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Surgery for metastases for esophageal-gastric cancer in the real world: Data from the AGAMENON national registry

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ABSTRACT

Introduction: The effect of surgery for metastases in patients with esophagogastric cancer is unknown, given the lack of randomized clinical trials; likewise, the criteria for selecting eligible patients remain to be determined.
Methods: This registry evaluates the results of patients with advanced adenocarcinoma of the stomach, distal esophagus, or gastro-esophageal junction from 32 centers. To assess selection criteria and prognostic factors, a state arrival extended Markov proportional hazards (PH) model was used.
Results: 1792 subjects were analyzed, 5% of whom (n = 92) underwent surgery for metastasis. The most common surgeries were peritoneal (29%), hepatic (24%), and distant lymph nodes (11%). Subjects chosen for metastasectomy had higher survival rates, HR 0.34 (95% CI, 0.06–0.80, $p = 0.021$). Patients who underwent surgery had a mOS since metastasectomy of 16.7 months (95% CI, 12.5–22.4). The 1-

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and 3-year relapse rates following R0 resection were 58% and 65%, respectively. Median time since R0 metastasectomy until relapse was 8.4 months (95% CI, 7.6–23.7). The 3-year OS after surgery was 30.6% (95% CI, 19.3–40.4). Duration of chemotherapy prior to surgery (months) increased mortality (HR 1.04 [95% CI, 1.01–1.07]), $p = 0.009$. The only significant interaction involved the use of anti-HER2 therapy.

Conclusion: The AGAMENON registry suggests that subjects with limited metastatic disease, selected on a clinical basis, can benefit from early surgeries. Prospective trials are needed to confirm these data.

Introduction

Esophagogastric cancer has a poor prognosis, given its tendency to relapse following potentially curative surgery (5-year disease-free survival approximately 50% in node-positive tumors) and that distant metastases are present in 35% of the cases at the time of debut [1,2]. In advanced tumors that overexpress or amplify human epidermal growth factor receptor 2 (HER2), the combination of cisplatin–fluoropyrimidine–trastuzumab is standard of care in first line, with median overall survival (mOS) of some 14 months [3]. In HER2-negative tumors, no chemotherapy schedule is considered of choice and mOS rarely exceeds 12 months [4,5]. There is a theoretical rationale in favor of performing surgery for metastases in selected cases (e.g., debulking, elimination of resistant clones, symptom relief, better delivery of chemotherapy, oligometastases, etc.). Several small trials have recently reported that patients with a low tumor burden could have a favorable prognosis after chemotherapy followed by resection [6,7]. However, the effect of metastasectomy on OS is debatable, given that no well-powered randomized trials focusing on this issue have been conducted [7,8]. The observational studies available are of cohorts from specialized centers or limited by their small sample size and suspicion of magnification of effect due to selection biases, no effective control of confounding variables, or time-dependent bias [9–11].

The uncertainty is further amplified because esophagogastric tumors behave heterogeneously in both biological and clinical terms (e.g., depending on HER2 status or Lauren histological type), requiring an individualized approach [12–15]. There are currently no clear selection criteria to determine which subjects are more likely to benefit from surgery.

Furthermore, data regarding the effect of interactions between histopathological characteristics and different therapies, including surgery, are currently scant or all together nonexistent, despite being of interest and subject to study [11,12] Despite attempts to correlate histological traits with outcomes, it is still unclear whether these variables are prognostic or predictive of efficacy of surgery for metastases [16]. Hence, it is important to ascertain the role of these variables in decision-making.

In short, all these doubts may translate in daily practice as missed opportunities or overtreatment. Registries of real-world data can contribute to generate hypotheses and put forth selection criteria to inform the development of clinical trials. With this background, we aimed here to describe the pattern of use of metastasectomies in clinical practice, as well as the main selection criteria and prognostic factors.

Material & methods

Study design & patients

Patients are from the multicenter, observational study AGAMENON in which 31 Spanish and one Chilean centers participate. The registry's design, methodology, and considerations as to its quality have been reported elsewhere [12,17–20]. Information is entered via a web-based data collection tool that contains filters to assure its reliability, avoid errors, protocol violations, and unjustified missing data. The information is monitored online and by telephone.

