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Original article

Low muscle attenuation is a prognostic factor for survival in metastatic breast cancer patients treated with first line palliative chemotherapy

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ABSTRACT

Background: Low muscle mass (LMM) and low muscle attenuation (LMA) reflect low muscle quantity and low muscle quality, respectively. Both are associated with a poor outcome in several types of solid malignancies. This study determined the association of skeletal muscle measures with overall survival (OS) and time to next treatment (TNT).

Patients and methods: A skeletal muscle index (SMI) in cm^2/m^2 and muscle attenuation (MA) in Hounsfield units (HU) were measured using abdominal CT-images of 166 patients before start of first-line chemotherapy for metastatic breast cancer. Low muscle mass (SMI <41 cm^2/m^2), sarcopenic obesity (LMM and BMI ≥30 kg/m^2) and low muscle attenuation (MA <41 HU and BMI <25 kg/m2 or MA <33 HU and BMI ≥25 kg/m2) were related to OS and TNT.

Results: The prevalence of LMM, sarcopenic obesity and LMA were 66.9%, 7.2% and 59.6% respectively. LMM and sarcopenic obesity showed no significant association with OS and TNT, whereas LMA was associated with both lower OS (HR 2.04, 95% CI 1.34–3.12, p = 0.001) and shorter TNT (HR 1.72, 95% CI 1.14–2.62, p = 0.010). Patients with LMA had a median OS and TNT of 15 and 8 months respectively, compared to 23 and 10 months in patients with normal MA.

Conclusion: LMA is a prognostic factor for OS and TNT in metastatic breast cancer patients receiving first-line palliative chemotherapy, whereas LMM and sarcopenic obesity are not. Further research is needed to establish what impact LMA should have in daily clinical practice.

1. Introduction

Muscle mass decreases from 40 years of age and onwards, with approximately 8% total muscle mass loss per decade [1]. In several diseases there is an association between low muscle mass and outcome, irrespective of the exact underlying mechanism [2]. Also, the quality of muscle, measured by the attenuation (density) of muscle by computed tomography (CT) reflecting the accumulation of adipose tissue in muscles, may be of prognostic value [3]. Also in cancer patients, there is increasing attention to the potential prognostic role of low muscle mass (LMM) and low muscle attenuation (LMA). The association of LMM as well as LMA with impaired survival has been well established in several tumor types [4–9]. In addition, in cancer patients, LMM and LMA are associated with worse disease-related outcomes in terms of postoperative complications [10] and treatment toxicity [5,11].

In most oncological studies muscle mass and attenuation are mostly determined by CT-scanning, which is considered the gold standard to measure muscle parameters. The CT-based method of muscle measurement relies on the assumption that muscle cross-sectional area is strongly correlated to total body muscle mass

Abbreviations: HU, Hounsfield unit; LMA, Low muscle attenuation; LMM, Low muscle mass; OS, Overall survival; SMI, Skeletal muscle index; TAMA, Total abdominal muscle area; TNT, Time to next treatment.

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[4,12] and muscle measurement can be easily conducted using CT-images acquired during routine care. However, despite increasing knowledge on the prognostic impact of skeletal muscle measures in several tumor types, this is relatively unexplored in breast cancer patients. Furthermore, due to the lack of a standardized method of muscle measurement, results from studies in other tumor types cannot be extrapolated to a breast cancer population.

To our knowledge, two studies so far have investigated the association between muscle measures and survival in patients with metastatic breast cancer. In the first study involving 55 metastatic breast cancer patients treated with third line capecitabine after failure of taxanes and anthracyclins, LMM resulted in a shorter median time to tumor progression (62 days vs. 105 days, HR 1.9, 95% CI 1.0–3.5, $p = 0.05$), but its association with the clinically more relevant overall survival and the impact of muscle quality on outcome was not assessed [5], while in some studies, muscle quality was associated with outcome, while muscle mass was not [13,14]. In the second study involving 40 metastatic breast cancer patients treated with taxanes as first line chemotherapy, patients with LMM seemed to have shorter overall survival (30 vs. 40.3 months, $p = 0.07$) and time to treatment failure (6.2 vs. 9.2 months, $p = 0.18$), but the difference did not reach statistical significance. In the same study, muscle attenuation also did not show a significant association with overall survival and treatment failure, but no cut-off was used to identify patients with the lowest muscle quality. Due to the small sample size, a type II error to detect possible clinically relevant survival differences could not be ruled out, and only patients treated with taxanes were investigated [9]. Given this, the prognostic impact of skeletal muscle measures in metastatic breast cancer needs further evaluation.

