Impact of the number of therapy lines on survival in advanced gastric and esophagogastric adenocarcinoma - a real-world retrospective analysis from Croatia

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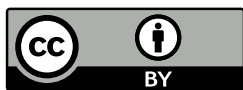
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The aim of the study was to conduct a retrospective database analysis to understand the current treatment patterns and outcomes to plan potential improvements in therapy delivery and patient selection. The electronic patient medical records of 225 patients with advanced gastric and esophagogastric adenocarcinoma treated at two Croatian high-volume tertiary centers from January 2018 to December 2021 were analyzed. Patients ineligible for chemotherapy (66 of 291, 22.7%) due to poor general condition or co-morbidities were not included in the study. The median overall survival (OS) for the whole cohort was 11.0 months (95% confidence interval (CI) 9.7–12.0). Of the 225 patients who received first-line therapy, 47.6%, 16.9%, and 3.1% received second-, third-, and fourth-line therapy, respectively. Survival correlated significantly with the number of treatment lines received (p<0.001), with a median OS from diagnosis of 7.8 (95% CI 6.6–9.4), 12.0 (95% CI 10.0–14.0), and 20.0 months (95% CI 18.0–23.0) for patients receiving 1, 2, and ≥3 lines of treatment, respectively. This study confirmed the positive impact of the number of chemotherapy lines on OS. This highlights the importance of the ratio of patients receiving multiple lines of therapy as well as the availability of new and effective drugs in real-life clinical practice. The selection of optimal therapy for each patient in the first-line therapy is important because a significant number of patients do not receive second-line therapy.

Key words: gastric cancer; esophagogastric carcinoma; real-world data; chemotherapy lines; overall survival

Gastric cancer (GC) is the fifth most common cancer worldwide, accounting for 5.6% of all new cancer cases and the fourth leading cause of cancer mortality, contributing to 7.7% of all cancer deaths [1]. Incidence rates are highest in Eastern Asia and Eastern Europe, whereas rates in Northern America and Northern Europe are low [1, 2]. GC was responsible for 798 new cases and 665 deaths in 2020 in Croatia, ranking sixth for incidence in men and tenth in women [3]. The incidence of noncardiac GC has been declining over the last half-century in Western populations, mainly due to changes in dietary and drinking habits, while the incidence of distal esophageal and esophagogastric adenocarcinoma has been increasing [4].

The prognosis of GC is poor, with a 5-year overall survival (OS) of approximately 20–33% [5, 6]. Approximately 80% of patients are diagnosed at an advanced stage [5]. The median OS of patients treated only with the best supportive care is 3–5 months [5]. Although esophagogastric cancer (EGC) and GC differ in terms of risk factors, carcinogenesis, and epidemiologic patterns, their treatment in the advanced setting is quite similar [7, 8]. Until recently, standard treatment in the first-line setting consisted of a platinum-fluoropyrimidine doublet with the possible addition of either an anthracycline or a taxane [9, 10]. Currently, taxane-based triple chemotherapy (ChT) is not recommended due to higher levels of toxicity [8]. In HER2-positive tumors, the addition of trastuzumab to ChT has improved OS and represents a standard care [11]. Recently, with the evolution of precision oncology, immune checkpoint inhibitors are improving treatment outcomes even more. Nivolumab in combination with oxaliplatin-fluoropyrimidine ChT resulted in significant improvement in OS versus ChT alone in patients with a programmed death-ligand 1(PD-L1) combined positive score (CPS) ≥5 [12]. Randomized trials with pembrolizumab in microsatel-

lite instability-high (MSI-H) GC have also shown survival improvement of patients [13, 14]. Regarding the second-line paclitaxel and anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, ramucirumab, ramucirumab alone and taxane or irinotecan monotherapy have demonstrated a survival advantage compared with the best supportive care [15–18]. Third-line treatment with trifluridine/tipiracil has shown better survival in patients with GC than best supportive care [19]. The results of trastuzumab deruxtecan after progression on trastuzumab therapy in randomized control phase II trials are promising [20].

