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Symptom Management and Supportive Care

Impact of Obesity on Quality of Life, Psychological Distress, and Coping on Patients with Colon Cancer

David Gomez,[a] Paula Jimenez-Fonseca,[a] Aránzazu Manzano Fernández,[b] Patricia Cruz Castellanos,[c] Maria Valero Arbizu,[d] Ruth Martínez Cabañes,[e] David Lorente Estellés,[f] Estrella Ferreira,[g] Jorge del Rio,[a] Teresa García García,[h] Alberto Carmona-Bayonas,[i] Caterina Calderon[j]

[a]Department of Medical Oncology, Hospital Universitario Central de Asturias, ISPA, Oviedo, University of País Vasco, País Vasco, Spain; [b]Department of Medical Oncology, Hospital Universitario Clínico San Carlos de Madrid, Madrid, Spain; [c]Department of Medical Oncology, Hospital Universitario La Paz, Madrid, Spain; [d]Department of Medical Oncology, Hospital Quirónsalud Sagrado Corazón, Sevilla, Spain; [e]Department of Medical Oncology, Hospital Universitario Fundación Alcorcón, Madrid, Spain; [f]Department of Medical Oncology, Hospital Provincial de Castellón, Castellón, Spain; [g]Department of Clinical Psychology and Psychobiology, Faculty of Psychology, University of Barcelona, Barcelona; [h]Department of Medical Oncology, Hospital General Universitario Santa Lucia, Cartagena, Spain; [i]Department of Medical Oncology, Hospital Universitario Morales Meseguer, University of Murcia, IMIB, Murcia, Spain; [j]Department of Clinical Psychology and Psychobiology, Faculty of Psychology, University of Barcelona, Barcelona, University of País Vasco, País Vasco, Spain

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Body mass index • Cancer • Chemotherapy • Obese • Quality of life • Recurrence

Abstract

Background. Despite the causal relationship between obesity and colon cancer being firmly established, the effect of obesity on the course of cancer calls for further elucidation. The objective of this study was to assess differences in clinical-pathological and psychosocial variables between obese and nonobese individuals with colon cancer.

Materials and Methods. This was a prospective, multicentric, observational study conducted from 2015–2018. The sample comprised patients with stage II–III, resected colon cancer about to initiate adjuvant chemotherapy with fluoropyrimidine in monotherapy or associated with oxaliplatin and grouped into nonobese (body mass index <30 kg/m^2) or obese (≥30 kg/m^2). Subjects completed questionnaires appraising quality of life (European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire), coping (Mini-Mental Adjustment to Cancer), psychological distress (Brief Symptom Inventory 18), perceived social support (Multidimensional Scale of Perceived Social Support), personality (Big Five Inventory 10), and pain (Brief Pain Inventory). Toxicity, chemotherapy compliance, 12-month recurrence, and mortality rate data were recorded.

Results. Seventy-nine of the 402 individuals recruited (19.7%) were obese. Obese subjects exhibited more comorbidities (≥2 comorbidities, 46.8% vs. 30.3%, p = .001) and expressed feeling slightly more postoperative pain (small size-effect). There was more depression, greater helplessness, less perceived social support from friends, and greater extraversion among the obese versus nonobese subjects (all p < .04). The nonobese group treated with fluoropyrimidine and oxaliplatin suffered more grade 3–4 hematological toxicity (p = .035), whereas the obese had higher rates of treatment withdrawal (17.7% vs. 7.7%, p = .033) and more recurrences (10.1% vs. 3.7%, p = .025). No differences in sociodemographic, quality of life, or 12-month survival variables were detected.

Conclusion. Obesity appears to affect how people confront cancer, as well as their tolerance to oncological treatment and relapse. ***The Oncologist*** 2021;26:e874–e882

Implications for Practice: Obesity is a causal factor and affects prognosis in colorectal cancer. Obese patients displayed more comorbidities, more pain after cancer surgery, worse coping, and more depression and perceived less social support than nonobese patients. Severe hematological toxicity was more frequent among nonobese patients, whereas rates of withdrawal from adjuvant chemotherapy were higher in the obese cohort, and during follow-up, obese patients presented greater 12-month recurrence rates. With the growing and maintained increase of obesity and the cancers associated with it,

Correspondence: David Gomez, M.D., Department of Medical Oncology. Hospital Universitario Central of Asturias, ISPA, 33011 Oviedo, Universidad del País Vasco, País Vasco, Spain. Telephone: 34 985106121. e-mail: gomelio009@hotmail.com Received October 22, 2020; accepted for publication January 12, 2021; published Online First on February 13, 2021. http://dx.doi.org/10.1002/onco.13687

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including colorectal cancer, the approach to these more fragile cases that have a worse prognosis must be adapted to improve outcomes.

