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Gender differences in tumor characteristics, treatment allocation and survival in stage I–III pancreatic cancer: a nationwide study

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ABSTRACT

Introduction: Sex and gender are modulators of health and disease and may have impact on treatment allocation and survival in patients with cancer. In this study, we analyzed the impact of sex and gender on treatment allocation and overall survival in patients with stage I-III pancreatic cancer.

Methods: Patients with stage I-III pancreatic cancer diagnosed between 2015 and 2020 were selected from the nationwide Netherlands Cancer Registry. Associations between sex and gender and the probability of receiving surgical and/or systemic treatment were examined with multivariable logistic regression analyses. Overall survival was assessed with log rank test and multivariable Cox proportional hazard analysis.

Results: Among 6855 patients, 51.2 % were female. Multivariable logistic regression analyses with adjustment for known confounders (age, performance status, comorbidities, tumor location, tumor stage and previous malignancies) showed that females less often received systemic chemotherapy compared to males (OR 0.799, 95 %CI 0.703–0.909, $p < .001$). No difference was found in the probability for undergoing surgical resection. Furthermore, females had worse overall survival compared to males (median OS 8.5 and 9.2 months respectively, 95 % CI 8.669–9.731).

Conclusion: This nationwide study found that female patients with stage I-III pancreatic cancer significantly less often received systemic treatment and had worse overall survival as compared to males. Disparities in pancreatic cancer care can be decreased by recognizing and resolving potential obstacles or biases in treatment decision-making.

1. Introduction

Pancreatic cancer is the seventh leading cause of cancer-related death with an estimated 466,000 deaths globally in 2020. The incidence is rising with approximately 1 % per year and is higher in males than in females [1–3]. In the Netherlands, the pancreatic carcinoma incidence rate per 100.000 person years (revised ESR) in 2019 was 18.05 for males and 15.21 for females [4]. The significant impact that sex and gender have on health and the course of disease of non-sex-related cancers has been increasingly recognized [5]. A growing body of literature suggests that sexual dimorphisms on multiple levels including genetic, epigenetic, immune-, hormonal and metabolic mechanisms and effects at the cellular and systemic level may have a significant effect on the risk, treatment response and outcome of non-sex related cancers [6]. A recent commission in The Lancet discussed the multiple levels of interaction between gender and cancer [7]. Several other studies reported that females tend to have better response rates and longer survival when undergoing anti-cancer treatments [8–14].

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In addition to potential differences in tumor biology or treatment effects, differences in treatment allocation, potentially influenced by sex and/or socially constructed gender, may impact stage-specific outcomes. Previous studies indicate that older and female patients with pancreatic cancer experience prolonged waiting times for surgical care after symptom detection, and recent research highlights older age, female sex, African Americans, and patients with more comorbidities as significantly prone to non-standard-of-care treatments [15,16].

In the Netherlands, the healthcare system, in theory, permits equal access to care for both male and female patients regardless of income or health status. This is ensured through a system of mandatory health insurance and government regulations. However, in a recent nationwide study of patients with metastatic pancreatic cancer, females less often received systemic treatment while having a better overall survival [17]. Studies which systematically analyze the impact of sex and gender on treatment allocation and survival in patients with localized and locally advanced (stage I-III) pancreatic cancer are currently lacking. The aim of the present study is to compare the impact of the patients' sex and other patient and tumor characteristics on treatment allocation and overall survival between female and male patients with stage I-III pancreatic cancer in a nationwide cohort. The hypothesis that sex and gender have a multidirectional effect on treatment allocation and survival.

2. Methods

2.1. Study design and data collection

This study comprises a nationwide, retrospective, cohort study, using data of the Netherlands Cancer Registry (NCR), a population-based registry containing information about all cancer in the Netherlands (i.e. 17 million people). Cancers are notified to the NCR using the Dutch Nationwide Pathology Databank (PALGA) and the Dutch National Hospital Care Registration (LBZ, hospital discharges and outpatient visits). Data on stage and treatments are routinely obtained by trained registrars of the NCR from electronic patient files in all Dutch hospitals. Annual linkage with the Municipal Administrative Database provided information of the vital status (updated 1 February 2022). Patients $\geq$ 18 years diagnosed between January 1, 2015 and December 31, 2020 with invasive stage I-III (probably) pancreatic adenocarcinoma (PAC) were included (ICD-O-3 topography C25 excluding C25.4, morphology codes in Supplementary materials), also comprising patients without microscopic verification. For a subgroup of patients participating in the prospective Dutch Pancreatic Cancer Project (PACAP) cohort [18], additional clinical data was available on marital status and educational level. All patients included in PACAP provided written informed consent for participation and linkage of their data to the NCR. The study proposal was approved by the privacy board of the NCR and the scientific committee of the Dutch Pancreatic Cancer group [19]. Medical ethical approval was not required. This study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

