Myosteatosis is associated with poor physical fitness in patients undergoing hepatopancreatobiliary surgery

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Abstract

Background: Body composition assessment, measured using single computed tomography (CT) slide at L3 level, and aerobic physical fitness, objectively measured using cardiopulmonary exercise testing (CPET), are each independently used for perioperative risk assessment. Sarcopenia (i.e. low skeletal muscle mass), myosteatosis (i.e. low skeletal muscle radiation attenuation) and impaired objectively measured aerobic fitness (reduced oxygen uptake) have been associated with poor post-operative outcomes and survival in various cancer types. However, the association between CT body composition and physical fitness has not been explored. In this study, we assessed the association of CT body composition with selected CPET variables in patients undergoing hepatobiliary and pancreas surgery.

Methods: A pragmatic prospective cohort of 123 patients undergoing hepatobiliary and pancreas surgery were recruited. All patients underwent preoperative CPET. Preoperative CT-scans were analysed using a single CT-slice at L3 level to assess skeletal muscle mass, adipose tissue mass and muscle radiation attenuation. Multivariate linear regression was used to test the association between CPET variables and body composition. Main outcomes were oxygen uptake at anaerobic threshold ($\dot{V}O_2$ at AT), oxygen uptake at peak exercise ($\dot{V}O_2$ peak), skeletal muscle mass and skeletal muscle radiation attenuation (SM-RA).

Results: Of 123 patients recruited (77 males (63%), median age 66.9± 11.7, median BMI 27.3± 5.2), 113 patients had good quality abdominal CT-scans available and were included. Of the CT-body composition variables, SM-RA had the strongest correlation with $\dot{V}O_2$ peak (r = 0.57, p <0.001) and $\dot{V}O_2$ at AT (r = 0.45, p <0.001) while skeletal muscle mass was only weakly associated with $\dot{V}O_2$ peak (r = 0.24, p <0.010). In multivariate analysis, only SM-RA was associated with $\dot{V}O_2$ Peak (B = 0.25, 95%-CI 0.15-0.34, p <0.001, R^2 = 0.42) and $\dot{V}O_2$ at AT (B = 0.13, 95%-CI 0.06-0.18, p <0.001, R^2 = 0.26).

Conclusions: There is a positive association between preoperative CT SM-RA and preoperative physical fitness ($\dot{V}O_2$ at AT and at Peak). This study demonstrates that myosteatosis, and not sarcopenia, is associated with reduced aerobic physical fitness. Combining both myosteatosis and physical fitness variables may provide additive risk stratification accuracy and guide interventions during the perioperative period.

Keywords: Body composition, cardiopulmonary exercise testing, physical fitness, sarcopenia, myosteatosis, oxygen uptake.

Background

Despite improvement in surgical techniques, multimodal cancer therapies and perioperative care, morbidity and mortality after major hepatobiliary and pancreas (HPB) cancer surgery still pose substantial challenges. Accurate perioperative risk assessment prior to major cancer surgery is not personalised and is still substantially variable in the precision of outcome prediction. Identifying patients who are at risk of poor outcomes is a priority in order to facilitate shared decision making, inform prehabilitaion and co-morbidity management initiatives before surgery, and guide intra- and post- operative care. Various scoring systems exist for the risk stratification of these patients, however few are objective. The importance of objectively measured aerobic physical fitness (using cardiopulmonary exercise testing - CPET) [1] and objectively defined body composition variables such as sarcopenia [2–5] or myosteatosis [6] (using routinely performed abdominal computer tomography (CT) scanning) as major contributors to poor post-operative outcomes and death have so far been studied separately.

Cardiopulmonary exercise testing (CPET) provides an objective assessment of physical fitness through evaluating cardio-respiratory function under the stress of exercise mimicking the stress of major surgery. This has been widely adopted in the UK as a pre-operative test to objectively evaluate perioperative risk [7] and international guidelines for CPET conduct have recently been published [8]. The ability of CPET to identify patients at risk of poor outcomes is used clinically to guide perioperative care and clinical decision-making, as well as informs the shared-decision making process [1,9]. We have previously reported that selected CPET variables such as oxygen uptake at estimated lactate threshold or anaerobic threshold ($\dot{V}O_2$ at AT) and at peak exercise ($\dot{V}O_2$ peak) are associated with worse outcome following colorectal surgery [10–12] and neoadjuvant cancer treatments [13,14]. Poor physical fitness is highly prevalent in HPB cancer patients and associated with poor post-operative outcomes and survival [15–19].

