European Journal of Cancer 187 (2023) 114–123

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Sex differences in treatment allocation and survival of potentially curable gastroesophageal cancer: A population-based study

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Received 24 December 2022; Received in revised form 31 March 2023; Accepted 4 April 2023
Available online 8 April 2023

KEYWORDS
Gastric cancer;
Oesophageal cancer;
Surgery;
Survival;
Sex

Abstract ***Background:*** Although curative treatment options are identical for male and female gastroesophageal cancer patients, access to care and survival may vary. This study aimed to compare treatment allocation and survival between male and female patients with potentially curable gastroesophageal cancer.
Methods: Nationwide cohort study including all patients with potentially curable gastroesophageal squamous cell or adenocarcinoma diagnosed between 2006 and 2018 registered in

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https://doi.org/10.1016/j.ejca.2023.04.002

the Netherlands Cancer Registry. The main outcome, treatment allocation, was compared between male and female patients with oesophageal adenocarcinoma (EAC), oesophageal squamous cell carcinoma (ESCC), and gastric adenocarcinoma (GAC). Additionally, 5-year relative survival with relative excess risk (RER), that is, adjusted for the normal life expectancy, was compared.

Results: Among 27,496 patients (68.8% men), most were allocated to curative treatment (62.8%), although rates dropped to 45.6% > 70 years. Curative treatment rates were comparable among younger male and female patients (≤70 years) with gastroesophageal adenocarcinoma, while older females with EAC were less frequently allocated to curative treatment than males (OR = 0.85, 95% confidence interval [CI] 0.73–0.99).

For those allocated to curative treatment, relative survival was superior for female patients with EAC (RER = 0.88, 95% CI 0.80–0.96) and ESCC (RER = 0.82, 95% CI 0.75–0.91), and comparable for males and females with GAC (RER = 1.02, 95% CI 0.94–1.11).

Conclusions: While curative treatment rates were comparable between younger male and female patients with gastroesophageal adenocarcinoma, treatment disparities were present between older patients. When treated, the survival of females with EAC and ESCC was superior to males. The treatment and survival gaps between male and female patients with gastroesophageal cancer warrant further exploration and could potentially improve treatment strategies and survival.

1. Introduction

With over one million new cases in 2020, gastric cancer is the 5th most common cancer accounting for 5.6% of all new malignancies worldwide [1]. Oesophageal cancer ranks 7th, with over half a million new cases in 2020 (3.1%) [1]. Together, they are one of the leading causes of cancer death, accounting for 13.2% of all cancer deaths worldwide [1]. Globally, incidences of gastric and oesophageal cancer vary greatly between male and female patients, with generally higher incidences in male patients [2].

Gastroesophageal cancers can be treated with curative intent if tumour infiltration into surrounding organs and distant metastasis are absent [3,4]. For oesophageal cancer, curative treatment options are esophagectomy with or without neo-adjuvant therapy, definitive chemoradiotherapy, or endoscopic resection for superficial node-negative tumours [4]. For gastric cancer, curative treatment options are gastrectomy with or without perioperative or adjuvant chemotherapy, or endoscopic resection for superficial node-negative tumours [3]. However, only patients allocated to these curative treatment options can benefit from them.

Allocation to the different treatment options is usually influenced by clinical factors such as age, performance status, tumour histology and stage, and guidelines do not distinguish between sexes [3–5]. However, studies in various cancer types suggest differences in treatment allocation between male and female patients, with potential impact on survival. For example, female patients with advanced gastroesophageal cancer are less frequently allocated to palliative treatment, and – despite higher tumour stages – females with colorectal cancer are less frequently treated with adjuvant chemotherapy [6,7]. Furthermore, Dutch population-based studies addressing the impact of hospital of diagnosis on the probability of receiving treatment for gastroesophageal cancer observed sex disparities, with 66% of male patients with oesophageal cancer undergoing treatment with curative intent compared to 53% of females [8], and 71% of males with gastric cancer undergoing surgery compared to 66% of females [9].

While others have evaluated survival differences between male and female patients among the surgically treated gastroesophageal cancer population [10,11], sex differences in treatment allocation and its impact on survival of potentially curable gastroesophageal cancer remains largely unknown. This study examined differences in allocation to curative treatment and long-term survival between male and female patients with potentially curable gastroesophageal cancer using a national cohort.