Eligibility criteria include adults (≥18 years) with histologically-confirmed adenocarcinoma of the distal esophagus, gastroesophageal junction, and stomach, with metastases or unresectable disease, who received at least one cycle of polychemotherapy (two or more agents) in first line between January 2008 and March 2017. Adenocarcinomas of the distal esophagus were eligible, in light of their molecular similarity with gastric cancer [21]. The registry excludes subjects who received perioperative chemotherapy in the six months prior to initiating treatment for advanced disease. Other exclusion criteria were patient participation in a clinical trial with non-standard therapy, prior use of treatments for advanced disease, and the history of another synchronous malignancy. Subjects having undergone surgery did so at any time, without restriction for their recruitment, and received treatment according to the real-world practice at each institution.

The study was approved by a multicenter Research Ethics Committee. All patients still alive at the time of data collection provided signed, informed consent in writing.

Variables & outcomes

The primary aim was to describe the pattern of use of metastasectomies in clinical practice. Other exploratory objectives were selection criteria and prognostic factors. OS was defined as the time elapsed between beginning chemotherapy until all-cause mortality. A dual secondary endpoint was disease-free survival and OS2, defined as beginning with the time of R0 resection until tumor relapse or demise due to any cause, respectively. Oligometastatic disease was defined as that which affects 1 or 2 organs with 1 or 2 metastases per organ. Both the Lauren histological classification as intestinal (IT) or diffuse (DT) subtype, as well as HER2 immunohistochemistry were evaluated locally and centralized review was not required. Tumors with signet-ring cells were reclassified as DT as per standard criteria [22]. Lymphatic metastases in hepatoduodenal, retropancreatic, mesenteric, and para-aortic territories were categorized as distant disease, in line with the AJCC-TNM classification, 7th edition. Twenty-one routinely available, potential confounding factors were chosen, with prognostic effect according to at least one prior publication (Annex Table 1) [20]. Tumor response was assessed at 3 and 6 months by the researchers, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

Statistical methods

A multi-state model was designed and is presented in graph-form in Figure Annex 2. To evaluate the effect of surgery for

metastases, a state arrival extended Markov proportional hazards (PH) model was used (this model takes into account all the confounding factors, and the time it takes for surgery to occur) [23]. The assumption of proportionality of hazards was evaluated by means of the Schoenfeld test. Specific covariates were used for each clinical status (e.g., surgery or demise). Step functions were applied on different time intervals when required [24]. The analyses were performed with RStudio (RStudio, Inc., Boston, MA, USA), including the mstate, etm, cmprsk, and survival software packages [25–29].

Results

Patients

Out of a total of 2549 registered subjects, 1792 patients were evaluable for this analysis (Figure Annex 1). In 78% (n = 1392), metastases were detected at the same time as the primary tumor. Just over 5% (n = 92) of the patients underwent metastasectomy after a median of 5 months (95% confidence interval [CI], 4.1–5.9) since initiating chemotherapy. Fig. 1 illustrates the flow through the multi-state model. Median age was 64 years and most subjects (70%) were male. The series' baseline characteristics are displayed in Table 1. Among the characteristics associated with greater propensity toward metastasectomy we found young age, being female, better functionality (ECOG-PS), low tumor volume, and surgery for the primary cancer, among others. HER2 status, the use of trastuzumab, or Lauren subtype were not associated with the likelihood of surgical intervention. At the time of analysis, 82% of the patients had passed away (n = 1464), with a median OS of 10.4 months (95% CI, 10.0–11.1).

Description of metastasectomies

Table Annex 2 shows the breakdown of the surgeries, the most common being peritoneal (29%, n = 27), hepatic (24%, n = 22), and distant lymph nodes (12%, n = 11). Several different locations were involved in 20% of the surgeries. The distribution of sites is related to the Lauren classification (e.g., 36% of hepatic metastasectomies correspond to diffuse subtype neoplasms vs. 65% of peritoneal surgeries). With respect to the grade of resection, R0 was achieved in 64% (n = 59), R1 in 14% (n = 13), and macroscopically incomplete or R2 in 22% (n = 20). In the case of hepatic metastases, resection was unilobar in 86% (19 of 22), and 1 or 2 lesions were resected in 82% (18 of 22). Surgery for hepatic metastases was accompanied by locoregional techniques (e.g., radiofrequency ablation) in 59% (13 of 22). Insofar as peritoneal disease is concerned, the median peritoneal carcinomatosis index (PCI) was 9 (range 1–21). Hyperthermic intraperitoneal chemotherapy (HIPEC) was used in 55% of the surgeries for peritoneal metastases (15 of 27).

