Visceral Adiposity is Associated with Increased Risk of Anastomotic Leakage Following Surgery for Colorectal Cancer

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ABSTRACT
This study investigates if body fat parameters, including visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), total adipose tissue (TAT) and body mass index (BMI), are correlated with increased risk of complications following surgery for colorectal cancer. Retrospective study of 54 consecutive patients undergoing elective resectional surgery for colorectal cancer with curative intent. A consultant radiologist reviewed all pre-operative CT scans and calculated body fat parameters using GE software. Primary outcomes were anastomotic leakage and 30 day mortality. Secondary outcomes included length of operation, number of lymph nodes retrieved, medical complications and duration of hospital stay. There were 5 leaks (9.3%) and 3 deaths (5.6%). Out of the four fat parameters, only VAT was significantly associated with an increased risk of developing anastomotic leakage (P=0.0341). The fat parameters were not significantly associated with any other outcome. Although male sex was associated with higher VAT (p=0.001), it was not an independent risk factor for leakage (p=0.380). Increased VAT is associated with a greater risk of anastomotic leakage following resection surgery for colorectal cancer. Further studies are warranted to investigate if pre-operative radiology may be used to stratify high-risk patients who may benefit from a temporary diverting stoma.

INTRODUCTION
Many surgeons associate obesity with adverse outcomes, and there is perceived increased technical difficulty when operating on patients with a larger body habitus. Body mass index (BMI) has traditionally been used as a surrogate marker for patient obesity. However, recent studies examining the relationship between BMI and complications following colorectal cancer surgery provide conflicting results. 1-4

The limitations of using BMI as a marker of intra-abdominal obesity are two-fold. First, it does not discriminate between muscle and fat mass, and second, it does not identify the distribution of fat within the body. There is increasing evidence that visceral fat, as opposed to subcutaneous fat, should be considered as different organs; for example, visceral fat generates inflammatory cytokines e.g. TNF-a, and is correlated with insulin resistance. Increased VAT is also associated with the metabolic syndrome and increased cardiovascular risk. 5

Visceral adipose tissue (VAT) has been used as a better marker of intra-abdominal obesity than BMI and as a predictor of complications following surgery. It has been associated with increased intra-abdominal infection, mortality and hospital stay following open gastrectomy for cancer 6 and pancreatic fistulae formation following total gastrectomy. 7 In a study including patients after gastric or colorectal cancer surgery, intra-abdominal fat was associated with increased medical and surgical complications. 8 In a specific cohort of patients undergoing laparoscopic resectional surgery for sigmoid colorectal cancer, increased VAT was found to be associated with an increased risk of wound infection and longer hospital stay. 9

This study aims to assess whether body fat parameters, including visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), total adipose tissue (TAT) and body mass index (BMI), are correlated with adverse outcomes, including anastomotic leakage, in patients undergoing open and laparoscopic surgery specifically for colorectal cancer.

METHODS
This was a retrospective study of 54 consecutive patients undergoing open and laparoscopic elective resectional surgery for colorectal cancer with curative intent over a 6 month period (April to October 2008) at a single centre. Data were obtained from JANUS, a web-based patient management and morbidity and mortality database. Patients’ electronic and paper notes were cross-checked to identify any complications arising after discharge from hospital. Exclusion criteria included abdominoperineal excision of rectum, emergency surgery, palliative intent, TEMS, inflammatory bowel disease and previous stenting. Primary outcomes were anastomotic leakage, confirmed by clinical and radiological examination, and 30 day mortality. Secondary outcomes included length of operation, number of lymph nodes retrieved, medical complications and duration of hospital stay. All operations were performed or supervised by one of five consultants with experience in open and laparoscopic colorectal surgery.

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obesity in patients with colorectal cancer has previously been validated. A consultant radiologist reviewed these scans and calculated the area of VAT and SAT at a horizontal section halfway between the lower costal margin and upper margin of the iliac crest, using an AW Volumeshare 2 workstation (GE, UK) (Figure 1a). A 1 cm thick volume of data was selected and loading into the ‘reformat’ part of the software. The volume of voxels with an attenuation of between -190 and -30 was recorded for the whole section (Figure 1b). Voxels outside the abdominal cavity were then removed and the measurement repeated (Figure 1c). As this was a 1cm thick section, this ‘volume’ measurement was the same as the surface area. VAT was defined as intra-abdominal adipose tissue within the abdominal cavity. SAT was defined as adipose tissue external to the abdominal cavity. Total adipose tissue was calculated as the sum of VAT and SAT. BMI was calculated from data obtained from JANUS. CT examinations were performed using GE Lightspeed scanners (4 or 16 slice). The following parameters were used kV 120, mA 300, spiral acquisition, 2.5-5mm slice thickness, after oral and IV contrast at 60s.

