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Postoperative Complications Do Not Impact on Recurrence and Survival after Curative Resection of Gastric Cancer

Short title: Impact of Postoperative Events

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Abstract (word count 241)

Background: The influence of major postoperative complications on the oncological outcome in patients with upper gastrointestinal (GI) cancer remains controversial. We assessed the impact of complications on recurrence and survival after curative gastric cancer resection.

Methods: A retrospective review of a prospectively maintained database was undertaken to identify patients undergoing R0 resections between 1990 and 2009. Patients were categorized by presence of any complication Clavien-Dindo (CD) $\geq$ II, sepsis or intra-abdominal sepsis. Cox regression analyses to relate complications and clinico-pathological variables to time to recurrence (TTR) and overall survival (OS) were performed.

Results: A total of 271 patients were included with a median follow-up of 149.9 months (range 140.1-159.9). Complications CD $\geq$ II occurred in 162 (59.8%) patients, sepsis in 66 (22.5%), and intraabdominal sepsis in 37 (13.6%). Tumor recurrence developed in 88 (32.4%) patients. At multivariate analysis, independent predictors of short TTR were pTNM stage (IIIB-IIIC vs. IA-IIA) (hazard ratio [HR]=37.55, 95% confidence interval [CI] 17.57-80.24; $p<0.001$), D1 lymphadenectomy (HR=3.14, 95% CI 1.94-5.07; $p<0.001$), and male gender (HR=1.65, 95% CI 1.06-2.57; $p=0.026$). In relation to OS, multivariate analysis identified pTNM stage (IIIB-IIIC versus IA-IIA, HR= 10.28, 95% CI 6.51-16.23; $p<0.001$), male gender (HR=1.64, 95% CI 1.17-2.31; $p=0.005$), age (HR=1.03, 95% CI 1.02-1.05; $p<0.001$), and adjuvant therapy (HR=0.55, 95% CI 0.37-0.83; $p=0.004$) as independent predictors.

Conclusions: Evidence provided by this study does not support a negative impact of postoperative complications CD >II, sepsis, and intraabdominal sepsis on the oncologic outcome after curative gastric cancer resection.

Key words: gastric cancer; postoperative complications; recurrence; survival

Introduction

Gastrointestinal cancer surgery is associated with high rates of postoperative complications. It has been suggested that these complications may promote tumor recurrence and decrease long-term survival, particularly in colorectal cancer surgery [1-3]. This relationship appears to be stronger for infectious complications [4]. Conflicting results have been reported regarding the association between postoperative complications and poor survival after resection of oesophageal cancer [5-7]. A more consistent relationship, however, has recently been described for gastric cancer resection, mainly in series from Eastern Asia, although differences in classifying or grading complications make these results still unclear [8-12]. It appears plausible that these results can be extrapolated to Western series where the incidence of overall and infectious postoperative complications, as well as the percentage of cases with advanced stages (II-III) are higher as compared with Eastern Asia series [13].

Clinical and experimental data suggest that persistent systemic inflammatory response by infectious complications may promote tumor recurrence and progression after cancer surgery [14,15]. It is worthwhile to assess the impact of septic events (sepsis and intraabdominal sepsis) uniformly classified on the oncologic outcome of patients undergoing curative gastric cancer resection.

The purpose of the present study was to examine the effects of postoperative complications especially those associated with a systemic inflammatory response, on recurrence and long-term survival after curative surgery for gastric cancer.

Methods

Study population

Between January 1990 and December 2009, 315 consecutive patients with gastric adenocarcinoma underwent R0 resection at the Gastrointestinal Surgical Units of Hospital Universitario del Mar and Hospital Clínic, in Barcelona, Spain. A specialized team following similar perioperative protocols over the time frame of the study performed gastric resection with associated lymphadenectomy. Given the time span of patients included in the study, the extent of lymphadenectomy varied but D2 dissection without splenectomy was commonly performed. The Institutional Review and Boards of both participating hospitals approved data collection and analysis.

Clinicopathological data and follow-up status for all operated patients were collected from a prospectively maintained database, which was common to both institutions. Two experienced pathologists (M.I., M.C) re-reviewed all diffuse and mixed type adenocarcinomas to identify signet ring cell (SRC) types, defined according to World Health Organization criteria [16]. Tumors were re-classified according to the seventh UICC/TNM classification system [17].