Introduction

Obesity has been recognized as one of the leading health challenges worldwide and is associated with an increased risk of cancer [1]. It is estimated that 20% of all tumors can be attributed to obesity and that obesity accounts for 14% of all cancer deaths in men and 20% among women [2, 3]. Obesity is present in 6%–19% of all oncology patients who receive chemotherapy [4]. Some authors believe that excess weight is a poor prognostic factor for certain types of tumors, such as colon, prostate, or breast [5–7]. Brown and Meyerhardt concluded that obesity entails a worse prognosis, specifically in cancers of the gastrointestinal tract [8].

There is a causal relation between excessive adiposity and the risk of developing cancer [9]. Obesity, defined as a body mass index (BMI) of ≥30.0 kg/m^2, negatively affects cancer progression, mortality, and survival [3, 10, 11]. Likewise, an increment in the risk of recurrence has been reported for every 5 kg/m^2 in BMI in male patients with colon cancer (1.36, 95% confidence interval [CI], 1.50–3.31) [6] and in female sufferers of breast cancer (1.12, 95% CI, 1.08–1.16) [10].

An elevated BMI can affect treatment selection, surgery, choice of chemotherapy dosage, and patient inclusion in clinical trials [3, 12]. Thus, it can negatively impact surgical outcomes, with greater morbidity due to increased risk of infection and delayed healing, as well as hindering optimal lymphadenectomy, with the risk of inadequate staging and cancer treatment [1, 13]. Dose-capped chemotherapy is generally prescribed (capped at body surface area of 2 m^2), for fear of excess toxicity, with the consequent risk of treatment being less effective [13, 14].

Cancer survivors, with or without obesity, are at greater risk for developing a second neoplasm, as well as cardiovascular problems, diabetes, and other complications [15, 16]. Patients with cancer are often sedentary and suffer cardiovascular disease, which can contribute to weight gain or undermine weight control [17, 18]. Furthermore, hormonotherapy and corticosteroid use to prevent chemotherapy-related toxicity and control symptoms can lead to weight gain in individuals with cancer [6].

Obesity has been linked to a proinflammatory state that causes nociceptive hypersensitivity with a heightened perception of pain [19, 20] and psychological distress [21, 22]. Belcher et al. have correlated a higher BMI, lower level of education, greater neuroticism, and less social support with self-controlled behavior and greater anguish [22]. Obesity has been associated with increased depression that fosters weight gain [23].

In light of the above, it appears that obese individuals constitute a vulnerable group that might benefit from personalized care and more intensive follow-up. Despite the evidence pointing toward worse evolution of the disease, to the best of our knowledge, there are no studies that appraise the psychological and clinical-pathological profile of the obese participants with colon cancer who initiates adjuvant chemotherapy, despite its being the third most common tumor and its close tie to obesity.

This study sought to examine the differences in clinical-pathological and psychosocial variables between individuals with stage II–III colon cancer who receive adjuvant chemotherapy with and without obesity.

Subjects, Materials, and Methods

Patients and Design

The data derive from a prospective cohort of patients with nonmetastatic colon cancer from the multicohort NEOCOPING study promoted by the Continuous Care Group of the Spanish Society of Medical Oncology and carried out in 17 Spanish medical oncology departments.

Individuals >18 years of age with resected, stage III and high-risk stage II colon cancer and eligible for adjuvant chemotherapy were consecutively included. Those who had received preoperative chemotherapy or radiotherapy and those with any condition that impedes comprehension of or participation in the study were excluded.

Subjects were treated with fluoropyrimidine in monotherapy or coupled with oxaliplatin with the choice of scheme and dose intensity as per the investigator's criteria and local clinical practice. Patients were treated according to uniform, standard criteria, without changes in clinical practice during the study period (2013–2018) [24].

This study was approved by the Institutional Research Ethics Committee of each hospital and the Spanish Agency for Medicines and Health Products (number L34LM-MM2GH-Y925U-RJDHQ); informed consent for voluntary participation was obtained in writing from all subjects prior to performing any study procedure. STROBE guidelines were used to ensure the reporting of this study [25].