With respect to timing relative to surgery on the primary tumor, both procedures were synchronous in 55% of the cases (n = 50); 38% (n = 35) underwent surgery for the primary first, whereas in 1 case metastasectomy was performed first, and in 6% (n = 6), palliative metastasectomy was recorded without resection of the primary tumor. Most patients who underwent surgery for metastases (92%, n = 85) received chemotherapy prior to the surgical procedure; median treatment duration was 4.5 months. At least one line of chemotherapy was administered to 68% following surgery. As regards the evaluation of response, 57% (n = 54) underwent surgery prior to the first CT, 28% (n = 26) after the first CT, and 13% (n = 12) after the second CT.

Postoperative complications were recorded in 19% of the patients (n = 18): infection (n = 10), bleeding (n = 4), respiratory distress (n = 3), and adhesion-related disorder (n = 1). Three of the patients who underwent surgery died due to postoperative complications.

Multi-state model

A state arrival extended Markov PH model was designed. The factors that increased surgeries in this model were oligometastatic disease, not being in progression, and having a good general/

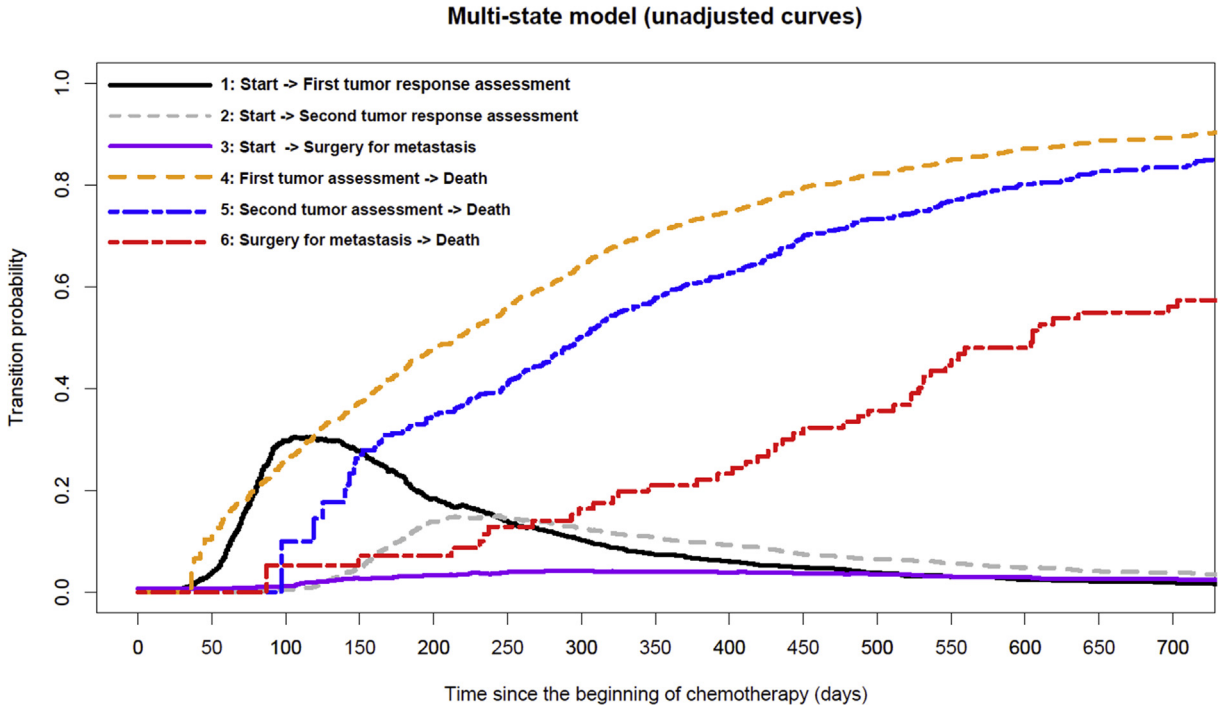

Fig. 1. Aalen-Johansen estimates of all state occupation probabilities. A 'clock forward' approach was used that begins counting when chemotherapy is initiated.

Table 1
Baseline characteristics of patients with or without surgery for metastases. P-values were derived from Fisher's exact tests, except for continuous variables, for which the Kruskal–Wallis test was used. Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group Performance status scale, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemistry, FISH = fluorescence in situ hybridization. The missing data for the HER2 variable are explained by the fact that they are cases diagnosed and treated prior to the publication of the ToGa trial [3].

