

World Journal of *Gastrointestinal Oncology*

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MINIREVIEWS

- 1892** Go-Ichi-Ni-San 2: A potential biomarker and therapeutic target in human cancers
Shan DD, Zheng QX, Chen Z
- 1903** Neoadjuvant therapy in resectable pancreatic cancer: A promising curative method to improve prognosis
Zhang HQ, Li J, Tan CL, Chen YH, Zheng ZJ, Liu XB

ORIGINAL ARTICLE

Basic Study

- 1918** Transcriptional factor III A promotes colorectal cancer progression by upregulating cystatin A
Wang J, Tan Y, Jia QY, Tang FQ
- 1933** VCAN, expressed highly in hepatitis B virus-induced hepatocellular carcinoma, is a potential biomarker for immune checkpoint inhibitors
Wang MQ, Li YP, Xu M, Tian Y, Wu Y, Zhang X, Shi JJ, Dang SS, Jia XL
- 1949** Overexpression of ELL-associated factor 2 suppresses invasion, migration, and angiogenesis in colorectal cancer
Feng ML, Wu C, Zhang HJ, Zhou H, Jiao TW, Liu MY, Sun MJ
- 1968** Interleukin-34 promotes the proliferation and epithelial-mesenchymal transition of gastric cancer cells
Li CH, Chen ZM, Chen PF, Meng L, Sui WN, Ying SC, Xu AM, Han WX
- 1981** Cuproptosis-related long non-coding RNAs model that effectively predicts prognosis in hepatocellular carcinoma
Huang EM, Ma N, Ma T, Zhou JY, Yang WS, Liu CX, Hou ZH, Chen S, Zong Z, Zeng B, Li YR, Zhou TC

Retrospective Study

- 2004** Multi-slice spiral computed tomography in differential diagnosis of gastric stromal tumors and benign gastric polyps, and gastric stromal tumor risk stratification assessment
Li XL, Han PF, Wang W, Shao LW, Wang YW
- 2014** Predictive value of a serum tumor biomarkers scoring system for clinical stage II/III rectal cancer with neoadjuvant chemoradiotherapy
Zhao JY, Tang QQ, Luo YT, Wang SM, Zhu XR, Wang XY

Observational Study

- 2025** Role of sex on psychological distress, quality of life, and coping of patients with advanced colorectal and non-colorectal cancer
Pacheco-Barcia V, Gomez D, Obispo B, Mihic Gongora L, Hernandez San Gil R, Cruz-Castellanos P, Gil-Raga M, Villalba V, Ghanem I, Jimenez-Fonseca P, Calderon C

- 2038** Droplet digital polymerase chain reaction assay for methylated ring finger protein 180 in gastric cancer

Guo GH, Xie YB, Jiang T, An Y

Prospective Study

- 2048** Long-term follow-up of HER2 overexpression in patients with rectal cancer after preoperative radiotherapy: A prospective cohort study

Chen N, Li CL, Peng YF, Yao YF

META-ANALYSIS

- 2061** Combining of chemotherapy with targeted therapy for advanced biliary tract cancer: A systematic review and meta-analysis

Bai XS, Zhou SN, Jin YQ, He XD

CASE REPORT

- 2077** Disseminated carcinomatosis of the bone marrow caused by granulocyte colony-stimulating factor: A case report and review of literature

Fujita K, Okubo A, Nakamura T, Takeuchi N

CORRECTION

- 2085** Correction to "Genome-wide CRISPR-Cas9 screening identifies that hypoxia-inducible factor-1a-induced CBX8 transcription promotes pancreatic cancer progression *via* IRS1/AKT axis"

Teng BW, Zhang KD, Yang YH, Guo ZY, Chen WW, Qiu ZJ

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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Observational Study

Role of sex on psychological distress, quality of life, and coping of patients with advanced colorectal and non-colorectal cancer

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Abstract

BACKGROUND

Patients with advanced gastrointestinal cancer must cope with the negative effects of cancer and complications.

AIM

To evaluate psychological distress, quality of life, and coping strategies in patients with advanced colorectal cancer compared to non-colorectal cancer based on sex.

METHODS

A prospective, transversal, multicenter study was conducted in 203 patients; 101 (50%) had a colorectal and 102 (50%) had digestive, non-colorectal advanced cancer. Participants completed questionnaires evaluating psychological distress (Brief Symptom Inventory-18), quality of life (EORTC QLQ-C30), and coping strategies (Mini-Mental Adjustment to Cancer) before starting systemic cancer treatment.

RESULTS

The study included 42.4% women. Women exhibited more depressive symptoms, anxiety, functional limitations, and anxious preoccupation than men. Patients with non-colorectal digestive cancer and women showed more somatization and physical symptoms than subjects with colorectal cancer and men. Men with colorectal cancer reported the best health status.

