Influence of Visceral Fat in the Outcomes of Colorectal Cancer

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Keywords

Visceral fat · Obesity · Colorectal cancer · Morbidity · Survival

Abstract

Aim: To determine the relationship of visceral fat (VF) with the surgical outcome of the patients with colorectal cancer (CRC) submitted to curative surgery. **Methods:** Retrospective analysis of all patients submitted to CRC surgery during 3 years with a minimum of 5 years of follow-up. We assessed the length of hospital stay, complications, pathologic reports, surgical re-interventions and hospital re-admissions, relapses, survival time and disease-free time. VF was calculated based on patients' pre-operative CT-scan. The patients were divided into quartiles according to the VF area. Linear regression models and logistic regression models were used to establish a relationship between VF and all data collected. **Results:** The study included 199 patients (129 with colon cancer [CC] and 70 with rectal cancer). The average area of VF was 115.7 cm². Patients with CRC revealed a direct relationship between VF and postoperative complications ($p = 0.043$), anastomotic leakage ($p = 0.009$) and re-operation ($p = 0.005$). The subgroup of patients with CC had an inverse as-

sociation between VF and lymph nodes harvested ($p = 0.027$). Survival analyses did not reveal significant differences. **Conclusion:** VF has an influence on postoperative complications, anastomotic leakage and re-operation. A negative influence of VF on lymph nodes harvested was observed on CC patients.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide [1]. Obesity is a global health growing problem. According to the World Health Organization, 39% of adults aged 18 years and over were overweight in 2014, and 13% were obese [2]. In Portugal, like most developed countries, the prevalence of overweight is more than 50% [3, 4].

Although body mass index has been used as one of the most reliable anthropometric indices of obesity because of its simplicity and objectivity, it does not reflect body adipose tissue accumulation, especially intra-abdominal or visceral fat (VF) tissue, and is not always consistent with VF area [5].

Waist circumference has been suggested to be a better marker for central obesity and is easier to obtain from patients. However, in some studies, it was proven to be insufficient to distinguish between subcutaneous and visceral fat [6]. A single slice area is sufficient to measure the abdominal fat [7]. Different levels are described in literature, but VF and subcutaneous fat quantification can be easily measured by single slice CT-scan going through the umbilicus [8].

Gastrointestinal surgeons know that the amount of fat can greatly influence the technical difficulty during abdominal surgery [9]. The increase of VF has been associated with a significant increase of surgical wound infection, anastomotic leak, re-interventions and an increase in post-operative hospital stay when compared to VF free patients [10–13]. However, other studies did not agree with this influence of VF [14]. The influence of VF on survival also remains unclear.

The main propose of this study is to evaluate the impact of VF on 30-days morbidity, tumor features and 5-year survival on patients undergoing CRC surgery with curative intent.

Material and Methods

Study Design and Selection of Patients

A retrospective study that included all patients submitted to a curative CRC surgery at Hospital de Braga during 3 consecutive years (between January 2007 and December 2009) was conducted. Of the 355 patients reviewed, 45 patients were excluded because they were operated in an emergency setting and 27 patients were excluded because they had a metastatic disease at presentation (Dukes D). Of the remaining 283 patients, 84 were excluded because they had CT scans from outside hospitals and images were not available for analysis (Fig. 1).

Data Collection

Detailed information was obtained from the clinical records, which included demographic information, length of hospital stay, complications at 30-days (Clavien-Dindo Classification), re-operation or readmission at 30-days, anastomotic leakage and pathological reports. Anastomotic leakage was defined as an abscess or air near the anastomotic site that was diagnosed based on endoscopic and radiologic findings together with clinical symptoms and signs such as a change in drainage color or signs of peritonitis that required re-operation or antibiotic treatment (e.g., in patients with colorectal anastomotic leak submitted to anterior resection with protective ileostomy and no sign of sepsis).

Patient follow-up was conducted during 5 years or until death or the last contact date. Tumor recurrence, place of recurrence and date of recurrence were recorded.

A single cross-sectional scan at the level of the umbilicus was selected for fat quantification. A scientific image-analysis programme, ImageJ, was used for subcutaneous and VF area measure (<http://imagej.nih.gov/ij>). Subcutaneous fat was defined as fat that

Fig. 1. Flowchart of the patients included in the study.

is superficial to the abdominal wall musculature, whereas VF is deep in the muscular wall and includes the mesenteric, subperitoneal and retroperitoneal parts (Fig. 2). For statistical analysis, VF area was divided into 4 quartiles.