2. Methods

Nationwide data were acquired from the Netherlands Cancer Registry (NCR), containing data of all newly diagnosed malignancies in the Netherlands. Data on diagnosis, patient characteristics, tumour and treatment specifications were extracted from the medical hospital records by NCR data managers. Distribution of tumour location was coded according to the International Classification of Diseases for Oncology (ICD-O-3) [12]. Tumours were staged according to the TNM classification of the International Union Against Cancer valid at the time of diagnosis [13–15]. Vital status was obtained annually through a linkage with the Dutch Personal Records Database, with follow-up until the 1st of February 2021.

This study obtained approval from the NCR. No informed consent, opt-out procedure or ethical approval was required under Dutch law. This paper adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational cohort studies [16].

2.1. Patients

All patients with a primary solitary potentially curable gastroesophageal adenocarcinoma or squamous cell carcinoma, that is, without tumour infiltration into surrounding organs and distant metastasis, diagnosed between 2006 and 2018 were included. Patients with clinically unknown lymph node status (cNx) were included for analyses, since, regardless of clinical N-stage, curability is based on tumour infiltration (clinical T-stage) and the presence of distant metastasis (clinical M-stage). Patients with unknown tumour infiltration (cTx) and distant metastasis (cMx) were also included, as it was hypothesised that, in case of tumour infiltration into surrounding organs or distant metastasis, this would have been identified during the general diagnostic work-up and would have been reported for most patients. Although for some registered with cTx and cMx, complete staging might have been discontinued in absence of treatment perspective. Patients with carcinoma in situ (cTis) were excluded.

2.2. Treatment

Curative treatment was defined as an endoscopic or surgical resection for gastric cancer, and as an endoscopic or surgical resection, or definitive chemoradiotherapy for oesophageal cancer [3,4]. An endoscopic resection was only considered potentially curative for superficial (cT1/x), node-negative tumours (cN0/x). A surgical resection could be combined with perioperative, neo-adjuvant or adjuvant therapy consisting of chemotherapy or chemoradiotherapy. Definitive chemoradiotherapy, defined as concurrent chemoradiotherapy without subsequent surgical resection, was only considered potentially curative for oesophageal squamous cell carcinoma.

2.3. Outcomes

The primary end-point was allocation to curative treatment. Secondary end-point was 5-year relative survival, which was estimated as the observed overall survival, calculated from date of diagnosis until date of death or last follow-up, adjusted for survival of the general Dutch population [17]. All comparisons were performed between male and female patients after stratification for tumour location and histology, resulting in three groups; oesophageal adenocarcinoma, oesophageal squamous cell carcinoma and gastric adenocarcinoma.

2.4. Statistical analysis

Mann-Whitney U or Student's t tests for continuous variables, and $\chi 2$ tests for categorical variables were used when applicable to examine differences in baseline characteristics. Multivariable logistic regression analyses were performed to assess sex differences in allocation to curative treatment after correction for age, year of diagnosis, clinical T and N-stage, tumour location, differentiation, and histological subtype, providing odds ratios (ORs) with 95% confidence intervals (95% CIs), presented for the overall group and stratified by age (≤70 and > 70 years).

To account for sex differences in general life expectancy, relative survival with 95% CI was assessed as the overall survival of included patients, divided by the expected survival in the general Dutch population matched on age, sex, and year, according to the Pohar Perme method [17]. To assess the association between sex and risk of death, multivariable relative excess risk (RER) with 95% CI was estimated using the relative survival adjusted for age, period of diagnosis, clinical T and N-stage, tumour location and histological subtype.

Sex differences in Body Mass Index, the presence of comorbidities, and American Society of Anesthesiologists score were estimated for a subgroup of patients diagnosed 2015–2018.

Missing data were described for each value in the relevant table. STATA version 14.2 (StataCorp, College Station, TX, USA) was used to assess relative survival. SPSS Statistics version 28.0 (Armonk, NY) was used for further statistical analyses. Two-sided p values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

In total, 27,496 patients were included, of whom 68.8% were male (Figure 1, Table 1). For all groups, female patients were older at diagnosis. Cardiovascular comorbidities were more frequent in all male versus female gastroesophageal cancer patients, and diabetes was more frequent in male patients with oesophageal squamous cell carcinoma (Supplementary Table 1). Clinical T and N-stage were higher in males with oesophageal adenocarcinoma and squamous cell carcinoma. Tumour differentiation and histological subtype differed only for gastric adenocarcinoma, with more poorly differentiated and more diffuse-type tumours in female patients (48.3% versus 45.0%, $p < 0.001$; 43.4% versus 33.5%, $p < 0.001$, respectively). In female patients, oesophageal tumours were less frequently located in the distal oesophagus (adenocarcinoma: 59.3% versus 70.3%, $p < 0.001$; squamous cell carcinoma: 31.3% versus 41.6%, $p < 0.001$), and gastric adenocarcinomas were more frequently located in the antrum (37.0% versus 32.5%, $p < 0.001$).

