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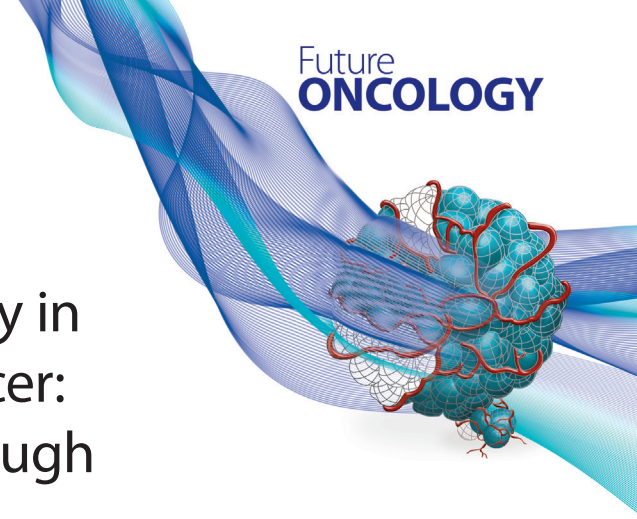

Selecting patients for gastrectomy in metastatic esophago-gastric cancer: clinics and pathology are not enough

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Aim: To evaluate the impact on overall survival (OS) of gastrectomy in asymptomatic metastatic esophago-gastric cancer. **Patients & methods:** Five hundred and thirteen patients were included. The role of surgery and other clinico-pathological factors was evaluated by univariate and Cox regression analyses. OS was the primary end point. **Results:** Multivariate analysis confirmed that gastrectomy was a predictor of longer OS ($p < 0.001$), as well as preserved performance status and benefit from first-line chemotherapy. None of the investigated clinico-pathological variables identified preferable candidates for surgery (all $p > 0.05$). **Conclusion:** Palliative gastrectomy might play a role in asymptomatic metastatic esophago-gastric cancer patients with good performance status who received benefit from first-line chemotherapy. Future prospective trials integrating tumor biology among inclusion criteria may help defining the optimal candidates.

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KEYWORDS
• chemotherapy • metastatic gastric cancer • palliative gastrectomy

Gastric cancer (GC) represents the fifth most common malignancy worldwide, accounting for 6.8% of the total cancer incidence and 8.8% of annual deaths from cancer in the world [1]. Surgery offers the only chance for cure, but its feasibility is limited to early stages of the disease. With the exception of eastern countries where aggressive surveillance is often implemented, however, most cases are detected when radical resection is no longer beneficial: indeed, in western regions up to 80% of patients with GC present with stage IV disease [1,2]. Systemic chemotherapy (CT) represents the most effective therapeutic option in these patients, since it significantly increased overall survival (OS) and positively impacted on quality of life (QoL) compared with best supportive care alone [2]. Nonetheless, the overall outcome remains dismal, median OS being in the range of 10–12 months in most studies [2] even after the introduction of effective biologic agents [3–6].

Up to half of all patients with metastatic GC present severe or impelling symptoms, such as obstruction, bleeding or perforation and in these cases surgical resection has an established role, supported by major guidelines [7,8]. In other malignancies (such as breast, kidney and colorectal cancers) resection of the primary tumor appears to have a positive prognostic impact in pauci-symptomatic or asymptomatic metastatic patients [9–11]. With regard to GC and gastro-esophageal junction cancer

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(GEJC), beyond palliation of the above mentioned gastrointestinal symptoms, the impact of surgical resection remains controversial due to the lack of evidence from randomized trials [12].

New interest about the role of surgery in advanced GC/GEJC patients has been recently awakened by improvements in surgical techniques [13] and better supportive measures that may be combined with systemic CT. Two randomized studies have recently evaluated the role of surgery in noncurable GC and both trials were closed before the planned accrual was reached. The GYMSSA trial, a single center prospective randomized trial conducted in the USA, compared gastrectomy, metastasectomy, hyperthermic intraperitoneal CT and systemic CT with systemic CT alone: the trial was prematurely stopped due to poor accrual after only 17 patients had been enrolled [14]. More relevantly, the REGATTA trial was a Phase III study conducted in 44 Asian centers among 175 patients with metastatic GC and a single non-curable factor [15], patients were randomly assigned to systemic CT alone or gastrectomy followed by CT. The study was closed after the first interim analysis had crossed the limits for futility. In contrast with this evidence, previous data from nonrandomized series suggested that surgery could be associated with an OS benefit in selected advanced GC cases [16]. Nevertheless, results of subgroup analyses from randomized trials and retrospective data do not allow for proper identification of potential candidates for surgery [15,17].

