The impact of sex on treatment and outcome in relation to histological subtype in patients with resectable gastric cancer: results from the randomized CRITICS trial

Caspers, I.A.; Slagter, A.E.; Lind, P.; Sikorska, K.; Wiklund, K.; Pontén, F.; ... ; Cats, A.

Received: 17 August 2023 | Accepted: 27 November 2023

DOI: 10.1002/jso.27554

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

The impact of sex on treatment and outcome in relation to histological subtype in patients with resectable gastric cancer: Results from the randomized CRITICS trial

Irene A. Caspers[1,2] | Astrid E. Slagter[3] | Pehr Lind[4] | Karolina Sikorska[5] | Katja Wiklund[4] | Fredrik Pontén[6] | Marianne Nordsmark[7] | Cornelis J. H. van de Velde[8] | Elma Meershoek-Klein Kranenbarg[8] | Johanna W. van Sandick[9] | Edwin P. M. Jansen[3] | Hanneke W. M. van Laarhoven[10] | Marcel Verheij[3,11] | Nicole C. T. van Grieken[2] | Annemieke Cats[1]

[1]Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, The Netherlands

[2]Department of Pathology, Amsterdam University Medical Center, Amsterdam, The Netherlands

[3]Department of Radiation Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, The Netherlands

[4]Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden

[5]Department of Biometrics, Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, The Netherlands

[6]Department of Immunology, Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

[7]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

[8]Department of Surgical Oncology, Leiden University Medical Center, Leiden, The Netherlands

[9]Department of Surgery, Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, The Netherlands

[10]Department of Medical Oncology, Amsterdam University Medical Center, Amsterdam, The Netherlands

[11]Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence
Annemieke Cats, Department of Gastrointestinal Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands.
Email: a.cats@nki.nl

Abstract

Background and Objective: This study aims to investigate the impact of sex on outcome measures stratified by histological subtype in patients with resectable gastric cancer (GC).

Methods: A post-hoc analysis of the CRITICS-trial, in which patients with resectable GC were treated with perioperative therapy, was performed. Histopathological characteristics and survival were evaluated for males and females stratified for histological subtype (intestinal/diffuse). Additionally, therapy-related toxicity and compliance were compared.

Results: Data from 781 patients (523 males) were available for analyses. Female sex was associated with a distal tumor localization in intestinal ($p = 0.014$) and diffuse tumors ($p < 0.001$), and younger age in diffuse GC ($p = 0.035$). In diffuse GC, tumor-positive resection margins were also more common in females than males (21% vs. 10%; $p = 0.020$), specifically at the duodenal margin. During preoperative chemotherapy, severe toxicity occurred in 327 (63%) males and 184 (71%) females ($p = 0.015$). Notwithstanding this, relative dose intensities were not significantly different between sexes.

Irene A. Caspers and Astrid E. Slagter contributed equally.

Conclusions: Positive distal margin rates were higher in females with diffuse GC, predominantly at the duodenal site. Females also experience more toxicity, but this neither impacts dose intensities nor surgical resection rates. Clinicians should be aware of these different surgical outcomes when treating males and females with GC.

KEYWORDS

gastric cancer, histopathology, Lauren classification, sex, sex differences

1 | BACKGROUND

Gastric cancer (GC) patients suffer from a poor prognosis since they are usually diagnosed at an advanced stage.[1] Treatment of this disease requires a multidisciplinary approach in specialized centers.[2,3] Currently, patients with resectable gastric cancer are treated according to a one-size-fits-all all principle. To better tailor GC treatment to the individual patient and tumor characteristics, it is important to identify clinically relevant subgroups of patients.

The Lauren classification is widely accepted for the classification of GC in clinical studies and for this purpose, distinguishes two major histological subtypes of gastric adenocarcinomas: intestinal-type GC and diffuse-type GC.[4] Intestinal-type GC and diffuse-type GC differ with respect to growth pattern, cellular morphology, and prognosis.[4] Patients with diffuse-type GC have worse survival and worse histopathological response to chemotherapy compared with patients with intestinal-type GC.[5] In addition, intestinal and diffuse-type GC also have different molecular profiles, as was first described in the Tumor Cancer Genome Atlas (TCGA).[6] Taken together, intestinal and diffuse-type GC are both clinically and biologically distinct subtypes of GC.

In recent years, it has become clear that the impact of sexual dimorphism in cancer patients has been underestimated. In several types of cancer, sex differences have been described with respect to epidemiology, biology, and treatment-related toxicities.[7] Males and females are not evenly affected by gastric cancer, as twothirds of gastric cancer patients are males.[1] Diffuse-type GC is more often diagnosed in females compared to intestinal-type GC and has been associated with younger age.[8,9] Likewise, female sex has been associated with a younger age of onset[9,10] and a more distal tumor localization[11] in gastric cancer patients. Only recently, a prolonged survival was reported for females compared to males with microsatellite instable GC.[12]

It has been hypothesized that sex differences in the epidemiology and histopathology of gastric cancer are multifactorial and include hormonal, environmental, genetic, and epigenetic factors.[13] Exposure to estrogens of either ovarian or exogenous origin, for example, has been associated with decreased risk of GC.[14] Furthermore, exposure to environmental risk factors, including diet patterns, smoking, alcohol consumption, and exposure to harmful industrial and occupational environments, have been associated with male sex.[15]

In several studies, including patients with hematological and solid cancers, females experienced more often severe toxicity during treatment with chemotherapy compared with males.[16–18] Recently, this has been reported in a pooled analysis of four randomized trials, including patients with advanced esophagogastric cancer treated with palliative intent. Especially, severe gastrointestinal toxicity occurred more frequently in females.[10]

Although the association between the histological subtype of GC and sex has previously been reported,[8,9] it remains currently unclear to what extent these factors are intertwined and to what extent each contributes to treatment outcomes in patients with potentially curative resectable gastric cancer. In the intention-to-treat analysis of the previously published CRITICS study, in which histology was one of the stratification factors, we have described survival differences among sexes between patients with resectable gastric cancer treated with postoperative chemotherapy versus chemoradiotherapy. To enhance our understanding of differences in compliance to treatment, chemotherapy-induced toxicity, and outcomes between sexes irrespective of histological subtype, we now present a post-hoc subgroup analysis of the CRITICS study.

