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ORIGINAL RESEARCH

Sex and gender disparities in patients with advanced gastroesophageal adenocarcinoma: data from the AGAMENON-SEOM registry

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Background: Recommendations for research articles include the use of the term sex when reporting biological factors and gender for identities or psychosocial or cultural factors. There is an increasing awareness of incorporating the effect of sex and gender on cancer outcomes. Thus, these types of analyses for advanced gastroesophageal adenocarcinoma are relevant.

Patients and methods: Patients with advanced gastroesophageal adenocarcinoma from the Spanish AGAMENON-SEOM registry treated with first-line combination chemotherapy were selected. Epidemiology, characteristics of the disease, treatment selection, and results were examined according to sex.

Results: This analysis included 3274 advanced gastroesophageal adenocarcinoma patients treated with combination chemotherapy between 2008 and 2021: 2313 (70.7%) men and 961 (29.3%) women. Tumors in females were more frequently HER2-negative (67.8% versus 60.8%; $P < 0.0001$), grade 3 (45.4% versus 36.8%; $P < 0.001$), diffuse (43.3% versus 26.5%; $P < 0.0001$), and signet ring cell histology (40.5 versus 23.9%; $P < 0.0001$). Peritoneal spread was more common in women (58.6% versus 38.9%; $P < 0.0001$), while liver burden was lower (58.9% versus 71.1%; $P < 0.0001$). There were no significant differences in treatment recommendation. Treatment doses, density, and duration were comparable between sexes. Women experienced more diarrhea (46% versus 37%; $P < 0.0001$), neutropenia (51% versus 43%; $P < 0.0001$), and anemia (62% versus 57%; $P < 0.0001$). After a median 59.6-month follow-up [95% confidence interval (CI) 54.5-70.8], there were no statistically significant differences between the sexes in progression-free survival [6.21 months (95% CI 5.8-6.5 months) versus 6.08 months (95% CI 5.8-6.3 months); log-rank test, $\chi^2 = 0.1$, 1 df, $P = 0.8$] or in overall survival [10.6 months (95% CI 9.8-11.1 months) versus 10.9 months (95% CI 10.4-11.4 months); log-rank test: $\chi^2 = 0.6$, 1 df, $P = 0.5$].

Conclusion: This sex analysis of patients with advanced gastroesophageal adenocarcinoma from the AGAMENON-SEOM registry receiving first-line polychemotherapy found no differences in survival. Although women had worse prognostic histopathology, metastatic disease pattern, and greater toxicity, treatment allocation and compliance were equivalent.

Key words: gastroesophageal cancer, sex, gender, survival, toxicity

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INTRODUCTION

Gastroesophageal cancer is the fourth leading cancer worldwide, accounting for 8.7% of all cancers with almost 1 700 000 estimated new cases diagnosed in 2020. It is also the second foremost cause of cancer death, comprising 13.2% of all cancer deaths with 1 312 869 estimated deaths in 2020.[1] Spain is expected to see an estimated 9681 new gastroesophageal cancers diagnosed in 2021, the sixth in cancer incidence; similarly, there were 6756 estimated deaths attributable to this kind of cancer and is the fourth cause of cancer deaths.[1]

Gastroesophageal cancer affects men more frequently,[2] as attested to by the fact that in Spain the difference was greater in esophageal (1895 cases in men versus 473 in women, 4/1 ratio) than in gastric cancer (4506 cases in men versus 2807 in women, 1.6/1 ratio) in 2021. Likewise, the estimated gastroesophageal cancer deaths in Spain for 2021 were more common in men; again, the difference was greater in esophageal (1452 deaths in men versus 320 in women) than in gastric cancer (3016 deaths in men versus 1968 in women).[1]

Sex and gender are important determinants of health inequalities. They are not only clinicopathological features of disease and health care needs, but also affect differences in treatments, adherence, and therapeutic outcomes and tolerability. While sex and gender are often used interchangeably, they are not equivalent concepts: sex is a biological variable that defines species (including humans) as male or female (or intersex) according to their reproductive organs, based on their chromosomal assignment. By contrast, gender refers to the socially constructed norms that determine roles, relationships, and positional power of individuals throughout their lifetime. Both concepts are interrelated and impinge upon health and well-being in different ways.[3]

The causes of the disparities in incidence and outcomes between men and women with gastroesophageal cancer may be based on either biological (i.e. sex) or sociocultural (i.e. gender related) factors. The biological factors include differences in the distribution of molecular or genetic subtypes. Gender-based factors can encompass individual exposure to risk factors such as obesity, smoking, and alcohol, but also treatment options and opportunities, as well as factors associated with the need for and access to health care.[4]

Consequently, epidemiological and therapeutic research on gastroesophageal cancer may be influenced by the preponderance of men,[1,2,5-7] but data regarding the impact of sex on survival outcomes are inconclusive.[6,8,9] Apart from raw epidemiological and therapeutic results, usually considering sex differences in subgroup analyses, a deeper evaluation of diagnosis, patterns of disease at diagnosis, and treatment strategies could help to explore and explain how gender, beyond sex, may influence disease presentation, treatment approach, and, ultimately, treatment outcomes.

Historically, women were excluded from clinical trials in certain circumstances and therefore, medical research has been centered on male physiology.[10] A simple way to evaluate gender bias is to identify if, for the same disease, providers make the same efforts for both. When both sexes are not offered the same quality of treatment and care for the same medical complaints, or when the different manifestations of disease are not considered on the basis of sex, patients' outcomes can be expected to be worse.[3] Along the same line, the Sex and Gender Equity in Research (SAGER) guidelines[11] have been designed to guide authors in preparing their manuscripts, but they are also useful for editors, as gatekeepers of science, to integrate the assessment of sex and gender into all manuscripts as part of the editorial process.[10,12] Recommendations for reporting in research articles include the use of the term sex when reporting biological factors and gender when reporting gender identities or psychosocial or cultural factors.[12] Ideally, the increased interest in the importance of sex and gender from funders and editors for all research should result in improved reporting of these considerations.[13,14]

Sex differences in cancer biology and treatment deserve more attention and systematic investigation. Interventional clinical trials evaluating sex-specific dosing regimens are necessary to improve the balance between efficacy and toxicity for drugs with significant pharmacokinetic differences. Especially in diseases or disease subgroups that exhibit significant differences in epidemiology or outcomes, men and women with non-sex—related cancers should be considered biologically distinct patient groups for whom specific treatment approaches warrant consideration.[15]

This real-world data analysis using data from the Spanish AGAMENON-SEOM registry aims to expand knowledge about how sex and gender may influence patients with advanced gastroesophageal adenocarcinoma, as well as how they impact physicians from diagnosis to treatment outcomes, to expose areas in which there is room for improvement to avoid health care disparities.