2.2. Variables and outcomes

NCR data consisted of patient (i.e. sex, age, WHO performance status (PS), comorbidities, previous malignancies), tumor (i.e. location, tumor stage) and treatment characteristics (i.e. type of resection, systemic treatment and radiotherapy). In the NCR, sex is classified at birth as male, female or hermaphrodite. Therefore, in-line with what was measured in this study, and in consideration of the absence of any data on the gender of the included patients, we use the terms sex and male/female when referring to the study participants wherever possible. However, in situations where treatment allocation is discussed, for which not exclusively biological sex, but as well the patients and physicians' attitudes and choices play a role, which may be influenced by gender, we used sex and gender to acknowledge the relevance of these two distinct concepts [21]. Given that none of the patients included in our cohort had gender-affirming surgery, we assume that patients born with male sex were of masculine gender and of female sex feminine gender, respectively. Age was categorized into $\leq$ 59, 60–69, 70–79 and $\geq$ 80 years. Comorbidities were categorized as 0, 1 or $\geq$ 2 comorbidities. Primary tumor location was classified as head, body, tail or other/non specified, according to the ICD-O-3 guidelines. Tumor stage was based on the pathological tumor-node-metastasis classification at the time of registration (UICC TNM 7th edition during 2015–2016, 8th edition during 2017–2020 [22,23], supplemented with clinical TNM. Surgical resection was defined as a resection with or without (neo)adjuvant chemo(radio)therapy. Systemic therapy was started, either (neo)adjuvant (therapy provided in combination with surgical resection) or palliative chemo(radio)therapy (therapy in patients who did not underwent surgical resection). The main reason documented in patient files for receiving best supportive care (BSC) without cancer-directed treatment was categorized into five categories: 1) patient related (previous health status: comorbidity, performance status, other cancer); 2) tumor-related (short life expectancy, expected rapid progression, high tumor load); 3) choice-related (patient's or family's wish or refusal); 4) other; and 5) unknown. The primary outcome parameter was overall survival (OS), defined as the time from diagnosis until death (any cause) or the end of follow-up (emigration or 1 February 2022).

2.3. Statistical methods

Baseline characteristics were obtained using descriptive statistics. Categorical variables were presented as numbers and percentages. Continuous data were presented as median values with interquartile range (IQR). Differences in patient and tumor characteristics between male and female patients were tested for statistical significance using a Chi-square test. The association between the patients' sex and the probability of receiving cancer-directed treatment (surgery, systemic) was determined with multivariable logistic regression analyses with adjustment for age, performance status, comorbidities, tumor location, tumor stage and previous malignancies. Overall survival was determined with Kaplan-Meier analysis with the corresponding Log-Rank test and multivariable Cox proportional hazard analysis with adjustment for age, performance status, comorbidities, tumor location, tumor stage and previous malignancies, and stratified for age (<60 years, 60–69 years, 70–79 years and $\geq$80 years). Subgroup analyses were performed in patients who received cancer-directed treatment (surgery, systemic therapy) and who received BSC. Sensitivity analysis was performed with linked NCR-PACAP data. To address multiple testing, a Bonferroni correction was performed. This correction involves adjusting the significance threshold by dividing it by the number of groups tested in (i.e. overall and four age groups). Consequently, two-sided p-values below 0.01 (0.05/5) were considered statistically significant. Analyses were performed using the latest version of IBM SPSS statistics (IBM Cop Armonk, NY, USA).

3. Results

3.1. Patient characteristics

In total, 6855 patients were included from the NCR of whom 3511 (51.2 %) were females. Females were older compared to males (median 74 years, IQR: 67–81 vs. median 72 years, IQR: 64–79; $p < .001$), had worse performance status ($p < .001$) and less comorbidities ($p < .001$, Table 1).

3.2. Treatment

In total, 2351 patients (34.3 %) underwent surgical resection and 2772 patients (40.4 %) received systemic treatment (1192 patients, 17.5 %: systemic therapy only). Five hundred twenty-two patients (7.6 %)

Table 1
Patient, tumor and treatment characteristics.

