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Palliative Resection for Advanced Gastric and Junctional Adenocarcinoma: Which Patients will Benefit from Surgery?

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ABSTRACT

Background. Whereas palliative chemotherapy offers a median survival of approximately 10 months in advanced gastric and junctional adenocarcinoma (AGJA), the survival impact of primary tumor resection is controversial. Our purpose was to identify which AGJA patients benefit from palliative resection.

Methods. In 3,202 AGJA patients scheduled for surgery in 21 French centers between 1997 and 2010, prognostic factors were identified in palliative group and the impact of each combination of these factors on survival was studied.

Results. Surgery was defined as palliative due to solid organ metastasis (5.6 %), localized (4.6 %) or diffuse (2.3 %) peritoneal carcinomatosis (PC), or incomplete tumoral resection (12.8 %). Median survival of AGJA patients resected with a palliative intent ($n = 677$) was longer than in nonresected patients ($n = 532$; 11.9 vs. 8.5 months, $P < 0.001$). Multivariable analyses identified ASA score III-IV ($P < 0.001$) as a predictor of postoperative mortality and solid organ metastasis ($P = 0.009$), localized PC ($P = 0.004$), diffuse PC ($P = 0.046$), and signet ring cell histology (SRC; $P = 0.02$) as predictors of survival. Only ASA I–II patients with incomplete resection without metastasis or PC, one site solid organ metastasis without PC, or localized PC without SRC had a survival benefit after palliative surgery with median survivals from 12.0 to 18.3 months. Nonresected ASA I–II patients with same risk factors had median survivals from 3.5 to 8.8 months ($P < 0.05$ for each).

Conclusions. In AGJA, patient and tumor-related factors should be used to select candidates for palliative surgery in association with chemotherapy.

At the time of diagnosis, advanced gastric and junctional adenocarcinomas (AGJA) most commonly present with locally advanced or metastatic disease and they remain a leading cause of cancer-related death worldwide.[1,2]

Surgery is the treatment of choice for nonmetastatic and resectable tumors and may offer the chance of long-term survival; however, the role of palliative surgical resection in AGJA is questionable. For such patients, a median survival without resection of 3 to 5 months can be anticipated.[3] Palliative systemic chemotherapy has been shown to enhance both patients' survival and quality of life, offering in most trials a median survival of approximately 10 months.[3,4] In such advanced disease, surgical resection is usually recommended in cases with problematic symptoms, such as obstruction or bleeding, to provide best palliation and improve patients' quality of life. Beyond these cases, the impact of palliative resection in AGJA remains controversial due to poor evaluation and a lack of clarity that it provides a significant benefit. Palliative resection, combined with systemic therapy, should be

The study was conducted on FREGAT (French Eso-Gastric Tumors) working group—FRENCH (Fédération de Recherche EN CHirurgie). The collaborators group is given in Appendix.

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considered if it can provide symptomatic relief and improve survival, whilst at the same time be associated with an acceptable rate of postoperative morbidity and mortality.[5–8] Some older publications suggest that age and the number of metastatic sites may help to define which patients will benefit from palliative surgical resection;[9,10] however, these broad selection criteria need to be better defined as the approach to gastric cancer and patient' selection is refined. The purpose of this study was to identify which patients with AGJA could benefit from palliative resection based on both the patient and tumor characteristics of a large multicenter cohort. For this, results of palliative surgery, predictors of postoperative mortality, predictors of palliative surgery, and survival of subgroups of patients will be determined.

PATIENTS AND METHODS

This retrospective national survey was conducted at 21 French surgical centers that registered all of their consecutive AGJA cases between January 1997 and January 2010. For each patient, investigators completed a standardized questionnaire, double-checked by independent observers, and all data was entered into a dedicated database. Surgery was defined as palliative in cases of solid organ metastasis, localized or diffuse peritoneal carcinomatosis (PC), or incomplete tumoral resection. Malnutrition was defined as a weight loss >10 % of baseline weight during a 6-month period.

