Body composition indices and tissue loss in patients with resectable gastric adenocarcinoma

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Abstract

Background Body composition analyses from computed tomography (CT) scans have been used to assess cachexia in cancer patients. We investigated body composition indices, tissue change and treatment outcome in patients with resectable gastric adenocarcinoma.

Methods A cohort analysis of all patients treated with curative intent for gastric adenocarcinoma in two Scandinavian university hospitals from 2008-2011 was performed (n=137). Body composition analyses were performed on CT images taken for routine diagnostics and staging. Both preoperative single scans and repeat CT examinations were analyzed.

Results Perioperative chemotherapy was given to 58 (42.3%) patients. Forty patients (29.2%) suffered severe postoperative complications and 70 (51.1%) patients died within three years. There was a significant reduction in patients’ lean tissue during neoadjuvant chemotherapy (p=0.001). There was no association between skeletal muscle tissue index and postoperative complications. Poorer survival was observed in patients with preoperative skeletal muscle tissue index within the lowermost quartile, independent of tumor characteristics and neoadjuvant treatment (HR=1.91, 95% CI 1.11-3.28, p=0.019).

Conclusions Patients lost lean tissue during neoadjuvant treatment for gastric adenocarcinoma. Low preoperative skeletal muscle index was not associated with postoperative complications, but strongly associated with poorer survival.

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Keywords: Body composition, Cachexia, Gastric cancer, Surgery

Received 06 November 2016 Accepted 16 March 2017

Introduction

Patients diagnosed with gastric cancer may suffer from cachexia involving muscle loss, which may progress during the course of treatment [1,2]. Resection for gastric cancer is associated with high morbidity and poor long-term prognosis [3]. While perioperative chemotherapy has been shown to increase survival [4], a high degree of toxicity has been reported [5].

Body composition indices based on computed tomography (CT) images have been used to evaluate muscle mass in cancer patients [6-8]. Many studies have reported an association between the relative amount of muscle tissue and morbidity or survival, while others again have failed to show this connection [8-12]. Low muscle mass, assessed from CT images, has also been linked to chemotherapy toxicity and postoperative morbidity [2,13,14]. While most studies on body composition indices have used only single CT examinations (performed at a single point-in-time) [8,10,12], changes over time in the amount of lean and fat tissue during neoadjuvant treatment have been described in patients with gastroesophageal and pancreatic cancer [1,2,15,16]. These changes have yet to be consistently linked to clinical outcome [1,2,15,16]. Cancer cachexia has been defined as a multifactorial syndrome with ongoing loss of skeletal muscle mass [17]. To what extent cancer cachexia can be evaluated through preoperative body composition indices from a single CT examination remains uncertain. Furthermore, it is
uncertain how these indices relate to disease stage. Information on these issues together with validated disease-specific cut-offs are of key importance for body composition indices to be used in an everyday assessment of treatment, risk and prognosis in cancer surgery.

Only a few studies on body composition indices have been performed on patients with resectable gastric adenocarcinoma [8,12]. This is noteworthy as low muscle mass is highly prevalent [12] and repeat CT examinations are available due to routine administration of perioperative chemotherapy [5,9].

We aimed to investigate preoperative body composition indices and association with tumor characteristics and treatment outcome. Furthermore, we aimed to investigate tissue change during neoadjuvant chemotherapy.

**Patients and Methods**

**Cohort**

A complete cohort of all patients who underwent gastric resection with curative intent for adenocarcinoma in the four-year period 2008-2011 in two Scandinavian referral centers (University hospital of Northern Norway, Tromsø, Norway and Karolinska University Hospital at Huddinge, Stockholm, Sweden) was retrospectively analyzed (n=137). Information on general characteristics, comorbidity, histopathological stage, chemotherapy treatment and -toxicity, postoperative complications and overall survival was retrieved from patient files.

