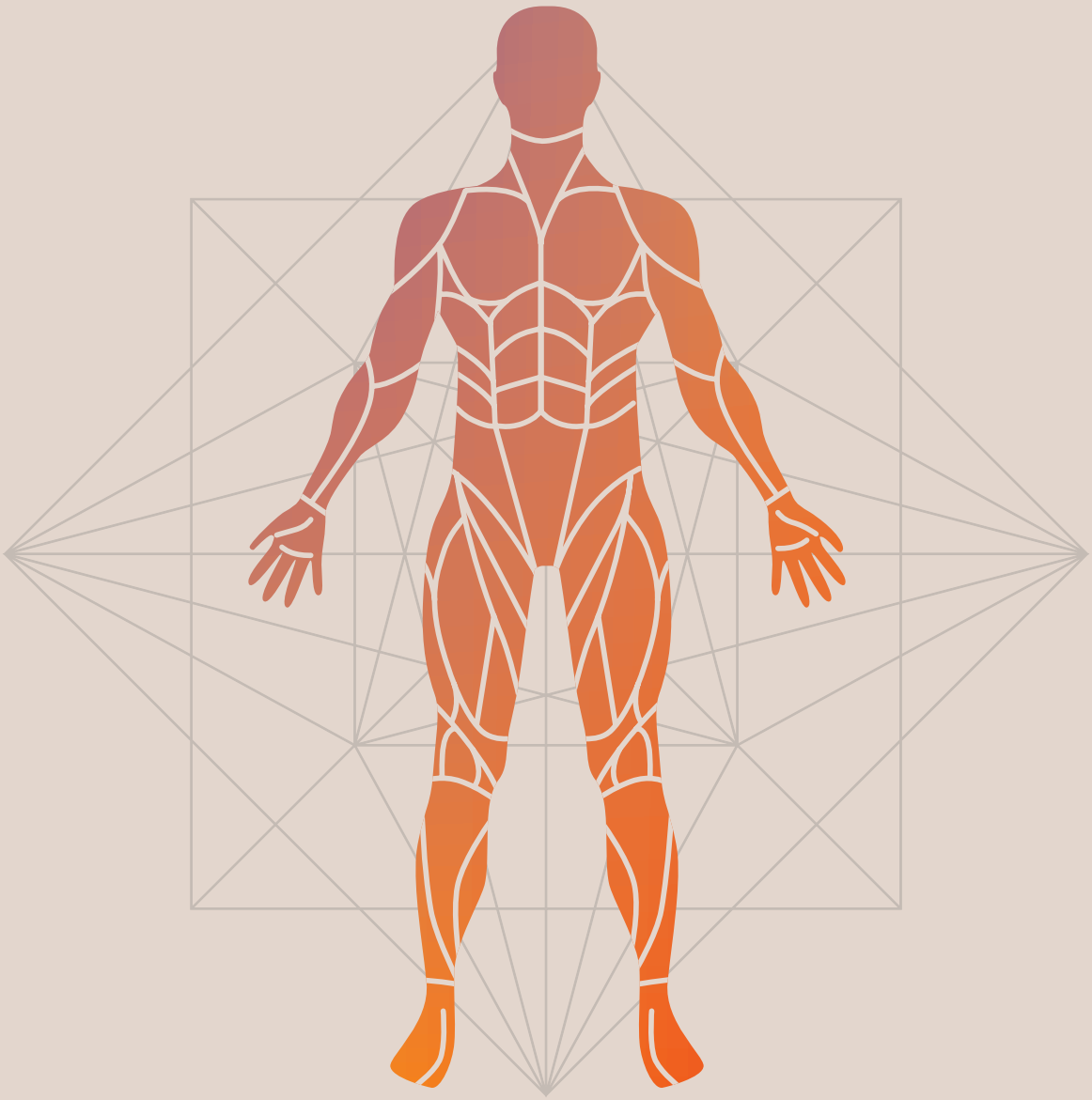
BODY COMPOSITION AND COMPLICATIONS IN ONCOLOGICAL SURGERY



COLIN HEUS

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Body composition and complications in oncological surgery

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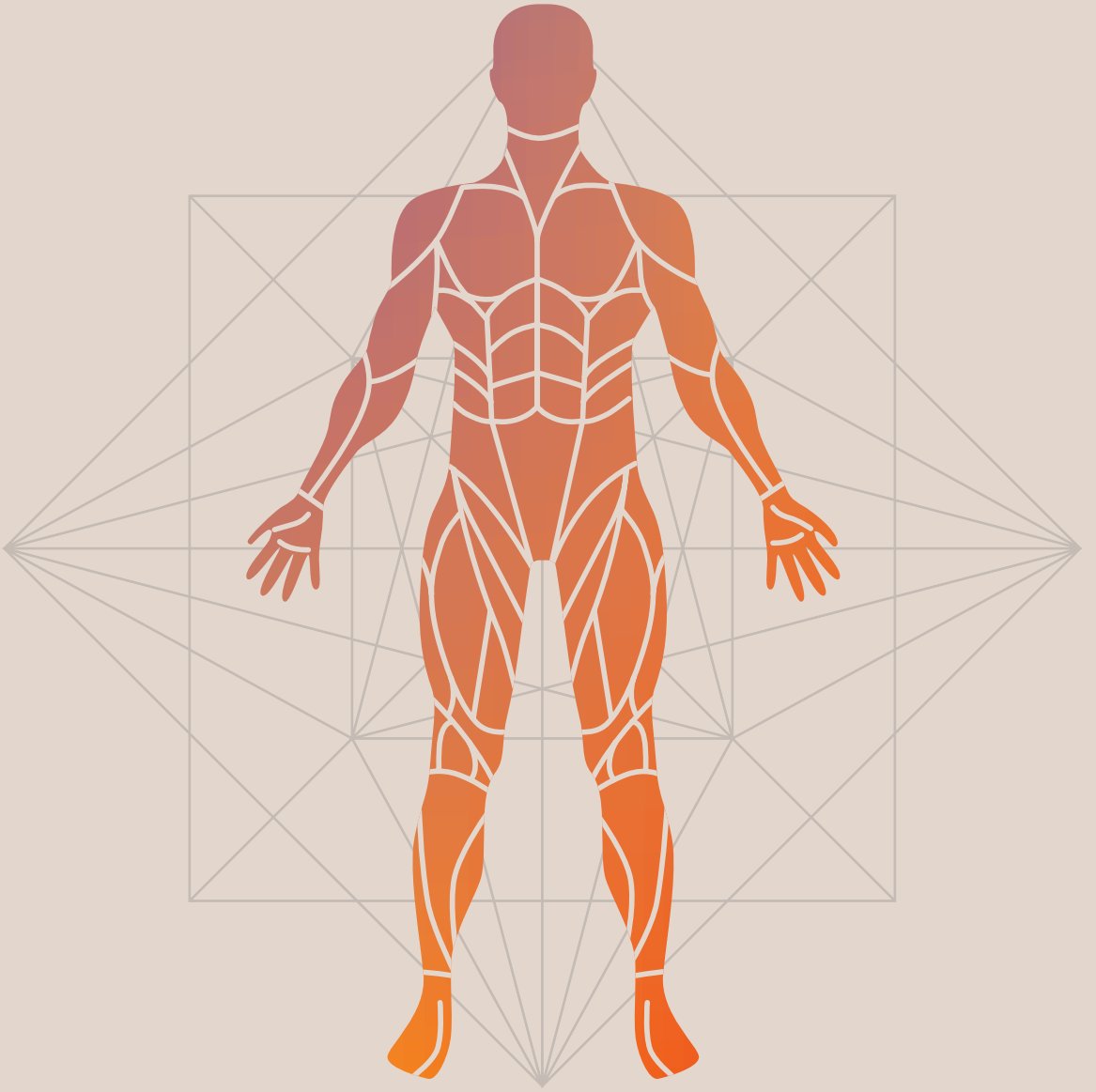

Chapter 1

General introduction

The relevance of visceral fat and muscle mass in surgery

In the last decades, an ever-increasing sedentary lifestyle with calorie overconsumption has influenced almost the entire world population. It has changed their bodies and their health. It is estimated by the WHO that in 2016, 1.9 billion people were overweight and this number is still increasing at an alarming rate. For example, while in 1981 already 27% of the Dutch population was overweight, currently over 44% are overweight[1]. Overconsumption of kiloJoules and reducing exercise or mobility not only cause an increase in body weight it also changes the composition of a body. It results in an accumulation of fat and it may lead to a loss of muscle tissue. This thesis focusses on the effects of these body composition changes on patients undergoing surgery.

The WHO is greatly concerned about the worldwide increase in obesity. The incidence of obesity has nearly tripled in the past 45 years. The effects of this increase in obesity is seen all over the world. Obesity is defined as a body mass index (BMI) above 30 kg/m^2. It is associated with an increased risk of diabetes mellitus, hypertension, cardio-vascular disease and multiple forms of cancer[2]. A consequence of the rising rate of obesity is that currently more people die of being overweight than being underweight[3]. Obesity used to be a wealth-related disease. However, an alarming rise of obesity is now also seen in low- and middle income countries. For example obesity in children under five years old has increased with 32,4 % in Africa. Many countries in Africa are now struggling with both undernutrition as well as obesity. The WHO has called out a global action plan to reduce obesity as a global pandemic. The global strategy of the WHO focusses on stimulating healthy diets and increased psychical activity to prevent obesity and obesity related problems. To prevent obesity a new guideline on psychical activity in children is released[3].

BMI is traditionally used to determine obesity but the use of it to determine actual health risk could be questioned. Obesity is diagnosed by using BMI. BMI consist of weight in the numerator and the square of body length in the denominator. A high BMI is associated with increased risk of disease in large groups of patients. The association for the individual patient, however, is debatable. We think that this is caused by the fact that BMI does not take body composition in account. To demonstrate why this could be important we will explain the meaning of body composition first. Body composition is a term that has several different meanings. Body composition describes the distribution of different types of tissue or matter in a body. Body composition describes how or of what is the body is composed. It can be described with different types of models[4]. These models divides the body in different kind of compartments, with different properties. For example, the atomic model divides the body in compartments of carbon, oxygen and hydrogen. When using the molecular model the compartments consist of water, fat, protein and mineral[4]. Which model is used in research depends of the properties that one wants to investigate.

In this thesis we focus on the functional model. The compartments in that model consists of fat tissue, muscle tissue and other tissues. These types of tissue all have different properties (I.E. metabolic and inflammatory) and therefore the distribution of these tissues are important. The compartment of fat tissue is often divided in a subcutaneous fat compartment and a visceral fat compartment. This extra division is made as visceral fat and subcutaneous fat are two very different entities with different important properties[5]. Therefore describing all fat tissue as one compartment is not exact. BMI does not take the ratio of these different compartments into account. The ratio of these compartments, or body composition, could be clinical important.

Visceral fat, subcutaneous fat and muscle tissue all have different properties in (patho-) physiology[5]. Imaging methods like CT, MRI and Dexa-scanning have recently boosted research on the association of the amount of fat in these compartments with disease development and treatment outcome. It has become clear that an increase in visceral fat can increase the risk of the development of metabolic and cardiovascular diseases (which were traditionally related to being overweight), but also of malignancies like colorectal cancer[6]. Visceral fat accounts only for about 10-15 per cent of the weight numerator in the BMI. BMI will therefore have some association with visceral fat mass but cannot discern between fat compartments, bone or muscle tissue[7]. The pathobiological changes underlying most of the "overweight' related diseases are insulin resistance and atherosclerosis. This is thought to be the result of an increase in visceral fat and not only increased weight. BMI therefore is not a focus of this thesis.

It is important to understand why an increased amount of visceral fat tissue is causing health risks and not just increased weight on itself. Visceral fat tissue has different metabolic and endocrine properties as compared to subcutaneous fat. Overwhelming evidence points to the existence of a chronic inflammatory status caused by visceral fat. This chronic inflammation is thought to cause the known health problems in obesity. The origin of this chronic inflammation is now recognized to reside in the expanding visceral fat depot and not in the subcutaneous fat depot. Expanding visceral fat, triggers the influx of macrophages and lymphocytes that invade the fat and start a chronic proinflammatory response characterized by cytokines like IL-1, IL-6, TNF. The immunologic contribution of adipocytes changes to a more inflammatory profile by lowering the anti-inflammatory adipokine adiponectin[5]. This inflammatory response has a key role in insulin resistance[8]. TNF-alpha for instance acts on the insulin receptor signaling pathway. When TNF-alpha is exogenously administrated an increase of insulin resistance is seen. Also, when removing TNA-alpha in diabetic mice insulin resistance improves[9]. This confirms the critical role of inflammatory factors in insulin systems. As mentioned, visceral fat tissue lowers the levels of adiponectin. This adiponectin has proven to act on the vascular wall, and has anti-ath-

erogenic functions. It prevents binding of monocytes when the vascular wall is damaged. Also, it induces proliferation of vascular smooth muscle[10]. In patients with coronary heart disease adiponectin levels are lower than matched patients without coronary problems. These reactions, following the inflammation in visceral fat, are thought to account for the increased health risks in visceral fat tissue. Unfortunately body composition cannot be calculated with BMI. It is clear that an increased amount of visceral fat causes increased health risks. Little is known about surgical risk in patients with increased amounts of visceral fat. In this thesis the surgical risk in patients with increased visceral fat tissue is investigated.

Muscle mass, also a compartment of body composition, could also be of importance in the pathophysiology of diseases. More exact, the loss of muscle mass could be important. It is known that myocytes, just as fat cells, have a role in metabolic and inflammatory processes. However, the role of sarcopenia as a contributing factor in many diseases is still under investigation. Sarcopenia, is the loss of muscle mass and is a frequent phenomenon in cancer patients. Sarcopenia is seen in up to 60 per cent of patients with colorectal cancer[11] and up to 54 per cent in patients with ovarian cancer[12]. There is still a lot unclear in the pathogenesis of sarcopenia. We do know that causes of sarcopenia include malnutrition and insulin resistance and is seen more in older patients[13].

In this thesis the effects of sarcopenia on surgical complications are studied. Therefore a more detailed explanation of the metabolic functions of muscle cells and the effects of the loss of muscle mass is needed. Low muscle mass is associated with reduced physical function, reduced tolerance for oncological treatment and reduced survival[12]. Loss of muscle mass is also associated with prolonged hospital stay and infectious complications and lower quality of life[14]. Muscle loss also effects the costs of healthcare. Steffl found that the costs of healthcare in older patients increased twofold with loss of muscle mass[15].

The effects of sarcopenia could be explained by the characteristics of muscle tissue. Muscle mass is an important tissue influencing the metabolic state of the body. Insulin targets muscle mass and with the loss of muscle mass insulin resistance can occur[16]. In contrast, loss of muscle mass can be accelerated by insulin resistance. In comparison to visceral fat mass chronic inflammation is also linked to loss of muscle mass. Increased levels of TNF-alpha and C-reactive protein are found in patients with sarcopenia[17]. Sarcopenia is therefore consequently associated with an increased risk of diabetes and cardiovascular diseases. Another result of muscle loss is the diminished protein and nutrient storage capacity. Recovery from surgical treatment requires these nutrients.

In summary, muscle cells and visceral fat cells influence the metabolic and inflammatory processes in the human body. It could be argued that these effects can influence one's recovery when undergoing surgery. Therefore this thesis focusses on the effects of visceral fat and muscle mass on surgical outcome in colorectal and ovarian cancer patients.

Measuring body composition

Body composition can be measured using different techniques. These techniques differ in cost, usability and reliability. The methods mostly used are anthropometry, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), CT-scan and MRI-scan. BIA uses the electrical properties of the body. The non-conducting properties of fat tissue and conducting properties of water are used to measure impedance. It is low cost and not invasive. On the downside these measurements are sensitive for ambient and skin temperature, transpiration and electrolyte changes. BIA also might underestimate fat mass and no quantification of (visceral) fat mass and muscle mass is determined[18]. Dexa scan uses x-ray with two different energies. Therefore two different component can be measured. It correlates well with body composition on CT-scan[19]. Dexa is however not always available in clinical circumstances. MRI-scan uses the magnetic properties of certain elements to produces images of the soft tissue. The results correlates well with other methods of measuring body composition[20]. MRI takes more time in comparison to CT-scan, and not all patients undergo MRI in the work-up for cancer treatment.

In this dissertation we will focus on CT-scan as a method to get more information on body composition. By using CT scans for this purpose, extra tests are avoided, because oncological patients often undergo a CT-scan as part of the routine workup in cancer. At the start of our research CT was the preferred method of measuring body composition in the research setting[21-23].

Although CT was the preferred method, little uniformity was used in measuring the body composition. The process of the measurement will be elaborated on in the following chapters. One goal of this thesis is to provide a uniform measuring protocol for using a CT-scan to determine body composition. Also different interpretations of the results were found. For example some used visceral fat as a continuous parameter when assessing surgical risk. Others used a cut-off to distinguish between visceral obese and non-visceral obese patients. Different cut-off levels were found for visceral obesity. This thesis will investigate these different cut-offs.

Treatment of colon, rectal and ovarian cancer

In The Netherlands each year approximately 12.000 individuals are being diagnosed with colorectal cancer of whom 4750 die of the disease[24]. The treatment of colorectal cancer

consists primarily of surgical resection of the tumor. This procedure can be performed both by laparoscopy or laparotomy. Patients with more advanced stage of the disease will subsequently be treated with chemotherapy. A large group of patients with stage II or III will receive neoadjuvant chemoradiation. Especially in the treatment of rectal cancer neoadjuvant chemoradiation is more common[25].

Ovarian cancer occurs in 1400 women each year in the Netherlands of whom 1000 die of the disease[24]. The majority of the patients are diagnosed with an advanced stage (FIGO stage III or more). The treatment for these women consists of a combination of debulking surgery and chemotherapy. The aim of debulking surgery is to remove all visible tumor. Chemotherapy is recommended both in the adjuvant and neoadjuvant setting. If optimal debulking can be achieved debulking surgery will be followed by adjuvant chemotherapy. In patients where an optimal debulking is not considered feasible, three course of chemotherapy will be followed by an interval debulking procedure again followed by three courses of chemotherapy[26]. In early stage disease patients are treated by surgical resection. Depending on the final (pathological) stage patients will get adjuvant chemotherapy. Most of the patients in an advanced stage are being treated with open surgery, while patients in early stage disease are frequently treated by minimal invasive techniques.

Postoperative complications

In general surgery postoperative complications occur can occur in up to 43%[27]. Often the impact of complications on recovery are mild. But, complications can have a serious impact on patients recovery. It is therefore important to understand how complications occur. This thesis focusses on finding a potentially underlying reason for an increased surgical risk. When an underlying cause of complications is found, a target for preventing these complications can be determined.

In patients treated for ovarian cancer a complication rate of 44% has been reported[28]. Up to 25% face a serious complication in the postoperative course[29]. In colorectal surgery a complication rate up to 33% in laparoscopic resection and over 38% in open resection is seen[30]. The rates increases even further when the surgery takes place after neoadjuvant radiation therapy[31].

Complications can result in a longer hospital stay, admission to the intensive care unit, another surgical treatment or the use of medication. Although rare, complications can also lead to mortality. Factors influencing the risk of complications include the patients' health or comorbidity prior to surgery and characteristics of surgery like surgical approach (open or laparoscopic procedure), type of resection and volume of tissue that was removed[27].

It is thought that obesity could be a risk factor for postoperative complications. However only 36% of studies find a higher frequency of complications in obese patients compared to non-obese patients[32]. We hypothesize however that an increase of visceral fat mass or a decrease in muscle mass could be more important in the risk of developing post-operative complication then obesity itself. The chronic state of inflammation of visceral obese patients could influence the inflammatory reaction following surgery. Also visceral obesity is linked with comorbidity like diabetes, which could influence the postoperative course. Sarcopenia is also linked with inflammation and comorbidity increasing the risk of complications. An hefty amount of visceral fat could also obstruct access to surgical site and therefore increase surgical risk. This last hypothesis will also be tested in this thesis.

Aims of this thesis

Little attention is paid in literature on the effect of body composition on surgical complications. Therefore our main objective of this thesis was to determine the importance of body composition on the occurrence of postoperative complications in colorectal and ovarian cancer patients. This was explored by reviewing the known literature about this subject and also by original research. Secondary we wanted to determine which cut-off value for visceral obesity is most valuable when assessing surgical risk in the same patients.

Outline of thesis

Part 1 Colorectal cancer. This part consist of three retrospective cohort studies in colorectal patients and one systematic review with meta-analysis.

Chapter two describes the results of a retrospective cohort study in 564 patients who underwent a colon cancer resection. The preoperative body composition is correlated with complications in these patients.

Chapter three provides the results of a systematic review and meta-analysis of the literature about body composition and complications in colorectal cancer patients.

Chapter four describes the retrospective cohort about body composition and complications in 406 rectal cancer patients.

In **Chapter five** we describe the results of a retrospective cohort about body composition and complications in patients undergoing chemoradiation therapy followed by resection. We also compared body composition before and after chemoradiation in these 74 patients. We also compared different cut-off values of visceral obesity in this publication to determine the most valuable cut-off value.

Part 2 Gynaecological cancer.

Chapter six describes a retrospective cohort study in 298 women with advanced ovarian cancer in which the association between body composition and surgical complications were analysed .

Chapter seven reviews the literature about body composition and complications in all types of gynaecological oncologic surgery.

Chapter eight provides discussion on the findings of this thesis and states recommendations for measuring and interpreting body composition.

Chapter nine summarizes the results of this thesis.

Chapter ten summarizes the results of this thesis in Dutch.

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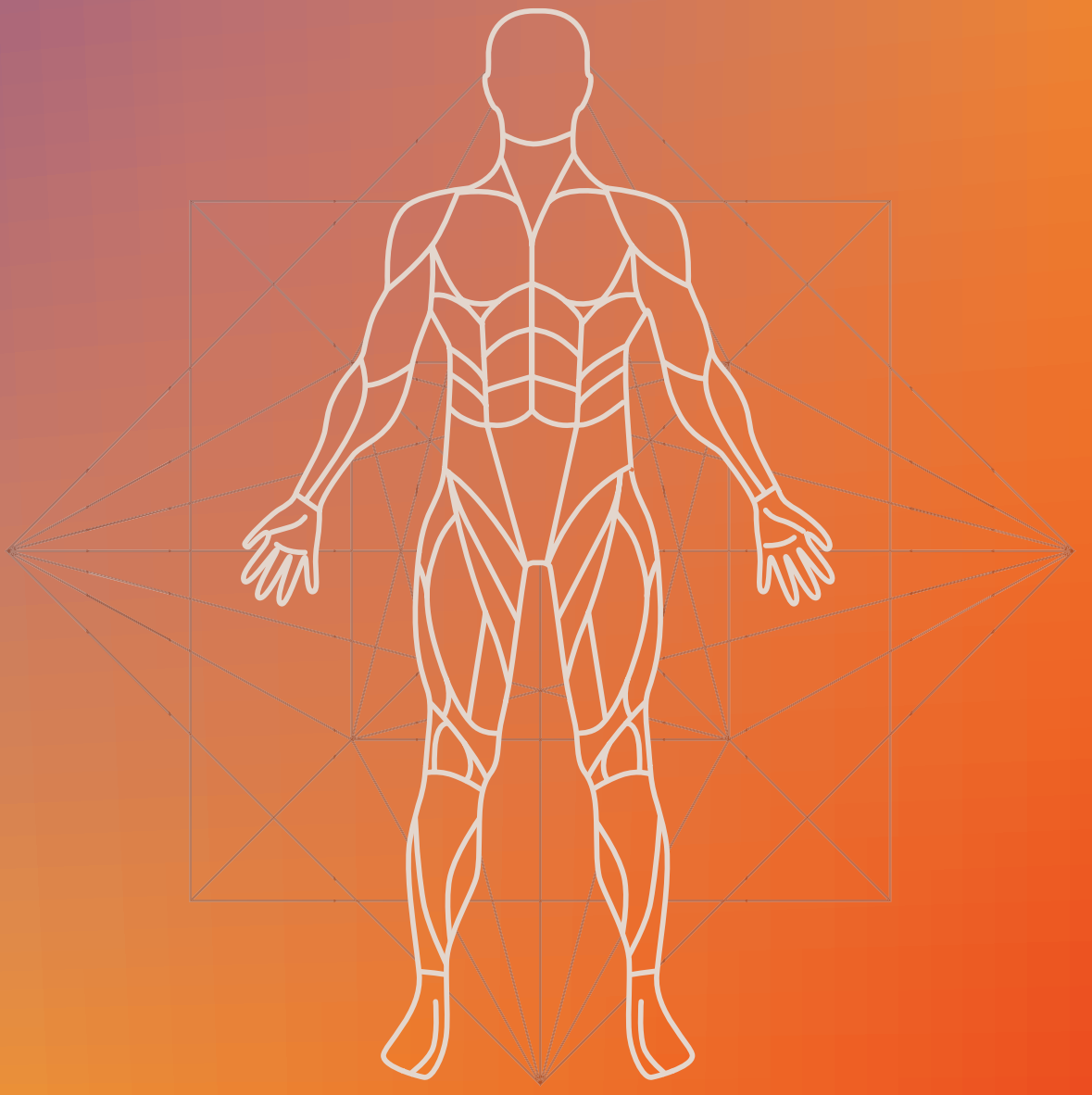
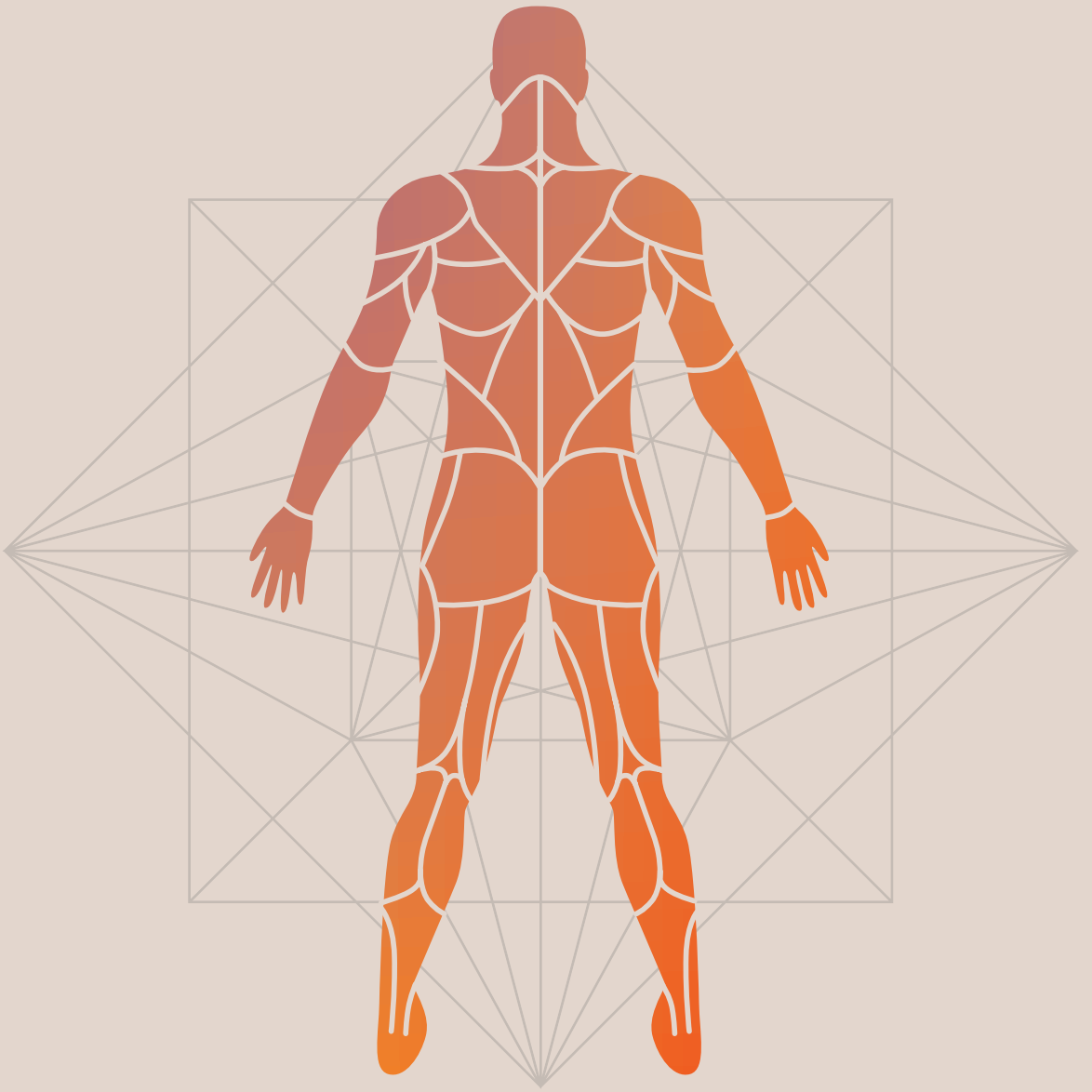
Part 1



Body composition and complications in colorectal surgery



Chapter 2

Visceral obesity, body mass index and risk of complications after colon cancer resection: A retrospective cohort study

Hamit Cakir
Colin Heus
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Surgery 2015

Abstract

Background

The aim of our study was to assess the influence of visceral obesity (VO), as measured by preoperative abdominal CT scan, in relation to body mass index (BMI) on the incidence of postoperative complications and duration of hospital stay after colon cancer surgery.