In the context of clinical trials carried out during the study period [18,19], patients with pathological stage (pStage) II/III disease were treated with adjuvant chemotherapy, which consisted of mitomycin C (MMC), 10-20 mg/m² i.v. bolus 4 courses (period 1990-1994) or MMC plus Tegafur 500 mg/m² p.o daily for 6 months (since 1995 to 2004). After 2004, adjuvant chemoradiation therapy was also indicated in patients with a high number of affected nodes.

Definition of Postoperative Complications

Complications were categorized into five grades according to the modified Clavien-Dindo (CD) classification [20]. If multiple complications occurred, the higher grade was used. For the purpose of this study, patients with CD $\geq$ II were considered as the “complication group”. Additionally, the Comprehensive Complication Index (CCI) was calculated as the sum of all complications that are weighted for their severity [21]. The final formula yields a continuous scale to rank the severity of any combination of complications from 0 to 100 in a single patient.

Perioperative blood transfusion (PBT) was defined as transfusion of allogenic red blood cells from 30 days before surgery until hospital discharge [22]. Indication of blood transfusion was left to the discretion of the treating physician. Sepsis was defined as an infection that had evoked a systemic inflammatory response syndrome (SIRS) [23]. Respiratory septic complications included pneumonia (defined as new or progressive infiltrate on chest X-ray, accompanied by fever/leukocytosis or leukopenia and purulent sputum, for which antibiotics treatment was started) and pleural empyema. Wound infection was defined as purulent drainage from the deep or superficial incision. Intraabdominal sepsis origins included anastomotic leakage (defined as full thickness gastrointestinal [GI] defect involving the anastomosis), duodenal stump fistula (bile or purulent drainage from a drain placed close to the duodenal stump), intraabdominal abscess (fluid collection diagnosed by ultrasound [US] or computed tomography [CT] with positive culture), pancreatic fistula (drain output with amylase content), and cholecystitis. Catheter-related bloodstream infection was defined as bacteraemia/fungemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a

peripheral vein and no other apparent source for the bloodstream infection except the catheter. Finally, catheter-related urinary tract infection (patient had an indwelling urinary catheter and positive urine culture) was also considered.

Follow-up

All patients were seen at the outpatient clinic by a medical oncologist and a surgeon at 3 months intervals during the first 2 years after operation, and every 6 months thereafter for 3 years. After 5 years, patients were followed every year. At follow-up patients underwent clinical examination, biochemistry with serum tumor markers (CEA and CA 19.9) and abdominal CT alternating with ultrasound examination every 6 months. More specific examinations (upper gastrointestinal endoscopy, laparoscopy, magnetic resonance imaging [MRI], or bone scintigraphy) were performed according to the patient's clinical condition. Histological confirmation of tumor recurrence was sought in all instances. Follow-up was extended to December 2012 ensuring a minimal potential follow-up of 36 months.

Statistical Analysis

Data are shown as frequencies and percentages for categorical variables or as median (interquartile range, percentile 25th-75th) for quantitative variables.

TTR was defined as the time from the date of surgery to the date of the first confirmed recurrence. OS was calculated from the date of surgery until death from any cause or the date of last follow-up in living patients. Median follow-up time was calculated using the reverse Kaplan-Meier method. Time to recurrence (TTR) and overall survival (OS) were the primary endpoints of the

study. Kaplan-Meier curves were plotted and compared using log-rank statistics. A Cox proportional hazards regression model was used to assess the effects of covariates on TTR and OS for both bivariate and multivariate analyses. Variables achieving a probability value of less than 0.1 in the bivariate analysis or those considered clinically relevant were subsequently entered in the multivariate proportional Cox hazards regression analysis. Then, variables without significance in the model were removed manually one by one, attending a possible confounding factor, until obtaining a final predictor model. Results are expressed as hazard ratio (HR) with 95% confidence interval (95% CI). Statistical significance was set at $P < 0.05$ (two-sided). The SPSS software package (SPSS Inc, Chicago, IL, USA), version 18.0, was used to manage patient data and to perform statistical analyses.