CONCLUSION

The degree of disease acceptance in gastrointestinal malignancies may depend on sex and location of the primary digestive neoplasm. Future interventions should specifically address sex and tumor site differences in individuals with advanced digestive cancer.

Key Words: Anxiety; Colorectal cancer; Depression; Gastrointestinal cancer; Sex

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Core Tip: Patients with advanced gastrointestinal cancer must cope with the negative effects of cancer and complications. However, data on psychological distress, quality of life, and coping strategies in patients with advanced colorectal cancer compared to non-colorectal cancer based on sex is lacking. This was a multicenter study conducted in 203 patients that completed questionnaires evaluating psychological distress, quality of life, and coping strategies before starting systemic cancer treatment. Based on these data, the degree of disease acceptance in gastrointestinal malignancies may depend on sex and location of the primary digestive neoplasm.

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INTRODUCTION

Background

Gastrointestinal cancers are among the most prevalent both worldwide and in Spain[1,2]. Colorectal cancer is the most frequent neoplasm in Spain in both sexes[2] with close to 65% survival at 5 years, although this rate declines in metastatic stages and in unresectable cancers[3]. The most common non-colorectal digestive cancers are pancreatic, gastric, and hepatocellular carcinoma, which are associated with a worse prognosis than colorectal cancer with a 5-year survival rate of < 5 years in the advanced scenery.

Individuals with advanced gastrointestinal cancer must face the negative effects (pain, malnutrition) and tumor-related complications (intestinal obstruction or hemorrhage). Advances made in recent years in anticancer treatment modalities to fight these cancers have managed to extend overall survival (OS) and control physical symptoms. Meanwhile, emotional distress in these cases has been correlated with diminished quality of life and with a negative impact on treatment compliance[4,5] and on oncological outcomes[6,7]. Furthermore, psychological suffering can aggravate vomiting and other side effects of systemic antineoplastic treatment and of the cancer itself[8-10]. For its part, the type of cancer and

surgery can affect the emotional distress and quality of life in individuals with a gastrointestinal neoplasm. In a Spanish prospective series, people with pancreatic-biliary cancer expressed more somatic complaints, depression, and anguish than those with colorectal cancer, whereas participants with gastroesophageal neoplasms suffered higher rates of depression, psychological distress, and hopelessness than those with colorectal cancer[11].

The relevance of contemplating sex and its influence on study outcomes is stated in the SAGER guidelines (Sex and Gender Equity in Research) designed to inform authors in preparing their manuscripts[12,13]. Sex, understood as going beyond its biological concept (chromosomal assignment) and founded on the basis of the roles and relationships established throughout the person's lifetime, is a sociodemographic variable that can give rise to differences in the evolution as well as the clinical and psychological aspects of cancer[14]. This is particularly relevant in cancers such as digestive neoplasms that have a higher incidence in men and in which there may be an underrepresentation of women who may experience a different evolution and coping style that call for specific approaches[15,16].

In the case of advanced gastroesophageal tumors, women have been seen to be less likely to receive systemic treatment with chemotherapy when the histology is adenocarcinoma with no difference among patients with squamous cell tumors. This impacts survival, in as much as men display increased OS in esophageal adenocarcinomas with no differences in survival rates by sex in cases of esophageal squamous cell carcinoma in some studies, while others attribute a higher incidence of cancers having an unfavorable and more aggressive histology among women[17-20]. As for pancreatic cancer, differences in the efficacy and toxicity of chemotherapy have been observed between men and women[21,22]. Women receiving FOLFIRINOX are older at the time of diagnosis and exhibit higher OS rates than men, despite requiring an earlier dose decrease due to early toxicity, which is possibly attributable to worse tolerance to systemic treatment. No study has investigated whether this poor tolerance is influenced by psychological factors[23].

Other clinical trials have revealed a trend toward higher progression-free survival and OS in women, although these findings were not statistically significant[23,24]. In individuals with localized colorectal cancer, a large-scale German study examined sex and found that the women were older than the men, had a more advanced stage at the time of diagnosis, and received a lower dose intensity of chemotherapy, despite having greater disease-free survival and OS[25]. The more advanced stage of disease among women might be due to the greater acceptance of endoscopic screening by men, among other reasons[26-28]. Therefore, women with digestive cancers are usually diagnosed at older ages than men and regardless of a lower rate of chemotherapy administration and greater toxicity in general, they display better survival rates without any study having been conducted to probe the cause behind such differences and whether psychological factors may play a role.

Three key psychological factors in cancer patients are psychological distress[6], quality of life[29-31], and coping[32,33]. Earlier studies have reported that up to 54% of people with colorectal cancer suffer anxiety and 27% suffer from depression[34-36] with higher incidences among women[37]. One study performed in subjects with gastrointestinal cancer in Spain reported that men with colorectal cancer have a worse quality of life, associated with physical performance and emotional and cognitive functioning[38]. Oppegaard *et al*[39] carried out a descriptive study focusing on sex differences in coping strategies and noted that women scored higher on positive reframing, religion, and instrumental support, while men scored higher for mood. Nevertheless, the question has never been studied as to whether these differences are due to the person's biological sex or if there are sex characteristics (acquired) or other biopsychosocial variables that modulate coping, emotional stress, and quality of life.

