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Original Research

Influence of sex on chemotherapy efficacy and toxicity in oesophagogastric cancer: A pooled analysis of four randomised trials☆

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KEYWORDS
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Abstract ***Background:*** Sex contributes to interpatient variability of chemotherapy metabolism and dose response, potentially influencing both efficacy and toxicity; however, comparative data on its effect on oesophagogastric cancer are lacking.

Patients and methods: Data for patients with advanced oesophagogastric cancer randomised to comparable first-line chemotherapy regimens within four United Kingdom prospective trials were pooled, and key demographic and outcome measures were compared between males and females.

Results: A total of 1654 patients were included: 1328 (80.3%) males and 326 (19.7%) females. Female patients were younger, had a significantly higher proportion of gastric tumours as opposed to junctional or oesophageal tumours and experienced significantly higher rates of a number of toxicities including nausea and vomiting, diarrhoea, stomatitis and alopecia. When adjusting for potential confounding factors, the risk of female patients experiencing grade ≥III gastrointestinal toxicity was greater (adjusted odds ratio = 1.50; 95% confidence interval = 1.07–2.12). Females also had a significantly higher incidence of serious adverse events on treatment and received comparatively less cycles of chemotherapy overall than males.

Conclusions: This represents the largest pooled analysis of the effect of sex on chemotherapy outcome and toxicity in advanced oesophagogastric cancer. The differential toxicity and

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adverse event rates observed suggest that sex may be an important modulator of treatment tolerability and safety in this tumour type.

1. Background

The impact of sexual dimorphism is a relatively underresearched area in oncology. There are major epidemiological differences in cancer susceptibility and survival between sexes, with men having increased risk and a poorer outcome for a number of non–sex-specific cancer types [1,2]. Possible hypothecated reasons include the influence of differential sex hormone levels and sex-based gene expression signatures, as well as differences in immune system composition and function affecting early tumour development [3]. There are also known sex disparities in the pharmacokinetic handling and clearance of anticancer drugs owing to a number of overlapping factors including variation in body composition, liver enzyme activity and haematological binding capacity, which result in higher achieved dose intensities for female patients [4–7]. Differences in chemotherapy toxicity have been observed across a range of tumour types including colorectal cancer, lung cancer, lymphoma and sarcoma, showing females to be more susceptible to treatment toxicity in general, including both subjective quality-of-life measures such as nausea and fatigue as well as objective measurable parameters of haematological toxicity [8].

Gastric and oesophageal cancers represent a challenging health problem globally, representing the third and sixth leading causes of cancer mortality, respectively [2]. Although the incidence of non–cardia gastric cancers has been decreasing in Western populations, the incidence of distal oesophageal and junctional adenocarcinomas is increasing [9]. Despite advances in both genetic characterisation and development of novel treatments, the outlook for advanced disease remains poor, with median overall survival (OS) not extending beyond 12 months in most trials. Chemotherapy remains the mainstay of first- and second-line treatment and a standard reference regimen in the first-line treatment consists of a fluoropyrimidine combined with a platinum agent, with the possible addition of an anthracycline or taxane [10–12]. Comparative data on the effect of sex on chemotherapy-related toxicity and efficacy in oesophagogastric (OG) cancer are lacking.

Four prospective randomised controlled trials (RCTs) conducted by the Royal Marsden Hospital and Upper GI Clinical Studies Group of the United Kingdom National Cancer Research Institute have investigated first-line chemotherapy in advanced OG cancer, each incorporating at least one arm consisting of a platinum/fluoropyrimidine/anthracycline triplet chemotherapy regimen [11,13–15]. The common inclusion criteria include age >18 years, Eastern Cooperative Oncology Group performance status 0–2, histologically confirmed advanced or inoperable OG cancer, adequate renal, hepatic and haematological function and no prior treatment in the advanced disease setting. Owing to their comparable design, large sample size and uniform trial population, these studies provide an opportunity to pool data to investigate the effect of sex on first-line chemotherapy treatment and outcomes in this tumour type.