Pretreatment Workup

Pretreatment investigations included a physical examination, standard laboratory tests, an esophagogastroduodenal barium study, a digestive endoscopy with biopsies, and a thoracoabdominal computed tomography (CT). Endoscopic ultrasound was not routinely performed according to center practice.

Surgical Approach

The surgical approach has been reported in detail elsewhere.[11] Briefly, in absence of solid organ metastasis or diffuse PC, an attempt for curative surgery was performed. For antropyloric tumors, a subtotal gastrectomy most often was performed, whereas for other gastric tumor locations a total gastrectomy was indicated, combined with an extended lymphadenectomy preserving the spleen and the pancreatic tail. Resection of the neighboring organs was performed in cases of suspected or confirmed neoplastic involvement. For tumor invading the esogastric junction, resection was extended to the esophagus using either a transthoracic or transhiatal approach with dedicated mediastinal lymphadenectomy.[12] According to results of previous publications that did not find any benefit for palliative surgery for multiorgan metastatic disease,[9,13] deliberate palliative surgery was considered in this study for patients with peroperative discovery of only one solid organ metastatic site and/or limited PC (defined as localized in cases of few metastases to the adjacent peritoneum or diffuse in cases of metastases to the distant peritoneum).[14] In this setting, the main goal was to remove the primary tumor with no systematic attempt for a complete resection of the macroscopic metastatic disease. Patients with more than one solid organ metastatic site and or with an extended PC (invasion of more than one abdominal region with numerous tumoral nodules) were referred for non surgical palliation. High-volume surgical centers were defined as centers with at least ten surgical procedures for AGJA per year.

Preoperative and Postoperative Treatments

Beginning in 2005 with the MAGIC study publication,[15] perioperative chemotherapy based on epirubicin-cisplatinum-fluorouracil (ECF) was proposed for tumors deemed to be resectable and staged IB and above. The following year, the CF regimen was proposed as an alternative to the ECF regimen.[16] Metastatic first-line postoperative chemotherapy was left to the discretion of the multidisciplinary specialists meeting, with regimes mainly based on either a doublet association of 5-fluorouracil-platinum therapy or 5-fluorouracil–irinotecan or a triplet association of 5-fluorouracil-platinum therapy in combination with epirubicin or docetaxel.

Histopathologic Analysis

Pathological staging was based on the sixth UICC/TNM classification.[17] Resections were designated as R0 when the clearance was complete. Otherwise the resection was defined as incomplete due to histological evidence of invasion of the longitudinal or lateral margins or macroscopic residual tumor. Signet ring cell adenocarcinomas (SRC) were adenocarcinomas in which the predominant component (more than 50 % of the tumor) consists of isolated or small groups of malignant cells containing intracytoplasmic mucins.[18] Advanced pTNM stages indicate stage III and stage IV tumors.

Follow-up

All patients surviving operation were followed until death or the time of closing the database (March 2010). During follow-up, patients underwent clinical examination, abdominal ultrasonography or CT, and chest radiography

approximately every 6 months for 5 years and annually thereafter. The survival status of the patients was determined in March 2010, and the median follow-up was 31.5 (range, 0.6–106.9) months. Eighty-one patients (7.7 %) were lost at follow-up.

Statistical Analysis

Statistical analysis was performed by using SPSS® version 15.0 software (SPSS, Chicago, IL). Data are shown as the prevalence, mean (standard deviation), or median (range). Continuous data were compared by using the Mann-Whitney *U* test. Ordinal data were compared by using the χ^2 test or the Fisher exact test as appropriate. Survival was estimated using the Kaplan-Meier method and included postoperative deaths. The predictive factors of survival were analyzed by Cox proportional hazard regression analysis using a stepwise procedure. To determine predictors of palliative surgery and of postoperative mortality, a stepwise logistic regression model was used, in which all covariates were adjusted simultaneously. The 0.1 level was defined for entry into the model except for redundant variables. ASA score was introduced into the model due to the clinical importance of this variable in the palliative context. Multivariate χ^2 and *P* values were used to characterize the independence of these factors. The hazard ratio (HR) and 95 % confidence interval (CI) were used to quantify the relationship between survival and each independent factor. All statistical tests were two-sided, with the threshold of significance set at $P < 0.05$. The study complied with the French National Health guidelines on research involving human subjects.

