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Impact of Body Composition on Surgical Outcome in Rectal Cancer Patients, a Retrospective Cohort Study

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Abstract

Background Obesity is becoming a bigger health problem every year. Current research shows that the obesity-related metabolic problems are strongly associated with visceral fat and not subcutaneous fat. Visceral obesity (VO) is associated with a worse postoperative outcome in multiple fields of abdominal surgery. On the other hand, muscle mass is related to better postoperative outcome. In rectal cancer patients, we studied the influence of visceral obesity and muscle mass on postoperative complications.

Methods The visceral fat area (VFA) and skeletal muscle area (SMA) were determined on preoperative CT scans in 406 patients. The preoperative comorbidity, per-operative outcome and postoperative complications were extracted retrospectively from the patient files. VO was defined as a VFA > 100 cm^2. Correlations between body composition, postoperative complications and LOS were studied.

Results In our study, 67% of the patients were classified as visceral obese. Mean body mass index (BMI) was higher in the VO group (26.6 ± 3.5 vs 23.5 ± 2.8; $p < 0.001$). Visceral obese patients had a higher prevalence of cardiac comorbidity (29% vs 13% $p = 0.001$), hypertension (36% vs 20% $p = 0.002$) and diabetes mellitus (16% vs 5% $p = 0.002$). In addition, VO patients had more operative blood loss (431 vs 310 mL; $p = 0.008$), longer operating time (166 vs 149 min $p = 0.003$) and more wound infections (14% vs 8% $p = 0.048$). Visceral obesity was associated with more complications (OR: 1.63 $p = 0.043$) and longer LOS (risk estimate: 1.18 $p = 0.009$).

Conclusion VO patients more often had a history of cardiac disease, hypertension and diabetes mellitus. Visceral obesity correlated with a worse outcome after surgery for rectal cancer.

Introduction

According to the WHO, the worldwide prevalence of obesity increases at an alarming rate [1]. This obesity epidemic causes health problems such as the metabolic syndrome and cardiovascular disease. Current research strongly suggests that these medical problems are causally linked to the accumulation of excess visceral fat (VF). In contrast to subcutaneous adipocytes that secrete anti-diabetic and anti-inflammatory hormones like leptin and adiponectin, visceral adipocytes produce pro-inflammatory cytokines like IL-6 and TNF-alpha [2]. Furthermore, VF becomes invaded by inflammatory cells contributing to the pro-inflammatory reaction [3]. The chronic state of inflammation in visceral obese (VO) persons is associated with the metabolic syndrome, cardiovascular disease and cancer [2–7].

Several studies have shown worse outcome in colorectal cancer patients with VO [8–10]. Most of these studies were

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conducted in the Asian population and investigated a mixed population of colon and rectal cancer patients. One study included only 46 rectal cancer patients [9]. In rectal cancer patients undergoing surgery after neoadjuvant chemotherapy, we recently showed significantly more peroperative blood loss, ileus and longer LOS in VO patients [8]. In another study on rectal cancer surgery, Ballian et al. showed delayed resumption of oral postoperative intake in VO patients but no effects on perioperative complications or LOS [11].

Another important tissue that may influence outcome after surgery is that of skeletal muscle. The loss of muscle tissue, or sarcopenia, has been associated with a higher rate of postoperative complications, an increased LOS and reduced quality of life in colorectal and liver surgery patients [12, 13]. Adequate muscle mass (MM) is a sign of good general metabolic condition and contributes to earlier recovery. Sarcopenia has been reported in 17 to 70% of colorectal cancer patients depending on their catabolic status [12–14].

Both VF and MM are easily determined on CT scan. As part of the standard workup for elective rectal cancer surgery, each patient undergoes a preoperative abdominal CT scan to screen for disseminated disease that can be used for body composition analysis. Here, we present data on the association of visceral fat and skeletal muscle mass with postoperative outcome in a large cohort of rectal cancer patients.

