Comparison between abdominal fat measured by CT and anthropometric indices as prediction factors for mortality and morbidity after colorectal surgery

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Abstract

Aim : **This study aims to determine which anthropometric (body mass index (BMI), waist-hip-ratio (WHR) and waist-to-height ratio (WHtR)) and radiological (visceral fat area (VFA) measured by CT scan) measurements of adiposity correlated better with postoperative outcome of colorectal cancer (CRC) surgery. We also assessed which of these measurements best predicted overall survival (OS) and disease-free survival (DFS).**

Methods : **Data from 90 consecutive Caucasian CRC patients who underwent surgery for colorectal cancer between 2010 and 2011 with a median follow-up of 53.25 months were analysed. The correlations of different adiposity measurements and postoperative outcomes were determined using logistic regression models and multivariate analyses.**

Results : **Higher WHtR ($p = 0.007$) and VFA ($p = 0.01$) significantly increased the risk of overall morbidity, especially of Clavien-Dindo III or IV. The WHtR correlated best with VFA ($p < 0.0001$), which is considered the gold standard for measuring visceral fat, whereas BMI ($p = 0.15$) was not a good predictor of postoperative morbidity.**

Multivariate analyses showed consistently significant results for postoperative complications for VFA in combination with all of the other variables analysed and for WHtR, confirming that VFA and WHtR were reliable independent prognostic factors of morbidity.

VFA had a significant effect on OS ($p = 0.012$) but did not correlate with DFS ($p = 0.51$).

Conclusions : **Both VFA and WHtR independently provided predictive data for potential postoperative complications after CRC surgery. In case CT scan was used for diagnostic purposes, VFA should be used in routine clinical practice.** (Acta gastroenterol. belg., **2018,** 81, **477-483**).

Keywords: morbi-mortality ; colorectal surgery ; waist to hip ratio ; waist to height ratio ; visceral fat area ; survival.

Introduction

Epidemiological studies have demonstrated a significant correlation between visceral obesity and the incidence of colorectal cancer (CRC) (1,2). Moreover, the association of visceral obesity with CRC was previously shown to lead to relatively poor oncological outcomes, although these findings are under debate (3-5). Visceral fat obesity is a risk factor for several metabolic disorders, including dyslipidaemia, hypertension and insulin resistance (6). However, it is still not clear whether visceral fat directly contributes to poor outcomes or is merely a surrogate marker of other pathological alterations. In addition, some studies suggested that obesity measured by body mass index (BMI) was responsible for increased morbidity and mortality rates after colorectal surgery (7,8). Wang et al. (8) recently showed that BMI was associated with survival among CRC patients following a U-shaped pattern, with both the obese and the underweight patients being associated with higher mortality after CRC diagnosis.

There are many different methods that can be used to quantify total body fat mass and distribution, ranging from anthropometric techniques to bioelectrical impedance analysis, CT and MRI. Most frequently, although many studies have clearly shown that BMI does not necessarily correlate well with visceral fat, basic anthropometric measures such as BMI are still the most commonly used parameters to define obesity (8-15). Analyses of other anthropometric parameters, such as waist-to-hip ratio (WHR) (15) and waist-to-height ratio (WHtR) (12), have therefore been used to determine whether they correlated better with visceral fat.

CT and MRI are currently the gold standards for the quantitative assessment of intra-abdominal adipose tissue (16). The assessment of body fat tissue by multi-slice volume MRI is considered to have the highest correlation with total body adipose tissue (17) but is limited by accessibility and cost. Although its results are comparable with those obtained using CT imaging (18), Seidell *et al.* (19) showed that CT and MRI yielded different absolute values of fat areas, especially concerning visceral fat areas (VFAs), even if ranking of individuals based on their fat areas was similar for both methods.

Abdominal CT scan is routinely performed for diagnostic purposes. CT-based visceral fat analysis takes advantage of these readily available images and could therefore be performed quickly and easily prior to surgery.

This study aimed to evaluate which measurements of body fat (CT scan or BMI, WHR or WHtR) best predicted morbidity after colorectal surgery. Data were then analyzed to identify the best predictor of overall survival (OS) and disease-free survival (DFS).