The main challenge of the treatment of advanced EGC and GC is a relatively short duration of response to treatment and often rapid deterioration of the patient's general condition, limiting further treatment. Nevertheless, several retrospective trials presented a survival advantage when that group of patients was treated with more treatment lines [21–23]. In this article, we report the treatment patterns and clinical outcomes of patients with advanced EG and gastric adenocarcinoma treated in two tertiary Croatian centers receiving at least one line of therapy. The aim of this article is to understand current treatment patterns and outcomes in the real-world patient population to improve further treatment as well as patient selection for optimal survival benefit.

Patients and methods

A retrospective analysis of patients treated with one or more lines of ChT due to advanced gastric and EG adenocarcinoma during the period from January 1st, 2018, to December 31st, 2021, in the Clinical Hospital Centers Zagreb and Split was performed. Patients treated only with supportive and symptomatic treatment were not included in this analysis. The cut-off follow-up date was December 31, 2022. Data were collected by a review of the electronic patient medical records. The clinicopathological data, treatment details, response assessment, and survival outcome were recorded.

The study was approved by the ethics committees of the participating institutions. The data were anonymized before the analysis, and the study was conducted in accordance with the World Medical Association Declaration of Helsinki of 1975, as revised in 2013 [24]. The study protocol was not preregistered, nor were the data reviewed centrally.

Endpoints. The primary efficacy endpoint was OS, defined as the time in months from the date of diagnosis of advanced disease to the date of death of any cause. OS data in living patients were censored at the time of the last data collection. The secondary efficacy endpoints were the objective response rate and disease control rate. The overall best response to treatment was estimated in compliance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria as stable or progressive disease and partial or complete response [25]. The overall response rate (ORR) was defined as the proportion of patients who had a partial

response (PR) or complete response (CR) to therapy. The disease control rate was defined as the proportion of patients with PR, CR, and stable disease (SD).

Statistical analysis. The differences in the clinicopathological characteristics of patients with GC and EGC as well as the difference in the percentage of ORR between patients with HER2-positive and HER2-negative tumors in first-line therapy were compared by using Pearson's chi-square test or Fisher's exact test where appropriate. OS was estimated using the Kaplan-Meier method with the log-rank test used to compare differences. All tests were two-sided and a p-value <0.05 was considered statistically significant. Subgroup analyses were undertaken to investigate the impact of multiple baseline characteristics and the number of treatment lines on OS by use of a Cox regression model. For the subgroup analysis of OS, the HR and 95% CI within each subgroup were summarized and displayed in the forest plot. All statistical analyses were conducted using the R environment for statistical computing and graphics, including the following libraries: tidyverse, survminer, ggsurvfit, ggsankey, and circlize.

Results

A total of 291 patients with advanced GC and EGC were identified. Sixty-six (22.7%) never received chemotherapy, and therefore, 225 patients remained for analysis. There were 161 (72%) males and 64 (28%) females. The median age was 65 years (range 25–83 years). At the beginning of the first-line treatment, the Eastern Cooperative Oncology Group performance status (ECOG PS) of patients was 0–1 in 93% (N=210). The stomach was the primary tumor site in 172 (76%) patients while EGC was the primary tumor site in 53 (24%) patients. At the beginning of the first-line therapy, 173 (77%) patients had *de novo* (initially) metastatic disease, 10 (4.4%) patients had unresectable locally advanced disease at first presentation, and 42 (19%) patients had recurrent disease. Forty patients with recurrent disease had distant metastases, and two had unresectable locally advanced disease. HER2-positive tumors were found in 28 (12%) patients. The median follow-up time was 11 months. The patients' characteristics are summarized in Table 1.

The most frequent metastatic sites were lymph nodes (116 patients, 31%), peritoneum and liver (85 patients each, 23%), although 51% of patients with metastatic disease had 2 or more metastatic sites (Figure 1).

