

Original Investigation

Predictive Factors of Postoperative Mortality After Junctional and Gastric Adenocarcinoma Resection

William B. Robb, MD; Mathieu Messenger, MD; Diane Goere, MD; Virginie Pichot-Delahaye, MD; Jeremie H. Lefevre, MD, PhD; Damien Louis, MD; Jérôme Guiramand, MD; Kevin Kraft, MD; Christophe Mariette, MD, PhD; for the FREGAT Working Group-FRENCH

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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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The French Eso-Gastric Tumors (FREGAT) Working Group-Fédération de Recherche en Chirurgie (FRENCH) members are listed at the end of this article.

Corresponding Author: Christophe Mariette, MD, PhD, Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Regional University Hospital Center, Place de Verdun, 59037 Lille CEDEX, France (christophe.mariette@chru-lille.fr).

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 hos-

pitals 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 antroploric 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			P Value
	All (N = 2670)	No Mortality (n = 2556)	30-d Mortality (n = 114)	
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). Dis-

crete 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%

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.

($n = 160$) (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.

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 trial⁸ 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 trial⁹ 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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Author Affiliations: Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Regional University Hospital Center, Lille, France (Robb, Messenger, Mariette); Faculty of Medicine, North of France University, Lille, France (Messenger, Mariette); Team 5 "Mucins, Epithelial Differentiation, and Carcinogenesis," Institut National de la Santé et de la Recherche Médicale, Unite Mixte de Recherche 837, Jean-Pierre Aubert Research Centre, Lille, France (Messenger, Mariette); Department of Digestive Surgery, Gustave Roussy Institute, Villejuif, France (Goere); Department of Digestive Surgery, Lyon University Hospital, Lyon,

France (Pichot-Delahaye); Department of Digestive Surgery, St Antoine University Hospital, Paris, France (Lefevre); Department of Digestive Surgery, Toulouse University Hospital, Toulouse, France (Louis); Department of Digestive Surgery, Paoli Calmette Institute, Marseille, France (Guiramand); Department of Digestive Surgery, Tours University Hospital, Tours, France (Kraft).

Author Contributions: *Study concept and design:* Robb and Mariette.

Acquisition of data: Messenger, Goere, Pichot-Delahaye, Lefevre, Louis, Guiramand, and Kraft.
Analysis and interpretation of data: Robb and Mariette.

Drafting of the manuscript: Robb, Kraft, and Mariette.
Critical revision of the manuscript for important intellectual content: Robb, Messenger, Goere,

Pichot-Delahaye, Lefevre, Louis, Guiramand, and Mariette.

Statistical analysis: Robb and Mariette.

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Study supervision: Goere and Mariette.

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Group Members: Members of the French Eso-Gastric Tumors (FREGAT) Working Group—Fédération de Recherche en Chirurgie (FRENCH) include Jean Pierre Arnaud, MD, and Dorothee Brachet, MD (Department of Digestive Surgery, Angers University Hospital, Angers, France); Jean Michel Balon, MD, and Sylvain Fabre, MD (Department of Digestive Surgery, Clinique Jules Verne, Nantes, France); Frédéric Borie, MD,

PhD, and Michel Prudhomme, MD (Department of Digestive Surgery, Nîmes University Hospital, Nîmes, France); Cécile Brigand, MD, PhD, and Manuel Fernandez, MD (Department of Digestive Surgery, Strasbourg University Hospital, Strasbourg, France); Nicolas Carrere, MD, PhD, and Damien Louis, MD (Department of Digestive Surgery, Toulouse University Hospital, Toulouse, France); Xavier-Benoit D'Journo, MD, PhD, and Pascal-Alexandre Thomas, MD, PhD (Department of Digestive Surgery, Nord University Hospital, Marseille, France); Pierre Dechelotte, MD, PhD (Department of Pathology, Clermont-Ferrand University Hospital, Clermont-Ferrand, France); Jean Robert Delpero, MD, and Jérôme Guiramand, MD (Department of Digestive Surgery, Paoli Calmette Institute, Marseille, France); Abdenaceur Dhari, MD, and Jean-Marc Regimbeau, MD, PhD (Department of Digestive Surgery, Amiens University Hospital, Amiens, France); Renaud Flamein, MD, Brigitte Gillet, RGN, Benjamin Mathieu, and Denis Pezet, MD, PhD (Department of Digestive Surgery, Clermont-Ferrand University Hospital), Aude Glaise, MD, and Bertrand Millat, MD (Department of Digestive Surgery, Montpellier University Hospital, Montpellier, France); Olivier Glehen, MD, PhD (Department of Digestive Surgery, Lyon Sud University Hospital, Lyon, France); Diane Goéré, MD, and Amine Souadka, MD (Department of Digestive Surgery, Gustave Roussy Institute, Villejuif, France); Marie Guilbert, RGN, Ariane Poisson, PharmD, and Florence Vandois, MD (Department of Digestive Surgery, Lille University Hospital, Lille, France); Noël Hutten, MD, and Kevin Kraft, MD (Department of Digestive Surgery, Tours University Hospital, Tours, France); Jérémie H. Lefevre, MD, and François Paye, MD, PhD (Department of Digestive Surgery, St Antoine University Hospital, Paris, France); Emmanuelle Leteurtre, MD, PhD (Department of Pathology, Lille University Hospital); Jean Yves Mabrut, MD, PhD, and Viginie Pichot-Delahaye, MD (Department of Digestive Surgery, Lyon University Hospital, Lyon); Bernard Meunier, MD, and Timothée Thiébot, MD (Department of Digestive Surgery, Rennes University Hospital, Rennes, France); Sophie Michalak, MD (Department of Pathology, Angers University Hospital); Francis Michot, MD, and Basile Tsilivlidis, MD (Department of Digestive Surgery, Rouen University Hospital, Rouen, France); Frédérique Peschard, MD, PhD (Department of Digestive Surgery, Ambroise Paré University Hospital, Boulogne-Billancourt, France); and Marc Pocard, MD, PhD (Department of Digestive Surgery, Lariboisière University Hospital, Paris).