RESULTS

Palliative Surgery

Among the 3,202 patients with AGJA scheduled for surgery, 1,209 (37.8 %) underwent a noncurative approach, with palliative surgical resection in 677 (21.1 %) and palliation without surgery in 532 (16.6 %) patients. Among resected patients, surgery was defined as palliative due to peroperative discovery of solid organ metastasis ($n = 150$, 5.6 %), localized ($n = 122$, 4.6 %) or diffuse ($n = 62$, 2.3 %) PC, or incomplete tumoral resection ($n = 343$, 12.8 %). To verify that surgery has a place in the palliative setting, we looked at median survival in AGJA patients resected with a palliative intent. Compared with patients who had palliation without surgery, the median survival was significantly higher in the palliative resection group (11.9 months (95 % CI 10.9–12.9) and 8.5 months (95 % CI 8.2–9.7), respectively, $P < 0.001$; Fig. 1) but significantly less than that of the curative surgery group (11.9 months (95 % CI 10.9–12.9) vs. 48.2 months (95 % CI 41.7–54.8), $P < 0.001$).

Having shown that palliative surgery offers an overall survival benefit, we aimed to identify tumoral variables that predicted palliative surgery by comparison of the curative and palliative surgical groups (Table 1). Based on univariate analysis in this surgical population, seven variables were found to be statistically associated with palliative resection: malnutrition ($P < 0.001$), gastric rather than a junctional location ($P < 0.001$), signet ring cell (SRC) histology ($P < 0.001$), pT ($P < 0.001$), pN ($P < 0.001$), pM ($P < 0.001$), and pTNM ($P < 0.001$) stages. Neoadjuvant chemotherapy administration, mainly based on fluorouracil-platinum therapy (87.6 %), with doublet (56.2 %) or triplet (in association with epirubicin 43.8 %), was not associated with a protective impact over palliative surgery occurrence (Table 1). Multivariate analysis identified three independent predictors of palliative surgery: advanced pT ($P < 0.001$, OR 1.58, 95 % CI 1.4–1.8) and pN ($P < 0.001$, OR 1.48, 95 % CI 1.3–1.7) stages and SRC histology ($P < 0.001$, OR 1.8, 95 % CI 1.4–2.3; Table 2).

Predictors of Postoperative Mortality

Having identified tumoral predictive factors associated with palliative resection, we identified which patient variables may influence a physician's decision regarding the value of palliative surgery. For this, through the surgically treated population ($n = 2{,}670$), we determinate factors

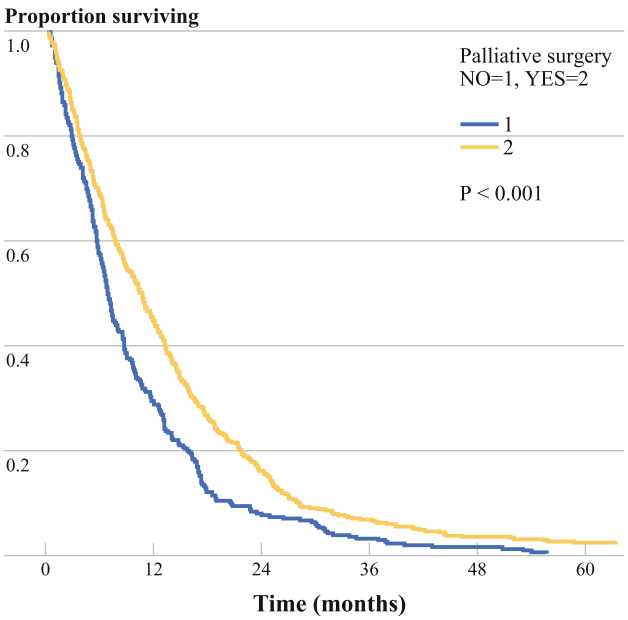

FIG. 1 Survival curves of patients that benefited from palliative surgical resection versus those who had palliative exclusive chemotherapy