METHODS

Study population and design

All the patient data were from the AGAMENON-SEOM registry of advanced gastroesophageal adenocarcinoma pertaining to the Spanish Society of Medical Oncology (SEOM in Spanish) with contributions from 40 Spanish and 1 Chilean center. The main characteristics of the registry, method, and data collection have been reported elsewhere.[6,7,16-27] In brief, the AGAMENON-SEOM is a registry sponsored by SEOM's Evaluation of Results and Clinical Practice section. It is an observational, noninterventionistic registry of the diagnostic—therapeutic approach according to each participating center's usual practice. The data are collected by means of an electronic case report form (http://www.agamenonstudy.com/). This website contains multiple filters to ensure data reliability, preventing inconsistencies and missing data. The researchers (PJF and ACB) monitor the data regularly and all cases are validated and verified before being closed.

Eligibility criteria and survival endpoints include patients with a histological diagnosis of locally advanced unresectable or metastatic gastroesophageal adenocarcinoma. All the patients must have received at least one cycle of polychemotherapy ($\geq$2 drugs). The target population suitable for tumor response analysis must also have measurable disease at baseline and at least one objective evaluation at 3 months, as per RECIST version 1.1. Individuals with an interval of $<$6 months since the end of adjuvant or perioperative chemotherapy and lacking at least 3 months of follow-up were excluded, unless the participant had died during this period. The study was approved by the Research Ethics Committees of all the centers involved. All patients still alive at the time of data collection provided written, signed, informed consent.

Variables

Epidemiological, histopathological, clinical, and therapeutic variables were obtained from the clinical history. The chemotherapy regimen, dose intensity, and number of cycles were chosen at the investigator's discretion. Outcomes were overall response rate (ORR) as per RECIST version 1.1 criteria evaluated locally by the researcher, overall survival (OS), progression-free survival (PFS), and toxicity classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. OS and PFS were defined as the time between initiation of treatment and all-cause mortality or progression, censuring those patients without any event at last follow-up. Tumor burden was categorized into five groups in the following way: group 1 (low burden): involvement of a single organ with 1 or 2 metastases, mild/microscopic peritoneal ascites not located elsewhere or not otherwise classified; group 2 (moderate): involvement of a single organ affected with 3-5 lesions or two organs affected with $<$3 lesions per organ; category 3 (high load): a single organ affected with $>$5 lesions or three or more organs involved, and category 4 (very high tumor burden): baseline sum of diameters $>$15 cm, moderate/severe ascites, peritoneal metastases with diffuses nodules $>$2-3 cm, or central nervous system metastases, or 3 or more bone metastases, or liver tumor burden $>$50%. Relative dose intensity was expressed as percentages and defined as the amount of drug per unit of time (expressed as mg/m^2 weekly) administered with respect to the amount scheduled for each regimen.

Statistics

Standard descriptive statistics were used, including absolute and relative frequencies, means, and medians. When appropriate, 95% confidence intervals (CIs) were provided and significance was considered at $P < 0.05$ in all statistical tests. Two-tailed P values were calculated. Survival probabilities were estimated by the Kaplan–Meier method. Multivariable Cox proportional hazards models were also used to assess the association between gender and survival-based endpoints. Covariates were chosen theoretically, based on the a priori plausibility of their association with prognosis. Distributions for continuous variables according to sex were compared with Kolmogorov–Smirnov tests. The binary results were evaluated using binary logistic regression. Continuous predictors (i.e. age) were analyzed via restricted cubic splines. The analyses were executed with R version 4.1.2,[28] including the survival package.[29]

RESULTS

Characteristics of patients and cancers according to sex

The database contains 3274 patients with advanced gastroesophageal cancer from 40 Spanish and 1 Chilean center and treated between 2008 and 2021. Baseline characteristics can be found in Table 1.

Most of the participants were male and only 29% ($n = 961$) were female. However, there was a higher percentage of females among younger patients (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100514). For instance, the percentage of women was 48% versus 27% in the $<$40- and $>$65-year-old age groups, respectively. The cases of women registers have not increased substantially from 2008 to the present (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100514). The biological profile of the tumors differs depending on gender. Women are more prone to developing HER2-negative, grade 3, diffuse, or signet-ring cell tumors. Primary cancers of the esophagus or gastroesophageal junction are uncommon in females. All of this is manifested in the pattern of dissemination with more ascites and peritoneal metastases, but less liver tumor burden in women. Carcinoembryonic antigen (CEA) biomarkers and neutrophil-to-lymphocyte ratio (NLR) exhibit slightly dissimilar distributions, with greater CEA elevations, but discreetly lower NLR in women (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100514). Females have lower body mass indices (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2022.100514), while men present more comorbidities. We have not detected differences in general status, number of metastatic sites, analytical values (hepatic testing, lactate dehydrogenase, albumin), or with respect to stage (locally advanced unresectable versus metastatic). The multivariable Cox proportional-hazards model yielded consistent results (see Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2022.100514).

Treatment

Treatment patterns varied only slightly on the basis of sex. Thus, a negligible tendency to use more FOLFOX in women versus men was observed (Table 1).