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Patients and Methods

Patient characteristics

The study was based on the retrospective analysis of 90 consecutive Caucasian patients included in our prospective, single-centre, institutional database who underwent colorectal resection for CRC. All patients were operated in a single centre between 2010 and 2011. In line with IRB regulations, informed consent was waived according to the retrospective, non-interventional design of the study.

The data collected for each patient included the following variables: patient characteristics (age, gender, BMI, waist circumference (WC), hip circumference (HC), height, and lifestyle factors), medical history, treatment details, including any preoperative neoadjuvant radio- and/or chemotherapy), intraoperative details, pathological features (tumor location and staging defined according to TNM classification), significant perioperative and postoperative events, and long-term follow-up with assessment of late complications. Preoperative CT scans were reviewed to determine fat mass.

The patients were followed up every 3 months during the first 2 years and then every 6 months for up to 5 years, with regular clinical examinations, blood tests including CEA monitoring, and radiological examinations using CT scan or ultrasound.

Quantification of adipose tissue

The two main compartments of body fat tissue distribution are the subcutaneous and visceral fat areas (SFA and VFA), the latter one including intraperitoneal and retroperitoneal adipose tissue, each with completely different metabolic characteristics.

Different methods are used to measure body fat, and each method differently evaluates the ratio between the two fat areas.

In our study, fat mass was assessed using 4 different methods based on anthropometric measurements performed at baseline recruitment (including weight, height, waist and hip circumferences) and on the preoperative abdominal CT scan.

1. BMI was calculated as weight in kilograms divided by the square of height in metres.
2. WHR was calculated as waist circumference (WC) divided by hip circumference (HC). Measurements were recorded in duplicate to the nearest 0.5 cm. The detailed measurement techniques were largely described in our previous study (15).
3. WHtR was calculated by dividing WC by height.
4. VFA was calculated using the preoperative CT images as data source.

CT scans used for the analysis were performed as part of the standard cancer staging before any therapeutic intervention. A transverse CT image from the third lumbar vertebra (L3) was analyzed for each patient, and the tissue area was estimated using Hounsfield unit (HU) thresholds and quantified with the Slice-O-Matic software, version 4.3 (Tomovision, Montreal, QC, Canada) (20). Assessment of the different adipose tissue areas was performed twice by one analyst in a blinded fashion, using the most commonly accepted CT-parameter ranges, inversely related to muscle fat content, of the pre-defined radiation attenuation Hounsfield Units (HU), i.e. from –190 to –30 HU (21). All CT images were analysed by a single trained observer, whose detailed measurements are presented in Figure 1.

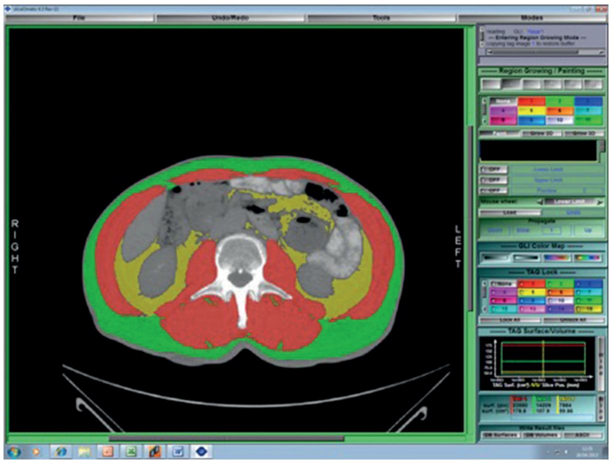

Fig. 1. — Slice-O-Matic Software for visceral fat analysis. Green area: subcutaneous adipose tissue. Red area: muscle. Yellow area: visceral adipose tissue. Whole-body fat mass (kg) = 0.042 x total adipose tissue at L3 (cm2) + 11.2
(adapted from HEYMSFIELD *et al.*, *Annu. Rev. Nutr.*,1997) (18).

For VFA measurements, the authors used the threshold for visceral obesity of 133 cm^2 for men and 91 cm^2 for women, as proposed in the literature (22).

Outcomes

Outcome data analyzed were the occurrence of severe postoperative complications as defined by a Clavien-Dindo (C-D) classification above or equal to grade III (23).