On the basis of this background, we reported our multicenter experience conducted in selected referral Italian centers with the aim to evaluate the impact on OS of primary tumor resection in advanced GC and GEJC patients without severe digestive symptoms and to identify those cases with the highest chances of benefit from an intensive approach in this setting.

Patients & methods

• Patient selection

We retrospectively collected clinical data of patients with metastatic GC or GEJC diagnosed between January 2002 and December 2015 and followed in 19 Italian centers. Main selection criteria for case inclusion were the following: histologically confirmed gastric or gastro-esophageal junction adenocarcinoma; locally advanced (unresectable) or metastatic disease at diagnosis; patients experiencing distant disease progression <6 months after a possibly radical resection of the primary tumor were also included in the surgical group; no major symptoms referred to the primary tumor (defined as complete gastric outlet obstruction, gastric perforation or bleeding requiring two or more transfusions of red cell concentrates per week); treatment with at least two lines of systemic CT for advanced disease (to allow for adequate exposure to the most effective cytotoxic and targeted agents), regardless of the regimens received; mandatory anti-HER2 therapy with trastuzumab in patients with known HER-2-positive disease; evaluable disease according to RECIST (version 1.0) criteria [18].

No restriction regarding the extent of lymphadenectomy was applied and D0–D2 resections were all included. No specific criteria for resection were applied and a decision to proceed to surgery was the result of the multidisciplinary evaluation of single cases in each center. As general rules shared among different centers, surgery was discussed in case of the following: highly motivated patients; anticipated risk of performance status (PS) deterioration if rapid tumor progression during CT occurred; significant benefit from first-line CT (complete or partial response).

As the aim of the study was to investigate the role of palliative surgery on primary tumor, we decided not to include in the resected group those patients submitted to radical (i.e., R0) surgery on both primary and distant nodal metastases, experiencing prolonged (i.e., >6 months) disease-free survival before recurrence. Indeed, in these patients, surgery did not represent a palliative procedure, but rather aimed to a curative intent.

All the patients signed a written informed consent form approved by the single institutional review committees, allowing treating physicians to collect all the data in a site-specific database. A uniform data collection form was then designed and shared among different centers: LF, EV and GA, who were responsible for data verification and clarification of potential inconsistencies, later merged single datasets.

• Statistical analyses

The primary end point of the current study was the evaluation of the impact on OS of resection of the primary tumor by univariate and multivariate analyses. Secondary end points included subgroup analyses according to available patient characteristics.

OS was defined as the time interval from the diagnosis of advanced disease to the date of death or last follow-up visit. Progression-free survival (PFS) was defined as the time from diagnosis of advanced disease to the date of disease progression or death, whichever occurred first. OS and PFS were estimated using the Kaplan–Meier method. Objective response rates were evaluated according to RECIST v.1.0 [18].

Statistical significance for both univariate and multivariate analyses was set at $p < 0.05$ for a two-sided test. The following parameters were included: resection of the primary tumor (yes vs no), gender (male vs female), age (≤65 vs >65 years), location of the primary tumor (gastro-esophageal junction/cardia vs fundus vs antrum vs pylorus), histology (diffuse vs intestinal), grading (G1 vs G2 vs G3), HER-2 status (positive vs negative), clinico-pathological subtype (proximal nondiffuse vs distal nondiffuse vs diffuse) [19], presence (yes vs no) of metastases in specific sites (liver, lung, lymph nodes and peritoneum), number of sites of metastases (evaluated as continuous variable), response to first-line CT (complete or partial response vs stable disease vs disease progression), first-line PFS (<6 vs ≥6 months) and Eastern Cooperative Oncology Group (ECOG) PS (0 vs 1 vs 2). Significant factors at univariate test were then challenged at multivariate analysis by stepwise Cox proportional hazards regression modeling. Statistical analyses were carried out employing the software package SPSS 19.0 (SPSS, IL, USA).