2. Patients and methods

Pooled analysis of data from patients treated with ECF, ECX, EOF or EOX chemotherapy (E: epirubicin; C: cisplatin; F: Fluorouracil (5FU); X: capecitabine; O: oxaliplatin) within the four included trials was undertaken [11,13–15]. Demographic, treatment, toxicity and efficacy data were recorded and compared between males and females. Toxicity data were recorded using National Cancer Institute Reporting of Adverse Drug Reactions and Common Terminology Criteria for Adverse Events, versions 2 and 3. Owing to variable data completeness, for comparison of overall and adjusted rates of toxicity, patients with complete data for anaemia, neutropenia, thrombocytopenia, infection, fever, nausea and vomiting, diarrhoea, stomatitis, taste alteration, alopecia, hand-foot syndrome, peripheral neuropathy, lethargy and depression were considered in a ‘combined analysis’ subgroup. Serious adverse events (SAEs) and dose data were available for patients from the two largest trials (REAL2 and REAL3) only (Fig. 1). The t-test and Mann–Whitney test were used to compare the means and distribution of normally and non-normally distributed continuous variables, respectively; the chi-square test was used for categorical variables; the log-rank test was used for survival rates. Multivariable logistic regression models were used to generate adjusted results for odds ratios (ORs) of overall and selected toxicities and efficacy outcome measures by accounting for the following factors: chemotherapy regimen, number of cycles received, age and baseline performance status. The significance level for statistical

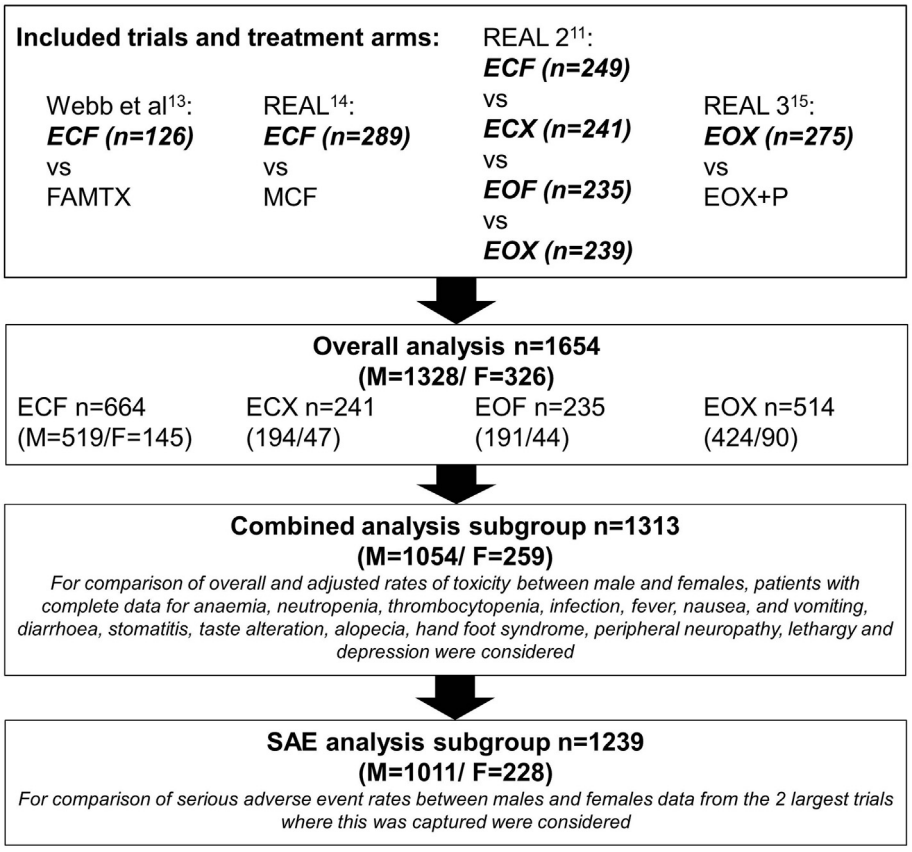

Fig. 1. Included trials and patients. E, epirubicin; C, cisplatin; F, 5FU; X, capecitabine; O, oxaliplatin; SAE, serious adverse event; M, mitomycin; A, doxorubicin; MTX, methotrexate.

tests was set at 0.05, and analysis was performed using Stata 13 software.

3. Results

3.1. Demographics

A total of 1654 patients were included: 1328 males (80.3%) and 326 females (19.7%). Patients were primarily drawn from the REAL2 trial [11], which provided 964 of 1654 (58.3%) patients, and the most common chemotherapy treatment included was the ECF regimen, used in 664 of 1654 (40.1%) included patients (Fig. 1). Females were younger (median age = 60 vs 62 years, respectively; p = 0.004) and had a significantly higher incidence of gastric tumours compared with junctional or oesophageal tumours (59.5 vs 35.9%, respectively; $p < 0.001$; Table 1).

