

**Aim of the study:** To analyse the influence of overweight and obesity in disease-specific survival (DSS) in rectal cancers at stages I–III in a population with high prevalence of overweight/obesity.

**Material and methods:** The population ( $N = 304$ ) consisted of Mexican patients with stage I–III rectal cancer during the period between 2009 and 2015. Patients were divided based on their body mass index (BMI) into normal weight 18–25 kg/m<sup>2</sup>, overweight 25–29 kg/m<sup>2</sup>, and obesity BMI > 30 kg/m<sup>2</sup> groups. Comparison of clinicopathologic features and survival analysis were performed.

**Results:** The median age was 58 years (interquartile range [IQR] 50–65) and the mean BMI was 26.03 ± 4.06 kg/m<sup>2</sup>. Patients in the obesity and overweight groups received a lower proportion of preoperative treatment and had a higher proportion of patients in stage II. Overweight patients had a lower baseline neutrophil/lymphocyte ratio and lower survival rate than patients with normal weight and with obesity (mean survival of 69.5 months vs. 81.15 months and 86.4 months, respectively). The estimated five-year DSS was 51% for the overweight group, 81% for the normal group, and 82% for the obesity group ( $p = 0.026$ ).

**Conclusions:** Patients with stage I–III rectal cancer in the overweight group showed a lower DSS compared to groups with normal weight and with obesity, with the last two being similar.

**Key words:** BMI, cancer, obesity, survival, rectal cancer.

Contemp Oncol (Pozn) 2018; 22 (3): 158–164  
DOI: <https://doi.org/10.5114/wo.2018.78937>

# Overweight but not obesity is associated with decreased survival in rectal cancer

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## Introduction

Rectal cancer along with colon cancer is a global problem, given that together they are the third most frequent cancer in incidence but the second in mortality, and this prevalence will increase in the next two decades as a result of aging and the expansion of populations in both developed and developing countries. The risk of rectal cancer varies from country to country and even within the same country, where subgroups may exist according to socioeconomic conditions or ethnicity. The risk also varies according to diet, lifestyle, and hereditary factors. Obesity has been associated with an increased risk of developing colon and rectal cancer [1] and has also been proposed as a factor that affects their prognosis [2]. However, the prognostic value of obesity in these patients is less established, with different studies describing associations in subsets of patients, and it has also been studied by mixing cases of both colon and rectum cancer. Considering the differences in the presentation and prognosis of colon carcinoma and rectal carcinoma, we consider it very important to study them separately.

On the other hand, Mexico has one of the largest (if not the largest) prevalence of obesity, increasing substantially since 1980 and affecting just over 30% of the population, and it is projected that by 2050 the proportion of obese men and women in Mexico will increase to 54% and 37%, respectively, with there being more obese people than overweight people [3].

In view of the great significance of both obesity and rectal carcinoma, this study aims to investigate the influence of overweight and/or obesity, at the time of diagnosis, on the clinicopathologic characteristics and the disease-specific survival rate of patients with rectal cancer in the Mexican population, where overweight and obesity predominates over normal weight. Our hypothesis is that overweight/obesity will be associated with lower survival rates compared to patients with normal weight.

## Material and methods

### Patients

The population consisted of patients who presented consecutively for the first time in our institution to receive care for rectal cancer during the period between 2009 and 2015. All patients older than 18 years who did not have a history of previous chemo or radiotherapy or another synchronous or metachronous tumour, or a history of a hereditary carcinoma, were included. Cases in stage IV were excluded because of their intrinsically worse prognosis and because their diagnosis and treatment protocols are very varied. The final sample consisted of 304 cases. The sample was obtained for non-probabilistic methods; however, statistical power was verified with G\*Power software (Universität Düsseldorf, Germany) to ensure the minimal group size reaching 80% of statistical power. Assuming that each group has

at least 55 cases and searching for a moderate size effect (0.3), the statistical power was 87%.

