Seminars in Cell & Developmental Biology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes

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ARTICLE INFO

Article history:
Received 1 September 2015
Accepted 2 September 2015
Available online xxx

Keywords:
Computed tomography
Cancer
Muscle
Fat

ABSTRACT

Cancer cachexia (i.e., skeletal muscle wasting with or without fat loss) relates to several adverse outcomes. Computed tomography (CT) cross-sectional images serve as an efficient biomarker for assessment of cachexia in cancer patients. We systematically reviewed literature reporting quantitative evaluation of the cross sectional area of the main tissues implicated in cancer cachexia, muscle and visceral, subcutaneous and inter-muscular fat in CT scans at the 3rd lumbar vertebra. Our main goal was to summarize CT-defined variation of muscle and fat and the relationship between these features and cancer outcomes such as chemotherapy toxicity, post-surgery complications and survival.

Contents

1. Introduction

Cancer cachexia is a multifactorial syndrome that is a consequence of elevated inflammatory response combined with alterations in metabolism and reduced food intake [1]. Cachexia-induced impaired food intake and altered metabolism result in disordered protein and energy balance [1]. Cancer cachexia-associated skeletal muscle wasting with or without fat loss, has consequential association with survival and quality of life [1].

Severe muscle depletion (termed *sarcopenia*) was first described as part of the frailty syndrome found in older individuals and was later shown to be prevalent in patients with cancer, chronic obstructive pulmonary disease, heart and renal failure [2]. Measurements of muscle and fat are not in the standard repertoire of oncologic medicine, however since emerging data suggests that measures derived from computed tomography (CT) images provide prognostic information in cancer patient populations, such measurements may be given future consideration as an efficient biomarker in research and clinical evaluation [3].

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http://dx.doi.org/10.1016/j.semcdb.2015.09.001
1084-9521/

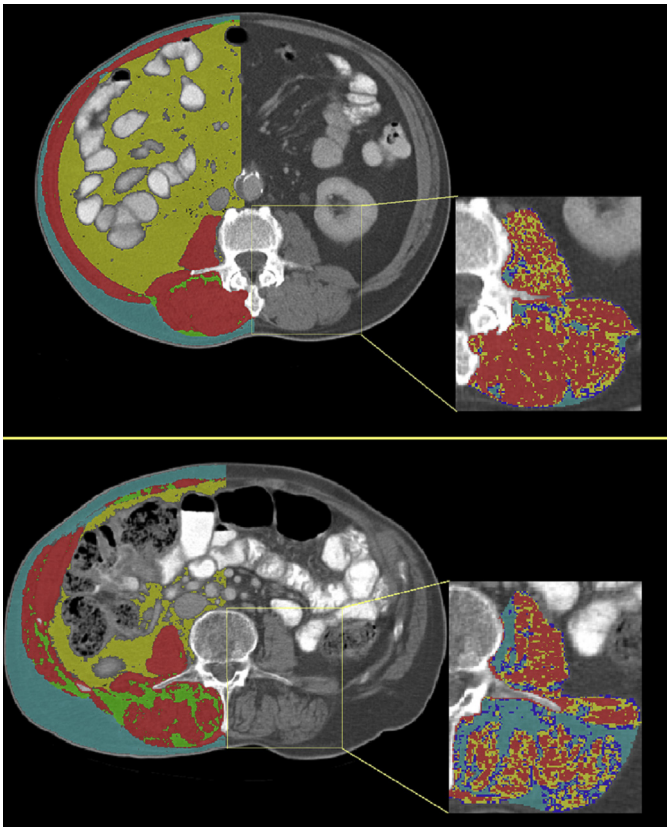

Fig. 1. Two cancer patients with different mean muscle attenuation and inter-muscular adipose tissue. *Main panels*: Total lumbar CT images (at 3rd lumbar vertebra level); attenuation ranges used for skeletal muscle (SM), −29 to +150 Hounsfield Units (HU); visceral adipose tissue, VAT, −150 to −50 HU; subcutaneous adipose tissue, SAT, −190 to −30 HU; inter-muscular adipose tissue, IMAT, −190 to −30 HU. *Insets*: Psoas and paraspinal muscles: attenuation ranges used for normal attenuation SM, +30 to +150 HU; and abnormal (reduced) attenuation muscle in two range [65]: [−29 to 0 HU; +1 to +29 HU] and IMAT, −190 to −30 HU. Patient in upper panel represents a typical (median) individual: male, BMI 22.5 kg/m^2, aged 69 y with sigmoid colon adenocarcinoma stage III. Overall SM = 164.9 cm^2 with mean attenuation 34.9 HU; VAT = 319.7 cm^2; SAT = 78.0 cm^2 and IMAT = 8.2 cm^2. Psoas and paraspinal normal muscle (inset) 65% of area is between +30 and +150 HU. Patient in lower panel has extensive fatty infiltration and extensive areas of abnormal attenuation: male, BMI 22.5 kg/m^2, aged 69 y with metastatic gastroadenocarcinoma. Overall: SM = 129.5 cm^2 with mean attenuation 23.3 HU; VAT = 58.7 cm^2; SAT = 114.0 cm^2; IMAT = 38.9 cm^2. Psoas and paraspinal normal muscle (inset) 34% of area is between +30 and +150 HU and remaining area is in abnormally low attenuation ranges between −29 and +29 HU. Neither patient had a history of diabetes or neuromuscular diseases.