3.2. Toxicity and adverse events

For toxicities captured commonly across all four trials, there was no significant difference in all-grade or grade ≥III toxicity between females and males (67.2 vs 62.8%; $p = 0.19$). Females experienced significantly higher rates of nausea and vomiting, both all-grade (89.3 vs 78.3%; $p < 0.001$) and grade ≥III (16.7 vs 9.5%; $p < 0.001$); all-grade diarrhoea (53.8 vs 46.9%; p = 0.027); all-grade stomatitis (49.5 vs 40.7%; $p = 0.004$) and all-grade alopecia (81.4 vs 74.3%; $p = 0.009$). Absolute rates of

Table 1
Patient characteristics.

Variable	Males (n = 1328)	Females (n = 326)	p value
Age (median, IQR)	62 (54–68)	60 (52–68)	**0.004**
Age category (%)			
<50 years	179 (13.5)	61 (18.7)	0.16
50–64 years	613 (46.2)	136 (41.7)	
≥65 years	536 (40.4)	129 (39.6)	
Performance status (%)			
0–1	1162 (87.5)	279 (85.6)	0.44
≥2	163 (12.3)	45 (13.8)	
Not recorded	3 (0.2)	2 (0.6)	
Primary tumour site (%)			
Oesophagus/OGJ	847 (63.7)	132 (40.4)	**<0.001**
Stomach	477 (35.9)	194 (59.5)	
Not recorded	4 (0.3)	0 (0)	
Histology (%)			
Adenocarcinoma	1208 (91.0)	282 (86.5)	0.06
Squamous cell	82 (6.2)	32 (9.8)	
Adenosquamous/ undifferentiated	20 (1.5)	5 (1.5)	
Not recorded	18 (1.4)	7 (2.1)	

IQR, interquartile range; OGJ, oesophagogastric junction.
Significant p-values are highlighted in bold.

grade ≥III neutropenia and febrile neutropenia were higher among females (45.1 vs 40.4% and 11.8 vs 7.7%, respectively), although significance was not reached. Males experienced significantly more all-grade peripheral neuropathy (49.3 vs 42.6%; $p = 0.03$). Females had a significantly higher incidence of at least one SAE on treatment (44.7 vs 35.8%; $p = 0.012$; Table 2). When adjusting for predefined factors, there was no difference in rates of grade ≥III overall or haematological toxicity between females and males; however, females were significantly more likely to experience GI toxicities (OR = 1.50; 95% confidence interval [CI] = 1.07–2.12; $p = 0.02$; Fig. 2; Supplementary Table S1). Considering toxicities of special interest potentially related to specific

Table 2
Toxicity and serious adverse event rates.

Toxicity		Males		Females		*p* value
		n	%	n	%	
Anaemia	All-grade	1212/1316	94.8	286/321	89.1	0.084
	Grade ≥III	147/1316	11.2	38/321	11.8	0.735
Neutropenia	All-grade	734/1162	63.2	184/288	63.9	0.820
	Grade ≥III	469/1162	40.4	130/288	45.1	0.140
Thrombocytopenia	All-grade	459/1316	34.9	106/321	33.0	0.530
	Grade ≥III	74/1316	5.6	16/321	5.0	0.653
Febrile neutropenia	All-grade	87/894	9.7	27/195	13.9	0.089
	Grade ≥III	69/894	7.7	23/195	11.8	0.064
Infection	All-grade	391/1306	29.9	97/317	30.6	0.818
	Grade ≥III	106/1306	8.1	24/317	7.6	0.748
Fever	All-grade	164/1250	13.1	49/298	16.4	0.135
	Grade ≥III	26/1250	2.1	7/298	2.4	0.773
Nausea and vomiting	All-grade	1024/1308	78.3	283/317	89.3	**<0.001**
	Grade ≥III	124/1308	9.5	53/317	16.7	**<0.001**
Diarrhoea	All-grade	612/1306	46.9	170/316	53.8	**0.027**
	Grade ≥III	81/1306	6.2	24/316	7.6	0.367
Stomatitis	All-grade	531/1305	40.7	157/317	49.5	**0.004**
	Grade ≥III	33/1305	2.5	14/317	4.4	0.072
Taste alteration	All-grade	581/1300	44.7	128/317	40.4	0.165
	Grade ≥III	0/1300	0	0/317	0	n/a
Hand-foot syndrome	All-grade	432/1305	33.1	109/316	34.5	0.638
	Grade ≥III	47/1305	3.6	8/316	2.5	0.346
Alopecia	All-grade	970/1304	74.3	258/317	81.4	**0.009**
	Grade ≥III	10/1304	0.8	6/317	1.9	0.069
Peripheral neuropathy	All-grade	644/1307	49.3	135/317	42.6	**0.030**
	Grade ≥III	30/1307	2.3	9/317	2.8	0.570
Lethargy	All-grade	1086/1213	89.5	261/292	89.4	0.942
	Grade ≥III	144/1213	11.9	43/292	14.7	0.184
Depression	All-grade	315/1301	24.2	92/316	29.1	0.072
	Grade ≥III	0/1301	0	0/316	0	n/a
Any toxicity[a]	All-grade	1051/1054	99.7	257/259	99.2	0.25
	Grade ≥III	662/1054	62.8	174/259	67.2	0.19
Occurrence of at least one SAE[b]		362/1011	35.8	102/228	44.7	**0.012**

