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Original Article

Visceral obesity is not correlated with lymph node metastases nor Colorectal cancer survival

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ABSTRACT

Introduction: The presence of lymph node metastasis in colorectal cancer is determinant for prognosis and for treatment planning. The relationship between visceral fat and the prognosis is not fully documented in the literature, so this study intended to evaluate whether there is a relationship between the presence of visceral obesity and the presence of lymph node metastases and the prognosis of patients with colorectal cancer.

Materials and methods: A sample of 68 patients who underwent surgery for colorectal cancer at Hospital de Braga between 1/1/2007 and 31/12/2007 was constructed, and their clinical and pathological data were recorded. Visceral fat, subcutaneous, and total fat areas were measured on preoperative computed tomography. Visceral obesity was defined as a ratio of visceral fat to total fat area >0.29. The ratio of metastatic lymph node (; number of metastatic lymph node/number of lymph node examined) was calculated.

Results: There was a significant association between visceral obesity and male sex ($p = 0.032$). Patient survival at 5 and 10 years of follow-up was higher in patients with subcutaneous obesity in both periods, but not significant. There was a significant association between the ratio of metastatic lymph node and survival at 5 and 10 years ($p = 0.03$ and $p = 0.002$, respectively), with higher survival when ratio of metastatic lymph node = 0% and worse for ≥ 18%.

Conclusion: In this study, no significant association was observed between visceral obesity and the number of metastatic lymph node, nor with survival at 5 and 10 years.

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Obesidade visceral não está correlacionada a metastases nos linfonodos ou cancer coloretal

Palavras-chave:
Câncer colorectal
Obesidade visceral
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RESUMO

Introdução: A presença de metastização ganglionar no câncer colorretal é determinante como fator de prognóstico e para planear o tratamento. A relação entre a presença de gordura visceral e o prognóstico não está totalmente documentada na literatura. Assim, pretende-se avaliar a existência de relação entre obesidade visceral e a presença de metástases ganglionares e o prognóstico de doentes com câncer colorretal.

Materiais e métodos: Construiu-se uma amostra de 68 doentes operados por câncer colorretal no Hospital de Braga, entre 1/1/2007 e 31/12/2007, e registaram-se os seus dados clínico-patológicos e de seguimento. As áreas de gordura visceral, gordura subcutânea e gordura total foram medidas na tomografia computorizada pré-operatória. Obesidade visceral foi definida como um razão da gordura visceral relativamente à área total de gordura >0,29. Calculou-se a razão de linfonodos metastizados.

Resultados: Verificou-se uma associação significativa entre obesidade visceral e sexo masculino (p = 0,032). A sobrevida dos pacientes, aos 5 e 10 anos de seguimento, foi superior naqueles com obesidade subcutânea em ambos períodos, contudo não significativa. Verificou-se uma associação significativa entre a sobrevivência em função da razão de linfonodos metastizados, aos 5 e 10 anos (p = 0,03 e p = 0,002; respectivamente), com maior sobrevivência quando a razão de linfonodos metastizados = 0% e pior quando ≥ 18%.

Conclusão: Neste estudo não se observou uma associação significativa entre a obesidade visceral e o número de linfonodos metastizados nem com a sobrevida aos 5 e 10 anos.

Introduction

According to the World Health Organization, in 2012 colorectal cancer (CRC) was the third most frequent neoplasm worldwide and the fourth cause of death due to neoplasia.[1] In Northern Portugal, it is the second most common neoplasm, with an incidence rate of 41.6%; in the district of Braga, the incidence is 34%.[2,3]

CRC stage at diagnosis is the main determinant of survival and the main predictor of mortality.[3,4] The TNM system is the most widely used staging system[3]; the presence of ganglion metastasis is a determining factor for the indication of adjuvant chemotherapy and an important predictor of global and disease-free survival[3,5]

Despite the lack of consensus, the literature presents an increasing number of studies correlating obesity with CRC, namely presentation in more advanced stages, carcinoembryonic antigen (CEA) level, morbidity and mortality rates, and hospitalization time.[6–10]

Neumann et al.[7] reported that obesity in patients with CRC can lead to the formation of adenomatous polyps, and for each increment of one unit in the body mass index (BMI) above 30 kg/m^2, there will be a 1% increase in the frequency with which these CRC precursor lesions are found.

