The Prognostic Impact of Trastuzumab Resistance and Body Composition Parameters in Metastatic Breast Cancer

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www.chestergibs.com
Print: Ridderprint BV
ISBN 978-94-6299-963-3

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Trastuzumabresistentie en lichaamssamenstelling:
Prognostische waarde bij uitgezaaide borstkanker

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

Woensdag 13 juni 2018 om 15:30 uur

door

Hánah Nicole Rier

geboren te Amsterdam
op 13 april 1987

Erasmus University Rotterdam

Promotiecommissie:

Promotor:	**Prof. dr. S. Sleijfer**
Overige leden:	**Prof. dr. J.N.M. IJzermans** **Prof. dr. J.L.C.M. van Saase** **Prof. dr. H.M.W. Verheul**
Copromotoren:	**dr. A. Jager** **dr. M-D. Levin**

De drukkosten van dit proefschrift werden vriendelijk gesponsord door:

Celgene B.V.

Erasmus Medisch Centrum

Het verschijnen van dit proefschrift en de CHARMING-studie werden mede mogelijk gemaakt en financieel ondersteund door:

Stichting ORAS (Oncological Research Albert Schweitzer Hospital)

Leerhuis en Wetenschapscommissie Albert Schweitzer ziekenhuis, Dordrecht

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Chapter 1

General introduction and outline of the thesis

Hánah N. Rier

Introduction

Cancer is the most common cause of death in the Netherlands and the Integral Cancer center of the Netherlands (IKNL) expects the incidence of cancer to increase in the upcoming years. In 2014, 104 patients per 100.000 people were diagnosed with cancer, compared to 57 per 100.000 people in 1990 [1]. Breast cancer is the highest prevalent cancer in the Netherlands, with 1 in 8 women developing breast cancer at some point during their life, and the second cause of death in women with more than 3000 deaths per year [2]. (Figure 1)

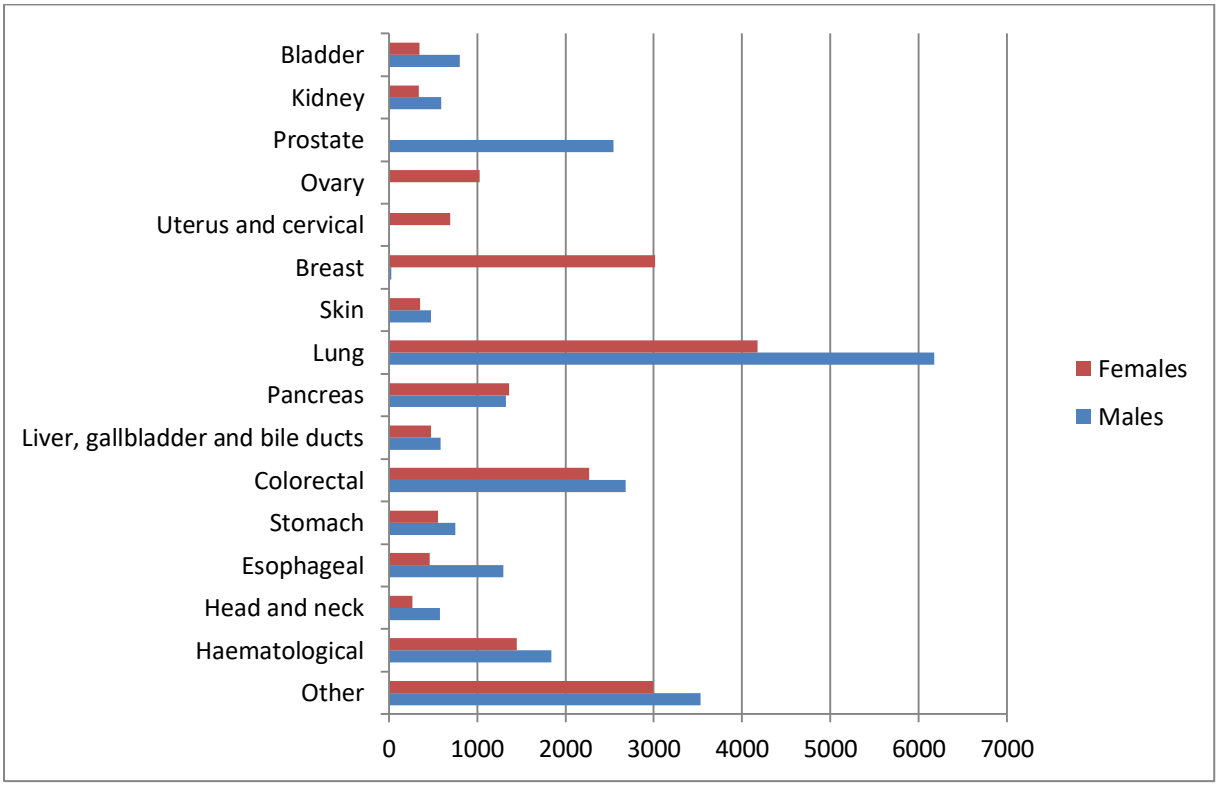

Figure 1. Numbers of cancer-related deaths in the Netherlands in 2014 [1].

Risk factors associated with breast cancer include obesity, smoking, alcohol use, null parity, early menarche, older age at first birth, a positive family history and genetic predisposition [3, 4]. The treatment of breast cancer is increasingly personalized and depends on the disease stage, the tumor type (i.e. hormone receptor status and the amplification level of the Her2 receptor), the age and the menopausal status of the patient. In general, surgery with or without radiotherapy is conducted in patients with primary breast cancer. In patients with a high relapse risk, perioperative systemic treatment is given consisting of chemotherapy, and/or

endocrine therapy in case of estrogen/progesterone receptor positivity and/or Her2-targeted therapy in case of Her2 receptor overexpression. Peri-operative systemic treatment is dependent on relapse risk, tumor characteristics and the age of the patient [5]. Metastatic breast cancer (MBC) is considered an incurable disease and systemic treatment with cytotoxic, endocrine and/or Her2 targeted agents is the cornerstone of the therapy.

Her2 targeted therapy in breast cancer`

In the literature, numerous subtype classifications for breast cancers exist. In the most commonly used system, breast cancer is categorized into the following subtypes: "Luminal A" (ER positive, Her2 negative, Ki-67 low, progesterone receptor high, low risk molecular signature), "luminal B" (ER positive and Her2 positive or ER positive and Her2 negative with either Ki-67 high or progesterone receptor low or high risk molecular signature), "Her2 positive" (ER negative) and "basal-like" (triple negative) [6]. These subtypes are partly decisive for the prognosis and the treatment strategy. The luminal A subtype is considered having the best prognosis and the triple negative subtype has the worst prognosis. In the pre-trastuzumab era, Her2 positive tumors were associated with rapid progression and poor prognosis, but since the introduction of Her2-targeted therapy, the survival of patients with Her2 positive breast cancer is comparable with hormone positive tumors [7]. Generally, low risk luminal A tumors are treated with endocrine therapy, luminal B tumors with endocrine therapy and possibly chemotherapy, and for Her2 positive and triple negative tumors, chemotherapy is indicated [8]. Treatment strategies differ, however, because of tumor- and disease characteristics and the preference of the patient. In the treatment strategies for the HER2-positive tumors, HER2 targeting agents such as trastuzumab, pertuzumab, T-DM1 and lapatinib play an important role. Trastuzumab is a monoclonal antibody binding to the extracellular segment of the Her2 receptor, resulting in inhibition of tumor proliferation [9].

Trastuzumab was approved for the treatment of Her2 positive MBC in 1998 after a substantial improvement of survival in these patients [10-13]. In a phase III trial involving 469 patients with Her2 positive MBC, participants were randomly assigned to receive chemotherapy or chemotherapy with trastuzumab. Patients receiving trastuzumab had a longer median time to disease progression (7.4 months vs. 4.6 months, $p < 0.001$), a larger percentage of overall response (50% vs. 32%, $p < 0.001$), and longer overall survival (25.1 vs. 20.3 months, $p = 0.046$) than patients receiving only chemotherapy [10].

The approval of trastuzumab for adjuvant treatment followed in 2006 after good efficacy and safety in clinical trials [14-18]. In the HERA trial (a phase III randomized open label trial) [16], treatment with trastuzumab for 1 or 2 years was compared with observation in 5102 patients. The addition of trastuzumab to adjuvant chemotherapy resulted in a significantly improved disease-free- and overall survival (HR 0.64, 95% CI 0.54 – 0.76 and HR 0.66, 95% CI 0.47 – 0.91 respectively) [19]. In the BCIRG-006 trial, trastuzumab with doxorubicin, cyclophosphamide and docetaxel or trastuzumab with docetaxel and carboplatin was compared with chemotherapeutic monotherapy (doxorubicin, cyclophosphamide and docetaxel). Both disease-free and overall survival rates were superior in the trastuzumab arms after a follow up of 5 years (84% and 81% vs. 75%, $p < 0.001$ and 92% and 91% vs. 87%, $p = 0.04$) [14].

