Original Investigation

Predictive Factors of Postoperative Mortality After Junctional and Gastric Adenocarcinoma Resection

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IMPORTANCE Postoperative mortality after junctional and gastric adenocarcinoma resection remains a significant issue.

OBJECTIVE To identify factors predictive of mortality within 30 days of junctional and gastric adenocarcinoma resection in a large national multicenter cohort.

DESIGN A retrospective study collecting data from a multicenter database of patients who underwent resection for junctional and gastric adenocarcinoma from January 1, 1997, through January 31, 2010. A stepwise logistic regression model was built to identify, by multivariate analysis, variables independently predictive of 30-day postoperative mortality (POM).

SETTING Nineteen university teaching hospitals in France.

PARTICIPANTS Two thousand six hundred seventy patients with available data.

MAIN OUTCOME MEASURES The primary end point was POM. Secondary end points included (1) late mortality (30-90 days after resection) and (2) postoperative morbidity.

RESULTS One thousand eight hundred ninety-six patients (71.01%) had gastric adenocarcinoma and 774 (28.99%) had junctional tumors. Neoadjuvant treatment was given to 655 patients (24.53%), and 114 patients (4.27%) died within 30 days of surgery. Postoperative mortality was higher in patients who experienced grades III and IV toxic effects during neoadjuvant treatment compared with those who did not (8.7% vs 2.9%, respectively; $P = .007$). Multivariate analysis revealed metastatic disease at diagnosis (odds ratio, 9.13 [95% CI, 3.29-25.35]; $P < .001$) and poor tolerance of neoadjuvant treatment (3.33 [1.25-8.85]; $P = .02$) as being independently predictive of POM. Centers performing at least 10 resections per year were found to be protective against POM (odds ratio, 0.29 [95% CI, 0.12-0.72]; $P = .008$).

CONCLUSIONS AND RELEVANCE This large national cohort study confirms that advanced disease heightens the risk of POM; centralization of junctional and gastric adenocarcinoma resection is warranted. The novel finding that grades III to IV toxic effects during neoadjuvant therapy increase POM has significant implications for decision making in this subgroup of patients.

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Postoperative surgical mortality after junctional and gastric adenocarcinoma (JGA) resection remains a significant factor in the patient treatment pathway. A recent European analysis of operative mortality after gastric resection revealed substantial geographic variation, with rates ranging from 5.2% to 16.0%.[1] This finding is consistent with other population-based studies demonstrating 30-day mortality rates ranging from 7.2% to 12.6%.[2]

Despite a decline in the incidence of gastric cancer during the second half of the 20th century, it remains the second most common cause of cancer-related mortality worldwide.[3] The declining incidence of distal gastric adenocarcinomas contrasts starkly with the marked increase in the incidence of adenocarcinoma of the esophagogastric junction and lower esophagus. The incidence of this tumor has increased more than 3.5-fold among white men in the United States from 1974 through 1994, with similar increases observed in other Western countries.[4,5] The evolving pattern of disease is likely to result from the complex interplay of many environmental factors.

Surgical resection is the mainstay of JGA treatment, with perioperative chemotherapy, adjuvant chemotherapy, and chemoradiation therapy all having shown survival benefit in European, Asian, and North American populations, respectively.[6] If curative surgery's advantage is to translate into improved long-term survival, then immediate postoperative mortality must be minimized. Consequently, the aim of this multicenter retrospective series was to evaluate 30-day postoperative mortality (POM) after the resection of JGAs and to identify factors predictive of 30-day POM, with the hope of helping to guide perioperative therapeutic planning.

Methods

Patients

We conducted a retrospective study to collect data from a multicenter database of patients undergoing resection of JGA. Data were collected from 19 French centers, from January 1, 1997, through January 31, 2010, and were available for a total of 2670 patients. All patients undergoing resection during the study period in each center were included. Patient details were collected by manual medical record review by a dedicated team with a second monitoring team auditing data capture to minimize missing data and control data quality. Patients were not included if surgical or pathological data required for analysis were missing; other missing data for minor variables are acknowledged in the Results section. Patients with a histological subtype other than adenocarcinoma were excluded from the study. The demographic and therapeutic variables analyzed are presented in **Table 1** and **Table 2**. Diagnostic investigations routinely included a physical examination, routine laboratory tests, a barium study, an esophagogastroduodenoscopy with biopsy, a thoracoabdominal computed tomographic scan, and a selective endoscopic ultrasonographic evaluation. Preoperative patient malnutrition was defined by weight loss of at least 10% of baseline body mass. For resection of JGAs, the definition of what constitutes a high-volume center has varied widely.[7] We arbitrarily defined hospitals as high volume if they performed more than 10 resections per annum. We assessed POM for 1997 through 2000, 2001 through 2005, and 2006 through 2010.