2 | MATERIALS AND METHODS

2.1 | Data acquisition

Patients with resectable GC who participated in the phase III open-label CRITICS trial were included in this analysis. In the CRITICS trial, 788 patients with resectable non-metastatic adenocarcinoma of the stomach or gastroesophageal junction (stage Ib–IVa, 6th edition TNM) were upfront randomized to receive preoperative chemotherapy and D2 surgery followed by either postoperative chemotherapy or postoperative chemoradiotherapy.[19,20] Randomization was performed with stratification for histological subtype according to Lauren, tumor localization, and hospital of inclusion. The methods and main results of the study have been published.[19,20] The CRITICS trial was carried out in agreement with the declaration of Helsinki. The study was approved by the Medical Ethical Committee of the Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital.

For this post hoc subgroup analysis, histological subtypes were reviewed by an expert pathologist (NCTvG) on pretreatment biopsies and resection specimens before this analysis. Tumors were classified according to Smyth et al.[21] as either

intestinal-type, diffuse-type, mixed type, or other type. In case the pretreatment biopsy was not available or inconclusive, the histological subtype determined on the resection specimen was used for final classification. Tumor regression grade according to the Mandard classification was also assessed on the resection specimens. Mixed and other subtype GC were excluded from this analysis due to limited numbers. TNM stages were retrospectively reviewed and updated to the 8th TNM classification, as described previously.[22]

2.2 | Outcomes

Baseline characteristics, surgical characteristics, pathological characteristics, and survival were analyzed separately for each histological subtype and compared between males and females. It was evaluated whether allocated treatment was equally distributed between sexes. Baseline characteristics included age, World Health Organization (WHO) performance status, and tumor localization. In the CRITICS trial, toxicities were prospectively collected and scored according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE; version 3.0). Pre- and postoperative severe toxicities (grade 3–5) and relative dose intensities (RDI's) were compared between males and females and stratified by histological subtype. Relative dose intensity was defined as $\frac{\text{dose received (mg)}}{\text{dose planned (mg)}} \times \frac{\text{time planned (days)}}{\text{time planned (days)} + \text{days of delay}} \times 100\%$. The following surgical characteristics were available and compared between sexes: potentially curative surgery rates, type of gastric resection, and extent of resection (R0 or R1). Survival analyses were performed comparing outcomes by (1) histological subtype, (2) sex, and (3) sex stratified by histological subtype. In addition, we compared outcomes per treatment arm (for the intention-to-treat population) stratified by sex and histological tumor type.

2.3 | Statistical analysis

Potential differences between sexes stratified by histological subtype were tested using Mann–Whitney *U* test for continuous variables and chi-square test or Fisher-exact test for categorical variables. We conducted a post hoc subgroup analysis for exploratory purposes, therefore, no adjustments for multiplicity were performed. The threshold for statistical significance was set at $p < 0.05$. Overall survival (OS) was defined as time from randomization in the CRITICS trial until death or censored at the time of the last follow-up. Recurrence-free survival (RFS) was defined as the time from randomization until progression or recurrence of disease or censored at the time of last follow-up. Survival was estimated using the Kaplan–Meier method, and groups were compared using the Log-rank test. Kaplan–Meier curves were ended if less than 10% of patients were at risk. All analyses were performed using R software version 4.0.3.

3 | RESULTS

3.1 | Data availability

Figure 1 shows a flowchart of the study. A total of 781 patients started preoperative chemotherapy and were evaluated for treatment compliance and toxicity, including 523 males and 258 females. Histological GC tumor type was available in 750 (95%) patients, including 323 (43%) intestinal-type, 333 (44%) diffuse-type, 35 (5%) mixed type and 59 (8%) other type. Histological tumor type was determined on biopsy specimens from 613 (82%) patients and on the resection specimen from 137 (18%) patients. The allocated treatment arm was equally distributed between males and females for intestinal-type GC ($p = 0.405$) and diffuse-type GC ($p = 0.503$).

3.2 | Baseline characteristics

Baseline characteristics are presented in Table 1. Diffuse-type GC was more frequently diagnosed in females. The proportion of diffuse-type GC was 42% in males and 66% in females ($p < 0.001$). For intestinal-type GC, age at diagnosis was equally distributed among males and females. For diffuse-type GC, females were diagnosed at a significantly younger age than males. Females had more often a distal tumor localization compared to males for both intestinal and diffuse-type GC.

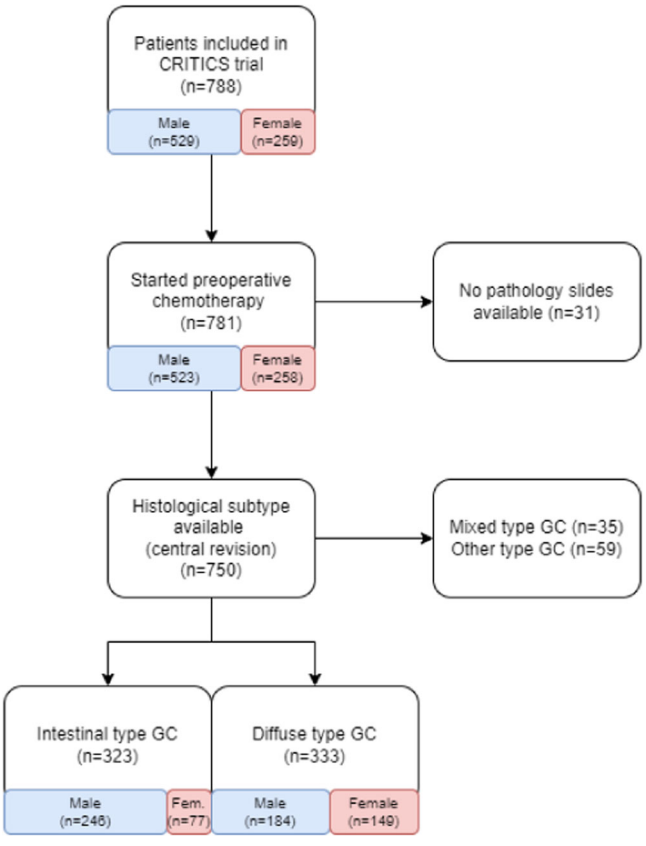

FIGURE 1 Flow chart of this study. GC, gastric cancer.

