



Conversion gastrectomy for stage IV unresectable gastric cancer: a GIRCG retrospective cohort study

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Abstract

Background The aim of this study is to report the experience with conversion surgery from six Gruppo Italiano Ricerca Cancro Gastrico (GIRCG) centers, focusing our analysis on factors affecting survival and the risk of recurrence.

Methods A retrospective, multicenter cohort study was performed in patients who had undergone conversion gastrectomy between 2005 and 2017. Data were extracted from a GIRCG database including all metastatic gastric cancer patients submitted to surgery. Only stage IV unresectable tumors/metastases which became resectable after chemotherapy were included in this analysis.

Results Forty-five resected M1 patients were included in the analysis. Reasons for being deemed unresectable at diagnosis were peritoneal involvement (PCI > 6) ($n = 38$, 84.4%), distant metastatic nodes ($n = 3$, 6.6%) and extensive liver involvement ($n = 4$, 8.8%). Median follow-up was 25 months (IQR 9-50). Median overall survival from surgery was 15 months and 1-, 3- and 5-year survivals were 57.2, 36.1 and 24%, respectively. Median progression-free survival was 12 months with 1- and 3-year survival of 46.4 and 33.9%, respectively. At cox regression analysis the only independent prognostic factor for OS was the presence of more than one type of metastasis (HR 4.41, 95% CI 1.72–11.3, $p = 0.002$). A positive microscopic resection margin was the only risk factor for recurrence (HR 5.72, 95% CI 1.04–31.4, $p = 0.045$).

Conclusions Unresectable stage IV GC patients could benefit from radical surgery after chemotherapy and achieve long survivals. The main prognostic factor for these patients was the presence of more than one type of extra-gastric metastatic involvement.

Keywords Stage IV gastric cancer · Conversion surgery · Palliative chemotherapy · Metastases · Gastrectomy · Survival

Introduction

Stage IV gastric cancer carries a poor prognosis. As per current guidelines [1, 2] the only therapeutic option for these patients could be palliative chemotherapy which may offer survivals up to 24 months [3]. However, there is growing literature reporting long survivals in those cases (stage IV gastric cancer) who responded to palliative chemotherapy and were subsequently submitted to gastrectomy [4–11]. In particular, this multimodal treatment, which was defined as conversion surgery, could be associated with significant improved survivals of more than 40 months when R0 resection could have been achieved [5, 11].

Still, literature about conversion surgery is scarce and studies are usually characterized by limited sample sizes and

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different definitions [7, 12]. In addition, to date, all but one study was performed on a cohort from a western center [7].

With this paper, we aim to report the experience of six GIRCG centers with conversion surgery, focusing our analysis on factors affecting survival and the risk of recurrence.

Materials and methods

Study design

A retrospective, multicenter cohort study was performed in patients who had undergone conversion gastrectomy April 1, 2005 and January 1, 2017 in 6 centers belonging to Gruppo Italiano Ricerca Cancro Gastrico (GIRCG) centers. Data were extracted from a GIRCG database including all metastatic gastric cancer patients submitted to surgery. Only stage IV GC which became resectable, (showing partial or complete response) after chemotherapy were included in this analysis.

Definitions

Patients' diagnosis, treatment and perioperative care were performed as recommended by GIRCG guidelines in all participating centers [2]. Conversion surgery was defined as a surgical treatment aiming at R0 resection for tumors that were deemed unresectable before chemotherapy. As per study protocol, the definition of an unresectable tumor/metastasis before chemotherapy was based on technical and oncological reasons and included: peritoneal cancer index (PCI) (as defined by Sugarbaker et al. [13]) > 6, bilobar hepatic metastases, nodal involvement outside D1-3 stations, technically unresectable metastases.

Staging laparoscopy was performed in all patients before chemotherapy. The re-assessment for resectability was based on the imaging performed during treatment at 3–6 months. Surgery was proposed only to those patients in whom gastrectomy and associated resections could have been potentially radical. In particular, the peritoneal involvement was considered for treatment only in case of PCI < 6 at exploration after palliative chemotherapy.

All specimens were histopathologically classified according to Lauren's microscopic criteria [14]. Tumor stage was presented as indicated by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) [15]. All cases were also grouped as proposed by Yoshida et al. [16].

