The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review

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Short title
Computed tomography to determine body composition and the influence of muscle mass on clinical outcome in abdominal malignancies

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Conflict of interest
The authors declare no conflict of interest.

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Abstract

Background
It is estimated there were 3.45 million new cases and 1.75 million deaths from cancer in Europe in 2012. Colorectal cancer was one of the most common, accounting for 13% of new cases and 12.2% of all deaths. Conditions causing reduced muscle mass, such as sarcopenia, can increase the morbidity and mortality of people with cancer. Computed tomography (CT) scans can provide accurate, high quality information on body composition including muscle mass. To date, there has been no systematic review on the role of CT scans in identifying sarcopenia in abdominal cancer. This review aimed to examine the role of CT scans in determining the influence of reduced muscle mass on clinical outcome in abdominal cancer.

Methodology
A systematic review of English-language articles published in 2000 or later was conducted. Articles included cohort, randomised controlled trials and validation studies. Participants were people diagnosed with abdominal cancer who had undergone a CT scan. Data extraction and critical appraisal was undertaken.

Results
Ten cohort studies met the inclusion criteria. Seven demonstrated that low muscle mass was significantly associated with poor clinical outcome, with six specifically demonstrating reduced survival rates. Eight studies demonstrated that a greater number of patients (27.3-66.7%) were identified as sarcopenic using CT scans compared to numbers identified as malnourished using Body Mass Index (BMI).

Conclusion
CT scans can identify reduced muscle mass and predict negative cancer outcomes in people with abdominal malignancies, where traditional methods of assessment are less effective.
Introduction

In Europe, 3.45 million new cases of cancer were identified in 2012 with recent statistics showing that cancer was responsible for 1.75 million deaths\(^1\). Colorectal cancer (CRC) was the second most frequent cause of death after lung cancer, accounting for 13\% of all new cancer diagnoses and 12.2\% of all deaths\(^1\). Improvements in diagnosis and treatment of CRC have increased survival rates, demonstrated by the recent increases in 5-year survival in Europe from 1999 to 2007\(^2\). Furthermore, harmful lifestyle issues can continue to persist after treatment, so creating a growing, vulnerable population group, with an increased demand for effective health care. Additionally, this population will be aging, with European statistics predicting that the percentage of all people aged 65 and over will increase from an average of 16\% in 2010 to 29\% in 2060\(^3\). Given that cancer risk and age show a strong association, it is assumed that the future cancer burden on health care provision is set to increase\(^4\).

In order to effectively manage this growing and aging cancer population, it is important that additional risk factors, which influence survival, are identified early so as to facilitate treatment and aim to improve cancer outcome. Recent data have demonstrated that nutritional status and food intake are strong predictors of quality of life\(^5\), length of hospital stay\(^6\) and rate of hospital readmissions\(^6\). Furthermore, nutritional interventions in curative oncological care contribute to reduced post-operative infection, better control of cancer related symptoms, shortened length of hospital stay and improved tolerance to treatment\(^7\).

Increasing evidence has highlighted the importance of measuring body composition to allow for a more comprehensive understanding of nutritional status\(^8\). Indeed, sarcopenia, a condition where muscle mass and strength is reduced, has been associated with poor clinical outcome in patients undergoing cancer treatments\(^9\)\(^10\). An increasing elderly population of
patients with cancer will mean the occurrence of sarcopenia will also rise\textsuperscript{11}, particularly in those patients who may already be suffering from some degree of muscle atrophy associated with the aging process. The criteria for diagnosing sarcopenia are: low muscle mass and either low muscle strength or low physical performance\textsuperscript{12,13}. For the purposes of this review the term sarcopenia will relate to a low muscle mass only, due to a lack of studies recording muscle strength or physical function when muscle mass data are collected.