		Total (N = 6855)	Males (n = 3344)	Females (n = 3511)	p-value
Age years, median (IQR)		72 (65–80)	72 (64–79)	74 (67–81)	< .001
Age in categories	< 60 years	947 (13.8)	522 (15.6)	425 (12.1)	< .001
	60–69 years	1644 (24.0)	844 (25.2)	800 (22.8)	
	70–79 years	2428 (35.4)	1226 (36.7)	1202 (34.2)	
	≥ 80 years	1836 (26.8)	752 (22.5)	1084 (30.9)	
WHO performance status	WHO 0–1	3199 (47.6)	1649 (50.3)	1550 (44.9)	< .001
	WHO 2	527 (7.8)	252 (7.7)	275 (8.0)	
	WHO 3–4	329 (4.9)	154 (4.7)	175 (5.1)	
	Unknown	2800 (41.6)	1222 (37.3)	1450 (42.0)	
Number of comorbidities	0	2624 (40.8)	1167 (37.4)	1457 (44.1)	< .001
	1	2223 (34.6)	1086 (34.8)	1137 (34.4)	
	≥ 2	1577 (24.5)	868 (27.8)	709 (21.5)	
	Missing	431 (6.3)			
Tumor location	Head of pancreas	5096 (74.4)	2480 (74.2)	2616 (74.5)	0.407
	Body of pancreas	694 (10.1)	340 (10.2)	354 (10.1)	
	Tail of pancreas	485 (7.1)	252 (7.5)	233 (7.1)	
	Other/unspecified	580 (8.4)	271 (8.1)	308 (8.8)	
TNM stage	0-1A–2B	1609 (23.5)	778 (23.3)	831 (23.7)	0.526
	2A–2B	2484 (36.2)	1160 (36.5)	1284 (36.6)	
	3	2159 (31.5)	1055 (31.5)	1104 (31.4)	
	Unknown	603 (8.8)	311 (9.3)	292 (8.3)	
Previous malignancies	No	5324 (77.7)	2585 (77.3)	2739 (78.0)	0.481
	Yes	1531 (22.3)	759 (22.7)	772 (22.0)	
Level of CA19–9, median (IQR)		280 (63–1125)	266 (67–1126)	292 (59–1115)	0.951

IQR, inter quartile range; WHO, world health organization.

received radiotherapy (203 patients, 2.9 %: (neo)adjuvant treatment; 251 patients, 3.7 %: in combination with chemotherapy; 70 patients, 1 %: radiotherapy only). Females less often underwent surgical resection (31.8 % vs. 36.9 %; p < .001) or received systemic treatment (36.5 % vs. 44.5 %; p < .001) compared to males. When stratified by age, only in the oldest age group females had statistically significant lower probability to undergo surgical resection or receive systemic treatment (7.7 % vs. 12.8 %; p < .001 % and 2.7 % vs. 5.1 %; p = 0.008, respectively, Fig. 1). In patients who underwent resection, there was no difference between males and females in the use of neo-adjuvant, adjuvant or both neo- and adjuvant chemo(radio)therapy (p = 0.822). In total, 3242 patients (47.3 %) received BSC (Fig. 2). When stratified by age, females significantly received BSC more often in the oldest age group (82.4 % vs. 89.5 %, p < .001). Similarly, when stratified by tumor stage, females received BSC more often across all stages. The main reason for receiving BSC was patient-related (36 %) for males and choice-related (40 %) for females (p < .001) (Fig. 3). Upon stratifying for age, this difference remained in the oldest age group (≥80 years).

Multivariable logistic regression analyses showed that among all patients, females had a lower probability of receiving systemic treatment compared to males (adjusted odds ratio [OR] 0.799, 95 % Confidence Interval [CI] [0.703–0.909], p < .001), but no difference was found for surgical resection (OR 0.917 [0.803–1.047], p = 0.199) (Table 2). Multivariable logistic regression analyses stratified for age showed that females ≥ 80 years had a lower likelihood of undergoing surgical resection and receiving systemic treatment compared to males.