Methods

Patients who underwent elective resection for colon cancer between January 1, 2006, and December 31, 2013, and had a preoperative CT scan were entered in the study. Visceral fat area (VFA) was determined by using the preoperative CT scan at the L3–L4 level. The effect of VO, defined as a VFA of >100 cm2, on postoperative complications and duration of hospital stay was analyzed.

Results

Of 564 included patients, 65% had VO. VO was associated with more anastomotic leakage (P = .04), pneumonia (P = .02), wound infection (P = .03), reoperations (P = .04), and longer duration of hospital stay (P = .05). Of patients with a BMI < 25 kg/m2, 44% had VO. In this group, VO was associated significantly with postoperative complications, cardiac (P < .01) and pulmonary (P = .01) comorbidity, hypertension (P < .01), and diabetes (P < .01). In the overweight (BMI 25–30 kg/m2) and obese (BMI > 30 kg/m2) groups, the rate of VO was much higher (81% and 90%, respectively), but was not associated significantly with complications or comorbidity, except for cardiac comorbidity (P < .02) in the BMI = 25–30 kg/m2 group. After multivariable analysis, VO was shown to be an independent predictor of anastomotic leakage and wound infection.

Conclusion

The association of VO with worse outcome after colon cancer surgery is most pronounced in patients with a BMI < 25 kg/m2.

Introduction

Obesity is a rapidly increasing problem, complicating the surgical treatment of colorectal cancer. Apart from the technical difficulties during resection, more postoperative complications and greater costs are reported in the obese population[1-3]. The way fat is distributed in the body influences the metabolic risk for the patient. Visceral fat is metabolically active and causes a chronic inflammatory status, increasing the risk of the metabolic syndrome characterized by insulin resistance, dyslipidemia, and hypertension[4-7].This may lead to an higher rate of complications after surgery in obese colon cancer patients[1,3]. To determine obesity, body mass index (BMI) is normally used, and patients with a BMI of >25 kg/m^2 are reported as at risk for developing postoperative complications.8 Recently, however, the use of BMI as a risk profiler for early postoperative outcome has been questioned and the focus turned to the impact of the accumulation of visceral fat[9-12]. Traditionally, intra-abdominal fat is indirectly measured by waist circumference or waist-to-hip ratio. These anthropometric methods give an indication of the amount of visceral fat, but they also measure metabolically inactive subcutaneous fat. Visceral obesity (VO) is determined with far more precision if the direct visceral fat area (VFA) is measured by CT[13]. A VFA of >100 cm^2 is associated with the metabolic syndrome14 and is a risk factor for poor outcome and longer hospital stay after colorectal operations[10-12]. Most data on VFA and postoperative outcomes come from Japanese patients, and little is known of its effect in the Western world.

The aim of our study was to assess the influence of VO, as measured by preoperative abdominal CT, in relation to BMI, on the incidence of postoperative complications and duration of hospital stay in a large cohort of patients with colon cancer.

Methods

Settings and study design

This retrospective cohort study was conducted at the Medical Centre Alkmaar, a general teaching hospital in The Netherlands. Patients who underwent an elective resection for colon cancer between January 1 2006 and December 31 2013 and had a preoperative CT scan to exclude metastases. Patients were treated according to the Enhanced Recovery After Surgery (ERAS) principles, and data were prospectively entered in the ERAS database[15]. Experienced gastrointestinal surgeons and their residents performed resection of colon cancer. Both open and laparoscopic resections were included in this study. Patients who underwent acute colonic resection or rectal resection were excluded.

Measurement of visceral fat

In this study, all patients underwent an abdominal CT scan preoperatively to screen for metastatic disease. VFA was determined by a single scan at the level of the umbilicus (L3–L4), which corresponds with total abdominal fat with 99% accuracy[13,16]. The CT images were transferred electronically to a central data system and retrieved at a workstation (Syngo MMWP VE40 A, Siemens AG, Munich, Germany). Adipose tissue was determined by threshold within the range of -140 to -50 Hounsfield units. VO was defined as a VFA of >100 cm^2.[14]

Patient characteristics and outcome variables

For the evaluation of the ERAS program in colorectal surgical patients, all relevant data were entered prospectively in a database. If necessary, additional information on outcome variables was obtained from the hospital administrative database and medical records. The following patient and surgery characteristics were evaluated: age, sex, type of surgery (laparoscopic or open), presence of a primary anastomosis, comorbidity (defined as cardiac or pulmonary comorbidity, hypertension, and diabetes), and BMI, divided into 3 groups: normal BMI (<25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2).

The outcome variables in this study were the occurrence of the postoperative complications anastomotic leakage, pneumonia, wound infection, urinary tract infection, the occurrence of reoperations within 30 days after surgery, and duration of hospital stay. The occurrence of an anastomotic leakage was evaluated only in those patients with a primary anastomosis. Duration of hospital stay was calculated from the day of surgery until the day of discharge.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Chicago, IL). Patient characteristics as well as postoperative outcomes were described as numbers with percentages in case of nominal and ordinal data, or as mean values with standard deviations in case of continuous data. Analyses for between-group differences were done for VO versus no VO, for the 3 BMI categories as well as for VO versus no VO within these BMI categories. Differences in nominal variables between groups (BMI categories and visceral versus no VO) were analyzed using the Chi-square or Fisher exact tests as appropriate. Differences in continuous variables between groups were analyzed using the independent samples t-test in case of a 2-group comparison and analysis of variance when >2 groups were compared. Continuous variables that were not distributed normally were transformed logarithmically before analysis. After analysis, back transformation of the means resulted in geometric means. The strength of the associations between VO, BMI categories, and VO within the BMI categories on the one hand and postoperative outcomes on the other were reported as odds ratios with 95% CI resulting from logistic regression analysis. When the logarithmically transformed duration of hospital stay was the outcome, a ratio of geometric means with a 95% CI resulting from linear regression analysis was reported. In this case, a ratio of geometric means can be interpreted as a risk ratio for prolonged hospital stay. For the comparison of the 3 BMI categories, the category of <25 kg/m^2 was chosen as the reference category.

To test the independent predictive value of VO, other patient characteristics, and laparoscopic surgery on the occurrence of any of the postoperative complications, reoperations, and duration of hospital stay, univariable and multivariable (linear and logistic) regression analyses were performed. All characteristics that were significantly associated in the univariable analysis ($P < .05$) were entered in a multivariable analysis. The final models incorporated all determinants with significant associations ($P < .05$). The risk estimates for the nominal outcomes variables are reported as odds ratios with 95% CIs. For the outcome duration of hospital stay, the risk estimate is a ratio of geometric means.

Results

Patient characteristics

VO and BMIA total of 564 patients were included (Table I). The mean age was 70 years (SD 11), and 51% of the patients were male. Mean BMI was 25.6 kg/m^2 and 65% of the patients were viscerally obese. Compared with the no VO group, more patients in the VO group were male ($P < .01$), were older ($P < .01$), and more had cardiac ($P < .001$) or pulmonary ($P < .01$) comorbidity, hypertension ($P < .01$), or diabetes ($P = .01$). A BMI of <25 kg/m^2 was found in 46% of the patients, 43% had a BMI of 25–30 kg/m^2, and 11% had a BMI of >30 kg/m^2.

Cardiac comorbidity and hypertension occurred more often in higher BMI groups. More overweight patients (BMI 25–30 kg/m^2) were male. Four patients had a BMI of <18.5 kg/m^2 without any comorbidity or complications. There was no difference in the frequency of laparoscopic surgery between groups. Figure 1 shows the relation between BMI and VFA.

Table 1. Patient characteristics for the total study population, visceral obesity (VO) groups versus no VO groups and body mass index (BMI) categories

Characteristic	Total study population (*n* = 564)	No VO (*n* = 197)	VO (n = 367)	*P* value	BMI < 25 kg/m^2 (*n* = 260)	BMI 25–30 kg/m^2 (*n* = 241)	BMI > 30 kg/m^2 (*n* = 63)	*P* value
Age (y), mean (SD)	70 (11)	68 (12)	71 (10)	<.01	71 (11)	70 (11)	68 (11)	.08
Male gender, *n* (%)	287 (51)	50 (25)	237 (65)	<.01	118 (45)	141 (59)	28 (44)	.01
Comorbidity, *n* (%)								
Cardiac	176 (31)	33 (17)	143 (39)	<.01	67 (26)	84 (35)	25 (40)	.03
Pulmonary	56 (10)	10 (5)	46 (13)	<.01	21 (8)	27 (11)	8 (13)	.37
Hypertension	196 (35)	49 (25)	147 (40)	<.01	83 (32)	81 (34)	32 (51)	.02
Diabetes	58 (10)	10 (5)	48 (13)	<.01	23 (9)	24 (10)	11 (18)	.13

VO is defined as a visceral fat area of >100 cm^2.

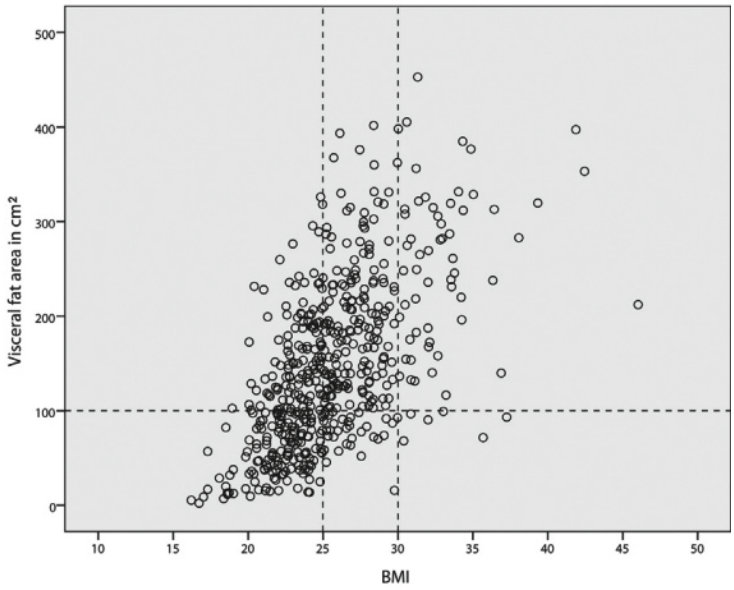

Figure 1. Relation between BMI and VFA

Patient characteristics: No VO versus VO within each BMI group

VO was found in 44% of the BMI < 25 kg/m^2 group, in 81% of the BMI 25–30 kg/m^2 group, and in 90% of the patients in the BMI > 30 kg/m^2 group. In the obese group, 10% had no VO. VO was associated with more advanced age in all BMI groups (Table II). Significantly more patients in the VO BMI < 25 kg/m^2 group had comorbidity, namely, cardiac comorbidity ($P < .01$), pulmonary comorbidity ($P < .01$), hypertension ($P < .01$), or diabetes ($P < .01$). In the BMI 25–30 kg/m^2 group, only cardiac comorbidity occurred more often ($P < .02$) in the VO than in the no VO group. In the obese group, no significant differences were found. The amount of VFA (mean ± SD) increased with higher BMI in the VO groups and no VO groups: VO group—BMI < 25 kg/m^2, VFA = 163.7 ± 50 cm^2, BMI 25–30 kg/m^2, 195.2 ± 68.2 cm^2, and BMI > 30 kg/m^2 259.9 ± 81.5 cm^2 ($P < .001$); no VO group—BMI < 25 kg/m^2, VFA 56.2 ± 26.8 cm^2, BMI 25–30 kg/m^2, 73.5 ± 21.3 cm^2, and BMI > 30 kg/m^2, 86.6 ± 13.3 cm^2 ($P < .001$).

Table 2. Patient characteristics for visceral obesity (VO) versus no VO per body mass index (BMI) category

	BMI <25 kg/m²			BMI 25–30 kg/m²			BMI >30 kg/m²		
Characteristic	**No VO (*n* = 145)**	**VO (*n* = 115)**	***P* value**	**No VO (*n* = 46)**	**VO (*n* = 195)**	***P* value**	**No VO (*n* = 6)**	**VO (*n* = 57)**	***P* value**
Age, mean (SD)	69 (12)	74 (9)	<.01	66 (14)	71 (10)	.04	65 (13)	68 (11)	.49
Male gender, *n* (%)	41 (28)	77 (67)	<.01	9 (20)	132 (68)	<.01	0 (0)	28 (50)	.03
Comorbidity, *n* (%)									
Cardiac	21 (15)	46 (40)	<.01	9 (20)	75 (39)	.02	3 (50)	22 (39)	.67
Pulmonary	6 (4)	15 (13)	.01	4 (9)	23 (12)	.55	0 (0)	8 (14)	1.00
Hypertension	35 (24)	48 (42)	<.01	11 (24)	70 (36)	.12	3 (50)	29 (51)	1.00
Diabetes	6 (4)	17 (15)	<.01	4 (9)	20 (10)	1.00	0 (0)	11 (19)	.58

VO defined as a visceral fat area of >100.cm ^{2}.

Postoperative outcome: VO and BMI

VO was associated with significantly more anastomotic leakage (P < .04), pneumonia (P < .01), wound infections (P < .03) and reoperations (P < .04), and greater duration of hospital stay (P < .05). There were no differences in outcome between the BMI groups (Table III).

Table 3. Postoperative outcomes for the total study population, visceral obesity (VO) groups versus no VO groups and body mass index (BMI) categories

Outcomes	Total study population (*n* = 564)	No VO (*n* = 197)	VO (*n* = 367)	Risk estimate* (95% CI)	*P* value	BMI <25 kg/m² (reference category; *n* = 260)	BMI 25–30 kg/m² (*n* = 241)	Risk estimate* (95% CI)	BMI >30 kg/m² (*n* = 63)	Risk estimate * (95% CI)	*P* value
Postoperative complications, *n* (%)											
Anastomic leakage †	36 (7)	7 (4)	29 (8)	2.3 (1.0–5.4)	.04	15 (6)	16 (7)	1.1 (0.6–2.4)	5 (8)	1.4 (0.5–4.0)	.82
Pneumonia	51 (9)	10 (5)	41 (11)	2.4 (1.2–4.8)	.02	23 (9)	22 (9)	1.0 (0.6–1.9)	6 (10)	1.1 (0.4–2.8)	.98
Wound infection	38 (7)	7 (4)	31 (9)	2.5 (1.1–5.8)	.03	19 (7)	15 (6)	0.8 (0.4–1.7)	4 (6)	0.9 (0.3–2.6)	.89
Urinary tract infection	23 (4)	8 (4)	15 (4)	1.0 (0.4–2.4)	.98	12 (5)	7 (3)	0.6 (0.2–1.6)	4 (6)	1.4 (0.4–4.5)	.40
Reoperation, *n* (%)	80 (14)	20 (10)	60 (16)	1.7 (1.0–3.0)	.04	36 (14)	38 (16)	1.2 (0.7–1.9)	6 (10)	0.7 (0.3–1.6)	.44
Duration of hospital stay, geometric means, *n* (%)	7.9 (1.9)	7.3 (1.8)	8.2 (1.9)	1.1 ‡(1.0–1.3)	.05	7.8 (1.9)	8.1 (1.8)	1.0 ‡(0.9–1.2)	7.8 (1.9)	1.0 ‡(0.8–1.2)	.79

VO defined as a visceral fat area of >100 cm 2.
**Odds ratio unless stated otherwise.*
† Analysis on data of 543 patients with a primary anastomosis (BMI < 25: non-VO, n = 140; VO, n = 108; BMI 25–30: non-VO, n = 44; VO, n = 190; BMI > 30: non-VO, n = 6; VO, n = 55).
‡ Ratio of geometric means.

Postoperative outcome: No VO versus VO within each BMI group

Only in the BMI < 25 kg/m² group was VO associated with more postoperative complications: anastomotic leakage (P = .06), pneumonia (P = .01), and wound infections (P < .03). Duration of stay was greater in the VO BMI < 25 kg/m² group (P = .08; Table IV).

Table 4. Postoperative outcomes for visceral obesity (VO) versus no VO per body mass index (BMI) category

Outcome	BMI < 25 kg/m²				BMI 25–30 kg/m²				BMI > 30 kg/m²			
	No VO (*n* = 145)	VO (*n* = 115)	Risk estimate * (95% CI)	*P* value	No VO (*n* = 46)	VO (*n* = 195)	Risk estimate * (95% CI)	*P* value	No VO (*n* = 6)	VO (*n* = 57)	Risk estimate * (95% CI)	*P* value
Postoperative complications, n (%)												
Anastomic leakage	5 (4)	10 (9)	2.8 (0.9–8.3)	.06	2 (4)	14 (7)	1.7 (0.4–7.8)	.74	0 (0)	5 (9)	—	1.00
Pneumonia	7 (5)	16 (14)	3.2 (1.3–8.0)	.01	3 (7)	19 (10)	1.6 (0.4–5.5)	.78	0 (0)	6 (11)	—	1.00
Wound infection	6 (4)	13 (11)	3.0 (1.1–8.0)	.03	1 (2)	14 (7)	3.5 (0.5–27.3)	.32	0 (0)	4 (7)	—	1.00
Urinary tract infection	7 (5)	5 (4)	0.9 (0.3–2.9)	.86	1 (2)	6 (3)	1.4 (0.2–12.2)	1.00	0 (0)	4 (7)	—	1.00
Reoperation, *n* (%)	16 (11)	20 (17)	1.7 (0.8–3.4)	.14	4 (9)	34 (17)	2.2 (0.8–6.6)	.14	0 (0)	6 (11)	—	1.00
Duration of hospital stay, geometric means, *n* (%)	7.2 (1.8)	8.4 (2.0)	1.2† (1.0–1.4)	.08	7.6 (1.8)	8.2 (1.9)	1.1† (0.9–1.3)	.49	6.6 (1.5)	7.9 (2.0)	1.2† (0.7–2.1)	.5

VO defined as a visceral fat area of >100 cm² .
** Odds ratio unless stated otherwise.*
† Ratio of geometric means.

Predictive factors for postoperative outcome

On univariable analysis, VO was associated significantly with the occurrence of anastomotic leakage, pneumonia, wound infections, and reoperations, as well as greater duration of hospital stay. On multivariable analysis, VO discriminated for anastomotic leakage (odds ratio [OR], 2.3; 95% CI, 1.0–5.4; P = .05), and wound infection (OR, 2.5; 95% CI, 1.1–5.8; P = .03). For pneumonia, only pulmonary comorbidity (OR, 2.3; 95% CI, 1.1–4.8; P = .03) remained discriminative after multivariable analysis. Pulmonary comorbidity (ratio of geometric means, 1.3; 95% CI, 1.1–1.6; P ≤ .01) and laparoscopic surgery (ratio of geometric means, 0.7; 95% CI, 0.7–0.8; P < .01) were multivariably associated with duration of hospital stay (Table V).

Table 5. Predictive factors for postoperative outcome

	Univariable analysis			Multivariable analysis		
Factor	**Predictive factor**	**Risk estimate* (95%CI)**	***P* value**	**Predictive factor**	**Risk estimate* (95%CI)**	***P* value**
Anastomic leakage †	VO	2.3 (1.0–5.4)	.05	VO	2.3 (1.0–5.4)	.05
Pneumonia	Age	1.0 (1.0–1.1)	.02			
	Male gender	2.1 (1.1–3.8)	.02			
	Pulmonary comorbidity	2.9 (1.4–5.9)	.01	Pulmonary comorbidity	2.3 (1.1–4.8)	.03
	VO	2.4 (1.2–4.8)	.02			
Wound infection	VO	2.5 (1.1–5.8)	.03	VO	2.5 (1.1–5.8)	.03
Urinary tract infection	Male gender	0.3 (0.1–0.8)	.02	Male gender	0.3 (0.1–0.8)	.02
Reoperation	Pulmonary comorbidity	2.8 (1.5–5.2)	<.01	Pulmonary comorbidity	2.6 (1.4–4.9)	<.01
	VO	1.7 (1.0–3.0)	.05			
Length of stay	Age	1.0 ‡(1.0–1.0)	<.01			
	Laparoscopic surgery	0.7 ‡(0.6–0.8)	<.01	Laparoscopic surgery	0.7 ‡(0.7–0.8)	<.01
	Pulmonary comorbidity	1.4 ‡(1.2–1.7)	<.01	Pulmonary comorbidity	1.3 ‡(1.1–1.6)	<.01
	VO	1.1 ‡(1.0–1.3)	.05			

VO , Visceral obesity.
** Odds ratio unless stated otherwise.*
† Analysis on data of 543 patients with a primary anastomosis.
‡ Ratio of geometric means

Discussion

The present data show that the negative association between VO and postoperative outcome in colon cancer patients was more pronounced in patients with a BMI of <25 kg/m^2. Unexpectedly, an high incidence of VO was found in this group of patients (44%), which emphasizes the relevance of this finding. In the groups of overweight and obese patients, VO was not associated significantly with postoperative outcome. Our findings shed new light on the impact of VO in relation to BMI, as a metabolic risk profiler for untoward postoperative outcome in colon cancer surgery.

To date, this is the largest cohort of colon cancer patients studied for the relation between VO and outcome after elective colon cancer surgery. In general, VO was associated with more comorbidity, a higher rate of postoperative complications and reoperations, and greater duration of hospital stay. These results are in line with the observations found by other authors. In colorectal surgery, VO has been related to postoperative cardiovascular and pulmonary complications, wound infections, and greater duration of hospital stay[3,17]. This association was found also in patients undergoing other types of abdominal surgery, such as gastrectomy, pancreatic surgery, and nephrectomy.[18-20]

The relevance of BMI compared with VO in determining a metabolic risk profile in colorectal cancer has been questioned in a number of studies[9,12,17]. Our data confirm this notion by showing that BMI in itself had no association with surgical outcome (Table III). However, in combination with VO, BMI < 25 kg/m^2 helped to further identify a group of colon cancer patients more at risk for postoperative complications. A similar association between lower BMIs and abdominal obesity is reported for the risk of death by Pischon et a[21] in a large European cohort of participants from the general population. In their study, waist circumference and waist-to-hip ratio were used as indirect measures of central obesity and were associated positively with risk of death. This association tended to be stronger in persons with a lower BMI. Although VO was measured indirectly, the strong similarity with our study in terms of relative risk for developing postoperative complications is striking. These indirect anthropometric measures of abdominal obesity do not discriminate between the relative contributions of subcutaneous and visceral fat. Indeed, this is of importance because visceral fat and not subcutaneous fat is now considered the major predictor of adverse events[22].

Nevertheless, considering the association of VO with untoward postoperative outcome, our results raise the question of why a higher rate of VO did not show a significant association with adverse outcomes in the overweight and obese groups. The differences between the lower and higher BMI groups may be related to a different immunologic response to colon cancer resection in the presence of VO. VO is characterized by a chronic inflammatory state

induced by the production of adipokines by visceral fat cells and proinflammatory cytokines from fat-infiltrated macrophages[6,23,24]. The mean VFA increased with higher BMI, both in the no VO groups and in the VO groups, indicating that fat had been accumulating for a longer time in the higher BMI groups. Here we speculate that VO-induced chronic inflammation is present more extensively and for a longer time in overweight and obese patients than in the patients with a BMI < 25 kg/m^2. The inflammatory response to abdominal surgery in patients with a chronic inflammatory state may be blunted according to the principle of acquired tolerance, which is best described for repeated cytokine and endotoxin exposure.25 Hypothetically, the proinflammatory response may, therefore, be more pronounced in patients with VO and a BMI of <25 kg/m^2 than in overweight and obese patients, leading to postoperative complications in patients with a lower BMI. In our multivariable analysis, VO was clearly associated with anastomotic leakage and wound infection, which suggests a link with an exaggerated inflammatory response. Further research on the principle of inflammatory tolerance in patients with VO and different BMIs is warranted.

The metabolic disturbances our patients presented with, such as cardiovascular disease, hypertension, and diabetes, were associated strongly with VO, confirming previous reports on the relation between the metabolic syndrome and VO.22 However, when stratified for BMI groups, these associations remained significant only in the BMI < 25 kg/m^2 group. Therefore, the worse outcome in the VO BMI < 25 kg/m^2 group may have been influenced by these metabolic disturbances. However, this is contradicted by the results of the univariable and multivariable analyses, which clearly showed that the only comorbidity factor related to complications was pulmonary comorbidity, and not those associated with the metabolic syndrome. Separate multivariable analysis in the BMI <2 5 kg/m^2 group confirmed the overall analysis (data not shown). We conclude that, despite the presence of more comorbidities in the VO low BMI group, this probably was not of direct influence on the risk of postoperative complications.

A limitation of the present study is its retrospective character, and results should be interpreted in this context. Database entry, however, was done prospectively as a routine part of our ERAS quality system, which minimized the loss of data.

In conclusion, according to our results, the negative effect of VO on postoperative outcome after colon cancer surgery is more pronounced in patients with a BMI of <25 kg/m^2 than in overweight and obese patients. The routinely performed preoperative CT scan can be used for screening the BMI < 25 kg/m^2 group for VO to identify a colon cancer population at significant risk for postoperative complications. Interventions need to be developed to quickly reduce visceral fat and applied in the weeks before colon cancer surgery to improve postoperative outcomes, especially in patients with a low BMI.

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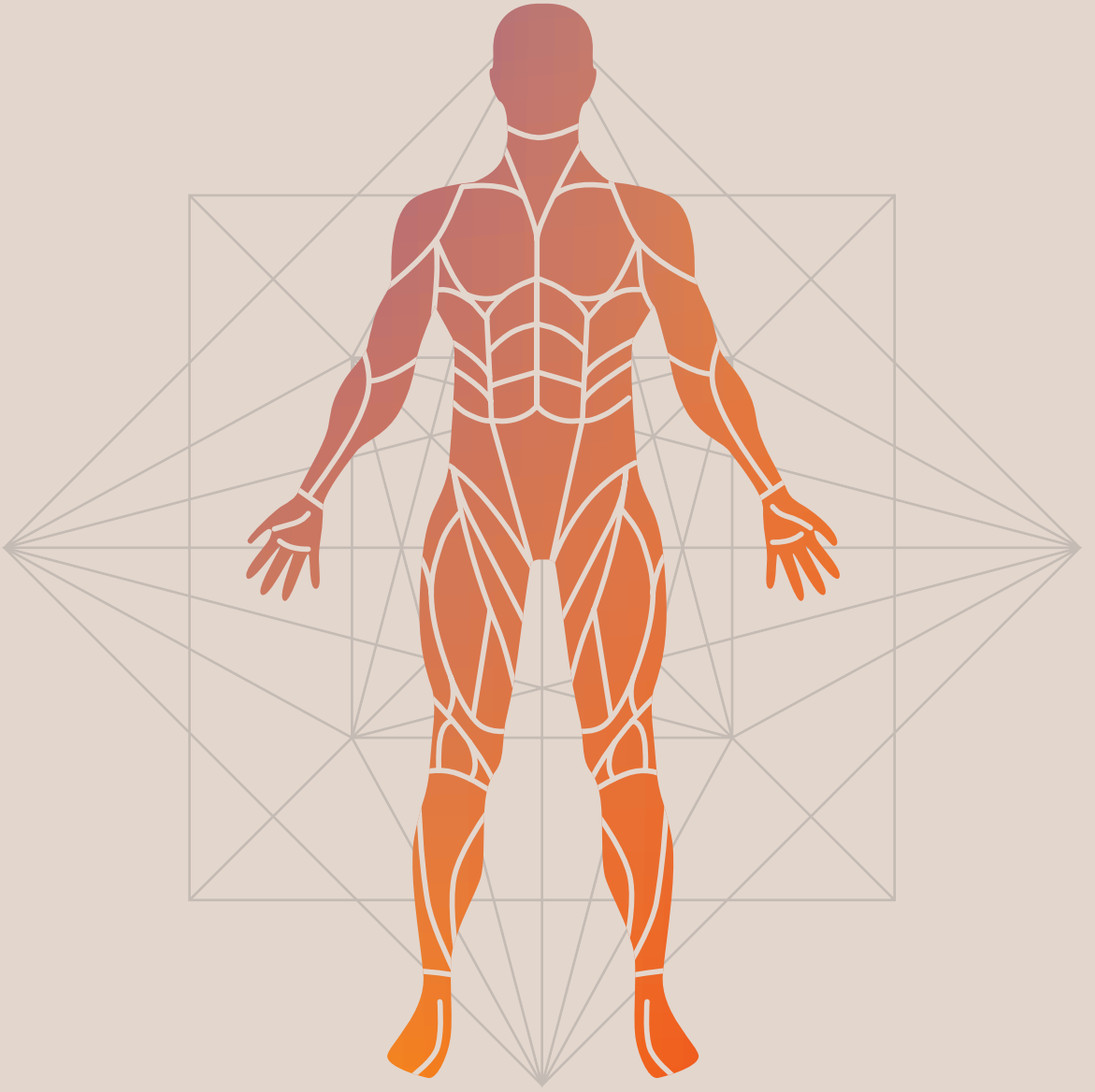

Chapter 3

Visceral obesity determined by CT scan and outcomes after colorectal surgery; a systematic review and meta-analysis

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Abstract

Background

Visceral obesity may affect outcome after colorectal surgery. The visceral fat area as determined by CT scanning is considered the standard in the detection of visceral obesity.

Method

A systematic review was performed of trials investigating the effect of visceral obesity on outcomes of patients with colorectal cancer with no radiotherapy or chemotherapy and measured by CT scanning. The main endpoints were primary hospital stay, morbidity, operative time and blood loss. Quality assessment and data extraction were performed independently by two observers.

