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Original Research

Impact of sex and age on chemotherapy efficacy, toxicity and survival in localised oesophagogastric cancer: A pooled analysis of 3265 individual patient data from four large randomised trials (OE02, OE05, MAGIC and ST03)

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KEYWORDS
Age;
Sex;
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Gastric cancer;
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Abstract ***Background:*** There is a lack of large-scale randomised data evaluating the impact of sex and age in patients undergoing chemotherapy followed by potentially curative surgery for oesophagogastric cancer.

Patients and methods: Individual patient data from four prospective randomised controlled trials were pooled using a two-stage meta-analysis. For survival analysis, hazard ratios (HRs) were calculated for patients aged <70 and ≥ 70 years, as well as between males and females. Mandard tumour regression grade (TRG) and, ≥grade III toxicities were compared using logistic regression models to calculate odds ratios. All analyses were adjusted for the type of chemotherapy received.

Results: 3265 patients were included for survival analysis (2668 [82%] male, 597 [18%] female; 2627 (80%) <70 years, 638 (20%) ≥70 years). A significant improvement in overall survival

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(OS) (HR: 0.78; p < 0.001) and disease-specific survival (DSS) (HR: 0.78; p < 0.001) was observed in females compared with males. No significant differences in OS (HR: 1.11; p = 0.045) or DSS (HR: 1.01; p = 0.821) were observed in older patients compared with younger patients.

For patients who underwent resection, older patients (15% vs 10%; p = 0.03) and female patients (14% vs 10%, p = 0.10) were more likely to achieve favourable Mandard TRG scores. Females experienced significantly more ≥grade III nausea (10% vs 5%; p≤0.001), vomiting (10% vs 4%; p≤0.001) and diarrhoea (9% vs 4%; p≤0.001) than males.

Conclusions: In this large pooled analysis using prospective randomised trial data, females had significantly improved survival while experiencing more gastrointestinal toxicities. Older patients achieved comparable survival to younger patients and thus, dependent on fitness, should be offered the same treatment paradigm.

1. Introduction

When combined, cancers of the oesophagus, oesophagogastric junction (OGJ) and stomach (oesophagogastric [OG] cancers) represent the second leading cause of cancer-related mortality worldwide [1]. For patients in Western populations with localised disease amenable to surgical resection, combination chemotherapy in a neoadjuvant or perioperative approach is commonly used with modest improvements in overall survival (OS) compared with surgery alone but with the cost of increased toxicity [2,3]. Responses to chemotherapy and clinical outcomes remain variable with approximately half of patients who undergo resection subsequently developing disease relapse, even with modern surgical technique [4].

The effect of sexual disparity on cancer incidence, aetiology and treatment has been relatively overlooked until recently but may be a key component of a precision medicine approach. Large epidemiological studies have demonstrated that sexual differences exist in cancer susceptibility and outcome with males having a higher incidence and poorer outcomes of several tumour types including OG cancer [1,5]. Whilst some of the differences in cancer incidence may be due to behavioural factors such as smoking and/or hormonal influences [6] (oestrogens are thought to have a protective effect in terms of the development of some cancers), it has also been suggested that differential sex-based gene expression signatures [7] and differing immune responses [8] may be important. Sexual disparity also affects the pharmacokinetic handling of cytotoxic chemotherapy drugs through differences in body composition [9], drug-metabolising enzyme expression [10], and drug-erythrocyte binding [11] with the data suggesting that higher dose intensities may be achieved in females compared to males.

In addition to sexual disparity observed in cancer incidence and outcome, age disparity also exists. OG cancers are predominantly a disease of older age with more than half of new cancers each year being diagnosed in people aged older than 75 years in the United Kingdom (UK) [12,13]. However, there is usually discrepancy in the use of treatment options compared with younger patients and outcomes are generally poorer for older patients [14,15]. The attribution of effects is complicated however by the increased impact of comorbidities in the elderly population, making it difficult to ascertain the reason for poorer outcomes in this patient group outside of clinical trials. Similar to the differences in drug handling observed between males and females, pharmacokinetic factors such as changes in body composition, reduced hepatic capacity and reduced renal perfusion [16] can also vary with increasing age, regardless of comorbidities, and may influence drug distribution, metabolism and clearance. The lack of older participants in clinical trials limits not only our knowledge about the pharmacokinetic handling of cytotoxic chemotherapy drugs in older patients but also the interpretation of clinical trial results into clinical practice.

Using four prospective randomised controlled trials (RCTs) evaluating the use of neoadjuvant or perioperative chemotherapy in operable OG cancer, we investigated the effect of sex and age on treatment outcomes.

2. Materials and methods

2.1. Methods

2.1.1. Patient cohorts

Individual patient data from four prospective RCTs evaluating neoadjuvant/perioperative chemotherapy for potentially operable OG cancer were included in this analysis: OE02, Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial (ISRCTN 93793971), OE05 (ISRCTN 01852072) and ST03 (ISRCTN 46020948). Individual trial design and results have previously been published, but in short:

OE02 recruited 802 patients between 1992 and 1998 with localised oesophageal cancer who were randomly allocated to receive two cycles of cisplatin and fluorouracil (CF[5-FU]) chemotherapy followed by surgery or surgery alone [2]; MAGIC investigated the use of perioperative chemotherapy (three cycles of epirubicin, cisplatin, 5-FU [ECF] pre- and post-operatively) compared with surgery alone in 503 patients with potentially resectable adenocarcinoma of the stomach, OGJ or lower oesophagus between 1994 and 2002 [3]; OE05 recruited 897 patients with operable oesophageal adenocarcinoma between 2005 and 2011 and randomised between two cycles of CF or four cycles of epirubicin, cisplatin, capecitabine (ECX) chemotherapy given pre-operatively [17]; ST03 investigated the addition of the antiangiogenic monoclonal antibody bevacizumab to perioperative ECX chemotherapy in 1063 patients with OG adenocarcinoma recruited between 2007 and 2014 [4]. Based on the lack of improved efficacy with bevacizumab, patients who received this drug were also pooled in this analysis.