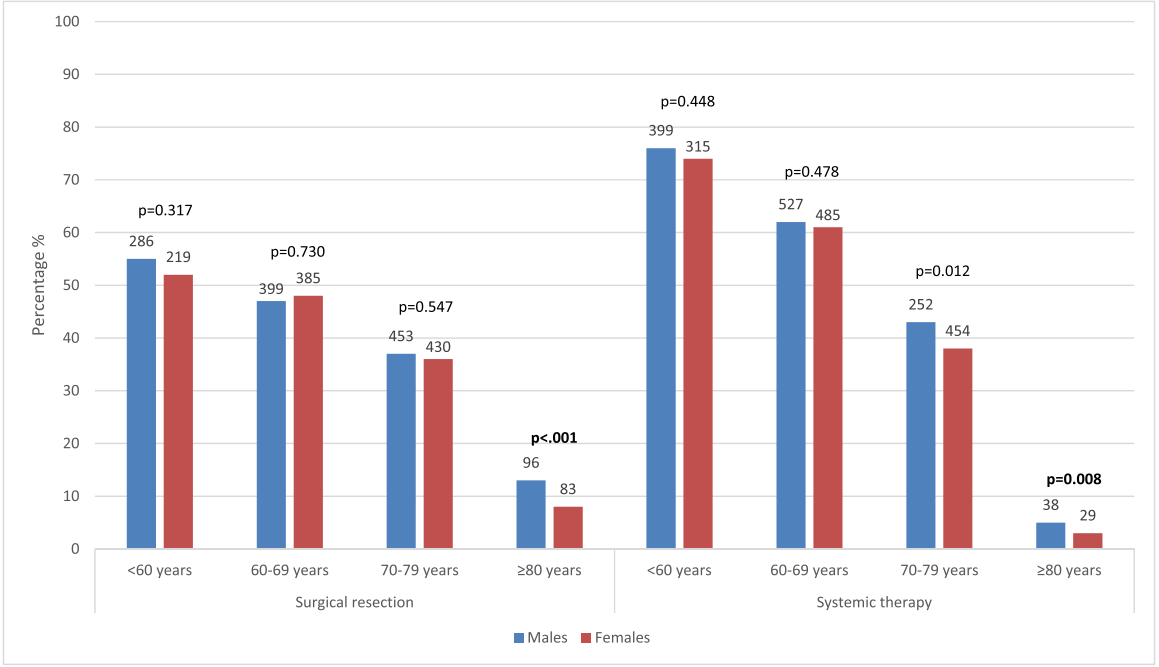

Fig. 1. Treatment allocation stratified by gender and age.

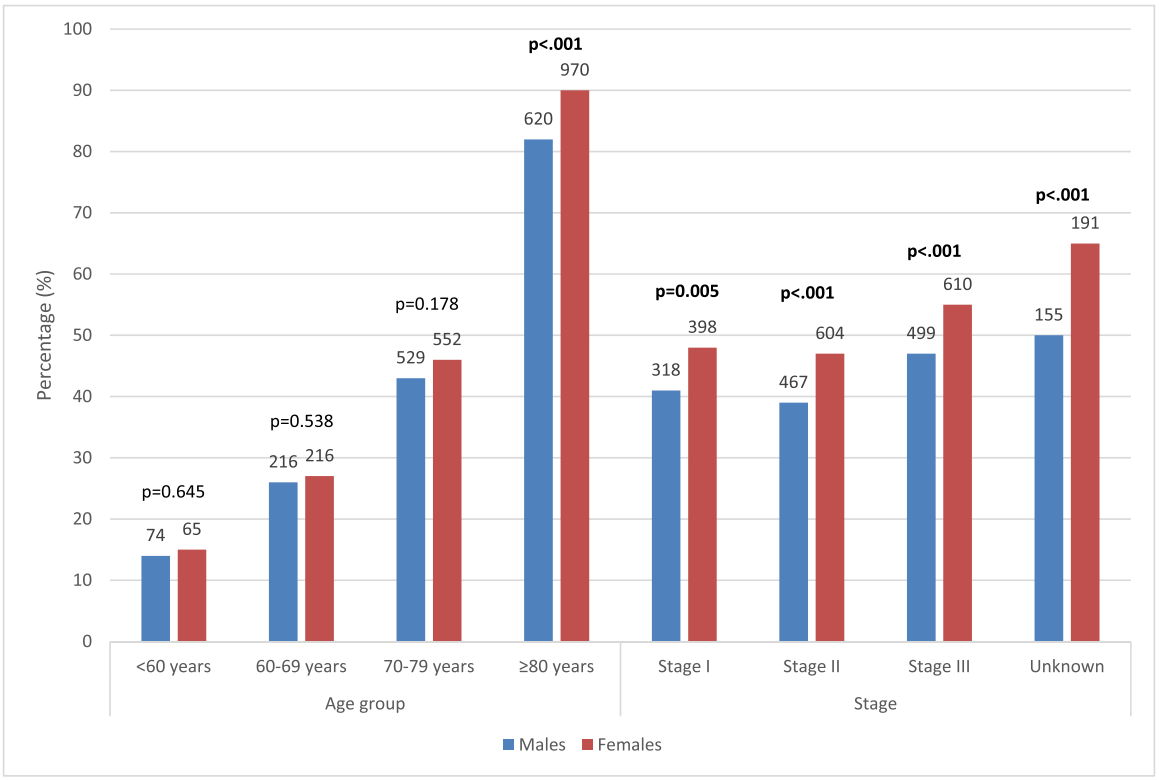

Fig. 2. Best supportive care stratified by age and tumor stage.