In non-smoking Korean women, CEA, which is overexpressed in CRC, was positively correlated with visceral obesity (VO) but not with subcutaneous obesity, although the mechanisms explaining this relationship remain unclear.[10]

In CRC, it has been demonstrated that the presence of VO is associated with longer surgical time,[8] higher morbidity,[6,8,9] and longer hospitalization time[8,9]; preoperative computed tomography (CT) can be used to quantify VO, helping to stratify at-risk patients.[8] Cakir et al.[9] documented that VO is significantly associated with anastomotic dehiscence, pneumonia, surgical wound infection, need for new surgical intervention, and longer hospitalization. VO is also associated with a lower incidence of lymph node metastases, probably due to the difficulty of access to deeper lymph nodes due to excess fat. However, Park et al.[6] found that the metastatic lymph node ratio (MLR; ratio between the number of metastatic lymph nodes and the number of lymph nodes examined) was only significantly associated with subcutaneous obesity (OS).

Thus, it is pertinent to assess whether VO, documented by preoperative CT, is associated with the presence of lymph node metastases and the prognosis of patients with CRC.

Methods

Patients and protocol

The studied population consists of the patients submitted to surgical treatment for CRC in Hospital de Braga from January 1, 2007 to December 31, 2007. Sample characterization was performed from an existing prospective database. The dates of death were updated as of June 12, 2017.

Of a total of 99 patients, 31 were excluded due to absence of/lack of access to preoperative CT.

Clinical–pathological data

The study collected individual (sex, age, tumor history, family history of CRC, and clinical presentation) and tumor data (location, macroscopic appearance, histological type, degree of differentiation, size, metastasis at diagnosis, number of lymph nodes assessed and metastasized, venous and lymphatic invasion, and pathological stage).

Tumor site was classified[11] as right colon (blind, ascending colon, colonic angle, and transverse colon), left (splenic angle, descending colon, and sigmoid colon) and rectum (between the anal margin and 15 cm in rigid proctoscopy).

The stage was defined based on the CRC TNM classification of the American Joint Committee on Cancer, 6th edition.

Each patient was followed-up until their death or the date of the last contact. In this study, the follow-up ended on June 12, 2017 (mean: 120 months).

The MLR was calculated. The cut-off point for MLR was set at 18%; patients were then stratified into MLR = 0%, MLR < 18%, and MLR ≥ 18%.[3,12,13]

Fat measurement

Subcutaneous fat was defined as that superficial to the muscles of the abdominal wall, while visceral fat was defined as that deep into the abdominal muscular wall (including mesenteric, retroperitoneal, and subperitoneal fat).[6]

Preoperative abdominal/pelvic CT was used to measure the fat area. The area of visceral fat was measured in an umbilical cross-section[6,14] by drawing a line immediately inside the abdominal wall, surrounding the abdominal cavity.[14] The same method was applied to calculate the total area of fat, this time drawing a line inside the skin. The ratio of visceral to total fat area (V/T) was then calculated, so as to use a single abdominal fat measurement that would be comparable with previous studies.[6] The cut-off point[6] was maintained at 29%, where V/T ≤ 29% indicated SO and V/T > 29% suggested VO.

Statistical analysis

The data were recorded in an Excel database and statistically analyzed through SPSS, v. 22.0 (SPSS Inc., Chicago IL, United States).

A descriptive analysis was carried out for all variables, and absolute value and relative frequencies were established. All correlations were analyzed for statistical significance using Pearson's chi-squared (χ^2) test and Fisher's exact test (when $n < 5$), and the results were considered statistically significant when $p < 0.05$.

Overall survival (OS) and disease-free survival (DFS) curves were determined using the Kaplan–Meier method and the log-rank test. SG was defined as the time period from the CRC diagnosis to death from any cause. DFS was defined as the interval from diagnosis to relapse.

The aforementioned data was collected under the approval of the Ethics Committee for Health of the Hospital de Braga; this approval had been previously obtained for previous studies (HSM 32/2013).

Results

Clinical–pathological characteristics

Table 1 describes the clinical–pathological characteristics of the sample.

Of the 68 patients in the sample, 67.6% were men and 32.4% women; 98.5% of the patients were over 45 years of age. A total of 16.2% of the patients presented history of tumors, and 10.3% of the sample had a family history of CRC. Of the total sample, 85.3% were symptomatic at presentation of the disease.

Regarding the characteristics of the tumor, 64.7% were located in the colon, 52.9% of the lesions were polypoid, and in 64.7% the tumor size was ≤4.5 cm. Histologically, all lesions were classified as adenocarcinomas; 50% were well differentiated, 76.5% presented subserosa and non-peritonized pericolic connective tissue involvement, 36.8% presented metastasized ganglia, 38.2% had venous invasion, and 54.4% had lymphatic involvement.