Results

Of the 315 eligible patients, 44 (14%) patients were excluded from the analysis for the following reasons: 18 received neoadjuvant therapy, 11 underwent surgery for gastric stump carcinoma, 6 patients presented with a synchronous primary tumor at the time of diagnosis, and 9 patients died before postoperative day 60. The demographic details and clinicopathological characteristics of the 271 patients finally included in the study are shown in Table 1.

Complications

One hundred sixty-two patients (59.8%) developed complications CD $\geq$ II (II: 116 [42.8%], IIIa: 23 [8.5%], IIIb: 13 [4.8%], IVa: 6 [2.2%], IVb: 4 [1.5%]). A comparison of patient's characteristics between groups with and without complications is depicted in Table 1. Median CCI was 20.9 (0-30.8) points. The PBT rate in the series was 45% (122 patients); only 7 patients received exclusively preoperative blood transfusion. In more than half of the patients with CD grade II (52%), PBT was the sole complication.

Sixty-six out of 271 patients (22.5%) developed 84 septic complications. Intra-abdominal sepsis was the most common event (37 patients; 13.6%), followed by respiratory sepsis (19 patients; 7.0%), catheter-related bloodstream infection (14 patients; 5.2%), urinary tract infection (8 patients; 2.9%), and wound infection (6 patients; 2.2%). Eleven of these patients had two or more septic events.

Follow-up

The median follow-up was 149.9 months (range 140.1-159.7). Nine patients (3.3%) were lost to follow-up. We confirmed by reviewing data from the National Mortality Register that 7 of these 9 patients died with a median survival of 157 months after surgery. At the end of the study, 87 patients died from gastric cancer recurrence, 59 due to causes unrelated to gastric cancer, 7 from unknown causes, and 2 (one with confirmed recurrence) were lost to follow-up. A total of 116 remained alive.

Recurrence and Risk Factors Related to the Time to Recurrence

During the follow-up period, a total of 88 (33.4%) recurrences occurred in 271 patients. Thirty-one patients developed recurrence within 12 months, 62 within 24 months, 73 within 36 months, 81 within 48 months, for a total of 85 at 5 years. Three patients developed late recurrences (74, 85 and 117 months after surgery; liver metastasis, bone metastasis and gastric stump relapse, respectively). The median time to death after the diagnosis of recurrence was 4.2 (range 1.9-9.2) months.

In the bivariate analysis, weight loss > 10%, tumor location other than in the antropylic region, total gastrectomy, diffuse-type adenocarcinoma, lymphatic invasion, vascular invasion, perineural invasion, advanced pTstage, advanced pNstage and advanced pTNM stage were all factors negatively influencing recurrence (*Table 2*). However, postoperative complications CD grade $\geq$ II, sepsis, intra-abdominal sepsis and PBT were not associated with a lower probability of being free of recurrence (*Figure 1*). Time to recurrence

curves stratified by pStage in patients with and without complications ($CD \geq II$, sepsis) did not show statistically differences (data not shown).

In the multivariate Cox regression analysis, male gender (HR 1.65, 95% CI 1.06-2.57; $p = 0.026$), extent of lymphadenectomy D1 (HR 3.14, 95% CI 1.94-5.07; $p < 0.001$), and advanced pTNM stage (IIB-IIIA versus IA-IIA HR 6.10, 95% CI 2.79-13.37; $p < 0.001$, IIIB-IIIC versus IA-IIA HR 37.55, 95% CI 17.57-80.24; $p < 0.001$) remained as independent negative factors for the development of recurrence disease.

Survival and Risk Factors Related to OS

The cumulative 1, 3, 5, and 10-year OS for the study cohort were 87.8%, 66.3%, 55.8% and 48.1% from the date of surgery, respectively.

The bivariate analysis retained age, weight loss $> 10\%$, cardiac co-morbidities, lymphatic invasion, perineural invasion, pT4 stage, pN stage, and advanced pTNM stage as factors negatively influencing overall survival (Table 3). OS was not significantly lower for patients who had complications $CD \geq II$, postoperative sepsis and intraabdominal sepsis than for those without. Patients not receiving PBT showed significantly higher OS (Figure 1).

Multivariate analysis identified age (HR 1.03, 95% CI 1.02-1.05; $p < 0.001$), male gender (HR 1.64, 95% CI 1.17-2.31, $p = 0.005$), and advanced pTNM stage (IIB-IIIA versus IA-IIA, HR 2.40, 95% CI 1.50-3.84; $p < 0.001$, IIIB-IIIC versus IA-IIA, HR 10.28, 95% CI 6.51-16.23; $p < 0.001$) as independent negative factors affecting survival. On the other hand, adjuvant therapy showed an independent protective effect (HR 0.55, 95% CI 0.37-0.83; $p = 0.004$).