Variables

Baseline characteristics collected included sex, age, American Society of Anaesthesiologists (ASA) score, type of

preoperative chemo- and/or radiotherapy, preoperative staging (pTNM). Operative variables collected included type of procedure and lymphadenectomy, additional resections, intraoperative multimodal treatments and number of lymph node harvested. Tumor-related variables included pathology stage (pTNM), resection margin status, tumor regression grade, Lauren's histotype and grading. Complications were all collected up to the day of discharge and graded according to Clavien et al. [17]. Progression-free survival (PFS) and overall survival (OS) were the primary outcome measures.

Statistical analysis

Continuous data were presented as median and interquartile range (IQR). The Kaplan–Meier curve was used to calculate survival rates. OS was calculated as the time between both diagnosis and surgery and death/last follow-up. PFS was defined as the time between surgery and the first evidence of disease recurrence/progression and was calculated for all patients excluding R2 resections. Cox regression was performed to find independent factors affecting survival after surgery. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated when required. Only variables with $p < 0.050$ at univariate analysis were entered in multivariable analyses in a stepwise manner. Follow-up was calculated as recommended elsewhere [18]. Analyses were performed with MedCalc Statistical Software (MedCalc Software bvba, Ostend, Belgium).

Results

In total, 287 stage IV GC patients were screened, of whom 242 were excluded for reasons (193 had no preoperative chemotherapy, 38 had preoperative chemotherapy for technically resectable disease, 11 had no details about preoperative period), leaving 45 patients for analysis. Patients' characteristics at diagnosis are presented in Table 1. Reasons for being deemed unresectable at diagnosis were peritoneal involvement ($n = 38$, 84.4%), distant metastatic nodes ($n = 3$, 6.6%) and extensive liver involvement ($n = 4$, 8.8%).

Operative variables are shown in Table 2. In 33 (73.3%) cases peritoneal resections were required while in 3 these were not performed due to the extent of the disease. Two patients with peritoneal involvement had complete response after palliative chemotherapy and peritonectomy procedures were not performed as no residual disease was found. Postoperative complications occurred in 18 (40%) patients; and they had a Clavien–Dindo grade above 2 in 14 cases (31.1%). Tumor-related variables are presented in Table 3.

Median follow-up was 25 months (IQR 9–50). Median overall survival was 15 months and 1-, 3- and 5-year survivals were 57.2, 36.1 and 24%, respectively (Fig. 1). Median

Table 1 Patients' characteristics at diagnosis

Age—median (IQR)	54 (48–61)
Female, <i>n</i> (%)	18 (40)
ASA > 2, <i>n</i> (%)	2 (4.1)
Tumor site, <i>n</i> (%)	
Upper third	6 (13.3)
Middle third	12 (26.7)
Lower third	18 (40)
Linitis	9 (20)
cT, <i>n</i> (%)	
cT3	9 (20)
cT4	33 (73.3)
Not available	3 (6.7)
cN, <i>n</i> (%)	
N0	10 (22.2)
N+	35 (77.8)
cM, <i>n</i> (%)	
M1	45 (100)
Positive peritoneal cytology <i>n</i> (%)	10 (22.2)
Yoshida types	
1	0 (0)
2	7 (15.5)
3	29 (64.4)
4	9 (20)
Types of palliative chemotherapy	
Cisplatin plus fluoropyrimidine	20 (44.4)
Epirubicin and Cisplatin plus fluoropyrimidine	9 (20)
Docetaxel and Oxaliplatin plus fluoropyrimidine	9 (20)
Other types	7 (15.5)

Table 2 Operative variables

Type of procedure, <i>n</i> (%)	
Total gastrectomy	33 (73.3)
Subtotal gastrectomy	12 (26.7)
Type of lymphadectomy, <i>n</i> (%)	
D1	4 (8.9)
D2	19 (42.2)
D3	22 (48.9)
Additional procedure, <i>n</i> (%)	
None	23 (51.1)
>1 additional resection	7 (15.5)
Colectomy	6 (13.3)
Splenectomy	5 (11.1)
Distal pancreatectomy	2 (4.4)
Small bowel resection	1 (2.2)
Distal splenopancreatectomy	1 (2.2)
HIPEC, <i>n</i> (%)	23 (51.1)

