



Original article

The impact of obesity on the histopathological characteristics of colorectal tumours. An observational study[☆]

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Background: To assess the influence of body mass index on the tumour characteristics of patients subjected to colorectal cancer surgery.

Materials and methods: Retrospective observational study. Patients subjected to curative elective colorectal cancer surgery at Hospital Josep Trueta of Girona (Spain), from 1990 to 2001.

Univariate and bivariate analyses were performed to evaluate differences in tumour characteristics with regard to body mass index.

Results: A total of 369 patients with colorectal cancer were included into the study, 213 (57.7%) with colon cancer, and 156 (42.3%) with rectal cancer. For colon cancer patients, when the BMI was higher than 25 kg/m², the tumour grade was worst ($P=.011$), and when BMI was above 30 kg/m² there were more lymph node metastasis. For rectal tumours, the higher the BMI, the more lymph node metastasis ($P=.041$), and higher tumour stage ($P=.023$).

Conclusions: Patients with a higher BMI have more lymph node metastasis when submitted to elective colorectal cancer surgery. In the case of colon cancer they also have worst tumour grades, and in the case of rectal cancer, a more advanced tumour stage.

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Impacto de la obesidad en las características anatomopatológicas de los tumores colorrectales. Estudio observacional

R E S U M E N

Palabras clave:

Índice de masa corporal
Obesidad
Neoplasia colorrectal
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Introducción: La obesidad es uno de los factores implicados en la génesis del cáncer colorrectal (CCR); sin embargo, no está claro cuál es el impacto que puede tener en las características anatomopatológicas de estos tumores una vez que se han desarrollado.

El objetivo de este estudio es determinar en nuestros pacientes cómo influye el índice de masa corporal (IMC) en las características histológicas de estos tumores.

Material y métodos: Estudio retrospectivo observacional. Se incluyó en el estudio a los pacientes intervenidos electivamente por CCR con intención curativa en el Hospital Universitario de Girona, España, durante los años 1990 a 2001. Se ha realizado un análisis descriptivo y bivariable para evaluar posibles diferencias en función del IMC por lo que respecta a los datos tumorales.

Resultados: Se incluyó en el estudio a 369 pacientes con CCR: 213 pacientes (57,7%) con cáncer de colon y 156 pacientes (42,3%) con cáncer de recto. En el caso de los tumores de colon, los pacientes con IMC mayor de 25 kg/m² tuvieron tumores peor diferenciados ($p = 0,011$), y los de IMC de más de 30 kg/m² tuvieron mayor afectación ganglionar que el resto. Para los tumores de recto, cuanto mayor fue el IMC mayor la afectación ganglionar ($p = 0,041$) y el estadio tumoral TNM ($p = 0,023$).

Conclusiones: Los pacientes con mayor IMC tienen mayor afectación ganglionar. En el caso del cáncer de colon son, además, tumores más indiferenciados, y en el caso del cáncer de recto son tumores en estadios más avanzados.

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Introduction

At present, the incidence rate of obesity in Western countries has reached epidemic proportions, and it is estimated that more than half of the European population between the ages of 35 and 65 is overweight or obese.¹ The tendency is similar in Spain, and obesity currently affects 13.2% of all men and 17.5% of all women aged 25 to 64.²

As we see with obesity, a higher incidence rate of some types of cancer is also being recorded in developed countries, particularly colorectal cancer (CRC).^{3,4}

The long-term prognosis for CRC depends on several factors, including the anatomical pathology characteristics of the excised tumours. Of these characteristics, tumour stage appears to be the main long-term prognostic factor.^{5,6}

If obesity has an effect on tumour stage at the time of diagnosis, or on the anatomical pathology characteristics of the surgical specimens, it has not been extensively analysed in medical literature. The purpose of this study is to evaluate our CRC patients to determine what impact body mass index (BMI) has on the anatomical pathology characteristics of the surgical specimen.

Patients and methods

The study included patients who underwent elective surgical procedures intended to cure CRC at Hospital Universitario of

Girona (Spain) between January 1990 and June 2001 (in these cases, there was no metastasis in neighbouring organs or affected lymph nodes outside of the tumour drainage area at the time of the surgery). Patients whose height and weight were not recorded before the procedure ($n=27$) were excluded, as were patients taking part in other studies during the time period in question.

The database for the General and Digestive Surgery Department prospectively records the data needed in order to analyse long-term survival of patients who undergo procedures intended to cure CRC.

The tumours were classified according to the TNM classification,⁷ and the Anatomical Pathology Department at Hospital Universitario of Girona carried out the histological study using conventional lymph node isolation techniques.

All recorded surgical procedures were carried out using general anaesthesia; the approach used was midline suprainfraumbilical laparotomy and the oncological resections were intended to cure the condition.