Influence of Complications Clavien-Dindo $\geq$ II, Sepsis, and Intraabdominal Sepsis on TTR and OS

Additional multivariate analyses adjusting each complication category (complications CD $\geq$ II, sepsis, and intraabdominal sepsis) for patient, disease and treatment-related variables were performed using two models (Table 4). In both models, complications CD $\geq$ II, sepsis, and intraabdominal sepsis were not associated with a significantly shorter time to recurrence or worse long-term OS.

Discussion

This study in 271 patients undergoing curative resection for gastric cancer does not provide evidence supporting that either postoperative complication classified as Clavien-Dindo $\geq$ II or sepsis or intraabdominal sepsis had a negative effect on tumor recurrence and OS. Advanced pathologic stage, however, remained as the most powerful predictor of recurrence and survival. Adjuvant therapy had a beneficial effect on OS.

The potential negative effect of postoperative complications and, in particular infectious complications, on long-term oncologic outcome after curative surgery for gastrointestinal cancer has been mainly examined in the setting of colorectal cancer [1-4]. A recent meta-analysis demonstrated that anastomotic leakage increases the risk of local tumor recurrence and reduces long-term cancer-specific survival after curative resection for rectal cancer [1]. Some groups have reported contradictory results especially when the impact of anastomotic leakage on tumor recurrence and survival was analyzed in patients after colonic anastomosis only.

Also, there is conflicting evidence regarding the effects of postoperative complications on long-term survival after resection for esophageal and gastric cancer. In esophageal cancer, four research groups have reported no effect of surgical complications on overall and disease-specific survival [5,24-26]. Four other studies [6,7,27,28], however, have found a correlation between postoperative complications and decreased OS, shorter time interval until death due to cancer and early recurrence.

To date, only seven studies, six of them from Eastern Asia, have analyzed the influence of postoperative complications on the oncologic outcome

in patients undergoing gastric cancer resection [8-10,12,29,30]. Their findings support a negative effect of anastomotic leakage [9,29], postoperative infection [8,30], intraabdominal infection [10], or complications Clavien-Dindo $\geq$ II [12] on recurrence and survival after gastric cancer resection. The results of the present study, however, do not replicate these findings, even in a more adverse scenario with a higher rate of complications and more advanced tumor stages (stages II-III, 74.6%). Postoperative complications occurred at a high rate of 61% in our study cohort, which is higher than what has been reported in series from Japan and Korea assessing the same question. It is of interest that PBT accounted for half of our reported Clavien-Dindo II complications (42.8%). The present study, confirming the results of two recent large series, shows that PBT is not an independent prognostic factor for OS in patients having curative gastric cancer resection [31,32].

As complications Clavien-Dindo $\geq$ II include not only infectious complications, we specifically assessed the impact of sepsis after carefully having identified all infections that induced a systemic inflammatory response syndrome, but even in this setting no impact on recurrence and long-term OS was found.

The present findings should be interpreted taking into account the limitation of the retrospective design of the study covering a 20-year period (1990-2009) and the relatively small series of patients. Although we are aware of the wide time span of the study and that this might include heterogeneity in the perioperative care of the patients, further adjustment per year of surgery in the multivariate models did not affect the results obtained (see models “2” in Table 4). It should be noted that patient data was collected prospectively by the

same surgeon (M.P), surgery was performed by a reduced specialised team leaded by the same surgeon (M.P) in both institutions, and the follow-up assessment was achieved, in collaboration with the same oncologists, with a high degree of compliance during the whole study period. The potential impact of adjuvant therapy variability was limited as we mostly used the same protocol. Taking into account the sample size and the event rate in the group of patients without postoperative complications, our study had a 80% of power to detect a 13% increase in 5-year overall survival and a 15% increase in 5-year recurrence-free survival due to complications classified as Clavien-Dindo $\geq$ II. Thus, besides the lack of a true association, the absence of a statistically significant association could be due to (i) the presence of an association smaller than those depicted above or, (ii) a type II error (20%). The apparent high mortality due to unrelated causes (59 patients) can be explained as the mean age of our patients was high at the time of surgery (almost 70 years) and the follow-up period was very long. In fact, the majority of patients died due to cardiovascular (47%) or respiratory (25%) causes. Despite the lack of an effect on recurrence and survival, a priority for improvement should be to reduce postoperative complications after curative gastric cancer surgery.