Data Analysis

Descriptive statistics are presented as absolute (n) and relative (%) frequencies for categorical variables, and mean (M) and SD for quantitative variables. The chi-square test was used to identify associations between dichotomous outcomes, and oneway analysis of variance was used to compare continuous variables. The Kaplan-Meier model with log-rank test was used to assess the impact of different characteristics on survival. A value of $p < 0.05$ was considered significant. All statistical analysis was performed with the IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA).

Ethical Issues and Informed Consent

This retrospective study is based on recorded data study. Informed consent was not able to be obtained from every patient, but this study design and use of data for the purpose intended was approved by the Ethic Committee of Hospital de Braga. The authors made sure to safeguard the anonymity and confidentiality of all the participants.

Results

The study included 199 patients with CRC with an average age of 68 years, of whom 124 (62.3%) were male. There were 129 patients with colon cancer (CC) and 70 with rectal cancer (RC). The clinicopathological characteristics of the patients are presented in Table 1.

Statistical analysis was performed for CRC patients group ($n = 199$) and for sub-groups of CC patients ($n = 129$) and RC patients ($n = 70$; Table 2).

The CCR group of patients presents significant differences in terms of 30-days morbidity ($p = 0.043$),

Fig. 2. Visceral fat (VF) quantification at ImageJ programme. **a** CT-scan. **b** Total fat measure (262 cm²). **c** VF measure (61 cm²).

Table 1. Clinicopathological characteristics of patients

Variables	CRC	CC	RC
Number of patients	199	129	70
Age, years	68.2±11.0	69.4±11.2	68.4±10.8
Gender, male, %	62.3	66.7	54.3
ASA, %			
ASA I	11.1	13.2	7.1
ASA II	60.3	55.0	70.0
ASA III	25.1	29.5	17.1
ASA IV	1.0	0.8	1.4
Missing	2.5	1.6	4.3
Laparoscopic surgery, %	3.5	4.7	1.4
Dukes classification, %			
Dukes A	19.1	16.3	24.3
Dukes B	40.7	45.7	31.4
Dukes C	40.2	38.0	44.3
Lymph nodes			
Positive, <i>n</i>	1±2.6	1±2.5	1±3.0
Harvest, <i>n</i>	11±8.1	11±7.8	11±8.7
≥12 lymph nodes harvested, %	37.7	39.7	33.8
Adjuvant QT, %	57.3	51.9	67.1
Post-operative hospital stay, days	10.0±11.0	9.8±10.8	10.3±11.4
30-days morbidity, %	25.1	24.0	27.1
Minor morbidity	15.1	14.7	15.7
Major morbidity	10.1	9.3	11.4
Anastomotic leak, %	7.5	7.0	8.6
Wound infection, %	17.6	16.3	20.0
30-days re-operation, %	7.0	7.0	7.1
30-days re-admission, %	4.0	3.9	4.3
5-years relapse, %	26.8	24.0	31.9
5-years mortality, %	38.2	37.2	40.0
Overall survival, years	5.2±2.6	5.2±2.6	5.3±2.5
Disease free survival, years	4.6±3.0	4.6±3.0	4.6±2.9
Total fat area, cm ²	303.6±119.3	291.7±114.8	325.6±125.0
Visceral fat area, cm ²	115.7±63.3	113.2±61.7	120.2±66.4

CRC, colorectal cancer; CC, colon cancer; RC, rectal cancer; ASA, American Society of Anesthesiologists Score.

anastomotic leak ($p = 0.009$) and re-operation ($p = 0.005$). Despite not being statistically significant, the patients with more VF area present a long post-operative hospital stay, and more wound infections. Pathologic variables (Dukes stage and lymph nodes) were not statistically different between the quartiles of VF area.

The analyses of the CC sub-group revealed significant differences in terms of anastomotic leak ($p = 0.008$) and re-operation ($p = 0.008$), like the in the CRC group. However, this sub-group also presented with significant differences on the number of lymph nodes harvested ($p = 0.027$) and the percentage of patients with at least 12 lymph nodes harvested ($p = 0.003$).