TABLE 1 Clinicopathological characteristics.

Variable	Intestinal-type GC			Diffuse-type GC		
	Male (n = 246)	Female (n = 77)	p-Value	Male (n = 184)	Female (n = 149)	p-Value
Baseline						
Age			0.274			0.035
Median (IQR)	65 (58–70)	66 (59–72)		60 (52–67)	57 (48–65)	
WHO PS			0.821			0.982
Missing	17	3		5	11	
WHO 0	164 (72%)	54 (73%)		136 (76%)	105 (76%)	
WHO 1	65 (28%)	20 (27%)		43 (24%)	33 (24%)	
Tumor localization			0.014			<0.001
GEJ	69 (28%)	15 (19%)		24 (13%)	4 (3%)	
Proximal	59 (24%)	11 (14%)		43 (23%)	19 (13%)	
Middle	54 (22%)	17 (22%)		58 (32%)	69 (46%)	
Distal	64 (26%)	34 (44%)		59 (32%)	57 (38%)	
Variable	**Male (n = 206)**	**Female (n = 66)**	**p-Value**	**Male (n = 144)**	**Female (n = 110)**	**p-Value**
Type of resection			0.167			0.285
Total gastric	95 (46%)	24 (36%)		84 (58%)	57 (52%)	
Subtotal gastric	76 (37%)	33 (50%)		54 (38%)	51 (46%)	
Esophagus-cardia	35 (17%)	9 (14%)		6 (4%)	2 (2%)	
Pathology						
R status			0.679			0.020
Missing	1					
R0	200 (98%)	64 (97%)		129 (90%)	87 (79%)	
R1	5 (2%)	2 (3%)		15 (10%)	23 (21%)	
pT stage			0.104			0.512
pT0	17 (8%)	7 (11%)		4 (3%)	1 (1%)	
pT1–T2	56 (27%)	26 (39%)		38 (26%)	33 (30%)	
pT3–T4	133 (65%)	33 (50%)		102 (71%)	76 (69%)	
pN stage			0.850			0.318
pN0	107 (52%)	37 (56%)		67 (47%)	56 (51%)	
pN1	40 (19%)	10 (15%)		23 (16%)	10 (9%)	
pN2	37 (18%)	11 (17%)		26 (18%)	17 (15%)	
pN3	22 (11%)	8 (12%)		28 (19%)	27 (25%)	
Mandard			0.464			0.077
Missing	19	7		12	16	
TRG 1–2	45 (24%)	17 (29%)		11 (8%)	15 (16%)	
TRG 3–5	142 (76%)	42 (71%)		121 (92%)	79 (84%)	

Abbreviations: IQR, interquartile range; GEJ, gastro-esophageal junction; TRG, tumor regression grade; WHO PS, World Health Organization Performance Score.

3.3 | Toxicity and treatment compliance

During preoperative chemotherapy, severe toxicity of any kind occurred more frequently in females (n = 184, 71%) compared to males (n = 327, 63%) (p = 0.015). The proportion of gastrointestinal, constitutional, and other types of toxicity was higher in females (Table 2). These results remained significant after stratification by histological tumor type, with the exception of constitutional toxicity in patients with intestinal-type GC (Supporting Information: Table S1). Postoperatively, severe toxicity of any kind occurred in 94 (56%)

TABLE 2 Pre- and postoperative grade 3–5 toxicities.

Preoperative CT	Variable	Male (n = 523)	Female (n = 258)	p-Value
	Hematological			0.999
	Grade 0–2	334 (64%)	165 (64%)	
	Grade 3–5	189 (36%)	93 (36%)	
	Gastrointestinal			<0.001
	Grade 0–2	416 (80%)	170 (66%)	
	Grade 3–5	107 (20%)	88 (34%)	
	Constitutional			0.021
	Grade 0–2	396 (76%)	175 (68%)	
	Grade 3–5	127 (24%)	83 (32%)	
	Vascular			0.274
	Grade 0–2	455 (87%)	217 (84%)	
	Grade 3–5	68 (13%)	41 (16%)	
	Other			<0.001
	Grade 0–2	443 (85%)	189 (73%)	
	Grade 3–5	80 (15%)	69 (27%)	
Postoperative CT	**Variable**	**Male (n = 168)**	**Female (n = 65)**	**p-Value**
	Hematological			0.879
	Grade 0–2	109 (65%)	43 (66%)	
	Grade 3–5	59 (35%)	22 (34%)	
	Gastrointestinal			0.063
	Grade 0–2	141 (84%)	47 (72%)	
	Grade 3–5	27 (16%)	18 (28%)	
	Constitutional			0.378
	Grade 0–2	134 (80%)	48 (74%)	
	Grade 3–5	34 (20%)	17 (26%)	
	Vascular			0.121
	Grade 0–2	164 (98%)	60 (92%)	
	Grade 3–5	4 (2%)	5 (8%)	
	Other			0.351
	Grade 0–2	152 (90%)	56 (86%)	
	Grade 3–5	16 (10%)	9 (14%)	
Postoperative CRT	**Variable**	**Male (n = 162)**	**Female (n = 83)**	**p-Value**
	Hematological			0.346
	Grade 0–2	145 (90%)	78 (94%)	
	Grade 3–5	17 (10%)	5 (6%)	
	Gastrointestinal			0.235
	Grade 0–2	134 (83%)	63 (76%)	
	Grade 3–5	27 (17%)	20 (24%)	
	Constitutional			0.545