Preoperative Treatment

Subsequent to the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial (MAGIC) study being reported,[8] perioperative chemotherapy consisting of epirubicin hydrochloride, cisplatin, and fluorouracil was included, from 2006, in the French guidelines for treatment of gastric adenocarcinoma of stages IB and higher. The subsequent presentation of the results of the Fédération Nationale des Centres de Lutte Contre le Cancer 94012-Fédération Francophone de Cancérologie Digestive 9703 provided an alternative to the epirubicin-cisplatin-fluorouracil regimen consisting of cisplatin and fluorouracil.[9] Preoperative treatment was usually initiated from 4 to 6 weeks after the first oncological consultation. Concomitant neoadjuvant radiotherapy was proposed for patients with locally advanced tumors predominantly involving the esophagus and according to center practice. Usually, 45 Gy was administered in 25 fractions of 1.8 Gy each (to convert to rad, multiply by 100). Patients categorized as having a good tolerance of neoadjuvant treatment were those who exhibited no toxic effects or experienced grade I or II toxic effects and those with poor tolerance of treatment evidenced by grades III and IV toxic effects, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[10]

Surgical Approach

Details of the surgical approach to resection have been described previously.[11] Briefly, for antropyloric tumors, a subtotal gastrectomy was most often performed, whereas for more proximal gastric tumors, a total gastrectomy was indicated, combined with an extended lymphadenectomy preserving the spleen and the pancreatic tail. A D0 lymphadenectomy was defined as fewer than 15 analyzed lymph nodes; D1 lymphadenectomy, 15 to 25 resected lymph nodes; and D2 lymphadenectomy, at least 26 resected lymph nodes. Extended resections were performed for suspected or confirmed neoplastic invasion and included resections of the liver, spleen, pancreas, and colon. For tumors invading the esophagogastric junction, resection was extended to the esophagus using a transthoracic or transhiatal approach with dedicated mediastinal lymphadenectomy,[6] or an esophagectomy was performed for proximal junctional tumors. In patients presenting with metastatic disease, surgery was performed to relieve or palliate gastric outlet obstruction, bleeding, or perforation.

Histopathological Analysis

Histological staging of tumors was based on the sixth edition of the International Union Against Cancer TNM classification,[12] which was the reference at the time of study accrual. Signet ring cell tumors were defined by the World Health Organization classification as those with more than 50% of the tumor having signet ring cell morphology.[13] A radical resection, with macroscopically and microscopically tumor-free margins, was defined as an R0 resection; a microscopically positive resection mar-