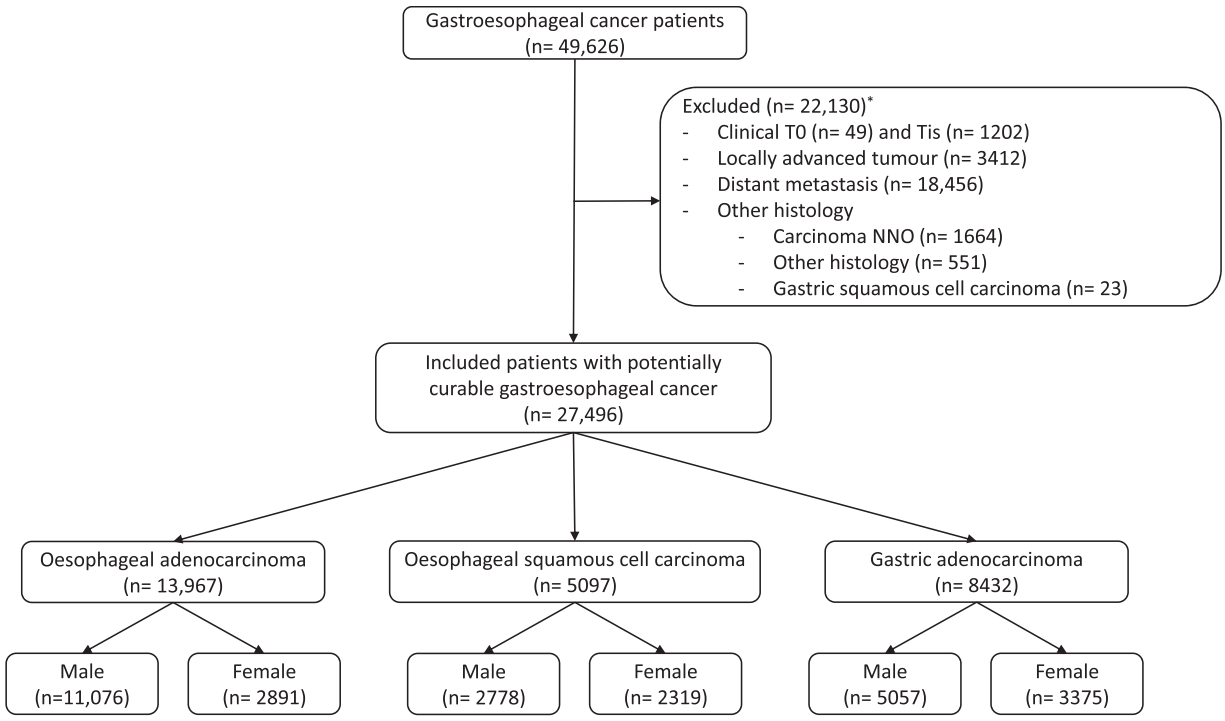

Fig. 1. Flowchart of inclusion. * Multiple reasons for exclusion may apply for one patient.

3.2. Treatment characteristics

Nearly two-thirds of patients were allocated to curative treatment (62.8%, Table 2), with a higher proportion among younger patients (≤70 years; 80.4%). Female patients with oesophageal and gastric adenocarcinoma were less frequently allocated to curative treatment than male patients (49.7% versus 62.4%, $p < 0.001$; 65.6% versus 68.9%, $p = 0.001$, respectively). For oesophageal adenocarcinoma this sex difference remained significant when adjusted for confounders (age, year of diagnosis, clinical T and N-stage, tumour location, differentiation and histological subtype), both in the overall (OR 0.84, 95% CI 0.75–0.93) and older patient group (OR 0.85, 95% CI 0.73–0.99), while no difference was present between younger patients. For oesophageal squamous cell carcinoma and gastric adenocarcinoma, adjusted curative treatment probability was comparable for both sexes (OR 1.13, 95% CI 0.98–1.30; OR 0.97, 95% CI 0.87–1.09, respectively) in the overall patient group.

Surgery was the most frequent applied curative treatment option (84.5%). Overall, male patients with oesophageal and gastric adenocarcinoma were more frequently allocated to surgery (55.7% versus 43.4%, $p < 0.001$; 66.8% versus 64.0%, $p = 0.010$), while surgical treatment rates were comparable between younger patients with adenocarcinoma. Surgically treated males with oesophageal and gastric adenocarcinoma more often received additional chemo(radio)therapy compared to females (78.1% versus 73.8%, $p < 0.001$; 47.7% versus 44.5%, p 0.020, respectively), while the use of additional chemo(radio)therapy was comparable between younger patients.