TABLE 2 (Continued)

Grade 0–2	121 (75%)	59 (71%)	
Grade 3–5	41 (25%)	24 (29%)	
Vascular			0.999
Grade 0–2	157 (97%)	81 (98%)	
Grade 3–5	5 (3%)	2 (2%)	
Other			0.353
Grade 0–2	140 (86%)	8 (82%)	
Grade 3–5	22 (14%)	15 (18%)	

Note: **Hematological** included anemia, leucopenia, neutropenia, lymphocytopenia, febrile neutropenia, and thrombocytopenia. **Gastrointestinal** included mucositis/stomatitis, heartburn/dyspepsia, dysphagia, anorexia, nausea/vomiting, diarrhea, constipation, bowel inflammation, and gastrointestinal fistula/obstruction/perforation. **Vascular** included cardiac arrhythmia, ischemic event, thromboembolic event, sudden death, and hemorrhage. **Constitutional** included weight loss, dehydration, dizziness, fatigue, hypertension, infection without neutropenia, insomnia, mood alteration, and pain. **Others** included allergic/dermatological reaction, alopecia, DPD deficiency, dyspnea, genitourinary obstruction, local complication, metabolic disorder, musculoskeletal disorder, neuro-/ototoxicity, and palmar-plantar.

Abbreviations: CRT, chemoradiotherapy; CT, computed tomography.

males versus 41 (63%) females in the chemotherapy group ($p = 0.323$) and in 72 (44%) males versus 39 (47%) females ($p = 0.705$) in the chemoradiotherapy group.

There were no significant differences in preoperative RDI's of epirubicin, cisplatin/oxaliplatin or capecitabine between males and females (Table 3). Postoperatively, overall lower RDI's were observed in females in the chemotherapy arm, but this was not statistically significant. In the postoperative chemoradiotherapy group, the median radiotherapy dose was 45 Gy (IQR 45–45 Gy) in both males and females ($p = 0.357$). Median RDI for cisplatin during chemoradiotherapy was high in both subgroups with a statistically, but not clinically, significant difference (97% [78%–100%] vs. 99% [88%–100%]; $p = 0.017$). Capecitabine RDI was comparable for males and females ($p = 0.825$). The RDI's stratified by histological subtype shows a similar pattern (Supporting Information: Table S2).

Potentially curative surgical resection was performed in 206 (84%) males and 66 (86%) females with intestinal-type GC ($p = 1.00$) and in 144 (78%) males and 110 (74%) females with diffuse-type GC ($p = 0.195$). Postoperative therapy after potentially curative surgical resection started in 153 (74%) males and 46 (70%) females with intestinal-type GC ($p = 0.465$) and in 119 (83%) males and 81 (74%) females with diffuse-type GC ($p = 0.082$).

3.4 | Histopathological tumor characteristics

Pathological tumor characteristics of resected specimens are displayed in Table 1. Females with diffuse-type GC had more often a tumor-positive resection margin (R1 resection) than males with diffuse-type GC (21% vs. 10%; $p = 0.020$). This tumor-positive resection margin often involved the duodenal end: in 65% of females and in 47% of males with diffuse-type GC. pTN-stages were similar between males and females with both intestinal-type and diffuse-type GC. For patients with intestinal-type GC, the pathological response rate was also similar for males versus females. (Near-) complete pathological response (TRG 1–2) was less often achieved in diffuse-type GC, and more outspoken in males with diffuse-type GC compared with females (8% vs. 16%; $p = 0.077$).

3.5 | Survival outcomes

The median follow-up time was 7.3 years. As expected, OS was significantly longer in patients with intestinal-type GC compared with patients with diffuse-type GC with 5-year OS rate estimates of 51% in intestinal-type GC and 34% in diffuse-type GC ($p < 0.001$) (Figure 2A). There was no significant difference in OS between males and females ($p = 0.130$) (Figure 2B). In addition, there was no significant difference in OS within subtypes of GC between males and females (Figure 2C,D). Figure 3 shows that the allocated treatment arm did not significantly influence OS on an intention-to-treat basis in all four subgroups.

4 | DISCUSSION

It is known that tumor characteristics of gastric cancer differ between sexes. In addition, the histological subtype is known to influence clinical outcomes. However, it is yet unclear whether an interaction exist between these two variables. As a significant—though unexplained—interaction between sex and treatment arm existed in the CRITICS study,[20] we here present data on the impact of both histological tumor type and sex on treatment-related toxicity in combination with compliance and efficacy of treatment in patients with resectable gastric cancer. We confirmed previously published reports showing that the female sex is associated with distal tumor localization in both histological subtypes and younger age in diffuse-type GC.[11,23] The current study shows that in both males and females, diffuse-type GC leads to high rates of tumor-positive resection margins (up to 21%), and that,

TABLE 3 Relative dose intensities (RDI).

Preoperative CT	**Variable**	**Male (*n* = 523)**	**Female (*n* = 258)**	***p*-Value**
	Epirubicin			0.792
	Missing	20	11	
	RDI (IQR)	96% (76–100)	96% (76–100)	
	Cisplatin/oxaliplatin			0.558
	Missing	20	11	
	RDI (IQR)	95% (82–100)	96% (80–100)	
	Capecitabine			0.094
	Missing	20	11	
	RDI (IQR)	91% (72–100)	90% (67–100)	
Postoperative CT	**Variable**	**Male (*n* = 168)**	**Female (*n* = 65)**	***p*-Value**
	Epirubicin			0.291
	Missing	7		
	RDI (IQR)	87% (64–99)	78% (61–98)	
	Cisplatin/oxaliplatin			0.186
	Missing	7		
	RDI (IQR)	87% (65–98)	78% (62–98)	
	Capecitabine			0.347
	Missing	7		
	RDI (IQR)	81% (55–94)	73% (51–92)	
Postoperative CRT	**Variable**	**Males (*n* = 162)**	**Females (*n* = 83)**	***p*-Value**
	Cisplatin			0.017
	Missing	5	2	
	RDI (IQR)	97% (78–100)	99% (88–100)	
	Capecitabine			0.825
	Missing	5	2	
	RDI (IQR)	87% (76–100)	90% (80–100)	

Abbreviations: CRT: chemoradiotherapy; CT, chemotherapy; IQR, interquartile range.

especially in females, the distal resection margin is dominantly involved. We also confirmed—as previously shown in patients with advanced esophagogastric cancer and other types of cancer—[16–18,24] that female patients experience more often severe toxicity during chemotherapy treatment, irrespective of gastric cancer subtype. We now show that this does, however, not result in significant dose adaptations as the RDI's between males and females were similar.