Evaluation of VO and SO

VO (V/T > 29%) was observed in 89.7% of patients, while OS (V/T ≤ 29%) was observed in 10.3% of patients.

Relation between clinical–pathological characteristics and VO

For the studied variables, it was observed that the male sex was significantly associated with VO ($p = 0.032$); 95.7% of the men in the present sample presented VO. In contrast, VO was observed in 77.3% of the women in the present sample. No other association was observed between VO and the remaining variables (Table 2).

Survival analysis

The Kaplan–Meier model was used to estimate five- and ten-year OS in VO and SO patients. Five-year OS was higher in SO patients, but this difference was not statistically significant ($p = 0.150$). A similar result was observed regarding ten-year OS ($p = 0.169$).

OS was also assessed regarding the MLR classification (MLR = 0%, MLR < 18%, and MLR ≥ 18%). It was observed that five-year OS was higher when MLR = 0% and worse in cases of MLR < 18% ($p = 0.03$). However, this negative effect on OS was only observed after about 50 months post-surgery; before that time, MLR ≥ 18% had a worse effect on survival (Fig. 1). Ten-year OS was significantly ($p = 0.002$) higher in patients with MLR = 0% and lower in those with MLR < 18%; however, this decrease in survival was only present at the end of the period considered, *i.e.*, over 100 months after resection. Until that date, survival was lower when MLR ≥ 18% (Fig. 2).

DFS

When comparing SO and VO patients, DFS was lower in the latter, but this difference was not statistically significant ($p = 0.236$).

Table 1 – Descriptive analysis of clinical–pathological characteristics of patients with CRC undergoing surgical therapy.

	Frequency (percentage) *n* (%)
Sex	
Male	46 (67.6)
Female	22 (32.4)
Age (years)	
≤45	1 (1.5)
>45	67 (98.5)
Tumor history	
Yes	57 (83.8)
No	11 (16.2)
Family history of CRC	
Yes	59 (86.8)
No	7 (10.3)
Presentation	
Asymptomatic	10 (14.7)
Symptomatic	58 (85.3)
Location	
Right colon	10 (14.7)
Left colon	34 (50)
Rectum	24 (35.3)
Macroscopic aspect	
Polypoid	36 (52.9)
Ulcerated	13 (19.1)
Infiltrative	10 (14.7)
Exophytic	3 (4.4)
Villous	1 (1.5)
CEA (ng/mL)	
≤10	54 (79.4)
>10	5 (7.4)
Metastases at diagnosis	
Yes	13 (19.1)
No	55 (80.9)
Tumor size (cm)	
≤4.5	44 (64.7)
>4.5	19 (27.9)
Histological type	
Adenocarcinoma	62 (91.1)
Mucinous adenocarcinoma	5 (7.4)
Signet-ring cell adenocarcinoma	1 (1.5)
Differentiation	
Well differentiated	34 (50)
Moderately differentiated	26 (38.2)
Little differentiated	3 (4.4)
Penetration	
Intramucosal carcinoma	1 (1.5)
Submucosal invasion	4 (5.9)
Muscular invasion	10 (14.7)
Subserosa/non-peritonized pericolic connective tissue invasion	52 (76.5)
Other organs or structures invasion	1 (1.5)
Ganglionar metastasis	
No	38 (55.9)
Yes	25 (36.8)
Venous invasion	
Absent	36 (52.9)
Present	26 (38.2)
Lymphatic invasion	
Absent	24 (35.3)
Present	37 (54.4)
TNM	
Stage I	12 (17.6)
Stage II	26 (38.2)
Stage III	24 (35.3)
Stage IV	6 (8.8)
Obesity	
Subcutaneous	7 (10.3)
Visceral	61 (89.7)

CRC, colorectal cancer; CEA, carcinoembryonic antigen.

DFS was assessed at three years, stratified by MLR (MLR = 0%, MLR < 18%, and MLR ≥ 18%). It was observed that DFS was higher when MLR = 0% and lower when MLR < 18%; however, this difference was not statistically significant ($p = 0.073$).

Discussion/Conclusion

CRC is a worldwide public health problem, representing the third most frequent neoplasm and the fourth leading cause of cancer death.[1] In the Northern region of Portugal, it is the second most common neoplasm.[2]

The clinical–pathological characteristics of the present sample were similar to those described in the literature[11–29]; CRC is more frequent in men[11,15,16] and in those aged over 45 years.[11,17–21] In fact, CRC is often defined as a disease of the elderly; advanced age is a risk factor for this neoplasm. In the present sample, 10.3% of patients had a family history of CRC. The literature indicates that a positive family history is strongly associated with CRC.[19,22] The figure documented in this study may be underestimated, as patients may not be aware of their family history.