In the first-line treatment, 204 (90.7%) patients received doublet therapy, predominantly a fluoropyrimidine/cisplatin doublet; 8 (3.5%) patients received triplet therapy, which included predominantly fluoropyrimidine/platinum doublets with the addition of either taxanes or an anthracycline; and 13 (5.8%) patients received single-agent therapy. Of the 255 patients, 107 (47.6%) subsequently received second-line treatment. Sixty-eight (63.6%) patients were treated with second-line doublet therapy, mainly with paclitaxel and ramuci-

rumab combination, whereas 39 (36.4%) patients received single-agent therapy. Of the 225 patients who had received first-line ChT, 38 (16.9%) subsequently received third-line treatment. Of these 38 patients, 21 (55.3%) received single-agent therapy, and 17 (44.7%) patients received doublet therapy. Seven (3.1%) patients received fourth-line therapy. The first-line, second-line, and third-line ChT regimens are shown in Figure 2.

There were no differences in baseline clinicopathological characteristics or the number of received treatment lines between patients with GC and EGC except for sex (p=0.014), the extent of the disease at the beginning of the first-line therapy (<0.001), the number of metastatic sites (p=0.045), and the location of metastatic sites (p<0.001). Namely, twice as many females were found to have GC (33%) than EGC (15%), and 53% of patients had one metastatic site and GC while only 37% had one metastatic site and EGC. Relapse was more frequent in patients with EGC (31% vs. 13%) and *de novo* metastatic disease was more frequent in patients with GC (85% vs. 66%). The peritoneum as the metastatic site was almost three times more frequent in patients with GC than in those with EGC (27% vs. 9.4%).

In the first-line setting, the overall best response was CR in 1.8%, PR in 25.8%, SD in 27.5%, and progressive disease (PD) in 44.9% (Table 2). The ORR was 46% in HER2-positive patients and 26% in HER2-negative patients (p=0.028). In the second-line setting, the overall best response was a CR in 0.9%, PR in 15.0%, SD in 29.9%, and PD in 54.2% of patients. In the third-line setting, the best overall response was a PR in 2.9%, SD in 22.8%, and PD in 74.3% of patients. Therefore,

Table 1. Patients' characteristics (N=225).

Characteristics	N (%)
Sex	
Male	161 (72)
Female	64 (28)
ECOG PS at 1st line therapy	
0	108 (48)
1	102 (45)
2	15 (6.7)
Site of primary tumor	
Stomach	172 (76)
EGJ	53 (24)
Disease extent at beginning of 1st line therapy	
De novo metastatic	173 (77)
Relapse	42 (19)
Unresectable locally advanced	10 (4.4)
HER2 status	
Positive	28 (12)
Negative	191 (85)
Not recorded	6 (2.7)
Lauren classification	
Intestinal	45 (20)
Diffuse	57 (25)
Mixed	17 (7.6)
Not recorded	106 (47)
Number of metastatic sites*	
1	105 (49)
≥2	108 (51)

Note: *N=213; Abbreviations: ECOG-Eastern Cooperative group; PS-performance status; EGJ-esophagogastric junction; HER2-human epidermal growth factor receptor 2
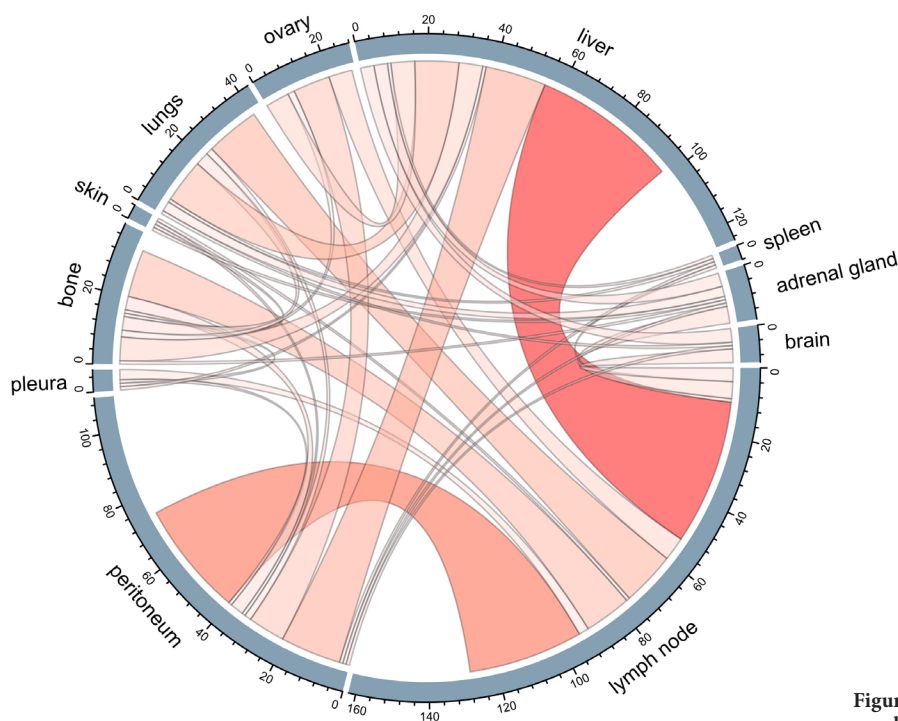