Variables and Measures

After the first appointment with the oncologist, during which the person was informed of the risk of relapse and indication for adjuvant therapy, the following variables were compiled: sex, age, BMI, comorbidities (Charlson index [26]), marital status, educational level, employment status, stage, time between diagnosis and surgery, time from surgery to chemotherapy, and type of surgery.

Subjects were grouped by the presence or absence of obesity, defined as BMI ≥30.0 kg/m^2. Chemotherapy prescribed in the first cycle to obese patients was classified as adjusted body surface area (BSA) of 2 m^2 (capping) or actual BSA (no capping). At the end of adjuvant treatment, maximum chemotherapy-related gastrointestinal, hematological, neurological, skin toxicity, and asthenia during treatment were all recorded. The maximum chemotherapy-related toxicity was defined as the highest grade of any toxicity experienced by each patient during the course of adjuvant chemotherapy, classified according to CTCAE v4.0 [27]. Early discontinuation of adjuvant treatment and the reasons for it were likewise collected. The reason for withdrawal of adjuvant therapy was collected as a

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Table 1. Baseline clinical-psychosocial characteristics of patients with and without obesity

Characteristics	Nonobese, *n* (%)	Obese, *n* (%)	*p* values
Total	323 (80.3)	79 (19.7	
Gender, male	204 (63.1)	46 (58.2)	.996
Age, mean, yr	63.6	62.3	.374
Marital status, married or partnered	242 (74.9)	62 (78.5)	.067
Education, primary	176 (54.5)	48 (60.7)	.371
Work, retired	215 (66.5)	49 (62)	.986
Type of organ resection			.581
Sigmoidectomy	126 (39)	32 (40.5)	
Hemicolectomy or total colectomy	197 (61)	47 (59.5)	
Tumor stage			.340
II	80 (24.8)	22 (27.8)	
III	243 (75.2)	57 (72.2)	
Adjuvant treatment			.318
Chemotherapy	313 (97)	75 (94.9)	
Chemo- and radiotherapy	10 (3)	4 (5.1)	
Anticancer treatment			.806
Fluoropyrimidine + oxaliplatin	238 (73.7)	59 (74.7)	
Fluoropyrimidine alone	83 (25.7)	19 (24)	
Dose capping			
Fluoropyrimidine + oxaliplatin		35 (59.3)	
Fluoropyrimidine alone		8 (42.1)	
Reject treatment	2 (0.6)	1 (1.3)	
Charlson index, ≥2 comorbidities	98 (30.3)	37 (46.8)	.001[a]

[a]Significantly different from zero at the .05 level (two-tailed).

categorical variable with five levels: completed therapy, toxicity, intercurrent problems, patient's desire, and others. Mortality and 12-month recurrence after having concluded treatment were examined.

Participants completed quality of life (QoL), psychological, and other questionnaires by themselves.

The European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire (EORTC QLQ-C30) is a reliable and validated measure of the quality of life of patients with cancer in multicultural, clinical research settings. This 30-item scale is divided into three subscales: functional, symptom, and global health status and/or QoL [28]. The Spanish version of the EORTC QLQ-C30 was used for data collection. A sample can be downloaded at the following URL: http://groups.eortc.be/quol/erotc-qlq-c30. Each item is ranked from 0 to 100. The higher the functional scale and global health status and the lower the symptom scale scores, the better the QoL (in this sample, $\alpha = 0.85$).

The Mini-Mental Adjustment to Cancer consists of 29 items classifying four coping strategies, helplessness, anxious preoccupation, positive attitude, and cognitive avoidance [29], and has been adapted for use with Spanish patients with cancer [30]. Items are scored on a 4-point Likert scale; higher scores indicate better coping strategies. Score on the Spanish version (Ω coefficients) varied from 0.76 to 0.90 [30].

The Brief Symptom Inventory 18 comprises 18 items categorized into three dimensions of psychological distress (somatization, depression, and anxiety) and rated on a five-point scale [31] and has been adapted to Spanish patients with cancer [32]. Raw scores are converted to T-scores based on sex-specific normative data. According to the cut-off values recommended by Derogatis [31], patients whose T-score ≥ 63 were considered as suffering from ''probable psychological anxiety, depression or somatization. The α coefficients were between 0.75 and 0.88 for the Spanish version among patients with cancer [32].