It was observed that 85.3% of the patients were symptomatic at diagnosis. This number may reflect a low/non-existent rate of adherence to screening programs.

Regarding tumoral site, a higher frequency of tumors was observed in the colon (64.7%) compared to the rectum, especially in the left colon (50%). These results are in line with the literature.[23,24]

Histologically, most lesions (82.4%) were adenocarcinomas.

Staging is the main prognostic factor, with implications for survival. Most patients were classified as stage II (38.2%), while 8.8% were classified as stage IV, a figure lower than that in the literature (20%). [25]

Table 2 – Relationship between clinical–pathological characteristics and visceral obesity.

	Subcutaneous obesity	Visceral obesity	
	n – positive (%)	*n* – positive (%)	*p*
Sex			0.032
Male	2 (4.3)	44 (95.7)	
Female	5 (22.7)	17 (77.3)	
Age (years)			1.000
≤45	0 (0)	1 (100)	
>45	7 (10.4)	60 (89.6)	
Tumor history			0.316
Yes	2 (18.2)	9 (81.8)	
No	5 (8.8)	52 (91.2)	
Family history of CRC			0.562
Yes	1 (14.3)	6 (85.7)	
No	6 (10.2)	53 (89.8)	
Presentation			0.582
Asymptomatic	0 (0)	10 (100)	
Symptomatic	7 (12.1)	51 (87.9)	
Location			0.412
Right colon	1 (10)	9 (90)	
Left colon	2 (5.9)	32 (94.1)	
Rectum	4 (16.7)	20 (83.3)	
Macroscopic aspect			0.524
Polypoid	5 (13.9)	31 (86.1)	
Ulcerated	0 (0)	13 (100)	
Infiltrative	2 (20)	8 (20)	
Exophytic	0 (0)	3 (100)	
Villous	0 (0)	1 (100)	
CEA (ng/mL)			1.000
<10	7 (13)	47 (87)	
≥10	0 (0)	5 (100)	
Distant metastases			0.331
Yes	7 (12.7)	48 (87.3)	
No	0 (0)	13 (100)	
Tumor size (cm)			1.000
≤4.5	4 (9.1)	40 (90.9)	
>4.5	1 (5.3)	18 (94.7)	
Histological type			0.810
Adenocarcinoma	7 (11.3)	55 (88.7)	
Mucinous adenocarcinoma	0 (0)	5 (100)	
Signet-ring cell adenocarcinoma	0 (0)	1 (100)	
Differentiation			0.632
Well differentiated	2 (5.9)	32 (94.1)	
Moderately differentiated	3 (11.5)	23 (88.5)	
Little differentiated	0 (0)	3 (100)	
Tumor penetration			0.718
T1	1 (20)	4 (80)	
T2	1 (10)	9 (90)	
T3	3 (6.3)	45 (93.8)	
T4	0 (0)	1 (100)	
Lymph node involvement			0.640
Absent	4 (10.5)	34 (89.5)	
Present	1 (4)	24 (96)	
Venous invasion			0.388
Absent	4 (11.1)	32 (88.9)	
Present	1 (3.8)	25 (96.2)	
Lymphatic invasion			0.290

Table 2 (Continued)

	Subcutaneous obesity	Visceral obesity	
	n – positive (%)	*n* – positive (%)	*p*
Absent	3 (12.5)	21 (87.5)	
Present	1 (2.7)	36 (97.3)	
TNM			0.675
Stage I	2 (16.7)	10 (83.3)	
Stage II	2 (7.7)	24 (92.3)	
Stage III	3 (12.5)	21 (87.5)	
Stage IV	0 (0)	6 (100)	
MRL (%)			0.347
0	6 (14.3)	36 (85.7)	
<18	0 (0)	9 (100)	
≥18	1 (5.9)	156 (94.1)	

CRC, colorectal cancer; CEA, carcinoembryonic antigen; MLR, number of metastasized lymph nodes/number of lymph nodes examined.