Body composition analysis using a single slice CT at the third lumbar vertebra (L3) is strongly correlated with total body skeletal muscle mass [20]. The area of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) can also be accurately estimated using this methodology. In addition, CT scans contain information about the radio density of a specific tissue type in Hounsfield units (HUs), which is referred to as radiation attenuation. Low muscle radiation attenuation is considered a surrogate of increased intramyocellular triglycerides, increased water content (i.e. muscle oedema), change in muscle structure, and dysregulated host systemic inflammatory response [21–23]. A recent review showed that skeletal muscle radiation attenuation, referred to as myosteatosis (SM-RA), is highly prevalent in cancer patients [23]. Sarcopenia and myosteatosis have been found to be independent prognostic factors of reduced survival and poor outcome after surgery or neoadjuvant treatments in various cancers including pancreas [4,24], colorectal [25,26], gastric [27], esophageal [28,29] and ovarian [30]. This relationship was less evident in colorectal liver metastasis patients [31–34]. It is hypothesized that changes in muscle tissue composition such as low SM-RA (myosteatosis) results in diminished muscle function phenotypically expressed as poor resilience that may potentially be reversed by improving activity levels or exercise interventions [5,35]. Therefore, low SM-RA is often reported as an indicator of “poor muscle quality”. However, the association between low skeletal muscle radiation attenuation and physical fitness has not previously been evaluated. We therefore aimed to assess the association of low skeletal muscle radiation attenuation (i.e. myosteatosis), low skeletal muscle mass (i.e. sarcopenia) and selected CPET variables (i.e. aerobic physical fitness) in a representative HBP population.

Methods

Subjects and data collection

All consecutive patients undergoing CPET and HPB surgery between January 2014 and January 2018, at the University Hospitals Southampton NHS Foundation Trust HPB Unit, UK were included in a prospective cohort and were eligible for inclusion. The study was reviewed and approved by the South East Scotland Research Ethics Committee (16/SS/0188) and is registered with clinicaltrials.gov (NCT03641118). All patients had a histological or radiological diagnosis of operable liver metastases (melanoma, colorectal, breast), periampullary carcinoma, hepatocellular carcinoma or benign disease necessitating major liver or pancreas resections. A minority of patients underwent neoadjuvant cycles of Capecitabine and Oxaliplatin prior to colorectal liver metastasis surgery. This represented a pragmatic prospectively collected patient cohort reflecting a busy tertiary HPB referral centre. All patients underwent CPET before surgery. Body composition was assessed using a pre-operative single computer tomography (CT) slice at the level of the third lumbar vertebra (L3). Patients without a good quality preoperative abdominal CT-scan were excluded. CT-scans were defined as poor quality if they had large radiation artefacts or profound muscle oedema. Preoperative plasma levels of haemoglobin, creatinine, albumin, and C-reactive protein (CRP) were assessed within 7 days of the planned surgery. The albumin and CRP levels were used to calculate the modified Glasgow Prognostic Score (mGPS) (36). Additional data collection included: sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, type of surgery, and histopathology diagnosis. Primary outcomes were $\dot{V}O_2$ at AT and $\dot{V}O_2$ peak ($ml.kg^{-1}.min^{-1}$). Secondary outcomes included one-year all cause mortality and length of hospital stay; both were measured from day of surgery.