Methods

Patients

This retrospective cohort study was conducted at the Northwest Clinics Alkmaar. All patients were included in the period from 2006 to 2013. Patients who underwent rectal resection for rectal carcinoma were included. Only patients with a preoperative CT scan of the abdomen were included. Patients were included regardless of their preoperative treatment with radiation therapy, chemo-radiation therapy or no neoadjuvant treatment. Some patients who underwent neoadjuvant chemo-radiation treatment were also included in an earlier study where the effect of chemo-radiation on body composition was measured [8]. A diverting loop ileostomy was constructed to protect the anastomosis in case of preoperative radiotherapy or chemoradiation. Neoadjuvant radiotherapy consisted of 5 sessions of 5 Gy. Chemo-radiation therapy consisted of 28 × 1.8 Gy and 1500 mg capecitabine twice a day for 5 weeks. Rectal resections in an acute setting were excluded.

Data collection

The patients' age, gender, BMI, comorbidity, type of surgery, surgical time, blood loss, length of stay (LOS), readmission and reoperation within 30 days and the in-hospital complications and mortality were extracted from patient files. The visceral fat area (VFA) and skeletal muscle area (SMA) were measured using the preoperative CT scan.

The primary endpoint was the occurrence of complications. Secondary outcome was perioperative blood loss and LOS. To define complications, the Clavien–Dindo classification was used. Complications were also separately defined as wound infection, pneumonia, urinary tract infection, anastomotic leakage and ileus.

Measurement of VFA and SMA

The VFA and SMA were measured by using the preoperative CT scan. These images were analyzed at a specific workstation (Syngo MMWP VE40A, Siemens, Germany). One transversal slice at the level of the intervertebral disk of L3–L4 was selected for the measurement of VFA and SMA. For visceral fat tissue, a threshold of − 140 to − 50 Hounsfield units (HU) was used [15–17]. Five to 60 HU were used for muscle tissue [18–21]. The researcher manually traced the VFA and the SMA. Subcutaneous fat area is the TFA with the VFA subtracted. The analyst was not informed about clinical outcome. Visceral obesity (VO) was defined, by the most commonly used definition, as a VFA $\geq$ 100 cm^2 [8, 10].

Surgical procedure

The surgical procedures were performed by trained gastrointestinal surgeons or by their residents. Patients were scheduled in a chronologic fashion depending on the availability of an operating room and a certified surgeon. Both laparoscopic and open routes were used. Surgical procedures include: low anterior resection (LAR), abdominoperineal resection (APR) and extended Hartmann procedure.

All patients were treated with antibiotic prophylaxis before incision. All patients had postoperative prophylaxis of thrombosis with low molecular weight heparin. Postoperative patients were treated according to the Enhanced Recovery After Surgery principle.

Patients were dismissed if they were able to mobilize, had sufficient intake, and the pain could be controlled with oral pain medication.

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Chicago, IL, USA). The Chi-square test or Fischer exact test was used for discrete data. The independent *t* test was used for continuous data. Continuous variables that were not normally distributed were logarithmically transformed before analysis. A p value < 0.05 was considered statistically significant.

Logistic or linear regression analyses were performed to calculate the predictive value of different variables on the occurrence of complications. SMA was used as a continuous variable in the regression analysis of complications and LOS.

The variables with p value < 0.05 in the univariable analysis were entered into a multivariable regression analysis. A ratio of geometric means and the 95% CI is given when a log-transformed parameter is used.

The work has been reported in line with the STROCSS criteria [22].

Results

A total of 406 patients were included in this study. Sixty-two percent (n = 253) of the patients were male. A total of 272 patients (67%) had a VFA > 100 cm [2].

Patient characteristics

Table 1 shows the patient characteristics. There were more male patients in the VO group. In the VO group, there were more patients with cardiac disease, hypertension and