The Multidimensional Scale of Perceived Social Support contains 12 items that assess perceived social support from three different sources (family, friends, and significant other) on a 7-point scale [33], It has been adapted to Spanish patients with cancer [34]. Total scores ranged from 7 to 84; higher scores indicate greater perceived social support. In this sample, α coefficients ranged from 0.84 to 0.91.

The Big Five Inventory 10 is a short version of the widely used BFI that identifies five traits (extraversion, neuroticism, openness to experience, agreeableness, and conscientiousness) [35]; it has been adapted to Spanish patients [36]. The lowest sum score possible is 10 and the highest is 50. The coefficient αreliability ranges from 0.75 to 0.83 [35].

The Brief Pain Inventory (BPI) was devised to quantify subjective severity of pain, as well as interference resulting from pain [37]. The BPI captures changes in pain; is easy to administer, and boasts the Expert Working Group of the European Association of Palliative Care's endorsement as a

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Table 2. Baseline psychosocial and clinical characteristics of patients with and without obesity

Characteristics	Nonobese, *n* (%)	Obese, *n* (%)	*p* value
Total	332 (81.6)	79 (19.7)	
EORTC QLQ-C30			
Functional scale	69.1 (12.3)	66.4 (15.5)	.122
Symptom scale	15.0 (13.1)	15.9 (14.4)	.587
Health status/QoL	72.6 (20.8)	71.4 (22.6)	.656
BSI-18 psychological scale			
Somatization	59.5 (6.1)	59.6 (7.1)	.889
Depression	58.9 (5.3)	60.6 (6.7)	.025[a]
Anxiety	60.6 (7.4)	61.5 (7.9)	.374
Psychological distress	61.8 (7.3)	62.8 (7.2)	.316
M-MAC coping			
Helplessness	18.3 (18.1)	25.4 (23.4)	.005[a]
Anxious preoccupation	37.2 (22.3)	25.4 (23.4)	.014[a]
Positive attitude	75.0 (16.6)	76.1 (18.5)	.648
Cognitive avoidance	52.8 (25.6)	52.1 (27.0)	.825
MSPSS social support			
Family	26.3 (4.5)	26.3 (2.3)	.946
Friends	23.1 (4.8)	21.7 (6.2)	.036[a]
Others	26.1 (3.2)	26.0 (3.6)	.848
Personality			
Extraversion	6.6 (1.9)	7.2 (1.9)	.034[a]
Conscientiousness	7.0 (1.8)	6.8 (2.0)	.616
Neuroticism	5.5 (2.0)	5.5 (2.1)	.979
Openness to experience	5.6 (2.1)	5.4 (2.1)	.463
Agreeableness	7.4 (1.4)	7.4 (1.7)	.971
BPI pain			
Pain severity	17.9 (21.4)	24.9 (23.9)	.040[a]
Pain interference	17.3 (21.4)	24.4 (22.1)	.037[a]
Perceived risk of recurrence			
Patient	33.3 (24.6)	38.7 (23.0)	.095
Physician	27.1 (17.2)	27.4 (16.4)	.859
Perceived risk of toxicity			
Patient	56.2 (21.5)	56.3 (24.8)	.976
Physician	11.2 (9.8)	10.9 (8.8)	.806

[a]Significantly different from zero at the .05 level (two-tailed).
Abbreviations: BPI, Brief Pain Inventory; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire; M-MAC, Mini-Mental Adjustment to Cancer; MSPSS, Multidimensional Scale of Perceived Social Support; QoL, quality of life.

pain measurement tool [38], adapted to Spanish patients with cancer [39]. Scores ranged from 0 to 100; higher scores indicate more severity or greater interference due to pain

Patients' and oncologists' perception of risk of relapse and of toxicity with adjuvant chemotherapy were scored on a 4-point Likert scale as being low, intermediate, high, or very high risk to make it easier for patients to express their definitive impression about these issues.