Aspects of nutritional status measurements may be masked, with many of the traditional assessment techniques providing results that may give a general idea of status but fail to pick up on more specific issues, such as sarcopenia. For example: food diaries rely on patients to self-report; body mass index (BMI) assumes a typical distribution of fat and muscle tissues; bioelectrical impedance analysis (BIA) relies on the patient to fast beforehand and for their internal fluid balances to be in equilibrium\textsuperscript{14}. Differences also exist between single frequency and multi frequency impedance measurements\textsuperscript{15}. Therefore, while the latter methods give an indication of nutritional status\textsuperscript{16}, they may not have the specificity to accurately identify changes in muscle mass and strength, which has been shown to lead to negative outcome in disease trajectory\textsuperscript{5-7}.

Computed Tomography (CT) scans can provide important quantitative information on muscle composition and distribution\textsuperscript{17} through their high pictorial quality, spatial accuracy, site specificity and the ability to measure fat and muscle content from one abdominal cross-sectional slice\textsuperscript{18}. Images from CT scans also distinguish between visceral and subcutaneous fat\textsuperscript{19} and are considered highly accurate in evaluating levels of fat, fat free mass and skeletal muscle\textsuperscript{20}. In addition to this, recent data suggest that CT scans can accurately measure changes in muscle mass in older populations\textsuperscript{21}. However, CT scans are not recommended as a
routine method of assessment or a stand-alone reason to determine body composition, as they are expensive and expose individuals to a small amount of radiation (10 mSv), which is the equivalent of 100 chest x-rays (0.1 mSv per x-ray).  

CT scanning is routinely used during diagnosis of abdominal tumours and therefore will be readily available for body composition assessment, without additional cost, patient radiation exposure or patient inconvenience. A previous review has highlighted the usefulness of imaging techniques to identify muscle wasting in chronic disease. However, to date, there has been no systematic review on the role of CT scans in specifically identifying sarcopenia in people with abdominal malignancies. This review aimed to evaluate the published evidence available on the role of CT scans in identifying low muscle mass (sarcopenia) in people with abdominal tumours and determine the role of body composition measurements in relation to clinical outcome.

**Methodology**

The systematic review followed the suggested criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidance. Studies were identified by searching electronic databases and scanning reference lists of relevant articles. This search was applied to Ovid MEDLINE (2000-present), PubMed (2000-present), and adapted for EMBASE, AMED, British nursing Index, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and Web of Science. Abstracts published in 2000 or later were hand searched from European Society of Parenteral Nutrition (ESPEN), British Association of Parenteral and Enteral Nutrition (BAPEN) and the American Association of Parenteral and Enteral Nutrition (ASPEN).
In each database, medical subject headings (MeSH) were used to search titles and/or abstracts. These headings included: Compute* Tomography, CT scan, cancer nutrition*, body composition, muscle, intra-abdominal fat and subcutaneous fat. This search was run in July 2014. The search Strategy for Medline (Ovid) is given in Figure 1.

Study Eligibility Criteria

Types of participants:
All adults (over 18 years) who had undergone one or more abdominal CT scans as part of their routine investigation and had a confirmed abdominal cancer diagnosis, including: liver, pancreas, colorectal, small bowel, bladder, ovarian and bile duct cancers.

Types of interventions:
Studies that used CT scans and specialised software to assess body composition in people diagnosed with an abdominal cancer (see figure 2). This included studies that compared the use of CT scans with other body composition analysis techniques, such as dual-energy x-ray absorptiometry (DXA), BIA or anthropometry.

Types of outcome measures:
Primary outcomes included: the incidence of sarcopenia determined by CT scans; patients’ clinical outcome; the incidence of malnutrition determined by traditional methods of nutritional assessment. The mean differences between the percentage of participants identified as sarcopenic and the percentage identified as malnourished were compared in relation to clinical outcome. Clinical outcomes included: morbidity and mortality; overall survival; treatment outcomes and cancer treatment complications.
Secondary outcome measurements:

Secondary outcomes included: skeletal muscle area and fat free mass area derived from CT scans; assessment of nutritional status; body mass index (BMI); weight loss; incidence of risk of malnutrition measured by a validated tool. The malnutrition universal screening tool (MUST) is an example of a validated tool, used by healthcare professionals. MUST states that an unplanned weight loss of more than 5% and a low BMI, combined with an acute disease effect score, can indicate malnutrition24 25.