All four trials were designed and managed by the Medical Research Council Clinical Trials Unit at University College London and assessed a similar patient population. These particular trials were chosen as they represent the largest randomised trials conducted in this patient population in the UK, and the clinical and pathological data were readily available to our group. The majority of patients were recruited from UK centres with MAGIC and OE02 including a small number of patients from other countries, which amount to less than 1% of the total population. There were no upper age limit restrictions in any trial and none included planned dose changes based on the age of patients.

2.1.2. Analysis of toxicity and tumour regression grade

Individual patient data were available from all four trials. Baseline patient demographic data common to all trials were age, sex and World Health Organisation (WHO) performance status. In addition, OE05 and ST03 included data on baseline tumour stage. In the OE02 trial, toxicity information was not recorded. MAGIC, OE05 and ST03 all recorded toxicity information on nausea, vomiting, diarrhoea and stomatitis in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. In addition, OE05 and ST03 both collected data on tinnitus, thrombocytopaenia, neutropenia, cardiac toxicity, loss of taste, infection (neutropenic), peripheral neuropathy, palmar-plantar erythrodysesthesia (PPE), renal toxicity, deep vein thrombosis (DVT) and pulmonary embolism.

Tumour regression grade (TRG) was assessed in accordance with the Mandard system [18] as follows: TRG 1 (complete regression/fibrosis with no evidence of tumour cells), TRG 2 (fibrosis with scattered tumour cells), TRG 3 (fibrosis and tumour cells with a dominance of fibrosis), TRG 4 (fibrosis and tumour cells with a dominance of tumour cells), and TRG 5 (tumour without evidence of regression). For all trials, central TRG review was available and was assessed by two independent experienced pathologists and a third if no consensus was agreed. Further disagreements were settled by a majority call. Central TRG data were available for 1799 (83%) of the 2165 patients who underwent surgical resection after neoadjuvant chemotherapy.

2.1.3. Statistical analysis

The primary outcome measure for this analysis was OS, and secondary outcome measures were disease-specific survival (DSS), Mandard TRG and incidence of grade $\geq$III toxicity. Data were analysed using a two-stage approach: first analysing data within trials and then combining the data across trials using a fixed-effects meta-analysis. To assess the impact of model choice on results, sensitivity analyses were also performed using a random-effects meta-analysis.

For the purposes of analysis, age was dichotomised into patients aged $<$70 years and patients $\geq$70 years. The decision to dichotomise age was driven by the fact that patients aged 70 years and older are often treated differently in the clinical setting, especially in the UK. The intent of the age analyses was predominantly to challenge/confirm this clinical approach.

OS was defined as the time from randomisation until death from any cause, with surviving patients censored at their date of last follow-up. DSS was defined as the time from randomisation to death from cancer, with surviving patients censored at their date of last follow-up, and patients dying of other causes censored at their date of death. Survival analyses were performed for all trial participants in the intention-to-treat population. Mandard TRG was categorised into responders (grade I or II) and non-responders (grade III–V) and was only analysed for patients who were randomised to a pre-operative chemotherapy treatment arm and subsequently underwent surgical resection. Toxicity analysis was only performed in patients who received at least one cycle of neoadjuvant chemotherapy in the MAGIC, OE05 and ST03 trials, as toxicity data were not collected in OE02.

Time to event outcome measures (OS and DSS) were analysed using a Cox model to obtain hazard ratios (HRs) for the effect of age and sex. Binary outcome measures (Mandard TRG and toxicity) were analysed using logistic regression models to obtain odds ratios. All models were adjusted for WHO performance status and the type of chemotherapy received (none, CF, ECF/ECX, ECX+bevacizumab). A further analysis of OS was performed to also adjust for baseline tumour stage (stage I and II vs stage III and IV, in accordance with Union for International Cancer Control TNM 6th edition) in patients recruited to OE05 and ST03 alone.

Fig. 1 shows the proportion of participants drawn from each study and the number of participants included in each analysis. To account for multiple testing, a *P*-value of <0.01 is taken to indicate statistical significance. No imputation of missing data was performed.

3. Results

3.1. Demographics

3265 patients were included; 2668 (82%) males and 597 (18%) females. Of all patients, 2627 (80%) patients were aged <70 years and 638 (20%) were aged ≥70 years. There was no significant difference in age range between males and females. 2234 (68%) of patients were of WHO performance status 0, 1008 (31%) were WHO 1, and 23 (1%) were WHO >1 (all recruited through OE02). 1861 (71%) of patients aged <70 years and 373 (58%) of patients aged ≥70 years had a performance status of 0. In addition, 1824 (68%) of males and 410 (69%) of females had a performance status of 0. Owing to the nature of the individual studies, some included predominantly oesophageal cancers and others predominantly gastric or OGJ cancers. However, once the studies were pooled the proportions of patients with oesophageal, OGJ or gastric cancer were relatively balanced across the whole group. The vast majority of patients had adenocarcinomas (92%) with the exception of 268 patients in OE02 who had squamous cell or undifferentiated carcinomas, but this represents only 8% of the total patients in this analysis. Baseline characteristics of included participants from each trial are shown in Table 1 and numbers of participants in each age/sex subgroup according to baseline characteristics and chemotherapy outcome are shown in Table 2.