Objectives

The aim of our study was to analyze whether there were differences between colorectal and non-colorectal digestive cancer in sociodemographic and/or clinical conditions and compared mental health status, quality of life, and coping between colorectal and non-colorectal digestive cancer patients depending on sex. We believe that these results may be useful to design specific preventive programs for each group.

MATERIALS AND METHODS

Study design

NEOetic is a multi-institutional (22 Spanish hospitals), prospective, observational study and is part of a cancer patient research program funded by the Spanish Society of Medical Oncology. The study was approved by the Ethics Committee of each institution and by the Spanish Agency of Medicines and Medical Devices (identification code: ES14042015).

Participants

The study was a cohort study, and participants were 18 years of age or older with unresectable, locally advanced, or metastatic cancer and were candidates for systemic antineoplastic treatment. For the purposes of this analysis, subjects with digestive cancers were regarded and grouped as being colorectal

(colon and rectum) and non-colorectal digestive (esophagus, stomach, pancreas, biliary tract, liver, anal canal).

Setting

Patients were invited to participate in the study at the first visit with the oncologist where they were informed of the treatment alternatives for their cancer. Participation was voluntary, anonymous, and did not affect patient care. All patients included in the study signed an informed consent for their inclusion. The study was undertaken according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines[40].

We screened 245 patients; 203 were eligible for this analysis and 42 were excluded (10 failed to meet the inclusion criteria, 13 met the exclusion criteria, and 19 had incomplete data at the time of analysis).

Variables and measures

Demographic and clinical data (age, sex, marital status, educational level, employment status, tumor location and stage, and treatment) were obtained and updated by the medical oncologist directly from the patients and from their records. The oncologist explained the questionnaires to the participant who completed them at home during the 1st month following diagnosis of advanced disease and prior to starting cancer treatment. The questionnaires used are validated and are described below.

Data sources/measurement

The Brief Symptom Inventory consists of 18 items divided into three dimensions (somatization, depression, and anxiety) as well as a total score, the Global Severity Index, which summarizes the respondent's overall emotional adjustment or psychological distress over the last 7 d[41]. Each item is rated on a 5-point Likert scale and Cronbach's alpha ranged between 0.81 and 0.90[42].

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) contains 30 items comprising four subscales: functioning, symptoms, health status, and global quality of life[43]. The response choices range from 1 (not at all) to 4 (very much), except for the health status scale, where responses range from 1 (very poor) to 7 (excellent). All scale scores are linearly transformed into a 0-100 scale. Higher scores on the functioning scales and global quality of life scale represent a higher level of functioning or quality of life. For the symptom scales, the higher the score, the greater the symptom burden. In this sample $\alpha = 0.85$ [44].

The Mini-Mental Adjustment to Cancer is a 29-item scale that assesses cancer-specific coping strategies as being adaptive (cognitive avoidance, fighting spirit, and fatalism) or maladaptive (helplessness and anxious preoccupation)[45]. When studying the psychometric properties of the Spanish translation of the scale, a 4-factor structure is found and used in this study; it includes helplessness, anxious preoccupation, and cognitive avoidance as well as a new subscale, positive attitude, that combines fighting spirit and fatalism[46]. Each item is rated on a 4-point Likert scale and Cronbach's alpha coefficients for each domain ranged from 0.62-0.88[46].

Statistical analysis

Descriptive statistics were used for demographic data and survey responses. Absolute frequencies were used for categorical data and mean and standard deviation for quantitative data. Additional descriptive analyses were performed, grouping patients by cancer type. We conducted bivariate χ^2 and t tests to examine differences between colorectal cancer and non-colorectal digestive cancer patients in terms of sociodemographic, clinical, and psychological characteristics.

A general linear model was created for each dependent variable (psychological distress, quality of life, and coping) with the different cancer type (colorectal and non-colorectal digestive); the effect of sex was probed, in addition to the interaction effect between sex and cancer type. All post-hoc tests were subjected to Bonferroni correction. All analyses were complemented with the corresponding effect size statistic. Reference values were established as 0.01, 0.06, and > 0.14 for small, medium, and large sizes, respectively, for the partial eta-square (η_p^2). Statistics were generated using a standard statistical software package IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Participants

The study admitted 203 patients recruited during 2021. There were 101 (50%) colorectal cancer sufferers, and 102 (50%) had a non-colorectal digestive malignance.