Characteristics	All (n = 1792)	No surgery for metastasis (n = 1700)	Surgery for metastasis (n = 92)	*P*-value
	N (%)	*N* (%)	*N* (%)	
Age, median (range)	64 (20–89)	65 (20–89)	57 (25–80)	<0.0001
Sex, male	1269 (71)	1211 (71)	54 (59)	0.01326
ECOG-PS, <2	1558 (87)	1468 (86)	90 (98)	0.00036
Primary tumor site				
Esophageal	119 (7)	117 (7)	2 (2)	0.17483
Gastroesophageal junction	214 (12)	204 (12)	10 (11)	
Stomach	1459 (81)	1379 (81)	80 (87)	
Histological grade				
Grade 1	181 (10)	177 (10)	4 (4)	0.02912
Grade 2	518 (29)	490 (29)	28 (30)	
Grade 3	730 (41)	682 (40)	48 (52)	
Not available	351 (20)	351 (21)	12 (13)	
Lauren Classification				
Intestinal	815 (45)	778 (46)	37 (40)	0.06740
Diffuse	741 (41)	693 (41)	48 (52)	
Unclassified	236 (13)	229 (13)	7 (8)	
HER2 overexpression				
No (IHC 0+, 1+, 2+, and FISH−)	1153 (64)	1086 (64)	67 (73)	0.44521
Yes (IHC 2+ & FISH+)	99 (6)	95 (6)	4 (4)	
Yes (ICH 3+)	200 (11)	192 (11)	8 (9)	
Not available	340 (19)	327 (19)	13 (14)	
Number of metastatic sites				
1	708 (40)	654 (38)	54 (59)	<0.0001
2	562 (31)	528 (31)	34 (37)	
3	288 (16)	285 (17)	3 (3)	
≥4	234 (13)	233 (14)	1 (1)	
Lung metastases				
No	1561 (87)	1473 (87)	88 (96)	0.06340
1–2	62 (3)	60 (4)	2 (2)	
3–5	62 (3)	62 (4)	0	
>5	107 (6)	105 (6)	2 (2)	
Liver metastases				
No	1130 (63)	1063 (63)	67 (73)	<0.0001
1–2	188 (11)	170 (10)	18 (20)	
3–5	147 (8)	142 (8)	5 (5)	
>5	327 (18)	325 (19)	2 (2)	
Other sites of metastases				
Bone	174 (10)	172 (10)	2 (2)	0.00988
Peritoneal	795 (44)	750 (44)	45 (49)	0.38970
Ascites	435 (24)	405 (24)	30 (33)	0.06122
Lymph node	858 (48)	829 (49)	29 (32)	0.00125
Neutrophil-lymphocyte ratio, median (range)	3.1 (0.1–37.0)	3.2 (0.1–37.0)	2.6 (0.6–9.3)	0.00042
Surgery of primary tumor	630 (35)	551 (32)	79 (86)	<0.00001
Chemotherapy, triplets	574 (32)	531 (31)	43 (47)	0.00270
Trastuzumab with first-line chemotherapy	255 (14)	243 (14)	12 (13)	0.87827

nutritional status (Table 2). A second response to chemotherapy incremented the possibilities of resection (HR 3.83) and entailed a positive prognostic influence, although said effect was not statistically confirmed in the post-surgical stratum (Table 2). In fact, longer duration of chemotherapy prior to surgery (months) increased mortality with HR 1.04 ($P = 0.009$).

After adjusting for different factors, the individuals chosen for surgery had longer survival times in this registry, HR 0.34 (95% CI, 0.06–0.80), $P = 0.021$) (Table 2). In a sensitivity analysis, the trend was similar in the subgroup with only oligometastatic disease (HR 0.38, $P = 0.050$). Thus, patients who had undergone surgery (n = 92) had a median OS from time of metastasectomy of 16.7 months (95% CI, 12.5–22.4), with no differences based on grade of resection. Moreover, 1- and 3-year disease-free survival following R0 resection was estimated to be 42% and 35%, respectively. The three-year survival rate for subjects who underwent metastasectomy was 30.6% (95% CI, 19.3–40.4) versus 8.4% (95% CI, 6.4–10.1) for the full series. HER2 status was not a selection criterion. However, there was evidence of the existence of a subgroup effect for OS according to HER2 status and administration of trastuzumab, without interactions with other variables (Fig. 2). As expected, the sensitivity analysis revealed signs of heterogeneity in the effect of each type of surgery, while the small size of the subgroups precluded formal pairwise comparisons (Fig. 3).