Body composition analysis depended on the availability of computed tomography (CT) images of sufficient quality. Hence, all patients with available preoperative CT images were included (n=116). A subgroup analysis was performed on those patients who received neoadjuvant chemotherapy with available CT images from oncological staging (pre-chemotherapy) and response evaluation (preoperatively) (n=45).

**Body composition analyses**

CT examinations were originally performed for routine diagnostics and staging. CT images were analyzed using Slice-O-Matic software V4.2 (Tomovision, Montreal-Canada) which permitted specific tissue demarcation using Hounsfield unit threshold of -29 to +150 for skeletal muscles [18], -150 to -50 for visceral adipose tissue [19], and -190 to -30 for subcutaneous adipose tissue [18]. Cross-sectional areas (cm²) were calculated for each tissue by summing tissue pixels and multiplying by the pixel surface area. A transverse CT image from the third lumbar vertebrae (L3) was assessed for each scan and tissue areas estimated [20]. All CT images were sent to Edinburgh, United Kingdom, and analyzed by a trained observer who was blinded to all clinical data (N.J.)

Cross-sectional area was normalized for stature (cm²/m²) [6] and indices were calculated for skeletal muscle tissue (SMT), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT). Total whole-body amount of lean tissue (FFM=fat-free mass) and fat tissue (FM=fat mass) were estimated from the following formulas [6]:

\[
\text{FFM} \text{ (kg)} = 0.3 \times \text{L3 Skeletal muscle area (cm}^2\text{)} + 6.06 \times \text{FM (kg)} = 0.042 \times \text{L3 Visceral and subcutaneous adipose tissue area (cm}^2\text{)} + 11.2
\]

**Definition of variables**

Resections were classified into total gastrectomy, subtotal gastrectomy and distal gastric resection with pancreaticoduodenectomy. Almost all procedures were performed as open surgery with D2 lymphadenectomy. Body mass index (BMI) was calculated from the following formula [21]:

\[
\text{BMI} \text{ (kg/m}^2\text{)} = \frac{\text{Weight (kg)}}{\text{Height}^2 \text{ (m}^2\text{)}}
\]

Obesity was defined as BMI above 30 kg/m² [7]. Comorbidity was assessed according to the American Society of Anesthesiologists (ASA) classification. Diabetes mellitus was defined as medically treated disease (insulin or oral medication). Abnormal serum – c-reactive protein (s-CRP) was defined as s-CRP above 5 mg/L. Post-resection histopathological stage was classified according to the TNM classification, 7th edition. The default definition of low muscle mass was according to the cut-off suggested by Mourtzakis et al [6], later supported by an international consensus panel [17] and the latest European society for clinical nutrition and metabolism (ESPEN) guidelines [22]. This cut-off represents a skeletal muscle tissue index more than two standard deviations from that of healthy young adults (<39 cm²/m² for women and <55 cm²/m² for men) [6]. We also performed analyses with the cut-off suggested by Martin et al [23], which defines low muscle mass relative to BMI: Skeletal muscle tissue index <41 cm²/m² for all women and <43 cm²/m² for men with BMI ≥25 kg/m²; and <53 cm²/m² for men with BMI ≥25kg/m². Furthermore, survival was analyzed for patients with skeletal muscle tissue in the lowermost quartile in our cohort (<35.4 cm²/m² for women and <43.3 cm²/m² for men). Sarcopenic obesity was defined as Skeletal muscle tissue index within the lowermost quartile in our cohort combined with BMI >30 kg/m². Visceral obesity was defined as L3 visceral adipose tissue area above 130 cm² [10].

Patients received perioperative chemotherapy according to the indications and standards described by Cunningham et al in 2006 [4], with a somewhat modified chemotherapeutic regimen [3] i.e. a combination of Epirubicin, Oxaliplatin or Cisplatin, and Capecitabin (EOX or ECX regimen). Three cycles, given every three weeks, were administered both neoadjuvant and adjuvant. Complications (within 90 days after surgery) were classified by the Accordion classification [24,25]. Severe postoperative complications were defined as one or more complication graded Accordion III or higher [24,25]. Overall survival was calculated from the date of index surgery and all patients were followed for three years or more.