TABLE 1 Univariate analyses of tumoral variables that predicted palliative surgery by comparison of the curative and palliative surgical groups

Variables		Surgery		
	$N = 2,670$ (%)	Palliative $N = 677$ (%)	Curative $N = 1,993$ (%)	p
Gender				0.16
Male	1,873 (70.9)	455 (67.2)	1,438 (72.2)	
Female	777 (29.1)	222 (32.8)	555 (27.8)	
Age (year)				0.95
≤ 60	953 (35.7)	260 (38.4)	693 (34.8)	
> 60	1,717 (64.3)	417 (61.6)	1,300 (65.2)	
ASA score				0.63
I–II	2,043 (76.5)	505 (74.6)	1,538 (77.2)	
III–IV	627 (23.5)	172 (25.4)	455 (22.8)	
Malnutrition				<0.001
Yes	507 (19)	183 (27)	324 (16.3)	
No	1,973 (73.9)	441 (65.1)	1,532 (76.9)	
Not specified	190 (7.1)	53 (7.9)	137 (6.8)	
Localization				
Gastric	1,896 (71)	528 (78)	1,368 (68.6)	<0.001
EGJ	774 (29)	149 (22)	625 (31.4)	
SRC histology				<0.001
Yes	1,171 (43.9)	392 (57.9)	779 (39.1)	
No	1,499 (56.1)	285 (42.1)	1,214 (60.9)	
Extended resection to the neighboring organs				<0.001
Yes	316 (11.8)	193 (28.5)	123 (6.2)	
No	2,354 (88.2)	484 (71.5)	1,880 (93.8)	
pTNM stage				<0.001
I	814 (30.5)	36 (5.3)	778 (39)	
II	455 (17)	48 (7.1)	407 (20.4)	
III	1,071 (40.1)	265 (39.1)	806 (40.5)	
IV	330 (12.4)	328 (48.5)	2 (0.1)	
pT category				<0.001
pT0	73 (2.7)	4 (0.6)	69 (3.5)	
pTis	36 (1.3)	0 (0)	36 (1.8)	
pT1	443 (16.6)	27 (4)	416 (20.9)	
pT2	820 (30.7)	125 (18.5)	695 (34.9)	
pT3	952 (35.7)	325 (48)	627 (31.4)	
pT4	346 (13)	196 (28.9)	150 (7.5)	
pN category				<0.001
pN0	945 (35.4)	80 (11.8)	865 (43.4)	
pN1	860 (32.2)	207 (30.6)	653 (32.8)	
pN2	529 (19.8)	204 (30.1)	325 (16.3)	
pN3	336 (12.6)	186 (27.5)	150 (7.5)	
pM category				<0.001
pM0	2,342 (87.7)	349 (51.6)	1,993 (100)	
pM1	328 (12.3)	328 (48.4)	0 (0)	
Neoadjuvant chemotherapy				0.757
Yes	655 (24.5)	169 (25)	486 (24.4)	
No	2,015 (75.5)	508 (75)	1,507 (75.6)	
Surgery center				0.221

TABLE 1 continued

Variables		Surgery		
	$N = 2,670$ (%)	Palliative $N = 677$ (%)	Curative $N = 1,993$ (%)	p
High volume	2,015 (75.5)	503 (74.3)	1,512 (75.9)	
Low volume	655 (24.5)	174 (25.7)	481 (24.1)	

Malnutrition indicates weight loss > 10 % of physical weight during a 6-month period

ASA American Society of Anesthesiologists; *SRC* Signet ring cell adenocarcinoma; *EGJ* Esogastric junction

TABLE 2 Multivariable analysis of independent predictors of palliative surgery

Variables	p	χ^2	OR	95 % CI
Advanced pT stage	<0.001	37.3	1.6	1.4–1.8
Advanced pN stage	<0.001	34.2	1.5	1.3–1.7
SRC histology	<0.001	18.7	1.8	1.4–2.3
Malnutrition	0.109	2.6	1.3	0.9–1.7
ASA score III–IV	0.119	2.4	1.2	1–1.4
Localization (EGJ vs. gastric)	0.227	1.5	0.8	0.6–1.1
Extended resection to the neighboring organs	0.667	0.2	0.9	0.5–1.7
Gender (male vs. female)	0.886	0.02	1	0.7–1.3
pM stage	0.992	0	0	0–10