Our study confirmed the previously reported more favorable survival of patients with intestinal-type GC compared to patients with diffuse-type GC (Figure 2A).[5,25] Several studies have associated female sex with a worse long-term survival in patients with gastric cancer.[9,11,26] These studies, however, did not take histological subtypes into account. In the present study, we show that long-term survival was comparable between males and females after stratification for histological tumor type (Figure 2B–D). The primary analysis of the CRITICS trial using a univariate analysis model revealed a better survival in response to perioperative chemotherapy in male GC patients, whereas female patients showed better survival in response to the combination of preoperative chemotherapy and postoperative chemoradiotherapy.[20] The present post-hoc exploratory subgroup analysis confirmed this trend in both the intestinal and diffuse types of gastric cancer (Figure 3). The results were not statistically significant, which may be due to the inherent smaller group sizes. It suggests that the differential response between males and females according to the different treatment modalities is irrespective of histological subtype.

As mentioned above, in female patients, gastric cancer is more frequently localized in the distal stomach, irrespective of the histological subtype. In this study, we show that female patients with diffuse-type GC, but not intestinal-type GC, are more often confronted with a microscopically irradical R1 resection than males.

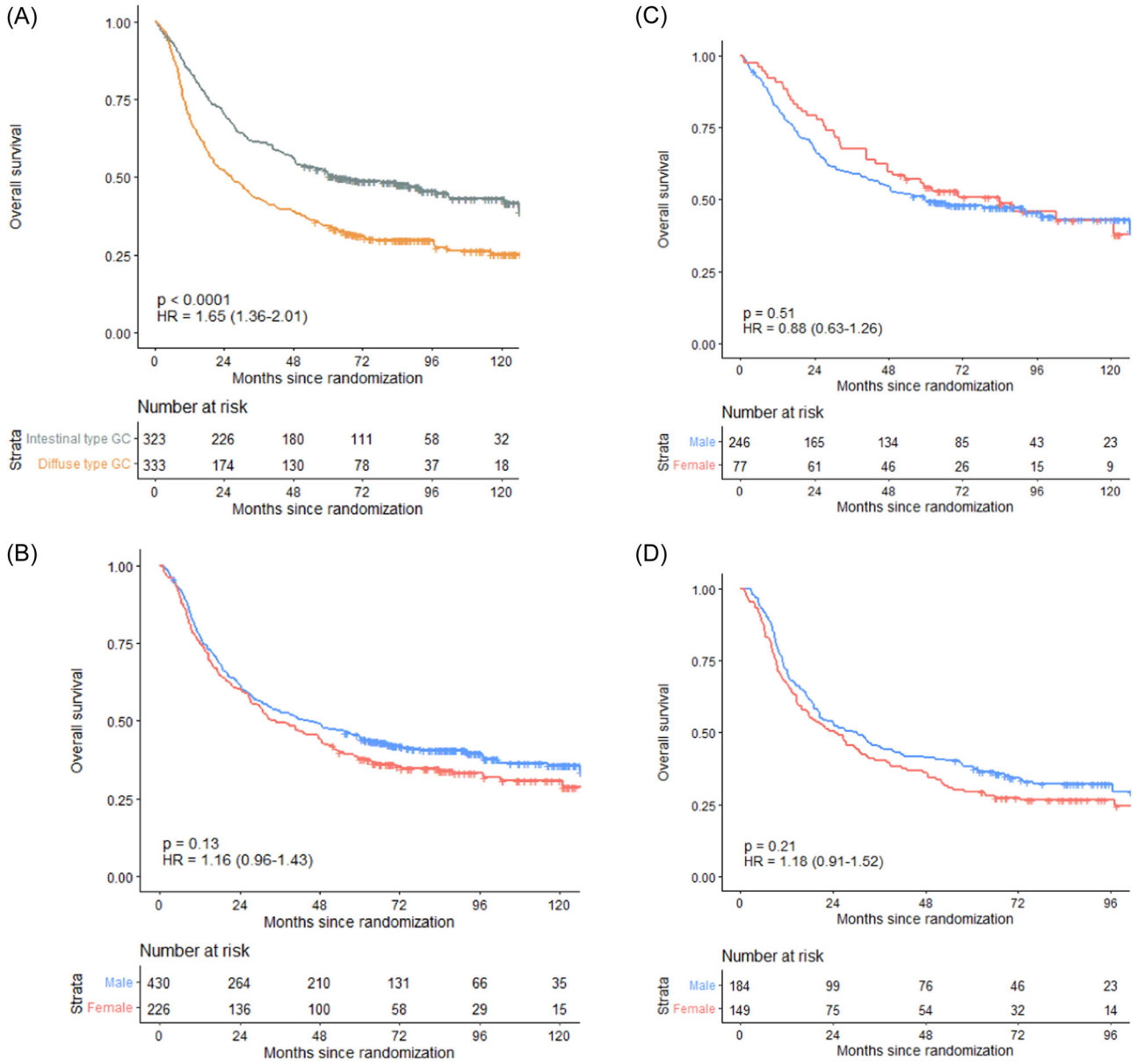

FIGURE 2 Overall-survival (A) intestinal versus diffuse-type gastric cancer (GC), (B) males versus females, (C) intestinal-type GC: males versus females, (D) diffuse-type GC: males versus females.