Results

Seven studies were eligible for analysis, including 1230 patients. Primary hospital stay (weighted mean difference 1.16 days, 95 % CI 0.0.05 to 2.28 days, $p=0.04$), morbidity rates (RR 0.15, 95 % CI 0.10 to 0.21, $p<0.00001$) and operative time (weighted mean difference 20.47 min, 95 % CI 12.76 to 28.17 min, $p<0.00001$) were significantly higher for visceral obese patients. No difference was found in blood loss.

Conclusion

Visceral obesity leads to a longer hospital stay, higher morbidity and longer operative time after elective colon surgery. These findings show that the preoperative CT scan for detecting disseminated disease can be used to assess visceral obesity and helps in risk profiling patients undergoing elective colon surgery.

Introduction

Colorectal resection for cancer is one of the most frequently performed surgical procedures in the world[1]. The associated complication rates are significant (15–20 %) and related to surgical and non-surgical causes[2]. In recent years, visceral obesity has been recognized as one of the possible non-surgical causes of postoperative complications and longer hospital stay after colorectal surgery[3]. Therefore, accurate determination of the amount of visceral fat may be of value in preoperative risk profiling in the colorectal cancer patient.

Body mass index (BMI) as a general measure of obesity is not always consistent with the amount of visceral fat and is distributed differently among various ethnic groups[4]. The waist circumference and the hip to waist ratio reflect visceral fat depots better, and strong correlations with cardiovascular disease and type 2 diabetes have been found [5,6]. A down side to these anthropometric measurements is the low reproducibility and variability. Using body imaging techniques, like computed tomography (CT), accurate volumetric fat measurement can be performed with high reproducibility[7,8]. In the preoperative work-up of the colorectal cancer patient, CT imaging of the abdomen is standard in the search for disseminated disease and could be of value in determining visceral fat determination.

Here, we present a systematic review and meta-analysis of studies investigating the effect of visceral obesity measured only by CT on outcomes of patients with colorectal cancer who did not receive chemotherapy or radiation.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[9]. Inclusion criteria for article selection were clinical trials measuring visceral fat with CT in patients undergoing colorectal surgery.

Search strategy

A clinical librarian performed a search in MEDLINE (PubMed), EMBASE (Ovid) and the Cochrane Database of Systematic Reviews. The final search was performed on 4 April 2014. The key words and MeSH terms used for MEDLINE were ("Colorectal Neoplasms"[Mesh] OR "Colorectal Surgery"[Mesh] OR "Colectomy"[Mesh] OR "Colonoscopy"[MeSH Terms] OR "Colonic Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR abdominal surgery[tiab] OR colorectal surgery[tiab] OR colon surgery[tiab] OR rectal surgery[tiab] OR colectom*[tiab] OR colonic cancer*[tiab] OR colonic neoplasm*[tiab] OR colon cancer*[tiab] OR colon neoplasm*[tiab] OR rectal cancer*[tiab] OR rectal neoplasm*[tiab] OR rectal tumor*[tiab] OR colorectal cancer*[tiab] OR colonoscopy[tiab]) AND ("Intra-Abdominal Fat"[Mesh] OR "Obesity, Abdominal"[Mesh] OR visceral fat*[tiab] OR intra-abdominal fat*[tiab] OR visceral adipose tissue[tiab] OR visceral fat[tiab] OR visceral obesit*[tiab] OR abdominal obesit*[tiab] OR central obesit*[tiab] OR "Obesity"[MAJR] OR "Obesity/complications"[MeSH Terms]) AND (Prognosis/Broad[filter] OR systematic[sb] OR "Predictive Value of Tests"[MeSH Terms] OR "Cohort Studies"[Mesh] OR "Validation Studies"[Publication Type] OR "Comparative Study" [Publication Type] OR "Evaluation Studies"[Publication Type] OR "Meta-Analysis as Topic"[MeSH Terms] OR predict*[tiab] OR complication*[tiab]). For EMBASE, the combination of Emtree terms used was ((colorectal tumor/ or colorectal surgery/ or exp colon resection/ or colonoscopy/ or exp colon tumor/ or exp rectum tumor) OR (abdominal surgery or colorectal surgery or colon surgery or rectal surgery or colectom* or colonic cancer* or colonic neoplasm* or colon cancer* or colon neoplasm* or rectal cancer* or rectal neoplasm* or rectal tumor* or colorectal cancer* or colonoscopy).ti,ab.) AND ((intraabdominal fat/ or abdominal fat/ or abdominal obesity/ or *obesity/ or obesity) OR (visceral fat* or intra-abdominal fat* or visceral adipose tissue or visceral obesit* or abdominal obesit* or central obesit*).ti,ab.) AND ((predictive value/ or cohort analysis/ or exp clinical study/ or validation study/ or comparative study/ or evaluation/ or "meta analysis (topic)"/ or major clinical study/ or controlled study/) OR ((predict* or complication*).ti,ab.). No hits were found in the keywords used searching the Cochrane Database.

Study selection

Two reviewers (HC and CH) independently selected relevant studies based on their titles and abstracts. Conference abstracts with no subsequent publication were disregarded. Full text articles were read by both reviewers. Duplicate publications and papers that reported on the same or parts of the same study population were excluded, in which case, only the largest or the most recent publication was included. Final inclusion required consensus; any differences in judgement were resolved by discussion. Only articles where the CT was used as a modality and where the patients did not receive chemotherapy or radiation were included.

Data extraction and quality assessment

Two reviewers (HC and CH) independently selected relevant studies based on their titles and abstracts. Conference abstracts with no subsequent publication were disregarded. Full text articles were read by both reviewers. Duplicate publications and papers that reported on the same or parts of the same study population were excluded, in which case, only the largest or the most recent publication was included. Final inclusion required consensus; any differences in judgement were resolved by discussion. The methodology of each trial was critically appraised by the two reviewers independently, using the Cochrane Collaboration's tool for assessing risk of bias as proposed by the Cochrane Collaboration[10]. Studies presenting the following data were selected: age, sex, American Society of Anaesthesiologist (ASA), morbidity, mortality, readmission, primary or total hospital stay.

Outcomes

Data were extracted from original articles only. The two reviewers (HC en HC) both extracted the data onto a data sheet. Primary hospital stay, morbidity and operative time and blood loss were the outcomes of interest.

Statistical analysis

To determine if a meta-analysis of the data was appropriate, clinical heterogeneity was assessed by comparing inclusion and exclusion criteria per study, the outcome parameters studied and baseline characteristics of the included patients. Methodological heterogeneity was assessed using the MINORS tool. Heterogeneity was tested using the χ 2 test and quantified with an I 2 (the proportion of total variance explained by heterogeneity). For dichotomous data, a risk ratio (RR) was calculated with a 95 % confidence interval (CI). For continuous data, a mean difference (MD) with 95 % CI was calculated based on the inverse variance method. A P value of <0.05 was considered statistically significant. Statistical analysis was done using Review Manager version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration 2011) and Comprehensive Meta-Analysis version 2.2.064 (Biostat, Inc., USA 2011).

Results

Description of included studies and methodological quality

The design of the included studies is described in Fig. 1. Of 1064 citations reviewed, 33 met our inclusion criteria. After title and abstract review, 26 studies were excluded. The remaining seven studies were investigated in detail. All papers used in the analysis were retrospective cohort studies and in English. All studies consisted of patients of the Japanese population. These studies were published between 2005 and 2013. They reported a total of 1230 patients: a visceral obese group of 488 patients and a visceral nonobese group of 742 patients. In Table 1, the demographics, patient characteristics and reported outcome of the studies are shown. In two studies, a significant difference was seen in age[11,12]. In four of the seven included studies, significantly more men were in the visceral obese group[4,12-14]. Only two studies reported about the ASA classification, and one showed significant less ASA I patients in the visceral obese group[11]. Tsujinaka showed a trend in amount of patients with ASA I ($p=0.066$)[4]. Five studies measured the VFA at the umbilicus level or at the disc space between the third and fourth lumbar vertebral bodies during the preoperative abdominal CT[3,4,13-15]. One study measured the VFA at the level of the fourth and fifth intervertebral space[11]. Rickles et al. measured the VFA at the level of S1 vertebrae[12]. In five studies, patients with a VFA of ≥100 cm2 were defined as visceral obese[3,12-15]. In the other two studies, a VFA of ≥130 cm^2 was considered as visceral obese[4,11]. The methodological quality of the included studies is listed in Table 2. All included studies had several limitations.

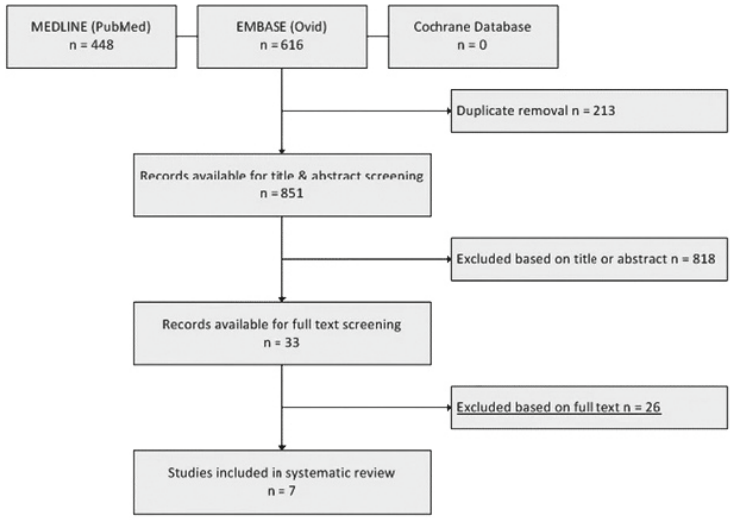

Figure 1.

Table 1. Demographics, patient characteristics and reported outcome of the studies

Patients (*n*)			Age (years)		Male gender (*n* (%))		ASA I (*n* (%))		Type of surgery	PHS (days)		Morbidity (%)		Operative time (min)		Blood loss (mL)		
Reference	Visceral obese	Visceral non-obese	Visceral obese	Visceral non-obese	Visceral obese	Visceral non-obese	Visceral obese	Visceral non-obese		Visceral non-obese	Visceral obese	Visceral non-obese	Visceral obese	Visceral non-obese	Visceral obese	Visceral non-obese	Visceral obese	Visceral non-obese
Ishii et al.	9	37	Not given	Not given	8 (88.9)*	16 (43.2)*	Not given	Not given	AR, APR, HM	22.0	16.0	7 (77.8)*	13 (35.1)*	387*	323*	156	112	
Kang et al.	29	113	67.5*	60.9*	16 (55.2)	73 (64.6)	16 (55.2)*	84 (74.3)*	All LS TEM	12.5	11.5	8 (27.6)	25 (22.1)	294.3*	254.1*	205.8*	102.5*	
Rickles et al.	111	108	69.1*	64.9*	71 (64.0)*	46 (42/6)*	Not given	Not given	Not defined	9.1	9.2	46 (41.4)	33 (30.6)	252	252	Not given	Not given	
Sakai et al.	25	54	66.1	70.6	14 (56.0)	29 (53.7)	Not given	Not given	IR, LH, RH, TR, SR, RR	Not given	Not given	13 (52.0)	6 (11.1)	210.1*	155*	158*	69.1*	
Tsujinaka et al.	68	65	65.5 median	64 median	49 (72.1)*	30 (46.2)*	38 (55.9)	47 (72.3)	All LS SR	12.0*	9.9*	22 (32.4)*	8 (12.3)*	224*	199*	74.5	69.9	
Watanabe et al.	144	194	66.2	64.8	107 (74.3*	72 (37.1)*	Not given	Not given	Not defined	11.3	11.2	37 (25.7)*	27 (13.9)*	197*	171*	45.1	35.6	
Yamamoto et al.	171	102	66.7	66.3	109 (37.4)	64 (62.7)	Not given	Not given	Not defined	Not given	Not given	Not given	Not given	261	270	376	401	

AR anterior resection, APR abdominoperineal resection, HM Hartmann, LS laparoscopy, TEM total mesorectal excision, IR ileocecal resection, LH left hemicolectomy, RH right hemicolectomy, TR transvers colectomy, SR sigmoidectomy, RR rectal resection
**p<0.05 (significant)*

Definitions of outcome measures

Primary hospital stay (PHS) or LOS was defined as hospital stay without including re-hospitalisation for complications, or no definition was given. Morbidity was defined as complications within 30 days of the first operation, or no definition was given. Operative time was defined as the duration of surgery, or no definition was given. Blood loss was defined as blood loss during surgery, or no definition was given.

Meta-analysis

The authors of seven studies were contacted for original data reported in mean and standard deviation for the purpose of this update and meta-analysis. Two of them did not provide the data for the analysis of PHS[3,15].

Table 2. Methodological quality

Adequate sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data addressed	Free of selective outcome reporting	Free of other sources of bias
Reference					
Ishii et al.	+	–	–	–	–
Kang et al.	+	–	–	+	–
Rickles et al.	+	–	–	–	–
Sakai et al.	+	–	–	–	–
Tsujinaka et al.	+	–	–	–	–
Watanabe et al.	+	–	–	–	–
Yamamoto et al.	+	–	–	–	–

Primary hospital stay

Five studies reported on primary hospital stay (Table 1). After pooling the data, a significant higher PHS was seen for the visceral obese group (weighted mean difference 1.16 days, 95 % CI 0.05 to 2.28 days, p=0.04) (Fig. 2).

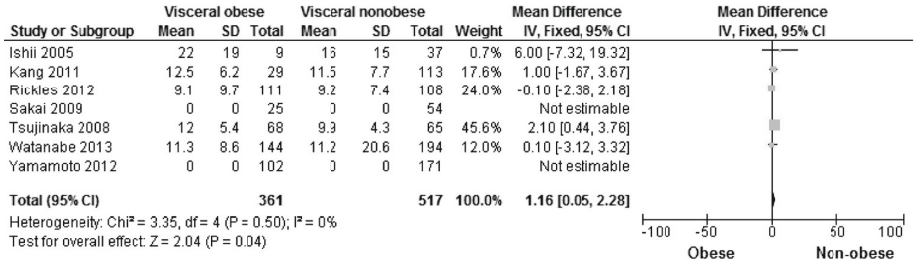

Figure 2. Primary hospital stay

Morbidity rates

Morbidity rates were reported in six studies and varied from 27.6 to 77.8 % in the visceral obese group and 11.1 to 35.1 % in the visceral nonobese group (Table 1). After pooling of the data, significantly lower morbidity rates were seen in the visceral nonobese group (RR 0.15, 95 % CI 0.10 to 0.21, p<0.00001) (Fig. 3).

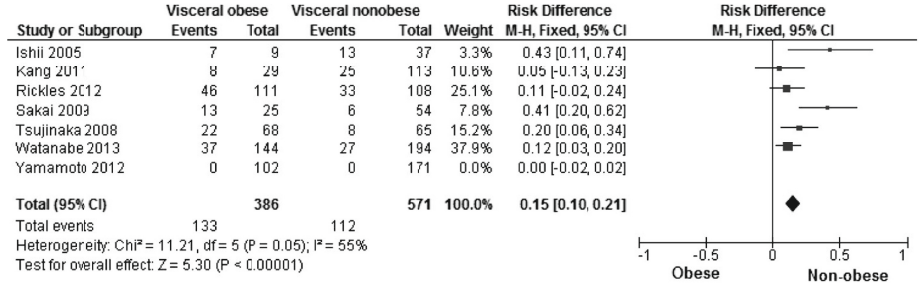

Figure 3. Morbity

Operative time

All studies reported on operative time (Table 1). Pooling of the data showed significantly longer operative time for the visceral obese group (weighted mean difference 20.47 min, 95 % CI 12.76 to 28.17 min, p<0.00001) (Fig. 4).

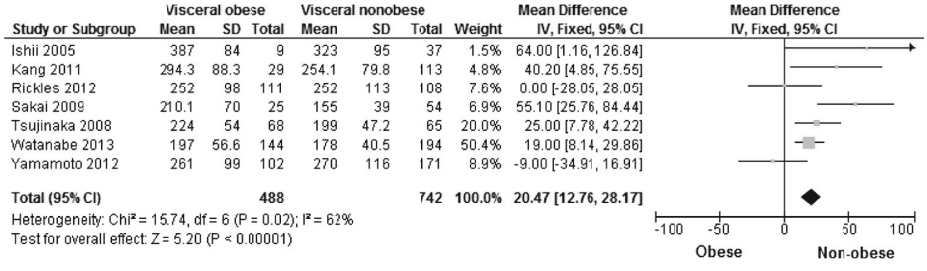

Figure 4. Operative time

Blood loss

Blood loss was reported in all included studies. The pooling of the data showed no difference in blood loss between both groups (weighted mean difference 4.64 mL, 95 % CI −16.84 to 26.12 mL, p=0.10) (Fig. 5).

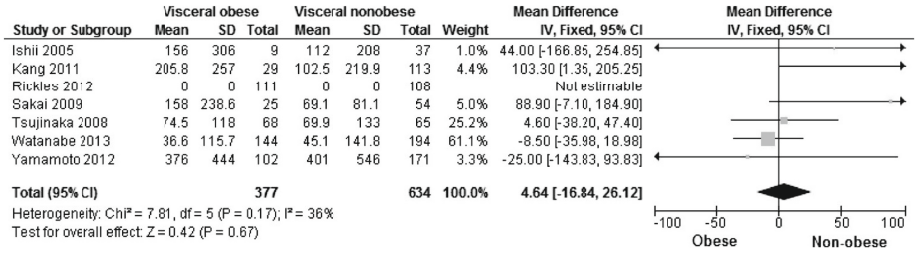

Figure 5. Blood loss

Discussion

This systematic review suggests that visceral obesity as determined by CT scan results in longer PHS, higher morbidity and longer operative time after elective colon surgery. No significant difference was observed in blood loss during surgery.

Obese patients represent a significant technical and metabolic challenge for the colorectal surgeon. Visceral obesity increases the risk of developing the metabolic syndrome possibly contributing to poorer outcome[16,17]. Indeed, several authors have reported that visceral obesity leads to higher numbers of wound hernia, pulmonary and cardiovascular complications, longer operative time and significantly lower disease-free survival after major colorectal surgery[18-20]. Almost all earlier studies use BMI or waist circumference as an indirect index of visceral obesity. However, direct visceral fat determination using CT scan is more accurate and was shown to better predict postoperative outcome after colorectal surgery than BMI[21,22].

Visceral obesity has been associated with worse outcome in other forms of surgery as well like gastrectomy, pancreatic resections and nephrectomies. For patients undergoing laparoscopy-assisted gastrectomy, VFA determined by CT scan was found to be more accurate than BMI in predicting operative time, blood loss, lower number of lymph nodes harvested and complications[23-25]. For open gastrectomy, more intra-abdominal infections were reported in patients with a high VFA[26]. Visceral obesity has been identified as a strong predictor of postoperative pulmonary complications after pancreaticoduodenectomy and of perioperative outcome in patients undergoing laparoscopic radical nephrectomy[27-28].

For accurate tumor staging and prognosis in rectal cancer surgery, adequate harvesting of lymph nodes in total mesorectal resection is important and more technically demanding in patients with visceral obesity[29-31]. From the studies in this review, only the study of four studies reported on lymph node retrieval which was lower in the visceral obese patients[3,11-13].

As stated before, BMI is not an accurate index to quantify intra-abdominal fat and thereby visceral obesity. One of the reasons is that BMI does not reflect the degree of a patients' visceral fat, because of the different fat tissue distribution between individuals and various ethnic groups[32]. For this reason, we reviewed only studies that used the CT scan as a method to analyse visceral adipose tissue. Schuster et al. conducted a review in which they investigated different modalities such as BMI, bioelectrical impedance analysis, dual energy X-ray, ultrasound, CT and MRI for visceral adipose tissue analysis[8]. They concluded that CT and MRI generate the most accurate, specific and comprehensive data in comparison with all other modalities. Because CT scanning is used for the preoperative determination of disseminated disease in patients with colorectal cancer, it can be used for VFA measurement as well.

Some problems however remain with the use of CT scanning for visceral fat determination. The first problem is concerned with the lack of an accepted attenuation Hounse Field Unit threshold for determining adipose tissue. In the literature, this threshold varies from −250 to −50, −190 to −30 or −140 to −40 HFU[33-35]. In only one study in our review, the threshold was given[7]. This complicates comparison of research data, and it is in this light that the results of the present review should be interpreted. The same accounts for the differences in the level of planimetric location of the VFA measurement. Most of the levels used are the umbilicus and the L4–L5 intravertebral space[36-38]. These levels are thought to correspond to the highest amount of adipose tissue accumulation[36-38].

No prospective RCTs have been performed at this moment, so the available data all come from retrospective cohort studies possibly leading to selection bias. In addition, these small studies are more likely to show larger treatment effects due case-mixed differences. Due to the beneficial reports in all included studies, a publication bias is also possible. The methodological quality of the studies was low. Furthermore, no study clearly defined their outcome measures, thereby increasing heterogeneity.

According to the present systematic review, visceral obesity leads to a longer hospital stay, higher morbidity and longer operative time after elective colorectal surgery without any chemotherapy or radiation. In the preoperative work-up of the colorectal cancer patient, CT imaging of the abdomen is standard in the search for disseminated disease, and the

assessment of visceral fat could be performed easily. This information is important in metabolic risk profiling the elective colorectal surgery patients and offers the opportunity to develop tailor-made intervention programs. Progress in this field of research is dependent on international standardisation of the technical details of VFA CT scan determination. Prospective randomised studies on the prognostic effects of VFA and surgical outcome are needed to further substantiate the conclusions of the present review and also the effects of chemotherapy and radiation on visceral obesity.

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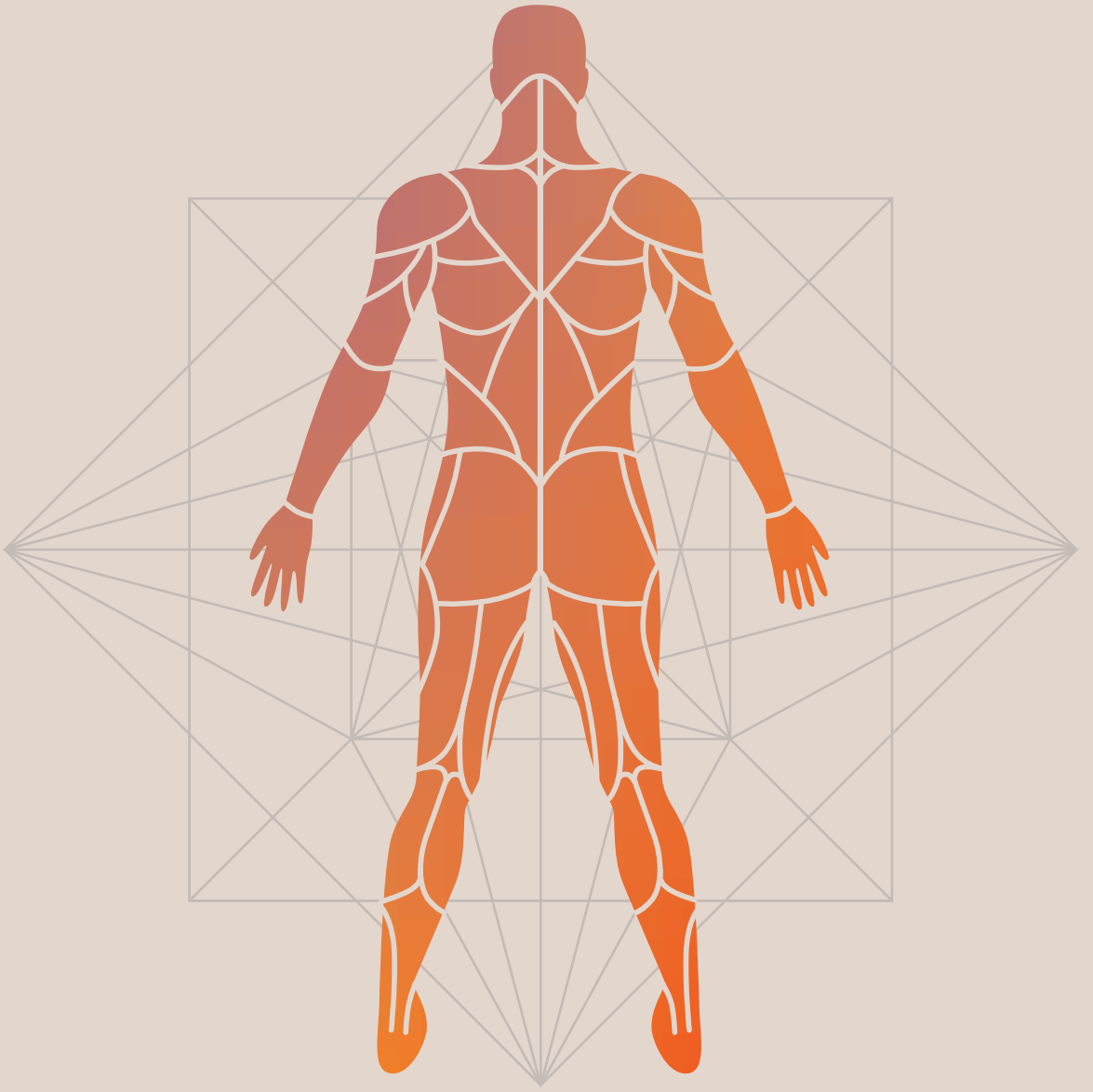

Chapter 4

Visceral obesity, muscle mass and outcome in rectal cancer surgery after neo-adjuvant chemo-radiation.

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Arjen Lak
Hiëronymus J Doodeman
Alexander PJ Houdijk

International Journal of Surgery, 2016

Abstract

Background

Preoperative chemoradiation has become a routine modality in the treatment of rectal carcinoma that may impair a patients general condition. In these patients, it is important to identify factors that influence postoperative recovery. Visceral obesity(VO) as a metabolic risk factor was studied in rectal cancer patients receiving preoperative chemoradiation.

Aim

The impact of VO on post-operative outcome in rectal carcinoma surgery after preoperative chemoradiation was studied. In addition, the effect of chemoradiation on body composition was studied.

Method

The visceral fat area(VFA), total fat area(TFA) and skeletal muscle area(SMA) were measured on cross-sectional CT-slides in 74 patients who underwent rectal cancer surgery after chemoradiation. CT-scans taken before and after chemoradiation were analysed. Associations between VFA, per- and postoperative complications were studied. A VFA of 100 cm^2 and 130 cm^2 was used to differentiate between non-VO and VO.

Results

Using a VO cut-off point of a VFA of 100 cm^2, the VO patients had more per-operative blood loss(471 mL vs 271 mL p = 0.020), a higher complication rate(10% vs 49% p = 0.001), more ileus(2% vs 28% p = 0.027) and a longer length of stay(9.7days vs 13days p = 0.027). When a VFA of 130 cm^2 was used, VO patients showed more complications(17% vs 55%, p = 0.001) and ileus(10% vs 32% p = 0.017).

During chemoradiation the SMA increased(Mean difference: 2.2 cm^2 p = 0.024), while the VFA showed no change.

Conclusion

It appears that VO is associated with co-morbidity and poor outcome in rectal cancer patients. Using different cutoff values for VO different associations with outcome were found. SMA increased during chemoradiation, a phenomenon that remains to be explained.

Highlights

- Visceral obesity is associated with co-morbidity and poor outcome in rectal cancer surgery.
- Visceral obesity is associated with more complications and a longer length of stay in rectal cancer surgery.
- Different cut-off values for visceral obesity different associations with outcome were found.
- Skeletal muscle area increased during chemoradiation, a phenomenon that remains to be explained.

Introduction

Preoperative chemoradiation followed by total mesorectal excision (TME) has become the standard treatment of locally advanced rectal cancer because of better local control and promising long-term results[1]. A downside of chemoradiation however, is the possible detrimental immunological and metabolic effects that may increase the risk of postoperative complications. Therefore, in these patients, identifying metabolic risk factors is important to direct strategies to optimize preoperative condition.

In recent years, visceral obesity has been identified as a significant metabolic risk factor that negatively influences surgical outcome in colon cancer, gastric cancer and pancreatic surgery[2-7]. Considering the increase in the number of obese patients, more knowledge on the effects of visceral obesity (VO) has become relevant. The negative effects of visceral adipose tissue are thought to be mediated by the state of chronic inflammation associated with cytokines such as TNF-alpha, IL-6 and IL-8 and the metabolic syndrome[8,9]. In the assessment of visceral obesity, the abdominal CT scan is helpful as it enables the direct measurement of Visceral Fat Area (VFA) with far more precision than the indirect anthropometric measurements like hip to waist ratio or body mass index (BMI). In Japanese studies, a VFA of >100 cm^2 has been associated with the metabolic syndrome and an increased number of complications after colorectal surgery but little is known from other parts of the world. Another relevant metabolic tissue that can be assessed by abdominal CT is skeletal muscle from the lumbar and psoas muscles. The loss of skeletal muscle or sarcopenia is associated with more postoperative complications, increased length of stay (LOS), lower survival and reduced quality of life [10-12].

In patients with locally advanced rectal cancer eligible for preoperative chemoradiation, an abdominal CT scan is performed in the search for disseminated disease before and after chemo-radiation with a time interval of approximately three months. In these patients the effect of VO on surgical outcome has not been studied before. In addition, it is not known whether chemoradiation has any effect on visceral fat or muscle mass.