Types of study design:

Studies were cohort, randomised controlled trials and validation studies. Studies were restricted to those published in the English language and those published after 1999, as technology for interpreting body composition is a relatively new innovation and not readily available prior to this date.

Study appraisal and synthesis

Eligibility assessment of selected papers was performed independently, in an un-blinded, standardised manner. Search results were transferred to EndNote X5 (Thomson Reuters, Philadelphia) and duplicates removed. Abstracts and titles were initially assessed against the inclusion criteria and those not meeting this were excluded. The full texts of publications meeting the criteria were reviewed to ensure compliance. Data were extracted using a form developed from the Cochrane data extraction template26. The form was piloted on two randomly selected, included studies and any appropriate amendments were subsequently made.
Information extracted from each of the selected publications included: the study aims, design and participant characteristics. Participant characteristics included: age, gender, BMI, weight loss, type of cancer, and cancer staging. The type of intervention was recorded including the method for measuring body composition, specialist software, definition of survival rate, definition of sarcopenia and clinical outcomes.

The quality of the methodology and validity of the results for each included paper were assessed using the Critical Appraisal Skills Programme (CASP) checklist. Different CASP tools are available for the type of study (RCT, validation, cohort) and the corresponding checklist was used to assess each study. Body composition measured by CT scans was examined according to quality components including: CT scan slice selected for analysis, training of analysts, blinding of analysts, repeat measures and observer inter and intra-reliability.

**Results**

There were 184 papers identified, of which ten studies met the inclusion criteria for the review. The search results are shown in the flowchart following the PRISMA guidelines\(^2\) (Figure 3). After screening titles, abstracts and reference lists the full texts of 23 citations were examined in detail. Of these, 13 studies failed to meet the inclusion criteria: 10 used CT scans to analyse fat mass only and so lacked detail in muscle mass and sarcopenia\(^27\text{-}36\); two presented cancers that were not specific to the abdominal region\(^37\text{-}38\) and one used CTs to examine organ size\(^39\).

**Study characteristics**
Of the ten studies selected for review, all were cohort studies: five were retrospective\(^{40-44}\) and five were prospective\(^{45-49}\). The included studies involved 2,584 participants and all further characteristics are detailed in Table 1. Of the ten trials; five were conducted in Canada\(^{40,41,45,47}\), one in the United States\(^{42}\), one in the UK\(^{43}\), one in France\(^{49}\), one in The Netherlands\(^{44}\) and one split across Norway and Canada\(^{48}\). All trials were based at a single oncology centre, except for one that included patients from 2 countries\(^{48}\) and one that conducted a multicentre study over 9 sites\(^{49}\).

The analysis of muscle and fat tissues in CT scans was observed in all studies. Six studies followed participants from diagnosis until death and the primary outcome was overall survival time in relation to CT scan analysis\(^{40,42,44,45,47,48}\). The primary outcomes of the four remaining studies included: occurrence of post-operative infections in relation to CT scan\(^{41}\); the capacity of CT to provide specific detail on different tissues\(^{46}\); level of inflammatory markers, including C-Reactive protein and albumin\(^{43}\); level of treatment toxicity\(^{49}\). In all studies, secondary outcomes included recognition of malnutrition by the identification of reduced muscle mass using CT scans and identification of those underweight using BMI. Assessment of malnutrition by the identification of substantial weight loss was only reported in two studies\(^{45,49}\).