The duration of the first-line regimens and the doses used are broadly equivalent except for a marginally lower relative dose intensity of platins in females (e.g. 77% versus 84% with cisplatin in FP3w; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100514). There were slight variations in the pattern of late management and successive cycles beyond 6 months. More surgeries for metastases were performed in women versus men: 5.6% ($n = 54/961$) versus 3.6% ($n = 85/2313$), $\chi^2 = 5.8$, 1 df, $P = 0.0157$. The most usual

Table 1. Baseline characteristics according to sex

Baseline characteristics	Total *n* = 3274 (100%)	Men *n* = 2313 (100%)	Women *n* = 961 (100%)	*P* value[a]
Age, years, median (range)	64 (20.8)	65 (20-89)	**63 (20-89)**	**0.0001**
Weight, mean (range)	68 (31-140)	71 (37-140)	**60 (31-115)**	**<0.0001**
Body mass index, mean (range)	25	25 (13-48)	**24 (13-48)**	**<0.0001**
Her2, *n* (%)				**<0.0001**
IHQ 0 or +1	2058 (62.9)	1406 (60.8)	**652 (67.8)**	
IHQ 3+	519 (15.9)	398 (17.2)	121 (12.6)	
IHQ 2+ and FISH +	210 (6.4)	174 (7.5)	36 (3.7)	
Unknown	487 (14.9)	335 (14.5)	152 (15.8)	
ECOG PS, *n* (%)				0.0542
0	773 (23.6)	550 (23.8)	223 (23.2)	
1	2034 (62.1)	1455 (62.9)	579 (60.2)	
2	467 (14.3)	308 (13.3)	159 (16.5)	
3	0	0	0	
Chronic comorbidities, *n* (%)				**<0.0001**
≥2	464 (14.2)	**384 (16.6)**	80 (8.3)	
Lauren type, *n* (%)				**<0.0001**
Intestinal	1365 (41.7)	1063 (46.9)	302 (31.4)	
Diffuse	1051 (32.1)	635 (26.5)	**416 (43.3)**	
Mixed	152 (4.6)	101 (4.4)	51 (5.3)	
Unknown	706 (21.6)	514 (22.2)	192 (20.0)	
Signet-ring, *n* (%)	942 (28.8)	553 (23.9)	**389 (40.5)**	**<0.0001**
Histological grade, *n* (%)				**<0.0001**
1	313 (9.6)	247 (10.7)	66 (6.9)	
2	863 (26.4)	671 (29.0)	192 (20.0)	
3	1287 (39.3)	851 (36.8)	**436 (45.4)**	
Not available	811 (24.8)	544 (23.5)	267 (27.8)	
Surgery for primary tumor, *n* (%)	1079 (33.0)	744 (32.2)	335 (34.9)	0.1464
Locally advanced, *n* (%)	173 (5.3)	133 (5.8)	40 (4.2)	0.5533
Location of primary tumor, *n* (%)				**<0.0001**
Esophagus	281 (8.6)	258 (11.2)	23 (2.4)	
Stomach	2552 (77.9)	1690 (73.1)	**862 (89.7)**	
Gastroesophageal junction	441 (12.5)	365 (15.8)	76 (7.9)	
Number of organs involved, *n* (%)				0.3864
1-2	2414 (73.7)	1695 (73.3)	719 (74.8)	
>2	860 (26.3)	618 (26.7)	242 (25.2)	
Metastasis, *n* (%)				**<0.0001**
Peritoneal	1463 (44.7)	900 (38.9)	**563 (58.6)**	**<0.0001**
Pulmonary	459 (14.0)	**362 (15.7)**	97 (10.1)	**<0.0001**
Hepatic	1216 (37.1)	**943 (40.8)**	273 (28.4)	**<0.0001**
Ascites	734 (22.4)	434 (18.8)	**300 (31.2)**	0.0671
Bone	330 (10.1)	248 (10.7)	82 (8.5)	**0.0103**
Nonlocoregional lymphatic	1412 (46.2)	**1102 (47.6)**	410 (42.7)	
Liver tumor burden, *n* (%)				**<0.0001**
No	2045 (62.5)	1362 (58.9)	**683 (71.1)**	
<25%	601 (18.4)	**465 (20.1)**	136 (14.2)	
25-50	375 (11.5)	**290 (12.5)**	85 (8.8)	
51-75	180 (5.5)	144 (6.2)	36 (3.7)	
>75%	73 (2.2)	52 (2.2)	21 (2.2)	
Tumor burden, *n* (%)				**<0.0001**
Low	503 (15.4)	362 (15.7)	141 (14.7)	
Moderate	551 (16.8)	397 (17.2)	154 (16.0)	
High	771 (23.5)	598 (25.9)	173 (18.0)	
Very high	1449 (44.3)	956 (41.3)	**493 (51.3)**	
Carcinoembryonic antigen, median (range)	4 (0-36000)	5 (0-16087)	3 (0-36001)	**0.0008218**
NLR, median (range)	3.2 (0.1-102)	**3.3 (0.1-102)**	3.0 (0.2-39)	**0.002362**
Albumin, *n* (%)				0.2085
Normal (>35 g/dl)	2142 (65.4)	1526 (66.0)	616 (64.1)	
30-35	522 (15.9)	359 (15.5)	163 (17.0)	
<30	245 (7.5)	162 (7.0)	83 (8.6)	
Not available	365 (11.1)	266 (11.5)	99 (10.3)	
Bilirubin baseline, *n* (%)				0.1097
Normal (<1.5 mg/dl)	3038 (92.8)	2132 (92.2)	906 (94.3)	
1.5-3	115 (3.5)	89 (3.8)	26 (2.7)	
3.1-5	21 (0.6)	17 (0.7)	4 (0.4)	
>5	20 (0.6)	18 (0.8)	2 (0.2)	
Not available	80 (2.4)	57 (2.5)	23 (2.4)	
Alkaline phosphatase (U/l), *n* (%)				0.4028
Normal	2162 (66.0)	1530 (66.1)	632 (65.8)	
Normal to 2.5 ULN	608 (18.6)	414 (17.9)	194 (20.2)	
2.5 to 5 ULN	205 (6.3)	145 (6.3)	60 (6.2)	