Statistical Methods

Descriptive analyses were used to characterize the patient sample in terms of demographic and clinical characteristics. Weight-based differences (nonobese: <30 kg/m^2 vs. obese ≥30kg/m^2) were examined using frequency scores; χ^2 and *t* tests gauged the differences between nonobese and obese subjects with respect to sociodemographic, clinical, and psychological characteristics. Cohen's *d* was used to calculate effect size. Cohen established a conventional interpretation of effect size in which *d* = 0.2 is considered a small effect; *d* = 0.5 is considered a medium-sized effect, and *d* = 0.8 is considered a large effect [40]. Logistic regression analysis was used to analyze the influence of weight loss on recurrence and toxicity using the forward Wald method for logistic regression. We applied Nagelkerke's R^2 to determine goodness-of-fit of the logistic regression model [41]. All statistical assessments were

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Table 3. Toxicity at the end of adjuvant chemotherapy

	Oxaliplatin-based chemotherapy, *n* = 297		Fluoropyrimidines in monotherapy, *n* = 102	
Adverse events	**Nonobese, *n* (%)**	**Obese, *n* (%)**	**Nonobese, *n* (%)**	**Obese, *n* (%)**
Total	238 (80.1)	59 (19.9)	83 (81.4)	19 (18.6)
Hematological toxicity				
Grade 1–2	75 (31.5)	32 (54.2)	24 (28.9)	5 (26.3)
Grade 3–4	30 (12.6)	4 (6.7)	1 (1.2)	0 (0)
p	.035	.035	.649	.649
Gastrointestinal toxicity				
Grade 1–2	113 (47.4)	25 (42.3)	30 (36.1)	6 (31.5)
Grade 3–4	10 (4.2)	4 (6.7)	3 (3.6)	0 (0)
p	.343	.343	.442	.442
Cutaneous toxicity				
Grade 1–2	97 (40.7)	26 (44)	30 (36.1)	7 (36.8)
Grade 3–4	3 (1.2)	1 (1.6)	6 (7.2)	0 (0)
p	.853	.853	.244	.244
Asthenia				
Grade 1–2	111 (46.6)	37 (62.7)	29 (34.9)	6 (31.5)
Grade 3–4	7 (2.9)	0 (0)	2 (2.4)	0 (0)
p	.129	.129	.522	.522
Neurotoxicity				
Grade 1–2	123 (51.6)	29 (49.1)		
Grade 3–4	19 (7.9)	6 (10.1)		
p	.567	.567		

two-sided and *p* values <.05 were deemed significant. Statistical analyses were performed using the IBM-SPSS 23.0 statistical software package for Windows PC.

Results

Baseline Patient Characteristics

This study analyzed outcomes among 402 participants with colon cancer receiving chemotherapy from 2015 to 2018. Mean follow-up was 26 months (range, 13–44).

Of the entire sample, 79 individuals (19.7%) were obese following cancer surgery and prior to commencing adjuvant chemotherapy. Table 1 presents the baseline characteristics of the obese and nonobese cohorts. No significant intergroup differences in sociodemographic characteristics or tumor stage were observed, although the percentage of participants living as a couple was higher among the obese, but statistical significance was not reached. Forty-seven percent of the obese sample had more than two comorbidities as per the Charlson index versus 30.3% of the nonobese (χ^2 = 10.723, *p* = .001). As for adjuvant chemotherapy, no differences were evidenced in the scheme administered to obese compared with nonobese groups; all received oxaliplatin-based (74.7% and 73.7%) or fluoropyrimidine in monotherapy (24 and 25.7%), *p* = .806. Dosages were capped in 35 (59.3%) of the obese participants treated with oxaliplatin and in 8 (42.1%) of those treated with fluoropyrimidine in monotherapy, no significant differences were detected (χ^2 = 2.022, *p* = .155). Obese patients who received uncapped doses had a median BSA of 2.3 (range, 2.2–2.7). In both groups, participants and oncologists perceived the risk of recurrence and toxicity similarly, although obese individuals tended to estimate a greater risk of relapse.

Baseline Characteristics of Obese and Nonobese Participants

No differences were evinced regarding quality of life between the obese and nonobese cohorts. Obese subjects displayed more symptoms of depression (*t* = −2.225, *p* = .025, Cohen's *d* = 0.28) and passive coping strategy (helplessness) (*t* = −2.810, *p* = .005, Cohen's *d* = 0.33), whereas the nonobese drew on more maladaptive coping based on anxious preoccupation (*t* = −2.475, *p* = .014, Cohen's *d* = .51). As for social support, the nonobese group perceived more support from friends than their obese counterparts (*t* = 2.103, *p* = .036, Cohen's *d* = 0.25), whereas there were no differences in perceived support from family or their milieu. The only difference observed concerning personality was greater extraversion in the obese group (*t* = 2.125, *p* = .034, Cohen's *d* = 0.31). Obese subjects had higher BPI pain scores on both variables, severity (*t* = −2.066, *p* = .040, Cohen's *d* = 0.02, small effect) and pain-related interference (*t* = −2.103, *p* = .037, Cohen's *d* = 0.02), see Table 2.