Figure 1. Metastatic sites of advanced gastric and esophagogastric cancer
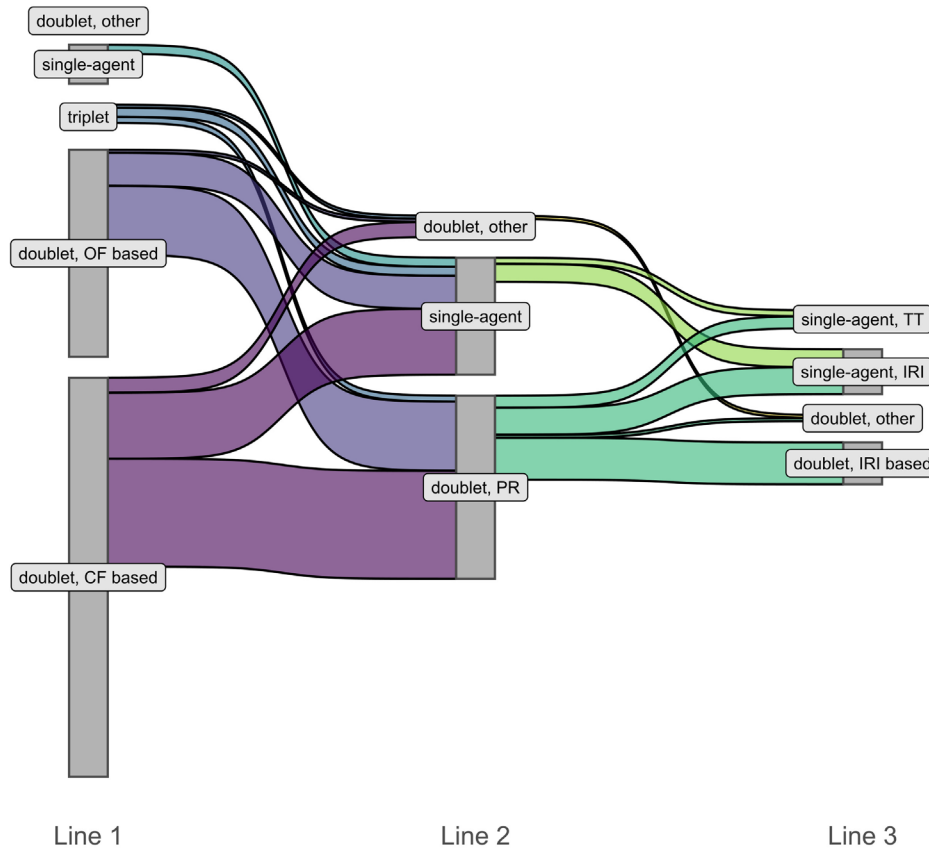
Figure 2. Treatment regimens received as first-line, second-line, and third-line therapy

Table 2. Variables stratified by treatment line.