Malnutrition indicates weight loss > 10 % of physical weight during a 6-month period

ASA American Society of Anesthesiologists; *SRC* signet ring cell adenocarcinoma; *EGL* esogastric junction; *CI* confidence interval; *OR* odds ratio

TABLE 3 Multivariable analysis of independent variables predictors of postoperative mortality

Variables	p	χ^2	OR	95 % CI
ASA score III–IV	<0.001	23.7	2.0	1.5–2.6
Palliative surgery	0.02	5.4	1.6	1.1–2.5
High-volume surgical center	0.28	1.2	0.8	0.5–1.2
Age > 60 years	0.289	1.1	1.3	0.8–2.1
Malnutrition	0.847	0.04	1.0	0.7–1.7

Malnutrition indicates weight loss > 10 % of physical weight during a 6-month period

ASA American Society of Anesthesiologists; *CI* confidence interval; *OR* Odds ratio

associated with postoperative mortality. In-hospital mortality rate was significantly higher in the palliative group compared with the curative group (8.6 % vs. 5.1 %, respectively, $P = 0.001$). Based on univariate analysis, eight variables were found to be statistically related to postoperative mortality: ASA score III–IV ($P < 0.001$), age > 60 years ($P = 0.001$), palliative surgery ($P = 0.002$), postoperative complication ($P < 0.001$), pT ($P = 0.006$), pM ($P = 0.009$), and pTNM ($P = 0.027$) stages and a low-volume surgical center ($P = 0.029$). Finally, two independent variables were found to be predictors of postoperative mortality in multivariate analysis: ASA score III or IV ($P < 0.001$, OR 2.0, 95 % CI 1.5–2.6) and palliative surgery ($P = 0.02$, OR 1.6, 95 % CI 1.1–2.5; Table 3). Postoperative mortality rate was threefold higher in ASA III–IV patients compared with ASA I–II patients (11.6 % vs 4.3 %, $P < 0.001$), justifying palliative resection only in ASA I–II patients.

Which Patients will Exhibit a Survival Benefit from Palliative Surgery?

Having demonstrated that palliative surgery independently increases the risk of postoperative mortality, we aimed to identify tumor associated prognostic factors in the palliative surgery group ($n = 677$, Table 4). Univariate analysis exhibited 12 variables statistically related to poor survival: ASA score III–IV ($P < 0.001$), malnutrition ($P < 0.001$), no extended resection to the neighboring organs ($P < 0.001$), advanced pTNM ($P < 0.001$), pT ($P < 0.001$) or pN stages ($P < 0.001$), pM1 stage ($P < 0.001$), peroperative discovery of a PC ($P = 0.002$), diffuse form of PC ($P = 0.012$), SRC histology ($P = 0.002$), low-volume surgical center ($P = 0.021$), and no postoperative chemotherapy administration ($P < 0.001$; Table 4). At least one cycle of postoperative chemotherapy was administered in 307 of 677 patients, based on a doublet association of 5-fluorouracil–platinum therapy or 5-fluorouracil–irinotecan in 74.2 % of cases, or a triplet association of 5-fluorouracil–platinum therapy in combination with epirubicin or docetaxel in 25.8 % of cases. Median number of cycles was four.[1–20] Postoperative radiotherapy was administered in 12.3 % of cases, mainly in association with 5-fluorouracil. More than half of the patients (54.7 %) did not receive postoperative treatment largely due to poor general status.