3.2. Toxicity and chemotherapy completion

Based on toxicities captured commonly across trials (Table 3), older patients experienced more ≥grade III neutropaenia (30% vs 22%; $P = 0.004$) than younger patients. Females experienced significantly more ≥grade III nausea (10% vs 5%; $P = <0.001$), vomiting (10% vs 4%; $P = <0.001$) and diarrhoea (9% vs 4%; $P < 0.001$) than males. No significant differences were seen in the occurrence of ≥grade III tinnitus, thrombocytopaenia, cardiac toxicity, loss of taste, infection/febrile neutropaenia, peripheral neuropathy, PPE, renal toxicity, DVT and pulmonary embolism.

Of the whole study population who were allocated to receive chemotherapy, 2246 patients (86%) completed the planned number of neoadjuvant chemotherapy cycles. A higher proportion of younger patients (87% vs 80%; $P < 0.001$) and males (87% vs 81%; $P = 0.001$) completed the planned number of chemotherapy cycles compared with older patients and females respectively.

3.3. Pathological treatment response (Mandard TRG)

There was no difference in the number of patients who underwent surgical resection between younger and older patients (84% vs 81%; $P = 0.03$), as well as between females and males (86% vs 83%; $P = 0.07$). For those patients who underwent surgical resection after neoadjuvant chemotherapy, older patients achieved similar rates of favourable Mandard TRG 1 and 2 scores as

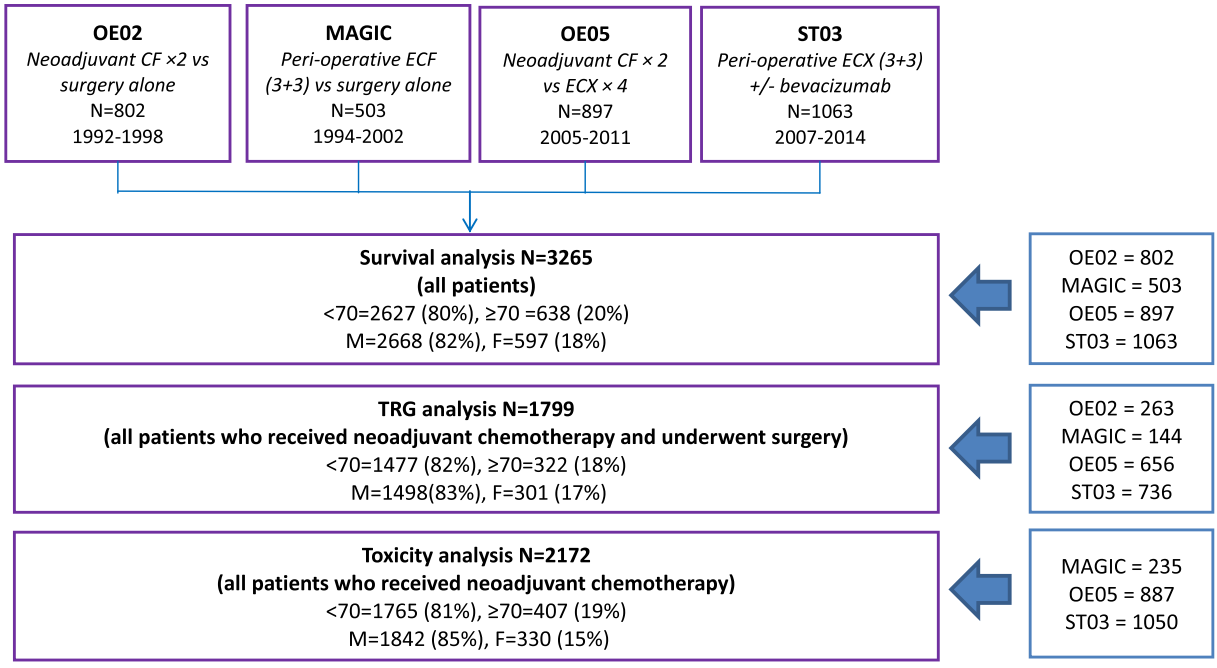


Fig. 1. Included trials and participants for each analysis.

younger patients (15% vs 10%; $P = 0.03$). Females also achieved similar rates of Mandard TRG 1 and 2 scores compared with males (14% vs 10%, $P = 0.099$).

3.4. Survival

A significant improvement in OS (28.6 vs 23.7 months, HR: 0.78 (0.70–0.88); $P < 0.001$) and DSS (35.3 vs 27.2 months, HR: 0.78 (0.69–0.88); $P < 0.001$) was observed in females versus males (Figs. 2 and 3). OS was similar between younger and older patients (24.5 vs 22.3 months, HR: 1.11 (1.00–1.24); $P = 0.05$) as was DSS (28.0 vs 28.0 months, HR: 1.01 (0.90–1.14); $P = 0.82$) (Figs. 4 and 5).

After adjusting for baseline stage in patients recruited through OE05 and ST03 only, female patients still had significantly improved OS (HR: 0.76 [0.63–0.91]; $P = 0.004$) and DSS (HR 0.75 [0.62–0.90]; $P = 0.002$) compared with male patients. In regards to age, no significant difference was seen in respect to OS (HR: 1.07 [0.91–1.25]; $P = 0.43$) or DSS (HR 0.99 [0.84–1.16]; $P = 0.87$).

In a separate analysis of the effect of sex on survival in the control arms of OE02 and MAGIC (i.e. in patients who underwent immediate surgical resection without any neoadjuvant chemotherapy; $N = 655$), females still demonstrated improved OS compared to males and this approached but did not meet statistical significance (HR: 0.83 [0.68–1.02]; $P = 0.07$).

All outcomes by sex and age analysis are summarised in Supplementary Table 1. No analysis showed evidence of significant heterogeneity of effect between trials. To assess the impact of model choice on the results, sensitivity analyses were performed using a random-effects

Table 1
Baseline patient and tumour characteristics for each trial.