BMI was calculated by dividing the patient's weight in kilograms and dividing it by height in metres squared ($BMI=kg/m^2$). These data were taken before the operation when the patient had been admitted to the surgical ward. This continuous variable has been divided into categories according to WHO criteria⁸: underweight $<18.5 kg/m^2$; normal weight $18.5-24.9 kg/m^2$; pre-obese (overweight according to the Spanish Society of Obesity Studies): $25-29.9 kg/m^2$, obese $>30 kg/m^2$.

Other study variables were age, sex, tumour location, surgical technique used, tumour stage according to the TNM classification (I, II, III), histological tumour type, degree of tumour differentiation, type of tumour infiltration, lymph nodes isolated, and lymph nodes affected by neoplasia.

Statistical method

Retrospective observational study. We performed an overall univariate analysis of all patients with CRC and a separate univariate analysis specific to colon cancer (CC) and rectal cancer (RC).

As a bivariate analysis, we analysed the effect of BMI on each of the listed variables using SPSS statistics software version 10.0 for Windows. The ANOVA test is used to evaluate overall differences among different groups, and the subsequent tests were completed using Scheffé's method. A *P* value less than .05 was considered significant. Possible differences for categorical variables between groups were analysed using Pearson's χ^2 test or Fisher's exact test. For all cases, we have realized several subsequent analyses to compare 3 BMI groups, and in one case, 2 groups of up to 25 kg/m² and up to 30 kg/m².

Results

Univariate analysis

We studied 369 patients who met the inclusion criteria; weight and epidemiological data is shown in Table 1.

There are no statistically significant differences among the different BMI groups with respect to sex, age, and surgical history, whether for CRC, CC, or RC.

Seven (1.9%) of the patients with CRC were underweight, 182 (49.5%) were of normal weight, 118 (32.1%) were overweight, and 61 (16.6%) were obese.

Colon tumour data

In most cases, the tumour type was adenocarcinoma (93.9%). Well-differentiated tumours made up 46.9% of the cases; 45.5% were moderately differentiated; and 3.8% were poorly differentiated. Neural or lymphatic infiltration was present in 0.5% and 6.1% of cases, respectively; both were present in 1.9%. There was no infiltration in 90.6% of the cases. The tumour location was the right colon in 87 cases (40.9%), left colon in 121 cases (56.8%), and 5 patients (2.4%) had double or triple neoplasias. The TNM was stage I in 10 patients (4.7%), stage II in 125 (58.7%), and stage III in 78 (36.6%).

Tumour data for rectal cancer

Adenocarcinomas made up 95.5% of the tumours that were studied. Tumours were well-differentiated in 66 patients (43.7%), 81 (53.6%) had moderately differentiated tumours, and 3 patients (1.99%) had undifferentiated tumours. We found no lymphatic or vascular infiltration in 84.6% of the patients. There were 29 cases (18.6%) of upper rectal tumours, 56 cases of mid rectal tumours, and 71 cases (45.5%) of lower rectal tumours. TNM was stage I in 5 patients (3.2%) with RC; 96 patients (61.5%) were in stage II; and 55 patients (35.3%) were in stage III.

Bivariate study

Table 2 shows a summary of the most remarkable findings.

In our series, 4.1% of the patients were in stage I, 59.9% in stage II, and 36.0% in stage III. The TNM classification by BMI group is shown in Table 3.

We noticed a few non-significant differences having to do with tumour location. Obese patients had a higher incidence rate of right colon tumours, although this was not statistically significant, and patients with a normal weight had more

Table 1 – Epidemiological and weight data

	CC	RC	CRC
n (%)	213 (57.7)	156 (42.3)	369 (100)
Males ^a	122 (57.3)	102 (65.4)	224 (60.7)
Females ^a	91 (42.7)	54 (34.6)	145 (39.3)
Age ^b	66.2 (9)	66.5 (11)	66.3 (10)
	36–87	30–86	30–87
Weight, ^b kg	66.9 (12)	67.3 (13)	67.1 (13)
	39–114	4–112	39–114
Height, ^b cm	161 (9)	162 (9)	162 (9)
	138–187	138–183	138–187
BMI, ^b kg/m ²	25.6 (4)	25.4 (5)	25.5 (4)
	18.2–37.1	16.9–49.7	16.9–49.8

BMI indicates body mass index; CC, colon cancer; CRC, colorectal cancer; RC, rectal cancer.

^an (%).

^bMean (95% standard error) (min–max).