## Methods

The clinical variables were obtained from the patient's electronic files and consisted of age, sex, use of chemotherapy, use of radiotherapy, type of surgical resection, surgery method, recurrence, follow-up time, and status at the last visit (dead or alive). Particularly, we define obesity as body mass index (BMI) equal to or greater than 30 kg/m<sup>2</sup>, overweight as BMI of 25 to 29.9 kg/m<sup>2</sup>, and normal weight as BMI < 25 kg/m<sup>2</sup>. Measurement of height and weight was performed during the study protocol of patients at the first or second visit and was carried out by the nursing staff or the doctor who conducted the interview. Clinical staging was based on computed tomography and endoscopic ultrasound and was performed following the TNM system in its seventh edition [4]. The pathological variables were obtained from the pathology archives of our institution. All specimens are analysed systematically following the protocol adopted by Quirke and validated in our institution [5, 6]. The 304 cases were divided into three groups for comparison based on the BMI, named normal weight (BMI < 25 kg/m<sup>2</sup>), overweight group (BMI of 25–29.9 kg/m<sup>2</sup>), and obesity (BMI > 30 kg/m<sup>2</sup>).

## Follow-up and outcome

All patients underwent a follow-up program that included outpatient visits every 1 to 6 months for physical examination and carcinoembryonic antigen tests, as well as chest X-rays, abdominal CT, and colonoscopy every 1 to 3 years after the operation. Local recurrence was defined as the existence of tumour located within the initial surgical field and confirmed by histology. The time for calculating survival was determined as the date of surgery for rectal cancer until the last visit or event occurrence. The prognosis was assessed based on disease-specific survival (DSS), and death as a result of rectal cancer was treated as an event. Death resulting from causes other than rectal cancer was treated as censored. No patient was lost in the follow-up during the first two postoperative years.

## Statistical analysis

The statistical analysis was made with SPSS ver. 23.0 (IBM, Armonk, New York, USA). Variables were tested for normality using the Kolmogorov-Smirnov test; thereafter, numerical variables were summarised by median with interquartile range (IQR) or median with standard deviation (SD) as appropriate. Categorical variables were summarised by counts and percentages. Data were compared by a one-way ANOVA or Kruskal-Wallis test for numerical variables, and the  $\chi^2$  test for categorical variables. Survival analysis was performed with the Kaplan-Meier test, and differences of survival between groups were assessed with the log-rank test. Stratified analysis was performed by clinical stage, neo-adjuvant treatment, and adjuvant therapy use. Independent association of obesity was assessed with a Cox regression model controlled for factors associated with poor survival in univariate analysis. For all tests, significance was settled at a *p*-value < 0.05.

## Ethic statement

This work was authorised by the Ethics and Research Committee of our institution, with a waiver of informed consent because of its retrospective nature (approval number: Rev/18/03). Likewise, the anonymity of the participants is guaranteed, and we conduct this work in accordance with the Helsinki declaration, with honesty, integrity, and impartiality.

## Results

### General characteristics of the population

Of the total population, 157 (51.7%) were men and 147 were women. The median age was 58 years (IQR 50–65), and the mean BMI was 26.03 ± 4.06 kg/m<sup>2</sup>. At the time of presentation, 88.75% of the cases correspond to a stage III, 6.25% to stage II, and 5% were in stage I. As initial treatment 78.9% of the patients received neoadjuvant chemoradiotherapy, reaching the pathological response complete 63 (26.3%) patients and downstaging 153 (63.7%). Regarding the pathological characteristics, 168 (55.3%) of the tumours were grade 1 and 77 (25.3%) grade 3, 71 (23.4%) cases had lymphatic vessel invasion, 31 (10.2%) venous vessel invasion, 57 (18.8%) had perineural invasion, and 126 (41.1%) lymph node metastasis.