An exploratory subgroup analysis was performed in order to assess interactions between treatment and subgroup in Cox regression model in terms of OS and was conducted using StataCorp 2016 Stata Statistical Software: Release 14 (TX, USA).

Results

• Patient characteristics & treatments administered

Data of 549 patients were collected, 36 patients were excluded because clinical data were not fully available and therefore 513 cases were finally included in the analysis (95 in the surgical group and 418 in the CT-only group, respectively; **Figure 1**). Characteristics according to surgical treatment are listed in **Table 1**. As expected, more patients in the nonresected group had two or more sites of metastases (53.6 vs 29.5%). Characteristics were generally well balanced between the two groups. Exceptions are represented by a higher prevalence of more than one site of distant disease and liver or lymph node metastases among patients treated with CT only. Of note, more patients in the CT-only group received either triplet or doublet combination therapy in first-line, however, less than 10% of the patients received single agent CT in both groups. Missing data in a significant proportion of patients could have impacted on the findings for specific characteristics, such as HER-2 status and clinico-pathological subtypes. With regard to the timing of surgery, 15 (15.8%) patients initially received CT and subsequently surgery, while 80 (84.2%) were initially resected and then treated with CT. Surgery consisted in total (n = 53, 55.8%) or partial (n = 42, 44.2%) gastrectomy and most patients received D2 lymphadenectomy (n = 84, 88.4%). Twenty-three (24.2%) patients in the resected group experienced early progression after an apparently radical surgery, and post-operative imaging revealed distant metastases in the first 90 days after resection in the majority of them (21 out of 23 cases).

• Palliative surgery & OS

At univariate analysis, patients who received gastrectomy reported a significantly longer median OS compared with non-operated patients (18.7 vs 13.5 months; $p < 0.001$). Other factors associated with better OS in our series were preserved ECOG PS, response to first-line CT and longer first-line PFS (all $p < 0.001$; **Table 2**). Indeed, no association with OS was reported for the other investigated parameters, such as presence of metastases at specific sites, number of metastatic sites, age, gender, primary tumor location, histology, grading, HER-2 status and clinico-pathological subtype (all $p > 0.05$, **Table 2**). Among resected patients, no difference in median OS was observed between patients receiving immediate surgery and then CT or those treated with CT first and then resection (18.5 vs 19.7 months; $p = 0.437$).

At multivariate analysis, all the four identified variables (surgery on primary tumor, PS, first-line response rates and PFS) retained a statistically significant correlation with OS **(Table 2)**.

• Subgroup analysis

Subgroup analysis was conducted in order to evaluate the interaction of surgical treatment with other variables and to identify potential