Discussion

The analysis of the surgeries of the AGAMENON national registry indicate that it is possible to select individuals on the basis of their clinical situation who have a good prognosis and can benefit from resection of their metastases. Approximately 1 of every 3 patients with R0 resection survived disease-free beyond 3 years, which is not accounted for by the remaining confounding factors evaluated. Specific clinical trials are needed to confirm this possible effect. As far as the timing of interventions is concerned, every month of delay until surgery increased the risk of death by 4%, despite the use of chemotherapy during that interval.

Table 2
Parameter estimates in the 'arrival extended' Markov PH model (multivariate analysis). The variables entered into the models are those with P<0.10 on univariate screening (Annex 1). Transitions can be consulted in the Annex to Fig. 2. Transitions #1 and #4 have not been represented, as they are not deemed clinically relevant. Each characteristic was modeled as a state-specific covariate, with a fixed effect for each arrival stratum (surgery or death). The 'arrival extended' Markov Stratified hazards model was stratified for each of these endpoints, including the effect of surgery and the time in reaching it [23]. Proportional hazards ratios test: global test, $\chi 2$ 2.53e+01, P = 0.999, all variables with P < 0.10. Abbreviations: PH = proportional hazards, HR = hazard ratio, ECOG PS = Eastern Cooperative Oncology Group Performance Status, HER2 = human epidermal growth factor receptor 2, LLN = lower limit of normal, RECIST = Response Evaluation Criteria In Solid Tumors.

Transition	Predictor	HR (CI 95%)	P-value
Start > Surgery (transitions 2, 5 & 7)	Histological grade 1	0.28 (0.10–0.82)	0.020
	ECOG PS ≥ 2	0.30 (0.07–1.23)	0.096
	HER2+ treated	1.17 (0.62–2.22)	0.611
	Albumin < LLN (g/L)	0.40 (0.18–0.89)	0.025
	Bone metastases	0.77 (0.18–3.28)	0.241
	Oligometastatic disease	3.32 (1.67–6.59)	<0.001
	Number of metastatic sites, <3	6.32 (2.32–17.5)	<0.001
	Lauren, diffuse	1.41 (0.91–2.20)	0.121
	Neutrophil-to-lymphocyte ratio	0.94 (0.85–1.04)	0.305
	First RECIST		
	Response	4.26 (2.17–8.32)	<0.001
	Stable disease	2.41 (1.05–5.50)	0.036
	Progression	0.35 (0.08–1.48)	0.156
	Second RECIST		
	Response	3.83 (1.75–8.37)	<0.001
	Stable disease	0.74 (0.17–8.37)	0.683
	Progression	–	0.977
Start > Death (transitions 3, 6 & 8)	Histological grade 1	0.70 (0.58–0.85)	<0.001
	ECOG PS ≥ 2		
	<180 days	2.46 (1.98–3.12)	<0.001
	≥180 days	1.44 (1.15–1.80)	0.001
	HER2+ treated	0.81 (0.68–0.95)	0.001
	Albumin < LLN (g/L)	1.13 (0.99–1.29)	0.057
	Bone metastases	1.11 (0.92–1.34)	0.731
	Number of metastatic sites, <3	0.84 (0.05–0.43)	0.006
	Oligometastatic disease	0.78 (0.69–0.88)	<0.001
	Lauren, diffuse	1.23 (1.09–1.38)	<0.001
	Neutrophil-to-lymphocyte ratio		
	<180 days	1.06 (1.04–1.08)	<0.001
	≥180 days	1.02 (1.00–1.03)	0.023
	First RECIST		
	Response		
	<360 days	0.50 (0.31–0.82)	0.006
	≥360 days	1.50 (0.74–3.04)	0.255
	Stable disease	0.77 (0.51–1.15)	0.212
	Progression		
	<360 days	3.68 (3.13–4.33)	<0.001
	≥360 days	2.43 (1.62–3.65)	<0.001
	Second RECIST		
	Response		
	<360 days	0.35 (0-18-0.67)	<0.001
	≥360 days	0.90 (0.67–1.22)	0.521
	Stable disease	1.15 (0.91–1.44)	0.219
	Progression		
	<360 days	2.60 (2.02–3.34)	<0.001
	≥360 days	2.15 (1.48–3.10)	<0.001
Surgery > Death (transition 9)	Histological grade 1	0.35 (0.04–2.85)	0.328
	ECOG PS ≥ 2	1.18 (0.22–12.8)	0.355
	HER2+ treated	0.21 (0.05–0.76)	0.017
	Albumin < LLN (g/L)	1.92 (0.71–5.13)	0.192
	Bone metastases	2.47 (0.45–12.4)	0.293
	Oligometastatic disease	0.14 (0.56–3.59)	0.451
	Number of metastatic sites, <3	4.16 (1.07–16.1)	0.039
	Lauren, diffuse	1.06 (0.58–1.91)	0.840
	Neutrophil-to-lymphocyte ratio	1.04 (0.89–1.21)	0.611
	First RECIST		
	Response	0.90 (0.36–2.24)	0.835
	Stable disease	1.06 (0.38–2.91)	0.907
	Progression	2.52 (0.59–10.7)	0.211
	Second RECIST		
	Response	1.04 (0.35–3.11)	0.933
	Stable disease	1.87 (0.64–5.48)	0.245
	Progression	2.46 (0.87–9.92)	0.088
	Prior time with chemotherapy (months)	1.04 (1.01–1.07)	0.009
Surgery for metastasis (all)	–	0.34 (0.06–0.80)	0.021