Two hundred (65.8%) patients underwent abdominoperineal resection, 69 (22.7%) a low anterior resection, 25 (8.2%) an intersphincteric resection, and 10 (3.3%) cases an exenteration; of the total, 160 (52.6%) were performed by laparoscopy. Sixty-five per cent of the cases had a complete mesorectal resection and 18.1% an almost complete resection, amounting to a total of 83.1% of adequate resections of the mesorectum. 88.2% of the cases had a surgical resection with negative margin, while 11.8% had a positive resection margin (microscopic).

### Characteristics of the groups

The characteristics of the groups are shown in Table 1; it can be seen that patients with obesity and overweight received a lower proportion of preoperative treatment because they also had a higher proportion of patients in stage II. On the other hand, overweight patients had a higher proportion of deaths and a lower baseline neutrophil/lymphocyte ratio, although with a statistical trend. The rest of the characteristics were similar among the groups.

### Survival analysis

The median follow-up of the patients was 25 months (IQR 15–42), in which time recurrence was recorded in 70 (23%) patients, while 43 (14.1%) died. During the study period, 12 cases had liver recurrence; seven (58.3%) were in normal weight patients, whereas three (25%) were presented in patients with overweight and two (16.7%) in patients with obesity. Overweight patients had a lower DSS than patients with normal weight and with obesity (Fig. 1), with a mean survival of 69.5 months, compared to 86.4 months for the obesity group and 81.15 months for the normal weight group. The estimated five-year DSS was 51% for the overweight group, 81% for the normal group,

**Table 1.** Basal characteristics and clinical outcomes of 304 patients with rectal cancer divided according to weight

Variable	Normal weight group (n = 127)	Overweight group (n = 122)	Obesity group (n = 55)	p*
Age, years (median [IQR])	58 (50–65)	57 (49–65)	58 (54–66)	0.383
Sex, n (%)				
Female	63 (49.6)	55 (45.1)	29 (52.7)	0.599
Male	64 (50.4)	67 (54.9)	26 (47.3)	
Body mass index, kg/m <sup>2</sup> (mean [SD])	22.24 (2)	27.17 (1.3)	32.25 (1.83)	< 0.001
Initial stage, n (%)				0.043
Stage I	1 (0.8)	1 (0.8)	3 (5.5)	
Stage II	4 (3.1)	10 (8.2)	5 (9.1)	
Stage III	122 (96.1)	111 (91)	47 (85.5)	
Neoadjuvance, n (%) (N = 240)				0.024
No	19 (15)	27 (22.1)	18 (32.7)	
Yes	108 (85)	95 (77.9)	37 (67.3)	
Downstaging, n (%) (N = 240)				0.983
No	39 (36.1)	35 (36.8)	13 (35.1)	
Yes	69 (63.9)	60 (63.2)	24 (64.9)	
Pathologic complete response, n (%) (N = 240)				0.053
No	86 (79.6)	69 (72.6)	22 (59.5)	
Yes	22 (20.4)	26 (27.4)	16 (40.5)	
Post-surgical tumoural stage, n (%)				0.138
pT0	21 (16.5)	26 (21.3)	15 (27.3)	
pT1	12 (9.4)	7 (5.7)	8 (14.5)	
pT2	37 (29.1)	24 (19.7)	9 (16.4)	
pT3	45 (35.4)	53 (43.4)	21 (38.2)	
pT4	12 (9.4)	12 (9.8)	2 (3.6)	
Post-surgical nodal stage, n (%)				0.899
pN0	75 (59.1)	71 (58.2)	32 (58.2)	
pN1	33 (26)	35 (28.7)	13 (23.6)	
pN2	19 (15)	16 (13.1)	10 (18.2)	
Histologic grade, n (%)				0.457
G1	21 (16.5)	24 (19.7)	14 (25.5)	
G2	77 (60.6)	63 (51.6)	28 (50.9)	
G3	29 (22.8)	35 (38.7)	13 (23.6)	
Hepatic recurrence, n (%)				0.461
No	120 (94.5)	119 (97.5)	53 (95.4)	
Yes	7 (5.5)	3 (2.5)	2 (3.6)	
Lymphatic vessel invasion, n (%)				0.768
No	95 (74.8)	96 (78.7)	42 (76.4)	
Yes	32 (25.2)	26 (21.3)	13 (23.6)	
Venous vessel invasion, n (%)				0.976
No	114 (89.8)	110 (90.2)	49 (89.1)	
Yes	13 (10.2)	12 (9.8)	6 (10.9)	
Perineural invasion, n (%)				0.637
No	105 (82.7)	96 (78.7)	46 (83.6)	
Yes	22 (17.3)	26 (21.3)	9 (16.4)	
Resection margin, n (%)				0.782
R0	111 (87.4)	107 (87.7)	50 (90.9)	
R1/R2	16 (12.6)	15 (12.3)	5 (9.1)	
Mesorectal quality, n (%)				0.430
Incomplete	24 (18.9)	19 (15.6)	8 (14.5)	
Near complete	18 (15)	28 (23)	8 (14.5)	
Complete	84 (66.1)	75 (61.5)	39 (70.9)	
No. of lymph nodes, median (IQR)	13 (10–18)	13 (9–17)	13 (8–19)	0.989
No. of lymph nodes with metastasis, median (IQR)	0 (0–2)	0 (0–1)	0 (0–2)	0.763
Neutrophil/lymphocyte ratio, median (IQR)	2.52 (1.91–3.5)	2.08 (1.63–3)	2.36 (1.8–2.94)	0.055
Surgery type, n (%)				0.252
Abdominoperineal resection	27 (21.3)	31 (25.4)	11 (20)	
Low anterior resection	86 (67.7)	75 (61.5)	39 (70.9)	
Exenteration	6 (4.7)	4 (3.3)	0	
Intersphincteric	8 (6.3)	12 (9.8)	5 (9.1)	