Characteristic	Trial				
	OE02 N = 802	OE05 N = 897	MAGIC N = 503	ST03 N = 1063	Total N = 3265
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Sex					
Male	603 (75)	810 (90)	396 (79)	859 (81)	2668 (82)
Female	199 (25)	87 (10)	107 (21)	204 (19)	597 (18)
Total	**802 (100)**	**897 (100)**	**503 (100)**	**1063 (100)**	**3265 (100)**
Age (years)					
Median	62	62	62	63	63
IQR	55–68	56–67	55–68	56–69	56–68
Range	30–84	27–81	23–85	28–82	23–85
<70	637 (79)	747 (83)	398 (79)	845 (79)	2627 (80)
≥70	165 (21)	150 (17)	105 (21)	218 (21)	638 (20)
Total	**802 (100)**	**897 (100)**	**503 (100)**	**1063 (100)**	**3265 (100)**
WHO performance status					
0	532 (66)	603 (67)	342 (68)	757 (71)	2234 (68)
1	247 (31)	294 (33)	161 (32)	306 (29)	1008 (31)
2	21 (3)	0 (0)	0 (0)	0 (0)	21 (1)
Total	**802 (100)**	**897 (100)**	**503 (100)**	**1063 (100)**	**3265 (100)**
cT-stage					
1	Data not available	8 (1)	Data not available	6 (1)	14 (0)
2		87 (10)		126 (12)	213 (6)
3		775 (86)		785 (74)	1560 (48)
4		27 (3)		58 (5)	85 (3)
Total		**897 (100)**		**975 (92)**	**1872 (57)**
cN-stage					
N0	Data not available	194 (22)	Data not available	217 (20)	411 (13)
N1+		695 (77)		748 (70)	1443 (44)
Total		**897 (100)**		**965 (91)**	**1854 (57)**
Tumour location					
Oesophageal	720 (90)	Data not available	73 (15)	144 (14)	937 (29)
OGJ	82 (10)		58 (12)	536 (50)	676 (21)
Gastric	0 (0)		372 (74)	383 (36)	755 (23)
Total	**802 (100)**		**503 (100)**	**1063 (100)**	**2368 (73)**
Histology					
Adenocarcinoma	533 (66)	897 (100)	503 (100)	1063 (100)	2996 (92)
Squamous	247 (31)	0 (0)	0 (0)	0 (0)	247 (8)
Total	**780 (97)**	**897 (100)**	**503 (100)**	**1063 (100)**	**3243 (99)**

OGJ, oesophagogastric junction; MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy; WHO, World Health Organisation; c, clinical stage.

Table 2
Patient characteristics and outcomes by age and sex subgroups.

Characteristic/outcome		<70		≥70		Total N (%)
		Male N (%)	Female N (%)	Male N (%)	Female N (%)	
Trial	OE02	490 (61)	147 (18)	113 (14)	52 (6)	802
	MAGIC	307 (61)	91 (18)	89 (18)	16 (3)	503
	OE05	675 (75)	72 (8)	135 (15)	15 (2)	897
	ST03	682 (64)	163 (15)	177 (17)	41 (4)	1063
	Total	2154 (66)	473 (14)	514 (16)	124 (4)	3265 (100)
WHO PS	0	1521 (71)	340 (72)	303 (59)	70 (56)	2234 (68)
	≥1	633 (29)	133 (28)	211 (41)	54 (44)	1031 (32)
	Total	2153	473	514	124	3265 (100)
cT-stage	1	9 (1)	2 (1)	3 (1)	0 (0)	14 (1)
	2	147 (11)	28 (13)	34 (12)	4 (8)	213 (11)
	3	1103 (84)	176 (83)	240 (81)	41 (84)	1560 (83)
	4	56 (4)	7 (3)	18 (6)	4 (8)	85 (5)
	Total	1315	213	295	49	1872 (100)
cN-stage	N0	279 (21)	51 (24)	71 (24)	10 (20)	411 (22)
	N1+	1024 (79)	160 (76)	220 (76)	39 (80)	1443 (78)
	Total	1303	211	291	49	1854 (100)
Tumour location	Oesophageal	593 (40)	161 (40)	130 (34)	53 (49)	937 (40)
	OGJ	481 (33)	75 (19)	105 (28)	15 (14)	676 (29)
	Gastric	405 (27)	165 (41)	144 (38)	41 (38)	755 (32)
	Total	1479	401	379	109	2368 (100)
Histology	Adenocarcinoma	2027 (95)	381 (81)	496 (97)	92 (75)	2996 (92)
	Squamous	114 (5)	88 (19)	14 (3)	31 (25)	247 (8)
	Total	2141	469	510	123	3243 (100)
Completed planned chemotherapy	No	209 (12)	56 (16)	72 (17)	27 (31)	364 (14)
	Yes	1553 (88)	287 (84)	346 (83)	60 (69)	2246 (86)
	Total	1762	343	418	87	2609 (100)
Underwent resection	No	341 (16)	61 (13)	99 (20)	20 (17)	521 (16)
	Yes	1786 (84)	402 (87)	402 (80)	100 (83)	2690 (84)
	Total	2127	463	501	120	3211 (100)
TRG response	1–2	112 (9)	34 (14)	39 (15)	8 (14)	193 (11)
	3–5	1121 (91)	210 (86)	226 (85)	49 (86)	1602 (89)
	Total	1233	244	265	57	1799 (100)

TRG, tumour regression grade; OGJ, oesophagogastric junction; MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy; WHO, World Health Organisation; c, clinical stage at baseline.

Table 3
Significant ≥grade III toxicities captured across three trials (MAGIC, OE05 and ST03).