Both surgical treatment rate and curative treatment probability were higher for younger females with oesophageal squamous cell carcinoma (47.3% versus male 42.2%, $p = 0.008$; OR 1.27, 95% CI 1.03–1.56), while being comparable in the overall group and among older patients with oesophageal squamous cell carcinoma.

3.3. Survival

Female patients with oesophageal and gastric adenocarcinoma had inferior 5-year relative survival (29.8% versus 33.5%, $p < 0.001$; 32.9% versus 35.9%, $p = 0.011$; respectively). When adjusted for confounders, survival of female patients with oesophageal adenocarcinoma was comparable to male patients in the overall group (RER 1.05, 95% CI 0.99–1.11), while superior to males in the group allocated to curative treatment (RER 0.88, 95% CI 0.80–0.96; Fig. 2). For gastric adenocarcinoma, adjusted survival was comparable to male patients in both the overall group (RER 1.02, 95% CI 0.96–1.08) and in the group allocated to curative treatment (RER 1.02, 95% CI 0.94–1.11). For oesophageal squamous cell carcinoma, adjusted 5-year relative survival was superior for female patients (overall RER 0.85, 95% CI 0.79–0.91; allocated to treatment RER 0.82, 95% CI 0.75–0.91).

Table 1
Baseline characteristics of included gastroesophageal cancer patients.

Characteristics		Oesophageal cancer						Gastric cancer		
		Adenocarcinoma			Squamous cell carcinoma			Adenocarcinoma		
		Male	Female		Male	Female		Male	Female	
		N = 11,076	N = 2891	*p*	N = 2778	N = 2319	*p*	N = 5057	N = 3375	*p*
		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Age	Years (SD)	68.4 (11.0)	72.3 (12.2)	< 0.001	68.5 (9.8)	70.5 (10.7)	< 0.001	71.8 (11.7)	72.7 (13.3)	0.003
cT stage										
	T1	752 (6.8)	213 (7.4)	< 0.001	113 (4.1)	111 (4.8)	< 0.001	276 (5.5)	157 (4.7)	0.284
	T2	2650 (23.9)	611 (21.1)		608 (21.9)	580 (25.0)		1226 (24.2)	817 (24.2)	
	T3	5075 (45.8)	1058 (36.6)		1285 (46.3)	951 (41.0)		768 (15.2)	486 (14.4)	
	T4	141 (1.3)	49 (1.7)		89 (3.2)	46 (2.0)		115 (2.3)	70 (2.1)	
	Tx	2458 (22.2)	960 (33.2)		683 (24.6)	631 (27.2)		2672 (52.8)	1845 (54.7)	
cN stage										
	N0	4353 (39.3)	1206 (41.7)	< 0.001	903 (32.5)	974 (42.0)	< 0.001	2626 (51.9)	1731 (51.3)	< 0.001
	N+	5350 (48.3)	1141 (39.5)		1582 (56.9)	1051 (45.3)		1302 (25.7)	779 (23.1)	
	Nx	1373 (12.4)	544 (18.8)		293 (10.5)	294 (12.7)		1129 (22.3)	865 (25.6)	
Tumour differentiation										
	Good	493 (4.5)	121 (4.2)	0.397	116 (4.2)	92 (4.0)	0.682	124 (2.5)	72 (2.1)	< 0.001
	Medium	2921 (26.4)	724 (25.0)		905 (32.6)	757 (32.6)		1004 (19.9)	538 (15.9)	
	Poor	3627 (32.7)	980 (33.9)		689 (24.8)	547 (23.6)		2278 (45.0)	1631 (48.3)	
	Missing	4035 (36.4)	1066 (36.9)		1068 (38.4)	923 (39.8)		1651 (32.6)	1134 (33.6)	
Histological subtype[a]										
	Intestinal	6866 (62.0)	1813 (62.7)	0.428	—	—		2428 (48.0)	1358 (40.2)	< 0.001
	Diffuse	1792 (16.2)	462 (16.0)		—	—		1695 (33.5)	1465 (43.4)	
	Mixed	250 (2.3)	56 (1.9)		—	—		194 (3.8)	129 (3.8)	
	Indeterminate	285 (2.6)	88 (3.0)		—	—		79 (1.6)	53 (1.6)	
	Missing	1883 (17.0)	472 (16.3)		—	—		661 (13.1)	370 (11.0)	
Clinical tumour location										
	Proximal	44 (0.4)	43 (1.5)	< 0.001	481 (17.3)	403 (17.4)	< 0.001	—	—	< 0.001
	Middle	358 (3.2)	224 (7.7)		924 (33.3)	1023 (44.1)		—	—	
	Distal	7785 (70.3)	1714 (59.3)		1157 (41.6)	725 (31.3)		—	—	
	GEJ/Cardia	2547 (23.0)	789 (27.3)		28 (1.0)	15 (0.6)		—	—	
	Overlapping	129 (1.2)	61 (2.1)		122 (4.4)	102 (4.4)		1088 (21.5)	753 (22.3)	
	Not specified	213 (1.9)	60 (2.1)		66 (2.4)	51 (2.2)		365 (7.2)	120 (3.6)	
	Fundus	—	—		—	—		232 (4.6)	86 (2.5)	
	Corpus	—	—		—	—		1030 (20.4)	705 (20.9)	
	Antrum	—	—		—	—		1643 (32.5)	1250 (37.0)	
	Pylorus	—	—		—	—		411 (8.1)	270 (8.0)	
	Curvatura minor	—	—		—	—		221 (4.4)	145 (4.3)	
	Curvatura major	—	—		—	—		67 (1.3)	46 (1.4)	