Continued

Table 1. Continued

Baseline characteristics	Total $n = 3274$ (100%)	Men $n = 2313$ (100%)	Women $n = 961$ (100%)	P value[a]
5-10 ULN	90 (2.7)	65 (2.8)	25 (2.6)	
>10 ULN	71 (2.2)	55 (2.4)	16 (1.7)	
Not available	138 (4.2)	104 (4.5)	34 (3.5)	
Lactate dehydrogenase (U/l), *n* (%)				0.7586
Normal	1825 (55.7)	1291 (55.8)	534 (55.6)	
Normal to 2.5 ULN	604 (18.4)	421 (18.2)	183 (19.0)	
2.5 to 5 ULN	154 (4.7)	116 (5.0)	38 (4.0)	
5-10 ULN	59 (1.8)	39 (1.7)	20 (2.1)	
>10 ULN	18 (0.5)	12 (0.5)	6 (0.6)	
Not available	614 (18.8)	434 (18.8)	180 (18.7)	
Platelets				0.6953
Normal (100,000-450,000/μl)	2883 (88.1)	2046 (88.5)	837 (87.1)	
High (>450 000/μl)	324 (9.9)	222 (9.6)	102 (10.6)	
Low (<100 000/μl)	33 (1.0)	23 (1.0)	10 (1.0)	
Not available	34 (1.0)	22 (1.0)	12 (1.2)	
Short-course regimens				**0.0452**
Oxaliplatin based	1451 (44.3)	992 (42.9)	**459 (47.8)**	
Cisplatin based	642 (19.6)	468 (20.2)	174 (18.1)	
Anthracycline based	595 (18.2)	421 (18.2)	174 (18.1)	
Docetaxel based	344 (10.5)	244 (10.5)	100 (10.4)	
Irinotecan based	57 (1.7)	46 (2.0)	11 (1.1)	
Others	185 (5.7)	142 (6.1)	43 (5.4)	
Detailed regimens				**0.0179**
CAPOX	729 (22.3)	521 (22.5)	208 (21.6)	
FOLFOX	689 (21.0)	449 (19.4)	**240 (25.0)**	
Anthracycline-based	606 (18.5)	429 (18.5)	177 (18.4)	
XP	425 (13.0)	319 (13.4)	115 (12.0)	
Docetaxel-based	346 (11.2)	256 (11.1)	110 (11.4)	
Cisplatin—5FU	200 (6.1)	146 (6.3)	54 (5.6)	
Carboplatin—5FU	75 (2.3)	62 (2.7)	13 (1.4)	
FOLFIRI	34 (1.0)	26 (1.1)	8 (0.8)	
Others	150 (4.6)	114 (4.9)	36 (3.7)	

Significance of bold values are relevant values to consider.
5FU, fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; IHQ, immunohistochemistry; NLR, neutrophil-to-lymphocyte ratio; ULN, upper limit of normal; XP, capecitabine + platinum.
[a]*P* values refer to comparisons by sex and are derived from χ^2 tests for categorical variables, and Wilcoxon test for continuous variables (e.g. age, NLR).

surgeries in women were peritonectomies (3% versus 1.3%, $\chi^2 = 6.2$, 1 df, $P = 0.0124$). There were no differences with respect to treatment to progression: 51% ($n = 1180$) of men versus 49% ($n = 471$) of women ($\chi^2 = 1.3$, 1 df, $P = 0.2441$) received second-line therapy.

Survival and response outcomes

A total of 2110 patients had measurable, response-evaluable disease. The 3-month RECIST version 1.1 evaluation in this group revealed complete response in 45 (2%), partial response in 893 (42%), stable disease in 550 (26%), and tumor progression in 622 (29%). When data from different schemes were pooled, a meager decrease of the ORR was observed in women: 45% versus 41%, common odds ratio 0.81 (95% CI 0.67—0.98; Mantel—Haenszel $\chi^2 = 4.09$, 1 df, $P = 0.04312$). When data are broken down by most common regimens, this tendency is similar to all regimens except for cisplatin-5FU, for which the ORR in females is 51% versus 41% in males (Figure 1).

In the 3274 individuals who were eligible for survival analysis, 2862 death events and 3038 progression events to first line were recorded, with median PFS and OS of 6.12 months (95% CI 5.9-6.3 months) and 10.8 months (95% CI 10.5-11.1 months), respectively. Median follow-up in those alive was 59.6 months (95% CI 54.5-70.8 months). No differences in PFS were observed based on sex, with a median of 6.21 (95% CI, 5.8-6.5) months and 6.08 months (95% CI, 5.8-6.3 months) in women and men, respectively (log-rank test, $\chi^2 = 0.1$, 1 df, $P = 0.8$). Likewise, no differences in OS were found by sex with a median of 10.6 months (95% CI 9.8-11.1 months) and 10.9 months (95% CI, 10.4-11.4 months) in females and males, respectively (log-rank test: $\chi^2 = 0.6$, 1 df, $P = 0.5$; Figure 2).

Toxicity for first line

The toxicity profile varies depending on patients' sex with more any grade gastrointestinal toxicity, neutropenia, and anemia among women (Figure 3). Thus, 46% women versus 37% men ($P < 0.0001$) had diarrhea (any grade); 51% women versus 43% men ($P < 0.0001$) exhibited neutropenia; 62% versus 57% ($P = 0.0002$) displayed anemia. As for National Cancer Institute-Common Toxicity Criteria grade 3-4 toxicity,women had more neuropathy (5% versus 3%; $P = 0.007$), neutropenia (24% versus 18%; $P < 0.0001$), emesis (5% versus 3%; $P < 0.0001$), and diarrhea (7% versus 5%; $P = 0.008$; Figure 4).

