Relationship between computed tomography-derived body composition, sex and post-operative complications in patients with colorectal cancer

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Abstract

Introduction: In the UK, colorectal cancer is the fourth most common cancer and the second most common cause of cancer death. Surgery is the primary modality of treatment but is not without complications. Post-operative complications have been linked to pre-operative of weight loss and loss of lean tissue, and also to obesity. Given sex differences in body composition, an examination of body composition and post-operative complications may provide valuable information. Therefore, the aim was to examine the relationship between male/ female body composition and post-operative complications in patients with operable colorectal cancer.

Methods: Patients **(**n=741) undergoing operation for colorectal cancer were examined. Pre-operative CT scans were used to define the muscle mass and quality, visceral obesity and subcutaneous adiposity. Post-operative complications, in particular, surgical site infection (SSI) and wound infection (WI) were considered as outcome measures.

Results: Male patients with greater subcutaneous adiposity had higher risk of SSI and WI ($p<0.01$ and $p\leq0.001$ respectively). On multivariate analysis, Postoperative Glasgow Prognostic Score (poGPS) on Day4 (OR 2.11, 95% CI 1.53 -2.92, P =0.001) laparoscopic surgery (OR 0.50, 95% CI 0.26-0.98, P =0.044) and subcutaneous adiposity (OR 2.71, 95% CI 1.26-5.82, P =0.011) remained significantly independently associated with overall SSI. Subcutaneous adiposity remained significantly independently associated with WI (OR 3.93, 95% CI 1.33-11.57, P=0.013). In female patients, however, no significant association was found between any body composition measure and complications.

Conclusion: This study showed that increased subcutaneous and visceral adiposity were associated with infective complications in male, but not female patients, after colorectal

cancer surgery. Therefore, it is important that sex be taken into account when evaluating the potential impact of body composition on post-operative outcomes in patients undergoing surgery for colorectal cancer.

Keywords: body composition, visceral obesity, sarcopenia, colorectal cancer, post-operative complication, surgical site infection, wound infection.

Introduction

Colorectal cancer is a common cancer in the UK and a leading cause of cancer death worldwide(1). Although surgery is an important aspect of the treatment of colorectal cancer, large proportion of patients develop complications after surgery, in particular infective complications. Surgical site infection (SSI) accounts for approximately 20% of all cases (2). SSI has been defined by the Centre for Disease Control and Prevention (CDC) as a post-operative infection within 30 days of surgery. SSIs includes wound infection (WI) and anastomotic leakage (AL) and it is a major burden to health services worldwide (3,4).

There is good evidence that the post-operative systemic inflammatory response (SIR) is linked to the development of post-operative infective complications following colorectal cancer surgery. A post-operative systemic inflammation score was developed based on the combination of CRP and albumin level, termed the post-operative Glasgow Prognostic Score (poGPS). Indeed, concentrations of C-reactive protein (CRP) above 150 mg/L and albumin levels below 25g/L on post-operative days 3 and 4 were consistently reported to be associated with post-operative infectious complications. (25). Furthermore, body mass index (BMI), in addition to tumour site, mGPS, and ASA grade influence the magnitude of the PoGPS on days 3 and 4 (25).

Obesity is well-known risk factor for the development of colorectal cancer. (5). In fact, many patients on diagnosis are overweight or obese. Furthermore, the development of infectious complications following colorectal cancer surgery is associated with obesity (26). A systematic review by Malietzis and coworkers in 2015 concluded that there was consistent evidence that visceral obesity was associated with an increased incidence of post-operative complications and poorer short-term recovery (7).

Most of the studies that investigated the role of body composition and colorectal cancer outcomes have used Computed tomography (CT) scans since it is part of their routine staging (6,7,8). This technique is recognized to have good specificity and precision regarding body composition analysis (24). However, given that body composition varies with gender, it is not clear what aspect of body composition underpins the relationship between obesity and post-operative complications. Moreover, gender is associated with differences in survival (9). However, to our knowledge, the relationship between body composition and post-operative infective complications has not been previously examined according to gender. The aim of this study was to examine the relationship between body composition and post-operative complications in male and female patients undergoing surgery for colorectal cancer.

Patients and Methods

Patients:

A complete cohort of all patients with colorectal cancer who underwent surgical resection with curative intent between March 2008 and June 2016 in a single centre were identified from a prospective electronic database.

Those patients with a preoperative CT scan, recorded height and weight and reported post-operative complication were included. ASA grading and pre-operative haematological and biochemical markers were recorded. All tumors were staged according to TNM 5^{th} edition. Ethical approval was granted from the West of Scotland Research Ethics Committee.

