a long tubular rubber padded body support placed along the chest and abdomen. Recently the multiple positioning-induced pressure points have been protected by using viscoelastic polymer products made of Akton (Action Products, Inc, Hagerstown, MD) to protect the position-induced pressure points. Once completed, the position is tested by rotating the operating table on each side . We use a surgical table that permits a 25-degree rotation on each side and maintains stability when the patient is in the horizontal supine position in which the entire body weight is completely off center with respect to the base of the bed. Complete distant anesthesiologic monitoring must be provided before draping because during the operation there is limited access to the patient. Abdominal exposure, after a xipho-umbilical laparotomy, is obtained either by using

Table S1 Frequency of greater curvature lymph node metastases reported in the literature

Author and year	Number of patients	Greater curvature lymph nodal metastases (%)			
		Total	4sa	4sb	4sd
Akiyama, 1995, (4)	179	18.9	–	–	–
Wang, 1993, (3)	42	26.1	31.8*	–	18.2*
Rüdiger Siewert, 2000, (2)	186	16.1	–	–	–
Feith, 2006, (46)	485	14	–	–	–
Fang, 2009, (5)	51	9.8	3.9	3.9	2
Leers, 2009, (47)	61	2	–	–	–
Yamashita, 2011, (9)	225	5.3	4	1.3	0
Hasegawa, 2013, (10)	95	6.3	1.1	2.3	3.5
Fujitani, 2013, (11)	86	10.4	7	3.5	0
Goto, 2013, (7)	42	7.1	2.4	4.8	0
Matsuda, 2014, (12)	55	3.6	3.6	–	–
Mine, 2015, (8)	288	5.2	–	–	–
Fukuchi, 2015, (6)	52	5.7	33.3**	13.3**	26.6**

*, frequency of lymph node metastasis expressed as the percentage of the number of patients with nodal involvement (22 patients). **, frequency of lymph node metastasis expressed as the percentage of the number of lymph nodes involved at stations #. 4–6 in 5 patients.



Figue S1 Right-side body, arm, and buttock supports. Reprinted from (48) with permission from Elsevier [or Applicable Society Copyright Owner].

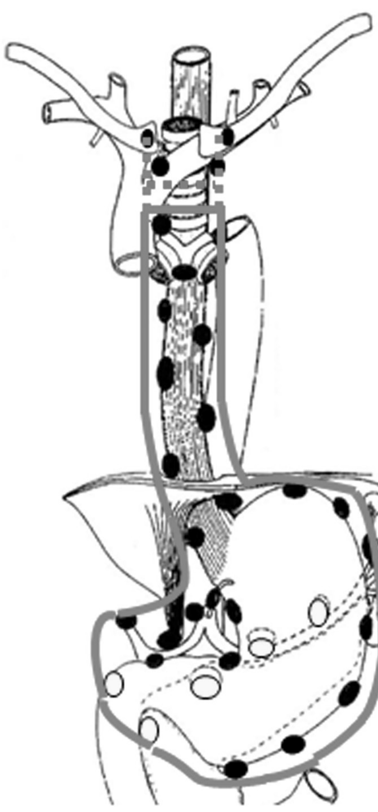


Figure S2 Resection and lymphadenectomy levels for patients receiving transabdominal total gastrectomy and right transthoracic esophagectomy at the azygos vein. The black line marks the en block resection comprehensive of thoracic and abdominal nodal stations. The black dotted line refers to station n° 2 left and right lymphadenectomy. Reprinted from (21) with permission from Elsevier (or Applicable Society Copyright Owner).

two upper hand retractor blades anchored to a bar with a parallelipid section, which is sustained parallel to the body by a custom bent rod locked, on the right side, to the rails of the table, or by using a Kent retractor system. Either of these systems is functional when the bed is in the right-rotated position to get the patient into the horizontal supine position.

A two-team operation may be carried out with one team working on the abdomen and one on the neck. The thoracotomic phase of the dissection is performed by rotating the bed to the left until the right chest up position is obtained.

Before the thoracotomy is started, the bed is split just below the scapula. The thoracotomy is performed through an anterolateral incision. The chest is entered through the fourth or fifth intercostal space, depending on the somatic features of the patient and on the target. To gain more exposure, the intercostal muscles are freed posteriorly from the upper border of the rib on the inferior side of the thoracotomy almost to the spine. Care is taken not to injur the sympathetic chain. Closure of the three surgical sites may be carried out simultaneously by partial left rotation of the table starting from the horizontal supine patient position.

Supplementary 2 Thoracic and abdominal lymph nodes

Lymphadenectomy was extended to the thoracic stations R2–4, 7–8–9, and L4, numbered according to Mountain's

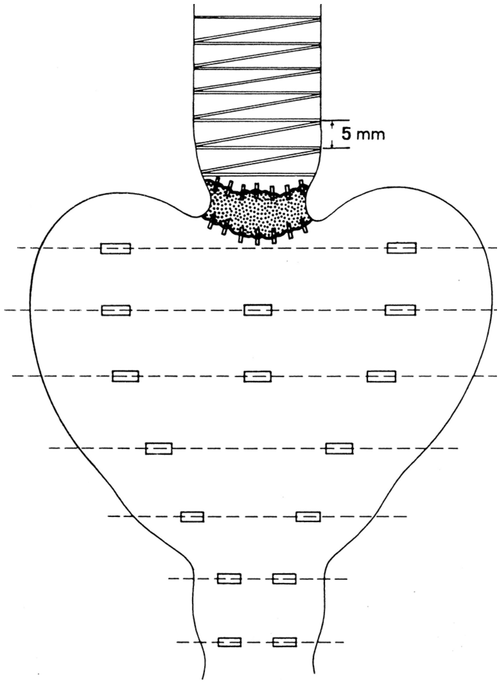


Figure S3 Surgical specimen pathology work-up.

classification (36) and to the abdominal stations 1–12, numbered according to the Japanese Research Society for Gastric Cancer (JRSGC) 1998 classification (37). Nodes were removed en bloc with the adjacent fat/connective tissue to achieve total lymphadenectomy. The surgical team labelled each lymph node when it was removed from the peripheral station and excluded fragments of the lymph nodes to avoid over-counting them.

Supplementary 3 Surgical specimen pathology work-up

Dedicated surgical pathologists performed or supervised every step of the surgical specimen work-up. Each surgical specimen was fixed in 10% buffered formalin. For the esophagus, full-thickness sections were acquired tangentially and transversally every 5 mm, from the oral margin of the tumour until the proximal shearing section, to study the pathways of intra-esophageal spread. The neoplastic diffusion into the stomach was assessed using 5-mm horizontal random samples of the lesser and greater curves from the cardia to the pylorus. The peritumoural tissues were also examined. Surgical pathologists performed or controlled the isolation and counted and labelled the lymph nodes from the surgical resection block.

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