Characteristics of Patient Groups with or Without Obesity at the End of Adjuvant Chemotherapy

Of the initial 402 cases, 12-month follow-up from the time of adjuvant chemotherapy completion was possible in 279 (69.4%).

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Of the 57 obese patients for whom 12-month follow-up data were available, 44 (83%) continued to be obese and 9 (17%) had lost weight during treatment and no longer met the criteria for obesity upon conclusion of adjuvant chemotherapy. As for the group of 222 nonobese participants with complete follow-up data, 213 (94.2%) remained nonobese and 13 (5.8%) fulfilled criteria for obesity at the end of adjuvant therapy.

Obese participants lost an average of 3.3 kg (SD = 5.6; 95% CI, 0.7–1.7), and the nonobese lost a mean of 1.2 kg (SD = 3.1, 95% CI, 2.1–4.5), revealing statistically significant differences (F = 10.049, p = .002, η^2 0.040).

There was an association between weight loss and cancer recurrence (Wald = 6.57, p = .01), such that Nagelkerke's R^2 suggests that 6.7% of the variability in recurrence is accounted for by weight loss, whereas no significant correlation was detected between weight loss and toxicity. Toxicity data were available for 321 nonobese and 78 obese patients upon completion of adjuvant chemotherapy (Table 3). Of the individuals treated with oxaliplatin and fluoropyrimidine, 238 (80.1%) were not obese and 59 (19.9%) were obese; among those treated with fluoropyrimidine in monotherapy, 83 (81.4%) were not obese and 19 (18.6%) were obese (X^2 = 0.074, p = .786). Nonobese participants treated with oxaliplatin-based schemes exhibited higher rates of grade 3–4 hematological toxicity (p = .035) than obese patients, whereas no significant intergroup differences were observed in digestive (p = .343), skin (p = .853), or neurological (p = .567) toxicity or with respect to asthenia (p = .129). Likewise, no differences were found in hematological toxicity between obese patients with and without dose capping who were treated with oxaliplatin-based chemotherapy (U = 235.5, p = .848, Monte Carlo significance [bilateral] = 0.069). There was no significant difference in toxicity between obese and nonobese subjects treated with fluoropyrimidine in monotherapy.

Adjuvant treatment was discontinued more often in the obese compared with the nonobese group, (χ^2 = 6.816, p = .033). This was mainly due to toxicity (15.2% vs. 6.5%) and, to a lesser extent, to intercurrent problems (2.5% vs. 1.2%).

In the 12 months following completion of adjuvant treatment, higher recurrence rates were confirmed in the obese versus the nonobese (10.1% vs. 3.7%, χ^2 = 5.024, p = .025). Despite a trend toward higher mortality rates in the first year among the obese vis-à-vis the nonobese, the scant number of events was insufficient to detect statistically significant differences (3.8% vs. 1.2%, p = .141). At 12 months of follow-up, four deaths had been recorded in the nonobese group, three from cancer recurrence and one from other cause, and three in the obese group, all related to cancer.

Discussion

This analysis of patients with resected, stage II–III colon cancer receiving adjuvant chemotherapy suggests that there are pathological and psychosocial differences between obese and nonobese individuals. In the psychological domain, obese subjects displayed more depression and greater helplessness, perceived less support from their friends, and were more extraverted than their nonobese counterparts; they exhibited no differences regarding quality of life before or after adjuvant treatment. Moreover, they suffered more comorbidities and greater pain severity and pain-related interference following cancer surgery. During adjuvant chemotherapy, the obese group presented less grade 3–4 hematological toxicity with oxaliplatin- and fluoropyrimidine-based chemotherapy and a higher rate of treatment withdrawal. Likewise, in the first 12 months of follow-up, they had more relapses without enough events to detect differences in survival, despite a trend toward greater mortality.