The aim of the present study was to assess the effects of chemoradiation on VFA and muscle mass and their relation to post-operative outcome in patients with rectal cancer.

Methods

Patients

All patients who underwent preoperative chemoradiation and rectal resection for locally advanced carcinoma and had a pre and post chemoradiation abdominal CT scan in the

period of 2006–2013 were included in this study. Chemoradiation consisted of 28 × 1.8 Gy (total of 50.4 Gy) and 1500 mg Capecitabine two times a day for the duration of 5 weeks. Surgery was scheduled 6–8 weeks after completion of chemoradiation. This retrospective cohort study was conducted at the Medical Centre Alkmaar, a general teaching hospital in the Netherlands. Experienced gastrointestinal surgeons and their residents performed resection of rectal cancer. Both open and laparoscopic resections were included in this study. Patients who underwent acute rectal resection were excluded.

Data collection

The data that were collected included, age, gender, BMI, type of surgery, co-morbidity, visceral fat area, total fat area and skeletal muscle area before and after chemoradiation, length of stay (LOS), readmissions and reoperations within 30 days and the 30-day morbidity and in-hospital mortality.

Primary outcome measures were perioperative blood loss, LOS, complications, and clinical outcome. Complications were defined as wound infection, pneumonia, urinary tract infection, anastomotic leakage and ileus. Length of hospital stay (LOS) was calculated from the day of surgery until the day of discharge. Clinical outcome was defined as re-admission and re-operation in 30days. Secondary outcomes were the differences in VFA, SMA and TFA between first and second CT-scan.

CT scan measurement of visceral fat area and muscle area

For the detection of disseminated disease, all patients underwent two CT scans before and after chemo-radiation prior to surgery. The images of the CT scan were electronically transferred to a centralized data system and retrieved at a workstation (Syngo MMWP VE40A, Siemens AG, München Germany). A single scan at the level of the intervertebral disc of L3-L4 was selected for quantification of the degree of visceral fat and skeletal muscle. A threshold of −140 to −50 for visceral fat was used which was comparable to previous studies [2,13-16].The range of 5–60 Hounsfield units was used for muscle tissue. The VFA and the skeletal muscle area (SMA) were manually traced by trained analysts and finally calculated by the software (Fig. 1, Fig. 2). The analysts were not informed with regard to clinical outcome. The pre and post chemoradiation scans were analysed in a random order.

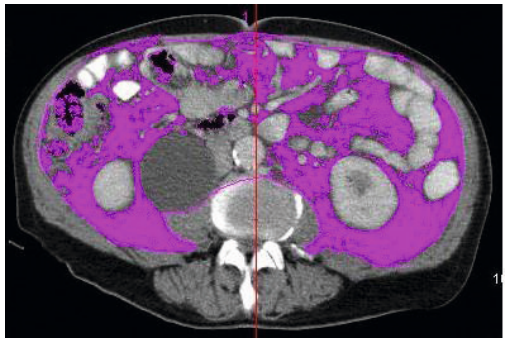

Figure 1. Measurement of the visceral fat area on the level of L3-L4

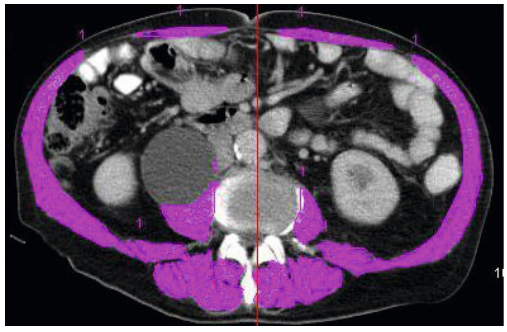

Figure 2. Measurement of the skeletal muscle area on the level of L3-L4

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Chicago, IL, USA).

For the comparison of dichotomous or categorical variables between groups, we used the Chi-square test or Fisher exact test where appropriate. For the comparison of the continuous variables between groups, we used the independent samples t-test. Continuous variables that were not normally distributed (LOS, Blood loss, VFA, TFA and SMA) were logarithmically transformed before analysis. After analysis back transformation of the means resulted in geometric means. A p-value < 0.05 was considered significant.

To test the independent predictive value of visceral obesity and patient characteristics on the occurrence of complications and LOS univariable and multivariable (logistic and linear) regression analysis were performed. The variables with p-value <0.05 in the univariable analysis were entered into a multivariable linear regression analysis. Effect sizes of significant predictive parameters were given with their 95% confidence intervals (CI).

Results

Seventy-four patients were included of who two patients eventually were not treated by surgery. However, their data were included in the analysis for preoperative co-morbidity and the impact of chemoradiation on the VFA and muscle mass. A low anterior resection was performed in 39 patients and an abdominoperineal resection was performed in 26 patients. Seven patients underwent an extended Hartmann procedure. An anastomosis was made in 33 patients (45%). Fifteen patients were treated laparoscopic. There was no significant difference between VO and non-VO patients in the number of laparoscopic procedures.

Impact of the chemoradiation on VFA,TFA and muscle mass

The mean period between the pre and post chemo-radiation CT scan was 101.0 days (SD:23 days). There was no difference in VFA (mean difference 2.0 cm^2, p = 0.53) and total fat area (mean difference 2.4 cm^2 p = 0.80) between the pre and post chemo-radiation CT scan. Surprisingly, the SMA significantly increased during chemoradiation with a mean difference of 2.2 cm^2 (p = 0.024). As the second scan is closer to the surgical procedure this scan was used for the analysis of the impact of VFA and muscle mass on surgical outcome.

Patient characteristics and postoperative outcome using VFA cut off = 100 cm^2 for VO

Table 1 summarizes the patient characteristics. Using VFA 100 cm^2 as a cut off, VO was found in 44 patients (60%) of who 30 (68%) were male. Of the 30 non-VO patients, 9 (30%) were male. Preoperative cardiac morbidity was significantly higher in the VO than in the non-VO group (27% and 0%, resp. P = 0.001). Visceral obese patients had more hypertension (7% vs 30%, p = 0.016) and diabetes (0% vs 16%, p = 0.037).

Table 1. Patient characteristics per group

	Total study population (n = 74)	VFA <100 cm² (n = 30)	VFA >100 cm² (n = 44)	*P*	VFA <130 cm² (n = 43)	VFA >130 cm² (n = 31)	*P*
Age in years, mean (SD)	64.0 (10.0)	61.2(8.0)	66.0(11.8)	0.042*	61 (11)	68 (7)	0.003*
Male sex, n (%)	39 (53)	9(30)	30 (68)	0.001*	20 (47)	19 (61)	0.209
Laparoscopic surgery, n(%)	15 (21)	5(17)	10(23)	0.538	7(17)	8(26)	0.366
Co morbidity, n (%)							
- Cardiac (%)	12 (16)	0 (0)	12 (27)	0.001*	1 (2)	11 (36)	<0.001*
- Pulmonary (%)	7 (10)	5 (17)	2 (5)	0.112	5 (12)	2 (7)	0.692
- Hypertension (%)	15 (20)	2 (7)	13 (30)	0.016*	4 (9)	11 (35)	0.006*
- Diabetes (%)	7 (10)	0 (0)	7 (16)	0.037*	2 (5)	5 (16)	0.122
Mean VFA $cm^{2,}$ (SD)	128 (81)	56 (29)	178(66)	NA	73 (36)	206 (60)	NA
Muscle mass in $cm^{2,}$ mean (SD)	58 (27)	48 (15)	66 (30)	0.001*	50 (16)	71 (33)	0.003*

VFA = Visceral fat area.
NA = not applicable.
**Statistically significant difference between corresponding groups (p ≤ 0.05).*

Table 2 summarizes postoperative outcome. Patients with a VFA >100 cm2 had significantly more per-operative blood loss than the VFA group <100 cm^2 (471 mL and 271 mL, resp. p = 0.020). In the VFA >100 cm^2 VO group, 21 patients (49%) had post-operative complications and in the non-VO group only 3 (10%) (p = 0.001, odds ratio of 8.3 (95% CI: 2.2–31.5)). Visceral obese patients had significantly more postoperative ileus (28% vs 7% p = 0.035). The LOS was significantly longer in the visceral obese group (13.0 days vs. 9.7 days, P = 0.027).

Table 2. Postoperative characteristics per group

	Total study population (n = 74)	VFA <100 cm^2 (n = 30)	VFA>100 cm^2 (n = 44)	*P*	VFA <130 cm^2 (n = 43)	VFA >130 cm^2 (n = 31)	*P*
Blood loss mL**	400	271	471	0.020*	338	427	0.341
Complications, n(%)	24 (33)	3 (10)	21 (49)	0.001*	7 (17)	17 (55)	0.001*
- Anastomic leakage, n(%)	3 (9)	1 (7)	2 (11)	0.658	1 (5)	2 (15)	0.547
- Pneumonia, n (%)	5 (7)	1 (3)	4 (9)	0.642	3 (7)	2 (7)	0.886
- Wound infection, n (%)	8 (11)	1 (3)	7 (16)	0.132	3 (7)	5 (16)	0.278
- Urinary tract infection, n (%)	5 (7)	1 (3)	4 (9)	0.642	1 (2)	4 (13)	0.158
- Ileus, n (%)	14 (19)	2 (7)	12 (28)	0.027*	4 (10)	10 (32)	0.017*
Readmission, n (%)	14 (19)	6 (20)	8 (19)	0.826	8 (20)	6 (19)	0.987
Reoperation, n(%)	10 (14)	2 (7)	8 (19)	0.159	3 (7)	7 (23)	0.064
Mortality, n (%)	4 (5)	2 (5)	2 (7)	0.692	4 (9)	0 (0)	0.135
LOS, geometric mean (SD)	12(1.8)	9.7 (1.6)	13 (1.9)	0.027*	10.4(1.7)	13.3(1.8)	0.068

VFA = Visceral fat area
LOS = Length of stay.
** statistically significant between corresponding groups (p≤0.05)*
***Geometric means*

Patient characteristics and postoperative outcome using VFA cut off = 130 cm2 for VO.

Table 1 summarizes the patient characteristics. Using a VFA of 130 cm2 as a cut off for VO, 31 patients (42%) were categorized in the visceral obese group of which 19 were male (61%). In the 43 non-VO patients, 20 were male (47%).

There was significantly more cardiac co-morbidity in the VO group (36%) than in the non-VO (2%; P < 0.001). A history of hypertension was more prevalent in VO patients (35% vs 9%; p = 0.006).

Table 2 summarizes postoperative outcome. In the VO group, significantly more postoperative complications were found (55% vs. 17%, p = 0.001). An odds ratio of 5.9 (95% CI: 2.0–17.3) was found for the occurrence of complications. In the VO patients more postoperative ileus occurred (32% vs 10%; p = 0.017). The difference in length of hospital stay between the non-VO group and the VO group did not reach statistical significance (resp. 10.4 and 13.3 days, p = 0.068).

Regression analyses for LOS and complications

Table 3 shows the univariable and multivariable regression analyses for the occurrence of a postoperative complication. A VFA >100 cm^2, a VFA >130 cm^2 and BMI were statistically significant in the univariable regression analysis. The multivariate analysis was performed independently for VFA >100 cm^2 and 130 cm^2. VO defined as a VFA >100 cm^2 gives an odds ratio of 5.78 (95CI: 1.38–24.2; p = 0.017) for the occurrence of postoperative complications in the multivariable analysis. In the multivariable analysis VO defined as a VFA >130 cm^2 gives an OR of 5.35 (95CI: 1.50–19.3; p = 0.011) for the occurrence of postoperative complications. BMI did not reach statistical significance in both multivariable analyses as a predictive value for complications.

Table 3. Predictive factors for the occurrence of complications

Predictive factor	Univariable analysis		Multivariable analysis	
	Odds Ratio (95%CI)	*P*-value	Odds ratio(95%CI)	*P*-value
VFA > 100 cm^2	8.27 (2.17–31.48)	0.002	5.78(1.38–24.2)	0.017
Body mass index	1.20 (1.03–1.39)	0.020	1. 10(0.93–1.29)	0.265

95%CI: 95% Confidence Interval.

Table 4. Predictive factors for length of stay

	Univariable analysis			Multivariable analysis		
	Predictive factor	Risk estimate[a] (95%CI)	P-value	Predictive factor	Risk estimate[a] (95%CI)	P-value
Length of stay	VFA > 100 cm^2	1.33(1.02–1.74)	0.039	VFA > 100 cm^2	1.24(0.95–1.64)	0.117
	Hypertension	1.47(1.06–2.05)	0.023	Hypertension	1.37(0.98–1.93)	0.070

95%CI: 95% Confidence Interval.
a Ratio of geometric means.

Discussion

In this study VO is associated with more co-morbidity, a higher complication rate and longer length of stay in patients undergoing rectal resection after chemoradiation for locally advanced cancer. After chemoradiation an increase in SMA was noticed whereas no effect on VFA or subcutaneous fat was found. Skeletal muscle area was not related to co-morbidity or outcome.

Our results on co-morbidity and postoperative complications in patients with visceral obesity confirm the findings of others in colorectal but also in gastric and pancreatic surgery[2,4-7,18]. Most of these studies, however, were performed in the Asian population and the present study is the first to report on the effect of VO on postoperative outcome in locally

advanced rectal cancer patients after chemo-radiation in a European population. Visceral obesity, is a risk factor for the metabolic syndrome[23-25] that represents a combination of cardiovascular risk factors including type 2 diabetes, obesity, hyperlipidaemia and hypertension[26]. The metabolic syndrome correlates with postoperative complications, as was demonstrated in liver transplant patients[27]. The higher incidence of cardiac co-morbidity and hypertension in the visceral obese rectal cancer patients is in line with these results. Clark et al. used the visceral fat/subcutaneous fat ratio to determine the effects of VO in rectal cancer patients after chemoradiation, showing a higher incidence of dyslipidemia and hypertension. Their study focused more on the long term effects of VO on tumor recurrence in rectal cancer patients treated with chemoradiation followed by surgery[28].

When using the VFA of 100 cm^2 or of 130 cm^2 as different cut off points for VO, a number of results turned out similar (Table 1, Table 2). At both cut off points, visceral obesity was associated with significantly more cardiac co-morbidity and a higher rate of postoperative complications. In contrast, LOS was significantly longer only in the VFA >100 cm2 group. In the regression analysis for complications both cut off points were of predictive value. In the regression analysis for LOS only VO defined as VFA >100 cm^2 was statistically significant. This indicates that using different VFA cut off points for VO, the risk profile for postsurgical problems in these patients will change. These results suggest that in terms of risk profiling the cut off of a 100 cm^2 is more valuable than the cut off of 130 cm^2.

Comparison to other studies using these VFA cut offs for VO in colorectal cancer patients show both similar and contrasting results with respect to surgical outcome. Kang et al., using the cut off VFA >130 cm^2 investigated the influence of VO in laparoscopic rectal cancer surgery in 142 patients. They showed more blood loss in the VO group but in contrast to our results, no difference in postoperative complications[17]. Using the VFA >100 cm^2 cut off point, Ishii et al. did not find more blood loss but in line with our results a higher rate of overall complications occurred in the visceral obese patients undergoing rectal cancer surgery[19]. It is of note, that in contrast to the high incidence of VO of 55.4% in our study, only 9 patients (19.5%) had VO in their study. This underscores the notion that geographical differences may influence body composition and related postsurgical outcome. In agreement with our results, Tsujinaka et al. showed more overall complications in colon cancer patients with VO using the cut-off point of 130 cm^2.[18] Sakai studied the effect of visceral obesity in 79 patients undergoing colorectal resection. More blood loss was found, when 100 cm^2 was used a cut off point[21]. From the above, we conclude that although different cut off points will result in an altered risk profile the average result points to a significant effect of an excess of visceral fat on outcome after colorectal surgery. All of the above studies however were performed in the Asian population probably contributing the differences in VO incidence and related changes in outcome. Larger

studies are needed to define a relevant cut off point for VO in surgical patients in terms of preoperative risk profiling.

This is the first study analyzing the effect of chemo-radiation on preoperative body composition in rectal carcinoma patients. Because two CT scans are taken before and after chemoradiation to screen for metastatic disease, its effect on VF and muscle mass could be studied. It pancreatic cancer patients, chemoradiation is accompanied by a decrease in SMA, VFA and subcutaneous fat[3]. In our rectal cancer patients, the amount of VFA was not influenced by chemoradiation. Pancreatic cancer is characterized by profound cancer cachexia that is not common in rectal cancer patients probably explaining this difference. In contrast, we found an unexpected increase in SMA after chemoradiation in our rectal cancer patients. This is an unprecedented finding and we have no clear explanation. The muscles that are measured are not in the field of radiation exposure therefore a direct influence of radiation can be discarded. One might speculate that chemoradiation decreases the inflammatory tumor state improving overall well being leading to more physical activity and muscle mass. We did not measure physical activity but this warrants further evaluation.

The CT scan was used in our study to measure visceral adipose tissue. Schuster et al. conducted a review to investigate the different modalities as BMI, bioelectrical impedance analysis, dual energy X-ray (DEXA), ultrasound, CT and MRI for visceral adipose tissue analysis[13]. They concluded that CT and MRI generate the most accurate, specific and comprehensive data in comparison with all other modalities. The umbilical level (L3-L4) was used to measure the VFA that corresponds to total abdominal fat with 99% accuracy and is used most frequently in the literature[13-20,29,30]. Using the preoperative CT scan that is made to screen for disseminated disease in rectal cancer patients can thus be used for the evaluation of VFA as metabolic risk factor.

The retrospective character and population bias are limitations of the present study and results should be interpreted as such. Database entry, however, was done prospectively, minimizing the loss of data. Another limitation is the small number of patients with locally advanced rectal cancer and results cannot be extrapolated to the group of rectal cancer patients as a whole.

Finally, it appears that visceral obesity is a risk factor for poor outcome after rectal carcinoma surgery in patients who underwent preoperative chemoradiation therapy. Determining the amount of visceral fat tissue using the routinely performed preoperative CT-scan is a simple method that may contribute to establish a preoperative metabolic risk profile in the rectal cancer patient. The increase in muscle mass of the psoas muscles after chemoradiation warrants further exploration.

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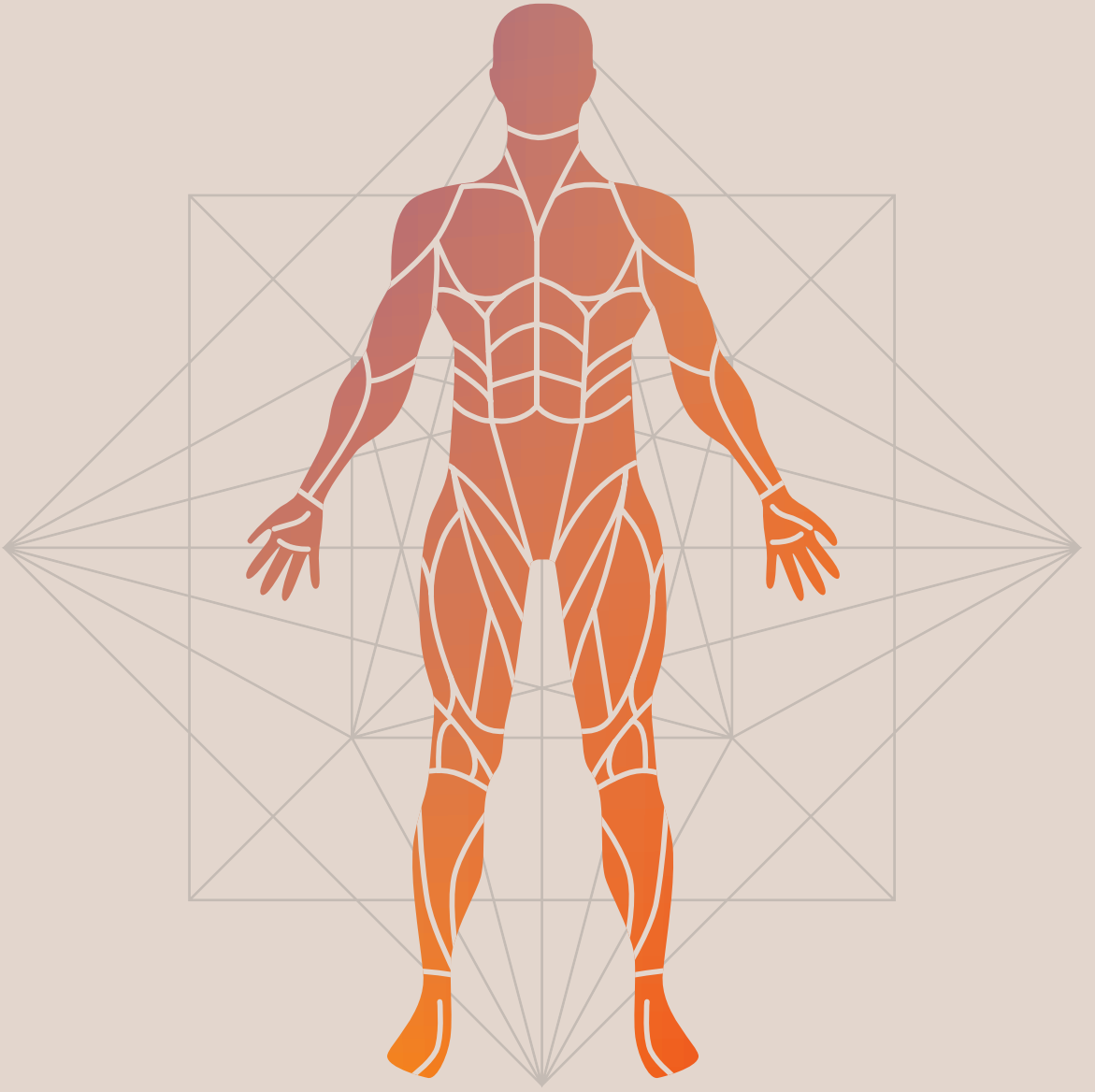

Chapter 5

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 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 per-operative 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[5]. A diverting loop ileostomy was constructed to protect the anastomosis in case of preoperative radiotherapy or chemo-radiation. Neoadjuvant radiotherapy consisted of 5 sessions of 5Gy. Chemo-radiation therapy consisted of 28 × 1.8Gy and 1500mg 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 ≥ 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$>100cm^2$.

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 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.

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*

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.

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*

Regression analysis for complications

Table 3 shows the logistic regression analysis for the occurrence of complications. Only laparoscopic surgery, VFA≥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≥100 cm^2 and laparoscopic surgery were significantly related with complications. Laparoscopic surgery decreased the risk for complications.

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		

Table 3. Factors associated with the occurrence of complications (continued)

Predictive factor	Univariable analysis OR (95% CI)	*p* value	Multivariable analysis OR (95 % CI)	*p* value
VFA>100 cm2	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)*

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]. 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.

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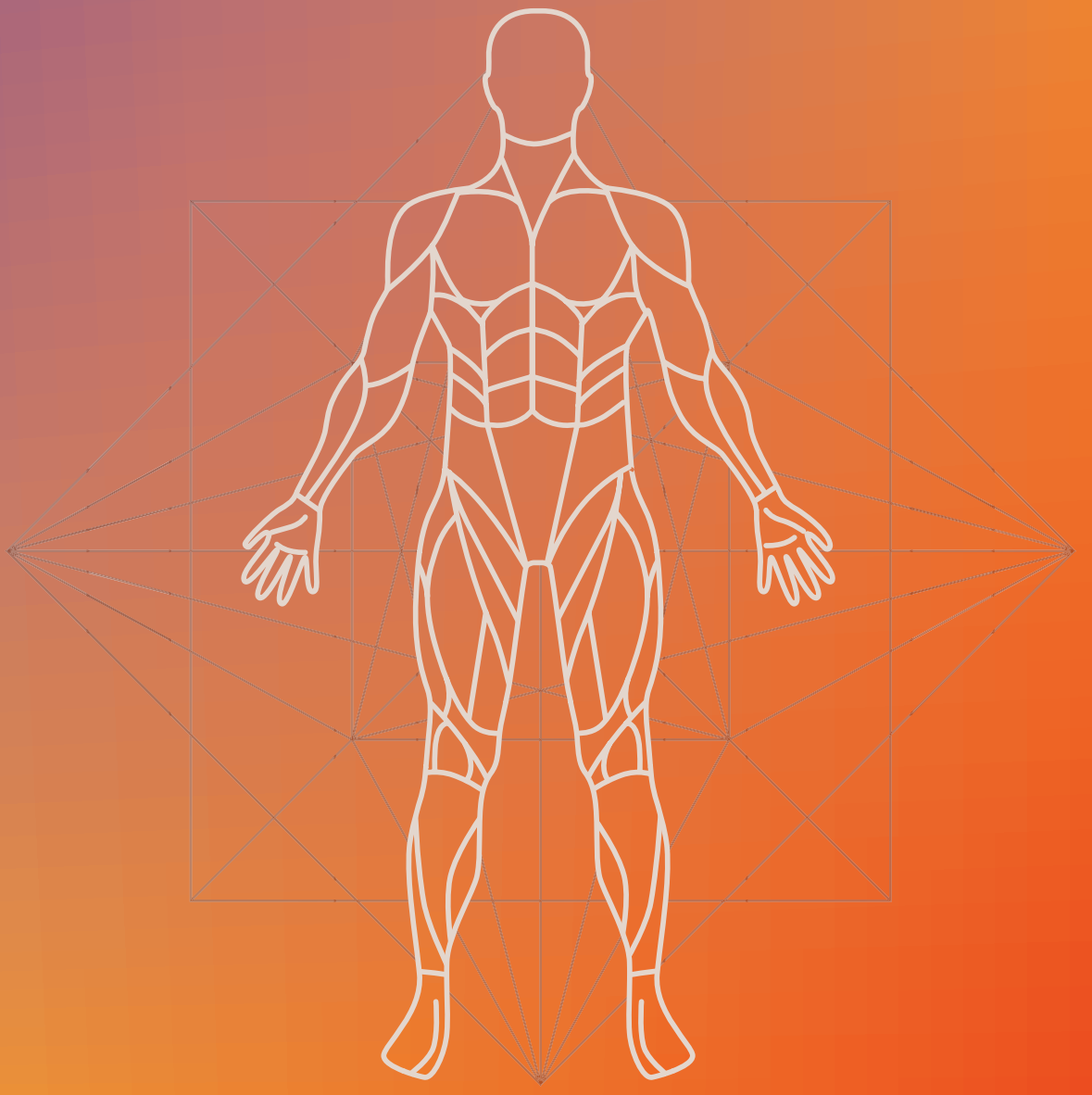
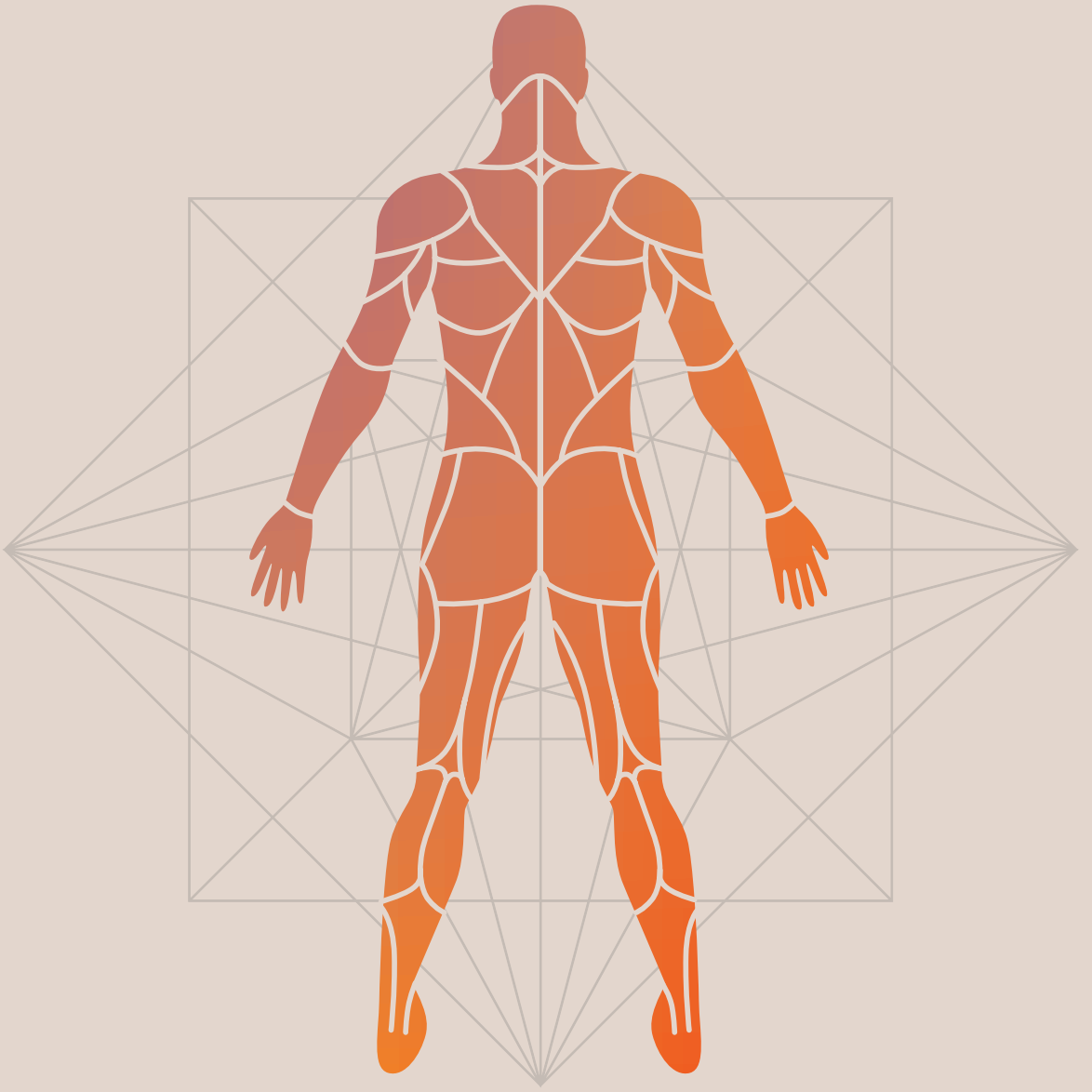
Part 2



Body composition and complications in gynaecological surgery



Chapter 6

Visceral obesity and muscle mass determined by CT scan and surgical outcome in patients with advanced ovarian cancer. A retrospective cohort study.