Table 1 Patients characteristics

	Total population N = 406	VFA < 100 cm^2 n = 134	VFA > 100 cm^2 n = 272	p value
Male n (%)	253 (62)	61 (46)	192 (71)	<0.001*
Age mean (SD)	67 (11)	65 (12)	69 (9)	<0.001*
Comorbidity				
Cardiac n (%)	97 (24)	18 (13)	79 (29)	0.001*
Pulmonary n (%)	47 (12)	12 (9)	35 (13)	0.247
Diabetes mellitus n (%)	50 (12)	7 (5)	43 (16)	0.002*
Hypertension n (%)	125 (31)	27 (20)	98 (36)	0.001*
BMI mean (SD)	25.5 (3.5)	23.5 (2.8)	26.6 (3.5)	<0.001*
VFA mean (SD)	142 (80)	56 (26)	185 (61)	<0.001*
SMA mean (SD)	85 (25)	76 (25)	90 (24)	<0.001*
SFA mean (SD)	184 (82)	153 (79)	199 (80)	<0.001*
Tumor characteristics n (%)				
T1	41 (10)	15 (11)	26 (10)	0.241
T2	130 (32)	46 (34)	84 (31)	0.207
T3	183 (45)	58 (43)	125 (46)	0.374
T4	11 (2.7)	4 (3)	7 (3)	0.430
Tis	3 (0.7)	2 (1)	1 (0.4)	0.355
Node characteristics n (%)				
N0	269 (66)	88 (66)	181 (67)	1.000
N1	81 (20)	28 (21)	53 (20)	0.756
N2	54 (13)	18 (13)	36 (13)	0.879
Metastasis				
M0	357 (91)	115 (86)	242 (89)	0.653
M1	35 (9)	16 (12)	19 (7)	0.106
Laparoscopic surgery n (%)	103 (25)	30 (21)	73 (27)	0.353
Conversion rate n (%)	9 (9)	3 (10)	6 (8)	0.901
Neoadjuvant treatment	370 (91)	125 (93)	245 (90)	0.285
Radiotherapy (%)	263 (65)	87 (65)	176 (65)	0.965
Chemo-radiotherapy (%)	107 (26)	38 (28)	69 (25)	0.520

*Statistically significant ($p < 0.05$) between VO and non-VO

Table 2 Peroperative and postoperative outcome

	Total population $N = 406$	VFA < 100 cm^2 $N = 134$	VFA > 100 cm^2 $N = 272$	p value
Blood loss**	387 (3)	310 (3)	431 (3)	0.008*
Operation time**	160 (1)	149 (1)	166 (1)	0.003*
Complications n (%)	182 (45)	46 (34)	136 (50)	0.003*
Wound infection	49 (12)	10 (8)	39 (14)	0.048*
Anastomotic leakage	16 (8)	3 (4)	13 (10)	0.173
Ileus	110 (27)	28 (21)	82 (30)	0.053
Urinary tract infection	41 (10)	16 (12)	25 (9)	0.374
Pneumonia	32 (8)	5 (4)	27 (10)	0.031*
Clavien–Dindo classification n (%)				
Grade 1	61 (15)	14 (10)	47 (17)	0.070
Grade 2	52 (13)	15 (11)	37 (14)	0.495
Grade 3	57 (14)	16 (12)	41 (15)	0.393
Grade 4	7 (2)	2 (1)	5 (2)	0.578
Reoperation in 30 days n (%)	70 (17)	18 (14)	52 (19)	0.163
Length of stay**	10.6 (2)	9.4 (2)	11.3 (2)	0.003*
Readmission in 30 days, n (%)	71 (18)	28 (21)	43 (16)	0.205
In-hospital mortality n (%)	14 (3)	3 (2)	11 (4)	0.564

*Statistically significant ($p < 0.05$) between VO and non-VO patients

**Geometric mean

diabetes. SMA was significantly higher in the VO group. Patients in the VO group were older. There was no difference in the number of laparoscopically operated patients or neoadjuvant treatment between the VO and non-VO groups. We also show the tumor and node characteristics, which not differ between VO and non-VO patients.

Per-operative outcomes and complications

Table 2 shows the peri- and postoperative outcome. Surgical time was significantly longer for patients with VO. In addition, there was more perioperative blood loss in the VO group. Fifty percent of the VO patients developed at least one complication compared to 34% of the non-VO patients. When scored by the Clavien–Dindo grading system, no significant differences were found between VO and non-VO patients. For specific complications, differences were found. More wound infections were seen in VO patients (14% vs 8%; $p = 0.048$). An overall in-hospital mortality of 3.4% was found with no differences between the groups. Patients with VO had a significantly longer LOS.

Regression analysis for complications

Table 3 shows the logistic regression analysis for the occurrence of complications. Only laparoscopic surgery, VFA $\geq$ 100 cm^2, subcutaneous fat area and BMI were significantly related to the occurrence of postoperative complications in univariable regression analysis. In the multivariable analysis, only VFA $\geq$ 100 cm^2 and laparoscopic surgery were significantly related with complications. Laparoscopic surgery decreased the risk for complications.