Whether this can be attributed to the combination of a distal tumor localization and diffuse histological subtype, or if other factors, such as differences in tumor biology or surgical techniques between men and women may contribute, cannot be definitively concluded based on our data. The vast majority of R1 resections in females involved the duodenal margin. The use of frozen sections of the duodenal margin is not common practice in the Netherlands, as Dutch surgeons generally aim to resect as close to the ampulla as possible. Additional peroperative diagnostic tests on frozen section margins may therefore lack surgical consequences since only in rare occasions an additional pancreaticoduodenectomy will be clinically feasible. Notwithstanding this, surgeons should, however, anticipate the increased risk of an R1 resection in female patients with diffuse-type GC and preoperatively evaluate the patients' fitness to undergo an extension of the operation to a pancreaticoduodenectomy in the event of an R1 resection, or refrain from doing so due to the increased morbidity associated with this procedure. Furthermore, alternative therapy strategies may help to reduce the R1 rate in the future. The TOPGEAR and CRITICS-2 trials, for instance, evaluate the value of preoperative chemoradiotherapy.[27,28] The results of these trials are still awaited and may provide more insight on the effect of preoperative chemoradiotherapy on R0 rate in female patients with diffuse-type GC.

Besides sex differences in epidemiology and histopathology of GC, our study also showed that females experience more often severe toxicity during preoperative chemotherapy treatment, specifically gastrointestinal, constitutional, and other toxicities such as palmar-plantar erythrodysesthesia. Similar observations have been

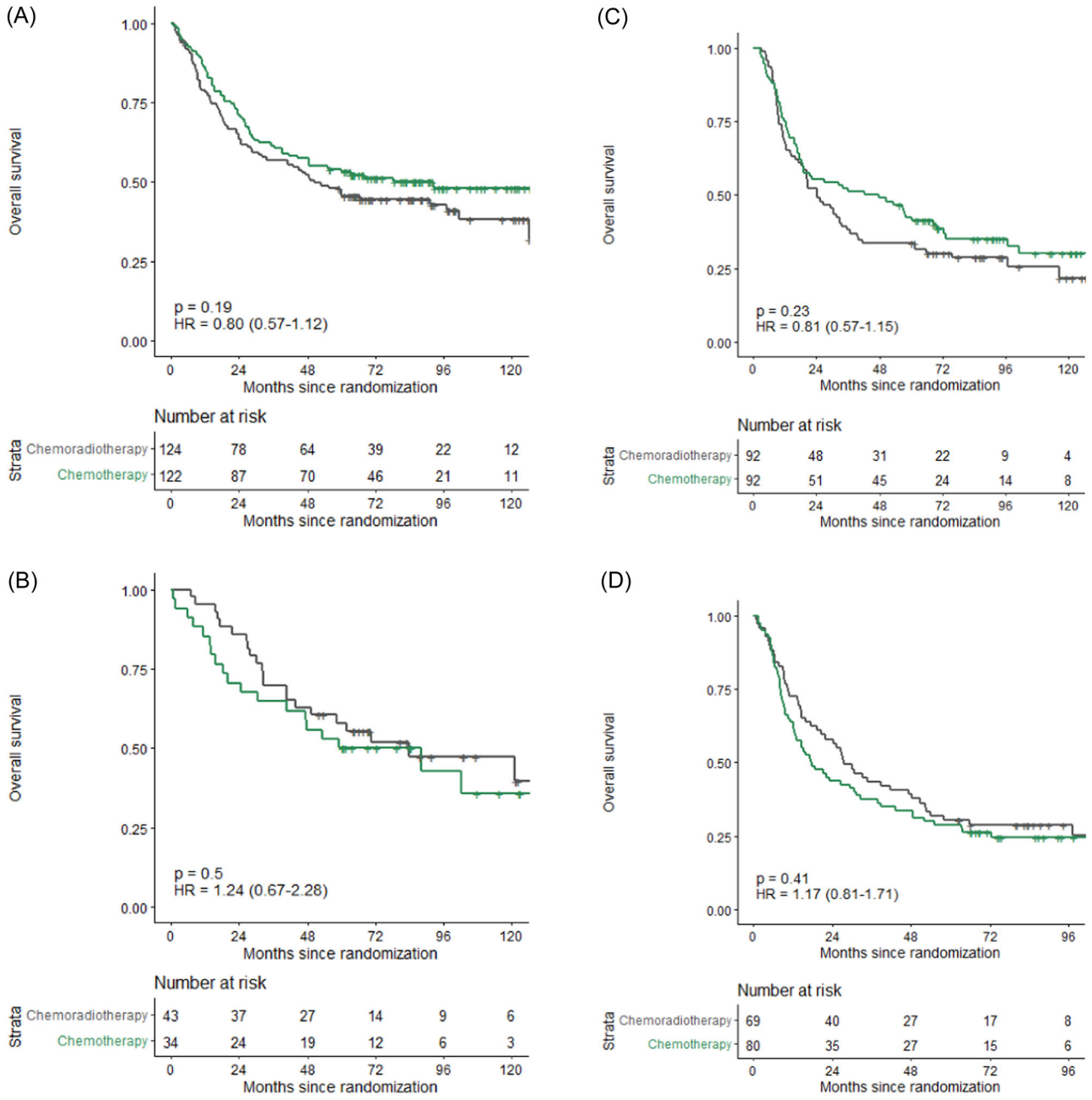

FIGURE 3 Overall-survival (A) male with intestinal-type GC: ITT postop CT versus postop CRT, (B) females with intestinal-type GC: ITT postop CT versus postop CRT, (C) males with diffuse-type GC: ITT postop CT versus postop CRT, (D) females with diffuse-type GC: ITT postop CT versus postop CRT. CRT, chemoradiotherapy; CT, chemotherapy; GC, gastric cancer; ITT, intention-to-treat.