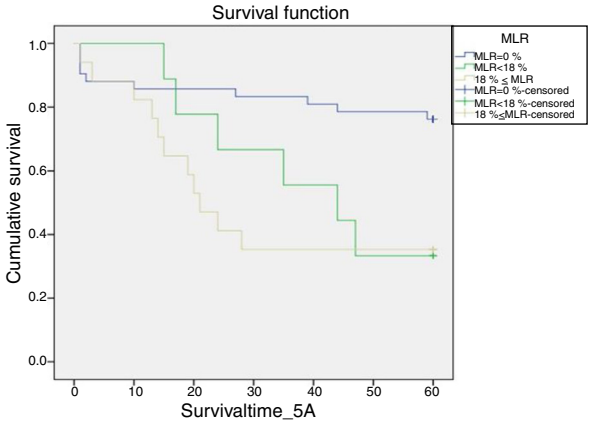

Fig. 1 – Five-year overall survival (OS) curves according to the MLR classification. The scale of the survival is in months (five years = 60 months). The Kaplan–Meier model was used to estimate survival per MLR category (MLR = 0%, MLR < 18%, and MLR ≥ 18%) for the 68 patients. Patients with MLR = 0% (blue line) had significantly ($p = 0.03$) better five-year OS, while those with MLR ≥ 18% (beige line) had poorer survival; however, only until approximately 50 months post-surgery. In the last ten months, approximately, MLR < 18% (green line) negatively contributed to OS.

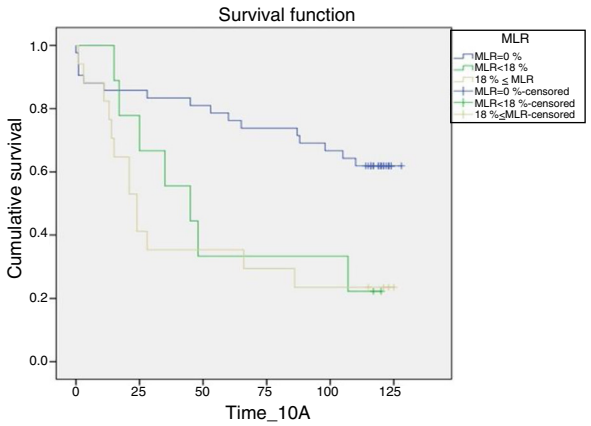

Fig. 2 – Ten-year overall survival (OS) curves according to the MLR classification. The scale of the survival is in months (ten years = 124 months). The Kaplan–Meier model was used to estimate survival per MLR category (MLR = 0%, MLR < 18%, and MLR ≥ 18%) for the 68 patients. Patients with MLR = 0% (blue line) had significantly ($p = 0.002$) better ten-year OS, while those with MLR ≥ 18% (beige line) had poorer survival. However, near the end of the study period, a reversal of the curves was observed, with MLR < 18% (green line) associated with worse survival.

Venous and lymphatic invasion, which are adverse prognostic factors, were observed in 38.2% and 54.4% of the present patients, respectively. The literature presents rates of vascular invasion between 10% and 89%.[26] These differences may be a consequence of the difficulty of diagnosing invasion and the different criteria used both in the identification of invasion and in the selection of patients.

Regarding tumor differentiation, in the present sample 50% of the CRC were well differentiated, in agreement with other studies.[27–29]

VO was present in 89.7% of patients, a figure higher than that reported by Park et al.[6] The only relationship observed was between VO and male sex ($p = 0.032$), a finding not previously described.[6]

Park et al.[6] associated the presence of lymph node metastases with a low V/T ratio. This finding was not observed in the present study ($p = 0.640$). This may be due to the reduced sample size, as well as the large difference between the VO and SO groups.

Five- and ten-year OS was estimated for VO and SO patients. Although survival was higher in SO patients in both periods, this difference was non-significant ($p = 0.150$ and $p = 0.169$, respectively), which may be due to confounding factors such as individual patient characteristics. The literature indicates[6] that VO patients tend to have better survival, which was not observed in the present study.

When OS was stratified by MLR, five-year OS was significantly ($p = 0.03$) higher when MLR = 0% and worse in cases of MLR ≥ 18%, but this latter finding only remained until

approximately 50 months after surgery, after which those with MLR < 18% presented worse OS. The same was observed at ten years, with worse survival when MLR < 18%, but only near the period considered.

No significant differences were observed regarding three-year DFS, whether regarding V/T or MLR, although this interval was lower in VO and MLR < 18%.

The main limitation of this study is its small sample size, as well as the large difference between the VO and SO groups. The retrospective nature of the present study implies incomplete data, which also leads to a selection bias (for example, only patients with preoperative CT were considered). A better definition of the cut-off point is also required to accurately classify VO by V/T, as there is a shortage of data in the literature.

In conclusion, in the present study no significant association was observed between VO and the number of metastatic ganglia, nor with five- and ten-year OS. Nonetheless, a significant association was observed between MLR and five- and ten-year OS. New studies, which take into account the limitations described here, are necessary to clarify these associations and bring new light to the study of CRC, aiming to provide the best treatment for each patient.

Conflicts of interest

The authors declare no conflicts of interest.

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