SAE, serious adverse event.
Significant p-values are highlighted in bold.
[a] Incorporating all patients with complete data for anaemia, neutropenia, thrombocytopenia, infection, fever, nausea and vomiting, diarrhoea, stomatitis, taste alteration, alopecia, hand-foot syndrome, peripheral neuropathy, lethargy and depression.
[b] Incorporating patients from REAL2 and REAL3 trials only.

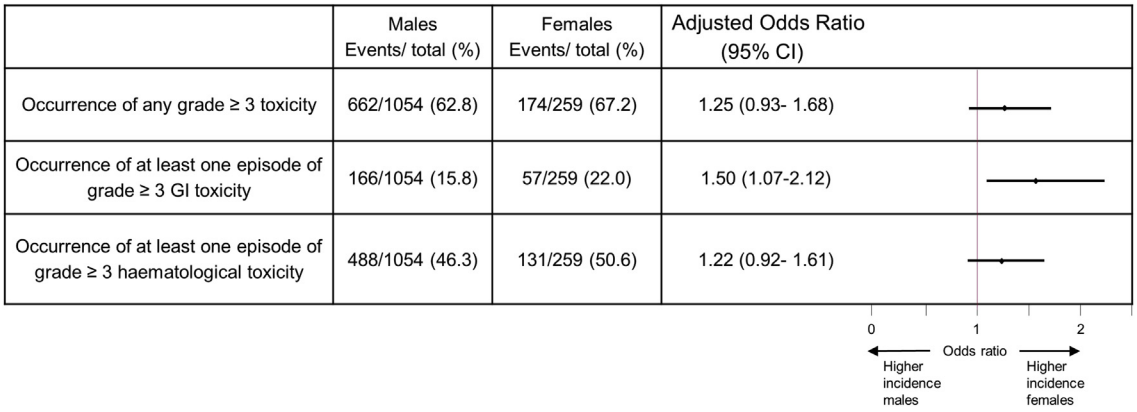

Fig. 2. Adjusted association between grade ≥III toxicities and sex. CI, confidence interval; GI, gastro-intestinal.

chemotherapy agents, there was no difference in rates of hand-foot syndrome or diarrhoea between male and female patients treated with capecitabine-containing regimens only or in rates of peripheral neuropathy in patients treated with oxaliplatin-containing regimens only (Supplementary Table S2).

3.3. Treatment duration and dose

Females received less chemotherapy overall than males, with a significantly higher proportion receiving only 1–3 cycles (30.1 vs 23.5%,) and lower proportion receiving ≥7 cycles (39.6 vs 45.9%,; $p = 0.02$, Table 1). The percentage doses of fluoropyrimidine, platinum and anthracycline delivered were lower for females; however, this did not reach statistical significance. There were no differences in the occurrence of dose delays or reductions (Table 3).