Table 1. Demographic and Perioperative Therapeutic Variables

Variable	Patient Groups, No. (%)[a] All (N = 2670)	No Mortality (n = 2556)	30-d Mortality (n = 114)	*P* Value
Age, y				
≤60	**953** (35.69)	928 (36.31)	25 (21.93)	.002
>60	**1717** (64.31)	1628 (63.69)	89 (78.07)	
Sex				
Male	**1893** (70.90)	1811 (70.85)	82 (71.93)	.80
Female	**777** (29.10)	745 (29.15)	32 (28.07)	
ASA score				
I	**745** (27.90)	726 (28.40)	19 (16.67)	<.001
II	**1298** (48.61)	1257 (49.18)	41 (35.96)	
III	**588** (22.02)	540 (21.12)	48 (42.11)	
IV	**39** (1.46)	33 (1.29)	6 (5.26)	
Weight loss, % of body mass				
<10	**1973** (73.90)	1896 (74.18)	77 (67.54)	.15
≥10	**507** (18.99)	480 (18.78)	27 (23.68)	
Unknown	**190** (7.12)	180 (7.04)	10 (8.77)	
Study period				
1997-2000	**666** (24.94)	644 (25.20)	22 (19.30)	.02
2001-2005	**932** (34.91)	900 (35.21)	32 (28.07)	
2006-2010	**1072** (40.15)	1012 (39.59)	60 (52.63)	
Tumor site				
Junctional	**774** (28.99)	742 (29.03)	32 (28.07)	.83
Gastric	**1896** (71.01)	1814 (70.97)	82 (71.93)	
Neoadjuvant treatment				
Yes	**655** (24.53)	632 (24.73)	23 (20.18)	.27
No	**2015** (75.47)	1924 (75.27)	91 (79.82)	
Grade III or IV toxic effects during neoadjuvant treatment[b]				
Yes	**92** (14.09)	84 (14.97)	8 (36.36)	.007
No	**491** (75.19)	477 (85.03)	14 (64.64)	
Unknown	**70** (10.72)	NA	NA	
Metastases/carcinomatosis at diagnosis				
Yes	**199** (7.45)	182 (7.12)	17 (14.91)	.002
No	**2471** (92.55)	2374 (92.88)	97 (85.09)	
Surgical procedure				
Subtotal gastrectomy	**1362** (51.01)	1310 (51.25)	52 (45.61)	.24
Total gastrectomy	**1308** (48.99)	1246 (48.75)	62 (54.39)	
Lymphadenectomy extent				
D0	**656** (24.57)	618 (24.18)	38 (33.33)	.18
D1	**914** (34.23)	879 (34.39)	35 (30.70)	
D2	**1100** (41.20)	1059 (41.43)	41 (35.96)	
Extended resection of adjacent organs				
Yes	**316** (11.84)	293 (11.46)	23 (20.18)	.005
No	**2354** (88.16)	2263 (88.54)	91 (79.82)	
Surgical center				
High volume	**2015** (75.47)	1937 (75.78)	78 (68.42)	.07
Low volume	**655** (24.53)	619 (24.23)	36 (31.58)	

Abbreviations: ASA, American Society of Anesthesiologists; NA, not applicable.

[a] Percentages have been rounded and might not total 100.

[b] Toxic effects of neoadjuvant therapy were defined according to the National Cancer Institute Toxicity Criteria scale (version 2.0) (n = 653).

gin, as an R1 resection; and a macroscopically positive resection margin, as an R2 resection. All patients with pTNM stage IV were considered to have an R2 resection. Tumors showing a complete pathological response were graded as pT0.

End Points of the Study

The primary end point of the study was POM, defined as death within 30 days of surgery. Secondary end points were (1) late mortality, defined as postoperative death from 30 to 90 days,

Table 2. Histological Variables of Resected Specimens[a]

Variable	Patient Groups			*P* Value
	All (N = 2670)	No Mortality (n = 2556)	30-d Mortality (n = 114)	
pT stage				
pTis	**36** (1.35)	35 (1.37)	1 (0.88)	.15
pT0	**73** (2.73)	67 (2.62)	6 (5.26)	
pT1	**443** (16.59)	432 (16.90)	11 (9.65)	
pT2	**820** (30.71)	788 (30.83)	32 (28.07)	
pT3	**952** (35.66)	906 (35.45)	46 (40.35)	
pT4	**346** (12.96)	328 (12.83)	18 (15.79)	
pN stage				
pN0	**945** (35.39)	908 (35.52)	37 (32.46)	.08
pN1	**860** (32.21)	832 (32.55)	28 (24.56)	
pN2	**529** (19.81)	498 (19.48)	31 (29.19)	
pN3	**336** (12.58)	318 (12.44)	18 (15.79)	
pM stage				
pM0	**2342** (87.72)	2252 (88.11)	90 (78.95)	.004
pM1	**328** (12.28)	304 (11.89)	24 (21.05)	
pTNM stage				
I	**814** (30.49)	783 (30.63)	31 (27.19)	.03
II	**455** (17.04)	440 (17.21)	15 (13.16)	
III	**1071** (40.11)	1027 (40.18)	44 (38.60)	
IV	**330** (12.36)	306 (11.97)	24 (21.05)	
Resection				
R0	**2224** (83.30)	2139 (83.69)	85 (74.56)	.009
R1	**312** (11.69)	295 (11.54)	17 (14.91)	
R2	**134** (5.02)	122 (4.77)	12 (10.53)	
Resection margins positive				
Yes	**247** (9.25)	231 (9.04)	16 (14.04)	.07
No	**2423** (90.75)	2325 (90.96)	98 (85.96)	
Proximal margin positive				
Yes	**163** (6.10)	152 (5.95)	11 (9.65)	.11
No	**2507** (93.90)	2404 (94.05)	103 (90.35)	
Distal margin positive				
Yes	**126** (4.72)	118 (4.62)	8 (7.02)	.24
No	**2544** (95.28)	2438 (95.38)	106 (92.98)	
Circumferential margin positive				
Yes	**171** (6.40)	159 (6.22)	12 (10.53)	.07
No	**2499** (93.60)	2397 (93.78)	102 (89.47)	
Signet ring cell histologic finding				
Yes	**907** (33.97)	875 (34.23)	32 (28.07)	.17
No	**1763** (66.03)	1681 (65.77)	82 (71.93)	
No. of lymph nodes dissected, median (range)	**22** (4-99)	22 (4-98)	18 (4-99)	.02
No. of invaded lymph nodes, median (range)	**2.0** (0-74)	2.0 (0-63)	4.0 (0-74)	.08
Ratio of invaded to dissected lymph nodes (range)	**0.1** (0.0-1.0)	0.1 (0.0-1.0)	0.2 (0.0-1.0)	.02