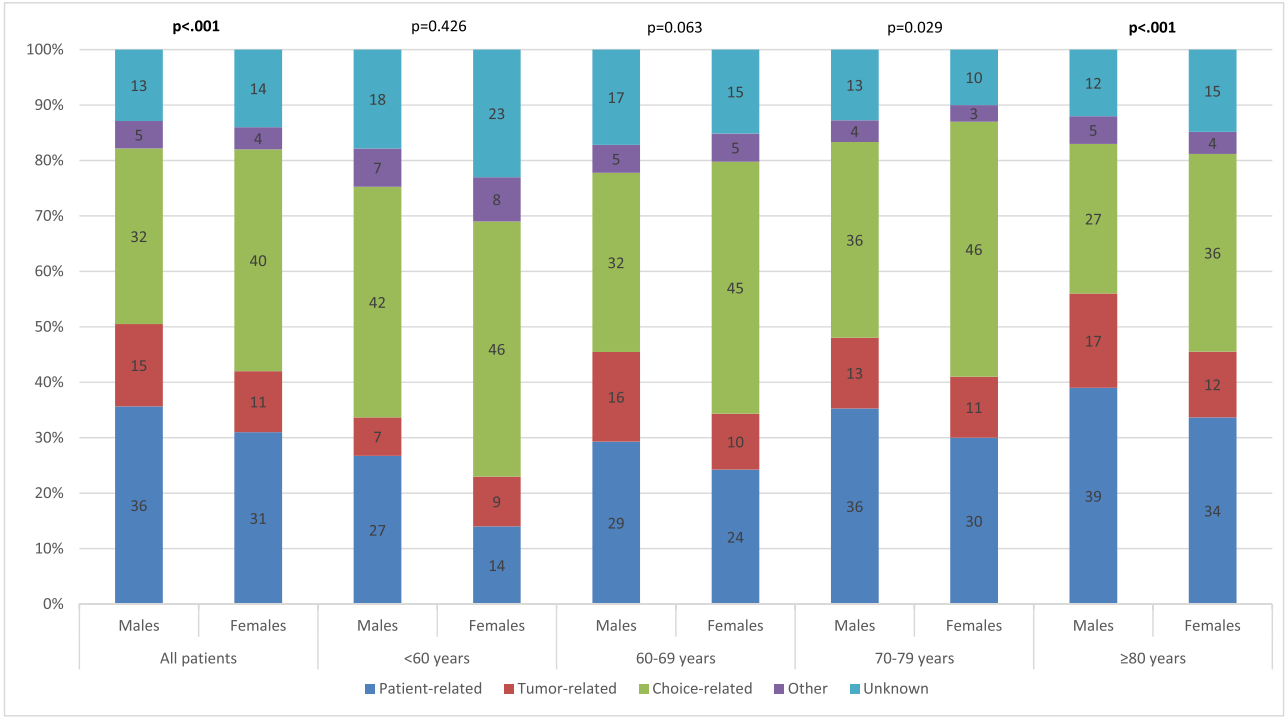

Fig. 3. Reason for best supportive care stratified by gender and age. Patient-related: comorbidity, performance status, other cancer; Tumor-related: short life expectancy, expected rapid progression, high tumor load; Choice-related: patient's or family's wish or refusal.

Additionally, females aged 70–79 demonstrated lower probabilities of receiving systemic treatment (Supplementary Table 1).

3.3. Survival

Median OS was 9.2 months (95 %CI: 8.7–9.7) for males and 8.5 months (95 %CI: 8.0–9.0) for females (p = 0.011, Table 3, Fig. 4A). Subgroup analyses are presented in Table 3 and Fig. 4A–D, but revealed

Table 2
Probability of receiving treatment [females vs. males (ref)].