cN: clinical N-stage; cT: clinical T-stage; GEJ: gastroesophageal junction; SD: standard deviation.
Due to rounding, percentages may not add up to 100%.
[a] Histological subtype is not applicable for oesophageal squamous cell carcinoma.

4. Discussion

This population-based study, including a total of 27,496 patients with potentially curable gastroesophageal cancer, reveals clinically relevant sex disparities in tumour localisation, biology, allocation to curative treatment and survival. With increasing concern for sex/gender-sensitive medicine, the observed treatment and survival disparities stimulate further consideration of sex/gender-specific effects in future trials and practice.

For both types of oesophageal cancer, tumours were more often located in the distal oesophagus in male patients, as compared to the mid oesophagus in females. For gastric cancer, tumours arising in males were more often located in the fundus, as compared to the antrum in females. In addition, a higher percentage of poorly differentiated and diffuse-type gastric cancer was observed in female patients. Both the observed differences in location and the higher percentage of diffuse-type and poorly differentiated cancers in females – which are in line with previous observations [18] – cannot be explained by sex differences in exposure to risk factors and lend further support to the concept of a sexual dimorphism [19], referring to differences in susceptibility and survival of cancers arising in both male and female as a result of biological differences. Not only are molecular subtypes of gastroesophageal cancers distributed in a characteristic way between male and female [20,21], a sexual dimorphism in gastric cancer has also been described at the level of the tumour microenvironment [22].

Table 2
Treatment characteristics of included gastroesophageal cancer patients, overall and stratified by age category (age ≤70 and > 70 years).

		Oesophageal cancer						Gastric cancer		
		Adenocarcinoma			Squamous cell carcinoma			Adenocarcinoma		
		Male	Female		Male	Female		Male	Female	
		N = 11,076	N = 2891	*p*	N = 2778	N = 2319	*p*	N = 5057	N = 3375	*p*
Treatment characteristics		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Curative treatment	Endoscopic resection	742 (6.7)	183 (6.3)	0.477	50 (1.8)	46 (2.0)	0.631	107 (2.1)	52 (1.5)	0.057
	CRT[a]	—	—		860 (31.0)	631 (27.2)	0.003	—	—	
	Surgery	6169 (55.7)	1255 (43.4)	< 0.001	881 (31.7)	761 (32.8)	0.402	3376 (66.8)	2161 (64.0)	0.010
	Surgery + C(R)T[b]	4815 (78.1)	926 (73.8)	< 0.001	663 (75.3)	570 (74.9)	0.869	1609 (47.7)	961 (44.5)	0.020
	Curative treatment	6911 (62.4)	1438 (49.7)	< 0.001	1791 (64.5)	1438 (62.0)	0.069	3483 (68.9)	2213 (65.6)	0.001
	Curative treatment probability[c]	OR 0.84, 95% CI 0.75–0.93			OR 1.13, 95% CI 0.98–1.30			OR 0.97, 95% CI 0.87–1.09		
		Male	Female		Men	Female		Male	Female	
Age ≤70 years		N = 6309	N = 1227		N = 1608	N = 1158		N = 2024	N = 1259	
Curative treatment	Endoscopic resection	436 (6.9)	87 (7.1)	0.821	22 (1.4)	25 (2.2)	0.112	36 (1.8)	14 (1.1)	0.129
	CRT[a]	—	—		525 (32.6)	361 (31.2)	0.412	—	—	
	Surgery	4574 (72.5)	875 (71.3)	0.395	679 (42.2)	548 (47.3)	0.008	1685 (83.3)	1060 (84.2)	0.478
	Surgery + C(R)T[b]	3704 (81.0)	700 (80.0)	0.500	513 (75.6)	409 (74.6)	0.712	1130 (67.1)	710 (67.0)	0.965
	Curative treatment	5010 (79.4)	962 (78.4)	0.426	1226 (76.2)	934 (80.7)	0.006	1721 (85.0)	1074 (85.3)	0.829
	Curative treatment probability[c]	OR 0.93, 95% CI 0.80–1.09			OR 1.27, 95% CI 1.03–1.56			OR 1.03, 95% CI 0.84–1.28		
		Male	Female		Male	Female		Male	Female	
Age > 70 years		N = 4767	N = 1664		N = 1170	N = 1161		N = 3033	N = 2116	
Curative treatment	Endoscopic resection	306 (6.4)	96 (5.8)	0.346	28 (2.4)	21 (1.8)	0.325	71 (2.3)	38 (1.8)	0.181
	CRT[a]	—	—		335 (28.6)	270 (23.3)	0.003	—	—	
	Surgery	1595 (33.5)	380 (22.8)	< 0.001	202 (17.3)	213 (18.3)	0.495	1691 (55.8)	1101 (52.0)	0.008
	Surgery + C(R)T[b]	1111 (69.7)	226 (59.5)	< 0.001	150 (74.3)	161 (75.6)	0.755	479 (28.3)	251 (22.8)	0.001
	Curative treatment	1901 (39.9)	476 (28.6)	< 0.001	565 (48.3)	504 (43.4)	0.018	1762 (58.1)	1139 (53.8)	0.002
	Curative treatment probability[c]	OR 0.85, 95% CI 0.73–0.99			OR 1.08, 95% CI 0.87–1.32			OR 1.08, 95% CI 0.94–1.25		