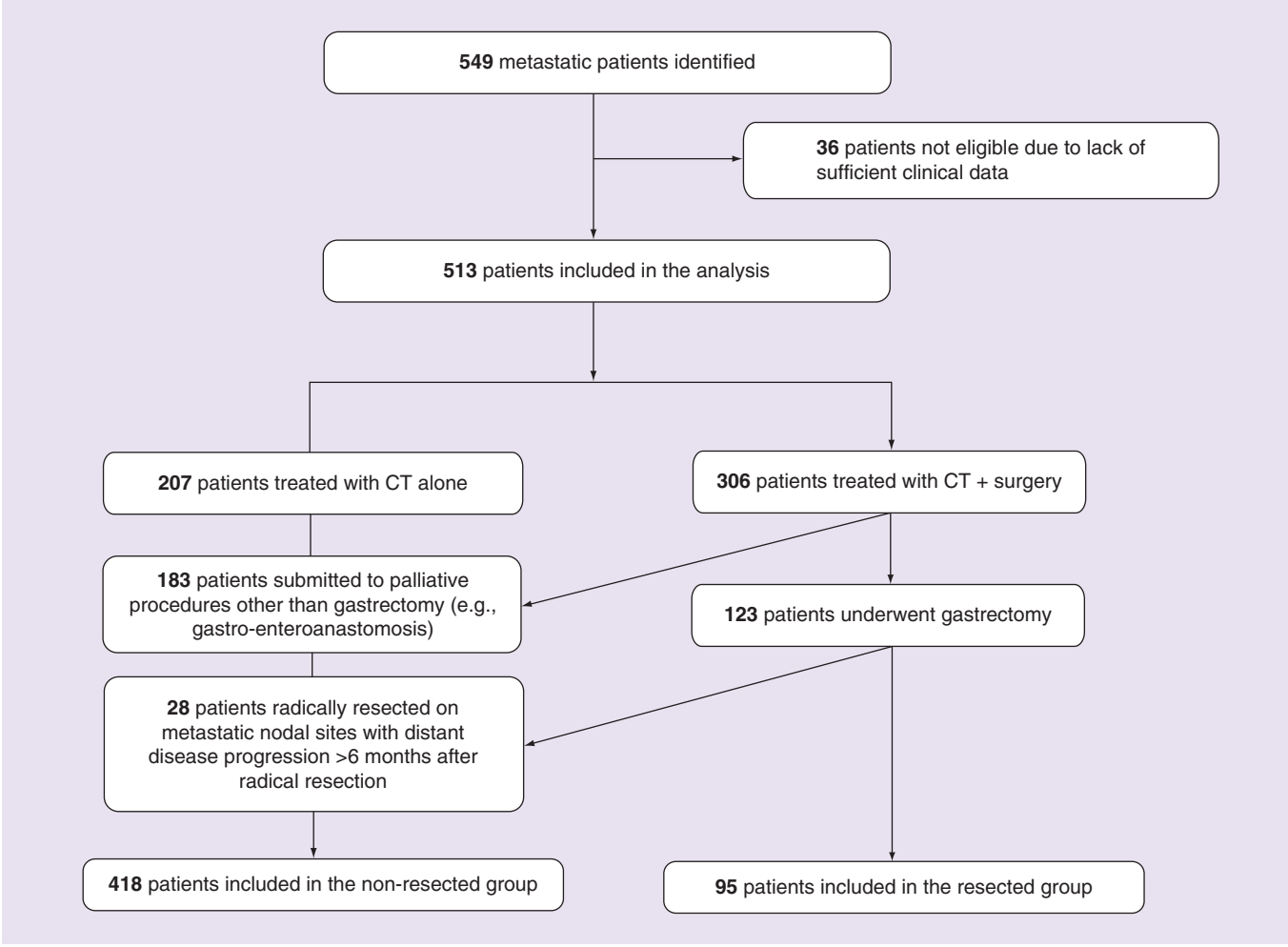

Figure 1. Study profile.
CT: Chemotherapy.

subsets of patients to be prospectively studied within future clinical trials. The following variables were investigated: ECOG PS, number of metastatic sites, presence of liver, peritoneal or lung involvement, sites of tumor origin, Lauren histology and clinico-pathological subtype. Results are reported in **Figure 2**, no significant interaction was observed for any of the investigated parameters.

Discussion

Patients with GC and GEJC not amenable to radical surgical resection have a dismal prognosis, systemic CT and in clinically and molecularly selected patients, targeted agents represent the mainstay of treatment [8]. Surgery should be considered when impelling or life-threatening symptoms related to the primary tumor might condition the overall prognosis or hamper the administration of effective systemic treatments [7,8]. Although the recently published REGATTA trial has not confirmed a survival benefit for surgery in asymptomatic patients with limited metastatic involvement treated with first-line combination CT [15], our results seem in line with those of other studies [7]. Actually, data from the present study confirm previous suggestions from limited series in a larger cohort of metastatic patients: indeed, resected patients treated with the most active available regimens could live longer than non-resected patients. Obviously, our results cannot represent a definitive proof in support of surgery on primary tumor in all advanced GC and GEJC patients, as this can be derived only from prospective randomized trials. However, findings are supported by multivariate analysis, which confirmed the independent role of surgery on OS

Table 1. Patient characteristics.