Descriptive data

The sociodemographic and clinical characteristics of both groups are displayed in Table 1. Of the total study population, 115 (56.7%) were men and 88 (43.3%) were women. The percentage of men *vs* women

Table 1 Patients' baseline characteristics, *n* = 203

Characteristic	Total		Colorectal, <i>n</i> = 101		Non-colorectal digestive cancer, <i>n</i> = 102		<i>P</i> value	λ
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
Sex							0.622	0.026
Men	115	56.7	60	59.4	55	53.9		
Women	88	43.3	41	40.6	47	46.1		
Age							0.028	0.081
≤ 65 yr	85	41.9	50	49.5	35	34.3		
> 65 yr	118	59.1	51	50.5	67	65.7		
Number of Elixhauser comorbidities (%)							0.344	0.033
≤ 4	81	39.9	37	36.6	44	43.1		
> 4	122	60.1	64	63.4	58	56.9		
ECOG							0.029	0.086
0	56	27.6	35	34.7	21	20.6		
1	138	68.0	62	61.4	76	74.5		
2	9	4.4	4	4.0	5	4.9		
Marital status							0.883	0.001
Married/partnered	167	86.6	87	86.2	92	87.0		
Not partnered	36	13.4	24	13.8	24	13.0		
Children							0.370	0.029
Do not have children	35	17.2	15	14.9	20	19.6		
Have children	168	82.8	86	85.1	82	81.4		
Educational level							0.521	0.010
Primary	112	55.2	58	57.4	54	52.9		
High school or higher	91	44.8	43	42.6	48	47.1		
Histology							0.001	0.129
Adenocarcinoma	180	88.7	98	97.0	82	80.4		
Others	23	11.3	3	3.0	20	19.6		
Metastasis							0.001	0.218
Locally advanced	32	15.8	1	1.0	31	30.4		
Metastatic disease	171	84.2	100	99.0	71	69.6		
Biomarker							0.001	0.196
No	161	79.3	66	65.3	95	93.1		
Yes	42	20.7	35	34.7	7	6.9		
Estimated survival							0.001	0.776
< 18 mo	108	53.2	14	13.9	94	92.2		
≥ 18 mo	95	4.8	87	86.1	8	7.8		
Treatment modality							0.001	0.339
Chemotherapy	139	68.5	45	44.6	94	92.2		
Combined	64	31.5	56	54.4	8	7.8		

ECOG: Eastern Cooperative Oncology Group.

in those with colorectal and non-colorectal digestive tract malignancies was 60 (59.4%) to 41 (40.6%) and 55 (53.9%) to 47 (46.1%), respectively. The median age was 65.7 years (range: 34–88, standard deviation = 9.6).

Outcome data

Colorectal cancer patients tended to be younger than those with non-colorectal, gastrointestinal cancer ($P = 0.028$, $\lambda = 0.081$). Additionally, colorectal cancer patients had a better Eastern Cooperative Oncology Group performance status than non-colorectal digestive cancer patients, 34.7% *vs* 20.6%, respectively ($P = 0.029$, $\lambda = 0.086$). Most participants were married or partnered (86.6%) with children (82.2%) and had a primary level of education (55.2%). All subjects were either retired or unemployed.

Of the patients with non-colorectal digestive cancer, the most common primary tumor site was the pancreas (54.9%, $n = 56$), followed by the stomach (22.5%, $n = 23$), esophagus (8.8%, $n = 9$), biliary tract (6.9%, $n = 7$), liver (4.9%, $n = 5$), and anus (2%, $n = 2$). Individuals with colorectal cancer were diagnosed with metastatic disease more often than unresectable, locally advanced cancer ($P = 0.001$, $\lambda = 0.218$); biomarkers to guide treatment options were more often available in these subjects ($P = 0.001$, $\lambda = 0.196$), and most received combined, systemic treatment with chemotherapy and a targeted drug ($P = 0.001$, $\lambda = 0.339$). The estimated 18-mo survival rate was 86.1% in colorectal cancer patients compared to 7.8% in patients with non-colorectal digestive cancer ($P = 0.001$, $\lambda = 0.776$).

Psychological distress

The general linear model results indicated significant differences in the levels of somatization ($F_{(1,202)} = 5.0244$, $P = 0.026$, $\eta^2_p = 0.025$), depression ($F_{(1,202)} = 15.747$, $P = 0.001$, $\eta^2_p = 0.073$), and anxiety ($F_{(1,202)} = 19.697$, $P = 0.001$, $\eta^2_p = 0.090$). The post hoc test showed significant differences in mean scores by sex, *i.e.* women manifested more depressive symptoms ($\eta^2_p = 0.073$) and anxiety ($\eta^2_p = 0.061$) than men. Patients with non-colorectal digestive cancer ($\eta^2_p = 0.020$) and women ($\eta^2_p = 0.025$) displayed more somatization than subjects with colorectal cancer and men. The model parameters and significant categories of each predicted variable are presented in Table 2 and Figure 1.