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Abstract

Objective

Visceral obesity (VO) is a risk factor for developing postoperative complications in patients undergoing abdominal oncological surgery. However, in ovarian cancer patients this influence of body composition on postoperative morbidity is not well established. The aim of this study is to assess the association between body composition and complications in patients with advanced ovarian cancer undergoing cytoreductive surgery.

Methods

Patients with FIGO stage 3 or 4 ovarian cancer between 2006 and 2017 were included. Visceral fat area, total skeletal mass and total fat area were measured on a single slice on the level of L3-L4 of the preoperative CT-scan. VO was defined as visceral fat ≥100cm2. The perioperative data were extracted retrospectively. A multivariate logistic regression analysis was performed to test the predictive value of multiple variables such as body composition, albumin levels and preoperative morbidity.

Results

298 consecutive patients out of nine referring hospitals were included. VO patients were more likely to be hypertensive (38% vs 17% $p < 0.001$), and to have an ASA 3 score (21% vs 10% $P = 0.012$). Complications occurred more often in VO patients (43% vs 21% $P < 0.001$). Thrombotic events were found in 4.9% of VO patients versus 0.6% of the non-visceral obese patients ($p = 0.019$). VO(OR: 4.37, $p < 0.001$), hypertension (OR:1.9, $p = 0.046$) and duration of surgery (OR: 1.004, $p = 0.017$) were predictors of post-surgical complications. Muscle mass is not a predictor of complications.

Conclusion

Visceral obesity is associated with a higher occurrence of complications in patients with advanced ovarian cancer undergoing cytoreductive surgery.

Highlights

- Visceral obesity predicts post-surgical complications in ovarian cancer patients undergoing cytoreductive treatment.
- Visceral obese patients have more hypertension and higher ASA scores.
- Patients with a normal BMI can be visceral obese and therefore have an higher risk of complications.

Introduction

Obesity is a risk factor for hypertensive diseases, diabetes mellitus, ischemic cardiac diseases and cancer[1]. It may also contribute to the occurrence of postoperative complications. A recent review including 118 studies that studied the association between obesity and complications showed that 36% of these studies found a difference between obese and non-obese patients in overall morbidity after major abdominal surgery, including surgery on gastric, rectal and liver cancer[2]. However, BMI only takes height and weight in account while it may be fat distribution that is the important factor associated with postoperative complications. Fat distribution and body weight are not absolutely related. Studies have shown that patients could have a high amount of body fat whilst having a normal BMI[3,4]. In these patients a relatively large percentage of their tissues consist of fat instead of muscle, bone or organ tissue. One study reported that 44% of the included patients with a normal BMI had too much fat tissue within the abdominal cavity and were considered visceral obese[4].

The higher complication risk is also considered to be linked to a state of chronic inflammation in visceral obese people. In this theory the adipose tissue is not only storing and mobilizing lipids, but is also functioning as an endocrine organ releasing cytokines, including pro-inflammatory molecules such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α). There is evidence of macrophage infiltration in adipose tissue, which can contribute to the state of chronic inflammation[8]. In theory, this chronic state of inflammation could influence the tissue response after surgery and thus cause complications. Also, visceral fat could possibly make surgical access to the target area more challenging leading to a longer operating time.

Visceral obesity is a predictor for postoperative complication[4,5]. With computed tomography (CT), it is possible to measure the visceral fat area accurately and correlate this with surgical outcome[6]. As CT of the abdomen is standardly performed to determine dissemination of disease in advanced ovarian cancer patients, visceral obesity can be easily assessed before surgery. The studies in patients with colorectal cancer show more post-surgical complications in visceral obese patients. Visceral obesity is associated with a longer hospital stay, higher morbidity rates and a longer operating time[7]. There is very little literature that compares the predictive value of BMI vs VO. However, an earlier study has also shown that more visceral fat is predictive for complications in patients also with a normal BMI of <25 kg/m^2.[4]

Low skeletal muscle mass is associated with postoperative complications in surgical oncology. A recent meta-analyses that includes 14,295 patients shows that preoperative

sarcopenia is associated with postoperative complications (OR: 1.44) and 30-day mortality (OR: 2.15)[21].

The incidence of postoperative complications after cytoreductive surgery in patients with ovarian cancer is described to be as high as 44% for overall complications [9] and 22% for serious complications[10]. For women with advanced ovarian cancer who are scheduled to have cytoreductive surgery it is important to assess the operative risk. When good predictors of complications are known, different strategies can be developed to lower this risk. Also, patients could be better informed with improved understanding of the risk of complications.

The aim of this retrospective cohort study is to determine the association of visceral obesity or muscle mass and post-operative outcome in patients with FIGO stage III or IV ovarian cancer.

Methods

A retrospective cohort study was performed in the network of the Centre for Gynaecologic Oncology Amsterdam (CGOA). The patients were referred from nine hospitals for treatment in the Amsterdam UMC. The Medical Research Involving Human Subjects Act did not apply to this study and the study was exempted by the Medical Ethics Committee.

All consecutive women with FIGO stage 3 or 4 ovarian cancer who underwent a primary or interval debulking between 2006 and 2017, and for whom a preoperative abdominal CT scan was available, were included in this study. Eligible women were selected from the oncology database of the CGOA. The patients who only underwent an explorative laparotomy or any other procedure than a primary or interval debulking were excluded from the study. Also patients who underwent acute surgery were excluded. Not all CT scans could be evaluated with the software package we had available. Therefore, patients with a non-compatible CT scan were excluded.

Patients were treated with low molecular weight heparin prophylaxis starting on the day of admittance until discharge. The patients were given prophylactic antibiotic treatment before incision. All surgery was performed by gynaecologic oncology surgeons, with at least five years experience in cytoreductive surgery.

The CT images were transferred electronically to a central data system and analyzed at a workstation (Syngo MMWP VE40 A Siemens Healthineers, Erlangen, Germany). The CT scans were analyzed prior to collection of any other data. The areas of interest for total

fat area, visceral fat area (VFA) and skeletal muscle area were manually traced on a single transversal slice at the level of the intervertebral disc of L3–L4[11,12]. VFA is defined as all fat tissue within the borders of the abdominal wall. Single slice measurements are strongly associated with the total volumes[13,14]. A predefined threshold of −150 to −40HU was used to measure adipose tissue and a threshold of 5 to 60 HU to measure skeletal muscle[4,5]. The visceral fat area, total fat area and skeletal muscle mass were then calculated. Visceral obesity was defined as a VFA of 100 cm^2 or higher[5]. One study compared both 100 cm^2 and 130 cm^2 and found that 100 cm^2 correlated best with complications. We used a BMI of 25 as a threshold for being overweight (WHO).

Independently from the assessment of the body composition, clinical data was collected from the patient records, outpatient and inpatient, by trained medical researchers. Information included patient characteristics(including length and weight), information of hospital admittance (length of stay, date of surgery, complications or adverse events), surgical details (type of surgery, operating time, total blood loss), histopathology of the tumor, American Society of Anesthesiologists (ASA) classification, World Health Organization (WHO) performance status and Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage. A complication was included if it was reported in the patients file as such by the physician or if the notes in the patient file showed a deviation of normal recovery. All complications occurring within 30 days after surgery were included and classified according to the Clavien Dindo classification (CDC)[15]. The Clavien Dindo scale is a widely used system with five classes of complications. The higher numbers accord to more serious complications (class V is death of a patient). We used this system to score complications and we scored the occurrence of any complication.

All statistical analysis was done using SPSS statistics v24 (IBM, Corp, Chicago, Illinois). Differences in baseline characteristics and outcome between the visceral obese (VFA ≥ 100 cm^2) and non-obese (VFA < 100 cm^2) group were compared using chi-squared test, Fisher exact test, independent t-test or a Mann-Whitney U test where appropriate. A p-value < 0.05 was considered to be statistically significant. To test the independent predictive value of visceral obesity and patient characteristics on the occurrence of complications, a univariate and multivariate logistic regression analysis was performed. BMI, age, smoking, comorbidities (such as cardiovascular status, hypertension, pulmonic problems and diabetes), type of surgery, duration of surgery, amount of blood loss, visceral obesity, skeletal muscle mass, total fat area, ASA classification, albumin level and WHO performance status were tested in the univariate analysis. The variables with a p-value < 0.05 in the univariate analysis were entered into a multivariate logistic regression analysis.

Results

A total 298 patients were included in the study. Of 570 patients deemed eligible to participate, in total 272 (48%) patients were excluded. Sixteen (3%) patients were considered not eligible for surgery. 256 (45%) patients were excluded as the scan of these patients were not-compatible with the software package used in this study. The excluded patients originated from all referring hospitals, although not all scans from these hospitals were incompatible.

Patient characteristics are shown in Table 1. Of the included women 122 (41%) were visceral obese and 176 (59%) non-visceral obese. The mean age of the population was 62 years (Range: 21–91 years). Visceral obese patients were older compared to non-visceral obese patients (64.9 years vs. 60.7 years p = 0.001). Visceral obese patients had a higher BMI in comparison with non-visceral obese patients (28.6 kg/m^2 vs. 23.4 kg/m^2, p < 0.001). Skeletal muscle mass and total fat area were higher in the visceral obese group of patients. The percentage of patients with hypertension was higher in the visceral obese group (38% vs. 17%, p < 0.001) and there were more patients with an ASA 3 classification (21% vs. 10%, p = 0.012). The non-visceral obese group included more smokers and more patients with ASA classification 1.

Table 1. Patient characteristics

	Total population	**Visceral obese**	**Not visceral obese**	***P*-value**
	***N* = 298**	***N* = 122**	***N* = 176**	
Age mean [SD]	62.4 [11.8]	64.9 [9.9]	60.7 [12.8]	**0.001**
BMI mean [SD]	25.5 [4.8]	28.6 [4.9]	23.4 [3.4]	**<0.001**
Length mean [SD]	1.68 [0.07]	1.65 [0.07]	1.66 [0.07]	0.359
Skeletal muscle mass mean [SD]	72.4 [15.9]	76.2 [17.7]	69.8 [14.0]	**0.001**
VFA median [IQRs]	82.9 [46–133]	151.99 [124–203]	54.67 [34–76]	**<0.001**
Total fat area median [IQRs]	286.1 [194–423]	432.0 [349–506]	214.4 [153–274]	**<0.001**
Albumin mean [SD]	41.19 [4.7]	41.08 [4.8]	41.27 [4.6]	0.740
Cardiac disease *n* [%]	37 [12.4]	19 [15.6]	18 [10.2]	0.169
Pulmonal disease *n* [%]	43 [14.4]	22 [18.0]	21 [11.9]	0.141
Diabetes Mellitus *n* [%]	22 [7.4]	11 [9.0]	11 [6.3]	0.369
Diabetes Mellitus I *n* [%]	2 [0.7]	0 [0]	2 [1.1]	0.515
Diabetes Mellitus II *n* [%]	20 [6.7]	11 [9.0]	9 [5.1]	0.239
Hypertension *n* [%]	75 [25.2]	46 [37.7]	29 [16.5]	**<0.001**
Smoking *n* [%]	67 [22.5]	21 [17.2]	46 [26.1]	**0.048**
ASA 1 *n* [%]	82 [27.5]	19 [15.6]	63 [35.8]	**<0.001**
ASA 2 *n* [%]	169 [56.7]	76 [62.3]	93 [52.8]	0.092
ASA 3 *n* [%]	43 [14.4]	25 [20.5]	18 [10.2]	**0.012**
Interval debulking *n* [%]	226 [75.8]	86 [70.5]	140 [79.5]	0.073

Table 1. Patient characteristics (continued)

	Total population *N* = 298	Visceral obese *N* = 122	Not visceral obese *N* = 176	*P* -value
FIGO IIIA *n* [%]	9 [3.0]	4 [3.3]	5 [2.8]	1.000
FIGO IIIB *n* [%]	6 [2.0]	4 [3.3]	2 [1.1]	0.231
FIGO IIIC *n* [%]	195 [65.4]	75 [61.5]	120 [68.2]	0.231
FIGO IV *n* [%]	88 [29.5]	39 [32.0]	49 [27.8]	0.443
WHO 0 *n* [%]	159 [53.4]	61 [50.0]	98 [55.7]	0.608
WHO 1 *n* [%]	78 [26.2]	34 [27.9]	44 [25.0]	0.394
WHO 2 *n* [%]	25 [8.4]	9 [7.4]	16 [9.1]	0.831
WHO 3 *n* [%]	2 [0.7]	-	2 [1.1]	0.520
WHO 4 *n* [%]	1 [0.3]	1 [0.8]	-	0.396

SD: standard deviation; IQR: interquartile range. Significance = P < 0.05.

Distribution between VFA and BMI is shown in Fig. 1. BMI and VFA only show a moderate correlation (r2 of 0.41). Nineteen per cent of the patients with a normal BMI is in fact visceral obese. Out of the patients considered overweight or obese 34% has a normal amount of visceral fat. (Fig. 2, Fig. 3.)

Table 2 summarizes the number of complications in the visceral obese and non-visceral obese group. In the total study group, 30% (n = 89) of the patients presented with one or more post-surgical complication. There was a significant difference between the number of complications in the visceral obese group compared to the non-visceral obese group (43% vs. 21%, p < 0.001). The patients in the visceral obese group suffered from more thrombotic events in comparison to the patients in the non-visceral obese group (6/122 4.9% vs. 1/176 0.6%, p = 0.019). The other types of complications did not differ significantly between the groups.

Table 2. Surgical outcome

	Total population	Visceral obese VFA > 100 cm^2	Non-visceral obese VFA < 100 cm^2	*P* value
	N = 298	*N* = 122	*N* = 176	
Blood loss median [IQRs]	400.0 [200.0–800.0]	400.0 [200.0–900.0]	400.0 [200.0–750.0]	0.357
Surgical time median [IQRs]	169.5 [135.0–221.3]	165.0 [135.0–220.3]	173.5 [134.3–229.0]	0.387
LOS median [IQRs]	7.0 [6.0–7.0]	7 [6.0–10.0]	7.0 [6.0–8.0]	0.271
Complication *n* [%]	89 [29.9]	53 [43.4]	36 [20.5]	**<0.001**
Wound infection *n* [%]	4 [1.3]	3 [2.5]	1 [0.6]	0.307
Ileus n[%]	25 [8.4]	13 [10.7]	12 [6.8]	0.217
Pneumonia *n* [%]	9 [3.0]	6 [4.9]	3 [1.7]	0.165
Urinary tract infection *n* [%]	13 [4.4]	7 [5.7]	6 [3.4]	0.389

Table 2. Surgical outcome (continued)

	Total population	Visceral obese VFA > 100 cm²	Non-visceral obese VFA < 100 cm²	*P* value
	***N* = 298**	***N* = 122**	***N* = 176**	
Thrombotic event *n* [%]	7 [2.3]	6 [4.9]	1 [0.6]	**0.019**
Abces *n* [%]	1 [0.3]	1 [0.8]	0 [0]	0.406
Sepsis *n* [%]	5 [1.7]	4 [3.3]	1 [0.6]	0.162
Complication	89 [29.9]	53 [43.4]	36 [20.5]	**<0.001**
Clavien Dindo I	45 [15.1]	26 [21.3]	19 [10.8]	0.730
Clavien Dindo II	36 [12.1]	23 [18.9]	13 [7.4]	0.492
Clavien Dindo III	5 [1.7]	1 [0.8]	4 [2.3]	0.153
Clavien Dindo IV	2 [0.7]	2 [1.6]	0 [0]	0.513
Clavien Dindo V / Mortality	1 [0.3]	1 [0.8]	0 [0]	1.000
Readmission <30 days *n* [%]	7 [2.3]	5 [4.1]	2 [1.1]	0.126
ICU admission *n* [%]	2 [0.7]	2 [1.6]	0 [0]	0.166
Revision operation *n* [%]	3 [1.0]	1 [0.8]	2 [1.1]	1.000

SD: standard deviation; IQR: interquartile range. Significance = P < 0.05.

Univariate analysis showed that BMI, hypertension, duration of surgery, visceral obesity, total fat area and albumin level were significant factors associated with the risk of complications after surgery. In multivariate analysis visceral obesity (OR 4.37, (range) p < 0.001) was an independent indicator for post-operative complications, as well as hypertension (OR 1.90, p = 0.046) and duration of surgery (OR 1.004, p = 0.017) (Table 3). Muscle mass was not an independent risk-factor for complications.

Table 3. Univariate and multivariate logistic regression analysis

	Univariate analysis	*P*-value	Multivariate analysis	*P*-value
	OR (95%CI)		OR (95%CI)	
BMI	**1.056 (1.003–1.112)**	**0.039**	1.012 (0.922–1.111)	0.799
Age	1.002 (0.981–1.023)	0.862		
Smoking	0.531 (0.276–1.022)	0.058		
Cardiac disease	0.707 (0.319–1.568)	0.394		
Hypertension	**2.165 (1.249–3.754)**	**0.006**	**1.903 (1.012–3.576)**	**0.046**
Pulmonal disease	1.501 (0.760–2.961)	0.242		
Diabetes	0.321 (0.321–2.248)	0.742		
Interval debulking	0.907 (0.511–1.609)	0.739		
Time of surgery	**1.004 (1.001–1.007)**	**0.019**	**1.004 (1.001–1.008)**	**0.017**
Blood loss	1.000 (1.000–1.001)	0.145		
Visceral obesity	**3.078 (1.839–5.152)**	**<0.001**	**4.365 (2.008–9.487)**	**<0.001**
Skeletal muscle mass	0.996 (0.980–1.012)	0.582		
Total fat area	**1.002 (1.000–1.003)**	**0.030**	0.998 (0.995–1.001)	0.246
ASA 1	0.833 (0.474–1.463)	0.525		

Table 3. Univariate and multivariate logistic regression analysis (continued)

	Univariate analysis	*P*-value	Multivariate analysis	*P*-value
	OR (95%CI)		OR (95%CI)	
ASA 2	1.082 (0.652–1.794)	0.760		
ASA 3	1.147 (0.571–2.301)	0.700		
Albumin	**0.946 (0.896–0.998)**	**0.043**	0.945 (0.891–1.001)	0.055
WHO 0	0.781 (0.461–1.323)	0.358		
WHO 1	1.228 (0.698–2.158)	0.476		
WHO 2	0.985 (0.407–2.382)	0.972		
WHO 3	2.108 (0.130–34.125)	0.599		

OR: odds ratio, 95%CI: 95% confidence interval, VO: visceral obese. Significance = P < 0.05.

Discussion

In this study visceral obesity defined as a VFA of ≥100 cm^2 was identified as a risk factor associated with postoperative complications (OR: 4.4) in ovarian cancer patients undergoing cytoreductive surgery. In addition, duration of surgery and hypertension were also significant predictors of post-surgical complications. Although the OR of duration of surgery seems low it is shown per minute. This is most likely a representation that more perioperative surgical problems correlates with more postoperative complications. High BMI and low muscle mass were not associated with a higher risk of complications. Our data support previous data that visceral obesity is a better predictor of complications than BMI. Determining body composition on a standard CT scan is a relatively easy and inexpensive method to define the elevated surgical risk in visceral obese patients. Even quicker and less time consuming are the recently developed automatic measurement tools. These automatically select the area of interest to measure the fat area [19]. This eliminates the need for a physician to handdraw the visceral fat area. We did not use an automatic measuring tool as it was not available in the research facility at the time.

In our study we found that 19% of the patients with a normal BMI was in fact VO. In literature it is known that 18–34% of patients with a normal BMI has too much visceral fat[22]. In our previously study in colorectal patients 44% of patients with a normal BMI was visceral obese. Fat distribution differs between men and women with men in general having a larger VFA. As we included only women in this study we find a lower amount of visceral obese patients as compared to the general population[23].

It is difficult to compare our results with previous research evaluating the relation between body composition and surgical complications. In the past, authors used a number of different protocols to determine body composition. The range of HU to differentiate be-

tween fat and muscle differs over the studies [4,9,16]. Also, most authors use the level of L3–L4 to measure the body composition. However, other levels are also used, for instance the umbilical level or level L4–L5. And even while CT-scan is the current the most frequently used method to determine body composition in preoperative patients, it appears that there still is no reference standard for measuring body composition on CT-scan. There are also differences in the definition of visceral obesity. In this study we used a single CT slice with a cutoff of 100 cm^2 to determine visceral obesity. It has been shown that the visceral fat area calculated on a single slice is strongly associated with total body fat volumes[13,14]. A study in rectal cancer patients compared two cutoff values to define visceral obesity. The authors showed that compared to a cutoff value of 130cm^2 visceral obesity defined as a VFA of ≥100cm^2 had a better correlation with postoperative complications[5]. We found several studies that evaluated the association of different measures of body composition and complication risk in women with ovarian cancer. However, most publishes studies include patients with different types of gynecological malignancy.

We did not find an association between muscle mass and complications. A previous study done by Silva de Paula et al. found a correlation between the radiodensity of muscle mass and complications in patients with ovarian and endometrial cancer[16]. They found that patients with a lower amount of high quality muscle mass were more likely to have postoperative complications in 250 patients. The muscle mass was divided in high-radiodensity and low-radiodensity. The high-density muscle mass was considered good quality muscle. We did not qualify the muscle mass that was measured. In line with our results another study did not find a relation between sarcopenia, or muscle mass and complications in patients with ovarian cancer[9].

Albumin level was not found to be of predictive value in complications. Lower albumin levels were the only significant predictor of complications in 82 women operated for FIGO stage IIIc or IV ovarian cancer in one study[17].Torres et al. studied a population of 82 women diagnosed with FIGO stage IIIC or IV ovarian cancer. A low albumin level was the only significant predictor of complications while higher subcutaneous of muscle fat was not[17]. Other studies in the past producing a risk model for complications in cytoreductive surgery also found a correlation between low albumin and complications [20]. In our study we did not find a correlation between albumin as a continuous variable and complications. Those studies used albumin as a discrete variable. This could explain the different outcome.

Visceral fat tissue is studied in published small number of papers. The results of those studies however are not conclusive. To summarize their results, two studies with a total of 298 patients did not find the amount of visceral fat tissue of predictive value of com-

plications[9,17]. One of those stydies found that low subcutaneous and muscular fat was associated with a longer length of hospital stay. This was defined as the fat mass in the muscular space and subcutaneous combined and below 77.21cm^2. This low subcutaneous and muscle fat was not associated with complications.

The only study with a correlation between fat and complications was from Nishikawa et al.. They studied a population of 115 patients with gynecological cancer, of which 24 patients were diagnosed with ovarian cancer. They assessed the usefulness of the abdominal wall fat index for predicting pulmonary embolisms. The abdominal wall fat index ratio of the maximum preperitoneal fat thickness to the minimum subcutaneous fat thickness and was determined using ultrasound. The abdominal wall fat index correlates closely with the visceral fat index measured by CT. This could be used as a tool for determining body composition. Patients with a higher abdominal wall fat thickness were at greater risk for developing pulmonary embolism. Visceral obesity could therefore be seen a risk factor for a pulmonary embolism as a post-surgical complication in these patients[18].

It is unclear to us why visceral obesity was correlated with wound infections in an earlier study[4].

Obesity is an epidemic that is affecting large parts of the world and this epidemic is not expected to improve in the near future. Gynaecologic oncologists will be confronted with increasing numbers of women who are viscerally obese. Our data suggest that this may also result in an increase in the number of postoperative complications. Prevention of obesity will likely have to come from public health policies and increased awareness amongst the public. In the meantime research could focus on establishing the pathophysiology of visceral obesity and the occurrence of surgical complications.

Our data could be used to identify patients with higher risk of postoperative complications. However, the time between the identification of ovarian cancer and the proposed surgical treatment is relatively short to achieve a meaningful reduction in visceral fat. Therefore a better approach seems to be to focus on exploring a method to decrease the complication risk in visceral obese patients.

The retrospective design from our study introduces some limitations. For the occurrence of complications we had to rely on the medical records. Women may not have consulted their gynaecologist for minor complications such as a urinary tract infection. This most likely underestimated the number of complications. However, we expect the reporting of complications not to be related to the amount of visceral fat and as such the risk of bias is considered low. Secondly, there were a number of CTs that could not be analyzed due

to an incompatibility between the data format of the CT image and the software used to determine VFA. It appears that the method of transferring the data on the disk differs in the same year in the same hospital. Therefore for this study we assume that the missing data were randomly distributed and the risk of selection bias is low as these problems occurred with patients of all referring hospitals. More importantly the baseline characteristics between the patients with a compatible scan and the patients with a non-compatible scan were not statistically different. When in the future VFA is to be used as a standard of care these compatibility issues clearly need to be solved.

This study has also some strengths. Our results are based on a large cohort of 298 women with ovarian cancer. Of these women 122 were considered visceral obese. Secondly, this study is the first one defining visceral obesity using a single cutoff of 100 cm^2. By categorizing patients in visceral obese and non-visceral obese patients instead of using VFA as a continuous outcome it improves the applicability in clinical practice.

In conclusion, our data supports the hypothesis that body composition is of importance in predicting complications in surgery performed to treat ovarian cancer.

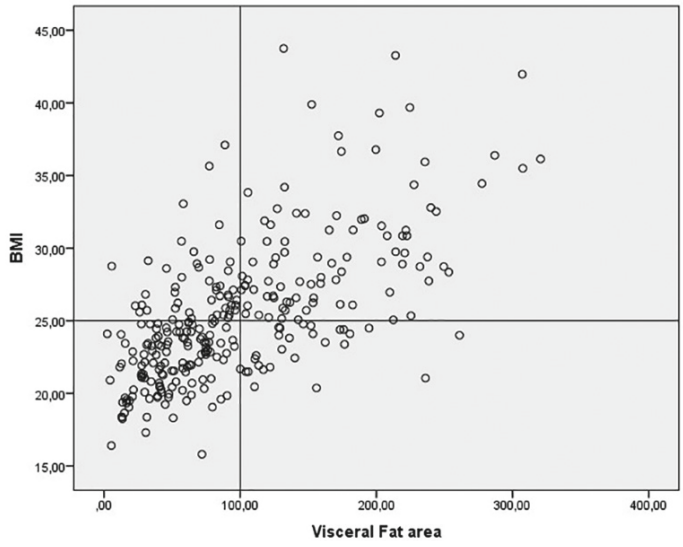

Figure 1. Relation between BMI (kg/m2) and visceral fat area (cm2) for the 298 patients. The lines indicate thresholds for visceral obesity (VFA ≥ 100 cm2) and overweight (BMI > 25 kg/m2)

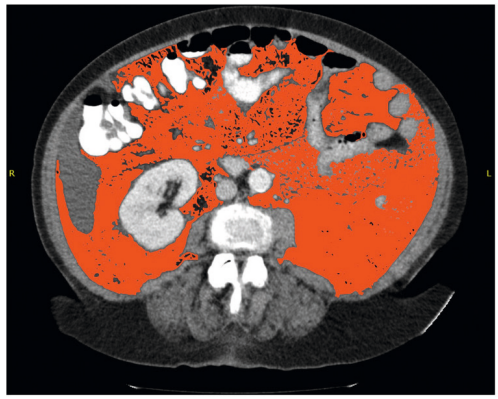

Figure 2. Schematic figure of measurement of VFA in a patient with a normal BMI of 21 kg/m^2 and a VFA of 236 cm^2

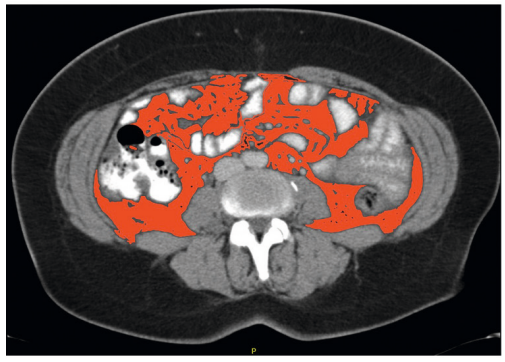

Figure 3. Schematic figure of measurement of VFA in a patient with obesity (BMI of 31 kg/m^2) and a normal VFA of 57 cm^2

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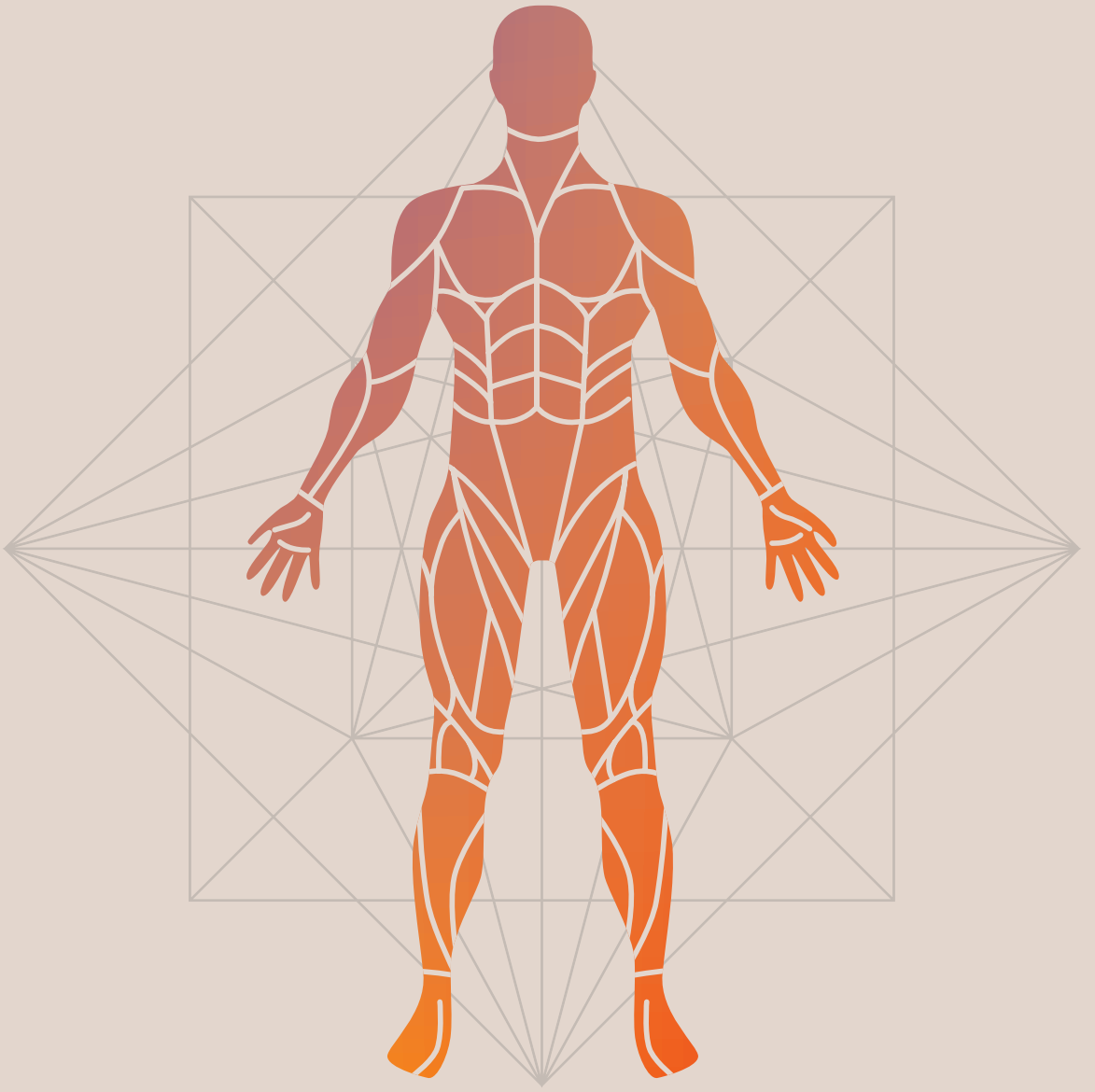

Chapter 7

Body composition and peri- and postoperative complications in patients with gynaecological malignancies: a systematic review.