Cardiopulmonary Exercise Testing (CPET)

CPET was conducted according to standardised methods published elsewhere by the Perioperative Exercise Testing and Training Society and endorsed by the Association of Respiratory Technology and Physiology (ARTP) in the UK [8]. In short, after resting spirometry (flow–volume loops), CPET on an electromagnetically braked cycle ergometer (Ergoselect 200; Ergoline, Bitz, Germany) comprised 3min resting (to allow gas exchange variables to stabilize), 3 min freewheel pedaling, and then a ramped incremental protocol until volitional termination followed by 5 min recovery data collection. Ventilation and gas exchange were measured using a metabolic cart. Heart rate, full disclosure 12-lead ECG, blood pressure and pulse oximetry were monitored throughout. Ramp gradient was based on a calculation using predicted freewheel $\dot{V}O_2$, predicted $\dot{V}O_2$ peak, height and age with the aim of achieving a 10 minutes ramp stage. All CPETs were analysed by experienced accredited perioperative CPET practitioners (DL/ME) who were blinded to CT-scan variables and clinical outcome variables.

CT-scan analysis

The preoperative CT-scan performed nearest to the date of surgery was selected for analysis (max 4 weeks before surgery and after completion of neoadjuvant chemotherapy). Abdominal CT-scans were analysed in an anonymized and blinded format by one researcher trained in body composition analysis (DVD) as described before [24]. Briefly, a single CT-slice at the level of the third lumbar vertebra (L3) was selected. CT-scans were assessed with sliceOmatic 5.0 (Tomovision, Magog, Canada) for Microsoft Windows®. Using predefined Hounsfield unit (HU) ranges, the cross-sectional areas (cm^2) of skeletal muscle (SM, -29 to 150 HU), visceral adipose tissue (VAT, -150 to -50 HU), and subcutaneous adipose tissue (SAT, -190 to -30 HU) were assessed. The cross-sectional area was then adjusted for height squared to calculate the L3-index (cm^2/m^2), which is strongly correlated with total body skeletal muscle and adipose tissue mass [20]. In addition, the average radiation attenuation (RA) in HU was assessed for all tissues (SM-RA, VAT-RA, and SAT-RA). A low radiation attenuation is associated with increased tissue triglyceride content [23]. Analyses were blinded to CPET and outcome variables.

Statistical analysis

Data were analysed using IBM SPSS statistics 23 for Microsoft Windows. Continuous data were compared using an independent t-test, the Mann-Whitney-U test was used for non-parametric variables and the chi-squared test was used for categorical variables. As the cohort size was too small for cut-point finding approaches such as optimum stratification, gender-specific cut-points were set at the median for each CT body composition and CPET variable [37]. The association of body composition and other clinical variables on CPET derived $\dot{V}O_2$ at AT and $\dot{V}O_2$ peak were assessed using linear regression. First, all clinical variables were tested separately in an unadjusted univariate model (model 1). Then, variables were ordered from lowest to highest p-value from model 1 and were added one-by-one to the multivariate linear regression model (model 2). After each addition, an F-test was performed to test wither the added variables significantly improved the model fit. If the F-test p-value was <0.05 the variable was kept in the model, otherwise it was removed. **Univariate and multivariate cox-regression and logistic regression were used for respectively overall survival and 1-year survival. Variables with a p<0.1 in univariate analysis were included into the multivariate analysis.** For correlations, Pearson's correlation coefficient was used (*r*) for normally distributed data and the Spearman correlation coefficient (r_s) for non-normally distributed data.

Results

Patients

One-hundred-and-twenty-three patients were included during the study. Liver resections consisted of liver metastases (39 patients; 1 benign; 15 neoadjuvant chemotherapy), hepatocellular carcinoma (5 patients) and other major liver resections (median 2 liver segments resected; 15 patients; 9 patients benign). Pancreas resections consisted of pancreatic neoplasms (29 patients; 5 benign), ampullary carcinoma (16 patients), cholangiocarcinoma (16 patients; 3 benign), intraductal papillary mucinous neoplasm (3 patients). Ten patients were excluded for CT-scan analysis because they did not have a suitable preoperative CT-scan available. Patient characteristics are shown in table 1, including the distribution among skeletal muscle mass, SM-RA and the main CPET parameters split into high and low groups at the gender specific medians for males and females respectively; Skeletal muscle mass: 50.7 cm^2/m^2 and 38.4 cm^2/m^2, SM-RA: 37.1 HU and 30.4 HU, $\dot{V}O_2$ at AT: 9.4 $ml.kg^{-1}.min^{-1}$ and 9.3 $ml.kg^{-1}.min^{-1}$, and $\dot{V}O_2$ peak 16.0 $ml.kg^{-1}.min^{-1}$ and 14.3 $ml.kg^{-1}.min^{-1}$. Patients with low skeletal muscle mass, SM-RA, low $\dot{V}O_2$ at AT and low $\dot{V}O_2$ peak were significantly older. No significant differences could be detected in body composition or fitness variables when comparing benign vs. malignant or liver vs. pancreas groups. Significantly lower haemoglobin was seen in the low $\dot{V}O_2$ at AT and $\dot{V}O_2$ peak groups, however no difference was found in skeletal muscle mass and SM-RA. No significant differences could be detected in CRP, GPS and white cell counts. However, there were weak correlations between SM-RA and both acute phase proteins CRP (r_s = -0.22, p = 0.02) and albumin (r_s = 0.19, p = 0.04).

