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Original article

The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma

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SUMMARY

Background & aims: Patients with pancreatic cancer have a poor prognosis, are often cachectic, and frequently demonstrate features of systemic inflammation, which may contribute to the phenomenon of myosteatosis. Analysis of body composition from CT scans has been used to study sarcopenia and its association with prognosis in a number of types of cancer, particular in combination with obesity. It has also been suggested that myosteatosis, defined as attenuated mean skeletal muscle Hounsfield units (HU), is associated with reduced survival in cancer. This study aimed to assess the association between body composition (sarcopenia and myosteatosis) and outcome in patients with unresectable pancreatic cancer.

Methods: All patients diagnosed with unresectable pancreatic cancer at Nottingham University Hospitals NHS Trust between 2006 and 2013 were considered for the study. A total of 228 patients were included retrospectively. Body composition was assessed using cross-sectional CT analysis to calculate a skeletal muscle index (SMI) for sarcopenia and use mean skeletal muscle HU for myosteatosis.

Results: The prevalence of sarcopenia in the whole patient group at baseline was 60.5% (138/228). Overall, patients who were sarcopenic had no significant difference in overall survival versus those who were not ($p = 0.779$). However, patients who were overweight/obese and sarcopenic had a significantly lower survival ($p = 0.013$). Of the 58 patients who were overweight or obese and sarcopenic, 32 were also myosteatotic. The prevalence of myosteatosis overall at baseline was 55.3% (126/228) and this was associated with significant reduction in overall survival ($p = 0.049$). Univariate Cox regression revealed myosteatosis but not sarcopenia to be predictive of reduced survival, however this relationship was lost on multivariate testing. Myosteatosis was associated with significantly greater levels of systemic inflammation (white cell count, neutrophil-lymphocyte ratio and C-reactive protein), anaemia and worsening of baseline blood urea. This relationship was not seen with sarcopenia.

Conclusions: This is the largest study on the association between body composition and survival in patients with unresectable pancreatic cancer and has shown that although sarcopenia alone did not have a bearing on survival, the presence of myosteatosis was associated significantly with the presence of systemic inflammation and reduced survival.

Abbreviations: CRP, C-reactive protein; CT, computed tomography; DICOM, digital imaging and communications in medicine; ESR, erythrocyte sedimentation rate; HU, Hounsfield units; NLR, neutrophil–lymphocyte ratio; SMI, skeletal muscle index; WHO, World Health Organisation.

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1. Introduction

Pancreatic ductal adenocarcinoma and distal cholangiocarcinoma are aggressive types of cancer with overall 5-year survival rates of less than 5%. The 5-year survival for patients treated with surgical resection is 4–8% and most patients with unresectable disease die within 9–15 months of diagnosis [1,2].

Pancreatic ductal adenocarcinoma is associated with both local and systemic inflammation, with previous studies demonstrating increased resting energy expenditure, most pronounced in those with increased acute phase response [3]. As a consequence, the prevalence of sarcopenia, severe weight loss [4] and cancer cachexia in this frail patient cohort is high [5], which is linked in part to poor survival [6,7]. Analysis of body composition from CT scans has been used to document the prevalence of both sarcopenia and myosteatosis and their association with prognosis in a number of different types of cancer [8–16].

Sarcopenia refers to a decrease in muscle mass, and resultant low muscularity which is quantifiable using cross sectional imaging [17]. CT-based cut-offs for the definition of sarcopenia have previously been established using regression equations from a heterogeneous group of cancer patients [11,16]. Sarcopenia is associated with poor clinical outcomes including increased risk of infection, loss of function and increased mortality [18]. In addition, sarcopenic patients have an increased risk of chemotherapy-related toxicity [8–10]. Recent evidence, however, has suggested that the relationship between sarcopenia and cancer outcomes may be mostly relevant in overweight or obese patients [12]. However, other studies have suggested that sarcopenia may not have a bearing on clinical outcome [18,19].