3.4. Efficacy

There was no difference between males and females in unadjusted progression-free survival (PFS; 6.68 vs 6.84 months; hazard ratio [HR] = 0.97; 95% CI = 0.85–1.10, $p = 0.62$; Fig. 3A) or OS (10.1 vs 9.61 months; HR = 0.98; 95% CI = 0.86–1.12, $p = 0.81$; Fig. 3B). The unadjusted overall response rate was higher in males, although significance was not reached (46.6 vs 40.4%; OR = 0.78 95% CI = 0.60–1.00; $p = 0.051$). When considering adjusted outcome measures using our multivariate model, the HR for OS became significantly better for females (HR = 0.83; 95% CI = 0.72–0.96; $p = 0.011$)and approached significance for PFS (HR = 0.87; 95% CI = 0.76–1.00; $p = 0.06$). Any trend towards an improved response rate among males was also lost (OR = 0.90, 95% CI = 0.67–1.21; $p = 0.48$; Supplementary Table S1).

4. Discussion

This is the largest pooled analysis of sex effect on outcome and toxicity undertaken in patients with advanced OG cancer treated with comparable first-line chemotherapy. Females experienced significantly higher rates of a number of predominantly gastrointestinal toxicities, as well as non-significantly higher rates of neutropenia and febrile neutropenia. When adjusting for potential confounders, the risk for females experiencing GI toxicity was significantly greater. A higher incidence of SAE occurrence and a trend towards female patients receiving less chemotherapy overall, both in terms of the absolute number of cycles and percentage dose received, may suggest that differentially experienced toxicities result in more potentially serious treatment complications and ultimately impact on chemotherapy delivery.

Similar disparities in toxicity have recently been noted in patients with colorectal cancer treated with 5FU-based chemotherapy regimens [16]. Females have been shown to have lower clearance of infusional 5FU, independent of relevant pharmacokinetic covariates such as age, body surface area and creatinine clearance, and the resultant higher achieved 5FU dose intensities may explain some of the observed differences in experienced toxicity [7]. Although sex differentials with anthracycline and platinum agents are less well characterised, there are data suggesting that male patients achieve higher anthracycline drug clearance while female patients experience a higher incidence of anthracycline-induced cardiotoxicity [17], as well as a higher incidence of cisplatin-induced emesis [18].

Many cytotoxic agents present a dose–response relationship where dose intensity correlates with efficacy, and a positive correlation has been described between female sex, response rates and survival for a number of chemotherapy treatments [19,20]. Furthermore, correlation between incidence of adverse events and response has been noted for both cytotoxic, targeted and immunomodulating therapies [21]. In our analysis, unadjusted absolute PFS and OS were similar between males and females, and indeed, males had an improved overall response rate, which approached statistical significance. In OG cancer, inherent differences in tumour biology between males and females may play a role in treatment response. In this cohort, females had a greater

Table 3
Chemotherapy dosing, delays and reductions.

Variable	Males	Females	*p* value
Number of cycles received			
Median	6	5.5	**0.02**
1–3	312/1328 (23.5%)	98/326 (30.1%)	**0.05**
4–6	397/1328 (29.9%)	95/326 (29.1%)	
≥7	610/1328 (45.9%)	129/326 (39.6%)	
Not recorded	9 (0.7%)	4 (1.2%)	
Mean (median) % dose delivered*			
Fluoropyrimidine	82.6 (100)	79.4 (93.0)	0.08
Platinum	84.8 (100)	82.6 (100)	0.37
Epirubicin	84.6 (100)	81.9 (99.2)	0.12
Reductions and delays*			
Any dose reduction	549/1011 (54.3%)	124/228 (54.4%)	0.98
Any dose delay	543/1011 (53.7%)	132/228 (57.9%)	0.25

*dose data from REAL2 and REAL3 trials only.
Significant p-values are highlighted in bold.

prevalence of gastric tumours as opposed to junctional or oesophageal tumours, and subgroup analyses of perioperative chemotherapy trials have suggested improved chemotherapy response in junctional tumours compared with true gastric cardia tumours [22–24]. Interestingly, after adjusting these efficacy outcomes using our multivariate model, the HRs for survival notably favoured females and any trend for difference in response rates was lost. This suggests that the similar absolute survivals observed were likely due to an imbalance in potential confounding factors between the two groups. This difference appeared to be primarily driven by the difference in the number of chemotherapy cycles received between males and females, as when this was removed from the model the adjusted survival HRs then became similar to the unadjusted results. An important caveat to this analysis is that we do not know the reasons for the shorter duration of treatment among females, which may be due to factors other than toxicity and tolerability such as progressive disease or the patient's and/or physician's choices around treatment discontinuation. Given the similar PFS and OS outcomes seen, it is not unreasonable to assume that it could be driven at least in part by the increased toxicity rates observed. A further limitation is that as these RCTs were performed over a long time period, not all prognostic factors now known to be relevant had data available; thus, we were unable to adjust for some known prognostic factors such as distribution of metastatic disease, blood and tumour marker abnormalities and more recently identified biological characteristics such as microsatellite instability [25,26]. Therefore, the difference in survival between males and females will require further validation in more contemporaneous RCT data sets, where all known prognostic factor data are collected.

