Higher muscle strength is associated with prolonged survival in older patients with advanced cancer

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Running head

Muscle strength and survival in older cancer patients

Implications for Practice

This study in older patients with advanced cancer shows that adequate muscle strength is associated with longer overall survival. The results of this study imply that muscle strength might be helpful in estimating survival, and therefore in identifying older patients who will benefit from anti-cancer treatment.

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Key words

- Muscle strength
- Aged
- Neoplasms
- Sarcopenia
- Muscle radiodensity
- Survival
- Body composition

Abstract

Background Identifying predictors of treatment toxicity and overall survival (OS) is important for selecting patients who will benefit from chemotherapy. In younger patients with cancer, muscle mass and radiodensity are associated with treatment toxicity and OS. In this study, we investigated whether muscle mass, radiodensity and strength were associated with treatment toxicity and OS in patients with advanced cancer, aged 60 years or older.

Materials and Methods Before starting palliative chemotherapy, muscle mass and radiodensity were assessed using CT scans and muscle strength using a hydraulic handgrip dynamometer. Treatment toxicity was defined as resulting in dose reduction and/or discontinuation of treatment. Multiple logistic and Cox regression analyses were performed to study potential associations of muscle mass, radiodensity and strength with treatment toxicity and OS, respectively.

Results 103 patients, aged 70 years, with advanced colorectal, prostate or breast cancer, participated. Muscle parameters were not significantly associated with treatment toxicity. Higher muscle strength was associated with longer OS (HR 1.03 (95%CI 1.00-1.05)). Muscle mass and radiodensity were not significantly associated with OS.

Conclusion Higher muscle strength at start of palliative chemotherapy is associated with significantly better OS in older patients with advanced cancer. None of the investigated muscle parameters were related to treatment toxicity. Future studies are needed to evaluate whether muscle strength can be used for treatment decisions in the elderly with advanced cancer.

Introduction

Systemic treatment of older patients with cancer is challenging, due to the heterogeneous condition and co-morbidity of this population, and a lack of knowledge caused by underrepresentation of this group of patients in clinical studies [1]. The high prevalence of treatment toxicity and the higher mortality rate caused by higher disease specific mortality and competing comorbidity, further complicate decision making in this population [2-4]. Knowledge of predictors for treatment toxicity and survival can contribute to the identification of patients who will benefit from treatment with chemotherapy. Low muscle mass and impaired muscle radiodensity have been found in adult patients with cancer and healthy older adults [5,6]. In adults with cancer, low muscle mass and increased fat infiltration of the muscle, reflecting lower muscle radiodensity (i.e. low muscle attenuation), have been observed in 15-55% of patients, and were found to be predictive for treatment toxicity and survival [5,7-11]. Decrease in muscle mass and muscle radiodensity is associated with ageing [6,12]. Depending on the definition, the prevalence of low muscle mass in older adults is up to fifty percent [13,14]. Muscle radiodensity is generally lower in older than in younger adults [6].

Because of the observed decrease in muscle mass and muscle radiodensity, both in patients with cancer and in patients at older age, it is likely that the combination of these two factors (cancer and old age) affect muscle parameters even more severely. Several studies have investigated muscle mass in patients with advanced cancer and reported age-related differences with conflicting results regarding prevalence of low muscle mass [5,8,10,15,16]. However, age-related differences in prevalence of low muscle radiodensity have not been reported in patients with advanced cancer.

Next to muscle mass and muscle radiodensity, muscle strength is a third important determinant of muscle depletion [17]. In the general population, muscle strength contributes to the identification of the most fit or – on the opposite – most vulnerable older patients [18-20]. Therefore, it may be a predictor of treatment toxicity and survival in older patients with cancer. In addition, muscle strength has been shown to be a predictor of poor clinical outcome in younger patients with advanced cancer [21].

In this study we prospectively studied the association of muscle mass, muscle radiodensity and muscle strength with both treatment toxicity and overall survival (OS) in a cohort of older patients with advanced cancer.

Materials and Methods

The present study was conducted as part of a large prospective study on nutritional status and muscle measures in patients with advanced cancer, at the VU University Medical Center (VUmc), Amsterdam, The Netherlands. A first analysis of these data was published in 2014 [22] and changes in muscle mass during treatment for metastatic colorectal cancer (CRC) were reported in 2016 [23].