Toxicity	Age				Sex			
	<70 No. (%)	≥70 No. (%)	Total No. (%)	P-value	Male No. (%)	Female No. (%)	Total No. (%)	P-value
Nausea	99 (6)	19 (5)	118 (5)	0.553	85 (5)	33 (10)	118 (5)	<0.001
Vomiting	92 (5)	14 (3)	106 (5)	0.183	74 (4)	32 (10)	106 (5)	<0.001
Diarrhoea	75 (4)	30 (7)	105 (5)	0.012	75 (4)	30 (9)	105 (5)	<0.001
Stomatitis	49 (3)	15 (4)	64 (3)	0.180	54 (3)	10 (3)	64 (3)	0.613
Neutropaenia (OE05 & ST03 only)	351 (22)	108 (30)	459 (24)	0.004	377 (23)	82 (28)	459 (24)	0.141
Infection or febrile neutropaenia (OE05 and ST03 only)	56 (4)	18 (5)	74 (4)	0.289	65 (4)	9 (3)	74 (4)	0.238

MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy.

meta-analysis. With the exception of the analysis of the effect of age on neutropaenia rates, all random-effects meta-analyses produced similar results to the fixed-effects models. For neutropaenia, the *p*-value for the effect of age was 0.004 for the fixed-effects analysis but 0.014 from the random-effects model. Our pre-defined cut-off for statistical significance was 0.01; therefore some caution is recommended when interpreting this result.

4. Discussion

This study, using patient-level data collected from four large prospective RCTs, represents the largest pooled analysis of the effects of age and sex on toxicity of neoadjuvant chemotherapy and survival in operable OG cancer. Females had statistically significant improved survival, both in terms of OS and DSS, compared to males including after adjustment for baseline stage. The survival difference between males and females in our study remained apparent, albeit less pronounced, when the control arms of OE02 and MAGIC (i.e. patients who underwent surgery without any neoadjuvant

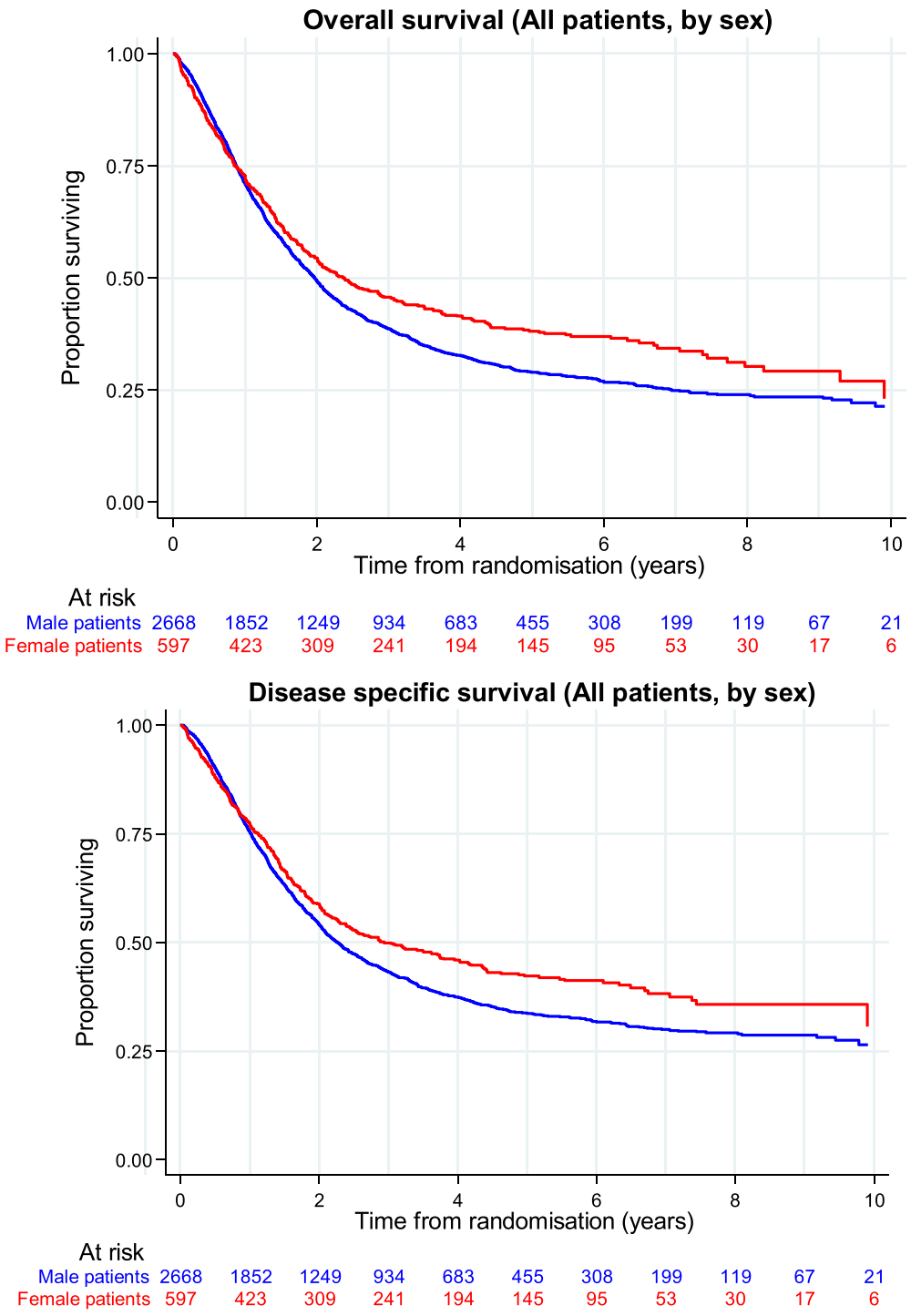


Fig. 2. Kaplan-Meier curves of overall survival (OS) and disease-specific survival (DSS) by sex.

chemotherapy) were analysed separately, and this approached but did not reach statistical significance. This result demonstrates that the prognostic effect of surgery is more pronounced in the study population who received neoadjuvant chemotherapy, suggesting a predictive effect from exposure to chemotherapy. The survival of patients aged 70 years and older was comparable to patients aged less than 70 years.