CRT: chemoradiotherapy; OR: odds ratio; Surgery + C(R)T: surgery in combination with chemo(radio)therapy.
[a] CRT is not considered potentially curative treatment for oesophageal and gastric adenocarcinoma.
[b] Proportion of surgically treated patients treated in combination with chemo(radio)therapy.
[c] Odds ratio for female compared to male, adjusted for age, year of diagnosis, clinical T and N-stage, tumour location, differentiation and histological subtype.

In addition, important sex differences in allocation to curative treatment were observed. For oesophageal adenocarcinoma, with 62% of male and only 50% of female patients allocated to curative treatment, this gap was most pronounced. Apart from an age difference between male and female patients with oesophageal adenocarcinoma, no differences in patient- or tumour characteristics could provide a rational explanation for the different treatment choices, and the observed difference in allocation to curative treatment remained significant after adjustment for age, year of diagnosis, clinical T and N-stage, tumour location, differentiation and histological subtype. Therefore, other factors must play a role.

For example, unconscious biases might be involved in treatment decisions. Sex/gender stereotyping may affect treatment recommendations, such as a perception of (older) females being more frail and needing protection from aggressive treatments [23,24]. Another example of unconscious bias is the observation that unmarried (oesophageal) cancer patients are less likely to undergo surgery [25–27]. Although generally attributed to patients' preferences, the evidence for this assumption is low [25,28], and the physician's contribution to these decisions has not been elucidated. In fact, humans are prone to stereotypes. Unconscious bias in physicians' attitude towards race and sex/gender are known to affect treatment decisions in various disciplines of medicine [29,30]. In organ transplantation, physicians have been shown to have biases against female patients [31]. Similarly, unconscious bias might as well affect physicians' recommendations to undergo treatment for gastroesophageal cancer and might also affect completion of the diagnostic process, possibly indicated by (significantly) higher percentages of cTx and cNx observed in female patients. As in cardiology, the development of treatment algorithms might reduce the treatment gap between male and female patients