made in patients with advanced gastric cancer[10] and in patients with other types of cancer.[18,24,29,30] In the current study, we show that these toxicities were irrespective of the histological subtype and, importantly, did not compromise the relative dose intensity of administered chemotherapeutic agents. Postoperative treatment-induced toxicities did not vary between males and females. This may be influenced by dose modifications at the start of postoperative chemotherapy and by the smaller group sizes. The explanation for higher toxicity rates in females compared to males might be sought in differential drug metabolism. For several types of drugs, up to >40% of sex-related differences in pharmacokinetics have been described between males and females.[31] Several studies have shown that females have a lower capacity to clear fluorouracil.[32–34]

Our study faces several limitations, of which the most important is that this is an exploratory, post-hoc subgroup analysis of the CRITICS trial which is not powered to find differences between males and females. While our study provides valuable insights into sex differences in clinicopathological characteristics and treatment outcomes, irrespective of histological subtype, the observed trends in survival differences should be confirmed in future studies. Another

limitation of our study is that the preferred chemotherapy regimen has shifted from using anthracycline-based treatment, as used in the CRITICS trial, to taxane-based treatment after the results from the FLOT4-AIO trial were published.[35] Future research should investigate the potential differences in chemotherapy-related toxicity and relative dose intensities between men and women treated with taxane-based chemotherapy regimens.

5 | CONCLUSION

In conclusion, both sex and histological subtypes have an impact on gastric cancer, its treatment, and outcome. Both intestinal and diffuse-type tumors are more often localized in the distal stomach in female patients. Moreover, especially female patients with diffuse-type GC are at a high risk of more than 20% encountering a microscopically irradical distal resection margin following resection. Surgeons should be aware of this phenomenon during preoperative evaluation and should consider the feasibility of extending the procedure if necessary before surgery. In addition, toxicity during preoperative chemotherapy is higher for females but does not seem to influence relative dose intensities. Pharmacokinetic analyses may help to optimize the doses of chemotherapeutical agents in females. Based on these results, we support the notion that males and females should be considered as distinct groups of patients and emphasize that clinicians should be aware of these differences in toxicity and surgical outcomes when treating males and females with GC.

AUTHOR CONTRIBUTIONS

Irene A. Caspers: Conceptualization; data curation; formal analysis; investigation; writing—original draft. **Astrid E. Slagter**: Conceptualization; data curation; formal analysis; investigation; writing—original draft. **Pehr Lind**: Writing—review & editing. **Karolina Sikorska**: Methodology; formal analysis; writing—review & editing. **Katja Wiklund**: Writing—review & editing. **Fredrik Pontén**: Writing—review & editing. **Marianne Nordsmark**: Writing—review & editing. **Cornelis J.H. van de Velde**: Writing—review & editing. **Elma Meershoek-Klein Kranenbarg**: Data curation; writing—review & editing. **Johanna W. van Sandick**: Conceptualization; writing—review & editing; **Edwin P.M. Jansen**: Conceptualization; Writing—review & editing. **Hanneke W.M. van Laarhoven**: Conceptualization; writing—review & editing. **Marcel Verheij**: Funding acquisition; conceptualization; data curation; methodology; investigation; writing—review & editing; supervision. **Nicole C.T. van Grieken**: Conceptualization; data curation; methodology; investigation; writing—review & editing; supervision. **Annemieke Cats**: Funding acquisition; conceptualization; data curation; methodology; investigation; writing—review & editing; supervision.

ACKNOWLEDGMENTS

We thank all patients, treating physicians, and research support staff in all participating centers. The CRITICS trial was financially supported by the Dutch Cancer Society, the Dutch Colorectal Cancer Group, and Hoffmann La Roche. The funding sources had no role in the design, collection, analysis, and interpretation of the data.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

TRIAL REGISTRATION CRITICS TRIAL

ClinicalTrials.gov identifier: NCT00407186. EudraCT number: 2006-00413032

ORCID

Irene A. Caspers http://orcid.org/0000-0003-2073-4485

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424. doi:10.3322/caac.21492
2. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:v38-v49. doi:10.1093/annonc/mdw350
3. NCCN Practical Guidelines in Oncology: Gastric Cancer version 5. 2017.
4. Laurén P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a Histo-Clinical classification. *Acta Pathol Microbiol Scand*. 1965;64:31-49. doi:10.1111/apm.1965.64.1.31
5. Petrelli F, Berenato R, Turati L, et al. Prognostic value of diffuse versus intestinal histotype in patients with gastric cancer: A systematic review and meta-analysis. *J Gastrointest Oncol*. 2017;8:148-163. doi:10.21037/jgo.2017.01.10
6. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513:202-209. doi:10.1038/nature13480
7. Özdemir BC, Oertelt-Prigione S, Adjei AA, et al. Investigation of sex and gender differences in oncology gains momentum: ESMO announces the launch of a gender medicine task force. *Ann Oncol*. 2022;33:126-128. doi:10.1016/j.annonc.2021.11.011
8. van der Kaaij RT, Koemans WJ, van Putten M, et al. A population-based study on intestinal and diffuse type adenocarcinoma of the oesophagus and stomach in the Netherlands between 1989 and 2015. *Eur J Cancer*. 2020;130:23-31. doi:10.1016/j.ejca.2020.02.017
9. Kim HW, Kim JH, Lim BJ, et al. Sex disparity in gastric cancer: female sex is a poor prognostic factor for advanced gastric cancer. *Ann Surg Oncol*. 2016;23:4344-4351. doi:10.1245/s10434-016-5448-0
10. Davidson M, Wagner AD, Kouvelakis K, et al. Influence of sex on chemotherapy efficacy and toxicity in oesophagogastric cancer: a pooled analysis of four randomised trials. *Eur J Cancer*. 2019;121:40-47. doi:10.1016/j.ejca.2019.08.010
11. Kalff MC, Wagner AD, Verhoeven RHA, et al. Sex differences in tumor characteristics, treatment, and outcomes of gastric and esophageal cancer surgery: nationwide cohort data from the Dutch