Table 2 – Tumour characteristics by body mass index

	CC	RC	CRC
Histological type	ns	ns	ns
Tumour stage, TNM	ns	ns	.023 ^c
Degree of tumour differentiation	ns	.011 ^a	ns
Type of tumour infiltration	ns	ns	ns
No. studied lymph nodes	ns	ns	ns
No. affected lymph nodes	ns	.043 ^b	.041 ^a

BMI indicates body mass index; CC, colon cancer; CRC, colorectal cancer; ns, differences not statistically significant; RC, rectal cancer; TNM, tumour neoplasia metastasis.

^aP when comparing patients with BMI <25 kg/m² and patients with BMI >25 kg/m².

^bP when comparing patients with BMI <30 kg/m² and patients with BMI >30 kg/m².

^cP when comparing 3 BMI groups.

left colon tumours. Rectal cancer was similar in proportion between both BMI groups.

In the initial analysis by BMI group, we found no differences in the degree of tumour differentiation.

Upon subsequently regrouping the patients into 2 BMI groups, we did find significant differences, as shown in

Table 3 – Body mass index and TNM tumour stage (P=.023) in rectal cancer

TNM stage	Normal weight	Overweight	Obese
I	2 (2)	3 (6)	0 (0)
II	56 (73)	24 (49)	12 (48)
III	19 (25)	22 (45)	13 (52)
n (%)			

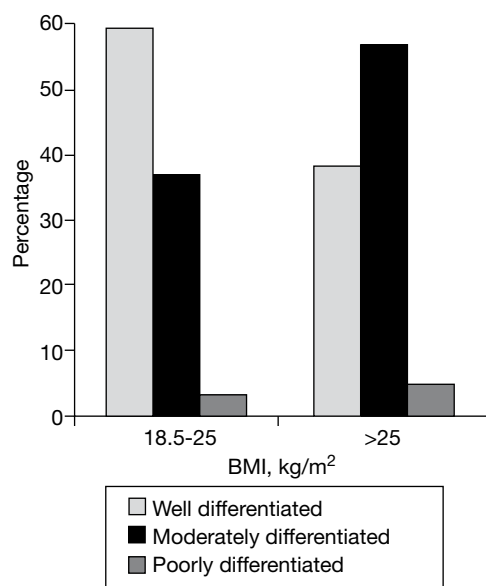


Figure – Body mass index and tumour differentiation (P=.011) in colon cancer.

Figure; patients with a higher BMI had more undifferentiated tumours.

Lymph nodes

There were no significant differences among the BMI groups when we analysed the number of examined and affected lymph nodes for the CRC series. In the subsequent analysis, however, we did detect increased lymph node involvement for CC where BMI exceeded IMC 30 kg/m² (P=.043) and in RC where BMI exceeded 25 kg/m² (P=.041). The mean number of lymph nodes is shown in Table 4.

Discussion

Pathological tumour type

In our series, as we see in medical literature, adenocarcinoma is the most common pathological type. It represents 93.9% of cases among patients with CC, and 95.5% of cases among patients with RC. All of the obese patients had an adenocarcinoma in both the CC and RC groups, but we found no significant differences among BMI groups. The explanation for our not finding any other histological types in obese patients may simply reside in the number of patients studied. We found no references in medical literature that indicate that BMI predisposes patients to a specific histological type of CRC.

Degree of differentiation

The more differentiated the tumour, the lower its cell division index. This gives a more favourable prognosis.⁹ We recorded 45.9% well-differentiated tumours, 49.2% moderately differentiated tumours, and 3% poorly differentiated tumours in the overall CRC series; data for the CC and RC analyses are very similar. Papp et al¹⁰ report that colorectal tumours are present in the following percentages according to their degree of differentiation: twenty percent well-differentiated tumours, 60% moderately differentiated tumours, and 20% poorly-differentiated tumours. These data are from patients

Table 4 – Body mass index and number of lymph nodes for colon and rectal cancer

	Lymph nodes	Underweight	Normal weight	Overweight	Obese
CC	Examined	12 (1.4)	13.6 (10.5)	12.0 (8.1)	12.8 (7.1)
		11-13	1-70	1-47	1-33
	Affected by neoplasia	1 (1.4)	1.1 (2.1)	0.9 (1.6)	1.2 (2.3)
RC		0-2	0-13	0-7	0-9
	Examined	12.4 (13.7)	12.0 (7.8)	9.7 (6.5)	12.1 (7.0)
		3-35	1-49	2-30	1-32
	Affected by neoplasia	0.2 (0.5)	1.0 (2.6)	1.6 (3.1)	1.6 (2.0)
		0-1	0-15	0-15	0-7
mean (95% SE) (min-max).					
CC indicates colon cancer; RC, rectal cancer.					

in the USA, and are generally not comparable to our data. In our area, we discover that Linares Santiago et al¹¹ found similar percentages to our own in their series in the province of Seville (47% well-differentiated tumours, 45.5% moderately differentiated tumours, and 7.5% poorly differentiated tumours). We must recall how difficult it is to classify tumours by their degree of differentiation, since different types of differentiation may exist inside the same tumour,⁹ and in normal daily practice at different hospitals, the degree of differentiation is quite subjective.¹²

In an initial analysis, we did not find significant differences in tumour differentiation among the 4 BMI groups, but when we assessed the degree of differentiation for CC patients of normal weight compared with those with a BMI over 25 kg/m² (overweight and obese), we found that patients with a higher BMI had more poorly differentiated tumours than patients of normal weight ($P=.011$).