Characteristics	Resected (n = 95); n (%)	Non-resected (n = 418); n (%)	p-value
Median age, years (range)	*66 (25–85)*	*64 (29–94)*	*0.304*[†]
≤70 years	66 (69.5)	312 (74.6)	
>70 years	29 (30.5)	106 (25.4)	
Gender			*0.091*
Female	38 (40)	129 (30.9)	
Male	57 (60)	289 (69.1)	
ECOG PS			0.660
0	25 (26.3)	127 (30.4)	
1	49 (51.6)	219 (52.4)	
2	19 (20)	71 (17)	
Not specified	2 (2.1)	1 (0.2)	
Primary tumor location			*0.120*[‡]
GEJC/cardia	27 (28.6)	153 (36.6)	
Fundus	8 (8.4)	66 (15.8)	
Antrum	35 (36.8)	133 (31.8)	
Pylorus	23 (24.2)	49 (11.7)	
Not specified	2 (2.1)	17 (4.1)	
Clinico-pathological subtype			*0.005*
Proximal non-diffuse	22 (23.2)	122 (29.2)	
Distal non-diffuse	27 (28.4)	57 (13.6)	
Diffuse	24 (25.3)	58 (13.9)	
Not specified	22 (23.2)	181 (43.3)	
Number of metastatic sites			*<0.001*
1	67 (70.5)	191 (45.7)	
>1	28 (29.5)	224 (53.6)	
Not specified	0 (0)	3 (0.7)	
Liver metastases			*<0.001*
Yes	29 (30.5)	189 (45.2)	
No	61 (64.2)	165 (39.5)	
Not specified	5 (5.3)	64 (15.3)	
Peritoneal metastases			*0.905*
Yes	36 (37.9)	147 (35.2)	
No	54 (56.8)	208 (49.8)	
Not specified	5 (5.3)	63 (15.1)	
Lung metastases			*1.000*
Yes	9 (9.5)	36 (8.6)	
No	81 (85.3)	318 (76.1)	
Not specified	5 (5.3)	64 (15.3)	
Lymph nodes metastases			*0.044*
Yes	36 (37.9)	186 (44.5)	
No	54 (56.8)	168 (40.2)	
Not specified	5 (5.3)	64 (15.3)	
HER-2 status			*0.039*
Negative	56 (58.9)	219 (52.4)	
Positive	7 (7.4)	66 (15.8)	
Not specified	32 (33.7)	133 (31.8)	
First-line CT			*0.013*[§]
Triplet	50 (52.6)	185 (44.3)	
Doublet	36 (37.9)	222 (53.1)	
Mono-CT	8 (8.4)	11 (2.6)	
Not specified	1 (1.1)	0 (0)	
Second-line CT			*0.349*
Triplet	10 (10.5)	35 (8.4)	
Doublet	41 (43.2)	210 (50.2)	
Mono-CT	42 (44.2)	160 (38.3)	
Not specified	2 (2.1)	18 (3.1)	
First-line PFS			*0.052*
<6 months	37 (38.9)	200 (47.8)	
≥6 months	58 (61.1)	195 (46.7)	
Not specified	0 (0)	23 (5.5)	
Response to first-line CT			*0.127*[¶]
Objective response	30 (31.6)	172 (41.1)	
Stable disease	32 (33.7)	113 (27)	
Progressive disease	29 (30.5)	127 (30.4)	
Not specified	4 (4.2)	6 (1.4)	

[†]Comparison for ≤70 versus >70 years.
[‡]Comparison for GEJC/cardia versus other.
[§]Comparison for triplet/doublet versus mono-CT.
[¶]Comparison for objective response versus other.
CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; GEJC: Gastroesophageal junction cancer; mono-CT: Single agent chemotherapy; PS: Performance status.

beyond conventional prognostic determinants such as PS and benefit from first-line CT.

More intriguingly, we tried to identify candidates with the highest chances of benefit from surgery, showing that none of the investigated subgroups had a significant interaction with surgery. Of note, the REGATTA investigators reported an apparent OS detriment from resection for tumor lesions located in the upper-third of the stomach and for patients with limited nodal involvement (i.e., clinical N0-N1) [15]. Our results do not confirm these findings. Some differences from the above-cited prospective study should be noted. First, eligibility criteria

Table 2. Univariate and multivariate analysis.