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Statistics

Statistical analyses were performed with SPSS v22 statistics software (IBM, NYC - USA). Normally distributed data were described with mean value and 95% confidence interval (95% CI). Non-normally distributed data were described with median value and interquartile range (IQR). Differences between groups and categories were analyzed with Student’s t-test, analysis of variance (ANOVA) and Pearson chi-square test. One-way t-test was used for analysis of two repeated measures. Non-normally distributed data were analyzed with Mann-Whitney U-test and Kruskall-Wallis test. Linear regression analysis was used to analyze the association between patient characteristics, disease stage and body composition indices. Logistic regression analysis was used to analyze the association between patient characteristics, body composition indices and postoperative complications. Overall survival was analyzed using Cox proportional hazard regression analyses; the assumption of proportional hazards was visually inspected by log-log survival curves. P-values <0.05 were considered statistically significant.

Results

Our cohort consisted of 137 patients with a median age of 70 years and of whom 77 (56%) were male. Perioperative chemotherapy was administered to 58 (42%) patients, 32 (55%) of these patients completed both neoadjuvant and adjuvant treatment. Total and subtotal gastrectomy were performed in 86 (63%) and 47 (34%) patients respectively. Distal gastric resection with pancreaticoduodenectomy was performed in four (3%) patients with distal gastric adenocarcinoma involving duodenum. The number of patients who died within three years was 70 (51%). Forty (29%) patients suffered severe postoperative complications.

Preoperative Computed Tomography (CT) images of sufficient quality were available in 116 patients and 49 (42%) of them received neoadjuvant chemotherapy. Of the 116 patients, 30 (26%) suffered severe postoperative complications and 58 (50%) died within three years. Baseline characteristics in patients with available preoperative CT images are given in Table 1.

Tissue loss during neoadjuvant chemotherapy

In patients treated with neoadjuvant chemotherapy (NAC) a median of ninety days (IQR: 77-103) passed between the initial diagnostic/staging CT and the preoperative CT examination. There was a significant loss of lean tissue during this period (p=0.001), with a median loss of 1.1 kg (IQR=0.2-3.1 kg) or 3% of the estimated lean tissue at the beginning of NAC. The proportion of patients with low muscle mass (SMT index below 39 cm²/m² for women and below 55 cm²/m² for men) increased from 58% prior to NAC and to 67% at the end of NAC. No significant loss of fat tissue (p=0.16) was observed. The distribution of tissue change during neoadjuvant chemotherapy are illustrated in Figure 1.

Preoperative body composition indices

A median of 23 days (IQR=9-43) passed between the preoperative CT examination and surgery. There was a strong correlation between the estimated amount of tissue (lean and fat tissue combined) from the CT images and total body weight reported in the patient file (r=0.89, p<0.001). Low muscle mass was present in 78 (67%) of the patients. Skeletal muscle tissue (SMT) index was higher in patients who did not receive chemotherapy prior to surgery, compared to patients who did (Estimated difference: 3.8 cm²/m², 95% CI=0.9-6.8, p=0.011, adjusted for age and gender). Diabetes mellitus was associated with a higher visceral adipose tissue (VAT) index. The estimated difference in VAT index between patients with (n=11) and without diabetes mellitus was 20.1 cm²/m² (95% CI=1.1-39.2, p=0.039, adjusted for age and gender). Older age was associated with lower SMT index (Table 2). Male gender was associated with a higher SMT index (Table 2). There was no association between comorbidity or tumor characteristics (histopathological examination of the resected specimen) and SMT index (Table 2).