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Submitted

Abstract

Background

In general abdominal surgery, the ratio of fat to muscle mass, or body composition measures, shows a stronger association with complications than body mass index. These studies include male and female patients. Women have a different body composition than men. Therefore, findings from general abdominal surgery cannot be extrapolated to women with cancer. The aim of this systematic review is to summarise the evidence on the association between body composition and peri- and postoperative complications in patients with gynaecological cancer.

Methods

Pubmed, Embase and the Cochrane Central database were searched in July 2021. Studies were eligible if they included patients undergoing surgery for gynaecological cancer and reported on the association between body composition (muscle or fat mass) and surgical complications. The quality of the studies was assessed using the Newcastle-Ottawa quality assessment scale. A best-evidence synthesis was used to summarise the level of evidence.

Results:

Ten studies were included that assessed muscle mass (n=6) or fat mass (n=6). We found strong evidence that there was no association between visceral fat and length of hospital stay. We found moderate evidence that a higher amount of good quality muscle was associated with a lower risk of postoperative complications. We found moderate evidence that there was no association between muscle or fat mass (i.e., muscle- or subcutaneous fat) and postoperative complications or fat mass and intraoperative complications. There was insufficient evidence for an association between visceral fat and intraoperative or postoperative complications, and for an association between muscle mass or -quality and length of hospital stay. There was high heterogeneity in the methods used to measure body composition.

Conclusion

The association between body composition, particularly adipose tissue and muscle quality, and complications suggests that these measures may be of interest in determining postoperative risk in women undergoing surgery for gynaecological cancer.

Introduction

Worldwide, more than 1.3 million women were diagnosed with gynaecological cancer in 2020, accounting for 16.5% of all new cancer cases[1]. Gynaecological cancers include cancers of the cervix, corpus uteri, ovaries, vulva and vagina. Treatment for gynaecological cancers includes surgery, chemotherapy, radiotherapy or a combination of these treatments. Surgery is an invasive treatment that can lead to peri- and postoperative complications such as surgical site infection, urinary tract infection or thromboembolic events in up to 43 per cent of cases[2]. A body mass index (BMI) greater than 25 kg/m^2 is associated with a 1.61 times greater likelihood of wound infection, longer operating time (10 minutes) and more complications (4% versus 21%) compared to a BMI of 25 kg/m^2 or less[3]. The main advantage of using BMI in clinical practice to classify surgical risk is that it requires only the quick and inexpensive measurement of body height and weight. However, BMI does not provide information on the distribution of fat and lean mass.

Previous studies have suggested the use of other body composition measures than BMI[4,6,8], for example those describing the absolute and/or relative contribution of different tissues to total body weight. This can be defined in several ways. One definition uses the ratio of adipose tissue to muscle tissue[4,5]. Other definitions further specify the fat mass in subcutaneous and intra-abdominal fat (or visceral fat). There is evidence that the amount of visceral fat or muscle tissue influences the risk of surgery. Several methods can be used to assess body composition, both in clinical practice and in research. The most commonly used methods are listed in Table 1.

BMI is not always a direct measure of body composition. Patients who are considered overweight based on their BMI (i.e., BMI ≥25 kg/m^2) may have low fat mass but high muscle mass, whereas patients with a normal BMI (i.e., BMI 18.5 - 25 kg/m^2) may have relatively high fat mass and low muscle mass. For example, in a study of patients with colorectal cancer, 44% of patients with a normal BMI (i.e., 18.5 - 25 kg/m^2) were visceral obese[6].

Models using measurements of adipose and muscle tissue may provide a more accurate estimate of the risk of developing postoperative complications than the use of BMI[6-8]. Most studies of body composition and postoperative complications have been conducted in male patients and have not included patients with gynaecological cancer[6,8-11]. Women have a different body composition than men[12,13]. Therefore, the results of the above studies cannot be used to estimate risk in patients with gynaecological cancer. The aim of this systematic review is to summarise the evidence on the association between body composition and peri- and postoperative complications in patients with gynaecological cancer.

Table 1. Overview of methods used for measuring body composition

Method	Description	Measurements	Specifics
Anthropometric measurements[30]	Non-invasive quantitative measurement of the body.	Waist-to-hip ratio; Waist circumference; Hip-circumference; Skinfold thickness.	Non-invasive and low cost; No quantification of visceral fat tissue or muscle tissue.
Bioelectrical impedance analysis (BIA)	Measurement of the electrical properties of the body. The non-conducting properties of fat tissue and conducting properties of water are used to measure impedance.	Fat Free mass; Total body water; Body fat mass.	Non-invasive and low cost; No quantification of visceral fat tissue of individual muscles; Estimation of fat (free) mass and total body water; Sensitive for changes in ambient and skin temperature, fasting, electrolyte changes, transpiration[32,33] BIA might underestimate fat mass[34]; Not standard in workup of oncology treatment.
Dual energy X-ray Absorptiometry (DEXA)	Uses X-ray with two different energies. The ratio in which different tissues absorb energy differ. By subtracting two images made with different energies separate tissues can be quantified.	Fat mass, Fat free mass; Visceral fat mass.	Low-dose x-ray (less than 10 microSievert); Quantification of body composition[35]; Good correlation with measurement on CT[36,37] Not always available in general practice; Not standard in workup of oncology treatment.
Computed tomography (CT) scan	Uses CT-scan to determine fat tissue and muscle tissue. Specific ranges of Hounsfield units are used to distinguish between fat and muscle. Most studies use one transverse slice.	Fat mass; Muscle mass; Muscle density;	Different methods are used in different studies. Field of interest (intra-abdominal cavity) could be manually traced or by automatically by specially designed software using radiodensity of the tissues; Can be used to quantify muscle and fat areas with high accuracy[38]; Single-slice measurement has a high correlation with whole-body composition.
Magnetic Resonance Imaging (MRI)	Uses different magnetic properties of nuclei of certain elements to produce soft tissue images.	Fat mass; Visceral fat mass; Subcutaneous fat; Muscle mass.	Need to undergo an MRI-scan. Can be used to quantify muscle and fat areas. Correlates well with other methods of measuring body composition.[39]

Methods

Literature search

A systematic search of Pubmed, Embase and the Cochrane Central database was conducted on 7 July 2021. Keywords related to gynaecological malignancies, surgery and body composition were used to identify studies that examined the association between body composition and peri- and postoperative complications in gynaecological malignancies. The search conducted in Pubmed can be found in Appendix A. This systematic review was conducted and reported according to PRISMA guidelines[14].

Study eligibility

Studies were included if they 1) included women who underwent surgery as the primary treatment for a gynaecological malignancy, or if they included patients with different types of cancer and reported results for gynaecological cancer separately 2) examined the association between body composition (within 3 months before or during surgical treatment) and peri- and postoperative complications (within 30 days after surgery), including length of stay, blood loss, conversion rate, and reoperation, and 3) assessed body composition using anthropometric tools (skinfold measurements and waist circumference and waist-to-hip ratio), dual-energy x-ray absorptiometry (DXA), bioimpedance analysis (BIA), computed tomography (CT), or magnetic resonance imaging (MRI). We excluded non-English articles, articles focusing only on BMI, letters, case reports, conference abstracts, reviews and editorials. There was no restriction on publication date.

Study selection and data extraction

After removal of duplicates, studies were selected on the basis of title and abstract by two researchers, independently (CH, SS). Full text screening of all selected studies was performed by two researchers, independently (CH, SS). Throughout the screening process, the researchers were blinded to each other's decisions. Disagreements between researchers were resolved by discussion with a third reviewer (LL) until consensus was reached.

General study details (i.e., title, author, year of publication, study methodology and design), study characteristics (i.e., sample size, age, comorbidity, histological type of cancer, disease stage, assessment and timing of body composition, study outcome and study results) were extracted by two reviewers (CH, SS) independently.

Risk of bias and statistical analysis

The quality of the evidence and the risk of bias were assessed independently by two researchers (CH, SS) using the Newcastle-Ottawa quality assessment scale.[15] This scale assesses the quality of studies in three domains: 1) selection of study groups and ascer-

tainment of exposure, 2) comparability of groups, and 3) ascertainment of outcome (see Table 2 for a full review). Study quality was assessed using the Newcastle-Ottawa quality assessment scale[15]. A maximum of four, two and three stars could be awarded in the domains 'selection', 'comparability' and 'outcome' respectively. A study was considered to be of good quality if it receives 3 stars for selection, 1 star(s) for comparability and 2 stars for outcome. Studies were of fair quality if they received two stars in the selection domain, one or two stars in the comparability domain, and two or three stars in the outcome domain. Studies were considered to be of poor quality if they received zero or one star in the selection domain, zero stars in the comparability domain or zero stars in the outcome domain.

A best-evidence synthesis was used to summarize the level of evidence. This synthesis considered the number of studies, the risk of bias of each study and the consistency of the study results[16]. The level of evidence was graded as follows: A) strong evidence, if there were consistent results in at least two studies with a low risk of bias, B) moderate evidence, if there were consistent results in one study with a low risk of bias and one or more studies with a high risk of bias, or in at least two studies with a high risk of bias, C) insufficient evidence, if there were inconsistent results in at least two studies (<75% of the studies showed results in the same direction (C1)) or if only one study was available (C2).

Table 2. Method used for quality assessment of included studies

Perspective	Stars
Selection (max. 4 stars)	
1. Representativeness of the exposed cohort	a. Truly representative (one star) b. Somewhat representative (one star) c. Selective group (zero stars) d. No description of the derivation of the cohort (zero stars)
2. Selection of the non-exposed cohort	a. Drawn from the same community as the exposed cohort (one star) b. Drawn from a different source (zero stars) c. No description of the derivation of the non-exposed cohort (zero stars)
3. Ascertainment of exposure	a. Secure records (e.g., surgical record) (one star) b. Structured interviews (one star) c. Written self-report (zero stars) d. No description (zero stars)
4. Demonstration that outcome of interest was not present at start of study	a. Yes (one star) b. No (zero stars)
Comparability (max. 2 stars)	
1. Comparability of cohorts based on the design of analysis controlled for confounders (maximum of two stars can be assigned)	a. The study controls for age (one star) b. The study controls for ASA score and comorbidities (one star) c. Cohorts are not comparable based on the design or analysis is not controlled for potential confounders (zero stars)

Table 2. Method used for quality assessment of included studies (continued)

Perspective	Stars
Outcome (max. 3 stars)	
1. Assessment of outcome	a. Independent blind assessment (one star) b. Record linkage (one star) c. Self-report (zero stars) d. No description (zero stars)
2. Was follow-up long enough for outcomes to occur (minimum of 30 days)	a. Yes (one star) b. No (zero stars)
3. Adequacy of follow-up of cohort	a. Complete follow-up all subjects accounted for (one star) b. Subjects lost to follow-up unlikely to introduce bias and ≥20% (one star) c. Follow-up rate <80% or no description of those lost (zero stars)

A maximum of 4, 2 and 3 stars could be awarded in the domains 'selection', 'comparability' and 'outcome' respectively. A study is judged of good quality if it receives ≥3 stars in the selection domain, ≥1 star(s) in the comparability domain and ≥2 stars in the outcome domain. Studies are considered of fair quality if they receive two stars in the selection domain, one or two stars in the comparability domain and two or three stars in the outcome domain. Studies are considered of poor quality when they received zero or one star in the selection domain, or zero stars in the comparability domain, or zero stars in the outcome domain.

Results

The primary search resulted in 2588 articles. Duplicates (N=462) were removed. After title and abstract evaluation, 24 articles were retrieved in full text to further examine the inclusion and exclusion criteria. After full text evaluation, 10 articles were included[17-26]. No additional studies were identified in the reference lists of the selected papers. Table 2 shows the characteristics and results of the included papers.

Table 3. Characteristics and outcome of studies

Author, year, country	Study design	Sample size	Cancer type and stage	Measurements	Methods	Outcome
Palomba, 2007, Italy	Prospective cohort	151	Endometrial cancer, FIGO IA-IV.	Intra-abdominal visceral fat CT, intra-abdominal fat US, subcutaneous fat US	Ultrasound: Distance between rectus muscle and the anterior wall of the aorta. CT: Level of L4/L5 intervertebral disc. HU: -190 to -30.	Early or late surgical conversion (laparoscopic to open)
Torres, 2013, USA	Retrospective cohort	82	Ovarian cancer, FIGO IIIC/IV.	Total muscle, subcutaneous + muscular fat, Visceral fat, total fat mass	CT-scan: Level of L3 vertebra, HU: Visceral fat: -150 to -50; Subcutaneous fat: -190 to -30; Skeletal muscle: -29 to 150.	Postoperative complications, LOS,
Kuroki, 2015, USA	Retrospective cohort	27	Endometrial cancer	Sarcopenia	CT-scan: Transversal slice on level L3 vertebra. Normalized for stature (cm2/m2). Sarcopenia: lumbar psoas < median (4.33 cm2).	Postoperative complications, readmission, LOS.
Kerimoglu, 2015, Turkey	Prospective cohort	94	Endometrial cancer	Percentage body fat	BIA: Elevated percentage body fat >32%	Surgical time, peri and postoperative complications, LOS
Silva da Paula, 2017, Brazil	Retrospective cohort	250	Endometrial and ovarian cancer	Muscle mass. Muscle quality	CT-scan: Transversal slice on level L3 vertebra; Hounsfield units muscle: -29 to 150. Sarcopenia: muscle mass <38.9 cm2	Postoperative complications, LOS
Rutten, 2017, Netherlands	Retrospective cohort	216	Ovarian cancer, stage II – IV	Sarcopenia, visceral adipose tissue,	CT-scan: Transversal slice on level L3 verterbra; HU used: muscle: -30 to 150; Sarcopenia: skeletal muscle index <38.37 cm/m2.	Postoperative complications

Table 3. Characteristics and outcome of studies (continued)

Author, year, country	Study design	Sample size	Cancer type and stage	Measurements	Methods	Outcome
Van der Zanden, 2021, Netherlands	Retrospective cohort	213	Ovarian cancer, stage III-IV, 70 years or older	Skeletal muscle area, skeletal muscle index, muscle density	CT-scan: Transversal slice on level L3 vertebra; Hounsfield units -29 to 150 for muscle. Low skeletal muscle: muscle index < 38.59 cm2/m2.	Post and perioperative complications.
Januszek, 2021, Poland	Prospective cohort	75	Endometrial cancer	Abdominal obesity	Waist-to-hip ratio, Waist circumference and hip circumference	LOS, surgical time, complications
Sehouli, 2021, Germany	Prospective cohort	226	Gynaecological cancer	Sarcopenia (muscle mass), fat mass	BIA: Sarcopenia: skeletal muscle index < 27%	Postoperative complications.
Heus, 2021, Netherlands	Retrospective cohort	298	Ovarian cancer, Stage III-IV	Visceral fat area, Total fat area, Skeletal muscle mass	CT-scan: Level of L3/L4 intervertebral disc. Hounsfield units used for Fat: -150 to -40 and Muscle: 5 to 60. Visceral obesity was classified as VFA >100cm2	Peroperative blood loss, surgical time, postoperative complications, LOS

Abbreviations: BIA; Bioelectrical impedance analysis:; CT: Computed Tomography; HU, Hounsfield Units; L3, Lumbar vertebra 3; LOS, Length of hospital stay; US, Ultrasound; VFA, Visceral Fat Area

Table 4. Newcastle-Ottawa Scale quality assessment

		Selection				Comparability	Outcome			Quality	
Author	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**2**	**3.1**	**3.2**	**3.3**	**Total score**	**Overall score**
Heus	2021	*	*	*	*	**	*	*	-	8	Good
Januszek	2021	*	*	*	*	*	*	*	-	7	Good
Kerimoglu	2015	*	*	*	*	*	*	-	-	6	Poor
Kuroki	2014	*	*	*	*	-	*	-	*	6	Poor
Palomba	2007	-	-	*	*	-	*	*	-	4	Poor
Rutten	2017	*	*	*	*	-	*	*	-	6	Poor
Sehouli	2021	*	*	*	*	-	*	*	*	7	Poor
Silva de Paula	2017	*	*	*	*	-	*	*	*	7	Poor
Torres	2013	*	*	*	*	**	*	*	-	8	Good
Zanden	2021	*	*	*	*	*	*	*	*	8	Good

Muscle mass and surgical outcomes

Seven studies assessed the association between muscle mass and complications[17-22,26]. These studies used different muscle measurements, different interpretations of these measurements, and different definitions of low muscle mass. Four studies used the term sarcopenia for low muscle mass, but the definition of sarcopenia varied between the studies[18-21]. One study used muscle area as a continuous variable instead of a dichotomous definition of sarcopenia[22]. Not all seven studies that used CT scans to examine body composition selected and measured the same muscles. Five studies measured all muscles on the slice used[17,19-22], while others one measured the psoas muscle[18].

There is moderate evidence of no significant association between muscle mass and postoperative complications, as five out of six studies showed no significant association (Table 4). We found insufficient evidence that muscle mass was significantly associated with length of hospital stay as these results were inconsistent. Of the three studies, one study found that a larger muscle area was significantly associated with shorter hospital stay (8 days versus 18 days) in patients with ovarian cancer[17], while two other studies in patients with endometrial cancer and ovarian cancer found no significant association[18,19].

Muscle quality and surgical outcomes

Two studies used CT scans to assess muscle quality based on the radiodensity of the muscle tissue. Based on these two studies, there is moderate evidence of a significant association between higher muscle quality as assessed by CT scan and a lower risk of postoperative complications[19,20]. One study assessed muscle quality in 250 patients with endometrial or ovarian cancer and showed that a lower high radiodense muscle tissue index was associated with more perioperative blood loss and (major) complications (OR: 3.6 - 6.5)[19]. The other study found that low muscle density was associated with a higher

risk of postoperative complications (OR: 2.83; 95%CI: 1.41-5.67) in 213 patients with stage III or IV ovarian cancer [20]. Insufficient evidence was found for the association between muscle quality and length of stay: this association was examined in one study that showed that patients with lower amounts of high-quality muscle and patients with high amounts of low-quality muscle had a longer hospital stay[19].

Visceral fat tissue and surgical outcomes

Visceral fat was assessed in five studies[17,21-24], one study used BIA[25], two studies used the waist-to-hip ratio [23,24], and four studies used a CT scan to determine the amount of fat[17,21-23]. One of these studies used CT and waist-to-hip ratio[23] .

There was strong evidence that visceral adiposity was not significantly associated with length of hospital stay, as found in two high-quality studies[17,22].

There was insufficient evidence for an association between visceral fat mass and postoperative complications, because the results were inconsistent. One study in ovarian cancer patients found that visceral obese patients were more likely to have complications (43% versus 20%; OR: 4.37; 95%CI: 2.01-9.49) and more thrombotic events (5% versus 0.6%) than non-visceral obese patients[22]. Another study found no significant association between visceral fat and postoperative complications in 82 patients with ovarian cancer[17].

There was insufficient evidence for an association between visceral fat and intraoperative complications or conversion rate, because these associations were examined in only one study each. A study of 298 patients with advanced ovarian cancer undergoing debulking surgery found that operating time and intraoperative blood loss did not differ between patients with visceral obesity and those without[22]. A study of 151 patients with endometrial cancer found a significant association with early conversion (OR: 2.18; 95%CI: 1.23-3.89)[23].

Other measures of fat mass and complications

We found moderate evidence that muscle fat and subcutaneous fat were not significantly associated with postoperative complications[17,25,26] and intraoperative complications [24,25]. There was insufficient evidence for an association between these types of fat and length of hospital stay as there were inconsistent results[17,24,25].

Table 5. Best-evidence synthesis

	Visceral fat mass				Other fat mass				Muscle mass				Muscle quality			
	N+	**N-**	**N0**	**LoE**	**N+**	**N-**	**N0**	**LoE**	**N+**	**N-**	**N0**	**LoE**	**N+**	**N-**	**N0**	**LoE**
Intra-operative complications			Heus[a]	C2			Kerimoglu[b], Januszek[a]	B								
Post-operative complications	Heus[a]		Torres[a]	C1			Kerimoglu[b], Torres[a], Sehouli[b]	B	Silva de Paula[b],		Kuroki[b], Rutten[,b], Torres[a], Heus[a], Sehouli[b]	B	Silva de Paula[b], Zanden[a]			B
Length of stay			Heus[a], Torres[a]	A	Januszek[a]	Torres[a]	Kerimoglu[b]	C1	Torres[a]		Kuroki[b], Silva de Paula[b]	C1	Silva de Paula[b]			C2
Conversion	Palomba[b]			C2												

Abbreviations: N+, positive association; N- negative association; N0, no association; LoE, Level of Evidence; A, Strong ev
idence ; B, Moderate evidence; C1 insufficient evidence, if there were inconsistent results in at least two studies (<75% of the studies showed results in the same direction; C2 insufficient evidence if only one study was available (C2).
a Studies of good quality
b Studies of poor quality

Discussion

This review synthesised the evidence on the association between body composition and complications in patients undergoing gynaecological oncological surgery. We found moderate evidence for an association between higher amounts of high-quality muscle and fewer postoperative complications. We found moderate evidence that there is no significant association between muscle- or fat mass and complications. Strong evidence for no significant association between visceral fat and length of hospital stay was found. Finally, there was insufficient evidence for an association between visceral fat and complications, and between muscle quality, muscle- or fat mass and length of hospital stay.

The association between muscle quality and risk of complications from gynaecological surgery found in this review supports previous findings from studies of gastrointestinal surgery[27-29]. In contrast, our results did not support previous findings in other types of surgery that higher muscle mass was associated with fewer complications and shorter length of hospital stay. This suggests that muscle quality may be more important than muscle mass. For example, Humaguchi et al. [30] found that more muscle of lower quality correlated with more surgical complications in patients with hepatocellular carcinoma. High lipid content in muscle (i.e., lower muscle attenuation) is thought to be associated with muscle weakness and poor function[40]. Lower muscle attenuation was found in patients with various comorbidities such as obesity or type II diabetes[41]. It is possible that these comorbidities may influence a patient's postoperative recovery. To fully understand the relationship between muscle measures and postoperative complications, more research is needed using a standardised measurement protocol and to understand the pathophysiological mechanism behind this association.

Our finding of insufficient evidence for an association between muscle mass and postoperative outcome is in contrast to findings in other areas of cancer surgery, such as hepatic resection or colorectal surgery, where loss of muscle mass and sarcopenia have been associated with fewer complications and longer hospital stay [7,31]. It is unclear why we did not find this association in gynaecological surgery. It may be that differences in definitions and measurement techniques make it difficult to make direct comparisons. The results of the gynaecological studies that investigated the association between muscle mass and postoperative complications were very different. Half of the trials that used sarcopenia as a measure of muscle mass found a significant association with postoperative complications, while the other half did not. The lack of a gold standard for defining sarcopenia makes it difficult to assess the value of sarcopenia in predicting the risk of surgery. This also highlights the need for a standardised protocol for measuring muscle mass and defining sarcopenia.

The value of visceral fat mass in postoperative risk assessment in gynaecological oncology patients is unclear. One study of 298 patients found a significant association[22], but another study of 82 patients did not [17]. It could be argued that the latter study may have been underpowered. The discrepancy in findings could also be related to the different measures of visceral fat, namely a continuous variable[17] versus a dichotomous variable distinguishing between visceral obese patients and non-visceral obese patients[22]. Therefore, further studies with larger numbers of patients in gynaecological surgery are needed to clarify the association between visceral fat and postoperative complications in this patient population.

In other areas of abdominal cancer surgery, several cohort studies and a meta-analysis have reported an association between visceral fat mass and postoperative complications[6,8]. Specifically, a retrospective cohort study showed that visceral obese patients undergoing colon resection had more anastomotic leakage (OR: 2.3) and more wound infections (OR: 2.5)[6]. In addition, the association between visceral obesity and complications after abdominal surgery seemed to be strongest in people with a normal BMI (i.e., 18.5 - 25 kg/m^2). In patients with colorectal cancer, visceral obesity was associated with a higher incidence of wound infection (11% versus 4%). In addition, patients with gastric cancer who were viscerally obese had more blood loss (240 versus 109 grams) and a longer operation time (294 versus 255 minutes) than patients with a healthy visceral fat mass[11].

A major difference between these previous studies and the present paper is that the current study focused only on women, who have a different body composition than men. Men generally have a higher percentage of visceral fat than women, while women generally have lower muscle mass. As a result, fewer patients with visceral obesity and high muscle mass have been included in studies of gynaecological cancers, reducing the power to detect associations between visceral fat and muscle mass and complications.

Visceral adipose tissue is metabolically and inflammatory active. Pro-inflammatory cytokines are secreted in this tissue. The macrophage invasion that follows this secretion causes chronic low-grade inflammation. This chronic inflammation is thought to increase the risk of developing metabolic syndrome, cardiovascular disease and several types of cancer[42]. The higher prevalence of these diseases in patients with visceral obesity is not exclusively correlated with the higher risk of complications in other studies. Visceral obesity is an independent predictor of complications in patients with ovarian cancer[22] and colorectal cancer[6,8]. Therefore, the chronic inflammatory state in patients with visceral obesity is thought to cause a different response to surgery.

We systematically analysed the available evidence in patients with gynaecological cancer. When interpreting the results of this study, it is important to note that there is large heterogeneity in the way that muscle mass and adipose tissue are measured. In particular, the definitions of sarcopenia and visceral obesity vary widely. There is a need for a single gold standard for measuring muscle mass and visceral adipose tissue and the definitions used. A study comparing methods of measuring body composition and their correlation with complications in gynaecological oncological surgery seems important. This article is the first to review the literature on body composition and complications in gynaecological oncology. Although broad inclusion criteria were used to include articles in this review, there is a lack of literature on this specific topic. As more data become available using consistent methods and definitions, the best-evidence synthesis could be replaced by a meta-analysis. This may provide a clearer answer about the association between body composition and complications.

In conclusion, measuring body composition may be important in determining peri- and postoperative risk in women undergoing surgery for gynaecological cancer. However, more research needs to be conducted to examine the value of body composition as a risk factor.