	Median OS (95%CI) (months)	Univariate analysis	Multivariate analysis	
		p-value	***HR (95%CI)***	***p-value***
Surgery on primary		*< 0.001*	*0.620 (0.487–0.790)*	*<0.001*
Yes	18.7 (16.8–20.6)			
No	13.5 (12.5–14.5)			
Response with first-line CT		< 0.001	0.833 (0.721–0.963)	0.013
Objective response	17.6 (16.2–19.0)			
Stable disease	14.6 (12.7–16.5)			
Progressive disease	10.4 (9.6–11.2)			
PFS with first-line CT		< 0.001	0.356 (0.278–0.456)	<0.001
<6 months	10.3 (9.8–10.8)			
≥6 months	19.4 (18.1–20.7)			
ECOG PS		< 0.001	0.617 (0.537–0.710)	<0.001
0	18.5 (16.6–20.4)			
1	14.2 (13.1–15.3)			
2	10.6 (9.4–11.8)			
Gender		0.279		NT
Male	13.9 (12.6–15.2)			
Female	15.2 (13.5–16.9)			
Age		0.218		NT
≤65 years	14.0 (12.8–15.2)			
>65 years	15.0 (13.5–16.5)			
Primary tumor location		0.105		NT
GEJC/cardia	15.2 (13.5–16.9)			
Fundus	12.9 (10.8–15.0)			
Antrum	14.2 (12.4–16.0)			
Pylorus	14.4 (12.6–16.2)			
Liver metastases		0.808		NT
Yes	14.6 (13.4–15.8)			
No	15.2 (13.7–16.7)			
Peritoneal metastases		0.727		NT
Yes	15.0 (13.3–16.7)			
No	14.6 (13.5–15.7)			
Lung metastases		0.120		NT
Yes	12.6 (11.2–14.0)			
No	15.0 (14.0–16.0)			
Lymph nodes metastases		0.111		NT
Yes	14.2 (12.5–15.9)			
No	15.0 (13.8–16.2)			
Metastatic sites		0.244		NT
1	15.5 (14.1–16.9)			
2	14.0 (12.5–15.5)			
3	13.1 (11.4–14.8)			
4	12.0 (7.4–16.6)			
Histology		0.664		NT
Intestinal	14.0 (12.7–15.3)			
Diffuse	13.7 (11.6–15.8)			
Grading		0.395		NT
G1	13.7 (11.4–16.0)			
G2	16.8 (15.1–18.5)			
G3	14.6 (13.3–15.9)			

CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; HR (95% CI): Hazard ratio (95% CI); NT: Not tested; OS: Overall survival; PFS: Progression-free survival; PS: Performance status.

Table 2. Univariate and multivariate analysis (cont.).

	Median OS (95%CI) (months)	Univariate analysis	Multivariate analysis	
		p-value	*HR (95%CI)*	*p-value*
HER-2 status		0.469		NT
Negative	15.0 (13.8–16.2)			
Positive	15.7 (11.3–20.1)			
Subtype		0.660		NT
Proximal non-diffuse	15.5 (13.5–17.5)			
Distal non-diffuse	15.4 (13.3–17.5)			
Diffuse	13.7 (11.6–15.8)			

CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; HR (95% CI): Hazard ratio (95% CI); NT: Not tested; OS: Overall survival; PFS: Progression-free survival; PS: Performance status.

definitely differ between the two experiences in terms of patient characteristics and surgical procedures, in REGATTA the enrolled patients had a single non-curable factor and a D1 lymphadenectomy was performed, while in our series a significant percentage of patients had two or more sites of metastases and D0–D2 resections were allowed. Second, subgroup analysis did not find an association between benefit from surgery and primary tumor location. In this regard, we indeed observed an apparent greater benefit of surgery in GEJC, even though the restricted number of patients is a limitation (as well as in the REGATTA subgroup analysis): we argue that differences in tumor biology between upper and lower tumors in the esophago-gastric tract should be taken into account [20,21]. Moreover, even in REGATTA, the study design did not provide patient stratification according to potentially relevant prognostic features. This criticism therefore hampers the conclusions of subgroup analyses in the trial, as it does not protect from potentially relevant imbalances between arms in key patient and disease characteristics. Of note, Lauren histology alone and also clinicopathological subtypes according to histology and location were not able to adequately select for surgical candidates in our analysis. As a prognostic role for molecular subtypes of GEJC and GC is emerging in earlier stages after resection [22], it could be of interest to prospectively validate an oncosurgical approach in the advanced setting stratifying patients for biological (rather than clinical or pathological) features.