Quality of life

Again, the general linear model results revealed significant differences on the functional ($F_{(1,202)} = 19.697$, $P = 0.001$, $\eta^2_p = 0.090$) and symptom ($F_{(1,202)} = 8.154$, $P = 0.005$, $\eta^2_p = 0.039$) scales. The post hoc test indicated that women presented more functional limitations than men ($\eta^2_p = 0.090$). Participants with non-colorectal, gastrointestinal cancer ($\eta^2_p = 0.030$) and women ($\eta^2_p = 0.039$) had more symptoms than those with colorectal cancer and who were men. The results revealed a significant effect of sex on symptom control. A statistically significant association between tumor type and sex in health status levels was observed, and men with colorectal cancer reported the best health status ($\eta^2_p = 0.025$) (Table 2 and Figure 1).

Coping strategies

In coping strategies, positive attitude and cognitive avoidance were the most widely used strategies by all patients included, and hopelessness was the least used (Table 2 and Figure 2). Differences were observed in the estimated mean scores for anxious preoccupation ($F_{(1,202)} = 6.722$, $P = 0.010$, $\eta^2_p = 0.033$) and positive attitude ($F_{(1,202)} = 4.389$, $P = 0.037$, $\eta^2_p = 0.022$). Post hoc tests showed that women presented more anxious preoccupation ($\eta^2_p = 0.033$) and less positive attitude ($\eta^2_p = 0.022$) than men.

DISCUSSION

Key results

In this study we analyzed the differences in emotional distress, quality of life, and coping by digestive tumor type and sex. Women displayed more depressive symptoms, anxiety, functional limitations, and anxious preoccupation than men. Individuals with non-colorectal digestive cancer and women exhibited more physical symptoms and somatization than patients with colorectal cancer and men, whereas men with colorectal cancer reported better health status. By type of cancer, participants with colorectal cancer are younger, treatment is more often adjusted by biomarkers, they receive more combined chemotherapy and a biological agent, their estimated survival is higher, and they have better general status at the time of diagnosis than subjects with non-colorectal digestive cancer.

Interpretation

As for coping strategy, women exhibited more anxious preoccupation and men exhibited positive attitude. These results might explain why women present more symptoms and worse functional status than men. Oppegaard *et al*[39] observed that women scored higher on denial, which has previously been associated with worse oncological outcomes, given the delay in seeking care, which in turn entails a diagnosis made at more advanced stages, with worse general status, and lower survival rates[47].

Table 2 Univariate general linear model for predicting psychological distress, quality of life, and coping strategies by tumor and sex

Scales	Colorectal cancer, <i>n</i> = 101		Non-colorectal digestive cancer, <i>n</i> = 102		ANOVA results, <i>F</i>		
	Men, mean (SD)	Women, mean (SD)	Men, mean (SD)	Women, mean (SD)	Tumor × sex	Tumor	Sex
Psych. distress (BSI) ¹							
Somatization	62.0 (6.3)	64.1 (8.0)	63.9 (6.7)	66.3 (8.1)	0.021	3.963	5.044
Depression	60.3 (6.6)	65.0 (6.6)	60.1 (5.5)	62.9 (7.5)	0.923	1.423	15.747
Anxiety	61.9 (7.8)	65.8 (8.3)	61.9 (6.8)	66.0 (8.3)	0.030	0.011	12.818
Quality of life (EORTC-QLQ-C30) ²							
Functional scale	79.6 (17.4)	62.3 (23.0)	70.8 (22.6)	60.8 (24.0)	1.427	2.781	19.697
Symptom scale	24.4 (22.9)	29.8 (19.4)	28.6 (17.8)	40.0 (22.1)	1.044	6.067	8.154
Health status scale	67.6 (22.6)	53.7 (27.9)	51.9 (23.5)	55.1 (32.8)	5.185	3.547	2.059
Coping with cancer (M-MAC) ²							
Helplessness	24.0 (22.9)	25.0 (21.9)	25.9 (22.8)	28.6 (25.6)	0.069	0.696	0.288
Anxious preoccupation	46.2 (24.4)	51.4 (18.8)	43.8 (19.0)	54.4 (23.6)	0.800	0.008	6.722
Positive attitude	83.4 (16.5)	76.8 (18.1)	79.2 (15.8)	74.9 (22.9)	0.186	1.364	4.389
Cognitive avoidance	66.6 (27.3)	60.6 (21.6)	64.3 (24.5)	60.2 (27.1)	0.036	0.192	1.758

¹T score.²Scale from 0 to 100.

ANOVA: Analysis of variance; BSI: Brief Symptom Inventory; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; M-MAC: Mini-Mental Adjustment to Cancer; SD: Standard deviation.

Furthermore, Oppegard *et al*[39] demonstrated that women scored higher on self-distraction as a detachment coping strategy, which had already been associated with a decreased sense of meaning of life in both women and men with cancer[48].