Variable	First-line	Second-line	Third-line*
Patients, N (%)	225 (100)	107 (47.6)	38 (16.9)
Treatment, N (%)			
Triplet	8 (3.5)	0 (0.0)	0 (0.0)
Doublet	204 (90.7)	68 (63.6)	17 (44.7)
Single	13 (5.8)	39 (36.4)	21 (55.3)
Median duration of treatment, months ± SD# (range)	5±4 (0–25)	3±4 (0–25)	3±2 (0–10)
Overall best response, N (%)			
CR	4 (1.8)	1 (0.9)	0 (0.0)
PR	58 (25.8)	16 (15.0)	1 (2.9)
SD	62 (27.5)	32 (29.9)	8 (22.8)
PD	101 (44.9)	58 (54.2)	26 (74.3)

Note: *N = 35 with radiological assessment of ORR;
Abbreviations: n-number; CR-complete response; PR-partial response;
SD-stable disease; PD-progressive disease; SD#-standard deviation

the disease control rates were 55.1%, 45.8%, and 25.7% in the first-, second-, and third-line therapies, respectively.

The median OS for the whole cohort from the date of diagnosis of advanced disease was 11.0 months (95% confidence interval (CI) 9.7–12.0) (Figure 3A). OS from the beginning of second- and third-line treatment was 5.9 (95% CI 5.0–7.3) and 5.4 months (95% CI 3.9–8.9), respectively. Survival correlated significantly with the number of treatment lines received (p<0.001), with a median OS from diagnosis of 7.8 (95% CI 6.6–9.4), 12.0 (95% CI 10.0–14.0), and 20.0 months (95% CI 18.0–23.0) for patients receiving 1, 2, and ≥3 lines of treatment, respectively (Figure 3B). OS was significantly improved in HER2-positive patients (17.0 vs. 10.0 months, p=0.007) (Figure 3C). Lauren classification and ECOG PS also had a significant impact on OS (Figure 4).

Discussion

For decades, stomach cancer has been among the most common causes of death from malignant solid tumors due to its late detection, high disease burden at diagnosis, and rapid progression to applied treatment with deterioration of the patient's general condition [1, 2, 5, 6]. Chemotherapy improves survival and quality of life for patients with locally advanced unresectable or metastatic GC [9, 10, 12]. Nevertheless, patients with GC who are treated with combination ChT historically had a median OS of less than 1 year

[26]. Substantial differences in the treatment and survival of patients with metastatic GC were found in a large population-based cohort from five European countries [27].

Unfortunately, in 2020, among the European Union member states, the highest standardized death rates for cancer were recorded in Hungary and Croatia with rates of at least 300/100,000 inhabitants [ec.europa.eu/eurostat/statistics-explained/index.php?title=Cancer_statistics]. Therefore, in addition to the fact that significant progress is necessary in the prevention and early detection of cancer in general, in order to improve poor statistics, it is necessary to treat advanced diseases as efficiently as possible.

This study provides a detailed description of patient characteristics, treatment patterns, and survival outcomes for real-world patients treated for advanced and metastatic GC and EG adenocarcinoma in Croatia. As expected, men were the dominant sex (75%), with a median age of 65 years, which is consistent with the results of other real-world data [21, 22, 28, 29]. The stomach was the most common location for cancer in our cohort (76%) as well as in the Chinese cohort (93%) [23], in contrast to real-life data from the British (37%), Dutch (29%), and Canadian (37%) populations defining differences in etiology and consequently in epidemiology in Croatia in comparison to other developed western countries [21, 22, 29]. Therefore, it is not surprising that the diffuse type was even slightly more common than the intestinal type in our cohort (25% vs. 20%), in contrast to the Dutch cohort of patients (21% vs. 45%) [29]. The incidence of relapse was similar to that in other real-life studies, while the incidence of locally advanced inoperable disease was slightly lower [21]. *De novo* metastatic disease predominated, which is in accordance with the results of other real-life studies [21, 22]. As in other real-life studies, lymph nodes, liver, and peritoneum were the most common metastatic sites of the disease [22, 23, 29]. The frequency of HER2-positive tumors in this study was similar to the frequency in the British study [21] but lower than that observed in other clinical studies [22, 29–31]. Since the higher frequency of HER2-positive tumors in EGC and intestinal cancers has already been shown, this can be explained by more frequent stomach cancers than EGC as well as by a relatively small number of intestinal cancers in our study [30]. However, the median OS was even better than that in other studies [11, 21].