HIPEC hyperthermic intraperitoneal chemotherapy

Table 3 Pathology variables

Residual disease, <i>n</i> (%)	
R0	30 (66.6)
R1	7 (15.5)
R2	8 (17.7)
Gastric margin status, <i>n</i> (%)	
R0	40 (88.9)
R1	5 (11.1)
pT	
T2	2 (4.4)
T3	15 (33.3)
T4a	23 (51.1)
T4b	5 (11.1)
pN	
N0	3 (6.6)
N1	5 (11.1)
N2	7 (15.5)
N3a	10 (22.2)
N3b	17 (37.8)
Nx	3 (6.6)
pM	
M1	45 (100)
Lymphnodes harvested <i>n</i> (%)	
< 16	3 (6.6)
15–29	2 (4.4)
30–44	13 (28.9)
45–59	13 (28.9)
60–74	13 (28.9)
> 75	1 (2.2)
TRG T site (<i>n</i> = 28)	
1b	7 (14.3)
2	8 (16.3)
3	13 (26.5)
Not specified	21 (42.8)
Lauren's histotype, <i>n</i> (%)	
Intestinal	11 (24.4)
Diffuse	29 (64.4)
Mixed	4 (8.8)
Not specified	1 (2.2)
Tumor grade	
G2	4 (8.8)
G3	34 (75.5)
Not specified	7 (15.5)

TRG tumor regression grade

OS calculated from diagnosis of GC was 20.6 months with 1-, 3- and 5-year survival of 78.2, 38.6 and 26.5%. Median PFS was 12 months with 1- and 3-year survival of 46.4 and 33.9%, respectively (Fig. 2).

At cox regression analysis the only independent prognostic factor for OS was the presence of more than one type of

Fig. 1 Kaplan-Meier curve of overall survival for the whole cohort

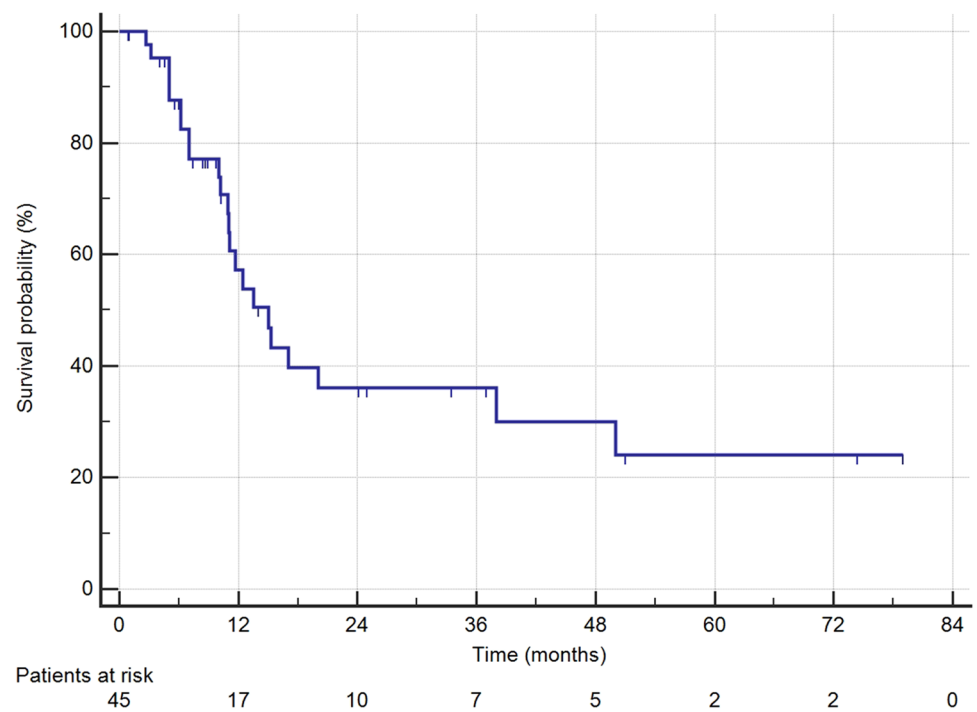
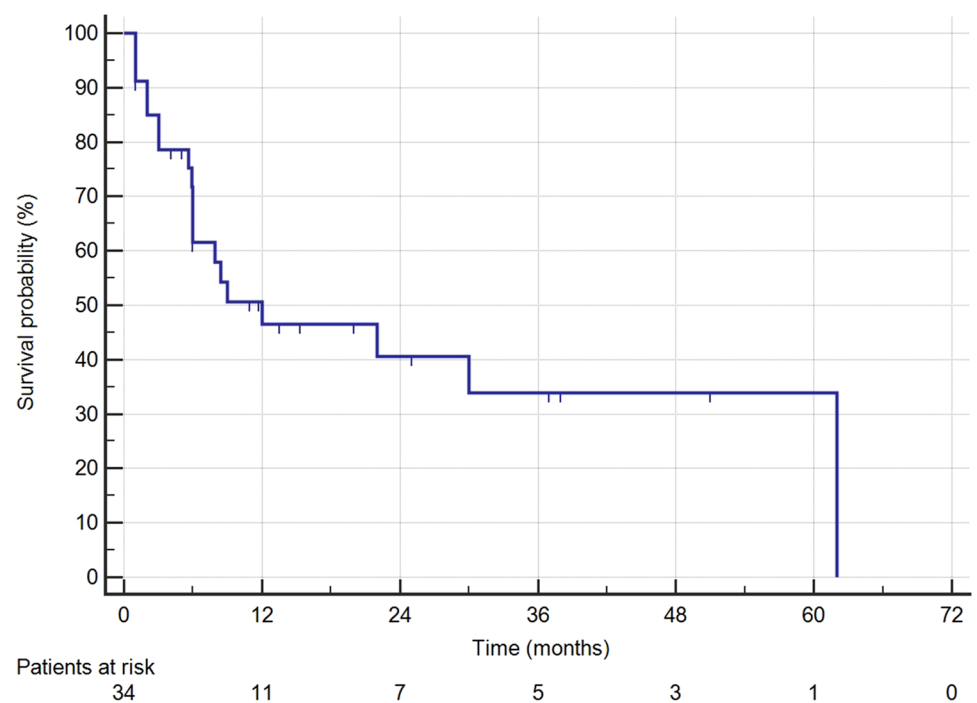