All 123 patients underwent CPET of which six patients were not able to achieve an anaerobic threshold (all six deceased at 1-year follow-up). No CPET related adverse events occurred. For both CT and CPET assessments there were significant differences between genders. In short, males had higher SM (p<0.001), VAT (p<0.001), SM-RA (p=0.001), and SAT-RA (p=0.048) while females had higher SAT (p<0.001), see figure 1. For CPET results, males had higher $\dot{V}O_2$ at AT (p<0.001), oxygen pulse ($\dot{V}O_2$/HR) at AT (p<0.001), ventilatory equivalent for carbon dioxide at AT ($\dot{V}_E/\dot{V}CO_2$ at AT) (p<0.001), work rate at AT (p<0.001), $\dot{V}O_2$ peak in $L.min^{-1}$ (p<0.001), $\dot{V}O_2$ peak adjusted for weight (p=0.033), $\dot{V}O_2$/HR at peak (p<0.001), and work rate at peak (p<0.001). Table 2 shows gender-specific comparisons for all CPET variables according to skeletal muscle radiation attenuation. Weight adjusted $\dot{V}O_2$ at AT for males (p=0.019) but not for females (p>0.05) was significantly higher in the high

SM-RA group. Weight adjusted $\dot{V}O_2$ peak was higher in the high SM-RA grouped for both males and females (males p=0.002; females p=0.008). A higher work rate at AT and peak were also seen in both groups at high SM-RA values, with significant differences in females (AT p=0.030 and peak p=0.016). Furthermore, a significantly lower $\dot{V}_E/\dot{V}CO_2$ slope for both males and females (males p=0.014 and females p=0.005) and $\dot{V}_E/\dot{V}CO_2$ at AT and peak (p=0.018 and p=0.025) for males was observed in the higher SM-RA groups.

Relationship between CT body composition and CPET variables

Univariate and multivariate linear regression results are shown in table 3. Of the CT body composition parameters, SM-RA had the strongest association with both weight adjusted $\dot{V}O_2$ at AT and $\dot{V}O_2$ peak in univariate analysis (R^2 = 0.20 and 0.33 respectively; correlations: r = 0.45 and 0.57 respectively, p<0.001, figure 2). Skeletal muscle mass only showed a weak association with $\dot{V}O_2$ peak (R^2 = 0.06; correlation: r = 0.24, p = 0.010). Other significant variables in univariate analysis were age, BMI, ASA > 2, VAT and SAT. However, in multivariate analysis only SM-RA and age were added to the model since adding additional variables did not result in a significant F change (p>0.05). In multivariate analysis, SM-RA was significantly associated with both weight adjusted $\dot{V}O_2$ at AT (B = 0.12, 95%-CI 0.06-0.18, p<0.001, R^2 = 0.26) and $\dot{V}O_2$ peak (B = 0.25, 95%-CI 0.15-0.34, p<0.001, R^2=0.42), see table 3. Other body composition variables such as sarcopenia were excluded from the model after the addition of age.