DISCUSSION

This analysis of the AGAMENON-SEOM registry in patients with advanced gastroesophageal adenocarcinoma is justified by the growing interest in exploring the sex- and gender-based differences in the diagnostic and therapeutic

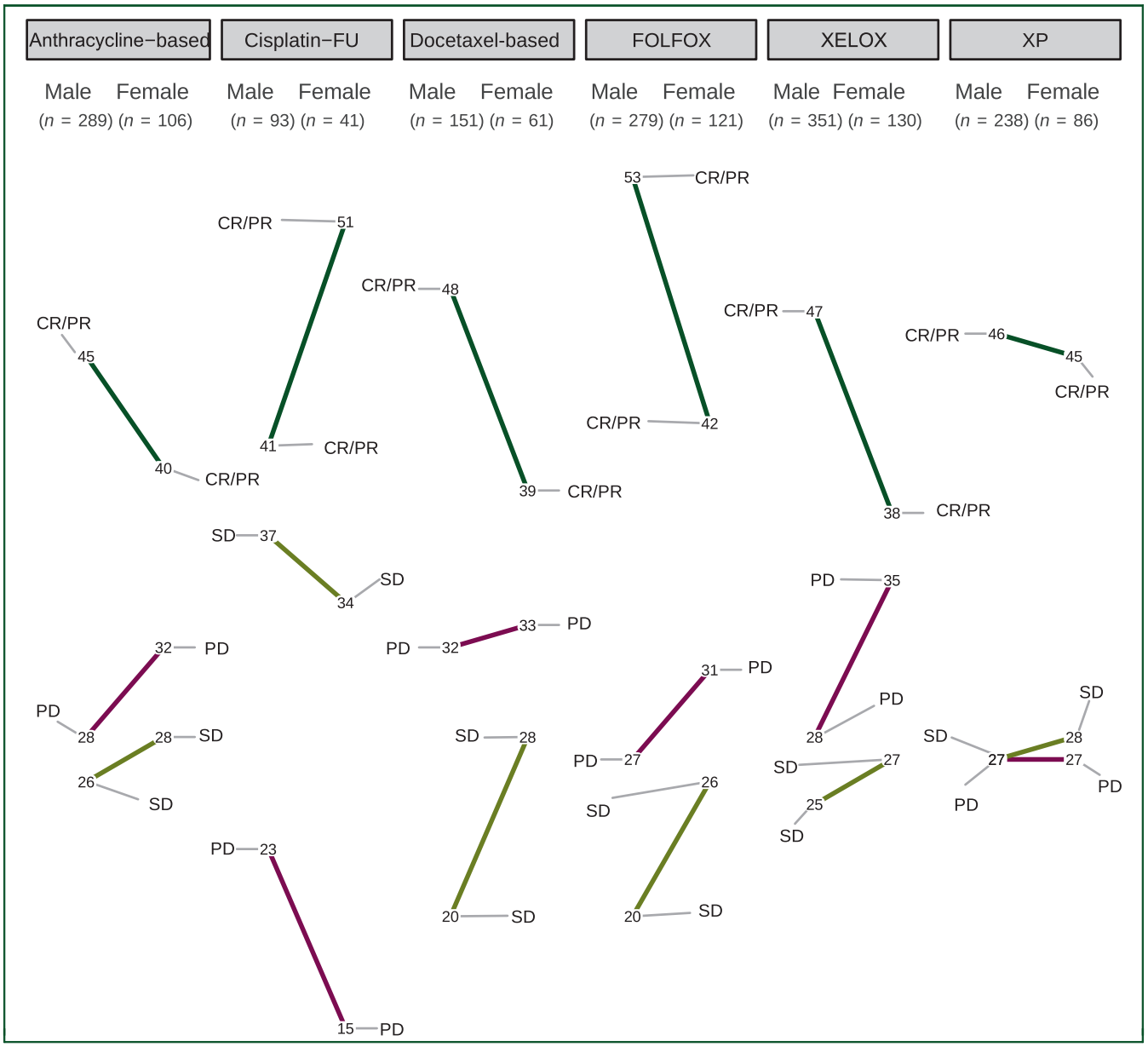

Figure 1. Slope plots with RECIST categories for males versus females.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

approach in individuals with cancer.[10] Several initiatives have been launched recently in this regard[30] and we are witnessing the publication of analyses derived from registries or clinical trials examining the impact of gender in this and other diseases with results that serve as food for thought.[4] In this scenario, the study we present here is the first to offer the perspective of sex and gender in a specific landscape of disease (advanced gastroesophageal adenocarcinoma) and with a premise (patients eligible for first-line combination chemotherapy). With this condition as our starting point, we probe the disease characteristics, as well as the selection, compliance, and treatment toxicity and survival results.

In our series, the relation between men and women tends to balance out in young patients and the proportion of males leaning toward a larger proportion of males at older ages. This fact, described by other series,[31] could be justified by the fact that tumors with a greater genetic predisposition are distributed equally across men and women, while those related to risk factors, with a cumulative influence, are more prevalent in men (Table 1 and Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100514). This has not changed over time in our series (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100514). Both environmental and genetic risk factors would contribute to the patterns of sex differences in gastroesophageal adenocarcinoma.[32] Accordingly, sex would condition the distribution at early ages in a homogenous manner, while gender would tend to favor the predominance of males at mature ages.