The change of the initial poor prognosis of Her2 positive breast cancer caused by trastuzumab led to an increase in the research of other Her2 targeting agents in both adjuvant and palliative setting. Currently, dual blockade of the Her2 receptor with trastuzumab and pertuzumab in combination with docetaxel is recommended as first line palliative systemic therapy in patients with Her2 positive MBC [20] after showing survival benefit in the CLEOPATRA trial [21]. In the EMILIA trial, trastuzumab-emtansine (T-DM1) or lapatinib was combined with capecitabine. T-DM1 showed superior efficacy than lapatinib in patients with progressive disease after treatment with trastuzumab and a taxane (HR for progression 0.65, 95% CI 0.55 – 0.77, $p < 0.001$, HR for overall survival 0.68, 95% CI 0.55 – 0.85, $p < 0.001$) [22]. Consequently, T-DM1 combined with standard chemotherapy is currently recommended as second line therapy in Her2 positive MBC [20]. Blockade of the Her2 receptor with more than one anti-Her2 agent in the adjuvant setting currently does not belong to the standard care yet, but recent trials suggest a possible benefit of the addition of pertuzumab to standard adjuvant trastuzumab therapy [23, 24]. In contrast, the combination of adjuvant lapatinib and trastuzumab has failed to provide further benefit so far [25].

The widespread application of trastuzumab in the adjuvant setting has substantially improved the outcome for patients with HER2-positive primary breast cancer. For those who despite the adjuvant treatment face a relapse, trastuzumab-based regimens are indicated. In this setting of advanced disease, patients have been pretreated with trastuzumab. Whether the benefit of trastuzumab is similar in this setting, as was seen in the initial publications of trastuzumab in the metastatic setting, remains unknown. Furthermore, a few concerns have risen regarding

the duration of systemic therapies in MBC and the selection of patients for these treatments. Cytotoxic regimens with anthracyclins and taxanes often induce cardiotoxicity, neuropathy and myalgia [26-28]. Her2 targeted therapy has extended the overall survival to more than 5 years in more than 10% of the patients with Her2 positive MBC [29] but is associated with cardiotoxicity and high costs. As patients live longer, the question rises how long anti-Her2 maintenance therapy should be continued. In addition, resistance to trastuzumab after initial response is an increasingly observed phenomenon and the mechanism of resistance is possible partly dependent of the sequence of previous treatment lines, thus differs between patients [30].

So, the selection of the right patient for the right treatment is essential but remains a challenge, especially in older cancer patients, who are more prone to develop treatment-related toxicities and where assessment of treatment risks can be difficult due to subclinical differences in physical reserve [31]. Increasing evidence suggests that treatment selection is not solely dependent of tumor biology, but also of patient-related clinical parameters, for example low muscle mass.

Body composition analysis as clinical prognostic factor for oncological outcomes.

Recently, low muscle mass has been independently associated with impaired overall survival in multiple tumor types [32-34] and a higher incidence of chemotherapeutic toxicity [35]. The use of muscle parameters in treatment decision making in cancer patients is a fast developing field of clinical research. Muscle mass deteriorates in all aging people due to age-related metabolic changes and age-related changes in muscle turnover [36]. It is considered the major component of age-related (primary) sarcopenia [37], a geriatric syndrome with multifactorial etiology presenting with low muscle mass and low muscle strength or impaired physical performance [38, 39]. Disease-related (secondary) sarcopenia, as occurs in cancer patients, accelerates muscle wasting and is mostly due to cachexia-related processes [40].
The combination of muscle mass, water and bone forms the lean body mass. Total body weight consists of the lean body mass (also called the fat-free mass) and the fat mass [41]. Recent studies have suggested that increased chemotherapeutic toxicity can occur in patients with muscle wasting, as the decrease of the lean body mass causes a lower distribution of chemotherapeutic drugs to this compartment and therefore higher systemic drug levels [35, 42]. However, standard measures of body weight, body mass index and body surface area are

insufficient to detect individual alterations of the lean body mass and the fat mass [43-45]. In body composition analyses, these compartments are measured separately, which is increasingly recognized as a new strategy to investigate the influence of muscle wasting on prognosis.

Muscle measurement using CT imaging.

Several imaging diagnostics can be used to obtain skeletal muscle measures, such as ultrasound, dual energy x-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), computed tomography (CT) and magnetic resonance imaging (MRI) [46, 47]. In oncological research, CT imaging is often preferred since this is considered the gold standard for muscle measurement [48], because the different muscle and adipose tissue depots can easily be quantified using only one slice at the L3 level [49] **(figure 2)** and because CT images are widely available in oncological care.

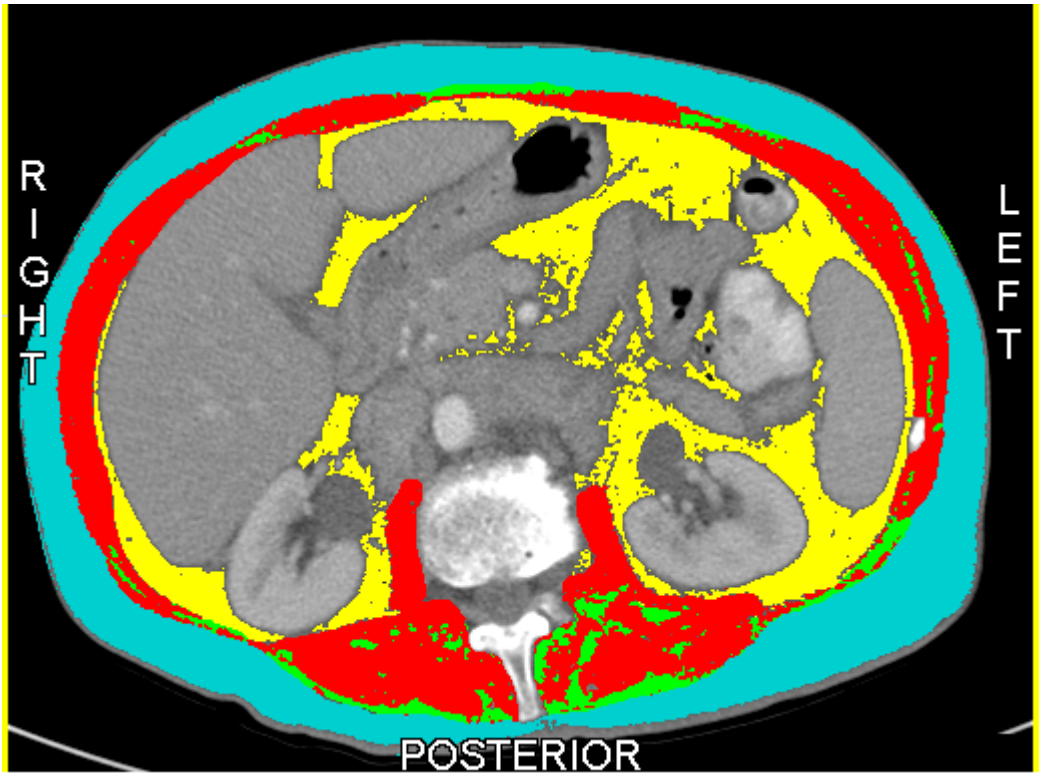

Figure 2. Body composition analysis using CT imaging at the L3 level

Red = Skeletal muscle tissue. **Green = Intramuscular adipose tissue**

Blue = Subcutaneous adipose tissue. **Yellow = Visceral adipose tissue.**

Knowledge regarding muscle strength and physical performance is necessary to diagnose sarcopenia [38]. The quality of muscle may be of prognostic value too, measured by the density of muscle, which reflects the infiltration of muscle by adipose tissue [50, 51].

Aim and outline of the thesis

The aim of this thesis was to evaluate the impact of several patient- and treatment related factors on the outcome of patients with metastatic breast cancer. The efficacy of anti-Her2 agents in the treatment of Her2 positive MBC is well established across clinical trials. However, the field of Her2-targeted therapy in Her2 positive MBC is rapidly evolving and sometimes previous cohorts of patients in clinical trials are therefore not representative anymore for the current daily clinical practice. In general, most patients in clinical trials were trastuzumab-naive before enrollment in the study according to current guidelines. As a result, the efficacy of retreatment with anti-Her2 agents after progressive disease on previous Her2-targeted therapy with the same agents remains unclear. In **chapter 2**, the efficacy of first line Her2-targeted based chemotherapy between patients relapsing after adjuvant trastuzumab and patients without adjuvant trastuzumab treatment is evaluated in a large multicenter retrospective study in the South Western part of the Netherlands.