In our study, slightly less than 50% of patients received second-line therapy, while only approximately one-third of those who were treated with second-line therapy received three or more therapy lines. Other real-life studies have shown that 39 to 55% of patients receive a second-line treatment, whereas 14 to 19% of patients receive three or more lines of therapy, defining gastric cancer itself and not only the quality of cancer care important for the success of patient's treatment [21, 23, 28]. In studies by Davidson et al. [21] and Gomez-Ulloa et al. [31], more than 60% of patients received triplet ChT. Both studies included patients treated before 2017. Meanwhile, the treatment paradigm has been changed
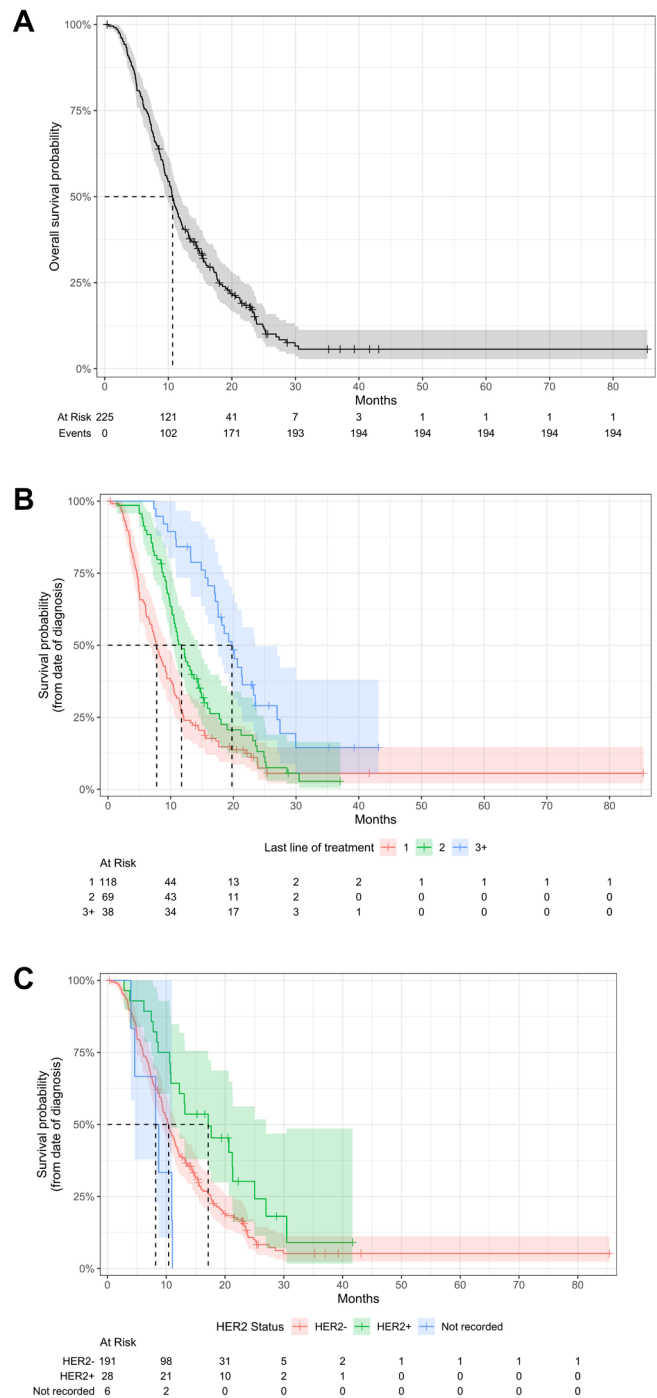

Figure 3. Overall survival A) for the whole cohort; B) stratified by the number of treatment lines; C) stratified by HER2 status.

