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

Kathelijn S. Versteeg
Susanne Blauwhoff-Buskermolen
Laurien M. Buffart
Marian A.E. de van der Schueren
Jacqueline A.E. Langius
Henk M.W. Verheul
Andrea B. Maier
Inge R. Konings

Submitted
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 both muscle mass and -quality, have been associated with treatment toxicity and OS. In the present study, we investigated whether muscle mass, -quality and -strength were associated with treatment toxicity and OS in patients with advanced cancer, aged 60 or older.

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

Results: 103 patients, aged 70 (SD 6.6) years, with advanced colorectal, prostate or breast cancer participated. Muscle parameters were not significantly associated with treatment toxicity. Compared to normative values, 21% had low muscle strength. Patients with adequate muscle strength had significantly longer OS than patients with low muscle strength (median OS 16.5 months vs 10.1 months (HR 1.75 (95% CI 1.02-3.00)). Muscle mass and -quality were not significantly associated with OS.

Conclusions: Adequate 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 quality have been described both in adult patients with cancer and in healthy older adults. In adults with cancer, low muscle mass and increased fat infiltration of the muscle, reflecting lower quality of muscle i.e. low muscle attenuation, have been observed in 15-55% of patients and were found to be predictive for treatment toxicity and survival (5-10). Decrease in muscle mass and muscle quality is associated with ageing (11,12). Depending on the definition, the prevalence of low muscle mass in older adults is up to fifty percent (13,14). Muscle quality is generally lower in older than in younger adults.

Because of the observed decrease in muscle mass and muscle quality, both in patients with cancer and 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 (6,8,9,15,16). However, age-related differences in prevalence of low muscle quality have not been reported in patients with advanced cancer.

Next to muscle mass and muscle quality, muscle strength is a third important determinant of muscle depletion (17). In the general population, muscle strength contributes to the identification of the 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 for poor clinical outcome in younger patients with advanced cancer (21).

In this study we prospectively studied the association of muscle mass, muscle quality 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 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

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 available within 40 days of start of treatment.

Body composition

Body weight, height and body mass index (BMI) 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 quality

All CT scans were obtained for clinical purposes. Muscle mass and muscle quality 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. cm²) and this value of muscle mass was normalized for stature (lumbar skeletal muscle index (SMI), cm²/m²) (24). Muscle quality, 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 quality were defined according to the sex- and BMI specific threshold values associated with low survival by Martin et al (5).

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). The test was performed 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, the patient was asked to perform 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 (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).
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 multiple 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 multiple logistic and Cox regression analyses, we adjusted for relevant confounders (defined as change of the regression coefficient of at least 10%).
Potential confounders included age, sex, comorbidity, cancer type and treatment line.
A p-value of \( \leq 0.05 \) 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 (± 6.6) and 66% were men (table 1).

**Table 1.** Patient characteristics (n=103)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>70.0 (6.6)</td>
</tr>
<tr>
<td>Sex (m)</td>
<td>68 (66)</td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37 (36)</td>
</tr>
<tr>
<td>1</td>
<td>53 (52)</td>
</tr>
<tr>
<td>2</td>
<td>9 (9)</td>
</tr>
<tr>
<td>unknown</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>54 (52)</td>
</tr>
<tr>
<td>Breast</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Prostate</td>
<td>34 (33)</td>
</tr>
<tr>
<td>Chemotherapy treatment line</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>77 (75)</td>
</tr>
<tr>
<td>2</td>
<td>17 (17)</td>
</tr>
<tr>
<td>3</td>
<td>7 (7)</td>
</tr>
<tr>
<td>( \geq 4 )</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index(^{17})</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>75 (73)</td>
</tr>
<tr>
<td>1</td>
<td>18 (18)</td>
</tr>
<tr>
<td>( \geq 2 )</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Polypharmacy, n (%)(^{a})</td>
<td>40 (39)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m(^2))</td>
<td></td>
</tr>
<tr>
<td>(&lt; 20 ) kg/m(^2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>20-24.9 kg/m(^2)</td>
<td>35 (34)</td>
</tr>
<tr>
<td>25-29.9 kg/m(^2)</td>
<td>53 (52)</td>
</tr>
<tr>
<td>( \geq 30 ) kg/m(^2)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Skeletal Muscle Index (cm(^2)/m(^2))(^*)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46.7 (7.5)</td>
</tr>
<tr>
<td>Women</td>
<td>38.4 (6.3)</td>
</tr>
<tr>
<td>Muscle attenuation (HU)*</td>
<td>31.5 (8.4)</td>
</tr>
<tr>
<td>Hand grip strength (kg)*</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39.8 (10.8)</td>
</tr>
<tr>
<td>Women</td>
<td>25.5 (7.0)</td>
</tr>
</tbody>
</table>

Abbreviations: HU: Hounsfield Units
\(^{a}\)Mean (sd)
\(^{a}\)Polypharmacy is defined as 5 or more different types of medication
Chapter 7

Approximately half of patients were diagnosed with CRC (52%) and 75% received first line cytotoxic treatment. Ten percent of patients had severe comorbidities and in 39% polypharmacy was present.