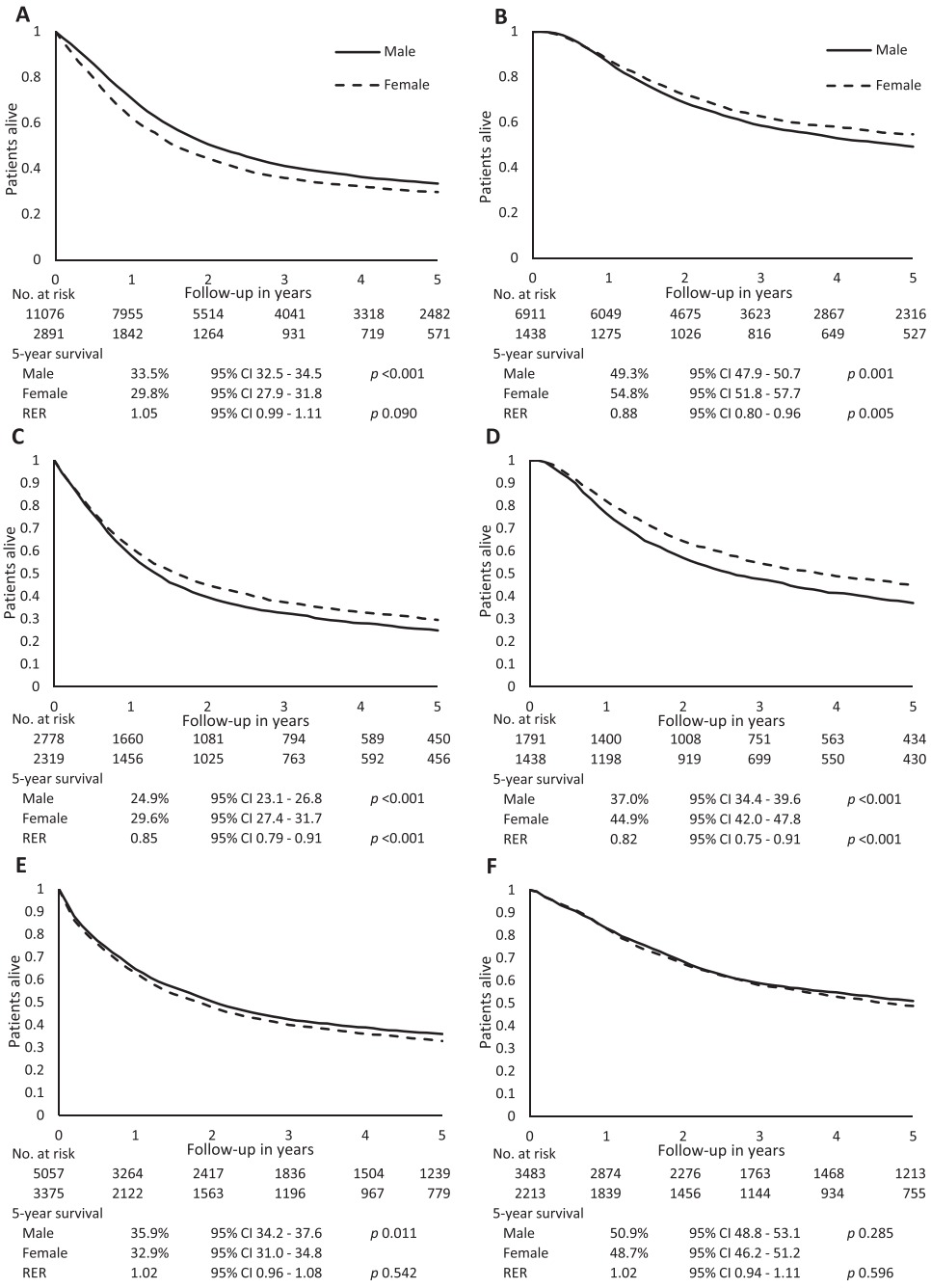

Fig. 2. Relative survival of male and female patients with oesophageal adenocarcinoma, oesophageal squamous cell carcinoma and gastric adenocarcinoma. Survival represented for all included patients with oesophageal adenocarcinoma (A) and those allocated to curative treatment (B). Survival represented for all included patients with oesophageal squamous cell carcinoma (C) and those allocated to curative treatment (D). Survival represented for all included patients with gastric adenocarcinoma (E) and those allocated to curative treatment (F). Solid lines represent relative survival for male, and dashed lines relative survival for female patients.

and could improve results [32]. However, further research is necessary to better understand the relative contribution of both patients' preferences and physicians' unconscious bias on treatment decisions for gastroesophageal cancer.

Unadjusted relative survival differed significantly between sexes of all three groups. Survival of males with oesophageal and gastric adenocarcinoma was superior to females, while survival of males with oesophageal squamous cell carcinoma was inferior to females. Although the under-treatment of females with oesophageal adenocarcinoma might have negatively influenced their survival, they showed similar relative survival to males when adjusted for confounders. In fact, when analysing relative survival only in those with oesophageal adenocarcinoma allocated to curative treatment, female patients showed superior relative survival. The observed treatment disparities, and the

moderate overall curative treatment rate of 63%, point to an opportunity to improve outcomes for gastro-esophageal cancer patients by consequently assuring their allocation to curative treatment whenever possible, irrespective of sex.