Myosteatosis is the process of infiltration of lipid into both the inter- and intramyocellular compartments [20,21] and can be estimated by the attenuation of skeletal muscle Hounsfield units (HU) on CT scanning. The conventional lower cut off for the normal attenuation of skeletal muscle is 30 HU [21,22], which is estimated to be two standard deviations below the mean skeletal muscle HU of young healthy people. There are a range of factors associated with attenuated muscle density including obesity [23], increasing age [24], male gender [25], type 2 diabetes mellitus [26], inactivity [27] and malignancy. Myosteatosis has also been linked to the host systemic inflammatory response [28], particularly neutrophil–lymphocyte ratio (NLR) in patients with colorectal cancer, but this relationship is not yet understood fully. Attenuated skeletal muscle density is prognostic of reduced survival independently in patients with malignancy of the lung and gastrointestinal tract [29].

The aims of this retrospective study, examining the role of measures of body composition in patients with unresectable pancreatic cancer and distal cholangiocarcinoma, were to examine the relationship between sarcopenia, myosteatosis, markers of systemic inflammation and survival.

2. Methods

All patients diagnosed with unresectable pancreatic ductal adenocarcinoma and distal cholangiocarcinoma managed at Nottingham University Hospitals NHS Trust between 2006 and 2013 were considered for the study. Patients with at least one abdominal CT scan taken at diagnosis and available for analysis were included. For patients in the palliative chemotherapy (gemcitabine-based throughout the duration of the study) group, a follow-up CT after commencement of chemotherapy, at a minimum of 60 days after the baseline CT, was also analysed. Blood results from within a week of the initial diagnostic CT scan were also collated. Patients with ampullary and duodenal carcinomas, neuroendocrine tumours or gastrointestinal stromal tumours were excluded. All patients had a diagnosis of cancer based upon histology and/or cytology; however, the precise tumour type (pancreatic ductal adenocarcinoma or distal cholangiocarcinoma) was not always known. Patient data were extracted from the electronic records of the Nottingham Information System and recorded by an investigator with no involvement in patient care. Missing data on patient height and weight were obtained from review of hospital case notes and data on survival by contacting the patients' General Practitioners. The conduct of the study was approved by the audit department of Nottingham University Hospitals and the need to obtain informed consent from patients was waived.

2.1. Body composition analysis

Electronic copies of CT scans taken routinely for clinical reasons were obtained from the hospital Picture Archiving and Communication System. Once accessed, the scans were anonymised, and one CT image slice at the third lumbar vertebra (L3) level was selected in Digital Imaging and Communications in Medicine (DICOM) format. The images were analysed by a single trained investigator using SliceOmatic 5.0 software (TomoVision, Montreal, Canada) to calculate the surface area of the specific tissue types: skeletal muscle tissue, visceral adipose tissue and subcutaneous/intramuscular adipose tissue. Within the L3 region are the following muscles: psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques and rectus abdominus.

SliceOmatic software relies on the variation in radiodensity of the different tissue types to identify and, thereby, quantify the surface area of the tissue present. The different tissue radiodensities are represented by specific HU thresholds: −29 to +150 for skeletal muscle [13], −150 to −50 for visceral adipose tissue [14] and −190 to −30 for subcutaneous and intramuscular adipose tissue [15]. Once the tissues were identified, the cross-sectional surface area (cm^2) of each tissue was calculated by the software [9]. Any change in tissue area was expressed as absolute change (cm^2). The mean HU measurement of all skeletal muscle within the L3 cross-section was recorded as a measure of myosteatosis, which was defined operationally as a mean skeletal muscle radiodensity of <33 HU in those with a BMI ≥25 and <41 HU in those with a BMI < 25 across the axial orthogonal view [29].

These data were used to estimate whole body stores of fat-free mass (FFM) and fat mass (FM) using regression equations [16] as follows:

$$\text{Total body fat-free mass (FFM) (kg)} = 0.3 \times \left[\text{skeletal muscle area at L3 } \left(cm^2\right)\right] + 6.06$$

$$\text{Total body fat mass (FM) (kg)} = 0.042 \times \left[\text{total adipose tissue area at L3 } \left(cm^2\right)\right] + 11.2$$

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