The research protocol was approved by the medical ethics committee of the VUmc and the study was performed according to the 1964 Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation.

Patients

In the large prospective study, eligible patients had advanced CRC, breast-, prostate- or lung cancer and were scheduled to receive the first cycle of (a new line of) palliative chemotherapy. Patients were excluded when treated with anticancer therapy within the last 30 days, with ascites or serious pitting edema, or when they were not able or willing to provide informed consent. Patients were recruited from the out-patient clinic and medical ward of the VUmc between October 2011 and July 2014.

For the current analysis we selected patients aged 60 years and older with CRC, breast- or prostate cancer who had an evaluable Computed Tomography (CT) scan of the abdomen available within 40 days of start of treatment. Because of absence of CT scans of the abdomen in the majority of patients with lung cancer, this group of patients was not included in this analysis.

Anthropometry

Body weight and height were assessed before the start of chemotherapy. Height was measured to the nearest cm using a stadiometer while the patient was standing barefoot and height was determined. Weight was measured within 0.2 kg on a calibrated scale (Seca type 888). BMI was calculated as the ratio of body weight (kg)/height (m)^2.

Muscle measures

Muscle mass and muscle radiodensity

All CT scans were obtained for clinical purposes. Muscle mass and muscle radiodensity were measured by analysis of electronically stored CT images. A certified investigator analyzed images using commercially available software: Slice-O-matic v 5.0 (Tomovision, Magog, Canada) on a single slice transverse CT image located at a standard vertebral landmark: L3 [24]. The software was used to specify the different tissues based on their anatomical features and pre-established thresholds of Hounsfield Units (HU). For skeletal muscle the range of HU is -29 to +150 HU and for intermuscular adipose tissue -190 to -30 HU [25].

Lumbar skeletal muscle measured at L3 is related to whole body muscle mass and is the sum of: paraspinal muscles (quadratus lumborum, erector spinae), psoas muscles, transversus abdominis, internal and external oblique and rectus abdominis [24]. The software computes surface areas of lumbar skeletal muscle (e.g. cm^2) and this value of muscle mass was normalized for stature (lumbar skeletal muscle index (SMI), cm^2/m^2)

[24]. Muscle radiodensity, which is also described as muscle attenuation, was measured using the muscle radiation attenuation rate (in HU).

Low muscle mass (low SMI) and low muscle radiodensity were defined according to the sex- and BMI specific threshold values associated with low survival by Martin et al [7].

Muscle strength

Hand grip strength is a valid indicator of general muscle strength and being a bedside method, it is the most frequently used clinical tool to determine muscle strength [26]. Hand grip strength was measured using a hydraulic hand dynamometer (Baseline, Fabrication Enterprises, USA). Patients performed the test while sitting with the shoulder adducted and neutrally rotated, elbow flexed at 90 degrees, forearm and wrist in neutral position. Patients were instructed to perform one practice contraction. Subsequently, each patient performed two maximal isometric contractions with the left hand and two with the right hand. Maximal hand grip strength was defined as the maximum value of 4 contractions and was recorded to the nearest 0.5 kg. Low muscle strength was determined by sex-specific cutoff values for maximal hand grip strength (<30.3 kg for men and < 19.3 kg for women) [27].

Treatment toxicity

Treatment toxicity was obtained from medical records and consisted of any toxicity leading to dose reduction or discontinuation of chemotherapy such as (febrile) neutropenia, neurotoxicity, gastrointestinal symptoms and fatigue. Treatment modifications due to other causes, for instance progressive disease or vacation were not taken into account. Treatment toxicity was dichotomized into present or absent. Furthermore, time until treatment toxicity and upfront dose reductions were noted. Early treatment toxicity was defined as toxicity occurring within 42 days (2 cycles of treatment).

Survival

OS data were obtained at least 1 year after inclusion of the last patient. Median length of follow up was 436 days (Interquartile range (IQR) 414). Patients who were still alive were censored on the date of last consultation. Six month OS was calculated.

Covariates

Demographic and clinical data were retrieved from medical records. Age, sex, cancer type and WHO/ECOG performance status were recorded before start of treatment with chemotherapy. Comorbidity was assessed by the Charlson Comorbidity Index (CCI) [28]. A score of ≥ 2 indicates severe comorbidity. Polypharmacy was defined as the use of 5 medications or more. Treatment line was defined as consecutive chemotherapy line and dichotomized, 1st line or ≥ 2 lines.