in favor of doublet therapy as a less toxic option with almost similar efficacy [8]. No significant differences were found in OS or time to second-line treatment between oxaliplatin- and cisplatin-based doublets [32]. Until the publication of the results of the RAINBOW study and the availability
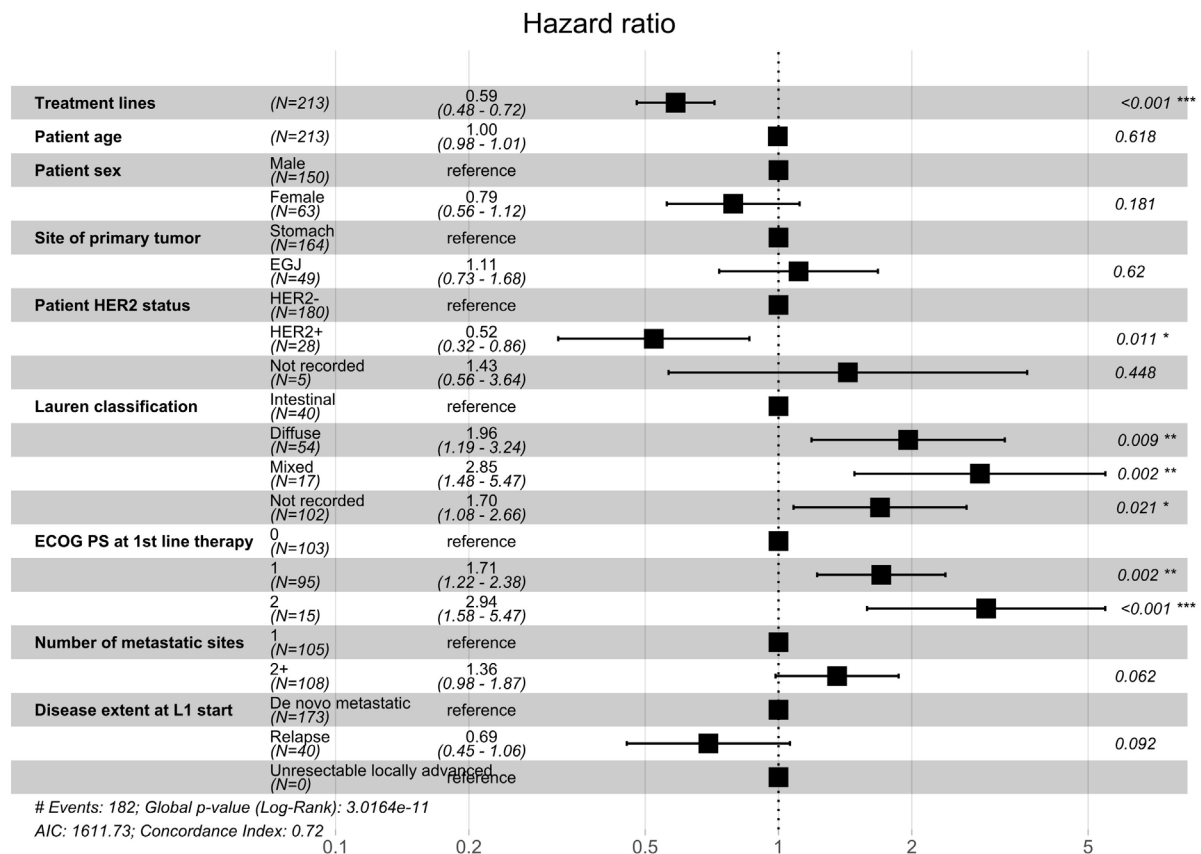
Hazard ratio