Discussion

This is the largest retrospective cohort study on the association of VO and outcome in exclusively rectal cancer surgery in a European population. Patients with VO had more intraoperative blood loss, postoperative complications and a longer LOS after surgery for rectal cancer. Visceral obesity was associated with more cardiac comorbidity, a higher prevalence of hypertension and more diabetes mellitus.

Our results confirm the findings by others on complications and comorbidity in visceral obese surgical patients [8, 10, 23]. Rickles et al. showed a significant correlation between VO, the occurrence of complications and a longer LOS in 219 colorectal patients. They reported more wound infections in visceral obese patients after surgery [23]. In line with our results, Ishii et al. also found more complications in VO patients ($n = 9$) in a small group of patients [9]. Furthermore, other studies came up with the same results of more complications in other fields of surgery such as gastric, liver and pancreatic surgery [24–27].

Table 3 Factors associated with the occurrence of complications

Predictive factor	Univariable analysis OR (95% CI)	*p* value	Multivariable analysis OR (95 % CI)	*p* value
Male gender	0.98 (0.66–1.47)	0.932		
BMI	1.08 (1.02–1.14)	0.011*	1.06 (1.00–1.13)	0.054
Age	0.99 (0.98–1.02)	0.818		
Cardiac comorbidity	1.28 (0.81–2.02)	0.291		
Pulmonary comorbidity	1.61 (0.87–2.97)	0.127		
Hypertension	1.00 (0.65–1.53)	0.994		
Diabetes mellitus	0.88 (0.48–1.60)	0.668		
VFA>100 cm^2	1.91 (1.25–2.93)	0.003*	1.63 (1.02–2.62)	0.043*
SMA	1.01 (1.00–1.02)	0.061		
Subcutaneous fat	1.003 (1.00–1.01)	0.028*	1.001 (0.99–1.004)	0.314
Laparoscopic surgery	0.43 (0.27–0.69)	0.001*	0.40 (0.25–0.66)	<0.001*
Neoadjuvant treatment	0.62 (0.31–1.24)	0.178		

*Statistically significant ($p < 0.05$)

Ballian et al. found that VO in 113 rectal cancer patients correlated with a delayed resumption of oral intake after surgery. In contrast to our results however, they did not find significant increases in per-operative blood loss, postoperative complications or LOS in VO patients [11].

Our finding of a higher prevalence of diabetes, hypertension and cardiac comorbidity in VO patients is in line with other studies on the relation between VO and the metabolic syndrome. Clark et al. found a higher incidence of diabetes, hypertension and hypercholesterolemia in VO rectal cancer patients [28]. Benoist et al. show a higher incidence of diabetes in obese patients undergoing colorectal surgery [29]. We also found a higher incidence of cardiac comorbidity in a group of VO patients undergoing colon resection [10]. A study performed in 2012 in 474 patients undergoing CT scan as part of colonographic evaluation also showed a correlation between VO and the metabolic syndrome [6]. Interestingly, VO-associated comorbidities like diabetes and hypertension were not related to postoperative complications in our regression analysis. In an earlier study, we also showed no effect of preoperative morbidity on complications in colon cancer patients [8]. A confounding factor that could contribute to a higher incidence of comorbidity in the VO patients is the higher age. Despite the higher incidence of comorbidity in VO patients, only a correlation between cardiac comorbidity and a longer LOS could be found. This strengthens the hypothesis that not the morbidity caused by VO, but a more direct effect of VO is the cause of a longer LOS and more complications. The accompanying chronic state of inflammation in VO may be involved in the development of perioperative problems. Patients with a VO-associated chronic state of inflammation perhaps have a different immunological response to surgery. This needs to be further evaluated as it may help to identify new perioperative strategies in preventing postoperative complications.