Various retrospective studies, pos hoc analyses of clinical trials, and metanalyses have compared survival and chemotherapy toxicity between obese and nonobese patients with cancer, primarily breast and colon cancers, yielding disparate data [14, 42–46]. In a systematic review, Carroll et al. examined the impact of obesity on adjuvant treatment of breast cancer. As in our series, obese subjects had more comorbidities. Furthermore, they reported data from five studies for which information about the dose administered was unavailable; in all of them, BMI correlated positively with reduced neutropenia [14]. Nevertheless, a post hoc analysis of the GAIN phase III trial in advanced breast cancer detected greater hematological toxicity, neutropenia febrile, and grade 3–4 thrombopenia in obese patients receiving full-dose chemotherapy compared with nonobese or obese subjects with adjusted-dose chemotherapy [42]. So far as we know, only one post hoc analysis of the phase III Intergroup 0089 treatment trial (INT-0089) explored toxicity, recurrence, and survival in a population comparable to our insofar as it comprised patients with stage II–III colon cancer receiving adjuvant chemotherapy, although their sample was divided into five BMI categories instead of two [43]. The chemotherapy used in that trial was 5-fluorouracil (5FU)-based chemotherapy modulated with levamisole versus high- or low-dose leucovorin, whereas in our case, subjects were given fluoropyrimidine (capecitabine or 5FU) in monotherapy or associated with oxaliplatin, a drug that is associated with greater hematological toxicity than fluoropyrimidines. In the INT-089 study, overweight and obese individuals experienced significantly lower rates of any severe toxicity (adjusted p for trend = .02) and lower rates of grade 2–3 nausea and grade 3–4 leucopenia compared with normal-weight patients, whereas the adjuvant chemotherapy completion rates did not differ. As in the INT-0089 study, we found less grade 3–4 hematological toxicity with oxaliplatin and fluoropyrimidine in the obese sample compared with the nonobese. In the INT-0089 trial, grade 3–4 leucopenia in the five categories ranged from 6.1% to 11.7%, and in our series, grade 3–4 hematological toxicity among obese compared with nonobese participants was 6.7% versus 12.6% in those receiving oxaliplatin and fluoropyrimidine (p = .035) and 0% versus 1.2% in those treated with fluoropyrimidine in monotherapy (p = .649). In one study with individuals who underwent chemotherapy for different neoplasms, Cox-Martin and others observed that the obese subjects displayed more peripheral neuropathy that negatively impacted the quality of life; a finding we have not observed [44]. Overall, the data point to asymmetric toxicity consequences depending on individual frailty, even with balanced toxicity rates. The higher number of

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chronic comorbidities for the obese in our series is compatible with the increased discontinuation rates of adjuvant chemotherapy due to toxicity in this population, despite the adverse events being only slightly unbalanced. In addition, there is the additive contribution of other specific factors in small groups of patients, including specific toxicities, such as asthenia of any grade, psychosocial factors, or maladaptive coping that will have a greater impact on the obese.

The INT-0089 trial, with follow-up until demise, found no differences in overall or recurrence-free survival based on BMI classes of normal-weight, overweight, and obese individuals. In contrast, we detected higher relapse rates in obese individuals without reaching statistical significance, which might be conditioned by the small number of events (3 of the 79 obese patients and 4 of the 323 nonobese patients died) and short follow-up (12 months). In a review published in 2019, greater mortality, mortality due to colon cancer, and recurrence in obese individuals were detected in two clinical trials in stage II–III colon cancer, NSABP C-04 and C-05 [6].

In our series, obese subjects expressed that they felt slightly more pain (small size-effect) following surgery that persisted at the beginning of adjuvant treatment, in line with published findings of a 2017 metanalysis, in which obese patients who underwent surgery for breast cancer were seen to experience more postoperative pain [47], and a 2019 study by Majchrzak et al., revealing that obese individuals had greater sensory pain after lung cancer surgery [48].

Whereas Speed-Andrews et al. detected evidence of a relation between decreasing BMI and improved quality of life and better cancer prognosis in 2009 [49], we have not noticed differences in quality of life between the obese and nonobese cohorts. Although obesity increases the incidence of colorectal cancer, studies on the association between weight change and prognosis are inconsistent [50, 51]. Our results indicate that weight loss contributes 6.7% to recurrence, although there may be confounding factors associated with weight loss, as well as the cancer itself. Consequently, further studies are needed to assess the relationship between weight change in patients with colon cancer and the prognosis of the disease.