Overall survival, mortality, and length of hospital stay

Low weight adjusted $\dot{V}O_2$ peak was associated with increased one-year mortality (21% vs. 8%, p=0.045) and increased length of hospital stay (13.9 ± 11.0 days vs. 10.6 ± 9.3 days, p=0.048) **in univariate analysis (see table 1). One patient (<1%) died within 30-days and 3 patients (2%) within 90-days (all will low SM-RA). However, in multivariate analysis there was only a trend (odds ratio**

2.99, 95%-CI 0.92-9.74, p-0.070). In multivariate cox-regression analysis there was also a trend for low weight adjusted $\dot{V}O_2$ peak and overall survival (hazard ratio (HR) 2.10, 95%-CI 0.98-4.51, p=0.056). As there was an association between $\dot{V}O_2$ peak and SM-RA we wanted to test whether a combination of low physical performance and myosteatosis would be a better predictor of overall survival and mortality. We therefore identified three patient phenotypes based $\dot{V}O_2$ peak and SM-RA: 1) high $\dot{V}O_2$ peak, 2) low $\dot{V}O_2$ peak only, and 3) low $\dot{V}O_2$ peak and myosteatosis (low SM-RA). Indeed, patients with both low $\dot{V}O_2$ peak and myosteatosis had significantly lower survival in multivariate cox-regression analysis (HR 2.42, 95%-CI 1.04-5.63, p=0.040), see table 4. There was no significant association with one-year mortality. The only other variable associated with lower survival was an elevated mGPS (≥1) (HR 2.37, 95%-CI 1.14-4.93, p=0.021).

Discussion

In this study, myosteatosis (low skeletal muscle radiation attenuation) was associated with reduced fitness ($\dot{V}O_2$ at AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$ slope) in both males and females while sarcopenia (low skeletal muscle mass) was not. SM-RA was associated with both weight adjusted $\dot{V}O_2$ at AT and $\dot{V}O_2$ peak in multivariate analysis. **Furthermore, combining low $\dot{V}O_2$ peak with myosteatosis (low SM-RA) was found to be a better predictor of overall survival than low $\dot{V}O_2$ peak or low SM-RA alone. Additionally, an elevated modified Glasgow Prognostic Score was associated with lower overall survival.** These novel finding demonstrates that CT-derived skeletal muscle radiation attenuation data are not only associated with skeletal muscle structure but also with skeletal muscle functioning.

Sarcopenia in a cancer population is multifactorial, and whilst tumour burden may be one of the contributing factors, poor physical fitness is a major factor. In addition, several studies in HPB populations demonstrated that particularly myosteatosis is associated with poor overall survival and increased surgical complications [24,38,39]. In the present study, the relationship between similar body composition and survival was not observed, as the present cohort was too heterogeneous for survival analysis. The approach of using a heterogeneous cohort provided a pragmatic snap-shot capture of the HBP patient population that lends itself easily to external validation in other patient cohorts. In a series of 1473 consecutive patients with lung and abdominal cancer, the presence of low SM-RA was a significant negative predictor. These were corroborated in a study by Rollins *et al.* [40] where the prevalence of myosteatosis in patients with unresectable pancreaticobiliary cancers was found to be 55.3%. Furthermore, myosteatosis but not sarcopenia was significantly associated with a reduction in overall survival and systemic inflammation. In the present study we were able to link myosteatosis with a high BMI and low fitness, but only found a weak correlation between myosteatosis and both CRP and albumin levels.

Although the relationship between myosteatosis, sarcopenia, and poor fitness was assumed, no study had ever set out to test this hypothesis. Interestingly, we observed that sarcopenia was only significantly associated with weight adjusted $\dot{V}O_2$ peak in univariate analysis but was excluded from the multivariate model after addition of age, suggesting the association was age-related rather than disease-related. In addition, while sarcopenia can be a result of muscle loss that occurred over time, a single time point assessment of a patients' muscle mass was previously shown not to be associated with actual muscle loss over time [30]. Indeed, skeletal muscle mass at a single timepoint is also affected by age, sex, race, build as well as disease, hence might not fully correspond with muscle strength/function [41]. Myosteatosis on the other hand, was associated with reduced fitness ($\dot{V}O_2$ at AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$ slope) in both multivariate analyses. Myosteatosis is generally regarded as the result of a pathologic process involving systemic inflammation and insulin resistance in disease states such as cancer cachexia or obesity [23]. Skeletal muscle insulin resistance, redox dysfunction and oxidative stress are associated with decreased glucose uptake and mitochondrial dysfunction, possibly leading to decreased muscle function and fitness [42–44].