Furthermore, the potential influence of body fat on OS and DFS was assessed.

Statistical analyses

The data were recorded using Microsoft Office Excel. The statistical analyses were performed using JMP software (version 10).

Descriptive statistics were calculated using frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables.

Anthropometric measures were tested as continuous variables instead of using predefined categories, which might be inadequate in the particular context of colorectal surgery, as the World health organization BMI subgroups were developed to assess global health status and not as a risk factor for postoperative complications.

The Kaplan-Meier method was used to estimate OS and DFS rates.

The statistical significance of any association between BMI, WHR, WHtR, with VFA and outcome measures was calculated using likelihood ratio tests. Predictions for the risk of complications were analyzed using logistic regression models adjusted for the 4 anthropometric markers. All *p* values below 0.05 were considered statistically significant.

The accuracy of the statistical models was measured using the Akaike information criterion (AIC), as lower AIC values indicate a model with minimal loss of information, although provide no information about how well a model fits the data in an absolute sense. The pseudo R^2 value is an extension of the R^2 measure in linear regression that expresses the percentage of variance explained by the model or the predictive value of the model. This measure includes values between 0 (no predictive value) and 1 (perfect prediction).

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards models to evaluate any association of the four fat tissue measurements with a hazard of death.

Pairwise correlations were used to screen for potentially significant associations between the 4 different body fat measurement methods.

Results

Patients and surgical characteristics

A total of 90 consecutive patients, 54 men and 36 women, who underwent colorectal surgery for cancer from 2010-2011 were included in this retrospective study. The median follow-up was 53.2 months (range: x - y months). Two patients were lost to follow-up due to emigration to another country (2/90 i.e. 2.2%, details can be found in Table 1).

Twenty-one (23,3%) of the 90 patients included in the present study underwent a right colectomy, 28 (31.1%) had a left colectomy whilst proctectomy was the surgery of choice for 41(45.5%) patients. Only 27 (30.0%) patients were managed according to an enhanced recovery programme.

All patients had R0 resections, and 6 (6.7%) patients simultaneously underwent a metastasis resection with complete tumor clearance. In total, 36 (40.0%) patients received postoperative chemotherapy, half of whom belonged respectively to the colonic and rectal patient groups.

Quantification of visceral obesity

Approximately half (48.9%)of the patients (n = 44) were overweight or obese according to their BMI, but only 12 (13.3%) patients had a BMI above 30. Thirty-four (63.0%) of the 54 men had a VFA above 133 cm², considered to correspond to visceral obesity in the literature (22). Yet 16 (47.1%), of these had a normal BMI, and only 2 (5.9%)were obese according to their BMI.

Only 13 (36.1%) of the 36 women had a VFA above 91 cm², although only 5 (13.9%) of these were obese according to their BMI.

All patients with VFAs above 133 cm² for men or 91 cm² for women had a WHR greater than 0.8 and a WHtR greater than 0.58.

The men had almost twice as much visceral fat area as the women (average 166.9 cm² vs. 78.9 cm²). The details

Table 1. — **Characteristics of the study population (n = 90)**

Patient characteristics	N (%)
Age (years)	
Mean (SD)	67 (13)
Median (range)	68 (41-89)
Gender	
Men	54 (60)
Women	36 (40)
Staging Colon	
I	10 (11.1)
II	19 (21.1)
III	16 (17.7)
IV	4 (4.4)
Staging Rectum	
I	14 (15.5)
II	12 (13.3)
III	12 (13.3)
IV	3 (3.3)
Comorbidity	
Cirrhosis	3 (3.3)
COPD	5 (5.5)
Diabetes	13 (14.4)
Type 1	3 (3.3)
Type 2	10 (11.1)
Metabolic syndrome	10 (11.1)
Ischemic heart disease	10 (11.1)
Neurological disorders	5 (5.5)
Pulmonary embolism	8 (8.8)
Smoker	10 (11.1)
Weight loss > 10% in 6 months	3 (3.3)
ASA Score	
I	2 (2.2)
II	58 (64.4)
III	30 (33.3)
IV	0 (0.0)
Previous abdominal surgery	22 (24.4)
Bowel preparation	53 (58.8)
Fleet	20 (22.2)
Moviprep	33 (36.6)
Surgical approach	
Open (laparotomy)	34 (36.6)
Laparoscopic	56 (63.3)
Conversion to Open	6 (6.6)
Surgical procedures	
Right colectomy	21 (23.3)
Left colectomy	28 (31.1)
Partial mesorectal excision	8 (8.8)
Total mesorectal excision	33 (36.6)
Enhanced recovery after surgery	27 (30.0)

COPD : Chronic Obstructive Pulmonary Disease ; ASA Score : American Society of Anesthesiologists Score.