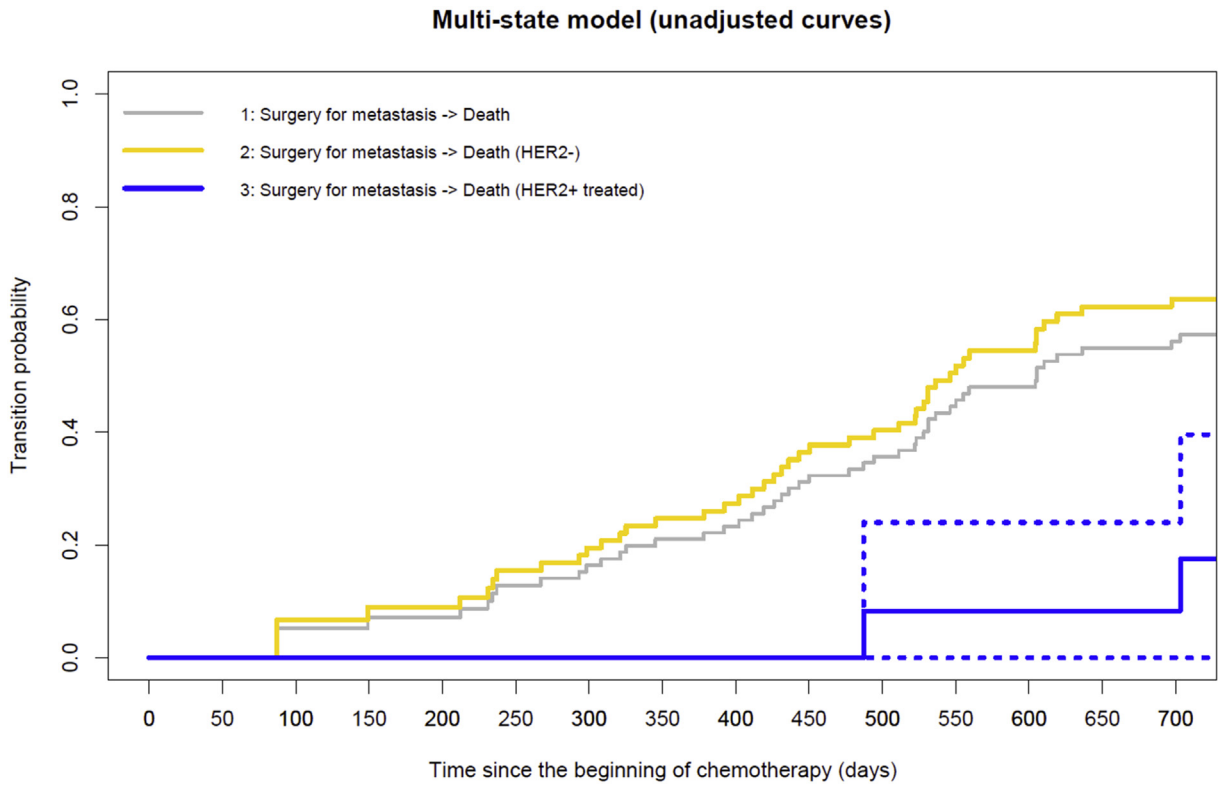

Fig. 2. Aalen-Johansen estimates for transition from surgery to demise based on HER2 status.