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and might not total 100.

and (2) postoperative morbidity, recorded as surgical or medical morbidity. The Clavien-Dindo Scale was used to grade the severity of postoperative morbidity.[14]

Statistical Analysis

Data analysis was performed using commercially available software (SPSS, version 15.0; SPSS, Inc). Data are shown as prevalence, mean (standard deviation), or median (range). Discrete variables were compared using the χ^2 test. Continuous variables were compared using the Mann-Whitney test. A stepwise binary logistic regression model was built to identify predictive factors of POM and postoperative morbidity. A *P* value of no greater than .10 on univariate analysis was required for entry into multivariate analysis of postoperative morbidity; in addition, only variables available at the time of surgery (excluding pathological variables and postoperative course events)

and non-redundancy between variables were required for entry into multivariate analysis of POM. All statistical tests were 2-sided, with the threshold for significance set at $P < .05$. The study was accepted by the regional institutional review board, and the database was registered on the Clinicaltrials.gov website.

Results

Study Population

This study included a total of 2670 patients who underwent resection of JGAs from January 1, 1997, through January 31, 2010 (1893 men and 777 women; ratio, 2.4). The median age at diagnosis was 65.4 (range, 19-99) years. The American Society of Anesthesiology (ASA) grade was I or II in 2043 patients (76.52%). Metastatic disease at initial presentation was identified in 199 patients (7.45%) during clinical staging investigations (n = 116) or at surgical exploration (n = 83). Of the 116 patients with metastatic disease at the time of presentation, 44 had liver metastases, 3 had lung metastases, 48 had evidence of carcinomatosis, and 21 had other disease. Of the 83 patients with metastatic disease discovered during surgical exploration, metastatic locations included carcinomatosis in 37, para-aortic lymph nodes in 20, liver in 19, and other locations in 7 (Table 1).

Preoperative and Perioperative Treatment

When preoperative chemotherapy was administered (655 patients [24.53%]), the regimen was based mainly on fluorouracil and a platinum agent (cisplatin), with doublet (290 patients [44.3%]) or triplet (in association with epirubicin; 138 patients [21.1%]) therapy used. Other combinations included epirubicin, oxaliplatin, and capecitabine (60 patients [9.2%]); fluorouracil and irinotecan hydrochloride (52 [8.0%]); fluorouracil and oxaliplatin (41 [6.3%]); and combinations in doublet or triplet forms with docetaxel (73 [11.1%]). Radiotherapy was proposed concomitantly in 217 patients (8.13%). Toxicity data were available for 632 patients receiving neoadjuvant treatment, of whom 214 had preoperative combined radiochemotherapy and 418 received chemotherapy only. Grade III or IV toxic effects were observed in 92 patients who received neoadjuvant treatment (14.0%). No difference was seen in the rates of observed grades III and IV toxic effects with the addition of radiotherapy (16.5% for chemotherapy vs 11.7% for radiochemotherapy; $P = .11$). Details of the delay between finishing neoadjuvant treatment and surgery were available for 364 patients who tolerated treatment well and 70 patients who exhibited grade III or IV toxic effects, with no difference being found ($P = .13$). Total gastrectomy was performed in 1308 patients (48.99%), including 209 patients who underwent a total esophagogastrectomy for extensive junctional tumors (Table 1).