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REFERENCES

1. Lepage C, Sant M, Verdecchia A, Forman D, Esteve J, Faivre J; EUROCARE working group.

Operative mortality after gastric cancer resection and long-term survival differences across Europe. *Br J Surg*. 2010;97(2):235-239.

2. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R. Cancer of the stomach: a patient care study by the American College of Surgeons. *Ann Surg*. 1993;218(5):583-592.

3. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol*. 2003;56(1):1-9.

4. Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. *Eur J Cancer Prev*. 1992;1(3):265-269.

5. Lord RV, Law MG, Ward RL, Giles GG, Thomas RJ, Thursfield V. Rising incidence of oesophageal adenocarcinoma in men in Australia. *J Gastroenterol Hepatol*. 1998;13(4):356-362.

6. Mariette C, Piessen G, Briez N, Gronnier C, Triboulet JP. Oesophagogastric junction adenocarcinoma: which therapeutic approach? *Lancet Oncol*. 2011;12(3):296-305.

7. Anderson O, Ni Z, Møller H, et al. Hospital volume and survival in oesophagectomy and gastrectomy for cancer. *Eur J Cancer*. 2011;47(16):2408-2414.

8. Cunningham D, Allum WH, Stenning SP, et al; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11-20.

9. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCO multicenter phase III trial. *J Clin Oncol*. 2011;29(13):1715-1721.

10. National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Cancer Therapy Evaluation Program: common terminology criteria for adverse events, version 3.0. March 31, 2003; published August 9, 2006. <http://ctep.cancer.gov>. Accessed February 16, 2013.

11. Messenger M, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C; FREGAT Working Group-FRENCH. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. *Ann Surg*. 2011;254(5):684-693.

12. Sobon LH, Wittekind C; International Union Against Cancer (UICC), eds. *UICC TNM Classification of Malignant Tumors*. 6th ed. New York, NY: Wiley-Liss; 2002.

13. Watanabe HJJ, Sobin LH. *Histological Typing of Gastric Oesophageal and Gastric Tumours: WHO International Histological Classification of Tumors*. 2nd ed. New York, NY: Springer-Verlag; 1990.

14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213.

15. McCulloch P, Ward J, Tekkis PP; ASCOT Group of Surgeons; British Oesophago-Gastric Cancer Group. Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. *BMJ*. 2003;327(7425):1192-1197.

16. Valenti V, Hernandez-Lizoain JL, Beorlegui MC, et al. Morbidity, mortality, and pathological response in patients with gastric cancer preoperatively treated with chemotherapy or chemoradiotherapy. *J Surg Oncol*. 2011;104(2):124-129.

17. Bouvier AM, Launoy G, Lepage C, Faivre J. Trends in the management and survival of digestive tract cancers among patients aged over 80 years. *Aliment Pharmacol Ther*. 2005;22(3):233-241.

18. Saif MW, Makrilia N, Zalonis A, Merikas M, Syrigos K. Gastric cancer in the elderly: an overview. *Eur J Surg Oncol*. 2010;36(8):709-717.

19. Sauvanet A, Mariette C, Thomas P, et al. Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. *J Am Coll Surg*. 2005;201(2):253-262.

20. Kokkola A, Louhimo J, Puolakkainen P. Does non-curative gastrectomy improve survival in patients with metastatic gastric cancer? *J Surg Oncol*. 2012;106(2):193-196.

21. Huang KH, Wu CW, Fang WL, et al. Palliative resection in noncurative gastric cancer patients. *World J Surg*. 2010;34(5):1015-1021.

22. Böttcher K, Siewert JR, Roder JD, Busch R, Hermanek P, Meyer HJ; German Stomach Cancer Study Group ('92). Risk of surgical therapy of stomach cancer in Germany: results of the German 1992 Stomach Cancer Study. *Chirurg*. 1994;65(4):298-306.

23. Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. *Med Care*. 2011;49(12):1076-1081.

24. Sakuramoto S, Sasako M, Yamaguchi T, et al; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357(18):1810-1820.

25. Ruol A, Portale G, Castoro C, et al. Effects of neoadjuvant therapy on perioperative morbidity in elderly patients undergoing esophagectomy for esophageal cancer. *Ann Surg Oncol*. 2007;14(11):3243-3250.

26. Fareed KR, Kaye P, Soomro IN, et al. Biomarkers of response to therapy in oesophago-gastric cancer. *Gut*. 2009;58(1):127-143.

27. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol*. 2007;8(9):797-805.