Table 2. — **Distribution of adipose tissue according to gender**

	Women Mean (+/- SD)	Men Mean (+/- SD)
Weight (kg)	67.12 (12.89)	81.20 (13.16)
Height (cm)	164.11 (7.24)	175.48 (6.91)
BMI (kg/m^2)	25.48 (3.73)	26.01 (4.80)
WHR	0.90 (0.08)	0.98 (0.06)
WHtR	0.56 (0.07)	0.57 (0.06)
VFA (cm^2)	83.18 (74.63)	166.97 (93.44)

BMI : Body Mass Index (kg/m^2) ; WHR : Waist-to-Hip Ratio ; WHtR : Waist-to-Height Ratio ; VFA : Visceral Fat Area (cm^2).

Table 3. — **Pairwise correlations between the four different methods of body fat measurement**

Variable by Variable	Correlation coefficient	p value
BMI vs. VFA	-0.0325	0.7611
WHR vs. VFA	0.5741	< 0.0001*
WHR vs. BMI	-0.1313	0.2175
WHtR vs. VFA	0.6854	< 0.0001*
WHtR vs. BMI	-0.1557	0.1429
WHtR vs. WHR	0.6179	< 0.0001*

*: statistically significant correlation ($p \leq 0.05$) ; BMI : Body Mass Index (kg/m^2) ; WHR : Waist-to-Hip Ratio ; WHtR : Waist-to-Height Ratio ; VFA : Visceral Fat Area (cm^2).

of the adipose tissue measurements using the different measurement techniques are summarized in Table 2.

By performing a pairwise correlation between the four different measurement methods for visceral fat (Table 3),

Table 4. — **Short and long term follow-up**

30-days postoperative Follow-Up	
30-days Postoperative Mortality	0
Post-operative complications	33 (36.9%)
Severity of postoperative complications (Clavien-Dindo Classification)	
≤ II	83 (92.2%)
≥ III	7 (7.7%)
Reoperation	
Emergency	3 (3.3%)
Late	4 (4.4%)
Hospital Stay	
Mean (+/- SD)	9.7 (6.2)
Long Term Follow-Up	
Recurrence Patterns	
Local	1 (1.1%)
Distant	21 (23.3%)
Follow-Up	
Mean (months) (+/- SD)	53.25 (24.6)
5Y-DFS	61/90 (67.7%)
OS	
Mean (months) (+/- SD)	54.5 (25)
Deaths	
Cancer	21 (23.3%)
Other causes	8 (8.8%)

5Y-DFS : five-year disease-free survival ; OS : overall survival.

we found a significant association between the WHR, WHtR and VFA but no relationship with the BMI.

Mortality and morbidity

In six cases, a conversion to laparotomy was necessary, mostly for locally advanced tumors that necessitated an "en bloc" resection of neighbouring structures. A conversion was necessary in only one case of an obese

Table 5. — **Univariate analysis of the risk factors for postoperative outcomes (anthropometric measures have all been tested as continuous variables)**

Variable Category	All Complications OR	p value	C-D Classification ^{3} III OR	p value
Gender (male)	1.42	0.42	1.56	0.33
Age	1.01	0.27	0.99	0.81
VFA	1.00	0.09	1.00	0.01
WHR	5.31	0.54	0.58	0.13
WHtR	9.57	0.04*	3.00	0.01*
BMI	0.93	0.18	0.97	0.15
Weight	1.01	0.43	1.01	0.06
Mechanical Bowel Preparation (Yes)	2.57	0.04*	5.47	0.13
ASA Score (ASA III)	1.23	0.64	2.15	0.65
Tumour Location (Right)	0.66	0.36	0.40	0.52
Surgical Approach (Laparotomy)	2.62	0.04*	0.23	0.33
Conversion to laparotomy (Laparoscopy)	0.32	0.31	2.20	0.98
ERAS (enhanced recovery after surgery)(No)	0.30	0.03*	0.32	0.02*