To individualize prognostic variables that can influence palliative resection decision-making, we included only pre

TABLE 4 Univariable analysis of tumor associated prognostic factors in the palliative surgery group

Variables	No. patients $N = 677$ (%)	Median survival (months)	95 % CI	p
Gender				0.106
Male	455 (67.2)	12.2	11–13.4	
Female	222 (32.8)	10.4	8.5–12.3	
Age (year)				0.100
≤ 60	260 (38.4)	12.5	11.2–13.7	
> 60	417 (61.6)	11.3	9.9–12.6	
ASA score				<0.001
I–II	505 (74.6)	12.6	10.7–14.6	
III–IV	172 (25.4)	7.7	3.9–13.1	
Malnutrition				<0.001
Yes	183 (27)	8.8	6.7–10.8	
No	441 (65.1)	13.1	11.3–14.8	
Not specified	53 (7.9)	ND	ND	
Localization				0.87
Gastric	528 (78)	11.8	10.7–12.9	
EGJ	149 (22)	12.2	10.5–14	
SRC Histology				0.002
Yes	392 (57.9)	11.2	10.2–12.2	
No	285 (42.1)	13	10.8–15.2	
Extended resection to neighboring organs				<0.001
Yes	193 (28.5)	13	11.7–14.3	
No	484 (71.5)	8.2	6.2–10.2	
pTNM stage				<0.001
I	36 (5.3)	55.7	7.1–104.3	
II	48 (7.1)	21	14.8–27.2	
III	265 (39.1)	12.8	11.5–14.1	
IV	328 (48.5)	9.7	8.3–11.1	
pT stage				<0.001
pT0	4 (0.6)	5.3	ND	
pT1	27 (4)	71.9	29.1–114.7	
pT2	125 (18.5)	13.3	10.9–15.8	
pT3	325 (48)	11.7	10.4–13	
pT4	196 (28.9)	10.2	8.5–11.9	
pN stage				<0.001
pN0	80 (11.8)	27.6	7.9–47.4	
pN1	207 (30.6)	12.4	10.7–14.2	
pN2	204 (30.1)	11.9	10.2–13.6	
pN3	186 (27.5)	8.7	6.8–10.6	
pM stage				<0.001
pM0	349 (51.6)	14	11.9–16.1	
pM1	328 (48.4)	9.8	8.4–11.3	
Solid organ metastasis				<0.001
Yes	184 (27.2)	8.6	6.7–10.5	
No	493 (72.8)	13	11.9–14.1	
Peritoneal carcinomatosis				0.002
Yes	122 (66.3)	10.2	8.2–12.3	
No	62 (33.7)	7	6–8	
If peritoneal carcinomatosis ($n = 184$)				0.012
Localized	165 (24.4)	8.6	6.4–10.8	
Diffuse	512 (75.6)	12.7	11.4–14	
Surgical center				0.021
High volume	503 (74.3)	12.3	11.2–13.4	
Low volume	174 (25.7)	10.2	8.8–11.7	
Preoperative chemotherapy				0.543
Yes	169 (25)	11.4	10.2–12.6	
No	508 (75)	12.1	10.9–13.3	
Postoperative chemotherapy				<0.001
Yes	301 (44.5)	15.3	12.4–18.2	
No	376 (55.5)	8.6	7–10.1	

ASA American Society of Anesthesiologists; *SRC* Signet ring cell adenocarcinoma; *EGJ* Esogastric junction; *ND* Not determined

Malnutrition indicates weight loss > 10 % of physical weight over a 6-month period

and peroperative variables in the multivariate analysis. Taking into account confounding factors, we identified four independent prognostic variables associated with poor survival: localized PC ($P = 0.004$, HR 2.7, 95 % CI 1.4–5.4), solid organ metastasis ($P = 0.009$, HR 2.5, 95 % CI 1.3–4.9), SRC histology ($P = 0.02$, HR 1.6, 95 % CI 1.1–2.3), and diffuse PC ($P = 0.046$, HR 1.4, 95 % 1.1–2.1; Table 5).

Having shown that (1) only ASA score I–II patients exhibited an acceptable postoperative mortality rate, and (2) tumor-related variables, such as localized PC, solid organ metastasis, SRC histology and diffuse PC negatively influence long-term survival, we proceeded to evaluate the median survival of each combination of these factors in the ASA score I–II patients (Table 6). We then compared median survivals obtained to the median survival usually reported after exclusive palliative chemotherapy (10 months) to identify which subgroups of patients may benefit from palliative resection.