In our study, women suffered more psychological distress in the form of anxiety and depression compared to men, and women with non-colorectal digestive cancer displayed more somatization than men and than women with colorectal cancer. Most studies have encountered similar results. Aminisani *et al*[49] evaluated psychological distress in a cohort of 303 colorectal cancer survivors from Iran. One-third of the study population presented depression and more than half of them exhibited anxiety; both conditions were more common among women than men. Sex differences in psychological distress have been reported by Gonzalez-Saenz de Tejada *et al*[50], revealing that men had less depression and anxiety. In The Netherlands, Braamse *et al*[51] found that women had higher levels of depression but not anxiety. Mols *et al*[30] observed that men suffered less anxiety and depression over time. Linden *et al* [52] examined anxiety and depression in a large cohort of oncological patients (*n* = 10153), including breast and gynecological cancer, and detected that women had more anxiety and depression than men, similar to our findings. Women have already been reported to exhibit greater acceptance of cancer of the reproductive organs compared to patients with gastrointestinal neoplasms[53]. Shapiro *et al*[54] published similar levels of depressive symptoms in individuals of both sexes with advanced cancer, and Goldzweig *et al*[15], in a cohort of 339 subjects with stage I-III colorectal cancer, reported greater psychological distress and impotence in men than in women, without knowing the reason for this disparity with respect to other studies. One of the most relevant points of our work is that it focuses specifically on gastrointestinal neoplasms and reveals that not only women (in general) but specifically those with non-colorectal digestive cancer are the ones who exhibit greater psychological distress.

Trinquinato *et al*[55] appraised quality of life in Brazilian patients with colorectal cancer undergoing chemotherapy and reported that chemotherapy negatively impacted men and women differentially. In their study, they found that cognitive function led to worse quality of life in men compared to women and that symptoms varied according to sex. Men had worse quality of life, due to sexual impotence and fecal incontinence, while in women, poor quality of life was associated with body image, abdominal pain, and dry mouth. Similarly, the women in our study had more functional limitations and more symptoms compared to men, with the corresponding impact of sex on the type of symptoms.

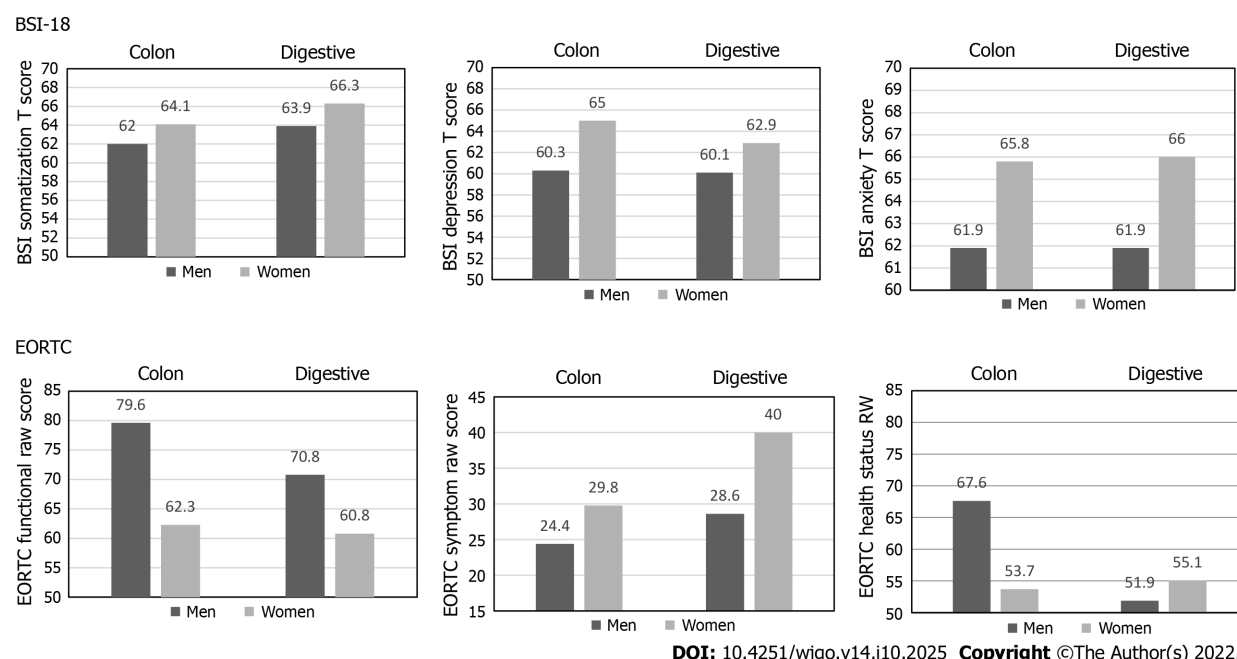


Figure 1 Scores obtained on the Brief Symptom Inventory-18, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for men vs women and for patients with colorectal vs digestive (non-colorectal) cancer. BSI: Brief Symptom Inventory; EORTC: European Organization for Research and Treatment of Cancer; RW: Raw.