Statistical Analysis

A preliminary analysis was performed to determine if any patient background characteristics or operative factors were independently associated with any of the fat parameters or surgical outcomes. Data were analysed using SPSS software, version 16. Fisher’s exact test was used to compare categorical variables. Mann-Whitney U test was used to compare observations from two groups. Linear regression was used to compare continuous variables. All continuous data are presented as mean (s.d.). p<0.05 indicated statistical significance.

RESULTS

The baseline characteristics, pathological findings and surgical procedures of the 54 patients included in the study are listed in Table...
Surgical results and post-operative outcomes are listed in Table 2. There were five anastomotic leakages (9.3%) after the following operations: two laparoscopic right hemicolectomies, one laparoscopic low anterior resection, one extended right hemicolectomy and one total colectomy with ileorectal anastomosis. All five leakages were diagnosed clinically with radiological confirmation. One patient was defunctioned with an end ileostomy and a mucous fistula. Another required an examination under anaesthesia (EUA) with rectal washout. One patient developed a leakage through the midline laparotomy wound and was managed conservatively with a wound manager and total parenteral nutrition (TPN). The other two patients were treated conservatively with antibiotics. Out of the 49 patients that did not develop leaks, 12 had temporary ileostomies.

There were three post-operative deaths (5.6%). One patient who had a low anterior resection developed atrial fibrillation followed by acute on chronic renal failure. The second patient had an anastomotic leakage after a laparoscopic right hemicolectomy, which was complicated by fatal bilateral pneumonia. The third patient underwent a laparoscopic high anterior resection but died from a massive pulmonary embolus secondary to deep vein thrombosis, despite stocking, calf compression and prophylactic heparin.

In our preliminary analysis, we investigated whether any patient or operative factors were associated with the individual fat parameters or post-operative outcomes. Older age was not significantly correlated with any of the four fat parameters, but was significantly associated with an increased risk of developing medical complications ($p=0.0071$). The male sex was significantly associated with a higher VAT ($p=0.001$), but not with any other fat parameter. Male sex was not an independent risk factor for leakage ($p=0.380$), nor any other post-operative outcomes. The method of access for operation was not significantly associated with any fat parameter, surgical result or post-operative outcomes. Risk of anastomotic leakage was not associated with age, sex or BMI. None of the four fat parameters were associated with increased operative time, and unlike Tokunaga et al., we did not find an association between any of the fat parameters and numbers of lymph nodes retrieved.

Visceral adipose tissue (VAT) ($p=0.0341$) was significantly associated with increased risk of anastomotic leakage (Figure 2), whereas subcutaneous adipose tissue (SAT), total adipose tissue (TAT) and BMI showed no significant relationship. In our study, we did not find any of the fat parameters to correlate with post-operative mortality, medical complications, or duration of hospital stay.
DISCUSSION

In this study of patients undergoing elective resectional surgery for colorectal cancer, including both laparoscopic and open procedures, raised VAT was associated with an increased risk of developing anastomotic leakage. This may be related to intrinsic patient factors and operative reasons. A higher VAT is associated with the development of metabolic syndrome, inflammation, oxidative stress, insulin resistance and atherosclerosis11-14 which could lead to poorer blood supply to the anastomosis and contribute to impaired wound healing. From a technical point of view, a patient with higher VAT and thicker mesentery may also make the operation more challenging and increase operating time.6,15,16

Although BMI has been widely used as a marker of obesity, it does not differentiate between SAT and VAT. There is increasing evidence that intra-abdominal obesity is more strongly associated with short-term outcomes following surgery than BMI6,9 and this is supported by our finding in our study that although there was a trend for increased BMI to be associated with anastomotic leakage, this was not found to be statistically significant (p=0.1065.)