In conclusion, our results do not support the hypothesis that postoperative complications Clavien-Dindo $\geq$ II, sepsis, and intraabdominal sepsis have a negative impact on the oncologic outcome after curative gastric cancer surgery, which seems to depend mostly on the pathological stage of the disease.

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Table 1. Clinicopathological characteristics of the study patients

	Entire group (n=271)	Non-complication group (n=109)	Complication group (n=162)	<i>P</i> ***
Year surgery				0.750
1990-1999	129 (47.6)	56 (51.4)	73 (45.1)	
2000-2009	142 (52.4)	53 (48.6)	89 (54.9)	
Gender				0.871
Male	160 (59)	65 (59.6)	95 (58.6)	
Female	111 (41)	44 (40.4)	67 (41.4)	
Age, mean (SD)	69 (7)	65.5 (13.6)	71.9 (10.5)	<0.0001
Comorbidities				
Diabetes	51 (18.8)	18 (16.5)	33 (20.4)	0.426
COPD	41 (15.1)	16 (14.7)	25 (15.4)	0.865
Weight loss				
<10%	241 (88.9)	97 (89)	144 (88.9)	0.979
≥10%	30 (11.1)	12 (11)	18 (11.1)	
Cirrhosis	8 (3)	3 (2.8)	5 (3.1)	0.979
Cardiovascular	121 (44.6)	38 (34.9)	83 (51.2)	0.008
ASA score				0.016
I	59 (21.7)	21 (19.2)	38 (23.4)	
II	157 (57.9)	74 (67.8)	83 (51.6)	
III	51 (18.8)	14 (13.3)	37 (23)	
IV	4 (1.5)	0 (0)	4 (2.5)	
Gastrectomy				0.868
Total	150 (55.4)	61 (56)	89 (54.9)	
Subtotal	121 (44.6)	48 (44)	73 (45.1)	
Lymphadenectomy				0.712
D1	88 (32.5)	34 (31.2)	54 (33.3)	
D2	183 (67.5)	75 (68.8)	108 (67.7)	
Splenectomy	57 (21)	23 (21.1)	34 (21)	0.982
Multivisceral resection	54 (19.9)	23 (21.1)	31 (19.1)	0.691
Adjuvant therapy	116 (42.8)	53 (48.6)	63 (38.9)	0.112
Tumor location				0.442
Antropyloric	134 (49.4)	51 (46.8)	83 (51.6)	
Non-antropyloric	137 (50.5)	58 (53.2)	79 (48.7)	
Laurén classification ^a				0.555
Intestinal	154 (56.8)	62 (57.4)	92 (59.3)	
Diffuse	100 (36.9)	44 (40.7)	56 (36.1)	
Mixed	9 (3.3)	2 (1.9)	7 (4.5)	
Signet-ring cell ^{a *}	26 (9.5)	15 (14.2)	11 (7)	0.057
Grade differentiation				0.903
Good	20 (7.4)	9 (8.3)	11 (6.8)	
Moderate	108 (39.9)	43 (39.4)	65 (40.1)	
Poor	143 (52.7)	57 (52.3)	86 (53.1)	
Lymphatic invasion	78 (28)	26 (23.9)	50 (31.6)	0.165
Vascular invasion	53 (19.6)	20 (18.3)	33 (21)	0.592
Perineural invasion	61 (22.5)	18 (16.5)	43 (27.4)	0.038
pT category**				0.605
pT1a	21 (7.7)	9 (8.3)	12 (7.4)	
pT1b	36 (13.3)	18 (16.1)	18 (11.1)	
pT2	32 (11.8)	12 (11)	20 (12.3)	
pT3	95 (35.5)	39 (35.8)	56 (34.6)	
pT4a	80 (29.5)	30 (27.5)	50 (30.9)	
pT4b	7 (2.6)	1 (0.9)	6 (3.7)	