Fig. 2 Kaplan-Meier curve of progression free survival



metastasis (HR 4.41, 95% CI 1.72–11.3, $p=0.002$) (Table 4) (Fig. 3). A positive microscopic resection margin was the only risk factor for recurrence (HR 5.72, 95% CI 1.04–31.4, $p=0.045$) (Table 5).

Discussion

Stage IV unresectable gastric cancer patients could benefit from surgery, which may offer prolonged survival.

More than 20 years ago, first, Nakajima et al. [8] described similar findings. Authors showed that unresectable

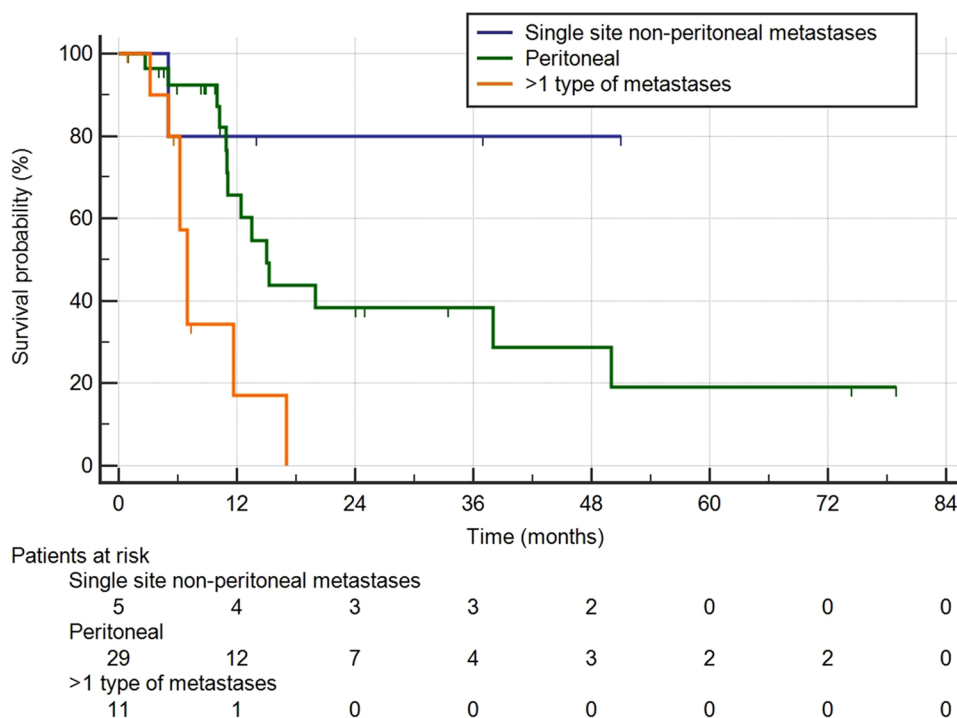
Table 4 Cox regression analysis of overall survival