Tumor histologies reveal a histopathological profile having a worse prognosis for women (diffuse, Her2-negative,

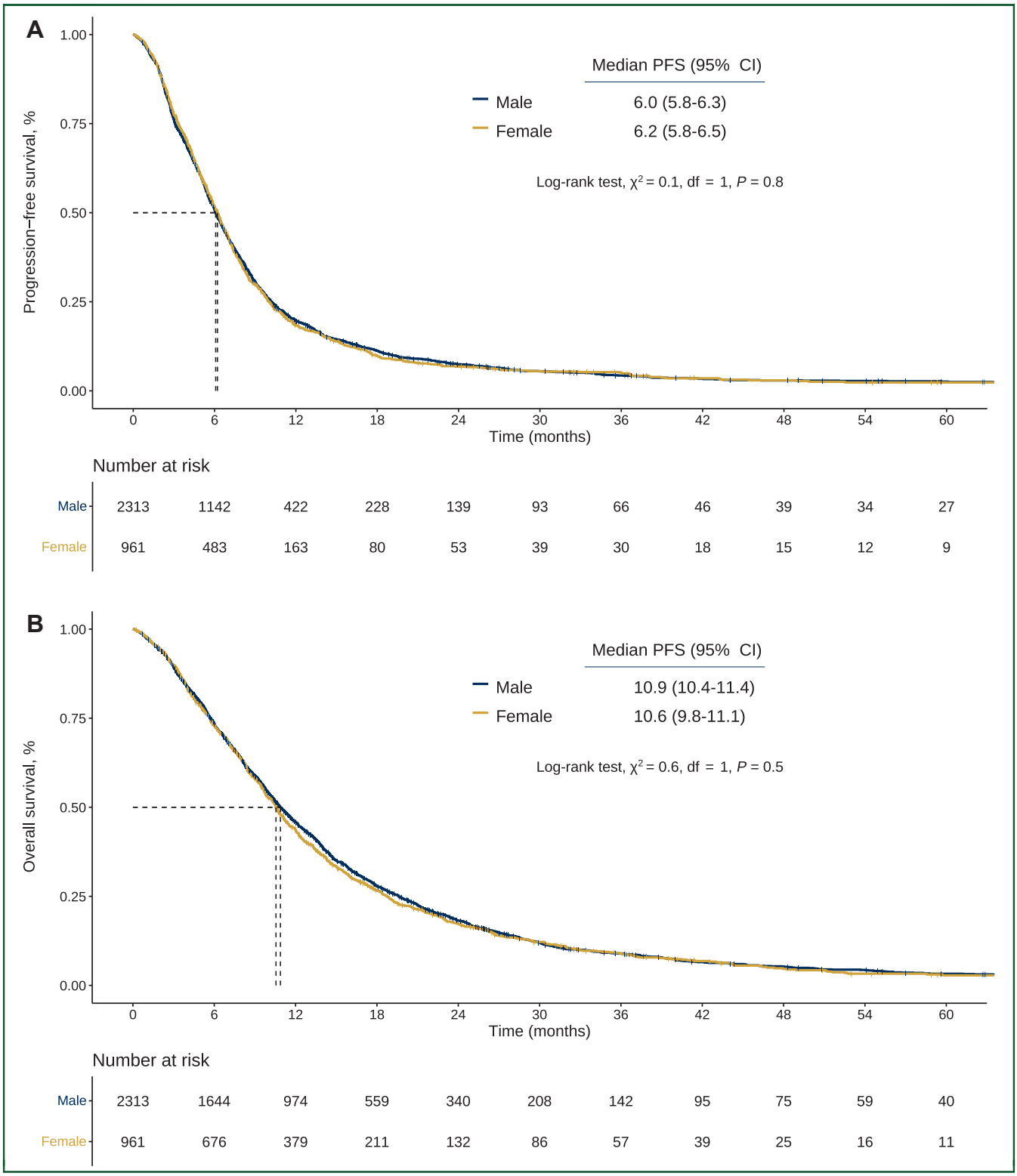

Figure 2. Survival functions stratified by gender. (A) Progressión free survival stratified by gender. (B) Overall survival stratified by gender.

G3, signet-ring cells). This aspect was unrelated to gender but to the biology of the disease itself (Table 1). Similarly, histopathological features in advanced esophagogastric adenocarcinoma in women point to a lesser association of the disease with exposure factors and to an increased likelihood of genetic predisposition.[33]

While in both sexes the most common location was the stomach, such was the case especially in women and an association between this location and the histopathological characteristics described earlier was noted.[34] Nevertheless, there were no differences with respect to distribution by locally advanced unresectable or metastatic disease.