The only factor predictive of benefit was the presence of a HER2-positive tumor treated with trastuzumab. However, a potential benefit of surgery cannot be ruled out, even with adverse histological prognostic factors such as the diffuse Lauren's type or high grade.

Our findings are in line with the literature in this field, albeit with certain nuances. Some authors have reported worse prognosis in patients with diffuse tumors or signet-ring cells [16,30], although it is not clear that they are prognostic or predictive, having not performed interaction tests. Bilobar disease is the most consistent prognostic factor following hepatic resections [31,32]. Nevertheless, most series did not stratify by Lauren subtype or HER2 status [33,34], which are key variables.

A meta-analysis has estimated a benefit from metastasectomy in terms of OS, with HR of 0.54, (95% CI 0.46–0.95), although most of the studies included are Asian [35]. These series confirm that surgery for metastases is capable of generating long-term survivors [36,37]. In one of the few European series published, Tiberio et al. estimated a 2-year survival rate of 10% following surgery for hepatic metastases [38]. In AGAMENON, OS at 3 years post-metastasectomy is 30% and most are disease-free during that time. However, unlike other series, we have not seen that the degree of resection impacts prognosis [39]. One possible explanation, in addition to the small sample size, is the administration of adjuvant techniques and postoperative treatment to these patients.

When considering the generalizability of these results, the reader must be aware that resections were performed in a minority (5%) of patients in this registry *versus* 22% in the systematic review by Gadde et al. [11]. This can condition the extrapolation of results in that they are highly selected patients: young, with good functional status, a single metastatic site, and in general, with chemosensitive tumors. Secondly, patients underwent surgery for metastases after a median of 5 months since starting chemotherapy. This is consistent with a recently published, phase II trial that concluded that subjects with oligometastatic disease who received neoadjuvant chemotherapy and later underwent metastasectomy exhibited apparently favorable survival rates [6]. Thirdly, most of the individuals who underwent hepatic or peritoneal resections received liver-directed therapies or HIPEC, which could affect these outcomes [40]. It must also be remembered that approximately half of the surgeries were synchronous with the resection of the primary, a particularity of this series. Finally, the data suggest that selection based on favorable clinical evolution (ECOG-PS 0–1 prior to intervention), as well as tumor response (RECIST criteria) can be tenable. It must be remembered that the delay in surgery appears to worsen outcomes; consequently, the optimal time to perform surgery might be between the first and second evaluation, similar to the AIO-FLOT3 study strategy [6].

On the other hand, in recent years, several studies have attempted to establish if the Lauren tumor classification, which characterizes gastric tumors as either intestinal or diffuse, is useful for individualizing therapy [13,14,41]. Some authors have found that the diffuse subtype has a worse prognosis [16,30]. In our registry, the Lauren subtype conditioned the procedures and displayed a prognostic effect on OS, but did not substantially influence the effect of metastasectomy. Though this hypothesis must be confirmed prospectively, the result is consistent with other studies [7,11].

Finally, our exploratory analysis has suggested a possible interaction between the effect of surgery and HER2 status, with the greatest benefit in HER2-positve tumors treated with trastuzumab (although HER2 negative tumors also appear to benefit). Should this be confirmed, as possible tentative explanations, maintenance with trastuzumab could be efficacious to prevent progression in micrometastatic disease. Moreover, rescue therapies following progression to first line for HER2-positve tumors have proven