It is notable that a recent pooled analysis of 3265 patients with early-stage OG adenocarcinoma treated with similar perioperative chemotherapy and surgery reported significantly improved disease-specific survival and OS in females compared with males, although again experiencing greater incidence of GI toxicity [27]. Thus, potential sex differentials in chemotherapy response and toxicity may be relevant in both early- and late-stage treatment.

Despite the historical nature of these data, our large patient sample drawn from prospective randomised trial databases still allows for robust comparisons to be made. Given that the mainstay of first-line treatment for this disease remains platinum- and fluoropyrimidine-based chemotherapy, with modern trials often combining investigational agents alongside such regimens, the results remain relevant to current clinical practice. Clinicians should be aware of the differential toxicities experienced by males and females to allow for more tailored education and supportive measures to

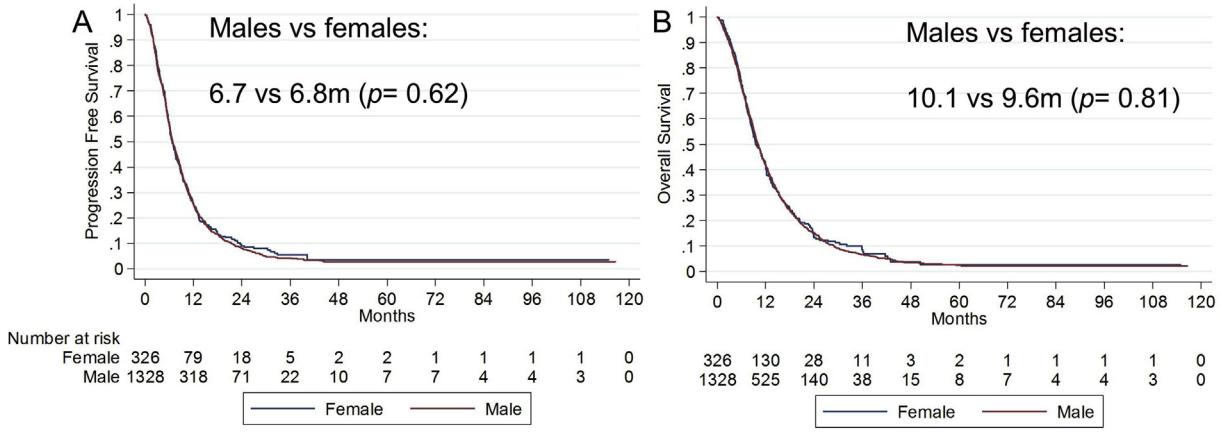

Fig. 3. (A) Progression-free survival and (B) overall survival.

improve patient experience and tolerability of treatment. A practical first step, for example, may be emphasising risk of GI toxicity to female patients and preemptively prescribing and encouraging early use of preventative symptom-control agents. Further research is necessary on the impact of sex on the relationship between dose, response and toxicity, as well as the underlying biological mechanisms driving such differences, as sex may warrant consideration as an important independent modulator of both treatment toxicity and outcome in this tumour type. If relevant sex disparities continue to be noted, trials investigating differing dosing strategies may be considered in the future to establish sex-specific treatment approaches.

Conflict of interest statement

Naureen Starling reports research funding from AZ, BMS and Merck and honoraria from AZ. David Cunningham reports research funding from Amgen, AstraZeneca, Bayer, Celgene, Merck Serono, MedImmune, Merrimack, Novartis, Roche and Sanofi. Ian Chau reports advisory board participation for Sanofi Oncology, Eli Lilly, Bristol-Meyers Squibb, MSD, Bayer, Roche and Five Prime Therapeutics and reports research funding from Janssen-Cilag, Sanofi Oncology, Merck Serono and Novartis and honorarium from Taiho, Pfizer, Amgen and Eli Lilly. Michael Davidson, Anna Dorothea Wagner, Kyriakos Kouvelakis, Henry Nanji, David Watkins, Sheela Rao and Clare Peckitt report no conflicts of interest.