The only factor associated with increased rate of severe postoperative complications was abnormal s-CRP preoperatively (OR=2.77, 95% CI=1.12-6.89, p=0.025). There was no association between BMI and postoperative complications (p=0.33). Neither SMT nor VAT index was associated with postoperative complications (both p-values >0.4, adjusted for age and gender).

More advanced tumor-stage and regional lymph node metastasis were both associated with poorer survival (Table 3). The administration of perioperative chemotherapy was not associated with overall survival (p=0.14). Higher preoperative SMT index was associated with improved survival (Table 3). Patients with SMT index within the lowermost quartile had poorer survival (HR=2.08, 95% CI=1.21-3.57, p=0.008, adjusted for age and gender), 21 (72%) of these patients died within three years. This association remained relatively unchanged when adjusted for age, gender, tumor characteristics and whether NAC was given or not (HR=1.91, 95% CI 1.11-3.28, p=0.019).

There was no association between low muscle mass and survival when using any other cut-offs (Table 3).
Body composition indices and tissue loss in patients with resectable gastric adenocarcinoma

Table 1 Baseline characteristics of patients with available preoperative computed tomography images (n=116), [1]Visceral adipose tissue area >130 kg/m²; cut-off for sarcopenia suggested by Mourtzakis et al: Skeletal muscle tissue index <39 cm²/m² for women and <55 cm²/m² for men, [2] Cut-off for sarcopenia suggested by Martin et al: Skeletal muscle tissue index <41 cm²/m² for all women, <43 cm²/m² for men with BMI <25 kg/m² and <53 cm²/m² for men with BMI ≥25 kg/m², [3] Patients with skeletal muscle tissue index within the lowermost quartile: <35.4 cm²/m² for women and <43.3 cm²/m² for men, c-CRP = serum – c-reactive protein, BMI = Body Mass Index, SMT = Skeletal Muscle Tissue, VAT = Visceral Adipose Tissue

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<tr>
<th>Variable</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>ASA 1</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>ASA 2</td>
<td>71 (61%)</td>
</tr>
<tr>
<td>ASA 3/4</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>s-CRP &gt;5mg/L</td>
<td>30 (26%)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>25.4 (4.4)</td>
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<tr>
<td>Obese (BMI &gt;30 kg/m²)</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>Visceral obese</td>
<td>57 (49%)</td>
</tr>
<tr>
<td>SMT index males (cm²/m²), mean (SD)</td>
<td>48.0 (7.5)</td>
</tr>
<tr>
<td>SMT index females (cm²/m²), mean (SD)</td>
<td>40.5 (6.6)</td>
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<tr>
<td>Sarcopenia, Mourtzakis</td>
<td>78 (67%)</td>
</tr>
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<td>Sarcopenia, Martin</td>
<td>52 (45%)</td>
</tr>
<tr>
<td>Sarcopenia, 1. Quartile</td>
<td>29 (25%)</td>
</tr>
<tr>
<td>Advanced T-stage (T3/T4)</td>
<td>71 (61%)</td>
</tr>
<tr>
<td>Lymph node metastasis (N+)</td>
<td>61 (53%)</td>
</tr>
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</table>

Table 2 The estimated impact of patient characteristics and disease stage on skeletal muscle tissue index. Linear regression analysis, adjusted for age and gender. Stratified on the administration of neoadjuvant chemotherapy. Estimated difference (95% confidence interval) in skeletal muscle tissue index (cm²/m²) compared with: - Patients with age <70 years (adjusted for gender only), - Women (adjusted for age only), - Patients with ASA1-2 (American Society of Anesthesiologists classification of comorbidity), - Patients with T1/T2 tumor stage (TNM, data from histopathological examination), - Patients with no lymph node metastasis (TNM, data from histopathological examination), Patients who did (n=49) or did not (n=67) receive neoadjuvant chemotherapy (NAC) were analyzed separately, due to the impact on preoperative skeletal muscle tissue index from the administration of NAC