Variable	n	OS			
		Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	p
Age*	45	1.01 (0.96–1.05)	0.467		
Sex					
Male	27	1.00	1.000		
Female	18	0.75 (0.31–1.84)	0.536		
ASA	43	1.00	1.000		
≤2	2	2.76 (0.63–12.1)	0.180		
>2					
cT					
cT3	9	1.00	0.000		
cT4	33	1.91 (0.56–6.49)	0.305		
cN					
cN0	10	1.00	1.000		
cN+	35	1.29 (0.67–2.51)	0.444		
Type of lymphadenectomy					
D1	4	1.00	1.000		
D2	19	0.46 (0.12–1.72)	0.253		
D3	22	0.27 (0.07–1.07)	0.065		
Additional resection					
No	23	1.00	1.000		
Yes	22	1.35 (0.58–3.13)	0.485		
HIPEC					
No	22	1.00	1.000		
Yes	23	0.85 (0.37–1.91)	0.689		
Postoperative complications					
No	27	1.00	1.000		
Yes	18	0.80 (0.33–1.94)	0.622		
Lymphnode harvested*	45	0.97 (0.93–1.01)	0.108		
Grading					
G2	4	1.00	1.000		
G3	34	1.04 (0.30–3.56)	0.949		
Lauren's hystotype					
Intestinal	11	1.00	1.000		
Diffuse	29	0.87 (0.37–2.32)	0.877		
Mixed	4	4.16 (1.01–17.2)	0.049		
pT					
pT<4	17	1.00	1.000		
pT4a-b)	28	1.5 (0.62–3.62)	0.365		
pN					
N0	3	1.00	1.000		
N1	5	0.63 (0.08–4.51)	0.649		
N2	7	1.39 (0.23–8.32)	0.721		
N3a	10	2.32 (0.48–11.3)	0.295		
N3b	17	1.11 (0.23–5.35)	0.897		
Radical treatment					
R0	30	1.00	1.000		
R1	7	0.93 (0.21–4.09)	0.922		
R2	8	2.24 (0.67–7.54)	0.194		
Type of metastasis					
Single site, non-peritoneal	5	1.00	1.000		
Peritoneal	29	4.37 (0.57–33.1)	0.156		
> 1 type	11	16.0 (1.91–134.7)	0.011	4.41 (1.72–11.3)	0.002

Table 4 (continued)

*Analyzed as continuous variables
 HIPEC hyperthermic intraperitoneal chemotherapy

Fig. 3 Kaplan-Meier curves of overall survival according to the type of extra-gastric involvement



GC could become resectable after intensive chemotherapy and found that long survivors were only in the group of patients who could have radical surgery after chemotherapy.

Since then, an increasing number of researchers tried to investigate the role of the combination of preoperative/palliative/induction chemotherapy followed by surgery in the treatment of advanced unresectable gastric cancer. Currently, literature demonstrated that so-called conversion surgery for unresectable stage III or stage IV gastric cancer was associated with longer survival than chemotherapy alone. The most recent studies on stage III/IV unresectable patients undergoing conversion surgery reported survivals ranging from 37 to 56 months [4, 5, 7, 9–11, 19–22].

The survival reported in our study is lower than those reported by others and this could be ascribed to the inclusion criteria we selected for our analysis. As such, our study population included only part of stage IV patients who had undergone chemotherapy plus surgery. In particular, we excluded from this study all stage IV GC patients who had chemotherapy plus surgery with $PCI \leq 6$, unilobar technically resectable hepatic metastasis, only positive cytology or positive nodal metastases in D3 stations. As a consequence, our inclusion criteria identified a selected population composed mainly by Yoshida type 3 and 4 patients for whom an extraordinary response to chemotherapy could have led to the complete resection of the primary tumor and the

peritoneal, nodal and liver metastases. As it has been highlighted by Yoshida et al. [16] and Yamaguchi et al. [11], peritoneal metastases in these cases may be technically resected but they often recur. In our study, a sub-population of Yoshida type 3 (macroscopic peritoneal dissemination without other organs involvement) patients showed unexpected survivals, being more than 35% alive 3 years after surgery. We believe that the results presented in this study may recommend not to exclude surgery a priori in selected advanced cases of stage IV GC.