Treatment lines	*(N=213)*	0.59 (0.48 - 0.72)		<0.001 ***
Patient age	*(N=213)*	1.00 (0.98 - 1.01)		0.618
Patient sex	Male *(N=150)*	reference		
	Female *(N=63)*	0.79 (0.56 - 1.12)		0.181
Site of primary tumor	Stomach *(N=164)*	reference		
	EGJ *(N=49)*	1.11 (0.73 - 1.68)		0.62
Patient HER2 status	HER2- *(N=180)*	reference		
	HER2+ *(N=28)*	0.52 (0.32 - 0.86)		0.011 *
	Not recorded *(N=5)*	1.43 (0.56 - 3.64)		0.448
Lauren classification	Intestinal *(N=40)*	reference		
	Diffuse *(N=54)*	1.96 (1.19 - 3.24)		0.009 **
	Mixed *(N=17)*	2.85 (1.48 - 5.47)		0.002 **
	Not recorded *(N=102)*	1.70 (1.08 - 2.66)		0.021 *
ECOG PS at 1st line therapy	0 *(N=103)*	reference		
	1 *(N=95)*	1.71 (1.22 - 2.38)		0.002 **
	2 *(N=15)*	2.94 (1.58 - 5.47)		<0.001 ***
Number of metastatic sites	1 *(N=105)*	reference		
	2+ *(N=108)*	1.36 (0.98 - 1.87)		0.062
Disease extent at L1 start	De novo metastatic *(N=173)*	reference		
	Relapse *(N=40)*	0.69 (0.45 - 1.06)		0.092
	Unresectable locally advanced *(N=0)*	reference		

 # Events: 182; Global p-value (Log-Rank): 3.0164e-11
AIC: 1611.73; Concordance Index: 0.72

0.1   0.2   0.5   1   2   5

Figure 4. Hazard ratios and 95% confidence intervals for OS in prespecified groups

of ramucirumab in everyday clinical practice, second-line monotherapy dominated [21, 31]. Only 6 (15.8%) patients were treated with trifluridine tipiracil in the third line in our study because the drug has been available for the treatment of metastatic GC and EGC in Croatia since June 2020.

The COVID-19 pandemic could potentially have influenced the lower ORR and disease control in all three lines of treatment in this study compared to the studies by Davidson et al. [21] and Sun et al. [23], but this requires further analysis. Another possible explanation is that none of the patients included in this real-life study were treated as part of a clinical trial, whereas in the study by Davidson et al. [21], one-fifth of patients (first line) to one-third of patients (2nd and 3rd lines) were included in clinical trials. As in other studies, we found a significantly better ORR in patients with HER2-positive disease than in HER2-negative disease [11], while this difference was not reported in the British cohort [21].

As expected, OS correlated significantly with the number of treatment lines. The median survival of the whole cohort as well as the median survival with respect to the number of treatment lines in this study correlate well with the results of other real-life studies [21–23]. In addition to HER2 status and number of lines of systemic therapy, ECOG PS and Lauren classification were shown to have a significant impact

on OS. The use of immunotherapy in combination with ChT in PD-L1-positive HER 2-negative tumors in the first-line therapy as well as in MSI-high tumors in the second-line therapy has recently shown further improvement in OS in clinical trials [12, 14]. Good results of trastuzumab deruxtecan after progression on trastuzumab in HER2-positive tumors were suggested previously in a phase II study [20] but have yet to be tested in a phase III study.

The biological and molecular features of GC have an impact not only on the response to the used ChT but, most importantly, on the selection of patients suitable for specific, targeted treatment [33, 34]. Although molecular subgroup testing is not yet in routine clinical practice, mismatch repair deficiency, PD-L1, and HER2 should be performed routinely, as these are strongly predictive biomarkers for available drug therapies that have a significant impact on the outcomes of patients with GC.

The limitations of our study, which may affect the interpretation of the results, include its retrospective design and the relatively small number of patients. The retrospective design of the study may lead to patient selection and consequent bias in the study results. In addition, the real-world setting is the main strength of our study and the cornerstone of its generalizability to real-life populations.

In conclusion, the use of multiple treatment lines in advanced GC and EGC has resulted in improved OS. In addition to new effective drugs, their availability as well as an individualized approach to treatment are necessary to further improve outcomes. The optimal choice of first-line treatment for each individual patient is of particular importance, given the high attrition rates between treatment lines.

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