Worldwide, females have a longer life expectancy than males and this trend has more recently been demonstrated in cancer survival too [5,19]. The large population-based EUROCARE-4 data set demonstrated that female sex was an independent predictor of survival in oesophageal and gastric cancer, as well as in a number of other cancers [20] and analysis of the Surveillance, Epidemiology and End Results database has

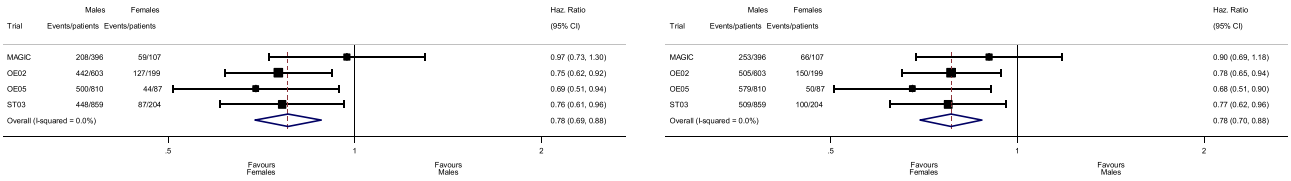
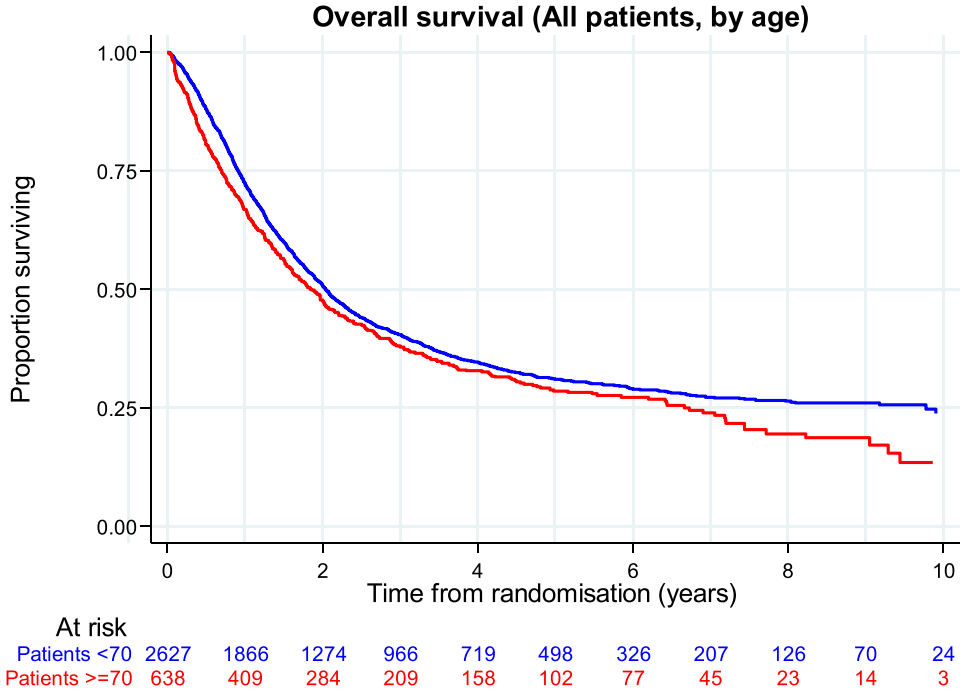


Fig. 3. Forest plots of DSS (left) and OS (right) benefit in females vs males. OS, overall survival; DSS, disease-specific survival.



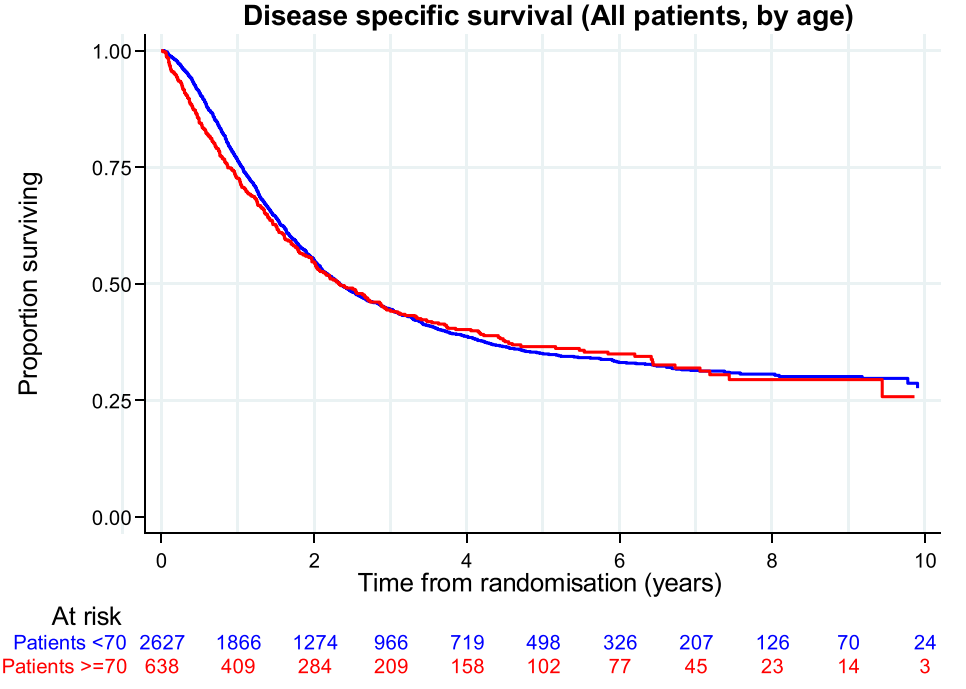


Fig. 4. Kaplan-Meier curves of overall survival (OS) and disease-specific survival (DSS) by age.