It seems that the degree of tumour differentiation may be influenced by the degree of local inflammation and by factors such as metallothionein¹³ (anti-apoptotic, antioxidant protein with proliferative, and angiogenic properties), which is also secreted by adipocytes,¹⁴ and leptin. The latter is a neurohormone which is also synthesised primarily in adipose tissue. It plays an important role in alimentary behaviour and energy expense in mammals. This cytokine is also present in tissues other than adipose tissue, such as digestive tract mucosa. Koda et al¹⁵ analysed the relationship between leptin and CRC and found increased leptin expression in the colonic mucosa near the tumour, which indicates that a progressive increase in the local expression of leptin occurs during colorectal carcinogenesis. When the tumours are not differentiated, the leptin concentration in their tissues is lower than in moderately differentiated tumours ($P=.002$). The study by Koda et al¹⁵ shows that increased local leptin levels may contribute to CRC growth and progression.

In our CR patients, we found no associations between BMI and the degree of tumour differentiation. Since there is no clear link between obesity and RC genesis,¹⁶ leptin, and metallothionein may not play an important role in RC.

Tumour stage

The differences that appear among the BMI groups are not statistically significant, but they are certainly clinically relevant; one is the fact that we did not record a single case of stage I CRC in an obese patient. This result indicates that obesity may have an effect on tumour stage at the time of diagnosis. We believe that obesity may contribute to disguising the symptoms, which leads to a delayed diagnosis, and thus fewer confirmed cases in stage I. Likewise, Ferrante et al¹⁷ stated that obese patients have a 25% lower probability of receiving a CRC screening than non-obese patients (OR, 0.75; 95% CI, 0.62-0.91).

Studied lymph nodes/affected lymph nodes

Even though over the years the number of lymph nodes that must be included in the surgical specimen has been shown to be an independent prognostic factor for survival,¹⁸ there is

still some debate over the minimum number of lymph nodes needed for a study. The number of lymph nodes isolated depends on the isolation method used, and some studies of RC also indicate that obesity may be a determining factor.¹⁹ Most authors and surgical associations currently recommend isolating a minimum of 12 lymph nodes for CRC to receive correct statistics.²⁰ In our series, patients with CC had a mean number of 12.9 lymph nodes examined, and the mean number of affected nodes was one. BMI was not shown to be influential in this aspect of CRC.

However, the significant association that we discovered between BMI and the number of affected lymph nodes in CC is relevant. This fact did not surface in the first analysis, but it is apparent when the normal weight and overweight patients are grouped together and compared with obese patients. Obese patients have significantly more affected lymph nodes than patients with a BMI <30 kg/m² in the case of CC ($P=.043$). Meyerhardt et al also found similar data, in which more lymph nodes are affected by neoplasia where BMI is higher.²¹ For RC, we examined a mean number of 11.3 lymph nodes and the number of affected lymph nodes was 1.3 (2.7); there were no differences among the different BMI groups. Görög et al¹⁹ classify their patients as BMI <25 kg/m² and BMI >25 kg/m² and isolate fewer lymph nodes for obese patients with a surgical specimen measuring less than 16 cm. We did not find any differences in the number of isolated lymph nodes. Our mean number of isolated lymph nodes is much higher than that of the abovementioned authors (11.3 vs 6.7) who attribute their findings to having a small number of cases and a large numbers of surgeons and pathologists involved in the process.

Where RC is involved, it seems that classic methods of identifying lymph nodes are hard to perform and less effective than with CC, due to the characteristics of mesorectal fat and the frequent metastasis to lymph nodes smaller than 5 mm, which normally are not isolated.²²

With RC, as with CC, we did not observe a larger number of affected lymph nodes in the first analysis, but there were significant differences ($P=.041$) in later tests when all patients with a BMI higher than 25 kg/m² and compared with patients of normal weight: patients with a higher BMI had more affected lymph nodes. Meyerhardt et al obtained the same results in their RC series.²³

Therefore, CRC patients tend to have more affected lymph nodes with a higher BMI. For CC, the tumours are more poorly differentiated, and for RC, the tumours are at later stages.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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