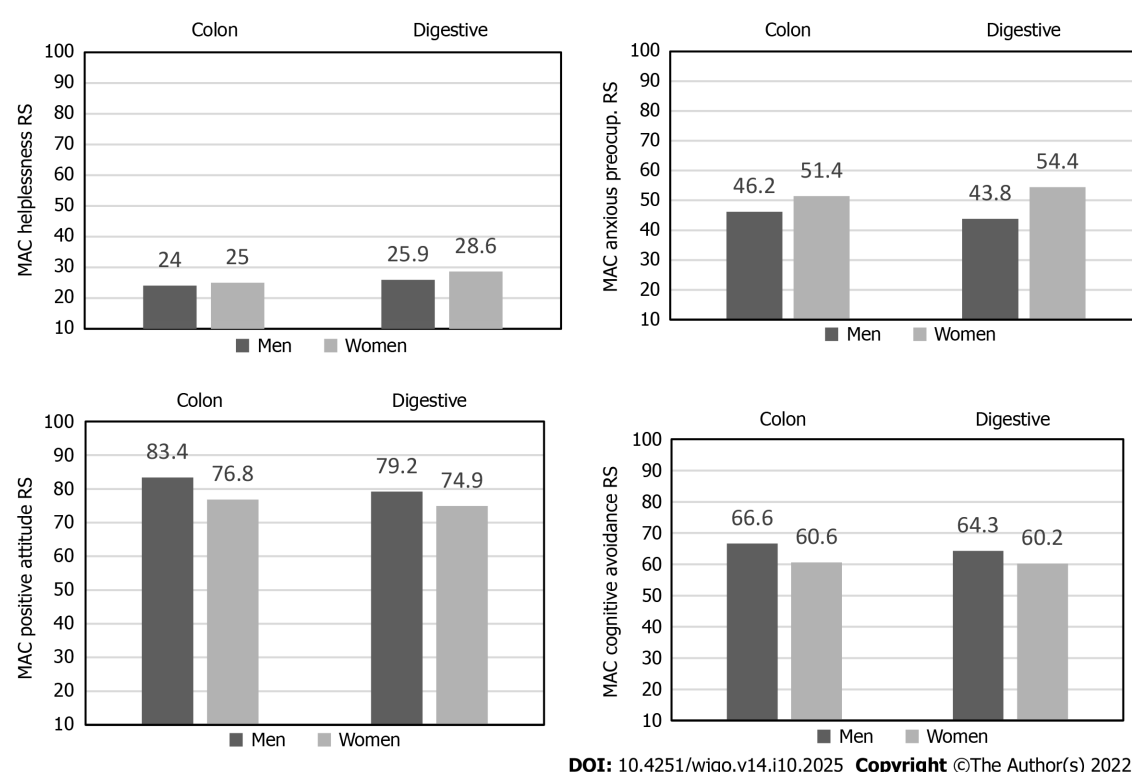


Figure 2 Scores obtained on the Mini-Mental Adjustment to Cancer scales for men vs women and for patients with colorectal vs digestive (non-colorectal) cancer. MAC: Mini-Mental Adjustment to Cancer; RS: Raw score.

Individuals with advanced colorectal cancer have a better prognosis than those with non-colorectal digestive cancer[2], and better patient-perceived quality of life might correlate with better acceptance of the disease, given the better prognosis and the presence of fewer symptoms. In our study, the participants with non-colorectal digestive cancers had more somatization symptoms than those with colorectal cancer, which may be attributable to the unfavorable prognosis. In a cohort of 378 individuals with colorectal, gastric, and pancreatic cancer, Czerw *et al*[56] reported that those with colorectal cancer

displayed an active behavior coping strategy compared to the subjects with non-colorectal cancer, who demonstrated a maladaptive coping behavior. In contrast, in our series, the strategies most widely used by the participants with advanced digestive tract cancers were positive attitude and cognitive avoidance, although the non-colorectal cancer group exhibited higher levels of helplessness, in line with outcomes observed by Czerw *et al*[56] in pancreatic cancer.

Colorectal cancer has the best prognosis among the main digestive tumors. However, neither the causes nor the prognostic differences in digestive cancers according to sex are well established. Colorectal cancer in women is located more often in the right colon than in men, which is a location associated with worse prognosis[57-59]. That being said, Schmuck *et al*[25] observed that the women included in a study of a cohort of people over 50 years of age had a better OS than men. The authors consider that these outcomes may have to do with the protective effect of women hormones against colorectal cancer, although there may be other causes for these prognostic disparities across sexes[60, 61]. In a sample of 13391 patients from a Norwegian cancer registry, men with gastroesophageal adenocarcinoma were more often assigned to potentially curative treatment compared to the women and had higher 5-year survival rates[16]. Kim *et al*[21] detected greater survival in women with advanced pancreatic cancer with worse tolerance of chemotherapy that has been linked to less clearance of cytotoxic drugs, such as 5-fluorouracil[62] and irinotecan[63-65], and with greater toxicity in women compared to men[66].