Table 1. Clinicopathological characteristics of the study patients (continued)

pN category**				0.979
<i>pN0</i>	123 (45.3)	50 (45.9)	73 (45.1)	
<i>pN1</i>	48 (17.7)	19 (17.4)	29 (17.9)	
<i>pN2</i>	40 (14.8)	17 (15.6)	23 (14.2)	
<i>pN3</i>	60 (22.1)	23 (21.1)	37 (22.8)	
pTNM stage**				0.737
<i>Ia</i>	48 (17.7)	23 (21.1)	25 (15.4)	
<i>Ib</i>	22 (8.1)	10 (9.2)	12 (7.4)	
<i>IIa</i>	48 (17.7)	17 (15.6)	31 (19.1)	
<i>IIb</i>	49 (18.1)	17 (15.6)	32 (19.8)	
<i>IIIa</i>	26 (9.6)	12 (11)	14 (8.6)	
<i>IIIb</i>	40 (14.8)	17 (15.6)	23 (14.2)	
<i>IIIc</i>	38 (14)	13 (11.9)	25 (15.4)	

*According to World Health Organization (WHO) criteria [16]. **According to the 7th edition of the International Union Against Cancer tumor node metastasis staging system [17]. COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists. ^aData for Laurén classification and signet-ring cell were missing in 8 patients. ***Pearson chi-square test.

Table 2. Bivariate Cox regression analysis for time to recurrence after curative gastrectomy for adenocarcinoma of the stomach

	Bivariate analysis		
	HR	95% CI	P
Gender (male)	1.28	0.83-1.97	0.263
Age, 1 year increment	1.00	0.99-1.02	0.346
Weight loss $\geq 10\%$	1.96	1.09-3.54	0.025
Cardiac co-morbidities	0.91	0.59-1.40	0.687
ASA score			
II	0.77	0.46-1.29	0.338
III-IV	0.81	0.42-1.57	0.548
Tumor location (Non-antropyloric vs. antropyloric)	1.53	1.00-2.34	0.049
Adjuvant therapy	1.41	0.93-2.15	0.103
Perioperative transfusion	1.27	0.83-1.93	0.256
Gastrectomy extent (Total vs. subtotal)	1.58	1.03-2.44	0.036
Splenectomy	1.09	0.65-1.81	0.738
Multivisceral resection	1.08	0.64-1.82	0.755
Lymphadenectomy extent (D1 vs D2)	1.19	0.77-1.86	0.424
Laurén (Diffuse vs. non-diffuse)	1.62	1.05-2.49	0.027
Lymphatic invasion	2.82	1.85-4.31	<0.001
Vascular invasion	2.07	1.31-3.28	0.002
Perineural invasion	2.38	1.53-3.71	<0.001
Differentiation grade (compared vs. good)			
Moderate	2.13	0.65-6.94	0.207
Poor	2.35	0.73-7.55	0.150
Signet-ring cell*	1.49	0.83-2.69	0.181
pT category** (compared vs. T1-T2)			
pT3	3.64	1.57-8.43	0.002
pT4	14.6	6.64-32.22	<0.001
pN category** (compared vs. pN0)			
pN1	2.73	1.28-5.81	0.009
pN2	6.32	3.14-12.74	<0.001
pN3	11.53	6.25-21.24	<0.001
pTNM stage** (compared vs. IA-IIA)			
IIB-IIIA	4.70	2.16-10.21	<0.001
IIIB-IIIC	22.30	10.93-45.50	<0.001
Clavien grade ($\geq$ II vs.0-I)	1.13	0.73-1.73	0.572
CCI (per point)	1.00	0.98-1.01	0.886
Sepsis	1.14	0.70-1.84	0.606
Intra-abdominal infection	1.04	0.56-1.91	0.905
Respiratory complications	1.07	0.56-2.01	0.832

Statistically significant results are shown in bold. *According to World Health Organization (WHO) criteria [16] **According to the 7th edition of the International Union Against Cancer tumor, node metastasis staging system [17]. ASA, American Society of Anesthesiologists; CCI, Comprehensive Complication Index. HR: hazard ratio; CI: confidence interval.

Table 3. Bivariate Cox regression analysis for overall survival after curative gastrectomy for adenocarcinoma of the stomach.