Table 2 shows the prevalence of low muscle measures for all patients, and for each cancer type separately.

<table>
<thead>
<tr>
<th>Table 2. Prevalence of low muscle measures, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer types (n=103)</td>
</tr>
<tr>
<td>Low muscle mass*</td>
</tr>
<tr>
<td>Low muscle quality^</td>
</tr>
<tr>
<td>Low hand grip strength</td>
</tr>
</tbody>
</table>

* Low muscle mass*: men BMI < 25: low SMI < 43 cm²/m²; men BMI ≥ 25: low SMI < 53 cm²/m²; women: low SMI , 41 cm²/m².

^ Low muscle quality^: BMI < 25: low muscle quality < 41 HU; BMI ≥ 25: low muscle quality < 33 HU.

Low muscle mass was present in 66% of patients, low muscle quality in 88% and low muscle strength in 21% of patients.

**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).
Higher muscle strength and prolonged survival in elderly

Table 3. Associations between muscle measures and treatment toxicity/overall survival (n=103)

<table>
<thead>
<tr>
<th></th>
<th>Treatment toxicity</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>SMI (cm²/m²)</td>
<td>1.01</td>
<td>0.97-1.06</td>
</tr>
<tr>
<td>Muscle quality (HU)</td>
<td>1.01</td>
<td>0.96-1.06</td>
</tr>
<tr>
<td>Hand grip strength (kg)</td>
<td>1.02</td>
<td>0.99-1.05</td>
</tr>
</tbody>
</table>

Abbreviations: SMI: skeletal muscle index (muscle mass); HU: Hounsfield Units

*Adjusted for sex, cancer type, baseline dose reduction

**Adjusted for sex, cancer type, treatment line

Adjusting for or narrowing treatment toxicity to early treatment toxicity, did not change this.

Overall Survival

Median OS was 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).
Figure 1. Kaplan Meier curve for association of low hand grip strength, defined as <30.3 kg for men and <19.3 kg for women, and overall survival

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 quality and muscle strength were predictive for treatment toxicity and survival in older patients treated with chemotherapy for advanced cancer. Adequate muscle strength predicted for significantly longer OS. Muscle measures and treatment toxicity were not related in this group of patients that were already selected to be treated with chemotherapy. The significant association between muscle strength and OS supports findings from a previous study in patients with advanced cancer aged 18 years and older (21). In healthy older adults, muscle strength is associated with OS as well (19). This implies that muscle strength can potentially contribute to estimating life expectancy, which may be used as one of the factors to select older patients for anti-cancer treatment.
Higher muscle strength and prolonged survival in elderly patients with advanced cancer: In several previous studies in younger patients with advanced cancer, muscle mass and muscle quality were significantly associated with OS (5-10). However, our finding that in older patients with advanced cancer muscle strength is more important in estimating survival 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 quality with OS in older patients is the high prevalence of low muscle mass and low muscle quality in our study compared to other studies in patients with cancer (5,9,10). We found that 66% of older patients with advanced cancer had low muscle mass and 88% had low muscle quality. These prevalence rates are higher than in younger patients with cancer (5), suggesting that in older patients with cancer, both natural ageing and cancer may contribute to loss of muscle mass and increase of fat accumulation in muscle. This implies that age-adjusted cutoff values for this group of patients are needed. Furthermore, the finding of the high prevalence of low muscle mass and low muscle quality 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 functioning and muscle strength and in addition less dose adjustments were required (35). Future trials should investigate whether improving muscle strength improves OS.

Although previous studies described an association between muscle mass, muscle quality and treatment toxicity, we did not find this association (8,25). 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. Prado and Barrett 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 (9;36). However, adjusting for cancer type did not change the association in this study. Secondly, the causes of treatment toxicity in older patients with cancer are numerous. In contrast to younger patients where treatment toxicity may solely be due to a pharmacokinetic effect caused by a decrease in muscle mass (9), treatment toxicity in older patients may also be related to the ageing of various 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, quality 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 have adjusted 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, patients treated for advanced CRC, breast or prostate cancer do survive significantly longer when having adequate muscle strength compared to patients with low muscle strength. Based on this finding, in future studies the clinical use of muscle strength for judging whether or not a patient should receive palliative treatment should be one of the factors to be evaluated to optimize treatment outcome in this elderly population.
Higher muscle strength and prolonged survival in elderly

References


30. Cooper R, Kuh D, Hardy R. Objective measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 2010;341:c4467