In addition to mechanisms at tumor site level leading to resistance, also body composition parameters in metastatic breast cancer might impact outcome. At this moment, the use of body composition parameters in oncological care is intensively studied, but the research field is hampered by the lack of a standardized muscle mass measurement and no consensus on a definition of sarcopenia. In **chapter 3,** a review of the literature is provided on the importance of muscle mass and body composition in cancer patients and the methods of muscle measurement. Most knowledge regarding the prognostic impact of body composition and muscle quality in cancer patients is generated in patients with abdominal malignancies as abdominal CT imaging is necessary for muscle measurement using the technique of analyzing a single slice. Studies investigating this in breast cancer are scarce, but might have clinical impact by improving clinical outcome, physical performance and quality of life in breast cancer in case of interventions targeting low muscle mass [52]. **Chapter 4** investigated the impact of low muscle mass and low muscle quality on time to next treatment and overall survival in patients with MBC undergoing first line palliative chemotherapy. In **chapter 5,** changes in body composition during chemotherapeutic treatment for MBC are described. The research field of body composition is especially clinically relevant in patients with higher risk

of complications, i.e. in older patients. Muscle parameters might be an additional help during risk assessment before the start of therapy. Therefore, in **chapter 6**, the association between different levels of sarcopenia prior to therapy and a decline of physical independence after chemotherapy in older cancer patients is studied. In addition, there is a need of alternative ways of evaluating skeletal muscle and body composition in case CT images are not available or when less invasive diagnostics are preferable, which is often the case in older people. Therefore, the association between muscle parameters and functional measures in elderly patients with a wide range of different cancers is reported in **chapter 6** as well. The main findings of this thesis and future directions for research are discussed in **chapter 7.**

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Chapter 2

First-line palliative treatment with trastuzumab in Her2 positive metastatic breast cancer is less effective after failure of adjuvant trastuzumab.

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Abstract

Background: Survival of patients with Her2-positive metastatic breast cancer (MBC) has improved dramatically since trastuzumab has become available, although the disease eventually progresses in most patients. This study investigates the outcome (overall survival (OS) and time to next treatment (TNT)) in MBC patients pre-treated with trastuzumab in the adjuvant setting (TP-group) compared to trastuzumab-naïve patients (TN-group) in order to investigate the possibility of trastuzumab resistance.

Patients and methods: Patients treated with first-line Her2-targeted-containing chemotherapy were eligible for the study. A power analysis was performed to estimate the minimum size of the TP-group. OS and TNT were estimated using Kaplan-Meier curves and multivariable Cox proportional hazards models.

Results: Between January 1, 2000 and June 1, 2014, 469 patients were included of whom 82 in the TP-group and 387 in the TN-group. Median OS and TNT were significantly worse in the TP-group compared to the TN-group (17 vs. 30 months, adjusted HR 1.84 (1.15 – 2.96), p = 0.01 and 7 vs. 13 months, adjusted HR 1.65 (1.06 – 2.58), p = 0.03)) after adjustment for age, year of diagnosis, disease-free interval, hormone receptor status, metastatic site and cytotoxic regimens.

Conclusion: First-line trastuzumab-containing treatment regimens are less effective in patients with failure of adjuvant trastuzumab compared to trastuzumab-naïve patients and might be due to trastuzumab resistance. The impact of trastuzumab resistance on the response on dual Her2-blockade with trastuzumab and pertuzumab and how resistance mechanisms can be used in the optimization of Her2-targeted treatment lines needs further investigation.

Introduction

Survival of patients with Her2-positive breast cancer has dramatically improved since trastuzumab has become available in both the (neo) adjuvant and palliative setting [1-3]. In the advanced setting, trastuzumab-based therapy is the cornerstone of antitumor treatment. Although significant improvement of survival has been reached with this strategy, most metastatic breast cancer (MBC) patients will eventually develop progressive disease. This might be due to resistance against chemotherapy, but might also be partly explained by resistance against trastuzumab, for example due to previous exposure to trastuzumab in the adjuvant setting. Recognizing patients with trastuzumab (acquired) resistance could be of value to prevent unnecessary trastuzumab administrations, thus reducing costs, and furthermore stress the need for developing new anti-Her2 treatment strategies.

In case acquired resistance to trastuzumab after previous exposure plays a role, it could be hypothesized that patients with prior exposure to adjuvant trastuzumab will have less clinical benefit from first line palliative trastuzumab-treatment compared with trastuzumab-naïve patients. A possible way to study this might be comparing long-term outcome between patients pretreated with trastuzumab and patients without previous trastuzumab. However, studies investigating this issue have shown conflicting results [4-7], possibly due to small numbers of patients [4,5], low numbers of events [6,7], or short duration of follow-up [7]. We have therefore performed a retrospective study to compare the efficacy of first-line Her2-targeted-containing chemotherapy between patients who did or did not undergo adjuvant trastuzumab-based treatment in a large number of patients, determined by a power analysis calculated prior to the start of the study, thereby guaranteeing a sufficient number of events (deaths). Detailed information on previous systemic treatment was collected and the influence of clinical prognostic parameters on the efficacy of retreatment with Her2-targeted-containing treatment schedules/therapy in palliative setting was determined.

Materials and methods

Study design

Consecutive patients who had received at least one dose of first-line Her2-targeted-containing chemotherapy because of Her2-positive MBC from January 1, 2000 to June 1, 2014 at seven hospitals in the Netherlands were eligible for the present study and retrospectively identified. Any first-line Her2-targeted-containing chemotherapy was allowed, irrespective of the anti-Her2 agent. Patients were excluded in case of pathologically proven Her2 negative MBC, incomplete clinical data in the patient record, or a second active malignancy in the five years prior to the initial breast cancer diagnosis. Only patients with combined chemotherapy and Her2-targeted therapy as first-line regimen were included because of two reasons. First, the beneficial effect of trastuzumab addition to first-line chemotherapy has been more pronounced than the beneficial effect of trastuzumab addition to palliative endocrine therapy. Second, the combination of an anti-Her2 agent with chemotherapy is independent of the hormone receptor status, and thus allows a larger population to be investigated.

Patients were divided into two groups: the trastuzumab pretreated (TP)-group, consisting of patients who were treated with adjuvant trastuzumab in the past and the trastuzumab-naïve (TN)-group, consisting of patients who were not treated with trastuzumab before the diagnosis of MBC. Patients in the TN-group had either relapsed after stage I-III primary breast cancer or presented with de novo stage IV disease. Because previous studies reported that the presentation with primary metastatic disease does not affect long-term outcomes, these patients were pooled [4,6]. The retrospective review of electronic patients records for the purpose of this study was approved by the central ethical review board (METC 15-046) in addition to the permission of omitting written informed consent.

Data collection

Trained investigators searched electronic medical records for patient and tumor characteristics, treatment patterns, and location of metastases. The end of follow up was January 1, 2015. Her2 receptor status was locally determined using immunohistochemistry (IHC) on the primary tumor or on a metastatic lesion if available. Tumors were classified as

Her2 positive if there was 3+ staining on IHC or 2+ staining confirmed with gene amplification by CISH/FISH in at least 10% of the tumor cells. Hormone receptors were locally tested and ER/PR positive MBC was defined as ≥10% of the primary breast tumor cells showing positive nuclear staining of estrogen and/or progesterone receptor. In case a biopsy had been performed from a metastatic lesion, the hormone receptor status was based on this material obtained by the biopsy. Tumor grade was determined on the primary breast tumor using the Bloom-Richardson grading system [8]. Tumor stage at initial presentation was scored using the 7th edition of the TNM classification for breast cancer [9]. At start of first-line Her2-targeted-containing chemotherapy, all radiological detectable sites of distant metastases per patient were described, that is bone, visceral (liver, lung and other intestinal sites), central nervous system, skin or lymph nodes.

Statistical analyses

A power analysis was performed to determine the required number of patients to detect a clinically relevant difference in survival between the TP-group and the TN-group, assuming that this difference is present. A hazard ratio (HR) of 1.47 for OS was assumed based on a study that reported impaired OS for patients in the TP-group compared with the TN-group [4]. This study was chosen for the power analysis because other studies investigating this subject were not available at the start of this study. With a power of 80%, a two-sided significance level of 5%, a survival rate of 40% at the end of follow up in the TP group (based on the median duration of follow up in our study), approximately 100 patients in the TP-group were needed to detect a HR of 1.47 for OS in the TP-group compared with the TN group. Based on the incidence of metastatic breast cancer, the patients of seven regional hospitals were included in this study.