Postoperative Mortality

The overall 30-day POM rate was 4.27% (n = 114), and the cumulative in-hospital mortality rate up until day 90 was 5.99% (n = 160) (Table 1 and Table 2). We found no difference in the mean delay to surgery after neoadjuvant treatment for patients with 30-day POM and those without (1.6 [1.8] and 1.4 [1.0] months, respectively; $P = .71$). The causes of death within 30 days are listed in **Table 3**.

Table 3. Causes of 30-Day POM

Causes of 30-d POM	No. (%) of Patients
Anastomotic leak or gastric conduit complication	35 (30.70)
Respiratory complications	22 (19.30)
Sepsis and multiple-organ failure	16 (14.04)
Cardiac complications	12 (10.53)
Mesenteric ischemia	4 (3.51)
Sequelae of leak from duodenal stump	3 (2.63)
Pancreatitis and sepsis	3 (2.63)
Others/unknown	19 (16.67)
All Causes	114 (100.00)

Abbreviation: POM, postoperative mortality.

On the basis of univariate analysis, the following variables available at the time of surgery were statistically related to POM: being 60 years or older ($P = .002$), increasing ASA score ($P < .001$), grade III or IV toxic effects during neoadjuvant treatment ($P = .007$), metastatic disease diagnosed preoperatively or perioperatively ($P = .002$), and extended resection ($P = .005$). The number of resections performed increased with time, and POM during the 3 periods studied increased (3.3%, 3.4%, and 5.6%, respectively; $P = .02$). For the entire study period, POM in high- and low-volume centers was 3.9% and 5.5%, respectively ($P = .07$).

Grade III or IV toxic effects during neoadjuvant treatment occurred in 92 patients and were mainly digestive, neurological, and hematological. Eight of these patients (8.7%) died within 30 days of surgery. In patients with good tolerance of neoadjuvant therapy (n = 491), 14 postoperative deaths occurred (2.9%), associated with a lower POM ($P = .007$).

On multivariate analysis (**Table 4**), metastatic disease diagnosed preoperatively or perioperatively (odds ratio, 9.13 [95% CI, 3.29-25.35]; $P < .001$) and poor tolerance of neoadjuvant therapy (3.33 [1.25-8.85]; $P = .02$) were independently predictive of POM. We found an independently protective factor in centers performing a high volume of resections (odds ratio, 0.29 [95% CI, 0.12-0.72]; $P = .008$).

Late POM and Postoperative Morbidity

From postoperative days 30 to 90, 46 patients died (1.72%). Nine of these patients died of the consequences of an anastomotic leak; 9, cardiorespiratory complications; 8, sepsis and multiple-organ failure; 5, hemorrhage; and 15, other or unknown causes.

Surgical morbidity occurred in 717 patients (26.85%), and 81 of these died within 30 days of surgery, for a POM rate of 11.3% ($P < .001$). Of 678 patients with medical morbidity, 59 postoperative deaths (8.7%) occurred ($P < .001$). A combination of surgical and medical morbidity occurred in 373 patients, and Clavien-Dindo Scale morbidity was associated with POM ($P < .001$). Grades 1, 2a, 2b, and 3 morbidity occurred in 133, 395, 311, and 73 patients, respectively.

Table 4. Factors Predictive of 30-Day POM Identified by Multivariate Analysis

Variable	χ^2 Value	OR (95% CI)	*P* Value
Metastases diagnosed preoperatively or perioperatively	18.05	9.13 (3.29-25.35)	<.001
High-volume center, ≥10 vs <10 cases	7.06	0.29 (0.12-0.72)	.008
Grade III or IV toxic effects during neoadjuvant treatment[a]	5.80	3.33 (1.25-8.85)	.02
Extended resection of adjacent organs	0.72	0.54 (0.13-2.24)	.40
ASA grade	0.45	1.26 (0.64-2.47)	.50
Age of patient, ≤60 vs >60 y	0.32	0.76 (0.29-1.98)	.57
Resection radicality (R0, R1, and R2)	0.01	0.99 (0.44-2.24)	.98

Abbreviations: ASA, American Society of Anesthesiologists; OR, odds ratio; POM, postoperative mortality.