	All patients		
	OR	95 % CI	p-value
Surgical resection			
Univariable	0.798	0.722–0.882	**< .001**
Multivariable	0.917	0.803–1.047	0.199
Systemic treatment			
Univariable	0.717	0.651–0.790	**< .001**
Multivariable	0.799	0.703–0.909	**< .001**
(Neo)adjuvant			
Univariable	0.768	0.686–0.859	**< .001**
Multivariable	0.900	0.782–1.036	0.144
Palliative			
Univariable	0.795	0.701–0.901	**< .001**
Multivariable	0.836	0.716–0.975	0.023

*Multivariable analyses adjusted for performance status, comorbidities, tumor location, tumor stage and previous malignancies.

no significant differences between males and females. After stratifying for age, no statistically significant differences in 3-year OS were observed (data not shown). In multivariable Cox regression analysis adjusted for patient and tumor characteristics, no significant survival difference was observed (hazard ratio [HR] 0.981 [0.929–1.035], p = 0.477) (Table 3). Furthermore, after additional adjustment for systemic treatment, females had a significantly better survival compared to males (HR 0.932 [0.883–0.984], p = 0.010). Upon stratifying for age, in the multivariable subgroup analysis of patients who underwent surgical resection, females demonstrated significantly better OS compared to males (Supplementary Table 2).

3.4. Sensitivity analysis: PACAP clinical data

The PACAP cohort consisted of 780 patients (11.4 % of the total study cohort), of whom 353 (45.3 %) were females. Median age was 67 years (IQR: 61–73) and females were slightly younger compared to males (67 vs. 68 years, p = 0.479) (Supplementary Table 3). Compared to males, females were more often living alone (24.6 % vs. 12.24 %, p < .001) and had a lower educational level (secondary/higher/university: 65.6 % vs. 52.2 %, p < 001). In this cohort, 498 (63.8 %) patients underwent surgical resection and 661 (84.7 %) patients received systemic treatment. Multivariable logistic regression analysis also including these additional variables showed no statistically significant difference in treatment allocation between males and females (Supplementary Table 4).

4. Discussion

This first nationwide multicenter cohort study investigated the impact of sex and gender on treatment allocation and survival in 6855 patients with stage I-III pancreatic cancer. Overall, females less frequently received systemic treatment compared to males. Differences can particularly be attributed to the oldest age group. Strikingly, nearly half of the patients in this cohort received BSC. The main reason for receiving BSC over curative intent treatment was patient-related for males and choice-related for females. Interestingly, in the BSC group, females demonstrated better overall survival, although not statistically significant. These findings confirm the hypothesis that the patients' sex, and possibly gender have a multidirectional effect on treatment allocation and survival in patients with stage I-III pancreatic cancer.

Since this study is the first in patients with stage I-III pancreatic cancer it is imperative to compare its findings with other patient categories and disease stages. In a Dutch cohort of patients with metastatic pancreatic cancer, females received systemic treatment less often than males [17]. Likewise, in a Dutch cohort of patients diagnosed with potentially curable gastroesophageal cancer, older females were less frequently selected for curative treatment compared to males [24]. This was also evident among females in a separate Dutch cohort of metastatic gastroesophageal cancer patients [25]. These consistent findings across diverse patient populations underscore the urgent need to better understand and address disparities in treatment allocation and outcomes in cancer care based on sex and gender.

Multiple factors may have contributed to the observed discrepancies in treatment allocation. First, females were generally older with likely poorer performance status at baseline. Despite adjustment in multivariable analysis, a notable difference in systemic treatment allocation persisted. However, stratified age analysis highlighted that the significant differences were primarily observed in the oldest age group, suggesting an influence of their older age among females in the cohort. Nevertheless, we must be cautious when interpreting these data as 41.6 % of the performance status data of the patients was unknown.

Table 3
Survival analyzed with Kaplan Meier with Log Rank test and Cox regression analyses [females vs. males (ref)].

	Months, median (95 % CI)			HR	95 % CI	p-value
	Males	Females	p-value			
All patients						
Univariable	9.2 (8.7–9.7)	8.5 (8.0–9.0)	0.011	1.068	1.015–1.124	0.011
Multivariable[a]				0.981	0.929–1.035	0.477
Multivariable[b] SR				0.962	0.911–1.015	0.153
Multivariable[b] ST				0.932	0.883–0.984	**0.010**
Underwent surgical resection						
Univariable	24.1 (22.3–25.9)	23.6 (22.1–25.2)	0.999	1.000	0.906–1.103	0.999
Multivariable[a]				0.983	0.886–1.091	0.746
Received systemic treatment						
Univariable	18.3 (17.2–19.4)	18.9 (17.7–20.0)	0.870	0.993	0.910–1.083	0.871
Multivariable[a]				0.995	0.909–1.088	0.905
(Neo)adjuvant						
Univariable	29.3 (27.0–31.6)	27.6 (25.4–29.7)	0.600	1.034	0.912–1.174	0.600
Multivariable[a]				1.059	0.927–1.209	0.400
Palliative						
Univariable	11.1 (10.4–11.8)	12.1 (11.1–13.0)	0.119	0.910	0.808–1.025	0.120
Multivariable[a]				0.943	0.834–1.066	0.349
Received best supportive care						
Univariable	3.1 (2.8–3.3)	3.3 (3.1–3.6)	0.044	0.931	0.868–0.998	0.045
Multivariable[a]				0.923	0.857–0.995	0.036

SR, surgical resection; ST, systemic treatment.
[a] Adjusted for age, performance status, comorbidities, tumor location, tumor stage and previous malignancies.
[b] Adjusted for age, performance status, comorbidities, tumor location, tumor stage, previous malignancies and treatment.

