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Original article

Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer

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SUMMARY

Background & aims: Recent research indicates that severe muscular depletion (sarcopenia) is frequent in cancer patients and linked to cachexia and poor survival. Our aim was to investigate if measures of skeletal muscle hold prognostic information in advanced non-small cell lung cancer (NSCLC).

Methods: We included NSCLC patients with disease stage IIIB/IV, performance status 0–2, enrolled in three randomised trials of first-line chemotherapy (n = 1305). Computed tomography (CT) images obtained before start of treatment were used for body composition analyses at the level of the third lumbar vertebra (L3). Skeletal muscle mass was assessed by measures of the cross sectional muscle area, from which the skeletal muscle index (SMI) was obtained. Skeletal muscle radiodensity (SMD) was measured as the mean Hounsfield unit (HU) of the measured muscle area. A high level of mean HU indicates a high SMD.

Results: Complete data were available for 734 patients, mean age 65 years. Both skeletal muscle index (SMI) and muscle radiodensity (SMD) varied largely. Mean SMI and SMD were 47.7 cm^2/m^2 and 37.4 HU in men (n = 420), 39.6 cm^2/m^2 and 37.0 HU in women (n = 314). Multivariable Cox regression analyses, adjusted for established prognostic factors, showed that SMD was independently prognostic for survival (Hazard ratio (HR) 0.98, 95% CI 0.97–0.99, p = 0.001), whereas SMI was not (HR 0.99, 95% CI 0.98–1.01, p = 0.329).

Conclusion: Low SMD is associated with poorer survival in advanced NSCLC. Further research is warranted to establish whether muscle measures should be integrated into routine practice to improve prognostic accuracy.

1. Introduction

In advanced cancer, estimates of individual patients' survival are essential for several reasons. These estimates are needed to select

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the appropriate treatment approach, provide adequate patient information, enable advance care planning, and ensure timely provided palliative care. This is particularly relevant for patients with a poor prognosis such as advanced non-small-cell lung cancer (NSCLC) patients.

NSCLC accounts for approximately 85% of new cases of lung cancer, the leading cause of cancer deaths worldwide [1]. The majority is diagnosed with advanced disease [2], and median overall survival is relatively short [3–5]. Although several prognostic factors have been identified in advanced NSCLC, performance status (PS) remains the cornerstone to guide treatment decisions in daily clinical practice [6]. There are, however, large variations in survival within each PS group, and to improve outcomes and avoid both over- and undertreatment, there is a need for more precise prognostic factors.

Cachexia, a wasting syndrome linked to loss of weight and appetite, is believed to account for 20% of cancer related deaths [7], and is frequent in NSCLC [8]. Severe muscular depletion is a more recently recognised indicator of cachexia and appears to be a strong negative prognostic factor in ageing, several chronic diseases [9], as well as in malignancies, irrespective of cancer diagnosis, stage and treatment [10]. The majority of cancer studies hitherto performed are, however, small and the most convincing evidence arises from colorectal cancer, hepatocellular carcinoma and other gastrointestinal cancers [10–13]. From two studies on mixed samples there are also indications that severe loss of muscle mass may be predictive of survival in lung cancer [13,14].

In studies on cancer patients, muscle mass has been quantified by the cross sectional muscle area on computed tomography (CT) scans, and severe loss of muscle mass is referred to by the term sarcopenia. There is to date no general agreement of cut points to define this entity [10]. To discriminate between sarcopenic and non-sarcopenic patients, survival related thresholds identified in the cohort under investigation have been used [12–16]. General muscularity varies with several factors including ethnicity, age, gender and prevalence of obesity, and the identified thresholds seem to vary accordingly between populations [12–16].

In non-cancer settings, the definition of sarcopenia has been expanded to include both muscle mass and function [17]. Hence the quality of the muscle mass in general and the skeletal muscle radiodensity (SMD) in particular has received attention [18]. Assessed by CT imaging, SMD is expressed as the mean Hounsfield Units (HU) of a measured cross sectional muscle area. Low values reflect increased fat deposits, and have been linked to obesity, diabetes and several negative outcomes in non-cancer patients, including reduced physical performance and increased risk of hip fracture [19]. Relatively recent studies have suggested that low SMD may also be a significant prognostic factor in cancer patients [13,20–22]. As for sarcopenia, there are no well-established thresholds to define abnormally low SMD [19].