Statistical Analysis

All analyses were performed using SPSS for Windows v. 22.0 (IBM Corporation, Armonk, USA). Descriptive statistics were used to describe the basic features of the data. Continuous data were tested for normal distribution and presented as mean and standard deviation (SD). Pearson's chi-squared test (χ^2) was applied to investigate statistical significant differences between groups when appropriate. Pearson correlation was used to investigate the correlation between SMI and hand grip strength. To investigate whether there was an association between muscle measures and treatment toxicity, univariable and multiple logistic regression analyses were applied. For this analysis muscle measures were investigated as continuous variables. Odds ratios and corresponding 95% Confidence Intervals (CIs) were reported.

To investigate median OS per tumor type, the Kaplan-Meier method was used.

Associations between muscle measures (continuous variables) and OS were investigated with univariable and multivariable Cox regression analyses. Hazard ratios and corresponding 95% CIs were reported.

To investigate the clinical value of muscle measures that were significantly associated with OS, we also studied the association of low versus normal muscle measures based on age and gender-based cutoff values, with OS using Cox regression analysis. Furthermore, the discriminative value of investigated cutoff values was examined by calculating the sensitivity and specificity as well as the area under the receiver operating characteristics (ROC) curve, with 0.70-0.80 representing fair and 0.80-1.00 representing good discrimination (28).

In the multivariable logistic and Cox regression analyses, we adjusted only for relevant confounders (defined as change of the regression coefficient of at least 10%) because of the sample size. Potential confounders included age, sex, comorbidity, cancer type and treatment line. In the final analyses age and comorbidity were not relevant and therefore not adjusted for.

A p-value of ≤ 0.05 was considered significant for all analyses.

Results

Of 364 patients included in the original study, 103 patients were eligible for the present analysis based on age, cancer type and available CT scan. The mean age of patients was 70.0 years (SD 6.6) and 66% were men (table 1). Approximately half of patients were diagnosed with CRC (52%) and 75% received first line cytotoxic treatment. Ten percent of patients had severe comorbidities and polypharmacy was present in 39%. The mean SMI was 46.7 cm^2/m^2 (SD 7.5) in men and 38.4 cm^2/m^2 (SD 6.3) in women. Mean radiodensity was 31.9 HU (SD 8.3) in men and 30.5 (8.8) in women. Mean hand grip strength was 39.8 kg (SD 10.8) in men and 25.5 kg in women (SD 7.0) Table 2 shows the mean muscle measures for all patients, and for each cancer type separately. Low muscle mass was present in 66% of patients, low muscle radiodensity in 88% and low muscle strength in 21%. There was a correlation between SMI and hand grip strength only in males (male p=0.003; female p= 0.137)

Treatment toxicity

Treatment toxicity occurred in 46 patients (46%), resulting in dose reduction in 27 patients and discontinuation of treatment in 19 patients. In total, 19 patients (18%) started treatment with a reduced dose upfront. The prevalence of treatment toxicity did not differ significantly between patients with and without baseline dose reductions (58% vs. 42%; p=0.199.) Thirty-seven percent of treatment toxicities were early treatment toxicities (within 42 days of treatment).

After adjusting for sex, cancer type and upfront dose reductions, we found no significant association of SMI (OR 1.04 95%CI 0.97-1.11), muscle attenuation (OR 1.03 95%CI 0.98-1.09) or muscle strength (OR 1.01 95%CI 0.96-1.06) with treatment toxicity (table 3). Adjusting for or limiting treatment toxicity to early treatment toxicity (within 42 days of treatment), did not change this.

Overall Survival

Median OS did not differ significantly per tumor type (14.8 months (95%CI 10.56-19.08) for patients with CRC, 15.0 months (95%CI 4.46-25.50) for breast- and 17.7 months (95%CI 8.17-27.31) for prostate cancer (p=0.986)).

After adjusting for sex, cancer type and treatment line, higher muscle strength was significantly associated with longer survival (HR 1.03 (95%CI 1.00-1.05)) (table 3). No significant associations were found for muscle mass and muscle attenuation with survival.

Furthermore, patients with normal muscle strength based on cutoff values had significantly longer OS than patients with low muscle strength (median OS 16.5 months vs OS 10.1 months (HR 1.75, 95% CI 1.02-3.00)) (figure 1) [23].