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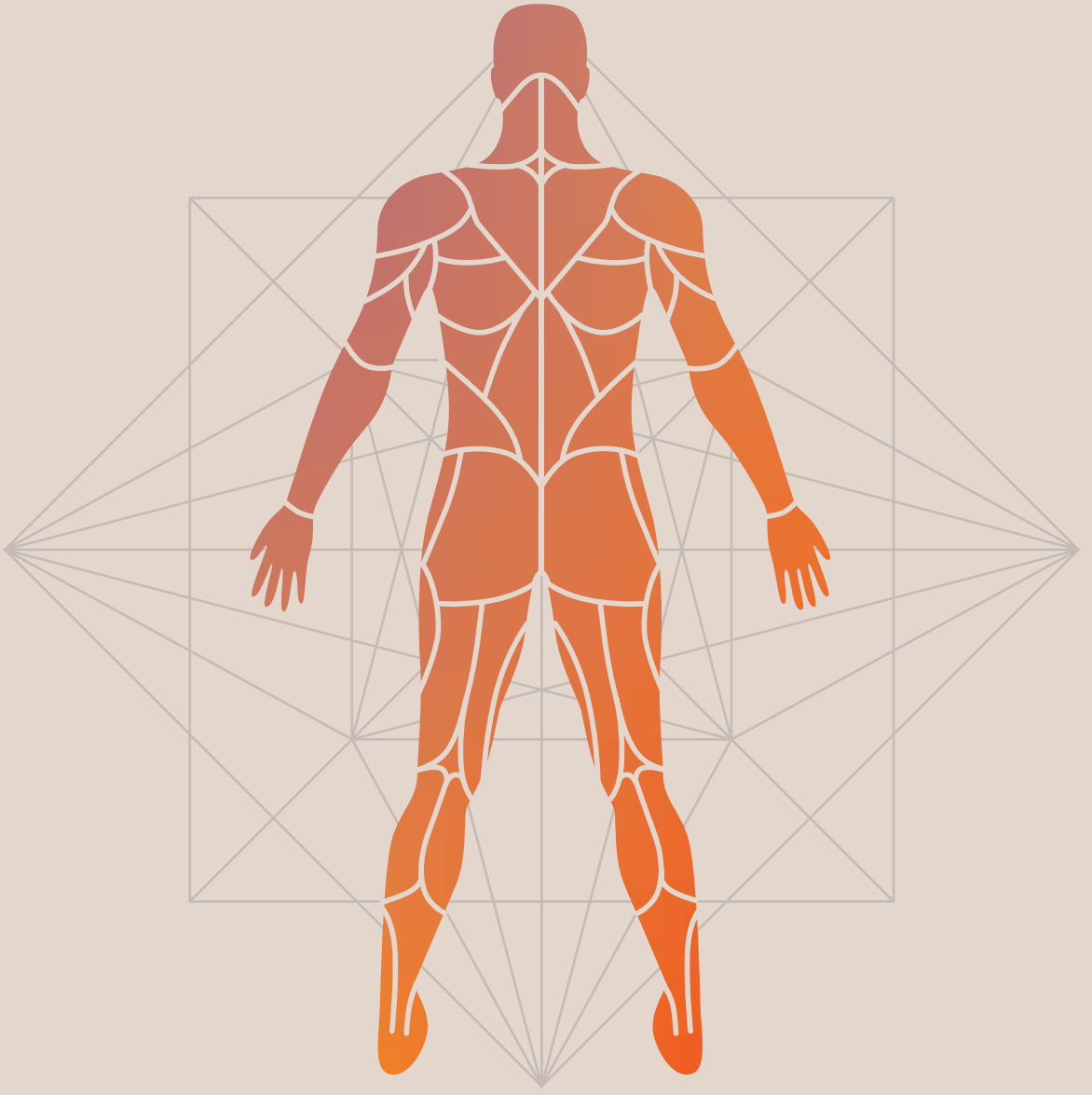

Chapter 8

General discussion and future implications

This thesis explores the relationship between measures of body composition and surgical outcome in patients with ovarian or colorectal cancer. When researchers use the term body composition, it can mean different things. It describes the relationship between the different components of the body. A more detailed explanation of body composition can be found in the introduction of this thesis. The focus of this thesis is specifically on the amount of visceral fat and muscle mass that a body contains. The evidence presented in this thesis suggests that visceral obesity in particular is strongly associated with operative risk in oncological surgery. In addition, BMI is not associated with surgical complications. Visceral obesity is an independent risk factor for surgical complications in patients with colorectal cancer and advanced ovarian cancer.

There is a great deal of heterogeneity in the way body composition is being measured in the current literature. There are also different definitions of visceral obesity and sarcopenia in that literature. This general discussion addresses this heterogeneity and proposes a unified measurement protocol. In this thesis we compared the two known cut-off values (100cm^2 and 130cm^2) above which people are defined as viscerally obese. The cut-off of 100 cm^2 is more strongly associated with surgical complications. This chapter provides further insight into the use of cut-offs for visceral obesity.

Visceral obesity and complications

It is important to understand why visceral fat might increase the risk of surgery in oncology patients. One hypothesis is that the inflammatory activity of visceral fat influences surgical risk. Visceral fat is known to secrete inflammatory factors that negatively influence a person's health. This is a complex process and, in addition to this inflammatory activity, other mechanisms are likely to be involved in the development of metabolic disease[1]. Increased inflammatory activity is found in visceral adipose tissue. Cytokine levels are elevated in visceral adipose tissue of metabolically unhealthy patients compared with levels in visceral adipose tissue of metabolically healthy patients[2]. The presence of inflammatory factors depends on the volume of visceral fat and is associated with metabolic disorders. It is thought that this chronic low-grade inflammatory state of visceral obesity contributes to the higher risk of surgical complications. Further research is needed to confirm this. The correlation between cytokine expression in visceral fat tissue removed during surgery and complication rates would need to be studied to verify this theory.

It could also be argued that the comorbidity of visceral obese patients influences their surgical risk. Patients with visceral obesity have more comorbidities such as diabetes, hypertension and metabolic syndrome[3]. These conditions could affect recovery from surgery in visceral obese patients. However, the chapters in this paper adjust for these

confounders. Even with these adjustments, the correlation between visceral obesity and complications was observed. Therefore, this hypothesis is disproved.

A third explanation for the association between an elevated visceral fat volume and complications is that the surgical procedure might be more challenging due to the amount of visceral fat. The visceral fat could limit access to the surgical area. If a procedure becomes more difficult, the duration of surgery would be longer. In a meta-analysis we found that visceral obesity was correlated with longer operation times in patients with colorectal cancer. In the study we did in rectal cancer patients, we also found a longer operation time in patients with visceral obesity. We did not find an association between visceral obesity and length of surgery in patients with advanced ovarian cancer. Research in other areas of abdominal surgery shows conflicting results. In gastric cancer, for example, several papers have given conflicting results about the length of surgery in patients with visceral obesity[4,5]. Based on this, there is evidence that surgical difficulty increases in patients with visceral obesity. However, it is not clear whether the duration of surgery also correlates with postoperative complications.

Variation in measurements and definitions in literature

An important part of this thesis is to understand the process of measuring body composition. There is a wide variation in the methods used to measure body composition. The literature describes MRI scans, DEXA scans, CT scans and other methods. It is important to establish a standardized protocol for body composition measurements. A consistent protocol makes it easier to compare data. For this thesis, the measurement of fat and muscle on preoperative CT scans was used. We found that there is no uniform method of measuring and defining body composition on CT scans. Variations are found in almost all steps of body composition measurement. Below we discuss these variations for each stage of the method.

Measuring body composition using CT involves a number of steps. The first is to determine which CT slice at which level of the body will be used to make the assessment. Most studies have used one or more transverse slices of the CT scan. Secondly, the area of interest should be decided. For example, when measuring visceral fat, the intra-abdominal cavity should be selected. This can be done manually or by an automated process using software. The third step is to determine the range of Hounsfield units that will distinguish the tissue of interest from other types of tissue. This will be discussed later. An illustration of the body composition measurement method used in this thesis can be found in chapters four and six.

The first variation found in the use of CT as a tool for measuring body composition is in the level of the chosen transversal slice of interest. Most studies use a single transverse slice of the CT scan to measure visceral fat and muscle mass. The chosen level of the slice varies between the lumbar disc 4-5 and the umbilicus[6-8]. It has been shown that the measurement of fat or muscle tissue on a transversal slice correlates well with the composition of the whole body[9,10]. This means that the amount of visceral fat found in one slice can serve as a proxy for the amount of visceral fat in the whole body. This is well studied for all the different levels used in the literature. Therefore, the differences in the chosen level may not be of significant clinical importance.

A second difference is the area of interest. When measuring fat or muscle area, it is necessary to define and identify the area of interest within the different body tissues are to be identified and measured. For example, when measuring visceral fat area, the measurement is usually limited to the intra-abdominal cavity. This area of interest can be delineated manually, as in this thesis, or by using specially designed software. This software automatically delineates the area of interest but requires manual confirmation and sometimes manual adjustment. Manual delineation and automated delineation by software give comparable results[11,12]. If the delineation is done by an experienced person, automatic software saves little or no time. Both methods give similar results and both can be used.

Another more important difference is the range of Hounsfield units (HU) used to identify different tissue types. Hounsfield units are the unit of measurement for radio density in CT scans. It is a relative measure of radio density and is used in the interpretation of CT images. The physical density of tissue is proportional to the absorption of the x-ray used in CT. The Hounsfield unit is calculated based on a linear transformation of the baseline attenuation coefficient of the X-ray beam. A grey scale can be calibrated on the basis of Hounsfield units[13,14]. Water is set at zero Hounsfield units and air at -1000 HU. Most tissue types are defined by a range of Hounsfield units. It is important to define what the range of HU is for the type of tissue being measured. If the range is too wide, other types of tissue may be included and the measurement will overestimate the absolute amount of the tissue of interest. If the range is too narrow, not all of the tissue of interest will be measured, resulting in an underestimate. Different ranges are used to define a particular tissue type. For fat tissue, ranges used include -250 to -50HU, -190 to -30HU and -140 to -40HU[15,16]. Most studies use the range of -150 to -50HU or -190 to -30HU to define adipose tissue. The origin of these ranges is not always clear. Already in 1988, the range of -190 to -30HU is referred to[17]. This publication is often cited. The other frequently used range (from -150 to -50 HU) dates back to 1983. In this study by Dixon, the fat area was measured using the -150 to -50HU range[18]. The authors described the difference in fat distribution between

men and women based on a sample of 25 people of each sex. We found no evidence to determine which range is better. However, mean HU for visceral fat has been measured in other studies and ranges between: -52HU[21] and -93HU[20]. The ranges used in this study differ only slightly from one of the most commonly used ranges. The measured adipose tissue correlates well with surgical complications in these patients. It also includes the mentioned mean HU reported in the literature, which should be included in the range. Therefore, we conclude that the range we used (-140 to -50HU) is adequate for measuring adipose tissue in a research setting and for predicting surgical risk.

The fourth variation is found in the definitions of visceral obesity and sarcopenia. Body composition measurements using CT scans give a surface area in square centimeters. When measuring visceral fat, this surface area is often referred to as visceral fat area. Most researchers, including ourselves, then use visceral fat area as a continuous determinant in analyses. Another option is to use a cut-off to determine whether a person has excessive amounts of visceral fat or , in other words, whether they have visceral obesity. Then use visceral obesity as a dichotomous determinant in the analysis. In this thesis we evaluated the two cut-offs used in the literature to define visceral obesity (100cm^2 and 130cm^2)[16,21]. We found that both cut-offs correlated well with complications. We also found that visceral obesity defined by the cut-off of 100cm^2 was a significant predictor of length of hospital stay. Visceral obesity defined by the 130 cm^2 cut-off did not correlate with length of stay. We concluded that a cut-off of 100 cm^2 should be used when using visceral obesity in risk profiling.

In the current literature, more arguments can be found for using a visceral fat area of 100 cm^2 as a cut-off point to define visceral obesity. The cut-off of 100 cm^2 is also used in studies to determine the health risks of visceral obesity. It seems more practical to use a similar cut-off for visceral obesity to determine both health risk and surgical risk. A VFA of 100 cm^2 or more is correlated with atherosclerotic changes in the carotid artery[21]. Despres et al published in 1993 that if a patient has a 2visceral fat area of more than 100cm^2, the risk profile for cardiovascular disease and diabetes changes negatively[23]. Another study showed that a person's cardiovascular risk increases with a visceral fat area of 100cm^2 or more[24]. This may be the reason why in Japan a visceral fat area of 100cm^2 or more is part of the definition of metabolic syndrome[25,26]. As this cut-off correlates with surgical risk as well as cardiovascular and metabolic risk, the 100 cm^2 cut-off for visceral obesity seems appropriate.

Another term that is being used in various ways in the literature is sarcopenia. The term sarcopenia is regularly used in studies that use CT scans to determine body composition. The use of this term and its translation to the amount of muscle mass on CT is challenging. Sarcopenia refers to the loss of muscle mass and muscle function. No information about muscle function can be derived from a CT scan. Therefore, a CT scan may not be the best way to detect sarcopenia. Muscle mass and muscle 'quality' can be measured using a CT scan. In the literature review in Chapter 8, we found that there is evidence that muscle quality correlates with surgical complications in gynaecological cancer patients. In the cohort studies in this thesis of patients with colorectal or ovarian cancer, muscle mass is not a significant predictor of complications. Further research is needed to establish the value of muscle mass and quality, as measured by CT scan, in predicting surgical complications.

Although not all of these differences may be clinically relevant, we strongly recommend the use of a standardised method of measuring (visceral) fat on CT scan to allow comparison between studies. We encourage further research into the measurement of muscle mass and its role in assessing surgical risk.

Clinical implications and prevention

Measuring visceral fat or muscle area is a simple and quick procedure. It only takes a few minutes and a measuring application to determine body composition on a CT scan. However, cancer patients have to undergo surgery at short notice. As a result, the time for reducing the amount of visceral fat is limited. Recent research suggests that a preoperative regime of exercise and caloric restriction could be beneficial, even if time is limited. Kashikara showed that a short weight loss program that included exercise and calorie restriction for 10 to 30 days reduced visceral fat area by 11 percent and reduced perioperative complications in patients with gastric cancer[27]. The same preoperative program was found to reduce visceral fat area by 18 per cent in colorectal cancer patients. These patients also had fewer complications after surgery[28]. Several studies have shown that preoperative exercise during neoadjuvant treatment is safe, feasible and improves fitness and quality of life[29,30]. This preoperative treatment is therefore something that needs to be explored further. It should be implemented as standard care as more positive evidence is gathered.

Obviously it is not only important to treat visceral obesity before surgery, but also to prevent visceral obesity. We have summarized the risks of visceral obesity in the introduction to this paper. Preventing or treating visceral obesity would remove a risk factor for developing cancer, metabolic syndrome and cardiovascular disease. To illustrate this theory, Hirashita surgically removed visceral fat from diabetic rats. As a result, the rats'

insulin resistance improved[31]. TNF-alpha levels were also reduced. In humans, the key to reducing visceral fat is exercise and limiting calorie intake[32]. Verheggen et al make it clear that regular exercise is associated with reduced amounts of visceral adipose tissue. In a review published in 2020, Ross et al concluded that 30-60 minutes of moderate intensity exercise per day, combined with a healthy and balanced diet, reduces the amount of visceral fat by 15-20 per cent in four to six months[33]. Verheggen et al showed that calorie restriction led to greater weight loss than exercise, but less reduction in visceral fat. Finally, other researchers have found that a 5 per cent reduction in weight through lifestyle interventions results in a 15 to 25 per cent reduction in visceral fat[34].

Societal implications and government actions

Participation in health education programs leads to a reduction in metabolic syndrome[35]. Subjects who participate in these programs show a reduction in visceral fat and a reduction in cardiovascular events[36]. Governments are trying to educate their citizens and improve the overall health of the population. Regular exercise and a healthy and balanced diet are part of the general advice in several western countries and should be encouraged by national or local governments to prevent visceral obesity and related health problems. This general advice in the Netherlands consists of 150 minutes moderate intensity exercise[37]. It is clear that the prevention of (visceral) obesity in early life has an impact on health for decades. The Dutch government agrees and therefore launched the National Prevention Agreement in 2018.[38] This prevention agreement focuses on reducing tobacco use, alcohol consumption and obesity in the Netherlands. As the prevention of obesity and the prevention of visceral obesity are mostly similar, it could be an important agreement to prevent the problems found in this thesis. Not only to prevent complications in surgery, but more importantly to reduce the risk of patients getting cancer in the first place, as visceral obesity is also associated with an increased risk of cancer. The Prevention Agreement has set targets to be achieved by 2040 and regular updates on progress are published. The main goal of the agreement is to reduce the percentage of people who are overweight from 50% to 38%. The main measures to achieve this goal are the reduction of the tax on fruit to zero percent, higher taxes on alcoholic beverages, and the so-called sugar tax. The government also wants to make agreements with food manufacturers to encourage healthier choices. The government also wants to encourage physical activity and improve the quality of food in schools and Increasing exercise and decreasing caloric intake will reduce visceral fat. It is therefore important that the objectives outlined in the agreement are achieved as soon as possible. For example, the sugar tax has already proven to be a successful measure. Several countries, including Denmark, Norway, Hungary and Mexico, have increased taxes on sugar-sweetened beverages or sugary foods. Mexico was the first country to implement this increased tax in 2014. This 1 peso per liter tax (11% price rise) resulted in a 12% decrease in the purchase of sugar sweetened

beverages[39] . This is expected to reduce the prevalence of obesity by 2.5%[40]. This should prevent 86 to 134 thousand cases of diabetes in Mexico. The tax on non-essential energy-dense foods in Mexico is expected to reduce average caloric intake by 17 kcal per day. This results in a weight reduction of 0.40 kg after one year[41]. In addition, Hungarian data show a 4% decrease in the average consumption of taxed sugary foods after the sugar tax was implemented. This sugar tax is a proven feasible and effective measure and there should be no reason to postpone its implementation in the Netherlands.

Although the results of measures such as the sugar tax are promising, progress towards the goals stated in the Dutch Prevention Agreement is not going as planned. The last update of the agreement dates from November 2020. In the area of overweight, 10 targets were set for 2020. Only two of the 10 goals have been achieved and one is almost achieved. The achieved goals are: agreements with producers of soda beverages about reducing calories per serving and the realization of 12 *Healty Neighborhoods*. There has also been an increase in the percentage of overweight and obese adolescents since the prevention agreement was published.

Two very important institutions where healthy eating should be the norm are schools and hospitals. However, even in these organizations, the implementation of health policies to reduce obesity has been very slow. The percentage of school cafeterias offering healthy food was 42% in 2020, while the target was 50%. It is worrying that less than half of the schools where young people need to be taught about healthy lifestyles provide healthy food.

Shockingly, only one hospital offered healthy food to patients, visitors and staff. Only 16% of hospitals (19/117) offered healthy food to patients. On a more positive note, 10 hospitals had started a pilot project for healthier food for patients[42].

In 2015 a plan was published to increase the time or amount of physical exercise in primary schools. However a report published in 2017 shows that no increase has been seen. Only 75% of schools provide 90 minutes of physical education. Money, time and staffing are cited in particular as barriers to giving more physical education.[43]

Organizations such as schools and hospitals are not able to implement measures to improve health. Why this does not work on a short notice needs to be investigated. It seems that a good initiative such as the Prevention Treatment is not enough to act quickly on the increasing prevalence of obesity in the world. One reason could be that most health programs or agreements are not enforced. Governments should take responsibility and enforce the agreements they have made to improve the health of their populations.

Recommendations for future research

This thesis presents evidence that visceral obesity is associated with increased surgical risk in patients undergoing oncological surgery. Prehabilitation shows promise in reducing surgical risk and should be further explored. It should be noted that most of these prehabilitation studies have been carried out in small groups of patients with predominantly male patients (70 to 90 per cent)[27-29,30]. In part 2 of this thesis we show that body composition differs between men and women. Recent data show that the body composition of women changes differently to that of men when exposed to exercise. Therefore, it is necessary to investigate the effect of prehabilitation on surgical outcome in an all-female population such as the gynaecological patient.

Furthermore, the effect of prehabilitation on visceral obese patients should also be investigated. Visceral obese patients are at higher surgical risk and may therefore benefit most from preoperative exercise and diet. However, we should be aware that it is very likely that prevention is the most effective method of overcoming the problems addressed in this thesis.

Conclusion and recommendations

Body composition measurements, especially the amount of visceral fat, could be used to predict the risk of surgery in patients undergoing cancer treatment. The predictive value of muscle mass is unclear. To improve the comparability of interpretation of results in future research, we recommend the use of a standardized method of body composition measurement. Based on the data presented in this thesis, we recommend the use of a transversal slice at a level between the third and fourth lumbar vertebrae. We suggest a range of Hounsfield units for adipose tissue from -140 to -50HU. Visceral obesity should be defined as visceral fat area ≥100 cm^2. Prevention of visceral obesity should be encouraged by focusing on regular physical activity and a healthy and balanced diet in the general population.

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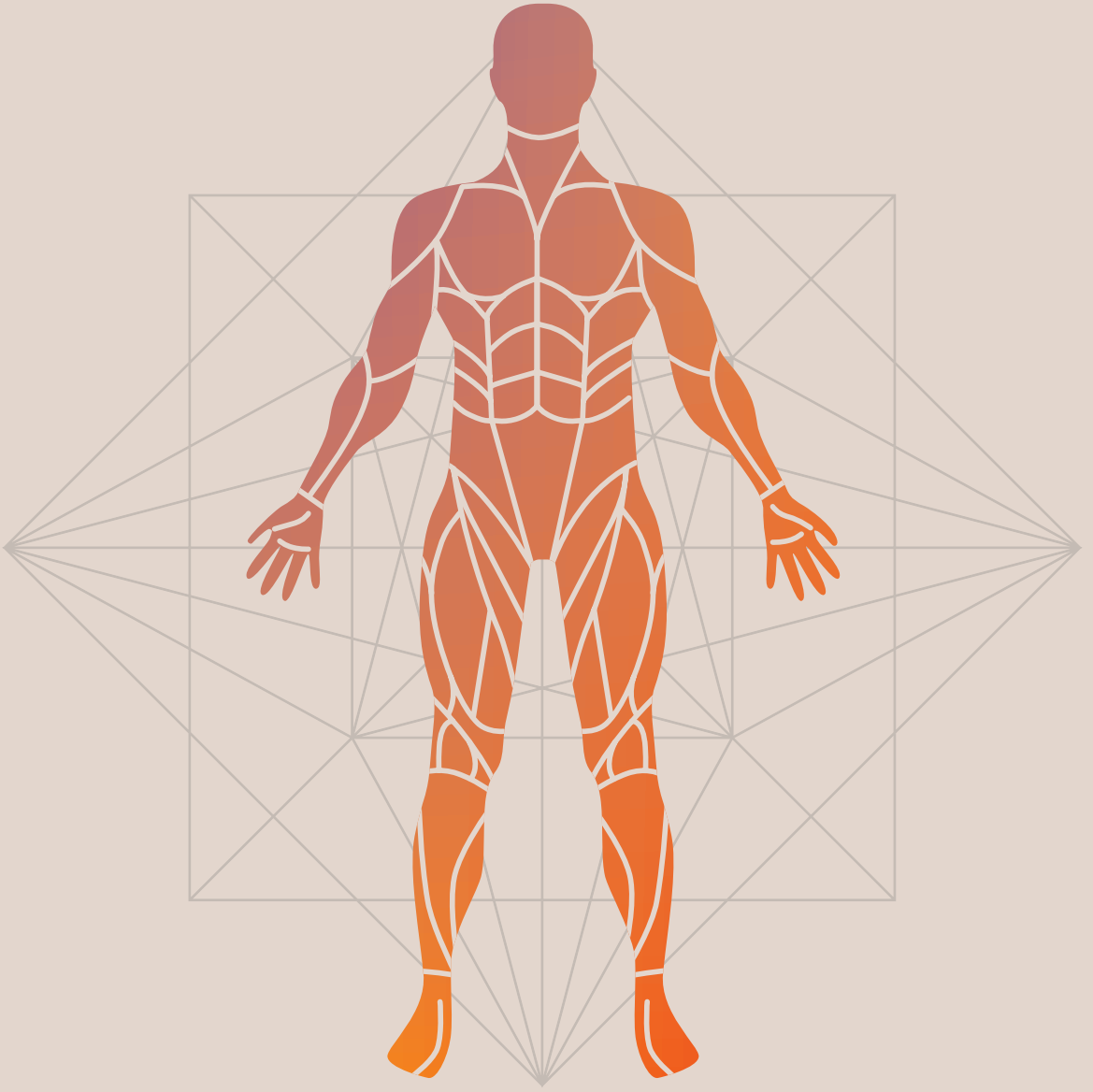


Chapter 9

Summary

This thesis reports on the use of body composition measurements on CT scan in correlation with surgical risk in patients undergoing surgical treatment for colorectal or gynaecological cancer.

The **first chapter** describes the outline and basis for the work in this thesis. It shows why it is thought that body composition measurements correlate better with surgical complications than body mass index. In summary, it is thought that it is not weight and height, but the composition of the body that is more important. This is due to the metabolic and inflammatory properties of visceral fat, subcutaneous fat and muscle mass. In particular, excess visceral fat can cause chronic low-grade inflammation, which can lead to metabolic syndrome and cancer, and may also make the body react differently to surgery. Body mass index does not correlate well with body composition.

Part one. The first part of the thesis covers the research carried out in patients with colorectal cancer.

Chapter two describes the outcome of a cohort study in 564 patient undergoing elective resection of the colon as a treatment of colon cancer. Recent research showed that body composition measurements, especially visceral fat, could be a better predictor of surgical complications. We retrospectively measured visceral fat area and muscle area on the preoperative CT-scan. We concluded that 65 per cent of these patients had visceral obesity. Patients with visceral obesity had significantly more anastomotic leakage, pneumonia, wound infection and reoperations. Visceral obesity was significant predictor of anastomotic leakage and wound infection. We also found that 44 per cent of patients with a BMI < 25 had an excessive amount of visceral fat. We therefore concluded that visceral obesity is related with complications in these patients and body mass index is not.

The systematic review in the **third chapter** reviews the known literature on visceral obesity and surgical outcomes in colorectal cancer surgery. We included seven trials with a total of 1230 patients. When we pooled the data collected from these studies, we found that visceral obese patients had a longer hospital stay with a mean difference of 1.16 days. Surgery took 20.5 minutes longer in these patients. Patients without visceral obesity had an odds ratio of 0.15 for developing a surgical complication compared to visceral obese patients. This shows that visceral obesity is correlated with surgical complications in colorectal cancer patients.

Chapter four reports on the results of a retrospective cohort study in 74 patients who underwent neo-adjuvant chemo-radiation therapy followed by a rectal resection. We compared the CT-scan before and after chemo-radiation and used the latter one in our

analysis concerning postoperative complications. We also investigated the difference of two cut-off points for visceral obesity (a visceral fat area of 100cm^2 and a visceral fat area of 130cm^2). We found an unexplained statistically significant increase of muscle area after chemo-radiation. We also found that having a visceral fat area >100cm^2 is an independent risk factor for developing postoperative complications (OR:5.78). Both cut-offs for visceral obesity correlated with complications, however only 100cm^2 correlated also with length of hospital stay. Therefore we conclude that 100cm^2 could be more valuable in the risk profile.

Chapter five describes the results of the most recent study in 406 rectal cancer patients. We found that 67 per cent of these patients were visceral obese. Patients with visceral obesity were more likely to have pre-operative cardiac comorbidity and more likely to have a history of hypertension. We found that patients with a visceral fat area of >100cm^2 had a longer surgical time (166 min vs 149min) and more peroperative blood loss (431 vs 310mL). Wound infections were more prevalent in the visceral obese patients(14 vs 8 per cent). Visceral obesity (VFA > 100cm^2) was a risk factor for complications (OR: 1.63). In this chapter we can also conclude that visceral obesity is correlated with postoperative complications and body mass index is not.

The **second part** shows the result of two studies in patients with gynaecological cancer. These diseases were chosen because they include only female patients, whereas patients with colorectal disease are predominantly male. The body composition of men and women is different, and therefore the effect of body composition on the postoperative course in these patients might be different from that in a sex-mixed group of patients.

A retrospective cohort study done in 298 patients with advanced ovarian cancer is described in **chapter six**. We used the same study design as in the first part of this thesis and performed this in this all-female patient group. We found that forty per cent of the included patients were visceral obese. This is lower compared to the patients in chapter two, four and five, possible due to the different body composition in women. We found that patients with visceral obesity suffered more often of hypertension than patients with normal amounts of visceral fat. Postoperative complications occurred in 20.5 per cent of the non-visceral obese patients and in 43.4 per cent of those with visceral obesity. We found that a thrombotic event occurred significantly more often in visceral obese patients (5 vs 0.6 per cent). Visceral obesity is an independent predictor of complications in these patients, along with hypertension and duration of surgery (OR:4.4).