**Risk of bias within studies**

All studies addressed a clearly focussed question and all except one\(^{46}\) focussed on either clinical or quality of life outcomes in relation to muscle mass measured using CT scans. All studies recruited the sample in an appropriate manner, with use of a cancer centre and an electronic database for identification of eligible patients and data collection. However, five studies recruited relatively small sample sizes\(^{40,42,46,48,49}\) in comparison to the other studies,
although one of these gathered data for seven years, which was the longest recruitment period\textsuperscript{40}. The largest sample size was 1474 and included all newly referred patients\textsuperscript{45}. In all studies, the recruited patients had a confirmed diagnosis of abdominal cancer and objective measurements were used to assess outcomes.

**Risk of bias within objective measures**

Objective measures were assessed for bias in each study and details are displayed in table 2. All studies selected the same CT slice at the third lumbar vertebral region (L3) for analysis, based on previous recommendations that established the skeletal muscle area at L3 to be highly correlated with total body skeletal muscle volume\textsuperscript{50}. Two studies demonstrated a particularly low risk of bias due to the use of pre-treatment CT scans; trained and blinded analysts; two consecutive L3 slices and intra-observer reliability\textsuperscript{40,45}. Bias was further reduced in one of these studies by tracking changes in CT scans over time, rather than measuring at a single time point\textsuperscript{40}. The remaining eight studies were vague about training and blinding of analysts and five of the studies failed to specify if any intra or inter-observer reliability tests had been carried out\textsuperscript{41,42,44,48,49}.

**Analysis of CT scans**

Slice-O-Matic software was used for the analysis of CT scans in all studies except for Richards et al (2012)\textsuperscript{43} and Vledder et al (2012)\textsuperscript{44}. One used a governmental free-ware programme (NIH ImageJ, v1.44, http://rbsweb.nih.gov.ij/) that was found to be comparable with Slice-O-Matic (Interclass correlation coefficient [ICC] 0.953, n=50)\textsuperscript{43} and one used a newly developed software (MeVisLab, v2.2.1, Bremen, Germany)\textsuperscript{44}. Skeletal muscle was quantified from CT scans in all studies and was recorded as skeletal muscle area. Participant height was used to standardise the muscle area and generate a muscle area index. The skeletal
muscle equation from Mourtzakis et al (2008)\textsuperscript{46} was used to estimate participant fat free mass. However, only four studies presented values for skeletal muscle area\textsuperscript{40,45-47} (Table 3).

**Body Composition evaluated by CT scanning and outcome**

Analysis of body composition in people with abdominal cancer by CT images was more precise than analysis by BIA and more readily available than DXA according to one study\textsuperscript{46}. This was due to the significant relationship of a single CT image to whole body fat free mass ($r=0.94$, $p<0.001$)\textsuperscript{46}.

Eight studies recorded clinical outcome in relation to body composition assessed by CT\textsuperscript{40-42,48}. One study recorded post-operative infection, rehabilitation and length of stay and demonstrated that an increase in each of these outcomes was significantly associated with the identification of sarcopenia\textsuperscript{41}. One study demonstrated an elevated systemic inflammatory response was significantly associated with a low muscle index ($p=0.01$)\textsuperscript{43}. Six studies recorded survival time as an outcome\textsuperscript{40,42,44,45,47,48} and all six demonstrated an association between low muscle mass and reduced survival time. This association remained significant in patients with a BMI > 30kg/m\textsuperscript{2}\textsuperscript{(Ref 47)} and in the presence of multiple factors (including muscle attenuation, weight loss and sarcopenia)\textsuperscript{45}. Notably all factors impacted on survival time regardless of BMI, although these factors were more strongly associated with reduced survival in patients with a BMI > 30kg/m\textsuperscript{2} or <20kg/m\textsuperscript{2} (Ref 45). It was also demonstrated that muscle loss was slower in those identified as sarcopenic at baseline compared to those identified as non-sarcopenic\textsuperscript{40}. However, the association between sarcopenia and survival time found in one study was not significant: 167 days survival in people with sarcopenia and 280 days in those who were not sarcopenic ($p=0.271$)\textsuperscript{42}. 
CT scan and BMI results compared