Previous studies examining the relationship between visceral obesity and complications following colorectal surgery have attempted to use indirect markers of visceral adiposity, such as waist circumference.17 Other studies that directly measured VAT used patient groups had limited inclusion criteria, for example, laparoscopic sigmoid colectomies,8 or included both gastric and colorectal cancer patients.9 Furthermore, most studies that have examined the relationship between VAT and complications following colorectal surgery have been in Japanese patients, and the results of these studies may not necessarily be directly applicable to the Western population. Our study focused specifically on patients undergoing resectional surgery for colorectal cancer, both open and laparoscopic, which reflects the workload of everyday practice in the UK, and demonstrates that VAT can be calculated relatively simply using radiological images that would have been obtained as part of the cancer investigational pathway.

Although alternative radiological methods such as MRI18 and ultrasound19,20 have been used to calculate VAT, the use of CT is still the gold standard.21-23 Newer techniques such as bioelectrical impedance analysis (BIA) have also been tested which estimate body composition based on opposition of flow of electric current through the body, but they have been shown to be inadequate predictors of VAT, especially in patients with high SAT.24,25

Many Japanese studies use the level of the umbilicus (L4/L5 level) to measure the area of VAT.26-28 but this level has not been shown to be the best marker of obesity-related health risk.29 We found that using the umbilicus as a level to measure VAT was highly variable as many of our patients were obese with a pendulous abdomen. We therefore calculated the amount of VAT and SAT at a fixed horizontal section, namely halfway between the lower costal margin and upper margin of the iliac crest. However, for 8 patients, part of the subcutaneous fat had been excluded from the field of view of the examination by the performing radiographer. The amount of subcutaneous fat was therefore underestimated in these patients. This is a limitation of this retrospective study. Studies examining the effects of VAT on surgical outcome have so far calculated VAT area using a single slice. However, it is possible to calculate the total volume of visceral adipose tissue,30 but it remains to be seen if total volume is significantly better at predicting outcomes of the surgery than VAT area at a single level.

Prior to resectional surgery for colorectal cancer, patients may be risk stratified according to their VAT levels, with patients at high risk of developing anastomotic leakages being offered a temporary diverting stoma. It is worth noting that all patients that leaked in this study had a VAT >200 cm², so this could be considered as a potential threshold. The paradigm of a critical VAT threshold (CVATT) has been proposed for the metabolic syndrome and insulin resistance,31 and a similar threshold may be identified for anastomotic leakage. However, different patient populations may have different amounts of intra-abdominal adipose tissue. For example, whereas our study population had a mean VAT of 195.1 cm², Japanese patients have a mean VAT of 73.0 cm².6 Thus, different cut-off points for VAT in different populations may be required, much like how obesity in the West is defined as a BMI >30, but in Japan the threshold is >25.32

The implications of a raised VAT may be more far reaching than just predicting short term surgical outcomes. Raised VAT is associated with an increased number of dysplastic aberrant crypt foci33 and adenoma formation,34,35 as well as an increased risk of developing colorectal cancer9,36 and reduced rates of disease-free survival in patients following surgery for resectable colorectal cancer.37 The link between increased VAT and neoplastic development is not clear, but may involve decreased adiponectin levels27 and increased insulin resistance34,35 and this is consistent with studies linking the activation of the insulin-like growth factor-1 (IGF1) pathway38,39 with colorectal cancer. Raised VAT could also be used to predict response to drug therapy as patients presenting with metastatic colorectal cancer with a higher VAT had a poorer outcome when given first-line Bevacizumab treatment, compared to patients with a low VAT.40

Although this study consists of a heterogeneous population of patients undergoing elective resectional colorectal surgery, our aim was to examine the relationship between VAT and surgical complications in a sample of patients that is representative of the workload performed in colorectal surgery today. Despite the relatively small number of patients in this study, we have found that raised VAT is significantly associated with an increased risk of anastomotic leakage. If the five patients in this study with raised VAT who subsequently developed anastomotic leakage had a covering ileostomy formed at the time of the initial operation, this would have prevented their leaks. It would be interesting to assess the effects of VAT on different patient subpopulations and types of operations in a larger patient group. Further studies are warranted to assess whether pre-operative radiology may be used to identify and stratify high-risk patients who may benefit from a temporary diverting stoma.

DISCLOSURES

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REFERENCES

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