<table>
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<th>No neoadjuvant chemotherapy (n=67)</th>
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<tr>
<td></td>
<td>Difference (95% CI) p-value</td>
<td>Difference (95% CI) p-value</td>
</tr>
<tr>
<td>Older age (&gt;70y)</td>
<td>-4.7 (-10.8/1.4) 0.13</td>
<td>-7.3 (-11.0/3.7) &lt;0.001</td>
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<tr>
<td>Male gender</td>
<td>9.7 (5.6/13.7) &lt;0.001</td>
<td>6.0 (2.7/9.4) 0.001</td>
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<tr>
<td>ASA 3-4</td>
<td>-0.3 (-8.1/7.4) 0.93</td>
<td>-1.5 (-5.2/2.1) 0.40</td>
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<td>T3/T4 stage</td>
<td>-2.2 (-6.4/2.0) 0.30</td>
<td>0.1 (-3.4/3.5) 0.98</td>
</tr>
<tr>
<td>N+</td>
<td>-2.6 (-6.7/1.5) 0.20</td>
<td>-2.1 (-1.2/5.4) 0.21</td>
</tr>
</tbody>
</table>

Table 3 The impact of selected risk factors, preoperative body composition indices and disease stage (histopathological stage in resection specimen)
on overall survival. Cox proportional hazard regression analysis, adjusted for age and gender. Statistically significant values (p<0.05) in bold writing: [1] Hazard ratio (95% confidence interval) for mortality within the follow-up period, [2] Cut-off for sarcopenia suggested by Mourtzakis et al.: Skeletal muscle tissue index <39 cm²/m² for women and <55 cm²/m² for men, [3] Cut-off for sarcopenia suggested by Martin et al.: Skeletal muscle tissue index <41 cm²/m² for all women, <43 cm²/m² for men with BMI <25 kg/m² and <53 cm²/m² for men with BMI ≥25 kg/m², [4] Patients with skeletal muscle tissue index within the lowermost quartile: <35.4 cm²/m² for women and <43.3 cm²/m² for men, [5] Visceral adipose tissue area ≥130 kg/m², [6] Tumor-stage according to TNM classification. Compared to patients with T1 and T2 tumors, s-CRP = serum – C-Reactive Protein, BMI = Body Mass Index, SMT = Skeletal Muscle Tissue, VAT = Visceral Adipose Tissue

<table>
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<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<td>ASA 1</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>ASA 2</td>
<td>1.71 (0.61-4.78)</td>
<td>0.31</td>
</tr>
<tr>
<td>ASA 3/4</td>
<td>2.40 (0.78-7.34)</td>
<td>0.13</td>
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<tr>
<td>s-CRP &gt;5mg/L</td>
<td>1.74 (1.00-3.05)</td>
<td>0.052</td>
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<td>BMI (continuous)</td>
<td>0.95 (0.89-1.01)</td>
<td>0.086</td>
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<tr>
<td>Obese (BMI &gt;30 kg/m²)</td>
<td>0.60 (0.28-1.25)</td>
<td>0.17</td>
</tr>
<tr>
<td>SMT index (continuous)</td>
<td>0.95 (0.92-0.99)</td>
<td>0.024</td>
</tr>
<tr>
<td>Sarcopenia, Mourtzakis¹</td>
<td>1.43 (0.79-2.61)</td>
<td>0.24</td>
</tr>
<tr>
<td>Sarcopenia, Martin¹</td>
<td>1.12 (0.68-1.86)</td>
<td>0.66</td>
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<tr>
<td>Sarcopenia, 1. Quartile²</td>
<td>2.08 (1.21-3.57)</td>
<td>0.008</td>
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<tr>
<td>VAT index</td>
<td>0.99 (0.99-1.00)</td>
<td>0.11</td>
</tr>
<tr>
<td>Visceral obese⁵</td>
<td>0.66 (0.38-1.16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Advanced T-stage (T3/T4)⁶</td>
<td>2.94 (1.65-5.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymph node metastasis (N+)</td>
<td>5.83 (3.24-10.48)</td>
<td>&lt;0.001</td>
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</table>

**Discussion**

We have demonstrated that patients suffer significant tissue loss during neoadjuvant chemotherapy treatment for gastric adenocarcinoma. Low muscle mass was highly prevalent in our patients compared to what has been reported in patients with other resectable gastrointestinal and hepatobiliary malignancies [8].