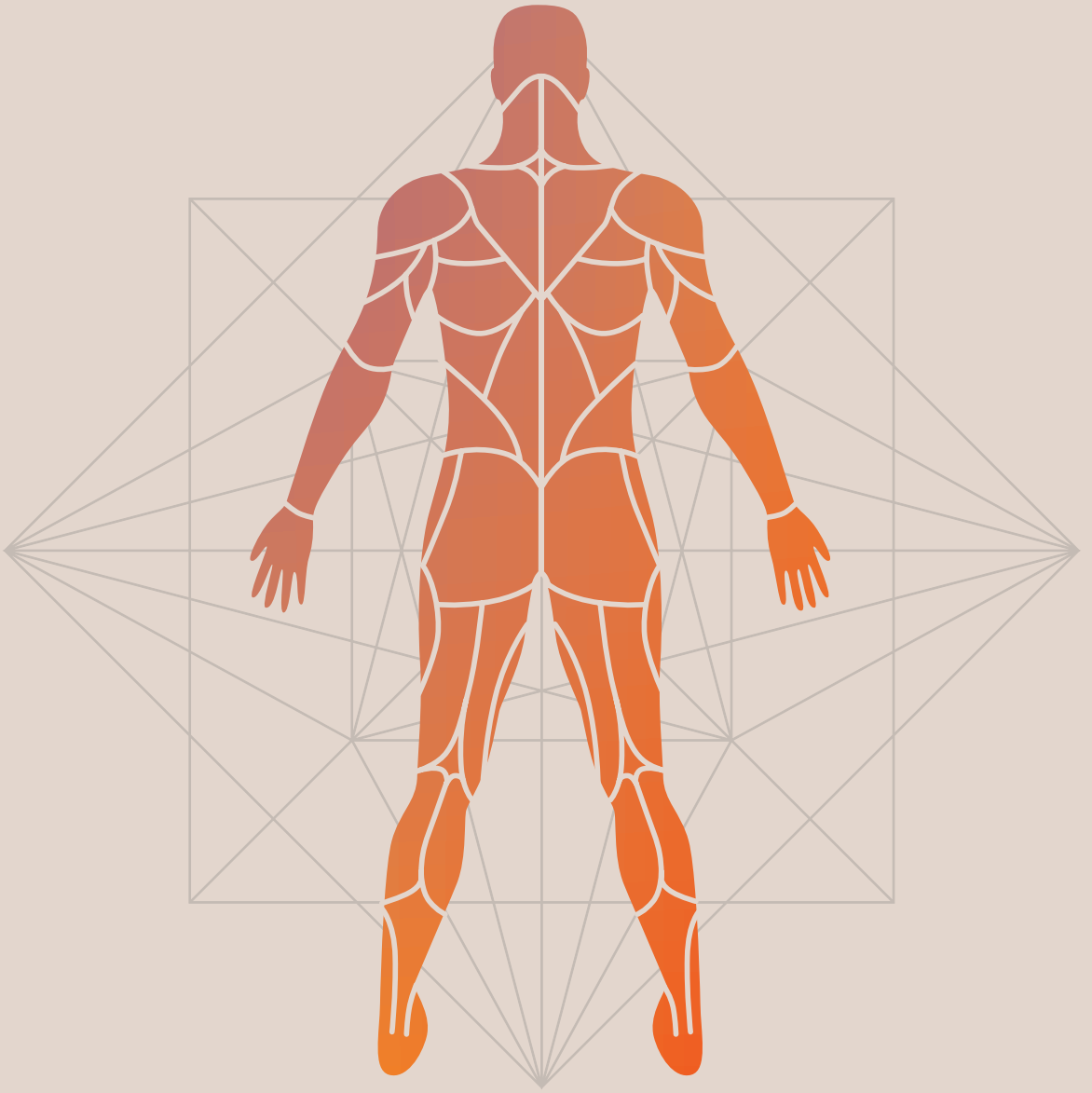
In **chapter seven** the known literature on the association between body composition measurements and postoperative complications in patients undergoing surgical treat-

ment in patients with gynaecological cancer is reviewed. We used best evidence synthesis to find the best evidence for a correlation as a meta-analysis was not possible due to the low amount of found studies. Also, the used methods differed widely between the studies and therefore pooling of the data was not possible. We included ten studies using different methods of measuring body composition. These included anthropometric measures such as waist circumference, bioelectrical impedance analysis and computed tomography (CT) scans. The trials included patients with ovarian or endometrial cancer. We found that there was strong evidence that there was no association between visceral fat and length of hospital stay. We found moderate evidence that there was no association between muscle or fat mass (i.e., muscle- or subcutaneous fat) and postoperative complications. There was insufficient evidence for an association between visceral fat and intraoperative or postoperative complications, and for an association between muscle mass or -quality and length of hospital stay. Some studies used muscle quality using CT-scan. We found moderate evidence that a higher amount of good quality muscle was associated with a lower risk of postoperative complications.

The general discussion is described in **chapter eight.** This chapter proposes a standardized protocol for measuring body composition using CT. It is important to use a protocol because there are currently a large number of different methods of measuring body composition in the published literature. As a result, the results of these studies are difficult to compare. A large part of the general discussion focuses on the prevention of (visceral) obesity. The importance of preventive measures taken by the (Dutch) government is discussed. It is concluded that it is important to prevent visceral obesity. Therefore, a healthy diet and physical activity should be promoted. The Dutch Prevention Agreement is criticized because the targets set out in the agreement are not being achieved quickly enough. The introduction of a sugar tax is also mentioned.

Conclusions of this thesis

- Visceral obesity is associated with postoperative complications in patients with colon, rectal and ovarian cancer.
- Body mass index, which is used currently, is not correlated with complications.
- An unexplained increase of muscle mass is seen after neo-adjuvant chemo-radiation therapy in patients suffering rectal cancer.
- A visceral fat area of 100cm^2 or higher should be the cut-off for visceral obesity
- A standardized protocol for measuring body composition should be used to improve comparison of results.
- There should be more focus on prevention of visceral obesity by the government, for instance by implanting a sugar tax.



Chapter 10

Summary in Dutch

Nederlandse samenvatting

Dit proefschrift beschrijft het gebruik van lichaamssamenstellingsmetingen op CT-scan in correlatie met chirurgisch risico bij patiënten die een chirurgische behandeling ondergaan voor colorectale of gynaecologische kanker.

Het **eerste hoofdstuk** beschrijft de opzet en de basis voor het werk in dit proefschrift. Het laat zien waarom het wordt gedacht dat metingen van de lichaamssamenstelling beter correleren met chirurgische complicaties dan de body mass index. Samengevat wordt gedacht dat niet gewicht en lengte, maar de samenstelling van het lichaam belangrijker is. Dit wordt toegeschreven aan de metabole en inflammatoire eigenschappen van visceraal vet, onderhuids vet en spiermassa. Met name overtollig visceraal vet kan een chronische laaggradige ontsteking veroorzaken, wat kan leiden tot het metabool syndroom en kanker, en er ook voor kan zorgen dat het lichaam anders reageert op een operatie. De body mass index is niet gecorreleerd aan de lichaamssamenstelling.

Deel 1. Het eerste deel beschrijft het onderzoek wat verricht is in patiënten met colorectale kanker.

Hoofdstuk 2 beschrijft de uitkomsten van een cohort studie met 564 patiënten die een electieve resectie van het colon ondergingen als behandeling van colonkanker. Recent onderzoek toont aan dat metingen van lichaamssamenstelling, met name van visceraal vet, een betere voorspeller kan zijn van chirurgische complicaties. Wij hebben retrospectief de viscerale vetoppervlakte en de spieroppervlakte gemeten op de preoperatieve CT-scan. Wij vonden dat 65 procent van de patiënten met kanker van het colon te veel visceraal vet heeft. Patiënten met teveel visceraal vet, ook wel viscerale obesitas genoemd, ervaarden significant vaker een naadlekkage, pneumonie, wondinfecties en moesten vaker een heroperatie ondergaan. 44 procent van de patiënten met een BMI onder de 25kg/m^2 had teveel visceraal vet. Concluderend vonden wij dat visceraal vet is gecorreleerd met complicaties in deze patiënten en BMI niet.

De systematische review in **hoofdstuk drie** beschrijft de literatuur over viscerale obesitas en chirurgische uitkomsten in patiënten met colorectale kanker. Er weren zeven trials geïncludeerd met in totaal 1260 patiënten. Door de analyse van de gecombineerde data van deze studies vonden wij dat de patiënten met viscerale obesitas langer opgenomen bleven in het ziekenhuis met een mediaan verschil van 1 dag. Tevens duurde de operatie gemiddeld 20.5 minuten langer. Patiënten zonder viscerale obesitas hadden een odds ratio van 0.15 voor het ontwikkelen van chirurgische complicaties in vergelijking met

patiënten die wel viscerale obesitas hadden. Dit laat zien dat viscerale obesitas is gecorreleerd met chirurgische complicaties in patiënten met colorectale kanker.

Hoofdstuk vier beschrijft de resultaten van een retrospectieve cohort studie met 74 patiënten die neoadjuvante chemoradiatietherapie ondergingen en daarop volgend een resectie van het rectum ondergingen. Wij vergeleken de CT-scan voor en na chemo-radiatietherapie en wij gebruikten de laatste scan voor de analyse naar postoperatieve complicaties. Tevens hebben wij in deze studie de twee afkapwaarden voor viscerale obesitas vergelijken (een viscerale vetoppervlakte van 100cm^2 en 130cm^2). Wij vonden een onverklaarde toename van spiermassa na chemoradiatie. Tevens vonden wij dat een visceraal vetoppervlakte van meer dan 100cm^2 een onafhankelijke risicofactor is voor het ontwikkelen van complicaties(OR 5,78). Beide afkapwaarden voor viscerale obesitas correleerde met postoperatieve complicaties. Echter alleen de afkapwaarde van 100cm^2 correleerde ook met de duur van de ziekenhuisopname. Derhalve concluderen wij dat de afkapwaarde van 100cm^2 de meest waardevolle waarde is in risicoprofilering.

Hoofdstuk vijf beschrijft de resultaten van de meest recente studie met 406 patienten met een rectumcarcinoom. In deze studie had 67 procent van de patiënten viscerale obesitas. Patiënten met viscerale obesitas hadden vaker cardiale comorbiditeit en hypertensie. Wij vonden dat patienten met een viscerale vetoppervlakte van 100cm^2 of meer een langere operatieduur (166 minuten vs 149minuten) hadden en meer peroperatief bloedverlies(431mL vs 310mL). Wondinfecties kwamen vaker voor(14 vs 8 procent). Viscerale obesitas is een risicofactor voor het ontwikkelen van complicaties (OR:1.63). Ook in dit hoofdstuk kunnen we concluderen dat visceraal vet is gecorreleerd met postoperatieve complicaties en BMI is dat niet.

In het **tweede deel** van dit proefschrift worden de resultaten van twee studies beschreven die werden verricht in patiënten met gynaecologische kanker. De lichaamssamenstelling verschilt tussen mannen en vrouwen en de invloed hiervan op het postoperatieve beloop wellicht ook. Derhalve werd gekozen voor ziekten met alleen vrouwelijke patiënten voor het tweede deel van dit proefschrift.

Een retrospectief cohortonderzoek bij 298 patiënten met gevorderde eierstokkanker wordt beschreven in **hoofdstuk zes.** Wij gebruikten dezelfde onderzoeksopzet als in het eerste deel van dit proefschrift en voerde dit uit in deze patiëntengroep die volledig uit vrouwen bestond. Wij vonden dat veertig procent van de geïncludeerde patiënten viscerale obesitas had. Dit is lager dan bij de patiënten in hoofdstuk twee, vier en vijf wat laat zien dat vrouwen een andere lichaamssamenstelling hebben dan mannen. Patiënten met viscerale obesitas hadden vaker last van hypertensie. Postoperatieve complicaties

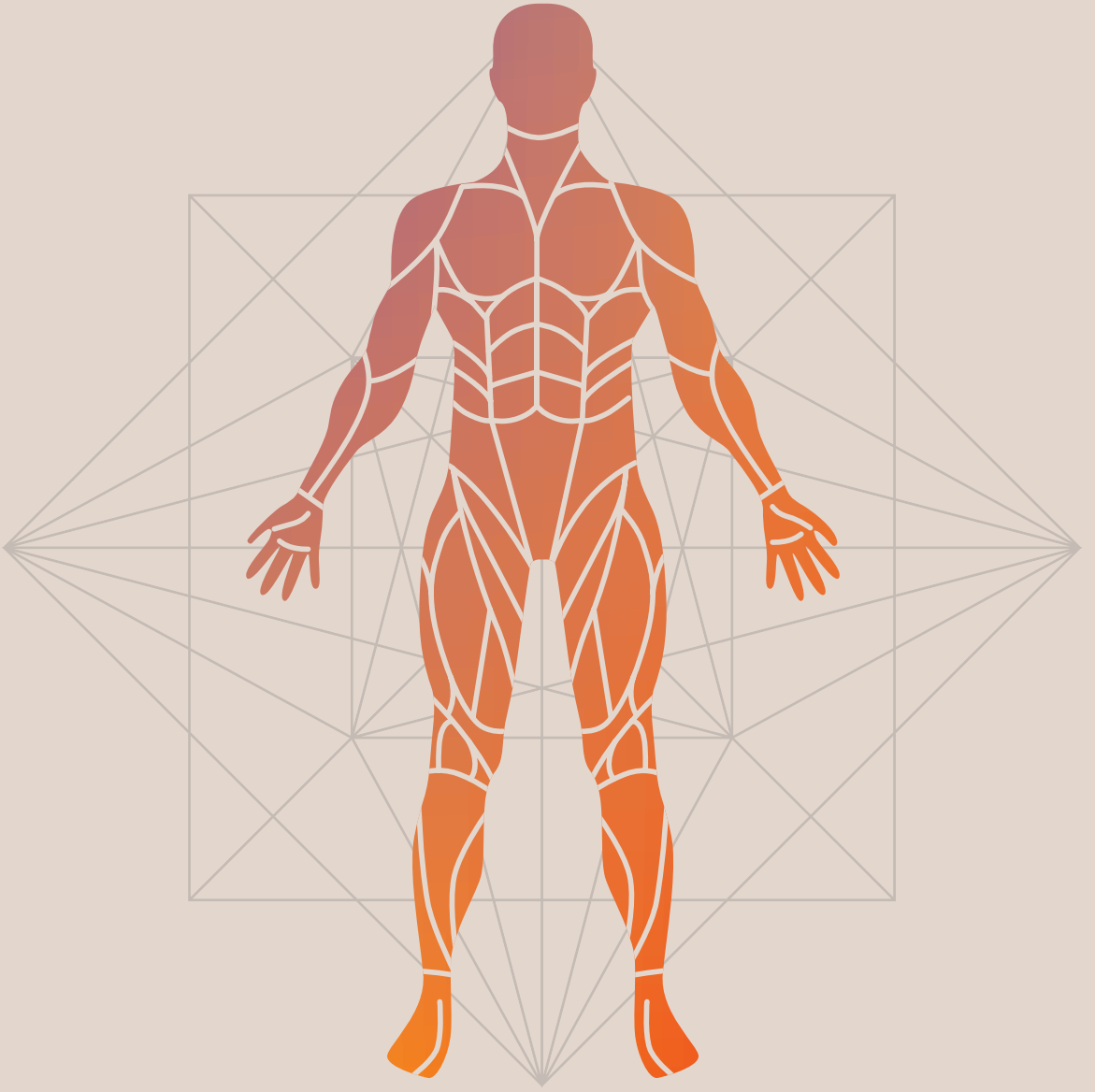
kwamen voor bij 20,5% van de patiënten die geen viscerale obesitas hadden en bij 43,4% van de patiënten die wel aan visceraal obesitas lijden. Wij vonden dat bij patiënten met viscerale obesitas vaker trombose voor kwam (5 versus 0,6 procent). Viscerale obesitas bleek, samen met hypertensie en operatieduur, een onafhankelijke voorspeller van complicaties (OR:4,4).

In **hoofdstuk zeven** wordt de bekende literatuur over de associatie tussen metingen van lichaamssamenstelling en postoperatieve complicaties bij patiënten die een chirurgische behandeling ondergaan voor gynaecologische kanker beoordeeld. We hebben gebruik gemaakt van een best evidence synthese om het beste bewijs voor een verband te vinden, aangezien een meta-analyse niet mogelijk was vanwege het geringe aantal gevonden studies. Ook verschilden de gebruikte methoden sterk tussen de studies, zodat samenvoegen van de gegevens niet mogelijk was. Wij hebben tien studies geïncludeerd waarin verschillende methoden werden gebruikt om lichaamssamenstelling te meten. Antropometrische metingen zoals tailleomtrek, bio-elektrische impedantieanalyse (BIA) en computertomografie (CT) scans werden gebruikt. De patiënten hadden eierstok- of endometriumkanker. Wij vonden dat er sterk bewijs is dat er geen verband bestaat tussen visceraal vet en de duur van de ziekenhuisopname. Wij vonden matig bewijs dat er geen verband is tussen spier- of vetmassa (d.w.z. vet is spieren of onderhuids vet) en postoperatieve complicaties. Er was onvoldoende bewijs voor een verband tussen visceraal vet en peroperatieve of postoperatieve complicaties, en voor een verband tussen spiermassa of -kwaliteit en verblijfsduur in het ziekenhuis. Sommige studies gebruikten de kwaliteit van de spiermassa gemeten op CT-scan. Wij vonden matig bewijs dat een grotere hoeveelheid spiermassa van goede kwaliteit samenhing met een lager risico op postoperatieve complicaties.

De algemene discussie kan worden gevonden in **hoofdstuk acht**. In dat hoofdstuk wordt een gestandaardiseerd protocol voor het meten van lichaamssamenstelling met behulp van CT-scan voorgesteld. Het is belangrijk om een protocol te gebruiken omdat er nu een groot aantal verschillende methoden worden gebruikt voor het meten van lichaamssamenstelling. Dit resulteert erin dat studieresultaten lastig te vergelijken zijn. Een groot deel van de discussie focust op de preventie van viscerale obesitas. Het belang van de genomen maatregelen door de nederlandse overheid wordt besproken. Geconcludeerd wordt dat het belangrijk is viscerale obesitas te voorkomen. Daarom moeten gezonde voeding en lichaamsbeweging worden bevorderd. Het Nationale Preventieakkoord wordt bekritiseerd omdat de doelstellingen uit het akkoord niet snel genoeg worden gehaald. Ook de invoering van een suikertaks wordt genoemd.

Conclusies van dit proefschrift:

- Viscerale obesitas is geassocieerd met postoperatieve complicaties bij patiënten met colon-, rectum- en ovariumkanker
- Body mass index, wat nu vaak gebruikt wordt in dagelijkse praktijk, is niet gecorreleerd met complicaties
- Een onverklaarde toename van spiermassa wordt gezien na neoadjuvante chemoradiatietherapie bij patiënten met rectumkanker
- Een viscerale vetoppervlakte van 100cm^2 of meer zou gebruikt moeten worden als afkapwaarde voor viscerale obesitas
- Een gestandaardiseerd protocol voor het meten van lichaamssamenstelling is van belang op resultaten met elkaar te kunnen vergelijken
- Er zou meer focus moeten komen op de preventie van viscerale obesitas door de overheid bijvoorbeeld door het invoeren van de zogenaamde suikertaks



Appendices

Portfolio
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Dankwoord

PhD Portfolio

Name PhD student:	Colin Heus
PhD period:	February 2012 – October 2023

Courses:

2020 Good Clinical Practice

Presentations:

2023 Progress report Amsterdam UMC

2022 Visceral obesity and muscle mass determined by CTscan and surgical outcome in patients with advanced ovarian cancer *Oncologiebespreking*

2014 Visceral obesity, body mass index and risk of complications after colon cancer surgery. *34th ESSO Congress, Liverpool*

2014 Impact of visceral obesity on outcomes after chemo-radiation therapy and surgery for rectal cancer. *International Student Congress of (Bio-)Medical Sciences, Groningen*

2013 Visceraal vet en uitkomsten bij oncologische rectumchirurgie na preoperatieve chemoradiatietherapie. *Chirurgendagen 31 mei 2013*

Poster presentation:

2013 Viscerale obesitas en uitkomsten na colorectale chirurgie: een systematische review en meta-analyse. Chirurgendagen 2013

Supervising:

Arjen Lak, medical student
Anna Smorenburg, medical student
Wouter Verduin, medical student

Curriculum Vitae

Colin Heus is geboren op 13 oktober 1990 in Haarlem. Hij groeide op in Alkmaar, met zijn ouders en oudere zus. Na de middelbare school in Alkmaar werd de studie Geneeskunde aan de Vrije Universiteit in Amsterdam gevolgd. In het begin van deze studie was hij overtuigd dat hij chirurg zou worden. Het duurde ongeveer vijf jaar voordat hij erachter kwam dat een carrière in de gynaecologie beter bij hem past.

Tijdens zijn coschappen begon Colin met het doen van onderzoek binnen de chirurgie onder de vleugels van dr Lex Houdijk. Later verlegde hij zijn focus naar de gynaecologie en werden prof dr Gemma Kenter en dr Luc van Lonkhuijzen toegevoegd aan zijn promotieteam. Onder leiding van deze groep werd al het onderzoek wat geresulteerd heeft in dit proefschrift voltooid.

Na het afronden van zijn studie Geneeskunde begon hij als basisarts in het Kennemer Gasthuis gevolgd door een ruime twee jaar klinisch werk in het AMC.

In 2018 begon Colin aan de medisch specialistische vervolgopleiding tot gynaecoloog in het Noordwest Ziekenhuis in Alkmaar. Onder begeleiding van opleiders dr Janne-Meije van Rijn, dr Annelies Rep en dr Joke Bais werden de eerste twee jaar van deze opleiding vervuld. In 2020 kwam hij weer terug in het AMC, nu als AIOS, met prof dr Joris van der Post en dr Guus Fons als opleiders. In het NWZ locatie Alkmaar zal hij de opleiding tot gynaecoloog afronden.

Colin woont in Alkmaar met Laura en hun dochter Doris. Een broer of zus voor Doris wordt verwacht in december 2023.

Dankwoord

Dan is het tijd voor een hoofdstuk waar ik erg naar uit gekeken heb, het dankwoord. Tien jaar onderzoek doen naast alle andere werkzaamheden kon ik niet alleen. Gelukkig heb ik om mij een fantastische vrienden, familie en collega's. Zonder hen was mij dit niet gelukt. Aan jullie is dit hoofdstuk gericht.

Beste Gemma, professor Kenter, enkele jaren geleden hadden wij onze eerste afspraak. Ik had al een aantal publicaties en met hulp van jou zou ik het wel even afmaken. Één jaar werd twee jaar en nog enkele tijd later is het mij dan toch gelukt. Ik ben heel blij dat ik toch onder jouw leiding dit project heb kunnen afmaken. Onze gesprekken waren duidelijk, to the point en no nonsense, precies zoals ik het fijn vind. Dank voor je hulp en motiverende gesprekken.

Beste Luc, dr van Lonkhuijzen, toen Gemma voorstelde om jou te betrekken bij mijn onderzoek leek mij dit gelijk een goed idee. Onze schrijfstijlen kwamen misschien niet overeen maar laten we het erop houden dat we elkaar goed aanvullen. Nadat je dan voor de zoveelste keer hetzelfde had uitgelegd over hoe ik iets beter kon opschrijven lukte het mij dan ook wel betere stukken te schrijven. Jouw deur stond altijd open voor kort en bondig overleg en dat waardeer ik enorm.

Dan Lex, dr Houdijk, ondertussen meer dan 10 jaar geleden hadden wij een afspraak. Ik zo groen als gras op onderzoeksgebied en jij had ondertussen al meerdere promovendi rondlopen. Het contrast kon niet groter. Ik moest en zou chirurg worden en onderzoek doen ging mij daar bij helpen. Jij koppelde mij aan Hamit en al snel resulteerde dit in enkele publicaties. De rest duurde wat langer, maar het resultaat mag er zijn. Jouw enfant terrible heb je mij wel eens genoemd, waarschijnlijk omdat ik weer eens een deadline niet gehaald had. Of was omdat ik toch ineens gynaecoloog wilde worden? Hoe dan ook ik ben blij dat je genoeg geduld hebt om dit project met mij af te ronden. Jouw enorme enthousiasme over het onderwerp gaf mij altijd weer een zet de goede richting op.

Ik wil de leescommissie bedanken voor hun tijd en inspanning om mijn proefschrift kritisch te beoordelen. In het bijzonder Ko van der Velden voor het meelezen met de inleiding en begeleiding in mijn tijd als ANIOS in het AMC, Rebecca Painter voor haar begeleiding in mijn academische opleidingstijd en Jaap Stoker voor begeleiding in een van de hoofdstukken en uitleg over de technische kant van de CT-scan.

Ik wil alle collega's bedanken met wie ik heb samengewerkt in het prachtige Alkmaar. Ik daar een heerlijke tijd gehad. In het bijzonder Janne-Meije, Annelies en Joke als opleiders. Jullie staan voor de AIOS en mede daardoor heb ik daar zo fijn gewerkt.

Ook de collega's in het AMC verdienen een bedankje, dankzij jullie heb ik mij jaren lang enorm thuis gevoeld. Speciale dank gaat uit naar Guus Fons. Jouw steun in mijn academische tijd heeft veel voor mij betekent en ik ben jou daar enorm dankbaar voor.

Lieve arts-assistenten met wie ik de afgelopen jaren heb gewerkt, jullie zijn geweldig. Michelle, Eva, Ravi en Martina wat heb ik met jullie gelachen! Minouk in de eerste week van onze kennismaking direct het licht uit doen in Hesp. Het was duidelijk, die Minouk die kan je er wel bij hebben. Vele biertjes volgden. Dank voor jouw luisterend oor en gezelligheid!

Dan mag "Clow", "Clow zonder Colin" of "de roddeleetclub" natuurlijk niet ontbreken! Vele namen van deze appgroep zijn gepasseerd net als vele restaurants en toetjes. Bouchra, Maud en Eva dank voor de gezelligheid de afgelopen jaren. Dat er nog maar veel etentjes mogen volgen.

Floris, jij hebt je rol als ceremoniemeester nooit kunnen vervullen maar wel als vriend. Als huisgenoten gingen we feestjes en het casino af. Altijd wel weer een goed gesprek afgewisseld met een goed feestje of samen op jacht op een muis in huis. Een van de stellingen heb ik ooit voor het eerst uit jouw mond gehoord en nooit meer vergeten.

Lieve Nada, wij hebben elkaar leren kennen tijdens de studie en de vriendschap is altijd blijven plakken. Soms met wat wisselend frequentie maar niet in kwaliteit. Ik ben blij me jou als vriend en dankbaar voor je adviezen.

iFriends, ik weet eigenlijk niet hoe deze naam ontstaan is. Maar een legendarisch groep mensen bij elkaar is het wel. Al sinds de middelbare school een hechte vriendschap. Vakanties, weekendjes weg en vele drankjes die ik voor geen goud had willen missen. Slechte grappen en goede gesprekken zijn jullie altijd voor te porren. Ik ben blij dat ik jullie tot mijn vrienden mag rekenen!

Lieve Nikki, mijn buddy in mijn eerste twee jaar van de opleiding en nu mijn paranimf. In mijn eerste paar weken stonden wij samen hetzelfde appartement te bezichtigen, jij kreeg het natuurlijk… Vrij vlot hierna werd jij mijn buddy om mij door de eerste periode heen te slepen en gelukkig kon ik hierna ook bij je terecht voor advies of sushi. Ik ben blij dat jij mijn paranimf bent en mij nu door deze dag kan slepen.

Margreet, Remco, Eleanor en Livia. Het voelt als een kadootje dat ik jullie bij Laura inbegrepen kreeg. Jullie interesse in hoe de voortgang ging met mijn proefschrift was altijd fijn. Margreet alle oppasdagen hebben er daarbij ook voor gezorgd dat ik onder andere aan mijn proefschrift heb kunnen werken.

Lieve Joost, Roos, Lise en Cato, wat een feest is het om jullie in mijn leven te hebben. Ik ben blij met elk moment dat ik bij jullie ben.

Mijn grote zus, jij bent niet voor niets mijn paranimf. Jij staat al je hele leven klaar voor mij en mama. Jij bent niet alleen belangrijk voor mij maar ook voor Laura en Doris. Lieve Nadine, ik ben blij dat jij naast me staat als ik mijn proefschrift verdedig, maar nog meer dat je altijd achter mij staat.

Lieve mama, ik ben blij met de onvoorwaardelijke liefde die jij hebt voor Nadine en mij. Jij staat altijd voor ons klaar, voor een kop koffie, een goed gesprek of (ongevraagd) moederlijk advies. Het was niet altijd makkelijk na het overlijden van papa maar ik ben super trots op hoe jij er voor hebt gezorgd dat Nadine en ik klaar waren voor het leven. Eigenlijk is een alinea in dit dankwoord is niet afdoende om mijn dank hiervoor te betuigen.

Lieve Laura, ik kan niet beschrijven hoe belangrijk jij voor mij bent. Motiverende teksten als “maar je doet er ook niet echt veel aan” en “is het nu dan af?” waren soms net de woorden die ik nodig had om door te zetten. Jij bent een fantastische partner en de beste moeder die Doris maar kan wensen. Ik ben blij dat jij mij, ondanks mijn vele afwezigheid, altijd weer naar het AMC hebt gestuurd om dit eindeloze project af te maken. Het is soms lastig met onze diensten om tijd voor elkaar te maken. Maar nu is het dan echt af en heb ik weer tijd om met jou en ons gezin tijd door te brengen, samen te zijn, bergen te trotseren en avonturen te beleven. En als de kerstboom staat dan begint ons volgende avontuur al.

Lieve Doris, papa wordt altijd enorm gelukkig als hij jou ziet. Vaak ben je lief, soms boevig maar altijd maak je mij blij.