All studies assessed nutritional status in participants using BMI (Kg/m²). The study that recruited obese participants only was excluded from this particular analysis as all participants had a BMI above 30. Another study was also excluded from this analysis as it failed to present data according to BMI categories. The remaining eight studies showed a greater number of patients identified as sarcopenic using CT scans compared to those identified as malnourished using BMI. These studies used BMI < 18Kg/m² indicate malnutrition with the exception of two studies, which used BMI < 20Kg/m² to indicate malnutrition. The mean percentage difference between numbers of patients identified as sarcopenic using CT and numbers identified as malnourished using BMI, ranged between 27.3 and 66.7%. Six studies used gender-specific, skeletal muscle index cut-points as suggested in a publication by Prado and colleagues (2008), two did not. Gender-specific ranges were used instead of specific cut-points in one study and gender specific skeletal muscle index cut-points taken from an earlier publication were used in another study (Table 4).

Body composition measured by CT scans compared to weight loss

Only two studies recorded if patients had a weight loss greater than 5%, which is considered indicative of malnutrition. One of these studies found that 33.3% of participants had lost greater than 10% of body weight, which was a larger percentage than those in the underweight BMI category (3.9%) but a lower percentage than those identified as sarcopenic by CT (70.6%). The other study found that 44.3% of participants lost greater than 8% of body weight and the percentage of people identified as sarcopenic using CT scans (40.9%) was a very similar. This study also considered overall survival in the presence of 3 prognostic body composition variables: > 8% weight loss; sarcopenia and low muscle
attenuation. Survival was shown to decrease significantly as the number of exhibited
prognostic factors increased.

Discussion

This is the first systematic review to evaluate the role of CT scans in identifying sarcopenia in
people with abdominal tumours. Seven of the ten studies included in the review,
demonstrated that clinical outcome in patients with abdominal malignancy was significantly
and adversely influenced by sarcopenia, as measured by CT scanning. In addition one study
demonstrated that treatment outcome in patients with abdominal malignancy was also
significantly and adversely influenced by sarcopenia. Clinical and treatment outcomes
measured included: survival time, post-operative infection, treatment toxicity
from chemotherapy, and systemic inflammation. The association between sarcopenia
and clinical or treatment outcome was not significant in one of the studies reviewed,
although, the small sample size and lack of intra-observer validated CT results limited the
ability to draw definitive conclusions from this study. Importantly, the number of people
identified as sarcopenic using CT was 27.3 to 66.7% higher than numbers identified as
malnourished using BMI. This highlights the importance of recording muscle mass
and muscle mass changes in relation to patient prognosis and outcome.

The paper by Martin et al. (2013), with a large sample size and a low risk of bias,
specifically demonstrated that CT imaging was useful in revealing muscle depletion in cancer
patients who were not necessarily thin or wasted in appearance. This showed the advantage
of CT scans over techniques such as MUST and BMI, which rely on whole body weight only.
In keeping with this, all reviewed articles demonstrated that CT scanning identified
tsarcopenia in a significantly higher proportion of patients than those deemed malnourished on
the basis of BMI alone. Furthermore, all studies demonstrated that sarcopenia could occur in patients across all BMI categories with three papers highlighting that some patients represented the body phenotype referred to as sarcopenic obesity (i.e. individuals who are objectively obese with a BMI >30 but also sarcopenic).\textsuperscript{42, 46, 47} With this in mind it is important to note the value of CT scans in identifying central obesity, which can have potential adverse effects in terms of malnutrition.\textsuperscript{52} One study highlighted that weight loss of more than 5% was associated with the identification of sarcopenia using CT scans\textsuperscript{45}, suggesting that percentage weight loss may be a useful indicator of underlying sarcopenia, although further work is required to confirm this finding, both in those with and without pre-existing obesity.