Ethical approval and consent to participate

As this was a retrospective study, patient consent to participate was not required. A protocol outlining the rationale, methods and statistical analysis plan was submitted and approved by the Royal Marsden Hospital Committee for Clinical Research before commencement of data collection and analysis and is available on request. The manuscript does not include any potentially identifiable patient images or data.

Consent for publication

All authors have given consent for publication.

Availability of data and material

Research data sets are available on request.

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Author contributions

M.D. and A.D.W. contributed to study concept. M.D. and A.D.W. contributed to study design. M.D., K.K., C.P., D.C., I.C., N.S., D.W. and S.R. contributed to data acquisition. M.D., C.P., K.K. and H.N. contributed to quality control of data and algorithms. M.D., C.P., K.K. and H.N. contributed to data analysis and interpretation. M.D., C.P., K.K. and H.N. contributed to statistical analysis. All authors contributed to manuscript preparation, editing and review. All authors were involved in writing the manuscript and provided final approval of the submitted version.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.010.

References

[1] Radkiewicz C, Johansson ALV, Dickman PW, et al. Sex differences in cancer risk and survival: a Swedish cohort study. Eur J Cancer 2017;84:130–40.
[2] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018. https://doi.org/10.3322/caac.21492.
[3] Clocchiatti A, Cora E, Zhang Y, Dotto GP. Sexual dimorphism in cancer. Nat Rev Cancer 2016;16(5):330–9.
[4] Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009;48(3):143–57.
[5] Hunt CM, Westerkam WR, Stave GM. Effect of age and gender on the activity of human hepatic CYP3A. Biochem Pharmacol 1992;44(2):275–83.
[6] Schrijvers D. Role of red blood cells in pharmacokinetics of chemotherapeutic agents. Clin Pharmacokinet 2003;42(9):779–91.
[7] 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(2):361–70.
[8] Özdemir BC, Csajka C, Dotto GP, Wagner AD. Sex differences in efficacy and toxicity of systemic treatments: an undervalued issue in the era of precision oncology. J Clin Oncol 2018;36(26):2680–3.
[9] Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013;19(34):5598–606.
[10] Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010;3(3):CD004064.
[11] Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358(1):36–46.

[12] Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24(31):4991–7.
[13] Webb a, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997;15(1):261–7.
[14] Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002;20(8):1996–2004.
[15] Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14(6):481–9.
[16] 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 erotic gastrointestinal group. JAMA Oncol 2018;4(7):1003–6.
[17] Kim H-I, Lim H, Moon and A. Sex differences in cancer: epidemiology, genetics and therapy. Biomol Ther (Seoul) 2018;26(4): 335–42.
[18] Liaw CC, Wang CH, Chang HK, et al. Gender discrepancy observed between chemotherapy-induced emesis and hiccups. Support Care Cancer 2001;9(6):435–41.
[19] Wheatley-Price P, Blackhall F, Lee SM, et al. The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials. Ann Oncol 2010;21(10): 2023–8.
[20] Elsaleh H, Joseph D, Grieu F, et al. Association of tumour site and sex with survival benefit from adjuvant chemotherapy in colorectal cancer. Lancet 2000;355(9217):1745–50.
[21] Abola MV, Prasad V, Jena AB. Association between treatment toxicity and outcomes in oncology clinical trials. Ann Oncol 2014; 25(11):2284–9.
[22] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11–20.
[23] Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29(13):1715–21.
[24] Al-Batran SE, 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):1948–57.
[25] Chau I, Norman AR, Cunningham D, et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer - pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004;22(12):2395–403.
[26] Zhu L, Li Z, Wang Y, et al. Microsatellite instability and survival in gastric cancer: a systematic review and meta-analysis. Mol. Clin. Oncol. 2015;3(3):699–705.
[27] Athauda A, Nankivell MG, Langley RE, et al. Impact of age and sex on chemotherapy (CTx) efficacy, toxicity and survival in early oesophagogastric (OG) cancer: a pooled analysis of 3265 patients from four large randomised trials (OE02, OE05, MAGIC & ST03). J Clin Oncol 2019;37(15):4022.