Continuous variables were described using medians and interquartile ranges (IQR). Categorical variables were described using percentages. Patient characteristics were compared between the TP-group and the TN-group using Mann-Whitney tests for continuous variables Fisher's exact tests for categorical variables with 2 categories and chi-square tests for categorical variables with more than 2 categories. The primary study endpoint was OS after start of first-line chemotherapy. OS was defined as the time between start of first-line Her2-targeted-containing chemotherapy and death of any cause. Patients were censored on January 1, 2015. The secondary study endpoint was time to next treatment (TNT), which was defined

as the time between the start of first-line Her2-targeted-containing chemotherapy and the start of a second treatment line because of disease progression. A switch to another regimen because of toxicity or patient demand was not considered a switch to second-line treatment. In case no second treatment line was started, TNT was until the date of documented disease progression or death, whichever came first. In all other cases, patients were censored at January 1, 2015. In this study, TNT was chosen as marker of progression-free survival to indicate the duration of clinical benefit, that is, the time until another treatment was deemed necessary by the treating physician to get disease control. The difference between TNT and the more commonly used time until documented disease progression (i.e. progression-free survival) was minimal, with less than 1 month in 82.5% of the entire study population and less than 2 months in 92.5%. OS and TNT were assessed using Kaplan-Meier curves and further explored by univariable and multivariable Cox proportional hazard models. To assess the effects of selection bias, the survival analyses were repeated with the following subgroups: 1. Exclusion of patients treated with lapatinib. 2. Exclusion of the patients presenting with brain metastases. 3. Exclusion of the patients treated before 2006. 4. Exclusion of the patients without adjuvant treatment with taxanes. The independent variables in the Cox proportional hazard models were included based on their prognostic relevance and were: age, year of diagnosis, the disease free interval (time between the initial breast cancer diagnosis and the occurrence of distant metastases), estrogen/progesterone receptor positivity, treatment with lapatinib, previous treatment with taxanes, the presence of brain metastases and the presence of visceral metastases. The proportional hazards assumption was assessed by including interaction effects of covariates and follow-up time in a Cox proportional hazard model with time-dependent covariates. Variance inflation factors were calculated to assess the degree of multicollinearity among the independent variables in the Cox proportional hazard models. A two-sided p-value of $p < 0.05$ was considered to be statistically significant. All analyses were conducted using SPSS version 24 (SPSS Inc.,Chicago, Illinois).

Results

Patient characteristics

Between January 1, 2000 and June 1, 2014, 753 patients with Her2 positive MBC were identified. After excluding patients who did not receive first-line Her2-targeted-based

chemotherapy (n = 259; see also below) and patients with incomplete clinical data (n = 25), 469 were included in the final analyses (**Figure 1)**, of which 82 in the TP-group and 387 in the TN-group**.** The median duration of follow-up was 30 months (range 0 – 165 months), starting at the diagnosis of distant metastases. The death rate in the entire cohort was 74%. No patients were lost to follow up.

Patients in the TP-group were slightly younger than patients in the TN-group (48.3 vs. 51.5 years, p = 0.02). All patients in the TP-group had received adjuvant chemotherapy (as this was combined with trastuzumab) compared with 41.1% of the patients in the TN-group. Patients in the TP-group more often had brain metastases at presentation of metastatic disease (11.0% vs. 0.5%) and were more often treated with other first-line anti-Her2 agents (i.e. lapatinib and pertuzumab) than with trastuzumab monotherapy (19.5% vs. 5.4%, p < 0.001). Hormone receptor status, nuclear grade of the primary tumor, and localization of metastatic sites were equally distributed over the two groups **(table 1)**.

Selection of patients treated with anti Her2-agents

The omission of first-line anti-Her2-based chemotherapy of the 259 excluded patients was mostly due to preferred anthracyclines without trastuzumab as first-line therapy (32.8%), poor clinical condition (19.7%), or no indication of chemotherapy yet (9.7%) **(Supplemental table 1)**. To investigate potential selection bias of the excluded patients, these were also divided into (a) patients having received adjuvant trastuzumab or having an indication for adjuvant trastuzumab without receiving it and (b) patients without an indication for adjuvant trastuzumab. Patient characteristics for both groups were compared with the TP and TN-group of the included patients, respectively, showing no selection of patients with prognostic negative characteristics in the TP-group and no selection of patients with prognostic positive characteristics in the TN-group **(Supplemental table 2).**

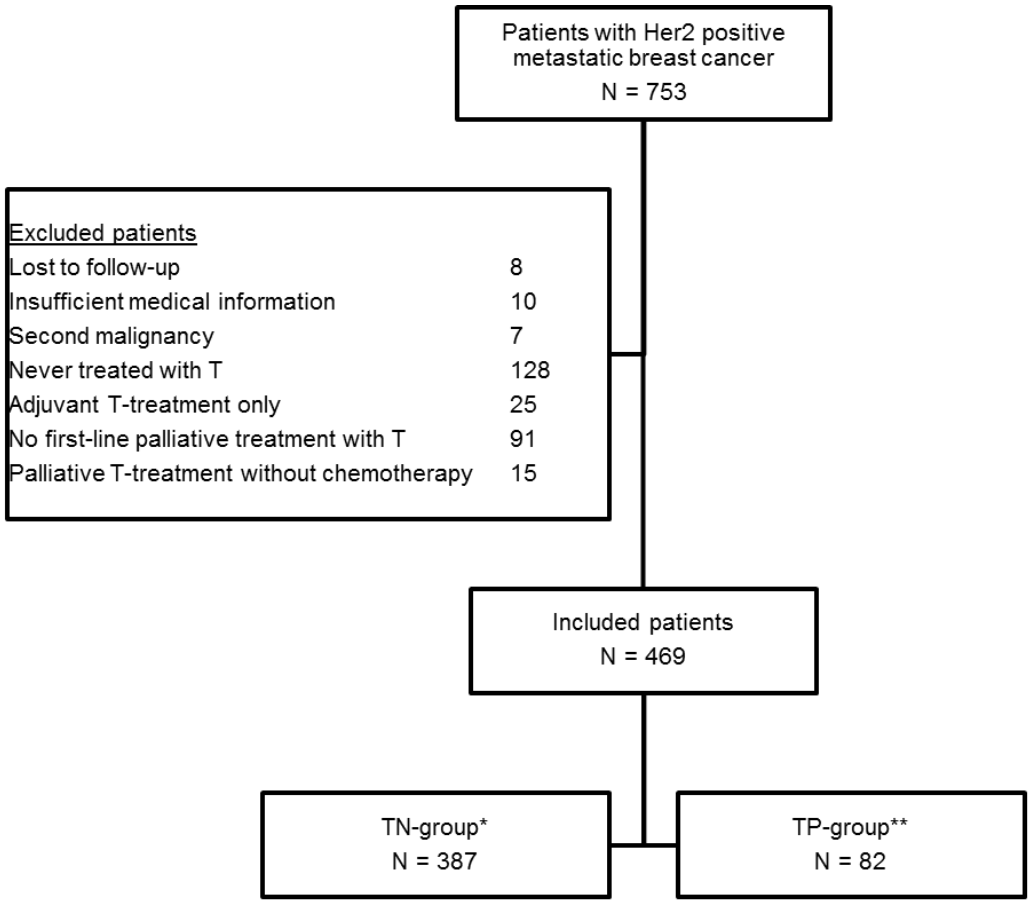


Figure 1. Flow chart patient inclusion

Overall survival and time to next treatment

Median OS was 17 months in the TP-group and 30 months in the TN-group (HR 2.00, 95% CI 1.51 – 2.63, p <0.001). Median TNT was 7 months in the TP-group and 13 months in the TN-group (HR 2.02, 95% CI 1.56 – 2.62, p < 0.001) **(Figure 2A and B)**. Dividing the TN-group into patients relapsing after stage I-III breast cancer and patients presenting with de novo stage IV disease did not affect the results (**Supplemental figure 1)**. Lapatinib instead of trastuzumab as first-line anti-Her2 therapy was administered in 19 patients (TP-group: n = 9, TN-group: n = 10); exclusion of these patients from the analyses showed similar results **(Supplemental figure 2)**, as well as the removal of the patients with brain metastases as first metastatic site (11 in the TP-group and 2 in the TN-group) to avoid negative selection bias of patients with brain metastases (OS 18 vs. 30 months, log-rank p < 0.001, TNT 7 vs. 13

Table 1. Patient characteristics

	TN-group (n = 387)	TP-group (n = 82)	P
Age (range) (y)	51.5 (25 – 84)	48.3 (24 – 72)	0.02
Diagnosis before 2006	241 (62.3)	21 (25.6)	<0.001
Hormone receptor status			0.72
• **Positive**	223 (57.6)	45 (54.9)	
• **Negative**	163 (42.1)	37 (44.6)	
• **Unknown**	1 (0.3)	0	
Tumor stage			<0.001
• **I**	53 (13.7)	3 (3.7)	
• **II**	120 (31.0)	40 (48.8)	
• **III**	80 (20.7)	39 (47.6)	
• **IV**	119 (30.7)	0	
• **Unknown**	15 (3.9)	0	
Nuclear grade			0.31
• **I or II**	95 (24.5)	19 (23.2)	
• **III**	160 (41.3)	44 (53.7)	
• **Unknown**	132 (34.1)	19 (23.2)	
Adjuvant chemotherapy			<0.001
• **None**	228 (58.9)	0	
• **Anthracyclines only**	125 (32.3)	10 (12.2)	
• **Taxanes only**	1 (0.3)	3 (3.7)	
• **Anthracyclines + taxanes**	14 (3.6)	69 (84.1)	
• **Other**	19 (4.9)	0	
Previous palliative endocrine therapy	82 (21.2)	17 (20.7)	1.00
First metastatic site			<0.001[a]
• **Bone**	67 (17.3)	17 (20.7)	
• **Visceral**[b]	79 (20.4)	11 (13.4)	
• **CNS**[c]	2 (0.5)	9 (11.0)	
• **Other**	41 (10.6)	10 (12.2)	
• **Multiple sites**	198 (51.2)	35 (42.7)	
Number of metastatic sites			0.47
• **1**	189 (48.8)	47 (57.3)	
• **2**	122 (31.5)	20 (24.4)	
• **3**	52 (13.4)	9 (11.0)	
• **>3**	24 (6.2)	6 (7.3)	
Disease-free interval[d] **(IQR**[e]**) (months)**	42 (20 – 78)	33.5 (21 – 46)	0.03
First line chemotherapy used in combination with Her2 targeted agent			<0.001
• **Anthracyclines**	7 (1.8)	0	
• **Taxanes**	317 (81.9)	51 (62.2)	
• **Capecitabine**	14 (3.6)	17 (20.7)	
• **Vinorelbine**	29 (7.5)	11 (13.4)	
• **Other**	9 (2.3)	2 (2.4)	
• **Unknown**	11 (2.8)	1 (1.2)	
Overall duration of palliative trastuzumab (IQR) (months)	16 (8 – 32)	9.4 (4 – 19)	<0.001
• **Unknown**	16	4	