Body composition indices from preoperative CT examinations were not associated with tumor characteristics and lower preoperative skeletal muscle tissue index was independently associated with poorer survival. The findings might indicate that low muscle mass is an independent indicator of poor prognosis in patients with resectable gastric adenocarcinoma.

We observed significant tissue loss during neoadjuvant chemotherapy. This might show that estimated tissue loss is quantifiable in patients receiving multiple CT scans for diagnostic and staging purposes and therefore may serve as a feasible continuous outcome in future studies on e.g. nutrition, prehabilitation and rehabilitation. There was a high correlation between the estimated body weight and the body weight reported in patients’ medical records. This confirms the validity of estimating whole-body tissue volumes from single L3 CT images.

Lower preoperative SMT index was not associated with complications after gastric resections which is in concordance with another recent study [12]. The pioneer studies of Windsor and Hill in the eighties demonstrated that preoperative protein depletion only constitutes a high risk of adverse outcome when such protein depletion is combined with functional impairment [26]. A more recent study has shown a remarkable association between the combination of sarcopenia, frailty and malnutrition, and complications after colorectal cancer surgery [14]. Preoperative body composition indices might be even more useful if combined with evaluation of functional impairment to assess the risk of morbidity after gastric resections.

Neither of the established cut-offs for low muscle mass [6;23], both frequently used in the recent years [11,12,15,22], were associated with survival in our study. This illustrates the importance of also using continuous variables wherever possible when assessing potential dose-response relationships [27]. The clinical impact of lower skeletal muscle tissue mass seems to depend on both populations, cancer type and stage [8,16], and appropriate cut-offs have to be developed and validated accordingly.

Increasing BMI was almost statistically significantly associated with increased survival and obesity was not associated with either postoperative complications or survival. This is consistent with the findings in several other recent studies and suggests that obesity is not associated with poor outcome after cancer treatment [12,28,29]. Visceral adiposity from CT images in our series was not associated with postoperative complications or survival. While visceral adiposity has been associated with diabetes [also confirmed in our study] and diabetes again has been associated with adverse postoperative outcome, evaluations of a direct association between adipose tissue indices and adverse outcome have shown conflicting results [10,12].

While the total number of patients in our study was limited, they represent a complete cohort of patients with resectable adenocarcinoma of the stomach during a four-
year period at two major Scandinavian university hospitals. As an unselected cohort, our data provide an insight into clinical aspects regarding body composition analyses in gastric cancer surgery.

Conclusions

Patients with resectable gastric cancer lost lean tissue during neoadjuvant chemotherapy. Lower preoperative skeletal muscle index was not associated with postoperative complications, but strongly associated with worse survival. Patients with skeletal muscle tissue index in the lowermost quartile in our cohort had a more than twofold risk of mortality within the follow up period.

Ethical considerations

Data retrieval, publication and dispensation from informed consent requirement, was approved by the Regional Committee on Research Ethics, Northern Chapter (REK V). The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle - Clinical Reports (von Haehling S, Ebner N, Morley JE, Coats AJ, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle - Clinical Reports. J Cachexia Sarcopenia Muscle Clinical Reports 2016; 1:e28:1-2.)

Conflicts of Interest

EK Aahlín, T Irino, N Johns, TB Brismar, M Nilsson, A Revhaug and K Lassen declare that they have no conflicts of interest.

References:


1998;351:871-875.