We therefore performed a study to assess the prognostic value of skeletal muscle measures in patients with metastatic breast cancer by determining the association of LMM, sarcopenic obesity and LMA with overall survival and time to next treatment after first line palliative chemotherapy in a real-world population of patients with metastatic breast cancer.

2. Materials and methods

2.1. Study design

This single-center retrospective study was performed at a regional hospital in the Netherlands. Patients diagnosed with breast cancer were identified using the pathology registry of our hospital between January 1, 2000 and June 1, 2014. Patients with distant metastases were identified from this database. Patients with abdominal CT-images within three months before the start of the first palliative chemotherapeutic treatment were included, regardless of tumor characteristics and treatment schedules. Exclusion criteria were: male sex, a second active malignancy and no palliative chemotherapy. Medical records were searched for patient characteristics, body composition parameters, such as height and weight, and data regarding clinical follow up. The primary study endpoint was overall survival (OS) and the secondary endpoint was time to next treatment (TNT) after first-line chemotherapy. OS was defined as the date of the first cycle of first-line chemotherapy to the date of death or the end of follow-up (January 1, 2016), whichever occurred first. Survival status was confirmed by reviewing the Dutch Cancer Registration (IKNL); patients still alive were censored at January 1, 2016. The IKNL publishes figures regarding the incidence and mortality of cancer patients and is therefore a reliable institution to confirm survival data. TNT was defined as the date of the first cycle of first line chemotherapy to the date of the start of the second-line systemic treatment (endocrine therapy or chemotherapy) or, in case of no second line treatment, to the date of documented disease progression or death, whichever came first. The switch to another regimen because of treatment intolerability or patient demand was not considered a change to second line treatment. Patients with none of these events were censored at January 1, 2016. The study was approved by our ethical committee.

2.2. Muscle measurements

Muscle mass was measured by CT-imaging (slice thickness 3 mm, Brilliance 64 CT or Brilliance 40 CT, Philips, Best, the Netherlands). All measurements were performed at one transversal CT-image at the L3 level using validated segmentation software (Slice-o-matic, Tomovision, Canada) [15]. To estimate muscle mass, total abdominal muscle cross-sectional area was measured in cm^2 and corrected for height, resulting in a lumbar skeletal muscle index (SMI) in cm^2/m^2. Mean muscle attenuation (MA) of all abdominal muscles at L3 was measured in Hounsfield units (HU). The HU-threshold for muscle tissue varied from −29 to +150 HU [4], as previously published. Low muscle mass (LMM) was defined as a SMI of $\leq$41 cm^2/m^2 [16]. Low muscle attenuation (LMA) was defined as <41 HU for patients with a body mass index (BMI) < 25 and < 33 HU for patients with a BMI $\geq$25 [16], using previously published cut-off points associated with survival after optimum stratification in patients with solid malignancies. Sarcopenic obesity was defined as the combination of LMM and a BMI $\geq$30 [4]. The inter-observer reliability between three trained investigators, as assessed with an intraclass correlation coefficient using a two-way random effects model and an absolute agreement definition, was 0.993. Hence, all muscle measurements were performed by one investigator.

2.3. Statistical analyses

Continuous variables were described as mean and standard deviation or as median and interquartile range (IQR). Categorical variables were described using percentages. Comparisons between included and excluded patients were performed using Mann-Whitney tests for continuous variables, Fisher's exact tests for dichotomous variables and chi-square tests for categorical variables with more than 2 categories. Associations between muscle parameters, age and BMI were evaluated using Spearman's rank correlation and multivariable logistic regressions with age and BMI as independent variables and LMM and LMA as dependent variables. The association of LMM, sarcopenic obesity and LMA with OS and TNT was determined using Kaplan-Meier curves. In univariable and multivariable Cox proportional hazard models for OS and TNT, the following patient characteristics were included as independent variables: age, body mass index, hormone receptor positivity, Her2Neu receptor positivity, year of diagnosis, time between initial breast cancer diagnosis and the occurrence of distant metastases, metastatic locations and number of metastatic sites. The multivariable Cox models included all patient characteristics as independent variables, and each muscle measurement was added to this model separately. The proportional hazards assumption was assessed by including interaction effects of covariates and follow-up time in a Cox proportional hazards model with time-dependent covariates. All analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA) with a two-sided significance level of 0.05.

3. Results

3.1. Patient characteristics

Initially, 380 patients with metastatic breast cancer undergoing