Another key point when discussing the role of primary tumor resection in the metastatic setting is the optimal timing of surgery. Our analysis did not find significant differences in OS between patients resected upfront and those resected after CT, but the number of patients in the latter group was limited and objective response after CT was not a decisive factor for surgery in this subset. As first-line CT is a major determinant of OS in GC [2] and on the basis of the negative results of REGATTA (which planned immediate surgery followed by CT) [15], we hypothesize that future studies should offer asymptomatic GEJC/GC patients systemic therapy first and then evaluate the role of surgery only among those achieving disease control. Recently reported data seem to support this approach [23]. Patients not responding to first-line CT have generally an extremely poor prognosis with second-line therapy and invasive procedures such as gastrectomy might further compromise nutritional status and QoL in this fragile population. Moreover, the higher activity of more modern chemotherapy combinations (such as the triplet regimen FLOT) could increase the number of patients reconsidered for surgery with promising results in terms of OS in selected cases [24].

Some caution is needed while interpreting the results of our analysis. The limitations of a retrospective analysis and some imbalances in patient characteristics between the two cohorts should be taken into account, definitive confirmation of our findings in randomized trials is therefore needed before implementing surgery in routine practice for stage IV GEJC/GC. Moreover, our patient population was treated with at least two lines of CT. With an increasing number of active drugs available, we hypothesize that surgery on primary tumor might help to maximize patient exposure to systemic therapy by preventing life-threatening or invalidating complications after initial disease control with first-line treatment. To account for potential bias inherent to retrospective studies, we confirmed our findings by multivariate analysis and evaluated subgroups by interaction test.