Patients with (1) diffuse PC, (2) metastasis combined with PC, or (3) localized PC of SRC had median survivals from 1.3 to 9.3 months. Patients with (1) incomplete resection

without either metastasis or PC, (2) one site solid organ metastasis without PC, or (3) localized PC without SRC had median survivals from 12.0 to 18.3 months, suggesting a palliative resection survival benefit for these patients.

Finally, to confirm that surgery offers a significant survival benefit for these subgroups, we looked at median survivals of each of the subgroups in the nonresected ASA I–II population (Table 6). Nonresected patients with (1) incomplete resection without either metastasis or PC, (2) one site solid organ metastasis without PC, or (3) localized PC without SRC had median survivals from 3.5 to 8.8 months ($P < 0.05$ for each), confirming the positive impact of palliative surgical resection for these patients.

DISCUSSION

In AGJA, surgical resection combined with pre and/or postoperative chemo(radio)therapy is the standard treatment in the curative setting, whereas palliative chemotherapy alone is usually proposed for AGJA offering a significant but modest survival benefit.[3] In this palliative setting, resection is highly controversial mainly due to poor evaluation of subgroups of patients that may benefit from such strategy.[19–23]

In the present study, median survival of AGJA patients resected with a palliative intent ($n = 677$) was significantly longer than in nonresected patients ($n = 532$; 11.9 vs. 8.5 months, $P < 0.001$), representing a survival gain of approximately one third in this devastating disease. The median survival with palliative chemotherapy alone is reported to be of approximately 10 months in the literature;[3] we found a median survival of only 8.5 months in this large series of unselected non resected AGJA. These results justify palliative surgery over exclusive chemotherapy in a group of patients who need to be carefully delineated. Four relevant predictors of prolonged survival were found. One was a patient-related factor, ASA I or II score, and the others were tumor-related factors, incomplete resection without metastasis or PC, one site solid organ metastasis without PC and localized PC without SRC. Our results neither support palliative surgical resection in ASA III–IV patients, due to a nonacceptable threefold higher risk for postoperative mortality, nor do they support palliative resection in patients who present with important metastatic tumoral spread. Such metastatic tumoral load includes those patients with diffuse PC or solid organ metastasis combined with PC, as well as patients with a limited peritoneal spread with SRC histology on diagnostic biopsy.

Age has been frequently reported as a significant variable to be taken into account for palliative surgery, with higher risk of postoperative mortality reported for patients

TABLE 5 Multivariable analysis of independent prognostic variables associated with poor survival that can influence palliative resection decision-making

Variables	p	χ^2	HR	CI (95 %)
Localized peritoneal carcinomatosis	0.004	8.5	2.7	1.4–5.4
Solid organ metastasis	0.009	6.8	2.5	1.3–4.9
Signet ring cell histology	0.020	5.4	1.6	1.1–2.3
Diffuse peritoneal carcinomatosis	0.046	3.9	1.4	1.1–2.1
ASA score III–IV	0.051	3.8	1.3	0.9–1.6
Advanced pTNM stage	0.984	0.1	1.0	0.8–1.3

ASA indicates American Society of Anesthesiologists

Advanced pTNM stage indicates stage III and stage IV tumors

TABLE 6 Evaluation of the median survival of each combination of identified factors in ASA score I–II patients who underwent palliative surgical resection ($n = 215$) or no resection ($n = 290$)