Table 1. Cont.

Variable	Normal weight group (n = 127)	Overweight group (n = 122)	Obesity group (n = 55)	p*
Laparoscopic resection, n (%)				0.252
No	60 (47.2)	63 (51.6)	21 (38.2)	
Yes	67 (52.8)	59 (48.4)	34 (61.8)	
Adjuvant treatment, n (%)				0.663
No	33 (26)	26 (21.3)	14 (25.5)	
Yes	94 (74)	96 (78.7)	41 (74.5)	
Follow-up (months), median (IQR)	26 (15–41)	24 (15–41)	25 (15–56)	0.627
Recurrence, n (%)				0.631
No	97 (76.4)	92 (75.4)	45 (81.8)	
Yes	30 (23.6)	30 (24.6)	10 (18.2)	
Mismatch repair status, n (%) (N = 176)				0.267
pMMR (proficient)	50 (67.6)	52 (72.2)	25 (83.3)	
dMMR (defective)	24 (32.4)	20 (27.8)	5 (16.7)	
Outcome, n (%)				0.033
Alive	114 (89.8)	97 (79.5)	50 (90.9)	
Dead	13 (10.2)	25 (20.5)	5 (9.1)	

\* $\chi^2$  test for categorical variables and Kruskal-Wallis test for numerical (except BMI – one-way ANOVA)

and 82% for the group with obesity. A stratified analysis was performed per stage, showing that the difference in survival persisted (Fig. 2A, 2B). Also, a stratified analysis was performed using neoadjuvant treatment (Fig. 2C, 2D) and adjuvant treatment (Fig. 2E, 2F), and the difference persisted. Finally, a multivariate analysis was performed with a Cox regression, without demonstrating an independent association of BMI with DSS.