*: statistically significant p value ($p \leq 0.05$) ; VFA : Visceral Fat Area (cm^2) ; WHR : Waist-to-Hip Ratio ; WHtR : Waist-to-Height Ratio ; BMI : Body Mass Index (kg/m^2) ; ASA Score : American Society of Anesthesiologists Score ; C-D Classification : Clavien-Dindo Classification.

Table 6. — **Multivariate analysis for postoperative outcomes. using age. gender. ASA score. ERAS. MBP. surgical approach and conversion as explanatory variables. goodness of fit and performance statistics**

	All Complications				C-D Classification		
	OR#	p value	AIC	PseudoR2	p value	AIC	PseudoR2
BMI	1.0645	0.306	124.2	0.14	0.323	296.2	0.25
WHR	0.0320	0.346	124.4	0.14	0.081	292.6	0.26
WHtR	0.0004	0.046	121.3	0.16	0.049*	291.3	0.27
VFA	0.9921	0.008**	118.3	0.19	0.001***	290.9	0.27

* : statistically significant p value ($p \leq 0.05$), ** : $p \leq 0.01$, *** : $p \leq 0.001$; BMI : Body Mass Index (kg/m^2) ; VFA : Visceral Fat Area (cm^2) ; WHR : Waist-to-Hip Ratio ; WHtR : Waist-to-Height Ratio ; ASA Score : American Society of Anesthesiologists Score ; C-D Classification : Clavien-Dindo Classification ; ERAS : enhanced recovery after surgery ; MBP : mechanical bowel preparation ; OR : odds ratios, #: per unit change in regressor ; AIC : Akaike Information Criterion.

male patient with rectal cancer due to difficult local anatomy.

Postoperative complications were mostly marked by postoperative ileus (n=9), surgical site infections (n =9), urinary infections (n =3) as well as 4 cases of anastomotic leak.

We observed no postoperative 30-days mortality. In total, 29 (32.2%) patients died during the follow-up period, due to cancer-related complications for 21(72.4%). of them

Twenty-one (23.3%) patients experienced recurrences, mostly in the form of hepatic metastases, pulmonary metastases, peritoneal carcinomatosis, cerebral metastases and pelvic local recurrence in one case. The results are summarized in Table 4.

Using univariate analysis, we tested clinically relevant factors that could influence postoperative morbidity (Table 5). VFA, WHtR, use of mechanical bowel preparation, open approach and lack of enhanced recovery after surgery (ERAS) techniques were significantly correlated with the occurrence of complications. In contrast, the univariate analyses of the other fat mass parameters did not reveal significant results.

Similar results were achieved using the same variables in relation to the C-D classification to differentiate less severe from severe complications.

The multivariate analysis combined the variables tested in the univariate analysis with each of the fat mass parameters. Both VFA and WHtR were observed to be independent prognostic factors of morbidity. The Akaike information criterion and the pseudo R^2 presented in Table 6 also showed consistently significant results for postoperative complications for both VFA and WHtR in combination with all of the other analysed variables.

Survival

Multivariable Cox regression analyses with the same factors used for the morbidity analyses together with each of the four visceral fat measurement methods showed that only VFA significantly influenced OS ($p = 0.012$) although it did not have an impact on DFS ($p = 0.51$). Neither WHR nor BMI showed any significant correlation with OS ($p = 0.20$ and 0.59, respectively) whereas there was only slight tendency of WHtR towards approaching statistical influence on OS ($p = 0.065$).

Discussion

Our study shows a significant positive correlation of visceral obesity, as measured by WHtR and VFA, on the occurrence of complications and their severity after colorectal surgery. On the other hand, we found a negative correlation with OS.