The RC sub-group presents no statistically different outcomes.

In terms of survival analysis, the Kaplan-Meier curves demonstrate that patients on the first and fourth quartiles have a slight better overall survival (Fig. 3) and disease-free survival (Fig. 4), although this difference is not significant (log-rank $p = 0.768$ and $p = 0.704$, respectively).

Discussion

The influence of VF on outcomes in patients who were submitted to curative CRC surgery remains controversial. One of the reasons that explain part of this disagreement

Table 2. Surgical and oncologic outcomes of CRC, CC, RC patients according to visceral fat area distribution into quartiles

	CRC (quartiles)					CC (quartiles)					RC (quartiles)				
	1st	2nd	3rd	4th	<i>p</i> value	1st	2nd	3rd	4th	<i>p</i> value	1st	2nd	3rd	4th	<i>p</i> value
Patients, <i>n</i>	50	50	50	49		33	35	34	27		17	15	16	22	
Age, years	66.1	69.8	70.9	69.3	0.155	67.2	69.9	71.7	68.7	0.409	64.0	69.6	69.2	69.9	0.327
ASA, %					0.241					0.497					0.108
ASA I	5.2	3.6	2.1	0.5		4.7	5.5	2.4	0.8		6.0	0	1.5	0	
ASA II	14.4	14.9	16.0	16.5		13.4	13.4	15.7	13.4		16.4	17.9	16.4	22.4	
ASA III	5.2	6.2	6.7	7.7		6.3	7.9	8.7	7.1		3.0	3.0	3.0	9.0	
ASA IV	0.5	0	0.5	0		0.8	0	0	0		0	0	1.5	0	
Postoperative hospital stay, mean, days	8.22	8.68	9.88	13.2	0.100	8.9	7.7	10.4	13.0	0.261	7.0	10.9	8.7	13.5	0.323
Dukes classification, %					0.507					0.733					0.795
Dukes A	3.5	6.0	5.0	4.5		3.9	5.4	3.9	3.1		2.9	7.1	7.1	7.1	
Dukes B	12.1	10.6	10.6	7.5		13.2	13.2	12.4	7.0		10.0	5.7	7.1	8.6	
Dukes C	9.5	8.5	9.5	12.6		8.5	8.5	10.1	10.9		11.4	8.6	8.6	15.7	
Lymph nodes															
Positive, <i>n</i>	1	1	2	1	0.790	1	1	1	1	0.998	1	2	2	1	0.586
Harvest, <i>n</i>	13	11	9	11	0.166	15	10	10	10	0.027	10	12	9	12	0.750
≥12 lymph nodes harvested, %	13.6	8.9	6.8	8.4	0.091	17.5	7.9	7.1	7.1	0.003	6.2	10.8	6.2	10.8	0.322
30-days morbidity, %	3.5	5.0	7.5	9.0	0.043	3.9	3.9	8.5	7.8	0.071	2.9	7.1	5.7	11.4	0.347
Minor morbidity, %	2.5	3.5	4.0	5.0	0.537	3.1	3.1	4.7	3.9	0.796	1.4	4.3	2.9	7.1	0.495
Major morbidity, %	1.0	1.5	3.5	4.0	0.115	0.8	0.8	3.9	3.9	0.067	1.4	2.9	2.9	4.3	0.875
Anastomotic leak, %	0.0	1.1	2.8	4.5	0.009	0.0	0.0	3.1	3.9	0.008	0.0	4.0	2.0	6.0	0.455
Wound infection, %	2.5	4.0	5.5	5.5	0.315	2.3	2.3	6.2	5.4	0.115	2.9	7.1	4.3	5.7	0.485
30-days reoperation, %	0.0	0.5	2.5	4.0	0.005	0.0	0.0	3.1	3.9	0.008	0.0	1.4	1.4	4.3	0.435
30-days re-admission, %	1.5	2.0	0.5	0.0	0.162	1.6	1.6	0.8	0.0	0.592	1.4	2.9	0.0	0.0	0.187
5-years relapse, %	5.7	7.2	8.2	5.7	0.575	4.8	5.6	8.0	5.6	0.622	7.2	10.1	8.7	5.8	0.271

CRC, colorectal cancer; CC, colon cancer; RC, rectal cancer; ASA, American Society of Anesthesiologists Score.

may be the different definitions of VF used in the articles published: VF area or volume [11, 14–17], ratio between VF and subcutaneous fat area [10], ratio between VF and total fat area [12] and ratio between VF and body surface area [9]. In addition, the same definition, like for example VF area, has different cut-off points in different papers [18]. There is a necessity to determine the cut-off point of VF that defines obese patients in order to be able to compare results from different studies. In this paper, we used quartiles because we think that in our population the division of patients into quartiles may be more accurate.