upper GI cancer audit. *Gastric Cancer*. 2022;25:22-32. doi:10.1007/s10120-021-01225-1
12. Quaas A, Biesma HD, Wagner AD, et al. Microsatellite instability and sex differences in resectable gastric cancer – a pooled analysis of three European cohorts. *Eur J Cancer*. 2022;173:95-104. doi:10.1016/j.ejca.2022.06.025
13. Lopes-Ramos CM, Quackenbush J, DeMeo DL. Genome-wide sex and gender differences in cancer. *Front Oncol*. 2020;10:1-17. doi:10.3389/fonc.2020.597788
14. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prevent*. 2012;21:20-38. doi:10.1158/1055-9965.EPI-11-0834
15. Chung HW. Analysis of demographic characteristics in 3242 young age gastric cancer patients in Korea. *World J Gastroenterol*. 2010;16:256-263. doi:10.3748/wjg.v16.i2.256
16. Singh S, Parulekar W, Murray N, et al. Influence of sex on toxicity and treatment outcome in small-cell lung cancer. *J Clin Oncol*. 2005;23:850-856. doi:10.1200/JCO.2005.03.171
17. Cristina V, Mahachie J, Mauer M, et al. Association of patient sex with chemotherapy-related toxic effects: a retrospective analysis of the PETACC-3 trial conducted by the EORTC gastrointestinal group. *JAMA Oncol*. 2018;4:1003-1006. doi:10.1001/jamaoncol.2018.0813
18. Klimm B, Reineke T, Haverkamp H, et al. Role of hematotoxicity and sex in patients with Hodgkin's lymphoma: an analysis from the German Hodgkin study group. *J Clin Oncol*. 2005;23:8003-8011. doi:10.1200/JCO.2005.205.60
19. Dikken JL, Jansen EPM, Cats A, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. *J Clin Oncol*. 2010;28:2430-2436. doi:10.1200/JCO.2009.26.9654
20. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19:616-628. doi:10.1016/S1470-2045(18)30132-3
21. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *The Lancet*. 2020;396:635-648. doi:10.1016/S0140-6736(20)31288-5
22. Caspers IA, Sikorska K, Slagter AE, et al. Risk factors for metachronous isolated peritoneal metastasis after preoperative chemotherapy and potentially curative gastric cancer resection: results from the CRITICS trial. *Cancers*. 2021;13:4626. doi:10.3390/cancers13184626
23. Anderson WF, Rabkin CS, Turner N, Fraumeni JF, Rosenberg PS, Camargo MC. The changing face of noncardia gastric cancer incidence among US non-Hispanic Whites. *JNCI: J Natl Cancer Inst*. 2018;110:608-615. doi:10.1093/jnci/djx262
24. Unger JM, Vaidya R, Albain KS, et al. Sex differences in risk of severe adverse events in patients receiving immunotherapy, targeted therapy, or chemotherapy in cancer clinical trials. *J Clin Oncol*. 2022;40(13):1474-1486. doi:10.1200/jco.21.02377
25. Tang C-T, Zeng L, Yang J, Zeng C, Chen Y. Analysis of the incidence and survival of gastric cancer based on the Lauren classification: a large population-based study using SEER. *Front Oncol*. 2020;10:1-10. doi:10.3389/fonc.2020.01212
26. Dijksterhuis WPM, Kalff MC, Wagner AD, et al. Gender differences in treatment allocation and survival of advanced gastroesophageal cancer: a population-based study. *JNCI: J Natl Cancer Inst*. 2021;113:1551-1560. doi:10.1093/jnci/djab075
27. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: a randomized, phase III trial of perioperative ECF chemotherapy with or without preoperative chemoradiation for resectable gastric cancer: interim results from an international, intergroup trial of the AGITG, TROG, EORTC and CCTG. *Ann Surg Oncol*. 2017;24:2252-2258. doi:10.1245/s10434-017-5830-6
28. Slagter AE, Jansen EPM, van Laarhoven HWM, et al. CRITICS-II: A multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resecta. *BMC Cancer*. 2018;18(1):877.
29. Van Den Berg H, Paulussen M, Le Teuff G, et al. Impact of gender on efficacy and acute toxicity of alkylating agent -based chemotherapy in Ewing sarcoma: secondary analysis of the Euro-Ewing99-R1 trial. *Eur J Cancer*. 2015;51:2453-2464. doi:10.1016/j.ejca.2015.06.123
30. Jiménez Fonseca P, Carmona-Bayonas A, Hernández R, et al. Lauren subtypes of advanced gastric cancer influence survival and response to chemotherapy: real-world data from the AGAMENON national cancer registry. *Br J Cancer*. 2017;117:775-782. doi:10.1038/bjc.2017.245
31. Anderson GD. Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. *J Women's Health*. 2005;14:19-29. doi:10.1089/jwh.2005.14.19
32. Gusella M, Crepaldi G, Barile C, et al. Pharmacokinetic and demographic markers of 5-fluorouracil toxicity in 181 patients on adjuvant therapy for colorectal cancer. *Ann Oncol*. 2006;17:1656-1660. doi:10.1093/annonc/mdl284
33. Milano G, Etienne MC, Cassuto-Viguier E, et al. Influence of sex and age on fluorouracil clearance. *J Clin Oncol*. 1992;10:1171-1175. doi:10.1200/JCO.1992.10.7.1171
34. Mueller F, Büchel B, Köberle D, et al. Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: results from a prospective population pharmacokinetic study. *Cancer Chemother Pharmacol*. 2013;71:361-370. doi:10.1007/s00280-012-2018-4
35. Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948-1957.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Caspers IA, Slagter AE, Lind P, et al. The impact of sex on treatment and outcome in relation to histological subtype in patients with resectable gastric cancer: results from the randomized CRITICS trial. *J Surg Oncol*. 2024;129:734-744. doi:10.1002/jso.27554