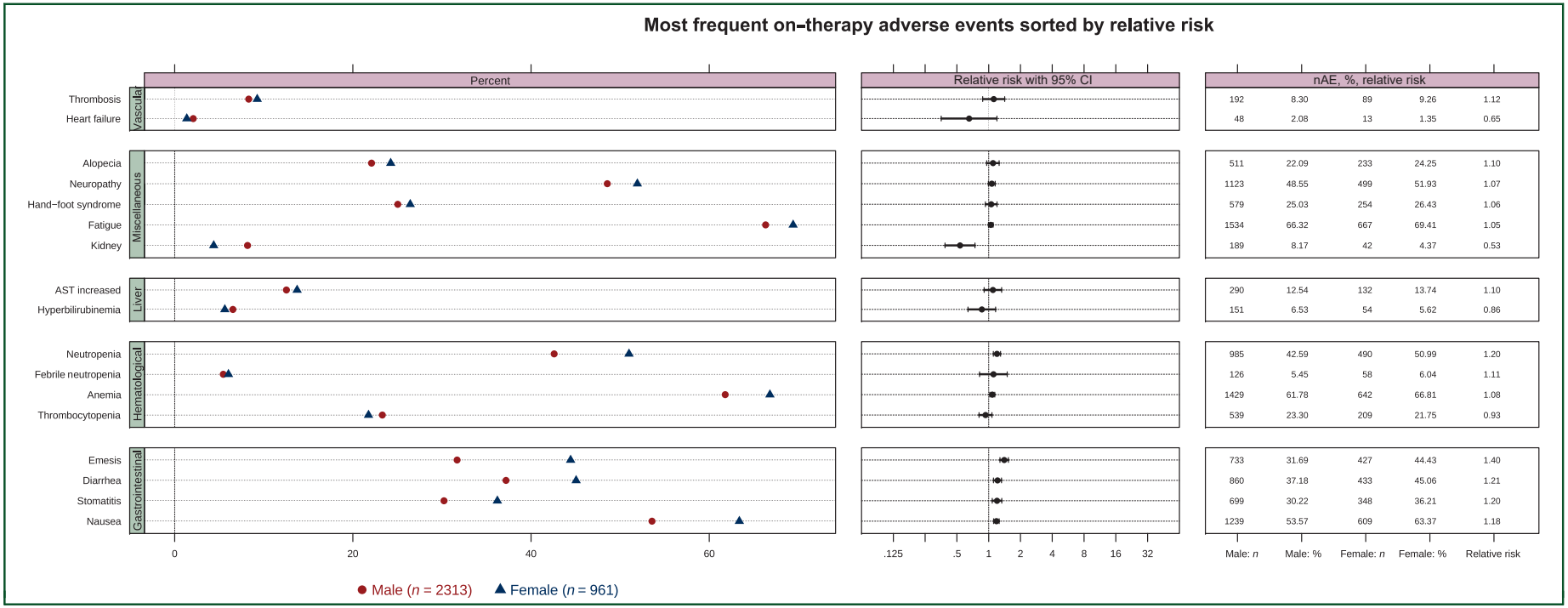

Figure 3. Amit plot toxicity by sex.
AST, aspartate aminotransferase; CI, confidence interval; nAE, number of adverse events.

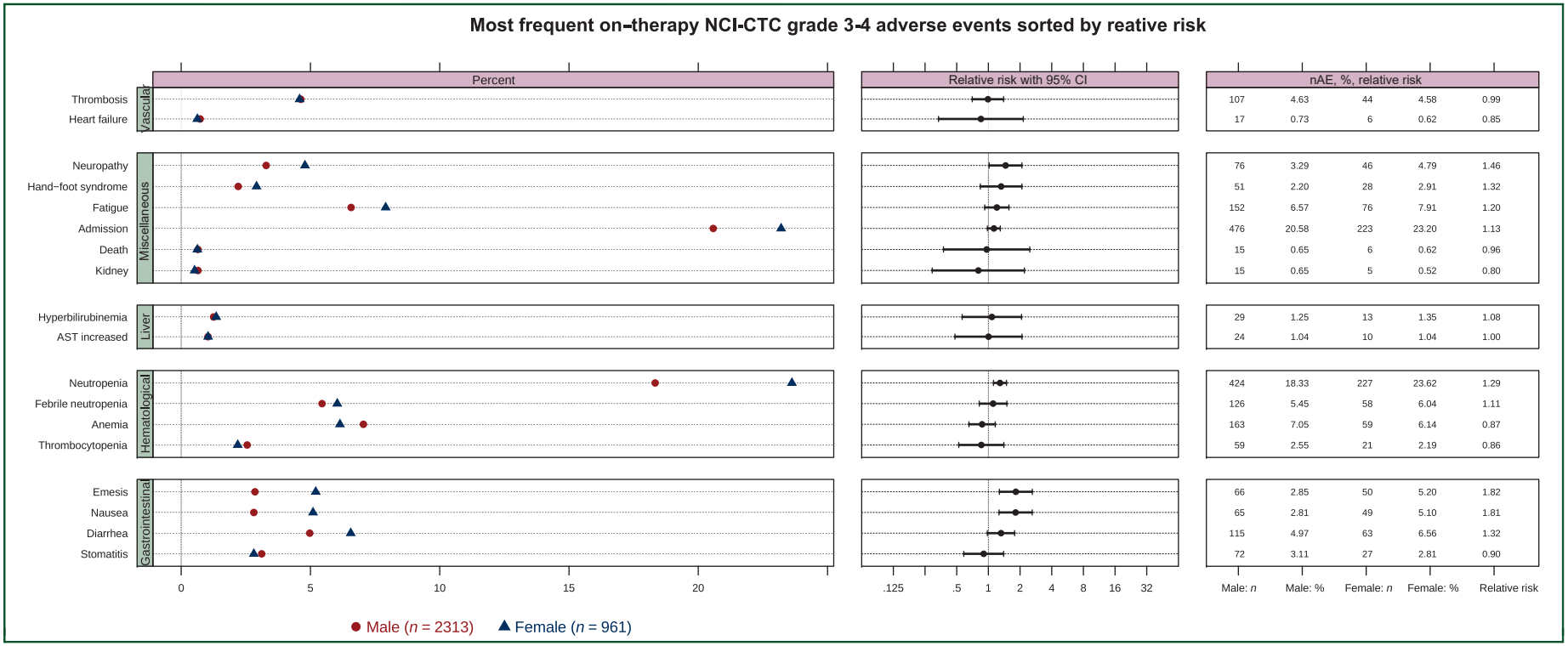

Figure 4. Amit plot for grade 3-4 toxicity by sex.
nAE, number of adverse events; NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

https://doi.org/10.1016/j.esmoop.2022.100514

Not only the histopathologic profile but also the metastatic disease profile of women was worse, with more peritoneal metastases (MTS) and ascites, and less MTS classically regarded as being less aggressive (lymph node and lung), with a higher proportion of disease with a greater tumor burden. No differences were observed with respect to the number of metastatic sites. Given that the pattern of peritoneal dissemination is associated with diffuse histology and signet ring cells, we identified a higher incidence of peritoneal metastases[35] and, given the proportions of histological type and peritoneal dissemination in our series, we can explain the differences in the pattern of dissemination as a consequence of histopathological characteristics (Table 1). An evaluation of metastatic sites, liver tumor burden, ascites, and peritoneal carcinomatosis suggests that the higher percentage of females with very high tumor burden is especially dictated by the peritoneal involvement. The association between histology, dissemination pattern, and tumor burden, coupled with the absence of differences in the number of metastatic sites and general status at diagnosis, does not support the association of the worse prognosis of disease for women with aspects attributable to gender, such as time to ascertain the reason for consultation, access to the health care system, health care services provided at diagnosis, among others.[3,36]

As for analytical variables, the slight increase in CEA in females compared with males contrasts with a lower NLR (favorable prognostic factor), despite a histology and spread of disease that have a predictably worse prognosis[6] (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100514).