Methods:

CT scans were obtained at single cross-sectional areas of third lumbar vertebrae (L3MA) (10). Patients with scans were taken more than 3 months prior to tsurgery were excluded from the study. The median and range for the interval between CT scanning and operation was 0.91 months (0.03-2.83). Scans with missing region of interest were excluded from the study. Each image was analysed using a program (NIH Image J version 1.47, http://rsbweb.nih.gov/ij/) (10).

The region of interest (ROI) measurements were taken of visceral fat (VFA), subcutaneous fat (SFA) (Figure 1), and skeletal muscle areas (SMA) (cm2) using standard Hounsfield Unit (HU) ranges (skeletal muscle -29 to +150, and adipose tissue -190 to -30) (Figure 2,3). These measurements were normalised for $height^2$ to produce indices; total fat index (TFI, cm^2/m^2), subcutaneous fat index (SFI, cm^2/m^2), visceral fat index (VFI, cm^2/m^2), and skeletal muscle index (SMI, cm^2/m^2). From the same ROI skeletal muscle radiodensity (SMD, HU) was measured.

Visceral obesity was defined as VFA >160cm^2 for men and >80cm^2 for women (22). High subcutaneous fat index (SFI) was defined as $\geq$50.0 cm^2 /m^2 in men and $\geq$42.0 cm^2 /m^2 in women (11). Sarcopenia was described by Caan and colleagues as an SMI<52.3 cm^2/m^2 if BMI<30kg/m^2 and SMI<54.3 cm^2/m^2 if BMI$\geq$30kg/m^2 in men and an SMI<38.6 cm^2/m^2 if BMI<30kg/m^2 and an SMI<46.6 cm^2/m^2 if BMI$\geq$30kg/m^2 in women (12). Myosteatosis was defined by SMD <41HU in patients with BMI <25kg/m^2 and <33HU in patients with BMI >25kg/m^2 (23).

Measurements were performed by two individuals (RD) and (AA) and inter-rater reliability was assessed in 40 patient images by interaclass correlation coefficients (ICCC) (TFA ICCC = 1.000, SFA ICCC = 1.000, VFA ICCC = 1.000, SMA ICCC = 0.998, SMD ICCC = 0.972).

BMI was classified: (underweight <20 kg/m^2, normal weight 20- 24.9 kg/m^2, overweight 25-29.9 kg/m^2, obese $\geq$30 kg/m^2)

Serum CRP (mg/L) and albumin (g/L) concentrations were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS was calculated as described previously (10). Preoperative neutrophil lymphocyte ratio (NLR) was calculated and values >5 were considered high.

Statistical analysis:

Categorical variables were analysed using χ^2 test for linear-by-linear association. The factors likely to influence SSI and WI were analysed using univariate and multivariate logistic regression analysis. Those body composition variables found to be significantly associated with overall SSI were entered into a multivariate model with other significant variables.

P values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

Results

In total, 832 patients with colorectal cancer were identified, and of these 91 were excluded due to missing eligible CT scan or anthropometric data. A total of 741 patients (410 males, 331 females) were analysed.

A comparison of baseline clinicopathological characteristics, host SIR, body composition and postoperative complications between male and female patients is shown in Table 1. There were no differences in clinicopathological characteristics and the SIR between male and female patients; mGPS and NLR (p=0.919 and p= 0.096 respectively). However, there were significant differences in body composition and in the development of post-operative complications. Specifically, more males had low subcutaneous adiposity compared to females (25% and 10% respectively, p<0.001), males had more sarcopenia compared with females (59% and 47% respectively, p<0.001), and had more myopenic obesity compared with females (10% and 5% respectively, p<0.001).

The relationship between body composition measures and complications in male patients is shown in Table 2. Male patients with high subcutaneous adiposity had a higher SSI rate and WI rate compared with those with low subcutaneous adiposity (p<0.01 and p≤0.001 respectively). Male patients with visceral obesity had a higher SSI rate compared with those with no visceral obesity (23% and 12% respectively, p<0.01) and had a higher WI rate compared with male patients with no visceral obesity (16% and 6% respectively, p<0.01). The WI rate in male patients with sarcopenia was less compared to those with no sarcopenia (9% and 19% respectively, p<0.01).

In male patients, the independent association of visceral obesity, sarcopenia and subcutaneous obesity with the SSI rate and the WI rate was examined in a binary logistic regression model (Table 3). On univariate analysis, age, TNM stage, PoGPS Day 3 and PoGPS Day 4, laparoscopic surgery, subcutaneous adiposity, visceral obesity and sarcopenia, were associated with SSI ($P<0.10$). On multivariate analysis, PoGPS Day4 (OR 2.11, 95% CI 1.53 -2.92, P =0.001) laparoscopic surgery (OR 0.50, 95% CI 0.26-0.98, P =0.044) and subcutaneous adiposity (OR 2.71, 95% CI 1.26-5.82, P =0.011) remained significantly independently associated with SSI.