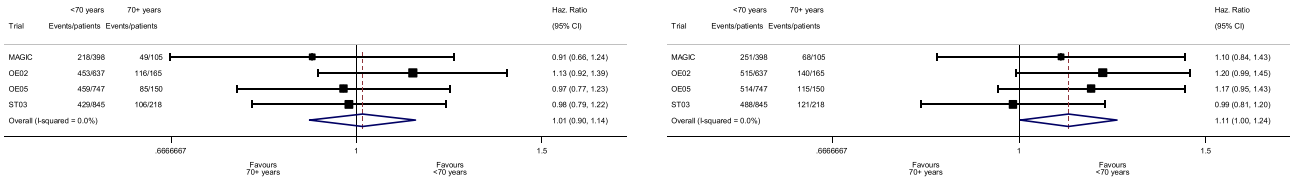


Fig. 5. Forest plots of DSS (left) and OS (right) in older vs younger patients. OS, overall survival; DSS, disease-specific survival.

revealed similar results for oesophageal cancer [21]. A survival benefit for females has also been observed in lung adenocarcinoma [22], although the converse has been observed in bladder cancer [23]. There remains limited data on the influence of sex on survival in operable OG cancer; a longer metastasis-free survival time for females undergoing pre-operative chemoradiation has been demonstrated; however, the number of participants in this study was small and females presented with earlier stage disease than males [24].

The molecular basis for differential cancer survival between males and females remains incompletely understood but is likely to be secondary to both inherent biological differences between the sexes, as well as tumour-specific molecular changes. Sex is one variable that influences both innate and adaptive immune responses which can hugely affect both pathogenesis, as well as prognosis from non-sex-specific cancers. Multiple putative mediators of immunity such as sex hormones, sex chromosome–linked genetic changes, metabolic and bacterial mediators, reproductive stage and environmental factors are thought to be differentially expressed in males and females at different stages of development and subsequently may influence the immune system in varying ways throughout the course of life [8]. Our increasing understanding of the complex interplay between immune cells and cancer cells, as well as the corresponding effect on tumourigenesis, therapeutic response and prognosis indicates that sex-specific immunological changes may contribute significantly to survival differences between males and females.

In regards to tumour-specific differences, Yuan et al. [7] analysed thirteen cancers of The Cancer Genome Atlas and identified a group of cancers with sex-biased gene expression signatures with 53% of clinically actionable genes. The majority of cancers in this group demonstrate sex-differential incidence and mortality, highlighting the significant impact that molecular-level understanding of the sex-effect can have on drug development, as well as clinical practice. The tumour-associated stroma may also play a key role in the disparity between tumours of males and females, for example, differences in expression of androgen and oestrogen receptors in the stroma of male and female patients with gastric cancer, and their correlation with tumour stage has recently been demonstrated [25]. Altogether, it is likely that a highly complex interplay between biological and environmental factors influences the improved cancer-specific survival for females which has been demonstrated in this and other studies, and the exact underlying mechanisms require further consideration.

In addition to the observed survival differences, toxicity rates and number of completed chemotherapy cycles also varied between males and females in our study. The occurrence of higher rates of toxicity in females has previously been reported for a number of different cytotoxic drugs and relates to both haematological and non-haematological toxicities [22,26,27]. Although the increased susceptibility of toxicities such as nausea and alopecia may be influenced by differing perceptions between females and males, differences in the occurrence of objective haematological parameters supports the notion of sex-specific variation in drug exposure and sensitivity. Within our analysis, the rate of severe gastrointestinal (GI)-specific toxicities was significantly increased in females although haematological parameters of toxicity, such as neutropaenia and thrombocytopaenia, were not. Recent results from a pooled analysis of 1654 patients with advanced OG cancer have also shown that females experienced more GI-specific toxicities than males when treated with equivalent first-line chemotherapy, although no significant survival differences were seen [27]. In both analyses, females completed fewer cycles of planned chemotherapy than males, suggesting that increased toxicity may impact on the effective administration of chemotherapy.

Despite the observed reduction in dose intensity for females and older patients in our analysis, both groups achieved similar rates of favourable regression as males and younger patients, suggesting that physiological differences contributing to sex and age-specific exposure to chemotherapy is adequate to induce comparable tumour responses despite a reduced overall dose. Previous studies support this theory by demonstrating a correlation between higher rates of toxicity, increased response rates and improved survival in females [28,29]. Independent of sex, a number of systemic anti-cancer therapies also display a toxicity-response relationship, whereby higher rates of toxicity are associated with better responses to therapy, an example of which is the skin rash associated with cetuximab [30]. As the maximum tolerated doses of cytotoxic drugs have

traditionally been determined through phase I and II studies which have a male preponderance, it may be that female patients are being treated with doses above those which will be efficacious but at the cost of increased toxicity. This supports the notion that effective dosage of systemic anti-cancer therapies should be determined on an individualised basis taking into account physiological and pharmacokinetic differences between patients of different sex and age.

A step forward in the personalisation of cytotoxic chemotherapy administration is through the incorporation of DPYD-genotype testing in patients planned to receive fluoropyrimidines. There is mounting evidence that the routine use of DPYD testing to guide dose adjustments in clinical practice and within clinical trials is feasible and of great benefit [31], and this practice has been adopted in many UK institutions. In addition, the routine use of UGT1A1 polymorphism testing occurs in many institutions to guide irinotecan dosing. The utilisation of therapeutic drug monitoring (TDM) of cytotoxic drugs, many of which have narrow therapeutic indices but highly variable pharmacokinetics, would be greatly informative for a personalised approach. However, the use of TDM is not commonplace in oncology owing to a number of issues including the use of combination chemotherapy regimens which make it difficult to establish therapeutic ranges for individual drugs, paucity of published data and analytical challenges with prodrugs to name a few [32]. There should be a continued effort to promote TDM guidelines in oncology practice and through clinical trials to evaluate the benefits of individualised chemotherapy.