CT and magnetic resonance imaging are ideal to quantify skeletal muscle as well as fat [visceral adipose tissue (VAT), subcutaneous AT (SAT), inter-muscular AT (IMAT)]. Precision of measures of tissue cross sectional areas with CT is excellent (0.4–1.5%) [4–6] providing sensitivity to detect changes over time. Taking advantage of CT images acquired in standard care or clinical trials, body composition of cancer patients has begun to be described. This analysis has a low incremental cost and is feasible and precise [2].

Most researchers used consistent methods for CT-defined cross sectional image analysis focusing on 3rd lumbar vertebra (L3) as a standard bony landmark (see Tables 1–3). Skeletal muscle [rectus abdominus, abdominal (transverse and oblique), psoas and paraspinal (quadratus lumborum, erector spinae)], IMAT, VAT and SAT appear at this level (Fig. 1). At *L3*, the cross sectional areas are linearly related to whole body mass of muscle (r^2 = 0.86) [7], VAT (r^2 = 0.89) [8], SAT (r^2 = 0.92) [8] as well as total adipose tissue (TAT) (r^2 = 0.93) [7]. Macroscopic IMAT within the fascial boundary of the muscle is quantified within the range of −190 to −30 Hounsfield Unit (HU) and is not included in the muscle cross sectional area. Muscle areas are typically quantified within a HU range of −29 to +150. HU ranges of −150 to −50 for VAT, and −190 to −30 for SAT [9] (Fig. 1). Specific software [e.g., Slice-O-Matic software (v.4.3, Tomovision, Montreal, Canada) or Image J software v1.42q (National Institutes of Health, http://rsb.info.nih.gov/ij)] are used to do this quantification.

The purpose of this work is to summarize published findings on CT-defined variation of muscle and fat at *L3* and the relationship between these features and cancer outcomes.

2. Materials and methods

To capture the literature on CT-derived body composition in cancer patients we used search terms for malignant disease [(cancer) or (neoplasm) or (carcinoma) or (tumor) or (tumor) or (malignant) or (metastasis)], computed tomography and body composition [(cachexia) or (wasting syndrome) or (weight loss) or (malnutrition) or (anorexia) or (skeletal muscle) or (skeletal muscle wasting) or (skeletal muscle loss) or (skeletal muscle depletion) or (sarcopenia) or (myopenia) or (lean body mass) or (adipose) or (adipose tissue) or (fat) or (fat loss) or (body composition)]. The search was conducted on MEDLINE from January 1st 1990 to January 15th 2015. Criteria for inclusion included human, adults (>18 y/o), cancer patient populations, English language and assessment by *CT scan* at *L3*. Articles were excluded if the quantification was done at a soft tissue landmark such as umbilicus or kidneys [10–12], or exclusively the psoas muscle [13] as these are not comparable to the rest of the literature. Reference lists of the identified articles were screened to find additional relevant publications. There were no exclusion regarding number of patients and type of study (retrospective, prospective or cross sectional). Data were extracted from the result sections, tables and figures of each article. As we did not aggregate the data, we did not ask for any extra data from the investigators. All statistical methods for summarizing the measurements [e.g. odds ratio (OR)] were included in our review and we did not conduct any further statistical analysis (such as data synthesis or additional subgroup analysis) on individual findings. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] flow diagram of our search strategy is shown in Fig. 2. All excluded articles were reviewed by SMRKB and VM to assure that they did not meet eligibility criteria.

3. Results

3.1. Overview

Fifty-three studies met the selection criteria (Fig. 2, Tables 1–3), including a total of 9138 patients. Data included tissue cross sectional areas (cm^2) for skeletal muscle, VAT and/or SAT, TAT and in 5/55 studies IMAT area was given [15–19]. Tissue areas were also normalized for stature (i.e., divided by the height in m^2). Skeletal muscle index (cm^2/m^2, SMI) is a representation of how muscular an individual is for their height. Mean skeletal muscle attenuation (MA) was reported in 5 articles [20–24], as some patients show greatly reduced attenuation values (Fig. 1), often with increased IMAT.

An early definition of sarcopenia was an absolute muscle mass >2 standard deviations below mean values for healthy young adults [25]. SMI may be treated as a continuous variable, but has also frequently been dichotomized (sarcopenic vs non-sarcopenic) with a statistical approach being used to identify threshold values below which low muscle mass associates with elevated risk of poor outcome (e.g., overall or disease-free survival). On early study Prado

Please cite this article in press as: Kazemi-Bajestani SMR, et al. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Semin Cell Dev Biol (2015), http://dx.doi.org/10.1016/j.semcdb.2015.09.001