In our analysis we found that more than one type of metastasis significantly affect prognosis. Similar findings were found by other authors [5, 10, 22], who showed that more than one non-curative factors were associated with a poor prognosis in unresectable GC patients. In light of those findings, it might be suggested not to proceed with surgery in those patients who have more than one district involved by metastases. Still, further data are required to confirm this hypothesis.

To date, the highest level of evidence about stage IV gastric cancer and the potential benefit of surgery in these patients is available thanks to the REGATTA trial [23]. This study showed that stage IV patients can benefit from surgery in terms of survival only when this is radical. Recently, these conclusions were also reached by the analyses of retrospective series of stage IV/unresectable patients undergoing

Table 5 Cox regression analysis of disease-free survival

Variable	n	PFS ^o			
		Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	p
Age*	34	0.99 (0.95–1.04)	0.744		
Sex					
Male	21	1.00	1.000		
Female	13	0.93 (0.38–2.29)	0.871		
ASA					
≤2	33	1.00	1.000		
>2	1	2.34 (0.29–18.4)	0.421		
cT					
cT3	7	1.00	1.000		
cT4)	25	2.33 (0.51–10.6)	0.275		
cN (cN0 vs cN+)		0.65 (0.31–1.36)	0.258		
Type of lymphadenectomy					
D1	3	§	0.069		
D2	13	2.37 (0.93–6.02)	1.000		
D3	18	1.00			
Additional resection					
No	16	1.00	1.000		
Yes	18	0.53 (0.20–1.34)	0.187		
HIPEC					
No	15	1.00	1.000		
Yes	19	0.69 (0.26–1.84)	0.469		
Postoperative complications					
No	24	1.00	1.000		
Yes	10	2.53 (0.16–1.20)	0.112		
Lymphnode harvested*	45	1.01 (0.97–1.06)	0.466		
Grading					
G2	4	1.00	1.000		
G3	24	2.99 (0.39–22.7)	0.292		
Lauren's hystotype					
Intestinal	10	1.00	1.000		
Diffuse	19	2.00 (0.63–6.39)	0.244		
Mixed	4	4.38 (0.95–20.2)	0.059		
pT					
pT < 4	12	1.00	1.000		
pT4a-b	21	2.19 (0.77–6.22)	0.141		
pN					
N0	3	§	0.594		
N1	2	§			
N2	5	0.66 (0.14–3.00)	0.438		
N3a	8	1.49 (0.54–4.12)			
N3b	14	1.00	1.000		
Radical treatment					
R0	30	1.00	1.000	5.72 (1.04–31.4)	0.045
R1	4	5.72 (1.04–31.4)	0.045		
Type of metastasis					
Single site, non-peritoneal	5	1.00	1.000		
Peritoneal	21	0.90 (0.19–4.16)	0.895		
> 1 type	8	3.29 (0.64–16.8)	0.153		

*Analyzed as continuous variables, § no cases of recurrence, calculated on 34 patients (of 37 R0-R1 patients, 3 did not have details about recurrence), HIPEC hyperthermic intraperitoneal chemotherapy

induction chemotherapy followed by surgery [5, 11]. Yamaguchi et al. [11] in their multi institutional study on 77 stage IV GC patients who had undergone conversion surgery found that median survival was 41.3 for R0 patients while it was 21.2 months for R1-2.

Our study, which is the largest in the western literature, confirmed that R0 conversion surgery was associated with a significantly longer PFS than R1 resections. In our opinion, this latter finding further highlights the importance of radical surgery in the attempt to improve survival in metastatic GC patients.

Current literature about conversion surgery lacks of standardized definitions as it was also highlighted by Terashima [12]: the criteria for initial determination of oncologically unresectable or determination of resectability post-chemotherapy are heterogeneous among studies and results should always be interpreted in light of these differences. An effort from the scientific community would be required to find common definitions, and thus, reliable results in future studies.

The main limitation of this study is that the long study period covers several advances in oncology and, thus, in the chemotherapy regimens adopted. This resulted in a heterogeneous population in terms of type of chemotherapy used which made it difficult to understand the real impact of a regimen in the achievement of complete/partial response.

In conclusion, conversion gastrectomy is a treatment option for selected patients with stage IV GC. The main prognostic factor for these patients was the presence of more than one type of extra-gastric metastatic involvement. A radical procedure was significantly associated with a reduced risk of recurrence.

Compliance with ethical standards

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Conflict of interest The authors declare that they have no conflict of interest.

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