Lack of physical activity and fitness is a major modifiable risk factor of ill-health [45] and premature death. There is a large epidemiological body of evidence supporting the notion that physical fitness has benefits in almost every context of health and disease, advocating better outcomes for fitter people [46]. Furthermore, physical *inactivity* is one of the leading public health issues we face [47,48] and its association with cancer risk is quite clear [49]. The biological bases underlying the associations between physical activity, fitness and cancer risk are incompletely defined [50]. The reliability and predictive value of perioperative objectively measured physical fitness using CPET in cancer patients is well established [1,51,52], with emerging evidence in pancreatic and hepatobiliary cohorts [15,18,19,53]. In this study we found that $\dot{V}O_2$ peak was the strongest predictor of adverse outcome (1-year mortality and length of hospital stay). **Combining CPET with CT data could provide a better prediction of clinical outcome compared with either of them alone, as we found that patients with both low $\dot{V}O_2$ peak and myosteatosis had significantly lower overall survival while low $\dot{V}O_2$ peak only was not significantly associated with overall survival.** Evidence of a higher physical activity and fitness after a cancer diagnosis and its treatments has been shown to reduce perioperative risk, improve quality of life and postoperative outcomes including survival [11,13,14,50,54,55].

Such data raise the obvious hypothesis: Can health outcomes be improved by peri-operative interventions targeted at improving body composition and physical fitness? Body composition and fitness modulation as a concept in surgical risk prediction is attractive due its potential reversibility. In elective surgical patients, there is a small window of opportunity from contemplation of surgery and tumour staging to the date of surgery. Tailored programmes during this period should be multi-faceted and targeted at individual patients' needs. A combination of strategies targeting poor muscle function, reduced physical fitness, secondary anorexia, inflammation, psychological health and poor nutrition have been suggested in the context of multimodal prehabilitation prior to cancer and major intra-abdominal surgery [56–61]. A large body of evidence exists utilising exercise to reverse loss of muscle mass and strength with ageing [62]. In addition, physical exercise improves muscular strength and ameliorates systemic inflammation in cancer patients [63]. Evidence relating to improving fitness with exercise in the perioperative period is also gaining momentum. Whilst reduced length of stay, post-operative morbidity and critical care dependency has been observed in cardiothoracic [64] patients undergoing prehabilitation programmes, there are limited data examining its subsequent impact on post-operative outcomes following abdominal surgery [59,65,66]. Moreover, understanding the underlying molecular mechanisms of muscle loss, interrogating distinct muscle phenotypes [67] and their relationship to cancer surgery morbidity and survival is urgently needed. This is key to inform the development of interventions and treatment strategies to mitigate against poor outcomes [35].

In conclusion, we found that myosteatosis and not sarcopenia (assessed by CT-scan) was associated with physical fitness (assessed with CPET) in a surgical HPB population. These data suggest that simple and fast analysis of myosteatosis on a single slice CT image provides information (albeit limited) on the patients' physical fitness. CT body composition combined with objectively measured fitness (CPET) might provide additive risk stratification benefits and guide personalised multimodal interventions during the perioperative period.

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Figure titles and captions

Figure 1 Gender-specific CT body composition

Boxes represent median and inter-quartile range. Whiskers are set at either the 25th or 75th percentile + 1.5 times the inter-quartile range (Tukey method). Dots represent outliers. * Significant p-value <0.05. CT=computed tomography, RA = radiation attenuation, SAT = subcutaneous adipose tissue, SM = skeletal muscle, VAT = visceral adipose tissue

Figure 2 Correlations and regression plots of skeletal muscle radiation attenuation with $\dot{V}O_2$ at AT ($ml.kg^{-1}.min^{-1}$) and $\dot{V}O_2$ peak ($ml.kg^{-1}.min^{-1}$)

Five patients did not reach their anaerobic threshold, these patients were excluded from this analyses. HU = Hounsfield unit, SM-RA = skeletal muscle radiation attenuation