Sexual disparity in cancer treatment efficacy can also be seen beyond traditional cytotoxic chemotherapy drugs. It has been shown that immune checkpoint inhibitors (ICIs) tend to be more effective in males than females [33,34], whereas ICIs combined with chemotherapy tends to be more effective in females [35]. This differential response to immune-modulating drugs is not entirely surprising, given the significant physiological differences which exist between male and female immune systems as described previously. Consequently, female tumours are considered by some to be 'immune hot' but display low tumour antigenicity, whereas male tumours are considered 'immune cold' but display high tumour antigenicity. In addition, it has been observed that females have a higher chance of exhibiting immune-mediated adverse events than males [36]. Taken together, it is becoming increasingly clear that immunotherapeutic strategies, in addition to systemic chemotherapy, may benefit from being tailored to the patient's sex.

As the majority of OG cancers in high- and middle-income countries are diagnosed in patients aged 70 years and older, it is now recognised that these cancers are predominantly a disease of older people. However, this population is under-represented in the trials included in this analysis, for example, only 3% of the OE05 participants were aged >75 years despite more than half of cancers being diagnosed in this age group in the UK. Owing to stringent trial eligibility criteria, almost all patients included in this analysis had a performance status of 0 or 1 and therefore represent a fit older population, hence these results may not be generalisable to all patients with OG cancer in the clinic. Nevertheless, these results are clinically important as they provide reassurance to clinicians and surgeons that fit older patients can be managed safely with the same curative treatment paradigm as younger patients and achieve comparable survival rates. These results are in keeping with a previous retrospective series, demonstrating comparable survival outcomes in patients aged ≥70 years treated with neoadjuvant chemotherapy and surgery in Germany [37]. A randomised phase II study conducted by the same group in patients aged ≥65 years showed that triplet chemotherapy was feasible in older patients with locally advanced or metastatic OG cancer but with the cost of increased toxicity and detriment on quality of life [38]. For palliative chemotherapy in advanced disease, tumour control and symptomatic improvement are more important driving factors for treatment, and clinical trials have now been designed to assess different regimens and dosages of drugs in older patients who may be frailer but still candidates for systemic therapy. The recently reported phase III GO2 study [39] demonstrated that reduced dose chemotherapy can achieve comparable survival to higher doses without compromising quality of life in frail older patients with advanced OG cancer. Based on our present study however, age alone should not be a discriminatory factor in determining chemotherapy regimen or dosage in patients with operable OG cancer.

A limitation of our study is the lack of uniform collection of baseline data, especially from the older studies (OE02 and MAGIC), which makes direct comparison of certain variables challenging. There is also a lack of information on potentially important confounding variables such as histopathological subclassification, baseline site of tumour and comorbidity index. In addition, although we have pointed towards a number of potential contributory factors accounting for survival differences between males and females based on available literature, information on these factors was not collected during the running of the included trials. This present study suggests more effort should be put into assessing these factors in future clinical trials. However, the large number of patients included in this analysis and the prospective collection of robust patient data through relatively uniform large clinical trials allows strong comparisons to be made, and this is a great strength. The use of individual patient-level data rather than aggregate data is also a strength of our study. The fact that our analysis includes significant numbers of patients in each subgroup of tumour site (lower

oesophageal, OGJ and gastric) enables these results to be relevant to all patients with OG cancer, which is important as current management regimens do not differentiate between these sites.

5. Conclusion

These results, drawn from four robust clinical trial data sets, suggest that sex as a readily available, cost-free, biological variable should be strongly considered in the stratification and interpretation of clinical trials as an independent regulator of chemotherapy efficacy and survival. The findings of this study suggest that clinicians should be aware of the differing toxicities and dose-response variability experienced by males and females as well as older and younger patients to provide education, tailor supportive measures, and improve tolerability of treatment for individual patients. Inherent sex-specific physiological differences are likely to account for the survival differences observed in this analysis however molecular characteristics of the tumour and stroma may also play a causative role. Further research is needed to ascertain any molecular changes which are potentially driving such differences in tumours between patients of differing sex.

Although males and females may both potentially benefit from sex-specific treatment strategies in operable OG cancer, age should not be a discriminatory factor and older patients, depending on fitness, should be treated with the same paradigm as younger patients.

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Conflict of interest statement

D.C. reports receiving research funding from Amgen, Sanofi, Merrimack, AstraZeneca, Celgene, MedImmune, Bayer, 4SC, Clovis, Eli Lilly, Janssen, Merck; sits on the scientific advisory board for OVIBIO. R.E.L. reports serving an advisory role for Bayer; receiving research funding from Bayer. I.C. reports serving on the advisory board for Eli-Lilly, Bristol Meyers Squibb, MSD, Bayer, Roche, Merck-Serono, Five Prime Therapeutics, Astra-Zeneca, Oncologie International, and Pierre Fabre; has received research funding from Eli-Lilly, Janssen-Cilag, Sanofi Oncology, and Merck-Serono; has received an honorarium from Eli-Lilly. N.S. has received research funding from AstraZeneca, BMS, and Pfizer; has received honoraria from Eli Lilly, Merck Serono, MSD Oncology, and Pierre Fabre; has received travel grants from AstraZeneca, BMS, Eli Lilly, Merck, Roche; has served on the advisory board for Pfizer, AstraZeneca, and Servier. A.A., M.N., D.A., H.I.G. and W.A. declare no competing interests.

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Appendix A. Supplementary data

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