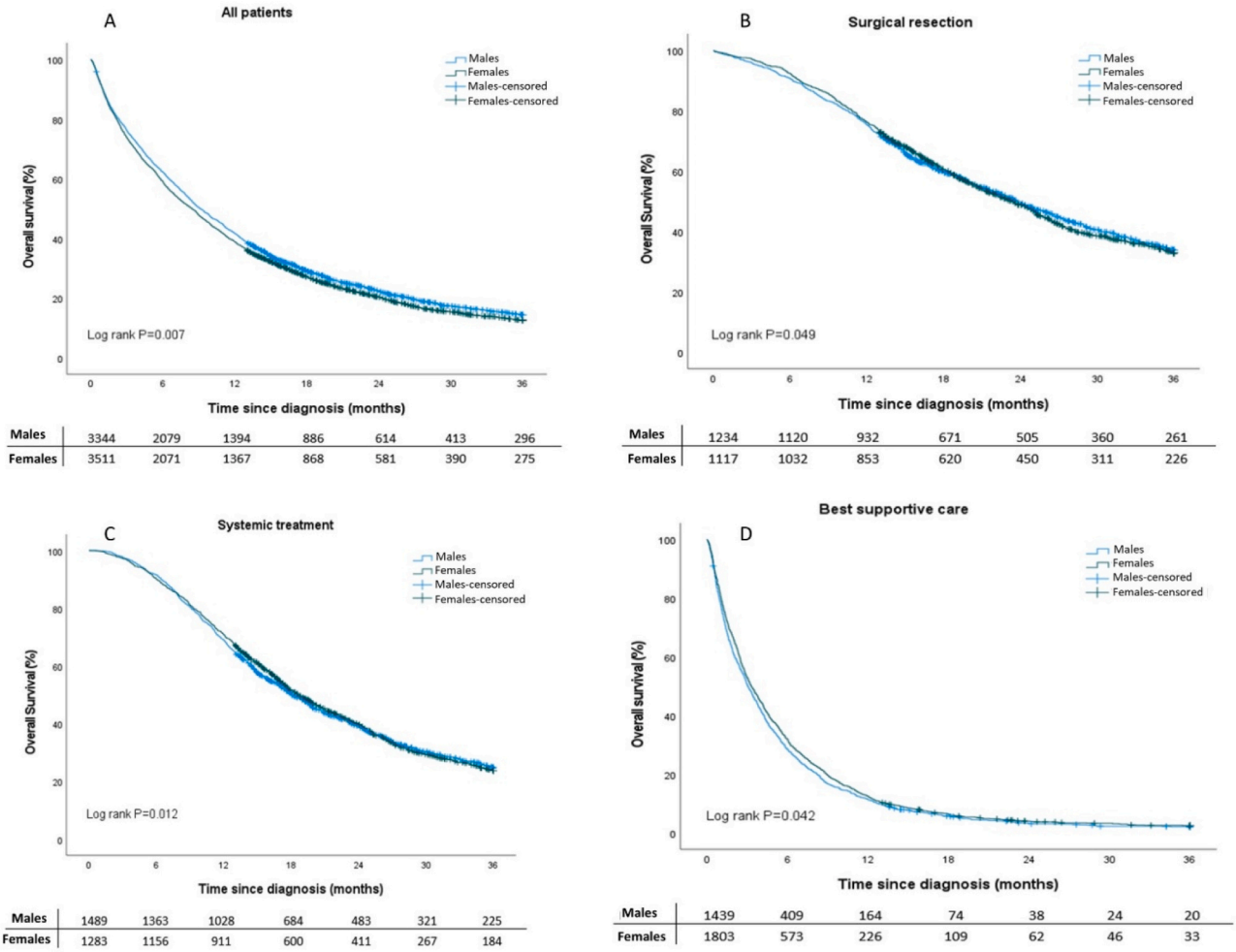

Fig. 4. A-D. Kaplan-Meier curves displaying 3-year overall survival stratified for gender in all patients (A), patients who underwent surgical resection (B), patients who received systemic treatment (C) and best supportive care (D).