[a] Toxic effects of neoadjuvant therapy were defined according to the National Cancer Institute Toxicity Criteria Scale (version 2.0).

Table 5. Factors Predictive of 30-Day Postoperative Morbidity Identified by Multivariate Analysis

Variable	χ^2 Value	OR (95% CI)	*P* Value
Age, ≤60 vs > 60 y	13.73	1.50 (1.21-1.85)	<.001
ASA score	13.79	1.29 (1.13-1.47)	<.001
Total vs partial gastrectomy	27.08	0.57 (0.46-0.71)	<.001
Extended resection of adjacent organs	10.22	1.55 (1.18-2.02)	.001
Period of study	9.65	1.21 (1.07-1.36)	.002
Sex	6.68	0.76 (0.62-0.93)	.01
Tumor location	4.89	0.72 (0.54-0.96)	.03
Malnutrition	0.67	1.10 (0.87-1.39)	.42

Abbreviations: ASA, American Society of Anesthesiologists; OR, odds ratio.

Early postoperative morbidity before day 30 was recorded for 1214 patients. In univariate analysis, early postoperative morbidity correlated with the later period of study ($P = .06$), male sex ($P < .001$), esophageal and Siewert types I and II lesions ($P < .001$), being older than 60 years ($P < .001$), high ASA grade ($P < .001$), weight loss of at least 10% of body weight ($P = .02$), extended resection ($P = .03$), and total gastrectomy ($P < .001$). Neoadjuvant therapy and the occurrence of grade III or IV toxic effects ($P = .46$ and $P = .23$, respectively) and the presence of metastatic disease at diagnosis, advanced cTNM stage, and resection radicality ($P = .60$, $P = .34$, and $P = .16$, respectively) did not result in higher rates of postoperative morbidity. The multivariate analysis of factors predictive of postoperative morbidity before day 30 is shown in **Table 5**.

Comment

Surgery for JGA endures as the most effective treatment in providing locoregional control of disease and a chance of long-term survival. Although perioperative staging, treatment, and care have all improved, the prognosis remains relatively poor. If surgery is to provide a maximal chance of long-term survival, then POM must be minimized and patient selection for surgical resection optimized. We undertook this study to identify the predictive factors for POM.

The 30-day POM was 4.27%, and the in-hospital mortality to 90 days was 5.99%, comparing favorably with many studies,[1,7,15,16] especially because we conducted a multicenter study. The following factors on univariate analysis were related to POM: age, ASA score, tolerance of neoadjuvant chemotherapy, metastatic disease diagnosed preoperatively or perioperatively, and extended resection. Increasingly, age is recognized as a factor that might increase risk but should not in itself prevent a rigorous surgical approach.[1,17,18] Although the ASA score is established as a reliable predictor of complicated postoperative course and death,[19] we did not find this to be so. The ASA score is limited by its subjectivity and wide interobserver variability, especially in a multicenter setting. The higher POM in the final period of study, during which more resections were performed, appears counterintuitive. This finding likely reflects a variety of differences in tumor and patient variables and resection patterns between high- and low-volume centers resulting from an ongoing process of centralization.

We found the presence of metastatic disease to be independently predictive of POM. Data regarding the value of palliative gastric resection come largely from retrospective series without real consensus regarding survival advantage.[20,21] However, a generalized consensus exists that a palliative resection can be recommended only for patients of reasonable physical condition, where metastatic disease is limited in extent, or where warranted by symptoms. Patients with advanced disease are often malnourished and have less physiological reserve, and the potential benefit of palliative resection needs to be balanced against the heightened surgical risks and the effect on quality of life.