Numerous studies have demonstrated a correlation between increased VFA and the presence of a metabolic syndrome (14,24,25). In addition to the known effect of storing excess calories, visceral fat is a very hormonally active tissue that releases different bioactive molecules and hormones also known as adipokines (26). Thus, VFA is a potentially interesting factor for pre-operative analysis of its impact on postoperative morbidity, even if the underlying mechanisms by which visceral obesity impacts CRC prognosis are unclear. Previous studies suggest that insulin can enhance IGF-I bioactivity, leading to cell proliferation and protecting cancer cells from apoptosis (27). Other factors associated with obesity, such as insulin-like growth factors, sex steroids, adipokines, obesity-related inflammatory markers, the nuclear factor kappa beta (NF-kappa B) system and oxidative stress, are also considered to be potentially linked to cancer mortality (28).

In addition to the metabolic role, mechanical and anatomical considerations, such as a narrow pelvis and the presence of more fat in men, may also negatively influence the outcome. For example, our study found that men had twice the women's level of visceral fat. This finding explains why operating on male patients is typically associated with greater technical challenges and worse oncological outcomes (29-31).

Quantifying VFA on CT scans is easy, consistent and can be automatically conducted (32) with automated or semi-automated software, in a reasonably short time. Of course, a CT scan involves radiation risks, and its indication should always be well considered. However, a preoperative CT scan is a standard in cancer diagnostics and can therefore be used to determine visceral fat quite easily and without any financial implications.

Both WHtR and VFA significantly influenced post-operative morbidity, which confirm the results of a previous study (12). These measurements showed better results than those for WHR, which was considered the best anthropometric method to predict morbidity risks (15).

In our series, we did not find any significant correlation between BMI and poor postoperative outcomes, which was supported by the finding that BMI did not accurately quantify visceral fat.

In our series, we did not find a correlation between BMI, WHR and OS, which was contradictory to the conclusions of some previous studies (24,25,33-35). Conversely, the only large cohort study (8) to examine the relationship between pre-diagnosis BMI/WHR and prognosis in 1,452 Asian patients with CRC concluded that BMI was predictive of OS and that WHR was not associated with OS.

These discrepancies may be explained by several factors, such as the use of different methodologies and study designs (e.g., in our study, we used linear measurement, whereas other studies used cut-off values), subdivision of the groups (e.g., gender), heterogeneity of the populations studied, including important differences in results between different races, and the number of patients included. Thus, there is a need to conduct further research of anthropometric measures to determine sound cut-off values based on larger homogenous cohorts.

In our study, we found a correlation between the presence of visceral fat and OS. VFA was an independent prognostic factor of OS, which was also reported in a previous study (36). However, in a similar study conducted with Asian patients (37), no association was found between visceral obesity and overall survival for colon cancer, although the results might be subject to a potential selection bias. This discrepancy underscores the need to investigate this aspect more deeply and with significantly larger cohorts to confirm the potential correlation of VFA with OS rates.

Our study did not show any correlation of DFS with fat mass measurements. No comparison with pre-existing studies could be performed due to the scarcity of available results to date, which indicated only a lower BMI as a promising predictor of recurrence in curative CRC patients (38-40).

Regarding the best surrogate measurement of visceral fat, the results of our study showed that VFA correlated best with WHtR, followed by WHR, confirming the conclusions of recent studies that indicated that WHtR correlated better with adipose tissue compartments and VFA than BMI or even WHR (12). Our study also confirmed the lack of correlation between VFA and BMI.

The strengths of our study include the prospective database, the standardized anthropometric assessment and the long-term follow-up. The main weaknesses of this study were the small number of patients and the retrospective design. We chose this approach because we tried to restrict the selection of patients to focus as much as possible on a homogenous group by including only Caucasian people with CRC. This approach was chosen in light of the findings that there are important race-dependent differences in the body fat distribution; for example, Asians may have a higher level of visceral fat than Caucasians with the same BMI (41) and thus higher CRC-specific morbidity than other subjects with the same standard values (8).

Building on the conclusions of this study, our next step will be to try to determine the cut off values for VFA that influence morbidity based on a significantly larger number of patients determined using statistical power analysis.

To conclude, both VFA and WHtR can independently provide vital predictive data for possible postoperative complications and OS after CRC surgery. In light of the potential predictive role of VFA and WHtR, exploring further improvements of currently used risk assessment scores by embedding these factors will certainly be useful.

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