Independent predictors of survival				Palliative resection ($n = 215$)			No resection ($n = 290$)		
Diffuse PC	Localized PC	Solid organ metastasis	SRC histology	No. of patients	Median survival (months)	95 % CI	No. of patients	Median survival (months)	95 % CI
No	No	No	No	34	16.3	3.7–21.8	43	8.8	5–12.6
No	No	No	Yes	12	12.5	11–13	23	8.5	3.2–10.8
No	No	Yes	No	65	14.3	13.2–15.3	75	8	6.6–9.6
No	No	Yes	Yes	28	12	11–13	10	4.1	2.7–5.5
No	Yes	No	No	15	18.3	17–18.9	8	3.5	0.1–7.5
No	Yes	No	Yes	8	9.3	8.3–10	6	4.5	2.2–9.5
Yes	No	Yes	No	15	9	7.9–9.9	6	6.5	4.1–9.8
No	Yes	Yes	No	9	1.3	0.9–5.6	48	7.6	4.7–10.9
Yes	No	Yes	Yes	11	9.2	4.5–12.3	7	1.9	0.1–6.1
No	Yes	Yes	Yes	18	7	5.5–14.1	64	6.5	4.4–8.6

PC Peritoneal carcinomatosis; *SRC* Signet ring cell; *ASA* American Society of Anesthesiologists

Advanced pTNM stages indicate stage III and stage IV tumors

older than 70 years.[3,24,25] As also reported in other pathologies, age no longer appears to be of significant prognostic value in recent series with more emphasis being placed on patient's performance status.[25–27] An ASA score of III or above is shown in our study to be the most important predictor of postoperative mortality, whatever the age, and also was associated with poor long-term survival.

Extension of the metastatic spread has been frequently correlated with poor survival in palliative surgery. This is illustrated by both the extent of the PC, with diffuse PC being associated with lower survival rates,[24] and also by the number of metastatic sites involved, with numerous publications reporting lower survival rates with multiple sites of metastatic disease.[3,9,24,25,28] It is for this reason that the present study investigated the role of palliative surgery only in patients with at most one solid organ metastatic site, with or without association with PC. This refined patient selection, and the large cohort, allowed us to identify subgroups of patients who should be eligible for palliative resection. Moreover, rather than solely an evaluation of the impact of individual factors on patient survival, our evaluation of the effect of a combination of these factors on patient survival allows for more rigorous selection and identification of the patients who will gain benefit from palliative resection. On this basis of the combined patient- and tumor-related characteristics, the optimal selection of candidates for palliative surgery may be performed. Another relevant and innovating finding is the prognostic impact of SRC in this situation, because even in the case of a localized PC, no survival benefit was found for palliative surgery. This is important because this peroperative discovery of PC is frequent in SRC,[18] with current systemic chemotherapy regimens thought to be of relatively poor efficacy.[11]

This study has some limitations. Its retrospective nature does not give us the opportunity to identify which parameters were taken into account prospectively by surgeons to proceed to palliative surgical resection for each individual. Moreover, even if a large number of patients has been included, number of events in each prognostic factor combination group could have been too low to reach statistical relevance. Finally, quality of life has been not evaluated and we may expect that it would be of great interest in this palliative setting, because survival benefit may be challenged by treatment toxicity. Some studies have reported an improved quality of life with palliative surgery,[29,30] and we may expect that optimal patient selection, as proposed here, may reinforce these data. Some very recent evidence shows that survival can be enhanced in the palliative setting by adding an anti HER2 therapy, such as trastuzumab in AGJA, leading to a median survival of 13.8 months compared with 11.1 months in the control group.[31] This therapeutic weapon was not available at the time of the present study. Moreover, the median survival of more than 10 months in the trial's control group suggests a selection of patients with better prognosis. This is reinforced by the median survival of 8.5 months observed in the nonresected group of our study. Finally, only approximately 15 % of patients exhibiting strong expression of HER2 can benefit from such targeted therapy and HER2 level of expression is usually not available at time of surgical exploration for AGJA deemed to be resectable, as included in the present study. In the future, an evaluation of the role of palliative surgery in HER2 patients may contribute to optimize the selection.

To conclude, this study offers some evidence that subgroups of patients may benefit from palliative resection instead of exclusive chemotherapy alone. In AGJA with peroperative discovery of locally advanced or metastatic disease, patients for whom palliative surgery will offer some survival benefit are ASA I-II patients with (1) incomplete primary tumor resection without metastasis or PC, (2) one site solid organ metastasis without PC, or (3) localized PC without SRC. Other clinical presentations have to be enrolled in exclusive palliative chemotherapy programs.

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APPENDIX

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