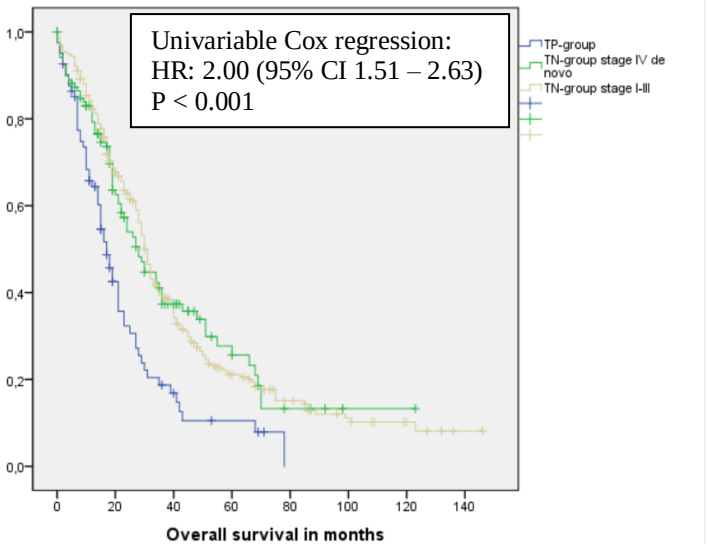
[a]When removing the patients with CNS-located metastases from this analysis, the first metastatic site did not differ between the groups (p = 0.43).
[b]Visceral: Liver, lung, pleural, peritoneal, pericardial, intestinal [c]CNS: Central nervous system
[d]Disease free interval: Time from initial breast cancer diagnosis until the diagnosis of distant metastases.
[e]IQR: Interquartile range
[f]Time to palliative treatment: Time from the diagnosis of distant metastases until the start of first-line palliative chemotherapy.

months, p < 0.001). In the multivariable Cox regression, OS and TNT in the TP-group were still shorter compared with the TN group (HR 1.84 for OS, 95% CI 1.15 – 2.96, p = 0.01 and HR 1.65 for TNT, 95% CI 1.06 – 2.58, p = 0.03, respectively) **(table 2-3)**. After assessing the proportional hazards assumption, a significant interaction was found between the development of brain metastases and the duration of follow-up. Therefore, brain metastases were modeled as a time-dependent covariate in the multivariate Cox regression. No other significant violations of the proportional hazards assumption were detected.

Median OS of ER+ vs. ER- patients in the TP-group was 18 vs. 15 months and in the TN-group 31 vs. 27 months (p = 0.91 and p = 0.20, respectively). Median TNT of ER+ vs. ER- patients in the TP-group was 7 vs. 6 months and in the TN-group 14 vs. 11 months, respectively (p = 0.79 and p = 0.42, respectively). However, when calculating OS from the first presentation of metastatic disease, median OS of ER- patients was significantly shorter than of ER+ patients (30 vs. 38 months, p = 0.01), suggesting that the prognostic advantage of ER positivity disappeared once first-line chemotherapy was indicated for disease control.

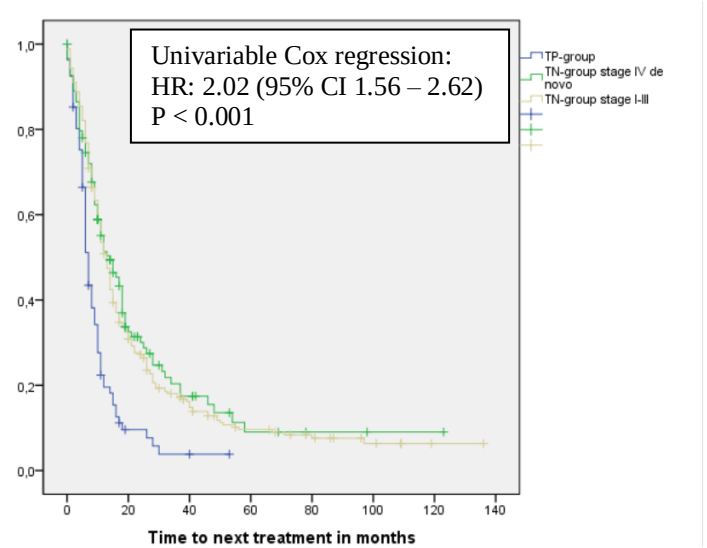
Since mid-2005, trastuzumab has been available for adjuvant treatment. Therefore, most patients in the TP-group were diagnosed with breast cancer after 2006, whereas the TN-group was largely exposed to older treatment regimens. Repeating the survival analyses with only the patients diagnosed after 2006 (TP-group: n = 61, TN-group: n = 146), in order to assess bias by difference in treatment regimens, still showed impaired OS and TNT in the TP-group. (16 vs. 29 months and 6 vs. 14 months, respectively (both log-rank p <0.001) **(Supplemental figure 3).**

a.



TP	82	24	8	3	0	0	0	0	Median OS: 17 months (95% CI 13.8 – 20.2)
TN stage I-III	268	174	84	40	22	12	6	1	Median OS: 30 months (95% CI 28.1 – 31.9)
TN stage IV de novo	119	61	27	13	4	1	1	0	Median OS: 28 months (95% CI 22.5 – 33.5)

b.



TP	82	5	2	0	0	0	0	0	Median TNT: 7 months (95% CI 6.1 – 8.0)
TN stage I-III	268	83	34	17	11	5	1	0	Median TNT: 13 months (95% CI 11.5 – 14.5)
TN stage IV de novo	119	29	12	4	2	1	0	0	Median TNT: 14 months (95% CI 9.3 – 18.7)

Abbreviations:

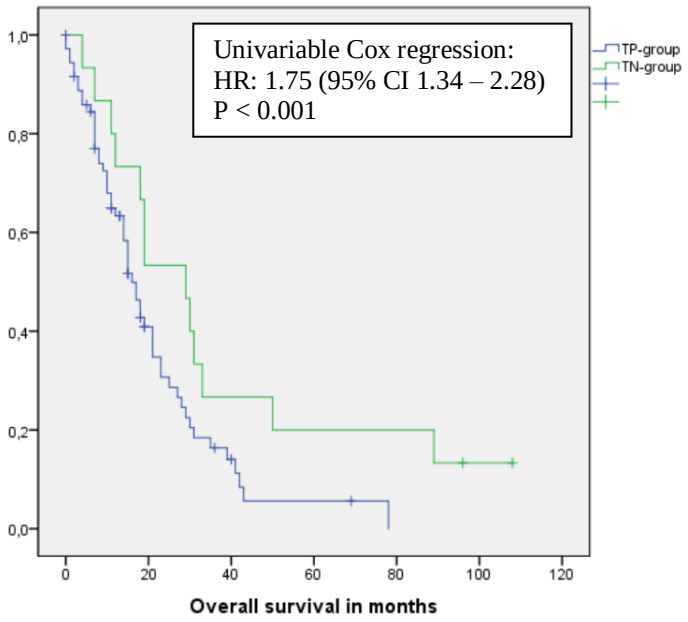
TP: Trastuzumab pretreated, i.e. relapsed after adjuvant trastuzumab-treatment; TN: Trastuzumab-naïve.