In VO patients, surgical procedures took longer and there was more blood loss. This could not be explained by differences in the type of surgery between the VO and the non-VO patients. The longer duration of surgery and more blood loss is a confirmation of previous findings in abdominal surgery. Tsujinaka et al. [18] found a longer operative time in visceral obese VO patients undergoing laparoscopic sigmoid resection; however, no difference in blood loss was found. In gastric cancer patients, Ueda et al. [25] showed a correlation between VFA and operative time as well as blood loss. Watanabe reported on significantly longer operative time in colon cancer patients [30]. It seems that compared to other abdominal procedures visceral obesity caused more blood loss in rectal cancer patients. This might be explained by VF obscuring the narrow surroundings of the pelvis complicating the procedure more when compared to procedures performed in the abdominal cavity. In 254 rectal cancer patients undergoing APR of LAR, Ballian et al. showed an association between obesity and a higher amount of per-operative blood loss, but only in patients who underwent a LAR. There was no difference in the duration of surgery, LOS or postoperative complications [31]. In agreement, our data also show that BMI is not associated with worse outcome in rectal cancer surgery. In addition, the present study showed no correlation between neoadjuvant chemo-radiation therapy and complications. This finding is supported by a study of Milgrom et al. [32] who also did not find an association between radiation therapy and 30-day morbidity after surgery in 461 patients.

In addition to specific complications, we also used the Clavien–Dindo system to enable comparison to international literature. In contrast to the higher rate of specific complications like wound infections and pneumonia, the Clavien–Dindo system showed no significance. It is unclear why the scores in the Clavien–Dindo system are not significant. Van Dijk et al. [33] showed more surgical site infections in VO patients undergoing surgery due to pancreatic cancer but also did not find an increase in complications in the Clavien–Dindo score. A drawback of this classification is that it only focuses on general complications, whereas specific inflammatory complications like wound infections and pneumonia are highly relevant in VO patients. The infectious complications could reflect altered immunological responses in a host with VO-associated chronic inflammatory state.

Sarcopenia has been associated with a higher rate of postoperative complications, an increased LOS and reduced quality of life in colorectal and liver surgery patients [12, 13]. In our group of patients, the correlation between SMA and short-term effects of surgery is not significant. Lieffers et al. found a correlation between depletion of SMA and infection in patients who underwent colorectal resection. Patients with sarcopenia also had a longer LOS. It seems that in their population sarcopenia is also correlated with comorbidity [13]. Our data are not in line with those findings. The study of Peng et al. states that sarcopenia can be a sign of frailty. They found a correlation between sarcopenia and complications as well as a longer LOS in 259 patients who underwent hepatic resection because of colorectal metastases [12]. Frailty often occurs in elderly patients. Our patients were older, and it could therefore be that the overall frailty was higher. The association between low SMA and complications can also be found in benign surgery. A study published in 2017, performed in 89 patients who underwent emergency surgery due to acute diverticulitis, shows a significant correlation between low SMA and surgical site infections and complications overall [34]. The different result between our study and others might be explained by the fact that there is still not a golden standard to measure SMA on a CT. There are differences in level of measuring and also in ranges of HU. Furthermore, we analyzed SMA as a continuous variable as others use SMA as a dichotomously. The cutoff points for sarcopenia differ between studies. A standardized method of measuring needs to be determined.

The strength of the present study is the large sample size in comparison with other studies. One of the limitations of the present study is its retrospective character. However, data entry in the database is done prospectively for quality assurance reducing lost data to a minimum.

Future research should focus on a possible treatment of VO in rectal cancer patients. Physical training is an effective method to decrease VO [35–37]. However, the time between diagnosis of rectal cancer and operative treatment is often too short for physical exercise to reduce VO. Therefore, modulating the chronic inflammatory state, with immunomodulating therapies for instance, may be an approach to improve postoperative outcome in the VO.

In conclusion, VO is related to a higher prevalence of cardiac comorbidity, hypertension and diabetes mellitus in rectal cancer patients. It is negatively associated with outcome after rectal cancer surgery. The measurement of VO is simple because all of these patients undergo a CT scan as part of the preoperative workup and as such can contribute to predicting the risk profile in rectal cancer patients.

Authors' contribution AH and CH designed the study. NB, WM and CH collected the data. HD and CH did the analysis of the data. CH and AH drafted the manuscript. All other authors critically revised the manuscript. All authors approved the final version. All authors agreed to be accountable for all aspects of the study.

Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest.

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