Alongside the observed treatment gap, other factors, most of which were accounted for in the adjusted survival analyses, may influence survival for male and female patients differently. More poorly differentiated and diffuse-type tumours were observed in female patients with gastric adenocarcinoma, both increasingly recognised as poor prognostic tumour characteristics [18,33,34]. On the contrary, fewer cardiovascular comorbidities were observed in female patients with gastroesophageal cancer. In addition, the lower clinical T and N-stages observed in female patients with oesophageal adenocarcinoma, result in a more favourable prognostic position [18,33–35] and direct even more attention towards the negative effect of the observed treatment gap.

Female patients with oesophageal squamous cell carcinoma showed superior relative survival, in line with a report describing SEER data [36]. Previous studies showed long-term oncological superiority of surgery compared to definitive chemoradiotherapy for oesophageal squamous cell carcinoma in non-Asian populations [37,38]. The observation that female patients with oesophageal squamous cell carcinomas were more frequently allocated to surgery, could have contributed to their superior survival. Additionally, these females had less cardiovascular and diabetic comorbidities, and more favourable tumour characteristics, with lower clinical T and N-stages, which could also have resulted in a survival benefit [35].

The relative survival of male and female patients was estimated using the Pohar Perme method [17]. This is of great added value given the survival difference between males and females in the general population. However, a limitation is its inability to include additional variables influencing mortality of the reference population, such as medical history.

Other limitations include the absence of additional potentially confounding variables in the NCR data, such as socio-economic status, marital status, ethnicity [39,40], and the presence of comorbidities, of which the latter is routinely collected since 2015 (included as subgroup analysis 2015–2018). The observed differences were addressed as sex differences (male/female) as hospital data were assumed sex assigned at birth, although a mutual influence of both sex-specific and gender-specific effects is most likely. Information regarding discrepancies between advised treatment and actual treatment, and reasons for deviating from guidelines were unfortunately not sufficiently registered in the NCR. In addition, distinction between intentional definitive chemoradiotherapy and neo-adjuvant chemoradiotherapy without subsequent surgery (e.g. due to progression or deterioration of performance status) was not possible.

In conclusion, this study reveals clinically relevant sex disparities in tumour biology, treatment, and survival of patients with potentially curable gastro-esophageal cancer, and illustrates different factors which may contribute to the survival differences. They include differences in tumour characteristics and treatment allocation, of which the latter may be also influenced by physicians' bias. The observation that – among patients with oesophageal adenocarcinoma – a significantly lower percentage of female patients was allocated to curative treatment is most striking and likely to influence their survival negatively. As a result, factors preventing patients from being allocated to curative treatment should be better understood and future practice should assure that curative treatment options are not missed without necessity, irrespective of sex.

Funding

Not applicable.

CRediT authorship contribution statement

Marianne C. Kalff: Conceptualisation; Data curation; Formal analysis; Methodology; Project administration; Software; Writing – original draft, review & editing. Willemieke P.M. Dijksterhuis: Conceptualisation; Data curation; Formal analysis; Methodology; Writing – original draft, review & editing. Anna D. Wagner: Conceptualisation; Methodology; Supervision; Writing – original draft, review & editing. Sabine Oertelt-Prigione: Conceptualisation; Methodology; Supervision; Writing – original draft, review & editing. Rob H.A. Verhoeven: Conceptualisation; Data curation; Formal analysis; Methodology; Software; Supervision; Validation; Writing – original draft, review & editing. Valery E.P.P. Lemmens: Conceptualisation; Methodology; Writing – review & editing. Hanneke W.M. van Laarhoven: Conceptualisation; Methodology; Supervision; Writing – original draft, review & editing. Suzanne S. Gisbertz: Conceptualisation; Methodology; Supervision; Writing – original draft, review & editing. Mark I. van Berge Henegouwen: Conceptualisation; Methodology; Supervision; Writing – original draft, review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Wagner has received consulting fees from BMS, Servier Suisse, Merck, MSD, Bayer, EMD Serono, Lilly, Celgene, Shire, Pierre-Fabre and Pfizer, non-financial support (travel fees) from Sanofi, AstraZeneca, AbbVIE and Ipsen and an educational grant from Roche to EORTC. Verhoeven has received unrestricted

research grants from BMS and Roche. Van Laarhoven has served as a consultant for BMS, Celgene, Lilly, and Nordic and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. Van Berge Henegouwen reports research grants from Stryker, in addition to consulting fees from Medtronic, Mylan BBraun, and Johnson and Johnson. The remaining authors have no conflicts of interest to report.

Acknowledgements

The authors thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry. Furthermore, we thank all participating hospitals in the Netherlands.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.04.002.

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