As for cancer treatment, according to a recent review by Slawinski et al., obese patients undergo more aggressive surgeries and are treated with full-dose chemotherapy without evidence of greater toxicity [13]. However, there are no specific analyses for this population subgroup, despite the fact that only 18% of all clinical trial participants are obese, which could impact outcomes.

Based on the above, our data point toward the obese constituting an entity unto itself that has worse outcomes, more comorbidities, more adjuvant treatment withdrawals, more depression, and worse coping strategies, all of which affect adjuvant chemotherapy in conditions of daily practice. Identifying the causes underlying these processes would allow strategies to be designed with the aim of mitigating their effect. In the meantime, the early detection of psychological symptoms (depression, passive coping strategies) may help medical oncologists refer obese patients with colorectal cancer to a psycho-oncologist to assist them in coping with their cancer and its treatment.

Our study has various limitations. First of all, obesity was determined 1 month after cancer surgery and prior to initiating adjuvant chemotherapy and defined in terms of BMI. A few cases of morbid obesity prior to surgery escaped detection, because of weight loss associated with the disease and surgery. In contrast, this increases the accuracy and reliability of the detection of subjects as obese, which yielded a similar percentage to that reported by other series. Second, we cannot rule out the possibility that some of the differences identified between obese and nonobese subjects are due to confounding variables not contemplated in this study (for instance, the regimen and dosage chosen as per the investigators judgment and not controlled for). Third, a larger sample of obese patients would be needed to confirm the differences found in our study. Fourth, the questionnaires were completed during the appointment prior to beginning adjuvant treatment, which does not capture the variation of parameters over time. A generic QoL questionnaire was used, rather than a specific one like the EORTC QLQ-CR29. However, the multidimensional assessment performed included several measures of symptoms, emotional state, and coping and helps to capture a substantial part of the perspectives of patients in this scenario. Furthermore, the self-report, subjective measures may be limited by response bias (social desirability, inaccurate memory, etc.), difficulty in fully comprehending the questionnaires, and the definition of depression and other psychosocial variables having been established by means of the questionnaires as opposed to a psychiatric evaluation. Fifth, this study did not include muscle mass measurements to estimate body composition and the presence of sarcopenia, which has been associated with cancer prognosis in several studies. Finally, the short patient follow-up period could have limited detection of differences in survival.

Conclusion

These findings indicated that obesity may impact how patients experience cancer and the course of the disease itself, which must be taken into account in the approach to and follow-up of this population. Thus, and in light of the paucity of evidence based on prospective data, future clinical trials should consider stratifying samples based on BMI.

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The study was approved by the Research Ethics Committee of the Principality of Asturias (January 19, 2015) and by the Spanish Agency of Medicines and Medical Devices (April 14, 2015).

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, noninterventionist trial.

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Signed informed consent was obtained from all patients.

Informed consent and approval by the competent national authorities include permission for publication and dissemination of data.

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Author Contributions

Conception/design: David Gomez, Paula Jimenez-Fonseca, Jorge del Rio, Teresa García García, Alberto Carmona-Bayonas, Caterina Calderon

Provision of study material or patients: David Gomez, Paula Jimenez-Fonseca, Aránzazu Manzano Fernández, Patricia Cruz Castellanos, Maria Valero Arbizu, Ruth Martínez Cabañes, David Lorente Estellés, Estrella Ferreira, Teresa García García, Alberto Carmona-Bayonas

Collection and/or assembly of data: David Gomez, Paula Jimenez-Fonseca, Aránzazu Manzano Fernández, Patricia Cruz Castellanos, Maria Valero Arbizu, Ruth Martínez Cabañes, David Lorente Estellés, Estrella Ferreira, Teresa García García, Alberto Carmona-Bayonas

Data analysis and interpretation: David Gomez, Paula Jimenez-Fonseca, Alberto Carmona-Bayonas, Caterina Calderon

Manuscript writing: David Gomez, Paula Jimenez-Fonseca, Aránzazu Manzano Fernández, Jorge del Rio, Alberto Carmona-Bayonas, Caterina Calderon

Final approval of manuscript: David Gomez, Paula Jimenez-Fonseca, Aránzazu Manzano Fernández, Patricia Cruz Castellanos, Maria Valero Arbizu, Ruth Martínez Cabañes, David Lorente Estellés, Estrella Ferreira, Jorge del Rio, Teresa García García, Alberto Carmona-Bayonas, Caterina Calderon

Disclosures

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