Figure 2. Fig. 2 Overall survival (a) and time to next treatment (b) in patients treated with first-line palliative anti-Her2 therapy

Effect of taxanes

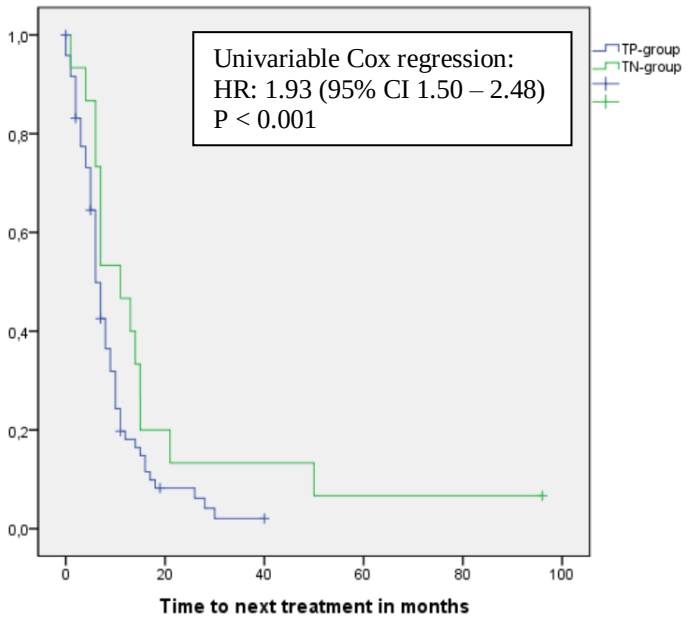
Previous adjuvant chemotherapy was administered in 159 patients (41.1%) in the TN-group and in all patients in the TP-group. In these patients, previous adjuvant chemotherapy consisting of taxanes was administered in 87.8% of the patients (n = 72) in the TP-group compared with 3.9% (n=15) in the TN-group. Due to the strong association between previous adjuvant taxanes and TP/TN-group, we found relatively high variation inflation factors for these two variables (3.1 and 3.2 respectively). To assess the effects of this multicollinearity, and to minimize the effect of possible taxane-resistance between both groups, we repeated the univariable survival analyses with only the patients relapsing after taxane therapy. We found that OS in the TP-group was still significantly shorter compared to the TN-group (17 vs. 29 months, log rank p = 0.048). The difference in TNT between both groups did not reach statistical significance (6 vs. 11 months, log rank p = 0.07) **(figure 3).** In the univariable Cox regression, previous taxane-exposure, which suggests resistance to taxanes, had a large association with OS and TNT (HR 1.75, 95%CI 1.34 – 2.28, p < 0.001 and HR 1.93, 95% CI 1.50 – 2.48, p < 0.001, respectively), but this was no longer statistically significant after adjustment for previous trastuzumab exposure in the multivariable Cox regression.

a.



TP-group and relapsed on adjuvant taxanes	72	20	6	1	0	0	0	Median OS: 16 months (95% CI 12.8 – 19.2)
TN-group and relapsed on adjuvant taxanes	15	8	4	3	3	1	0	Median OS: 29 months (95% CI 17.6 – 40.4)

b.



TP-group and relapsed on adjuvant taxanes	72	4	1	0	0	0	Median OS: 6 months (95% CI 4.9 – 7.1)
TN-group and relapsed on adjuvant taxanes	15	3	2	1	1	0	Median OS: 11 months (95% CI 5.7 – 16.3)

Figure 3. Overall survival (a) and time to next treatment (b) among patients with previous adjuvant treatment with taxanes

Table 2. Univariable and multivariable Cox proportional hazard models for overall survival.

	Univariable			Multivariable		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**P**
Age[a] (range) (y)	1.01	1.00 – 1.02	0.33	1.01	1.00 – 1.02	0.15
Diagnosis after 01.01.2006 vs. before 01.01.2006	1.21	0.97 – 1.51	0.09	0.99	0.75 – 1.30	0.94
DFI[b]	1.00	1.00 – 1.00	0.20	1.00	1.00 – 1.00	0.48
Hormone receptor status: positive vs. negative	0.86	0.69 – 1.06	0.15	0.88	0.70 – 1.10	0.88
Brain metastases vs. no brain metastases	1.02	1.01 – 1.54	**0.04**	0.88	0.61 – 1.25	0.88
Interaction between brain metastases and follow-up time (months)	--	--	**--**	**1.02**	**1.00 – 1.03**	**0.01**
Visceral metastases vs. no visceral metastases	1.25	1.01 – 1.56	**0.04**	**1.36**	**1.08 – 1.90**	**0.01**
First line lapatinib vs. trastzumab	1.62	0.99 – 2.64	0.05	1.36	0.82 – 2.28	0.24
Adjuvant taxane treatment vs. no previous taxane treatment	1.75	1.34 – 2.28	**<0.001**	1.16	0.74 – 1.83	0.52
Adjuvant trastuzumab vs. no adjuvant trastuzumab[c]	2.00	1.51 – 2.63	**<0.001**	**1.84**	**1.15 – 2.96**	**0.01**

[a]Age at initial breast cancer diagnosis
[b]Time from initial breast cancer diagnosis until the first diagnosis of distant metastases.
[c]TP-group vs. TN-group

Abbreviations: HR: Hazard ratio; CI: Confidence interval; DFI: Disease-free interval; CNS: Central nervous system.

Table 3. Univariable and multivariable Cox proportional hazard models for time to next treatment.

	Univariable			Multivariable		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age[a] (range) (y)	1.00	0.99 – 1.01	0.79	1.01	1.00 – 1.02	0.28
Diagnosis after 01.01.2006 vs. before 01.01.2006	1.08	0.89 – 1.32	0.43	0.86	0.67 – 1.11	0.25
DFI[b]	1.00	1.00 – 1.00	0.13	1.00	1.00– 1.00	0.12
Hormone receptor status: positive vs. negative	0.91	0.74 – 1.11	0.33	0.91	0.73 – 1.12	0.35
Brain metastases vs. no brain metastases	**1.33**	**1.09 – 1.63**	**0.01**	0.78	0.58 – 1.05	0.10
Interaction between brain metastases and follow-up time (months)	**--**	**--**	**--**	**1.04**	**1.03 – 1.06**	**<0.001**
Visceral metastases vs. no visceral metastases	1.10	0.90 – 1.35	0.36	**1.23**	**1.00 – 1.52**	**0.048**
First line lapatinib vs. trastzumab	1.59	0.97 – 2.58	0.06	1.36	0.82 – 2.26	0.23
Adjuvant taxane treatment vs. no previous taxane treatment	**1.93**	**1.50 – 2.48**	**<0.001**	1.41	0.92 – 2.15	0.11
Adjuvant trastuzumab vs. no adjuvant trastuzumab[c]	**2.02**	**1.56 – 2.62**	**<0.001**	**1.65**	**1.06 – 2.58**	**0.03**

[a]Age at initial breast cancer diagnosis
[b]Time from initial breast cancer diagnosis until the first diagnosis of distant metastases.
[c]TP-group vs. TN-group

Abbreviations: HR: Hazard ratio; CI: Confidence interval; DFI: Disease-free interval; CNS: Central nervous system.

Discussion

This study shows that patients receiving first line Her2-targeted-containing chemotherapy for Her2 positive MBC who were previously exposed to adjuvant trastuzumab had a shorter median OS and TNT compared to patients who were never exposed to trastuzumab at the time of diagnosing distant metastases. The unfavorable effect of prior trastuzumab exposure was independent of clinical and tumor characteristics and seems, at least partly, independent of pretreatment with taxanes.

Four retrospective studies have previously reported on this issue and showed conflicting results [4-7]. In two of these studies, some degree of shorter OS was reported in patients previously treated with adjuvant trastuzumab (univariable HRs 1.47 and 1.16) [4,6], although these associations were not retained after adjustment for other clinical risk factors. However, these could be false-negative observations, as the 95% confidence intervals of the hazard ratio of previous adjuvant trastuzumab treatment in these studies showed overlap with our 95% confidence interval (0.87 – 1.75 and 0.80 – 1.74 respectively, vs. 1.00 – 2.91 in our study). This implicates that no survival difference was detected, despite patients with relatively high hazard ratios of death. In the third study with 96 patients in the TP-group, 2-year overall survival was the only study endpoint and was not affected (HR 0.79, 95% CI 0.50 - 1.26) by previous adjuvant trastuzumab treatment [7]. A fourth study reported that patients with trastuzumab-retreatment also less often obtained long-term clinical benefit from re-introduction of Her2-targeted-based chemotherapy [5]. Although in line with our study results, this study had a short time of follow up after the registration of trastuzumab in adjuvant setting, which might have led to a negative selection of patients with relatively rapid development of distant metastases in the TP-group. Thus, small numbers of patients, short duration of follow-up, small number of events and possible selection bias could have influenced these previous study results.

The survival of the patients in our study seemed to be somewhat shorter when compared to prospective studies recently done in patients with Her2-positive MBC, including the CLEOPATRA- and RHEA-trials [10,11]. The median OS of our entire cohort was 28 months, compared with 37.6 months in the control-arm of the CLEOPATRA-trial [11]. The median OS of our trastuzumab-pretreated patients (TP-group) was 17 months, compared with 25 months in the RHEA-trial (which included only trastuzumab-pretreated patients). The median TNT in our study (TP-group: 7 months, entire cohort: 11 months) was comparable with the PFS of both the RHEA-trial (8 months) and the control-arm of the CLEOPATRA trial (12.4 months) [12].