## Discussion

We analysed the association of specific clinic-pathologic characteristics of rectal cancer and the prognostic influence of BMI categorised into normal weight, overweight, and obesity groups. Obesity and overweight groups were slightly more prone to present in earlier stages (stage I and II) and received neoadjuvant treatment in lower proportions. However, overweight patients died in a higher proportion than patients with obesity and normal weight.

In rectal cancer, a high BMI has been studied mainly as a risk factor or in surgical outcomes, and it is well demonstrated that surgical outcomes are very similar, establishing that surgical procedure does not strongly influence survival in patients with similar basal characteristics; if a difference in survival is found, it is probably due to the surgical procedure [7, 8].

A few studies have addressed the influence of BMI in the survival of rectal cancer patients. Chern *et al.* [7] showed in a series of 596 patients in stage I–III, non-statistical differences in DSS and overall survival (OS) between the obese (BMI > 30 kg/m<sup>2</sup>) and non-obese groups (BMI < 30 kg/m<sup>2</sup>). They found five-year DSS rates of 76% and 73% in patients without and with obesity, respectively ( $p = 0.75$ ) and five-year OS rates of 84% and 90% in patients without and with obesity, respectively ( $p = 0.92$ ). In addition, there was no statistically significant difference in local recurrence. Ballian *et al.* [9] did not find differences in DFS, but patients with BMI > 30 kg/m<sup>2</sup> had significantly

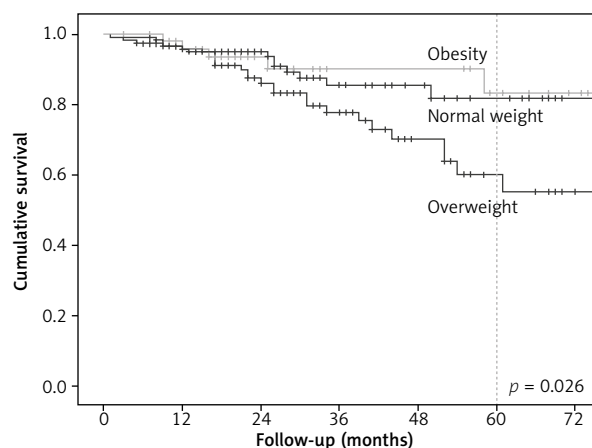
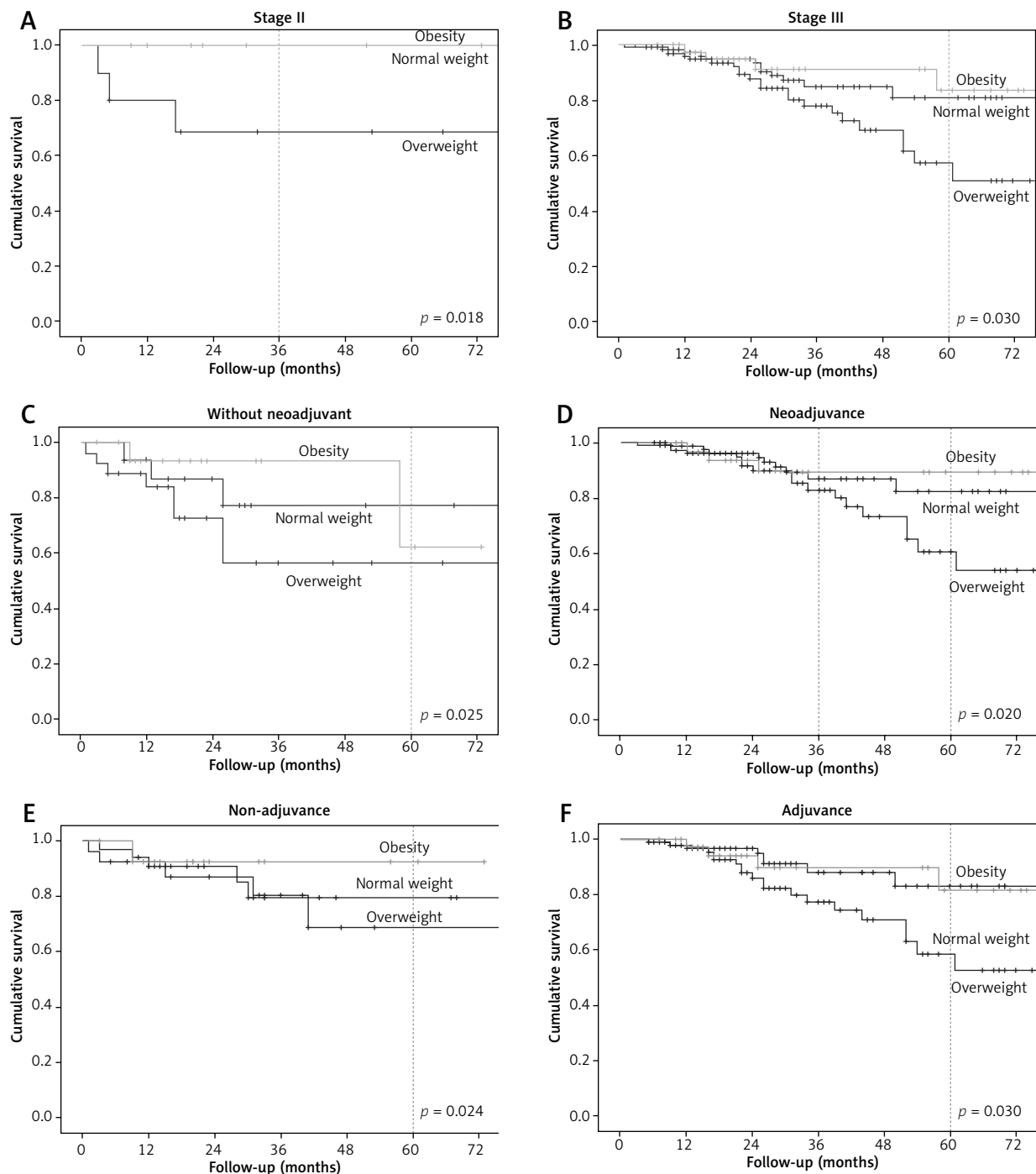