Furthermore, females or feminine patients seemingly more often preferred to receive BSC. This finding is in-line with previous observations [17,24,25]. However, it should be noted that this information was derived from caregiver reported phrases in patient files, introducing a significant potential for bias. Patient-caregiver discrepancies regarding treatment preferences, as well as potential caregiver biases or stereotypes, may contribute to variations in treatment decisions. Caregivers may consciously or unconsciously be influenced by their own biases or stereotypes related to gender roles or perceptions, which may impact their treatment recommendations [26–28]. For instance, older females are often stereotypically perceived as frail, leading to a reluctance to perform invasive surgical procedures [29]. Also, marital status appears to influence treatment decisions; unmarried patients face a higher risk of undertreatment and are less likely to receive surgery or radiotherapy despite being clinically indicated [30,31]. In fact, marital status is an independent prognostic factor of survival and married patients have an improved overall survival in several published series [32–34]. Interestingly, in the present study, no association was found between marital status and treatment allocation. This difference might be explained by the presence of other forms of social support, such as family or close friends.

Differences in tumor biology may influence treatment response [6,35–37]. For pancreatic cancer, studies have shown that compared to males, patients of female sex had a significantly higher disease control rate and significantly better overall survival when treated with chemo (radio)therapy [38,39]. In addition, other studies indicate that estrogen, the female sex hormone, may inhibit pancreatic cancer cell growth [40–42]. However, as most females in this population were older and thus most likely postmenopausal, the potential influence of estrogen is likely to be limited. In this patient population, undertreatment may negatively impact females' overall survival. The data demonstrated that (although not all tests statistically significant), in the overall population females have a slightly poorer overall survival. However, in multivariable analysis adjusted for patient and tumor characteristics and systemic treatment, females demonstrated better survival. While treatment may have positively impacted survival as expected, the observed lower rates of allocation to cancer-directed treatment in females may cause a health disparity. However, more important than the sex and/or gender differences in treatment allocation are the overall large percentages of patients (>40 %), even in the youngest subgroup (< 60 years, 14.7 %) who were not treated with surgery in this cohort of patients with non-metastatic pancreatic cancer. Partly because we could not identify patients with locally advanced pancreatic cancer (LAPC) properly and thus also included patients who could not potentially be treated with curative intent. Another possible explanation is that we included patients without microscopic verification and thus a high number of older patients with poor health status and poor survival. In post hoc analysis, it was found that 10 % of all patients died within 30 days after diagnosis (without any cancer-directed treatment), suggesting that a significant proportion may have been in a worse condition despite the absence of metastatic disease. Although the limited information on patient and tumor characteristics available in this study does not allow definitive

conclusions about the reasons for the low treatment rates, these figures are worrisome and deserve further analysis.

The study has several limitations, of which some merit attention. Firstly, the incidence of PAC is underestimated in the NCR. The missing patient group consists especially of elderly patients without pathological confirmation of cancer, with no cancer-directed treatment and with a very poor survival [43]. Therefore, patients were also stratified for receiving cancer-directed treatment. Secondly, the ''main reason for BSC'' and not receiving cancer-directed treatment was extracted retrospectively from the electronic patient file. The information recorded by the caregiver in the file is by definition an interpretation of patient statements or doctor-patient discussions, and thus prone for bias. Moreover, information regarding the gender of the caregivers, a factor that may also influence doctor-patient discussion and treatment allocation, was not assessed. Insufficient data hampers a complete understanding of the underlying factors contributing to the observed treatment allocation disparities. Therefore, future research should aim to collect self-reported data prospectively on the reason for choosing BSC. Furthermore, although we had access to unique data on marital status, other forms of social support were not assessed and therefore not considered.

In conclusion, this nationwide study investigating the impact of sex and gender on treatment allocation and survival in patients with stage I-III pancreatic cancer, found that almost half of the patients received BSC. Of the patients that received cancer-directed treatment, especially older females were less likely to receive systemic treatment compared to males. Our study highlights the general need to address sex- and gender disparities in cancer care, as these exist even in a country of theoretically equal access to care. They are likely to be much more important in countries with other health care systems and overall, more difficult access to care. Caregivers should thoroughly investigate reasons for BSC and strive to ensure equitable access to treatment for all eligible patients, regardless of sex, gender and age, and other causes of disparities. Identifying and addressing potential barriers in access to care or biases in treatment decision-making can help to reduce disparities in pancreatic cancer care.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114117.

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