	Bivariate analysis		
	HR	95% CI	P
Gender (male)	1.25	0.89-1.73	0.192
Age, 1 year increment	1.04	1.02-1.05	<0.001
Weight loss >10%	1.66	1.03-2.66	0.036
Cardiac co-morbidities	1.38	1.00-1.90	0.047
ASA score			
II	1.02	0.67-1.55	0.916
III-IV	1.56	0.96-2.57	0.075
Tumor location (non (Antropyloric vs. antropyloric)	1.17	0.85-1.61	0.336
Adjuvant therapy	0.89	0.65-1.24	0.506
Perioperative transfusion	1.38	1.00-1.91	0.051
Gastrectomy extent (Total vs. subtotal)	1.20	0.87-1.66	0.258
Splenectomy	1.07	0.73-1.57	0.721
Multivisceral resection	1.05	0.71-1.55	0.814
Lymphadenectomy extent (D1 vs. D2)	1.20	0.86-1.68	0.289
Laurén (Diffuse vs. non-diffuse)	1.39	1.00-1.94	0.051
Lymphatic invasion	1.74	1.24-2.46	0.002
Vascular invasion	1.47	1.00-2.18	0.051
Perineural invasion	1.83	1.27-2.65	<0.001
Differentiation grade (compared vs. good)			
Moderate	0.83	0.43-1.59	0.538
Poor	1.03	0.55-1.94	0.917
Signet-ring cell*	1.01	0.59-1.72	0.978
pT category** (compared vs. T1-T2)			
pT3	1.49	0.96-2.39	0.770
pT4	4.19	2.75-6.38	<0.001
pN category** (compared vs. pN0)			
pN1	1.68	1.03-2.73	0.037
pN2	2.99	1.87-4.76	<0.001
pN3	4.87	3.23-7.35	<0.001
pTNM stage** (compared vs. IA-IIA)			
IIB-IIIA	1.81	1.17-2.80	0.008
IIIB-IIIC	6.80	4.56-10.16	<0.001
Clavien grade (≥II vs 0-I)	1.21	0.87-1.69	0.250
CCI (per point)	1.01	1.00-1.02	0.182
Sepsis	1.19	0.83-1.71	0.354
Intraabdominal infection	0.90	0.55-1.47	0.660
Respiratory complications	1.13	0.71-1.78	0.611

Statistically significant results are shown in bold. *According to World Health Organization (WHO) criteria¹ [17] **According to the 7th edition of the International Union Against Cancer tumor, node metastasis staging system [18]. ASA, American Society of Anesthesiologists; CCI, Comprehensive Complication Index. HR: hazard ratio, CI: confidence interval.

Table 4. Multivariate Cox regression analyses for time to recurrence and overall survival adjusting for patient, disease and treatment factors.

	Time to Recurrence		Overall Survival	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Clavien-Dindo $\geq$ II				
* Model 1	0.93 (0.56-1.54)	0.779	0.76 (0.51-1.12)	0.167
**Model 2	0.99 (0.49-1.98)	0.971	0.72 (0.41-1.26)	0.254
Sepsis				
* Model 1	1.00 (0.55-1.83)	0.996	1.08 (0.70-1.67)	0.724
**Model 2	1.23 (0.68-2.25)	0.497	1.13 (0.73-1.75)	0.578
Intra-abdominal sepsis				
* Model 1	0.88 (0.43-1.82)	0.733	0.87 (0.49-1.52)	0.619
**Model 2	0.96 (0.45-2.01)	0.903	0.89 (0.50-1.56)	0.673

*Adjusted for patient and disease factors (age, gender, cardiovascular co-morbidities, ASA score, weight loss, tumor location, Laurén classification, signet-ring cell, grade of differentiation, lymphatic invasion, vascular invasion, perineural invasion, and pTNM stage).

**Adjusted for patient, disease and treatment factors (year of surgery, age, gender, cardiovascular co-morbidities, ASA score, Laurén classification, signet-ring cell, grade of differentiation, lymphatic invasion, vascular invasion, perineural invasion, pTNM stage, type of gastrectomy, extent of lymphadenectomy, splenectomy, multivisceral resection, adjuvant therapy, and perioperative blood transfusion).

HR: hazard ratio; CI: confidence interval.

Legends

Figure 1. Kaplan-Meier curves comparing time to recurrence and overall survival in patients with and without complications (A and C), and in patients with and without sepsis (B and D), respectively.