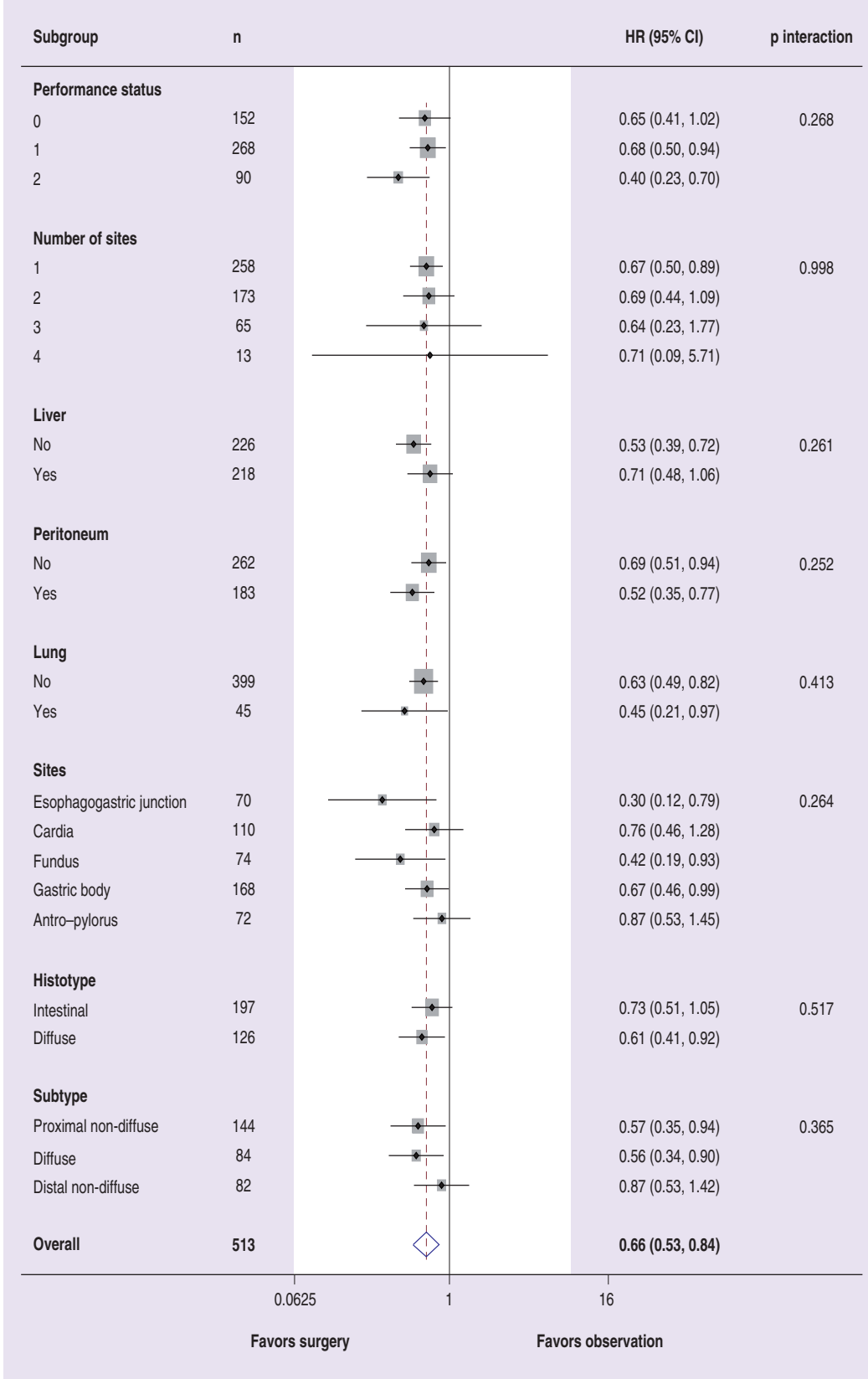

Figure 2. Subgroup analyses. Prognostic impact of gastrectomy among different subgroups defined by clinico-pathological features. HRs are shown with 95% CIs.
HR: Hazard ratio; 95% CI: 95% confidence interval.

Conclusion

In conclusion, our analysis suggests that surgery may have a role in selected advanced gastroesophageal cancer patients generally considered for palliative systemic therapy alone. However, as no definitive confirmation from randomized trials exists, such an approach cannot be recommended at present in all metastatic patients. Anyway, available evidence supports further research in the field and may guide the design of future trials in patients with preserved PS and responding after initial CT. Tumor molecular layout with potential prognostic importance and predictive value for CT should serve as stratification factor.

Future perspective

The treatment of advanced GEJC/GC is slowly but steadily improving thanks to the availability of new therapeutic agents and better supportive measures. It is therefore likely that improving the percentage of patients who achieve disease control in first- and second-line could increase the possibility of reconsidering surgery on primary tumor in a higher number of cases. This will open the way for further prospective research in the field and for the conduction of adequately sized randomized trials. Meanwhile, gastrectomy cannot be considered as a standard approach in asymptomatic GEJC/GC patients and a case-by-case decision should be based on the multidisciplinary assessment of any single patient.

As anticipated, if we would like to answer the open questions about the role of surgery in this setting, we should probably include benefit from upfront systemic therapy as a key selection factor, in order to avoid an aggressive surgical procedure in patients with lower chances of long-term survival and a potential detrimental impact on QoL. In this regard, the ongoing SURGIGAST trial randomizes patients without progressive disease after 2 months of CT to surgery or continuation of systemic therapy [25]. However, the most important step forward will probably be achieved by the introduction of molecular patient stratification and selection in future studies. As shown in the locally advanced disease setting, subgroups identified by different genetic alterations could be associated with different survival outcomes, as well as different response to treatment. As none of the conventional clinico-pathological criteria seems sufficient to reliably select patients for palliative gastrectomy, we believe that molecular features beyond the HER-2 status may be useful to open the way toward personalized surgery in upper gastrointestinal oncology.

Last but not least, as demonstrated by the relevance of PS as a major determinant of survival in any series in GEJC/GC, adequate and early supportive measures (e.g., nutritional support) should be part of the routine management of all patients and should be standardized to be included in the design of randomized trials.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

SUMMARY POINTS

- Surgery is an effective palliative approach in patients with symptomatic advanced esophago-gastric cancer, but its role in asymptomatic patients is still disputable.
- Retrospective series suggest that resected patients seem to live longer than patients treated with systemic therapy alone.
- We confirmed at multivariate analysis the positive prognostic role of gastrectomy in a large series of patients treated with modern chemotherapy regimens.
- Our subgroup analysis did not allow the identification of any clinico-pathological parameters to refine patient selection for an intensive oncosurgical approach.
- The integration of molecular biomarkers in future surgical studies in the advanced disease setting is warranted.

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