Two other factors that proved to be independently predictive of POM were surgical resection in high-volume centers and grades III to IV toxic effects of neoadjuvant therapy. Centralization of upper gastrointestinal tract cancer services is based on the belief that high-volume centers will improve the quality of surgical resection, reduce perioperative risk, and enhance patient survival. Our series confirmed that centers performing more than 10 resections per year were independently predictive of lower POM. Data correlating high-volume centers with survival beyond 30 days after JGA

resection are becoming more robust.[7] Differences in POM are likely not associated with large differences in complication rates, but rather with the ability of higher-volume centers to rescue patients from complications when they occur.[22,23] The literature on whether hospital volume affects longer-term survival is not decisive, and the definition of what constitutes high volume has varied widely.[7] For surgery to improve long-term survival, POM must be minimized, and the rationale for centralizing JGA resections appears valid.

The effect of preoperative chemotherapy on postoperative complications has remained controversial. Long-term survival depends not only on early diagnosis and the radicality of surgery but also on the use of a modern-multimodality oncological therapy.[8,24] The period of the present study (1997-2010) largely predated the European studies reporting on the long-term survival benefit and treatment efficacy of neoadjuvant therapy,[8,9] explaining the relatively low number of patients (655 [24.53%]) receiving this treatment. Despite this finding, grades III and IV toxic effects observed during the neoadjuvant phase have been identified as independently predictive of POM. This major finding has significant implications for planning surgical resection because surgery after poor tolerance of neoadjuvant therapy appears to augment patient risk. A paucity of literature addresses this issue. The European standard of care for JGAs is influenced by 2 randomized trials[8,9] of perioperative chemotherapy in patients with JGA. The MAGIC trial[8] randomized patients to 3 cycles of epirubicin-cisplatin-fluorouracil chemotherapy before and after surgery or to surgery alone. Its well-documented results report a significant 5-year survival benefit (36% vs 23%), an R0 resection rate of 69%, and a similar POM between the 2 groups (5.6% vs 5.9%), confirming the acceptability and place in the treatment algorithm of perioperative chemotherapy. At a very minimum, 23.8% of patients had grade III or IV toxic effects of treatment, and POM for this subset of patients is not reported. A second French randomized controlled trial[9] compared perioperative fluorouracil and cisplatin chemotherapy with surgery alone. Again, preoperative therapy significantly increased R0 resection rates (84% vs 73%; $P = .04$), with no difference in POM and a similar significant increase in overall survival at 5 years (38% vs 24%). A POM rate for the 37% of patients with grade III or IV treatment toxic effects is again not reported.

The only literature we found to support our findings comes from a smaller retrospective study of 238 patients undergoing esophageal resection after neoadjuvant treatment.[25] Patients with grade I or II toxic effects or no toxic effects had significantly lower POM compared with patients with grade III or IV toxic effects (1.1% vs 6.9%; $P = .03$), whereas neoadjuvant therapy was not predictive of POM ($P = .17$). This result closely mirrors our current findings, which we suggest may reflect the heterogeneity of this tumor group, in which molecular and enzymatic tumor expression may determine not only tumor response to therapy but also the likelihood of treatment toxicity.[26] In the future, trials should include an analysis of the effects of poor neoadjuvant treatment tolerance on perioperative and oncological outcomes. The identification of subgroups of patients likely to have grades III and IV toxic effects could help to define a tailored therapeutic algorithm according to individual risk. A strategy of interrupting neoadjuvant therapy in favor of immediate surgery has already been proposed in patients demonstrating a poor metabolic response to treatment.[27] A similar strategy could be of interest for patients who tolerate neoadjuvant treatment poorly or who manifest poor tolerance and poor metabolic response to neoadjuvant treatment. This possibility leads one to anticipate the era of effective individualized treatment.

This study has limitations. Its retrospective and multicenter nature leads to missing data that may introduce some bias. However, the very large sample size offers a unique opportunity to study a rare event, such as POM, and gives enough statistical robustness to identify its predictors. Moreover, the multicenter data collection allows more universal results. Furthermore, our assertion that grades III and IV toxic effects of neoadjuvant treatment are associated with higher POM assesses a smaller cohort because only 655 patients received this treatment. However, this variable is highly significant in multivariate analysis, suggesting its strong clinical importance.

In conclusion, this study of 2670 patients undergoing JGA resection during a 14-year period demonstrated an overall mortality rate of 4.27%. Metastatic disease, tolerance to neoadjuvant treatment, and hospital resection volume are independently predictive of POM. The finding that patients who tolerate neoadjuvant therapy poorly are at higher risk of postoperative death is novel and warrants further analysis in prospective trials with appropriate subgroup analysis.

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