On univariate analysis, age, ASA grade, TNM stage, PoGPS Day 3 and PoGPS Day 4 neoadjuvant therapy, laparoscopic surgery, subcutaneous adiposity, visceral obesity and sarcopenia, were associated with WI ($P<0.10$). On multivariate analysis, age (OR 0.57, 95% CI 0.37-0.90, p=0.015), TNM stage (OR1.45, 95% CI 1.01-2.09, p=0.043) PoGPS Day 3(OR 1.56, 95% CI 1.05 to 2.33, P=0.026), and subcutaneous adiposity (OR 3.93, 95% CI 1.33-11.57, P=0.013) remained significantly independently associated with WI.

The relationship between measures of body composition and complications in female patients is shown in Table 4. No significant association was found between any body composition measure and complications in female patients.The independed association between body composition and surgical site infection and wound infection in female patients with colorectal cancer presented in Table 5 as supplementary material.

Discussion

The results of this study clearly show that post-operative complication rate in obese patients with colorectal cancer was greater in males. In particular, subcutaneous adiposity in male patients was significantly associated with the development of surgical site infections and wound infections while in female patients there was no significant association. Therefore, the detrimental effect of obesity on post-operative complications would appear to be largely confined to male patients. This has implications for the post-operative management of obese patients with colorectal cancer.

The findings of this study may help to explain previous reports in large cohort studies that have observed that the occurrence of surgical site infection following surgery in males was approximately twice that in females (14). There are a number of potential mechanisms that may explain the consistent discrepancy in infective complication rates between males and females. Firstly, it may be that the surgical stress response differs between males and females. However, in the present study there was no significant difference in the magnitude of the post-operative systemic inflammatory response between male and female patients. Another plausible explanation is that sex hormones differently affect wound healing (14). However, in the present study being male or female per se was not associated with the development of infective complications. It may be that the differential impact of obesity in male and female patients on surgical site infective complications is due to the different distribution of adipose tissue in women and men (16). In particular, adipose tissue accumulate in the abdomen, the site of surgery in men, in contrast, in women the adipose tissue accumulate in thighs and hips. Fuente-Martín et al, (2013) showed that these differences are not limited to the distribution and amount of fat tissue, but also the metabolic response and function of adipose tissue differs between male and female. Specifically, males had increased proinflammatory immune cells in subcutaneous adipose tissue. They also have greater macrophage infiltration of subcutaneous adipose tissue (16). Indeed, BMI defined obesity is independently associated with a greater magnitude of the post-operative SIR, (poGPS). Taken together these differences may result in males being more prone to post-operative infective complications.

Previous studies have linked skeletal muscle wasting with post-operative infection, high recurrence rates, and poorer outcomes in cases of colorectal cancer. (11,17,18). Furthermore, Ebadi et al, (2017) reported that the longest survival was observed in sarcopenic patients with high subcutaneous adiposity (11). However, in our study we found that sarcopenic men had a lower wound infection rate, and this may be due to less subcutaneous fat tissue and therefore more favourable wound mechanics. Indeed, high subcutaneous adiposity at wound site has been reported to have reduced oxygenation compared with normal-weight patients, thus slowing the healing process and increasing susceptibility to infections (19). Decreased oxygen circulation increases the risk to surgical site infections, since wound healing requires high metabolic demands. In addition, immune cells have high oxygen demands, requiring oxygen for the formation of reactive oxygen species (20)

The main limitation of this study that it was retrospective, with patients identified from the electronic database. Therefore, body composition analysis was carried out only on those patients that had height, weight and a pre-operative CT available for analysis. A strength of the present study is that it is one of the largest studies to date examining the impact of body composition on post- operative outcomes in colorectal cancer.

In summary, the present study shows that obesity, in particular high subcutaneous adiposity and visceral obesity, was associated with the risk of SSI in men but not in women following colorectal cancer surgery. This should be taken into account for obese men undergoing such surgery since it may impact on greater length of hospital stay and requirement for clinical resources.

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Author contribution is as follows: AA, DM and CE designed research; AA, RD, SM and PH collect the data; AA and DM analyzed data and interpretation; AA wrote the paper; DM and CE manuscript editing; AA, CE and DM had responsibility for final content. All authors read and approved the final manuscript

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Figure legends

Figure 1. Body composition profile on a CT image at level of L3 vertebra. Reproduced from (24)