Fig. 1. Kaplan-Meier curves for disease-specific survival of 304 patients divided according to BMI categories. Patients in the obesity group (BMI  $\geq 30$  kg/m<sup>2</sup>) showed a mean survival of 86.4 months, normal weight patients (BMI < 25 kg/m<sup>2</sup>) showed a mean survival of 81.1 months, and patients in the overweight group (BMI 25–29 kg/m<sup>2</sup>) showed a mean of 69.5 months. The differences were tested with the log-rank test

longer OS (93% vs. 80%,  $p = 0.05$ ); however, multivariate analysis failed to show an independent association with OS. Gomez-Millán *et al.* [10] found that patients with BMI > 30 kg/m<sup>2</sup> were associated with a higher DFS (95% vs. 53%;  $p < 0.005$ ) than patients with BMI < 30 kg/m<sup>2</sup>. Seishima *et al.* [11] also found in a sample of 263 cases in Japan that the five-year DSS rates were 86.5 and 68.8 % in the BMI > 25 kg/m<sup>2</sup> and BMI < 25 kg/m<sup>2</sup> groups, respectively ( $p = 0.01$ ), but this difference was not independent in multivariate analysis.

The series dividing the BMI into four groups did not find significant survival differences. Sun *et al.* [12] found in a series of 522 patients that the five-year OS rates did not differ among groups of patients with BMI of < 25 kg/m<sup>2</sup>, 25–30 kg/m<sup>2</sup>, and > 30 kg/m<sup>2</sup> ( $p = 0.861$ ), but they found



**Fig. 2.** Kaplan-Meier curves for disease-specific survival of 304 patients divided according to BMI categories and stratified according to relevant characteristics. Patients in the overweight group (BMI 25–29 kg/m<sup>2</sup>) showed worse disease-free survival compared to patients in the normal and obesity groups. **A)** The survival difference persisted in stage II (the curves of the obesity and the normal group are superposed in the image), **B)** in stage III, **C)** in patients without neoadjuvant therapy, **D)** in patients with neoadjuvant therapy, **E)** in patients without adjuvant therapy, and **F)** patients with adjuvant therapy. For all figures, differences were compared using the log-rank test

that BMI > 25 kg/m<sup>2</sup> was associated with poorer T downstaging and thus poor local control following neoadjuvant chemo-radiotherapy in Asian patients. You *et al.* [13] in a series of 1873 Asian patients found no statistical difference for DFS among four BMI groups in the upper rectum ( $p = 0.14$ ) and lower rectum ( $p = 0.89$ ), but the five-year DSS rates were 67.6%, 78.9%, 77.4%, and 91.6% in underweight, normal, overweight, and patients with obesity

for upper rectal cancer, respectively; what is remarkable is that underweight and obese patients had a lower and higher five-year DSS rate, respectively, than the other groups. Denost *et al.* [14] found no differences in OS (five-year OS of 74%, 88%, 86%, and 88%, for underweight, normal, overweight, and patients with obesity, respectively,  $p = 0.724$ ), but importantly (as in our study) they considered important surgical/pathologic parameters like qual-

ity of mesorectum. In another study, De Felice *et al.* [15] also did not find significant differences in OS ( $p = 0.792$ ) or DFS ( $p = 0.807$ ) in patients stratified by BMI in four groups.

A convincing explanation for the influence of adiposity in cancer prognosis is difficult to find, and more intriguing is the fact that patients with obesity have similar disease-specific survival compared to patients with normal weight. It is postulated that adiposity is characterised by mild chronic inflammation, where white adipose tissue and resident macrophages secrete adipokines and cytokines, including tumour necrosis factor, interleukin (IL)-1, and IL-6 [16]. People with mild obesity may have sufficient nutritional reserves, which afford a more efficient metabolic state and thus allow proper inflammatory and immune responses to be evoked due to surgical stress [17] or metabolic stress because of the cancer. Although differences in metabolic tissues and immune responses may partly explain the different recurrence patterns observed for the groups with different BMI classifications, more research on this topic is required before this association can be confirmed.

An alternative explanation is that some works showed that the liver steatosis substantially decreases the risk of developing liver metastases, in both clinical observations as well in an experimental setting; this happens probably due to the changes in the microenvironment [18, 19]. Obese patients have a high frequency of liver steatosis and steatohepatitis, and then the probability of liver metastasis could be lower than normal weight patients. However, this information is controversial [20]. In our series, from 12 cases with liver recurrence, seven (58.3%) were presented in normal weight patients, whereas three (25%) were presented in patients with overweight and two (16.7%) in patients with obesity.

A patient with rectal cancer with overweight or obesity should require early adequate nutrition intervention because their status definitively does not exclude malnutrition. The evaluation of the baseline nutritional status of patients with rectal cancer should be a part of routine clinical practice [21].

The limitations of our study are the relatively short median follow-up period of 25 months – the calculated (not observed) five-year survival in our study is unlikely to capture adequately death from rectal cancer, which remains a significant threat for at least five years after resection.

## Conclusions

In conclusion, we found that patients with stage I–III rectal cancer in the overweight group showed a decreased survival rate, compared to groups with normal weight and with obesity, with the last two being similar. In addition, adiposity at the time of diagnosis could be a marker for patients who tolerated both preoperative chemo-radiotherapy and surgery, but there is an unsolved question as to why patients with “intermediate” adiposity (overweight but not obesity) had decreased survival.

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*The authors declare no conflict of interest.*

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**Submitted:** 17.04.2018

**Accepted:** 15.05.2018