Literature suggests that obese patients have a bigger risk of overall postoperative complications, surgical site infection, anastomotic leakage and colostomy complications [19–22]. A nationwide analysis from Sweden concluded that obese patients have increased post-operative complication rates [6]. A recent meta-analysis that aimed to determine the impact of visceral obesity on laparoscopic CRC surgery concluded that visceral obesity is associated with increased surgical difficulty and post-operative

morbidity [18]. However, a recent paper suggested that VF has no influence on intraoperative difficulties, post-operative complications, and postoperative recovery in patients with sigmoid colon or RC [14].

In our study, VF had influence on 30-days morbidity, anastomotic leak and re-operation rates on CRC patients with statistically significant differences. Patients with more VF area appear to have more wound infections and longer hospital stay; however, our results were not statistically significant. These results corroborated most of the literature already published that propose that CRC patients with higher VF are prone to have more complications.

However, the most relevant oncologic result of our data is that CC patients with higher VF have significant differences on the number of lymph nodes harvested and the percentage of patients with at least 12 lymph nodes harvested (accurate tumor staging). Current guidelines, like NCCN, for CC treatment suggest that a minimum of 12 lymph nodes need to be examined to establish N stage [23]. Those guidelines recommend that less than 12

Fig. 3. Overall survival analyzed by quartiles.

Fig. 4. Disease-free survival analyzed by quartiles.

lymph nodes retrieved constitute the high-risk factors for recurrence and adjuvant chemotherapy is beneficial to those patients [23]. Some papers concluded that the number of nodes harvested from patients with higher VF was significantly smaller [14, 17, 21] and others did not agree with this conclusion [10, 12]. This difference of lymph nodes harvested that we found on CC patients can have 2 explanations: VF increases surgical difficulty presenting as a problem for the surgeon to perform an accurate oncologic dissection and fat tissue adhering to the mesentery and makes the identification of the lymph nodes difficult for the pathologist [18].

The RC sub-group analysis did not retrieve any statistical differences. One of the explanations can be the lower number of patients included (70 patients).

The influence of VF on survival remains controversial. One recent review of the literature that analyzes the influence of VF and cancer survival encountered 6 papers of CRC patients, and only 4 of these papers related VF to survival [24]. Another review concluded that the increase in adiposity was associated with an increase of CC-related mortality and decreased the disease-free survival of CC in women and RC in men [25]. Other papers suggested that increased VF was a significant predictor of worst disease-free survival in patients with resectable CRC [10] and reduced overall survival in CRC patients receiving adjuvant chemotherapy [16]. In contrast, other works demonstrated that patients with higher VF tended to have better overall-survival than non-visceral obesity patients [12] and a meta-analysis concluded that there was insufficient evidence to prove the presence of a strong link between adiposity and survival [26]. Emerging literature reports the “obesity paradox” in cancer, which suggests that can-

cer survival is U-shaped and that extremes of weight may have better survival [27, 28]. Our results, although not statistically significant, show that patients on the first and fourth quartiles have a slight better overall survival and disease-free survival. We cannot explain why this happened, but maybe reflected some of the disagreement that exists around this.

The main limitations of this study include its retrospective design, which bears the issue of incomplete data and potential selection bias, and higher number of laparotomy, which does not reflect the current percentage of laparoscopy approach in CRC surgery.

Conclusion

The results suggest that VF increased likelihood of morbidity, anastomotic leakage and re-operations on CRC patients and lower number of lymph nodes harvest on the sub-group of CC patients.

The influence of VF in the number of lymph nodes harvested on CC patients are particularly interesting and should be verified in prospective trials with a larger set of patients. If the following studies support this difference in lymph nodes harvest, perhaps the most experienced surgeon and pathologist need to be called to deliver the best treatment to those patients.

Disclosure Statement

The authors certify that they have no conflicts of interest to disclose.

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