All studies demonstrated that CT scanning offers a viable and accurate tool to measure body composition. This has also been confirmed by a recent systematic review, which demonstrated that CT scan analysis techniques can be linked to outcomes in colorectal cancer patients.\textsuperscript{53} Risks of CT scanning include cost and radiation exposure; alternative techniques such as BIA may be advantageous in this regard. A recent large scale trial carried out using data from the National Health and Nutrition Examination Survey III (NHANES), successfully used BIA data to identify sarcopenia and sarcopenic obesity in a sample of 4652 healthy older volunteers.\textsuperscript{54} However, BIA may be inaccurate, due to the occurrence of fluid imbalances consequent to an underlying inflammatory process in patients with cancer.\textsuperscript{14} Indeed, since all individuals included in the studies analysed in this systematic review underwent a scan as part of their routine oncological care, CT scanning clearly offers a practical, precise and accessible method to identifying sarcopenia in large groups of patients with abdominal malignancies.
As studies were of heterogeneous design, indicated by: varied timescale; definitions of sarcopenia and outcome measures, it is difficult to make direct comparisons in the validity, prognostication and usefulness of CT scans. The quality of the studies varied considerably and the bias assessment has highlighted some interesting points to be aware of in relation to interpreting data from CT scans. One important point to consider is the defined reference values used for the assessment of muscle depletion, which varied amongst the studies in this review with all showing large variation between numbers identified as malnourished and numbers identified as sarcopenic. One of the smaller variations between malnourished and sarcopenic numbers (28.6%) was in the study by Richards et al. (2012)\textsuperscript{43}, which used gender-specific ranges instead of gender specific cut-points. One of the larger variation between malnourished and sarcopenic numbers (51%) was in the study by Mourtzakis et al. (2008)\textsuperscript{46}, which used gender specific skeletal muscle index cut points from an earlier publication\textsuperscript{51}. It is important to note that even though reference values for the definition of low muscle mass varied between studies, all studies ensured that the reference values were gender specific. This is important as the difference in muscle stores between men and women can affect the amount of muscle loss, with a smaller loss seen in those with smaller stores (women) compared to those with larger stores (men)\textsuperscript{55,56}. A recent review for the international consensus of cancer cachexia states that although there is paucity in muscle depletion reference values in relation to cancer-specific outcomes, the generally accepted rule is an absolute muscularity below the 5\textsuperscript{th} percentile\textsuperscript{57}. In terms of CT scans this is assessed in men, as <55 cm\textsuperscript{2}/m\textsuperscript{2} and women <39 cm\textsuperscript{2}/m\textsuperscript{2} (Ref\textsuperscript{57}).

Another important point is the use of CT scans in determining sarcopenia without testing for functional ability. Several papers have been produced which provide consensus definitions for sarcopenia, with the latest publications stating that the diagnosis of sarcopenia is the
combined presence of low muscle mass and low physical performance\textsuperscript{12,13}. In addition, a recent study carried out to assess definition of lean body mass deficiency in the elderly concluded that associations between estimates of body compositions and metabolic risks, inflammation and muscle function should be used to establish suitable cut-offs for defining sarcopenia\textsuperscript{58}. Indeed those who are more physically active or who have had a more active lifestyle previously may have larger muscle stores, particularly peripheral muscle. As CT scans do not measure peripheral muscle it may therefore be necessary to consider physical status and function. Therefore, any further work in this area should use appropriate muscle depletion reference values and combine CT scan outcomes with results of: functional tests; inflammatory readings and metabolic readings. Inclusion of these criteria will aid in minimising bias and standardising CT scan analysis guidance. Guidance in relation to analysts’ competency levels, training and application would potentially be useful for both clinicians and researchers.

In conclusion, the studies in this systematic review highlight the large changes in body composition that can occur in cancer, which are not always recognisable by physical appearance or by nutritional assessment using traditional techniques such as BMI. In order for this to be translated into clinical practice, future studies need have uniform endpoints and follow the consensus definition for the diagnosis of sarcopenia, including assessment of functionality. The future use of CT scans to identify sarcopenia will facilitate the identification of those at nutritional risk and will be useful for assessing the impact of targeted nutritional interventions.
References


Legend

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