Possible explanations for the shorter median OS in our study could be the differences in inclusion- and exclusion criteria, favoring the patients in both the CLEOPATRA- and RHEA-trials. In these studies, patients needed to have an ECOG performance status of 0 or 1, a relapse-free interval after adjuvant treatment of ≥6 months and a life expectancy of ≥3

months. These (prognostic positive) restrictions were not applied to our study cohort, which might have influenced OS.

We aimed to strengthen the interpretation of the analyses by investigating whether possible selection could have biased the current findings. Excluded patients could have caused a selection bias of preferentially poor prognosis patients in the TP-group or a selection bias of preferentially good prognosis patients in the TN-group, however, this was not observed when comparing the included and excluded patients **(supplemental table 2)**. Furthermore, patients in the TP-group more frequently had brain metastases as first presentation of metastatic disease than patients in the TN-group, possibly predisposing the TP-group to unfavorable outcomes. However, exclusion of these patients from the analyses still showed worse OS and TNT in the TP-group. Also possible selection by difference in treatment period was unlikely. A larger percentage of the TP-group compared to the TN-group was treated in recent time periods, so patients in the TP-group had a shorter disease-free interval (time between the initial breast cancer diagnosis and the development of distant metastases), but also could have benefited from newer recently developed anti-Her2 agents than the TN-group. Analyzing only the patients included after January 1, 2006, in order to compare patients with comparable disease-free interval and treated according to the same guidelines, did not alter the results. Finally, the TP-group more often received adjuvant taxanes (87.8% vs. 3.9%), possibly causing impaired sensitivity to taxanes in advanced setting, which might have contributed to the worse outcome in the TP-group. However, selecting only the patients who were treated with adjuvant taxanes still showed shorter OS and TNT in the TP-group. Altogether, after showing the comparable results in different subgroup analyses, we believe that the lower efficacy of first-line palliative trastuzumab in the TP-group is possibly due to less sensitivity to trastuzumab or resistance among a subset of MBC patients pretreated with trastuzumab.

This study was not designed to unravel exact mechanisms of resistance among treated patients, but nevertheless showed signs of possible clinically relevant unresponsiveness to trastuzumab (primary or acquired during previous adjuvant therapy), which could have implications for treatment decision making after short progression-free intervals in the palliative setting.

It must be noted that the current standard of care of first-line Her2-targeted therapy is dual Her2-blockade with trastuzumab and pertuzumab, instead of single trastuzumab, after the

results of the CLEOPATRA trial [12]. In this trial, trastuzumab pretreated patients seemed to have shorter PFS than trastuzumab-naïve patients, in both the pertuzumab-arm (16.9 vs. 21.6 months) and the control-arm (10.4 vs. 12.6 months). Although trastuzumab pretreated patients seemed to derive similar benefit from the addition of pertuzumab, as compared to trastuzumab-naïve patients, the benefit of dual Her2-blockade above trastuzumab monotherapy was not statistically significant in trastuzumab pretreated patients, as shown by the 95% confidence interval (HR 0.65, 95% CI 0.35 – 1.07). However, the number of patients with previous adjuvant trastuzumab was only 11% of the entire cohort, which could explain the loss of statistical significance. A future study is needed to determine the impact of trastuzumab resistance on first-line dual Her2-blockade in trastuzumab pretreated patients.

Several limitations of this study have to be mentioned. First, fewer patients than the needed number of patients determined by the power calculation were included. The main cause for this was the well known low incidence (about 10%) of developing distant metastases among patients in the TP-group, thus among those who were treated with adjuvant trastuzumab [13]. However, more events (deaths) occurred, so the power in our study was not substantially limited. Second, patients with lapatinib were included in this study, so the analysis was not restricted to only patients with trastuzumab retreatment. However, we chose to include all patients with any type of palliative first-line Her2-targeted therapy, in order to include a study population as close to the “real world” as possible. Furthermore, we provided a subgroup analysis without the patients treated with lapatinib, which showed similar results. Third, the loss of Her2 overexpression in distant metastases, which might result in trastuzumab unresponsiveness, could not be estimated due to the lack of metastatic biopsies. This has however been reported to be only 3-6% of the cases [14-16]. Fourth, first-line Her2-targeted therapy nowadays consists of the combination trastuzumab and pertuzumab [11], so cohorts treated with first line single Her2 blockade with trastuzumab will dissappear in the near future. However, the results of this study might still be useful, as single blockade of the Her2 receptor is still the standard of care in second line regimens and beyond. Finally, information about subsequent treatment lines and decisions was lacking, which also could affect survival. Nevertheless, this is not the case for TNT, which was clearly different between TN-and TP-group and was not affected by subsequent treatment lines.

Conclusion

First-line trastuzumab containing chemotherapy is less effective in patients treated with adjuvant trastuzumab compared to those not treated with adjuvant trastuzumab for primary breast cancer. Although resistance against taxane treatment could not be fully excluded, our study provides evidence that at least a subset of the patients derives less clinical benefit from Her2-targeted therapy, possibly due to trastuzumab resistance. Whether this resistance might also influence the response on dual Her2-blockade in first line treatment is currently unknown and needs further investigation.

Supplemental table 1. Omission of Her2-targeted therapy in the excluded patients (n = 259).

Patients never treated with anti-Her2 agents (n = 128)			
Reasons for omitting adjuvant Her2-targeted therapy		**Reasons for omitting first-line Her2-targeted therapy**	
Stage IV de novo	49 (38.3%)	Poor clinical condition	39 (30.5%)
Not available yet[a]	48 (37.5%)	Anthracyclins preferred[b]	22 (17.2%)
Endocrine therapy because of age	10 (7.8%)	No indication of chemotherapy yet because of limited metastatic burden	16 (12.5%)
No indication adjuvant chemotherapy	9 (7.0%)	Patient refusal	10 (7.8%)
Poor clinical condition	3 (2.3%)	No chemotherapy because of age	8 (6.3%)
Patient refusal	3 (2.3%)	Metastasis Her2 negative	1 (0.8%)
Low ejection fraction	2 (1.6%)	Low ejection fraction	1 (0.8%)
Unknown	2 (1.6%)	No insurance	1 (0.8%)
Primary tumor Her2 negative	1 (0.8%)	Unknown	30 (23.4%)
Early development of distant metastases	1 (0.8%)		
Patients without first-line anti Her2-based chemotherapy, adjuvant Her2-targeted therapy: yes (n = 25)			
Reasons for omitting adjuvant Her2-targeted therapy		**Reasons for omitting first-line Her2-targeted therapy**	
NA	NA	Poor clinical condition	7 (28.0%)
		Solitary brain metastases	5 (20.0%)
		Limited metastatic burden	4 (16.0%)
		Rapid progression after adjuvant trastuzumab	2 (8.0%)
		Metastatic lesion Her2 negative	2 (8.0%)
		Patient refusal	2 (8.0%)
		Unknown	1 (4.0%)
		Anthracyclins preferred	1 (4.0%)
		Low ejection fraction	1 (4.0%)
Patients without first-line anti-Her2-based chemotherapy, adjuvant Her2-targeted therapy: no (n = 91)[c]			
Reasons for omitting adjuvant Her2-targeted therapy		**Reasons for omitting first-line Her2-targeted therapy**	
Not available yet	61 (67.0%)	Anthracyclins preferred	62 (68.1%)
Stage IV de novo	26 (28.6%)	Unknown	18 (19.8%)
Low ejection fraction	1 (1.1%)	Anti-Her2 agents not common practice[d]	5 (5.5%)
Primary tumor Her2 negative	1 (1.1%)	Metastatic lesion Her2 negative	2 (2.2%)
No indication adjuvant systemic therapy	1 (1.1%)	Low ejection fraction	1 (1.1%)
		Tumor origin at first unclear	1 (1.1%)
		First chemotherapy, trastuzumab started at disease progression[e]	1 (1.1%)
Patients with first-line Her2-targeted monotherapy (no chemotherapy) (n = 15)[f]			
Reasons for omitting adjuvant Her2-targeted therapy		**Reasons for omitting first-line Her2-targeted therapy**	
Not available yet	8 (53.3%)	Poor clinical condition	5 (33.3%)
Stage IV de novo	3 (20.0%)	Limited metastatic burden	5 (33.3%)

No indication adjuvant systemic therapy	1 (6.7%)	Unknown	4 (26.7%)
Patient refusal	1 (6.7%)	Endocrine therapy because of age	1 (6.7%)

[a]Until July 2005
[b]Anthracyclins preferred as first line chemotherapy (between 2000 and 2005)
[c]Adjuvant treatment with trastuzumab was omitted in 90 of the 91 patients.
[d]Until July 2002
[e]Clinical trial
[f]Adjuvant treatment with trastuzumab was omitted in 13 of the 15 patients.