Generalisability

There are no data concerning sex differences in cancer perception among patients with advanced gastrointestinal malignancies, and previous studies that included patients with metastatic colorectal cancer and non-colorectal digestive cancer have not reported specific data in this regard[56,67]. Women have been underrepresented in gastrointestinal cancer research, and men have been underrepresented in cancer-associated psychosocial assessment[68]. The relevance of assessing sex differences stems from the fact that men and women have specific social, psychological, and physical characteristics that might compromise coping strategies and perceptions of quality of life.

Limitations

The present study has several limitations. First, the underrepresentation of some non-colorectal digestive cancer subtypes and the heterogeneity of the data could bias the overall estimates. Second, the questionnaires were completed during the appointment prior to beginning antineoplastic treatment, which does not capture the variation of parameters over time nor the causal relationship between variables. Third, the study only included patients from Spain and advanced stage cancers; thus, these results should be confirmed in patients from other countries and with cancers of other stages.

CONCLUSION

In conclusion, this study has detected differences in psychological distress, quality of life, and coping with cancer between women and men and between patients with colorectal and non-colorectal digestive cancers. Women and patients with non-colorectal gastrointestinal tract malignancies have more physical symptoms and somatization, and women suffer more psychological distress. These findings, if confirmed, suggest that sex and location of the primary digestive neoplasm should be considered in individualized communication with the patient to achieve a suitable approach to their psychological situation. Future studies should factor in sex and primary tumor site differences in advanced gastrointestinal cancer patients.

ARTICLE HIGHLIGHTS

Research background

Patients with advanced gastrointestinal cancer must cope with the negative effects of cancer and complications. Sex is a sociodemographic variable that can give rise to differences in the evolution as well as the clinical and psychological aspects of cancer.

Research motivation

To analyze whether there are differences between colorectal and non-colorectal digestive cancer in sociodemographic and/or clinical conditions and coping depending on sex.

Research objectives

To evaluate psychological distress, quality of life, and coping strategies in patients with advanced colorectal cancer compared to non-colorectal cancer based on sex.

Research methods

This was a multi-institutional prospective, observational study that evaluated patients with advanced digestive cancers; 203 patients were eligible for this analysis. Demographic and clinical data were obtained and the association between psychological distress, quality of life, and coping strategies and the role of sex and primary tumor site were analyzed.

Research results

Women exhibited more depressive symptoms, anxiety, functional limitations, and anxious preoccupation than men. Non-colorectal digestive cancer patients and women showed more somatization and physical symptoms than colorectal cancer patients and men.

Research conclusions

Disease acceptance in patients with advanced cancer of the digestive tract may be sex dependent.

Research perspectives

Future interventions should evaluate primary tumor site and sex differences in patients with gastrointestinal malignancies.

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FOOTNOTES

Author contributions: Pacheco-Barcia V, Calderon C, and Jimenez-Fonseca P developed the project, analyzed the data, and drafted the manuscript; The other authors recruited patients and provided clinical information, comments, and improvements to the manuscript; All authors participated in the interpretation and discussion of data and the critical review of the manuscript.

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Institutional review board statement: The study was approved by the Research Ethics Committee of the Principality of Asturias (May 17, 2019) and by the Spanish Agency of Medicines and Medical Devices (Identification code: L34LM-MM2GH-Y925U RJDHQ). The study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. This study is an observational, non-interventionist trial.

Informed consent statement: Signed informed consent was obtained from all patients.

Conflict-of-interest statement: Dr. Pacheco-Barcia reports grants from FSEOM and grants from Astra Zeneca during the conduct of the study; other from Eisai, other from Merck, other from Eli Lilly, other from Advanced accelerator applications, a Novartis company, grants from FSEOM and Merck, other from Roche, other from Eli Lilly, other from Bristol-Myers Squibb, other from Merck, other from Amgen, other from Merck Sharp and Dhome, other from Nutricia, other from Roche, other from Bayer, other from Amgen, other from Esteve, other from Eli Lilly, other from Roche, other from Bristol-Myers Squibb, grants from Ayuda Clínico Formativa AECC 2020, grants from FSEOM, outside the submitted work.

Data sharing statement: This database is available through a centralized web platform: www.neoetic.es. The code is available upon request to the authors. Code availability: Patients are identified by an encrypted code known only to the local researcher. The analysis code is available upon request to the authors.

STROBE statement: The study was undertaken according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

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