Sensitivity of low muscle strength in predicting six-month OS was 40% and specificity was 82%. The area under the ROC curve was 0.61.

Discussion

In this study, we evaluated whether muscle mass, muscle radiodensity and muscle strength were predictive for treatment toxicity and survival in older patients treated with chemotherapy for advanced cancer. Patients with higher muscle strength had longer OS than patients with lower muscle strength. Muscle measures and treatment toxicity were not associated with OS. The significant association between muscle strength and OS supports findings from a previous study in patients with advanced non-small cell lung and gastrointestinal cancer aged 18 years and older [21]. In healthy older adults, muscle strength was associated with OS as well [19]. This implies that muscle strength, as a frailty-marker, can potentially contribute to estimating survival, which may be used as one of the factors to select older patients for anti-cancer treatment [30,31]. However, although this study showed that cutoff values by Lauretani [27] for normal muscle strength can be used to predict OS, their discriminative value is low and may not be clinically useful [29]. This is mainly due to low sensitivity and a poor positive predictive value. The low sensitivity found in this study might be caused by a relatively high percentage of patients with upfront dose reductions who may have been fit to receive standard dosage [32].

In contradiction to younger patients with advanced cancer [5,7-11], muscle mass and muscle radiodensity were not significantly associated with OS in our group of older patients with advanced cancer. However, our finding that in older patients with advanced cancer muscle strength is more important in estimating OS than the muscle mass, supports previous findings of a cohort study among 2295 healthy older participants aged 70 years and older [18]. A possible explanation for the discrepancy in findings between muscle mass and muscle radiodensity with OS in older patients, is the relatively low muscle mass and low muscle radiodensity in our study compared to other studies in patients with cancer [7,10,11]. When cutoff values are used, prevalence rates of low muscle mass and low muscle radiodensity in our study population are higher than those reported in younger patients with cancer [7]. This suggests that in older patients with cancer, both ageing and cancer may contribute to loss of muscle mass and increase of fat accumulation in muscle. Therefore, age-adjusted cutoff values for this group of patients are needed. Furthermore, the finding of lower muscle mass and lower muscle radiodensity in this population raises the question whether improving muscle strength offers opportunities to improve OS, maintain functional independence or improve quality of life. In older community-based people exercise-based rehabilitation interventions or a resistance and aerobic exercise program have shown improvements in physical function and reduction in falls [33,34]. Moreover, in younger patients with breast cancer, it was shown that a combined supervised resistance and aerobic exercise program during adjuvant chemotherapy improved physical function and muscle strength and in addition less dose adjustments were required [35]. Future trials should investigate whether improving muscle strength improves OS.

In contrast to findings from previous studies[5,25], we found no significant association between muscle mass, muscle radiodensity and treatment toxicity. There are several possible explanations for the lack of significant associations. First, we included patients with three different cancer types and multiple treatment lines, therefore treatment regimens were heterogeneous. A previous study of Prado and Barrett [10;36] included a more homogeneous group of relatively young patients with respectively breast cancer

(55 patients, mean age 55 years) and CRC (51 patients, median age 65 years) with one type of treatment. However, adjusting for cancer type did not change the association in this study. Secondly, treatment toxicity in younger patients may solely be due to pharmacokinetic effects caused by decreased muscle mass [10], whereas in older patients pharmacokinetic effects are only partly responsible for causing treatment toxicity. Treatment toxicity in older patients may be multifactorial. Other possible causes are the ageing organ systems, such as the peripheral nervous system or bone marrow [37].

Strengths of this study are the simultaneous assessments of three important aspects of muscle, i.e. mass, radiodensity and strength, the specific focus on older patients with advanced cancer and the relatively large sample size. However, the inclusion of three cancer types may have resulted in heterogeneous treatment regimens. Although we did adjust for cancer type and treatment line, there may be some residual confounding affecting the association between muscle measures and treatment toxicity. Probably, most important, patients starting treatment with chemotherapy were selected, which may have resulted in a selected population with relatively high muscle strength.

In conclusion, in older patients treated for advanced CRC, breast or prostate cancer higher muscle strength is associated with longer OS. Therefore future studies should evaluate, the clinical use of muscle strength for judging whether or not a patient should receive palliative treatment to further optimize treatment outcome in this elderly population.

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