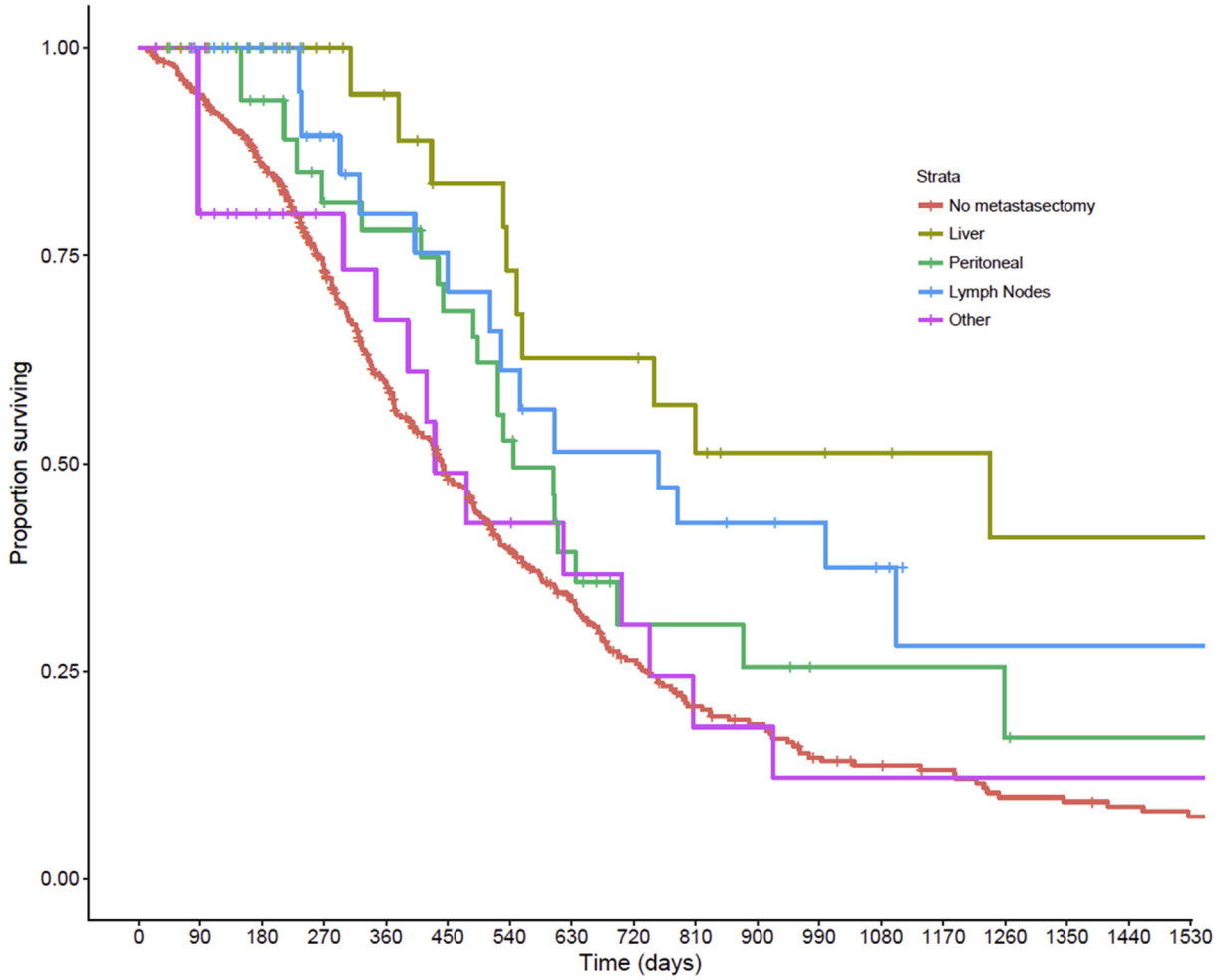

Fig. 3. Survival curves according to the type of surgery for metastases performed. The graph displays survival curves for each type of surgery, by a time-dependent graphing method.

inefficacious [42]; hence, metastasectomy during response to the first line of chemotherapy might be one of the interventions capable of consolidating response and prolong survival. However, given the small subgroup size (n = 12), the estimation is subject to uncertainty and must be understood as a 'hypothesis generator'.

Beyond the usual caveats associated with retrospective registries, our work has specific limitations. First of all, it is likely that some residual bias persists, since part of the information can be carried through time-dependent confounding factors (the RECIST criteria temporal variation has been contemplated here). The reader must be aware of the multiple factors that are difficult to capture and that nonetheless intervene in decision-making. Furthermore, the surgical procedures have been treated in aggregate, although it is true that every surgical technique and metastatic location has their idiosyncrasy. The aggregate analysis must therefore be taken as a general overview to be confirmed in future, more in-depth studies. While the sample size of our series (n = 92) is small, it is still comparable or superior to most previously published studies [6,7,11].

In short, lacking definitive clinical trials, our analysis has confirmed that it is possible to select patients on a clinical basis with a good prognosis as eligible for metastasectomy. These procedures were associated with 3-year survival rates of approximately 30%, while the most robust specific prognostic factor was time between initiation of chemotherapy and resection. The study also points to the hypothesis that the benefit may be greater in HER2-positve tumors that receive trastuzumab. These data can supplement the information contributed by clinical trials and aid in designing combined treatment strategies.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Research involving human participants

All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and subsequent versions. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.03.019.

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