The main aim of the present study was to test the hypothesis that measures of muscle mass and muscle radiodensity are independent prognostic factors for overall survival in advanced NSCLC patients receiving first line palliative chemotherapy, and hence are factors that should be considered in clinical practice to improve prognostic estimates.

2. Materials and methods

2.1. Patients

The study is based on three multicentre randomised controlled trials (RCTs) comparing first-line chemotherapy-regimens in advanced NSCLC [3–5]. Overall survival (OS), quality of life (QoL) and toxicity were the main endpoints. Disease free and progression free survival were not systematically registered. The main inclusion criteria were similar: chemonaive patients, age $\geq$ 18 years, stage IIIB/IV and performance status (PS) 0–2. RCT 1 (September 2003 to December 2004, n = 432) randomised patients to three cycles of carboplatin plus either vinorelbine or gemcitabine intravenously [3]. In RCT 2 (May 2005 to July 2006, n = 436), patients received four cycles of carboplatin plus either pemetrexed or gemcitabine [4]. RCT 3 (September 2007 to April 2009, n = 437) included patients who received three cycles of vinorelbine capsules plus either carboplatin or gemcitabine [5]. In all trials, patients $\geq$ 75 years had a 25% dose reduction. There were minor differences in the toxicity profiles, but no significant differences in QoL or OS (range: 6.3–7.3 months) between trial arms.

For inclusion in the present study we defined complete data on both muscle mass and radiodensity as mandatory, as well as data on appetite loss.

2.2. Assessments

Baseline data comprised demographic variables, stage of disease, histology, PS, height, weight and QoL. Laboratory values were restricted to haematological parameters, kidney and liver function. C-reactive protein (CRP) and s-albumin were not registered, neither was weight loss. QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) [23]. Diagnostic CT scans of the thorax/upper abdomen, taken within four weeks before chemotherapy commenced, was collected from 38 hospitals. All CT scans were performed with contrast enhancement and a tube voltage of 120 kVp was used for the majority. The CT scans were analysed using Slice-O-Matic software (v.4.3 Tomovision, Montreal, Canada) by three observers blinded for patient data. The first image in the caudal direction where both vertebral transverse processes at the level of the third lumbar vertebra (L3) were visible was used for manual outlining of the skeletal muscle and adipose tissue compartments. Muscle area at this level is shown to be strongly correlated to the corresponding whole body muscle masses [24]. Based on pre-established thresholds of HU in the range of −29 to +150 HU for muscle tissue, −150 to −50 HU for visceral adipose tissue and −190 to − 30 HU for subcutaneous and intramuscular adipose tissue [14], the cross-sectional areas (cm^2) of the outlined tissues were then calculated by the software.

As a measure of skeletal muscle mass, the total cross sectional skeletal muscle area (cm^2) was normalised for stature by dividing by height squared (m^2), and expressed as skeletal muscle index (SMI) (cm^2/m^2). Similarly, the adipose index (cm^2/m^2) was calculated based on the sum of the cross sectional visceral and subcutaneous adipose tissue areas (cm^2). Skeletal muscle radiodensity (SMD) was assessed as the mean radiodensity (HU) of the entire measured cross sectional muscle area at L3.

Body Mass Index (BMI) (weight (kg)/height (m^2)) was categorised: BMI < 20 as underweight, BMI [20,25) as normal weight, BMI [25,30) as overweight and BMI $\geq$ 30 as obesity [13]. To define appetite loss, we used the patients' baseline score for the item “Have you lacked appetite” from the QLQ-C30. The scores were dichotomised; with the score “not at all” indicating no appetite loss; while “a little”, “quite a bit” and “very much” defined appetite loss.

2.3. Statistics

Data from all RCTs were analysed jointly. Independent sample T-tests were used to investigate differences between groups on continuous variables. For categorical variables Pearson's chi-square tests were applied.

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