While there is a greater tendency to use oxaliplatin-based regimens and, more specifically FOLFOX, in women (Table 1), this is only justified in part by a decreased use of cisplatin. With this in mind, this tendency might be accounted for by the intention of protecting women from traditionally considered more toxic drugs.[37] Likewise, the greater frequency of comorbidities in males versus females might have affected the choice of regimens that potentially have a better toxicity profile, favoring equivalence with regimens applied in women.[38,39] The similarity in choice of regimens in men and women holds with regard to duration, cumulative dose, dose intensity, and dose density, as well as the reasons for discontinuing treatment. This is also the case with respect to the frequency of second-line treatment indication, detecting no statistically significant intergroup differences. The fact that our study population includes patients who received combination chemotherapy has kept us from properly exploring whether gender causes a difference in treatment recommendation, as demonstrated by the recent analysis of real clinical practice data, in which women were found to receive systemic treatment less often than men.[4]

The higher rate of surgery for advanced disease in women may be conditioned by the higher rate of peritoneal dissemination of disease in females and for which surgery is regarded as a treatment alternative that benefits survival.[40,41] Subsequently, most of the surgeries performed in the women in our series were peritonectomies.

The benefit of treatment in terms of RECIST version 1.1 response criteria is evidenced by the lower incidence of tumor regression in females compared with males, which is reflected in most regimens and more pronounced in regimens with oxaliplatin and/or docetaxel, and with the exception of cisplatin + fluorouracil, which was administered to only 6.1% of the sample (Figure 1). The slightly greater dose density of both chemotherapeutic agents in the cisplatin + fluorouracil regimen in women with respect to men does not appear sufficient to account for an overall trend toward greater response benefit of chemotherapy in men that, as we will see later and as previously reported, does not translate into a survival benefit.[42] This lower ORR in females may have to do with a higher percentage of diffuse cancers that are less chemosensitive.

In terms of toxicity, it is worth noting that, despite greater gastrointestinal toxicity, neutropenia, and anemia in women compared with men (Figure 3), these did not affect treatment duration, compliance, and density; accordingly, these did not impact survival outcomes. Although some toxicities may be subject to gender-influenced weighting, either because of how they are perceived by the patient or how they are recorded by the medical team, it would not justify our findings concerning toxicities with objective categorization by National Cancer Institute-Common Toxicity Criteria and/or blood test results. The relationship between antineoplastic treatment toxicity and sex has been analyzed and reviewed by other groups.[43,44] If we confine ourselves to gastroesophageal adenocarcinoma, the pooled analysis published by Davidson et al. in 2019,[45] including four randomized clinical trials in the UK, evidenced a higher overall incidence of toxicity, G3 gastrointestinal toxicity, and serious adverse events in women. Nevertheless, although in this analysis this higher incidence of toxicity was associated with fewer cycles of chemotherapy administered, this was not the case in our series. Later on, this same group reported the efficacy, safety, and survival analysis in localized gastroesophageal adenocarcinoma as per sex and age. While their results again documented a higher rate of G3 gastrointestinal toxicity in women, this was consistent with a higher survival expectancy for women,[46] which we also failed to find in our sample.

The absence of differences in terms of PFS and OS between women and men in our series, in a recognized circumstance of antineoplastic treatment equivalence in terms of regimens and their management, in the scenario of a disease with an a priori worse prognosis for women, enables us to put forward different hypotheses. On the one hand, there might be less of an adverse prognostic impact of classic histopathological factors, as well as peritoneal involvement in women with advanced gastroesophageal adenocarcinoma. On the other hand, women might benefit more from antineoplastic treatment, capable of reversing the initial disadvantage resulting from their worse prognosis. In any of the hypotheses posited, the consequence would be that sex and/or gender, in and of themselves, and the clinical pathological characteristics associated with them, should not condition our therapeutic attitude on the selection or intensity of treatment. Still, it is important to be

mindful of the aforementioned toxicity considerations, with the well-recognized higher incidence of adverse effects in women with gastroesophageal adenocarcinoma who receive chemotherapy treatment.[45,46] Moreover, considering that women have been underrepresented in relevant studies of first-line chemotherapy for advanced gastroesophageal adenocarcinoma as studies did not include a sex-specific analysis,[12,47,48] or due to the experimental arm potentially having less of a benefit for women,[49] stratification by sex is particularly necessary for a proper risk—benefit balance of treatment in women.[15]

Among the limitations of this study are the health care nature of the sample, with the repercussions that this can have on the recording of epidemiological variables, disease, and toxicities. Nevertheless, this may be an asset when assessing treatment patterns that may differ in clinical practice on the basis of gender. Second, although the standard first-line treatment for advanced gastroesophageal adenocarcinoma has been associated with combination chemotherapy, its composition has evolved over time, which may have played a role in the selection of different regimens in a study involving patients over a 13-year period. Conversely, the inclusion of patients who are candidates for first-line combination chemotherapy excludes other less intense treatments (monotherapy) and best supportive care alone, and precludes the analysis of a potential differential first-line therapeutic approach for one gender or patient and/or disease profile in this group in particular. This would presumably include the frailest and most elderly individuals. Having more information concerning the time of diagnosis, evolution of symptomatology, and access to the health care system would also be desirable, for the purpose of an in-depth analysis as to whether gender is a determining factor during the diagnostic process of advanced gastroesophageal adenocarcinoma. Finally, despite the large study population and the strong national representativeness of Spain, we cannot exclude the possibility that variability in clinical practice with respect to other countries or cultural differences may limit the external validity of our results.

In conclusion, the results of the AGAMENON-SEOM study of patients with advanced gastric adenocarcinoma treated with first-line polychemotherapy show that, despite the existence of subtle biological and clinical differences in the cancers according to sex, and the moderate impact this has on the selection of therapies, women with advanced gastroesophageal adenocarcinoma experience greater toxicity to obtain therapeutic results comparable with men. This analysis suggests the desirability of considering stratification and analysis by sex in studies of gastroesophageal adenocarcinoma in order to understand the risk-to-benefit ratio associated with this variable.

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