Abbreviations: NA: Not applicable

Supplemental table 2. Patient characteristics of the included vs. excluded patients in the TP-group (a) and the TN-group (b).

a. TP-group

	Included (n = 82)	Excluded (n = 28)	P
Mean age (range) (y)	48.3 (24 – 72)	51.2 (26 – 78)	0.58
Diagnosis before 2006	21 (25.6)	6 (21.4%)	0.80
Hormone receptor status			0.51
• **Positive**	45 (54.9)	13 (46.4%)	
• **Negative**	37 (44.6)	15 (53.6%)	
• **Unknown**	0	0	
Tumor stage			0.002
• **I**	3 (3.7)	2 (7.1%)	
• **II**	40 (48.8)	3 (10.7%)	
• **III**	39 (47.6)	23 (82.1%)	
• **IV**	0	0	
• **Unknown**	0	0	
Nuclear grade			0.41
• **I or II**	19 (23.2)	4 (14.3%)	
• **III**	44 (53.7)	17 (60.7%)	
• **Unknown**	19 (23.2)	7	
Adjuvant chemotherapy			0.07
• **None**	0	2 (7.1%)	
• **Anthracyclins only**	10 (12.2)	3 (10.7%)	
• **Taxanes only**	3 (3.7)	0	
• **Anthracyclin + taxane**	69 (84.1)	23 (82,1)	
• **Other**	0	0	
Previous palliative endocrine therapy	17 (20.7)	5 (17.9%)	1.00
First metastatic site			0.02
• **Bone**	17 (20.7)	3 (10.7%)	
• **Visceral[a]**	11 (13.4)	3 (10.7%)	
• **CNS[b]**	9 (11.0)	11 (39.3%)	
• **Other**	10 (12.2)	3 (10.7%)	
• **Multiple sites**	35 (42.7)	8 (28.6%)	
Number of metastatic sites			0.55
• **1**	47 (57.3)	20 (71.4%)	
• **2**	20 (24.4)	4 (14.3%)	
• **3**	9 (11.0)	3 (10.7%)	
• **>3**	6 (7.3)	1 (3.6%)	
Brain metastases	31 (37.8)	16 (57.1%)	0.08

Disease-free interval[c] (IQR[d]) (months)	33.5 (21 – 46)	24 (17 – 35)	0.04
Time to palliative treatment[e] (IQR) (months)	1 (0 – 6.25)	1.5 (1.0 – 7,25)	0.40
• **Not applicable**	0	24	
First palliative chemotherapy			<0.001
• **None**	0	23 (82.1%)	
• **Anthracycline**	0	3 (10.7%)	
• **Taxane**	51 (62.2)	2 (7.1%)	
• **Capecitabine**	17 (20.7)	0	
• **Vinorelbine**	11 (13.4)	0	
• **Other**	2 (2.4)	0	
• **Unknown**	1 (1.2)	0	

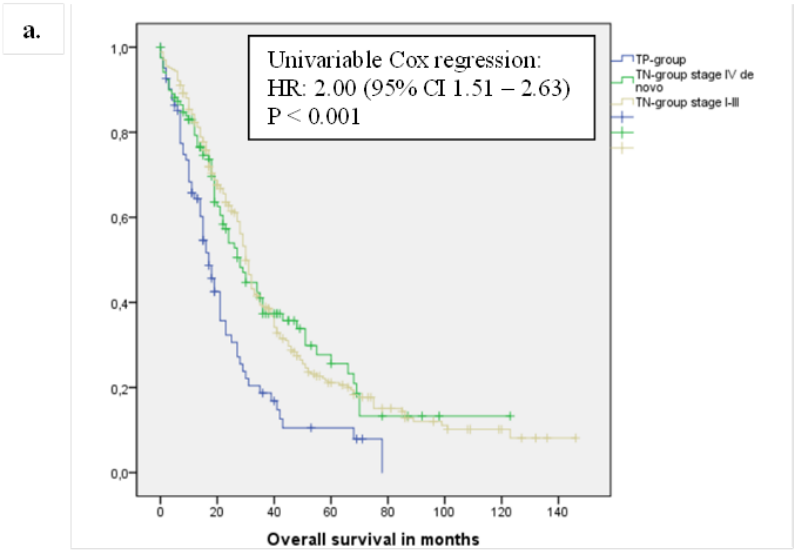
B. TN-group

	Included (n = 387)	**Excluded (n = 231)**	**P**
Mean age (range) (y)	51.5 (25 – 84)	56.1 (24 –92)	0.002
Diagnosis before 2006	241 (62.3)	165 (71.4%)	0.02
Hormone receptor status			0.03
• **Positive**	223 (57.6)	150 (64.9%)	
• **Negative**	163 (42.1)	74 (32.0%)	
• **Unknown**	1 (0.3)	7	
Tumor stage			0.20
• **I**	53 (13.7)	20 (8.7%)	
• **II**	120 (31.0)	69 (29.9%)	
• **III**	80 (20.7)	57 (24.7%)	
• **IV**	119 (30.7)	78 (33.8%)	
• **Unknown**	15 (3.9)	7	
Nuclear grade			0.73
• **I or II**	95 (24.5)	44 (19.0%)	
• **III**	160 (41.3)	82 (35.5%)	
• **Unknown**	132 (34.1)	105	
Adjuvant chemotherapy			0.08
• **None**	228 (58.9)	150 (64.9%)	
• **Anthracyclins only**	125 (32.3)	57 (24.7%)	
• **Taxanes only**	1 (0.3)	0	
• **Anthracyclin + taxane**	14 (3.6)	2 (0.9%)	
• **Other**	19 (4.9)	12 (5.2%)	
Previous palliative endocrine therapy	82 (21.2)	83 (35.9%)	<0.001
First metastatic site			0.01
• **Bone**	67 (17.3)	53 (22.9%)	
• **Visceral[a]**	79 (20.4)	38 (16.5%)	
• **CNS[b]**	2 (0.5)	8 (3.5%)	
• **Other**	41 (10.6)	18 (7.8%)	
• **Multiple sites**	198 (51.2)	101 (43.7%)	
• **Unknown**		13	
Number of metastatic sites			0.44
• **1**	189 (48.8)	117 (50.6%)	
• **2**	122 (31.5)	69 (29.9%)	
• **3**	52 (13.4)	23 (10.0%)	
• **>3**	24 (6.2)	9 (3.9%)	
• **Unknown**		13	
Brain metastases	144 (37.2)	54 (23.4%)	<0.001
• **Unknown**	1 (0.3)	3	
Disease-free interval[c] (IQR[d]) (months)	42 (20 – 78)	28.5 (16.8 – 52.3)	0.01
Time to palliative treatment[e] (IQR) (months)	1 (0 – 3)	1 (0 – 5)	0.63

• **Not applicable**		100	
First palliative chemotherapy			<0.001
• **None**	7 (1.8)	99 (42.9%)	
• **Anthracycline**	317 (81.9)	80 (34.6%)	
• **Taxane**	14 (3.6)	23 (10.0%)	
• **Capecitabine**	29 (7.5)	14 (6.1%)	
• **Vinorelbine**	9 (2.3)	1 (0.4%)	
• **Other**	11 (2.8)	9 (3.9%)	
• **Unknown**		5	

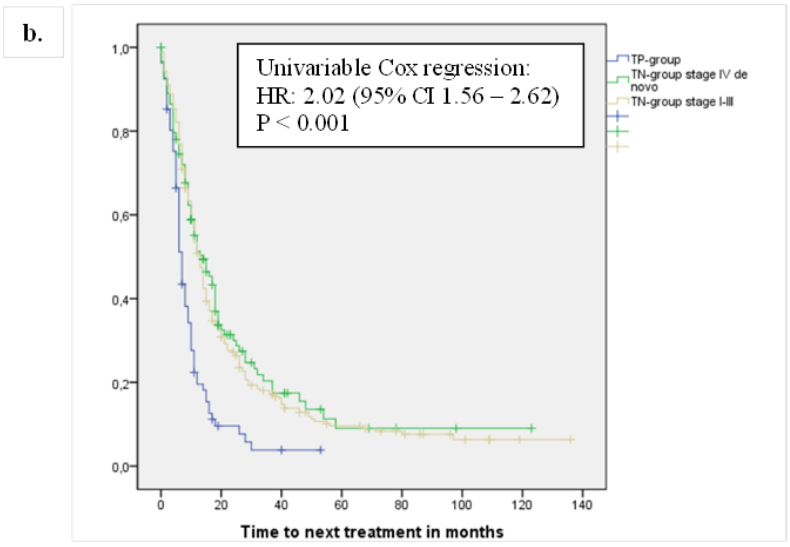
Supplemental figure 1. Survival of patients treated with first-line palliative anti-Her2 therapy.

A. Overall survival



TP	82	24	8	3	0	0	0	0	Median OS: 17 months (95% CI 13.8 – 20.2)
TN stage I-III	268	174	84	40	22	12	6	1	Median OS: 30 months (95% CI 28.1 – 31.9)
TN stage IV de novo	119	61	27	13	4	1	1	0	Median OS: 28 months (95% CI 22.5 – 33.5)

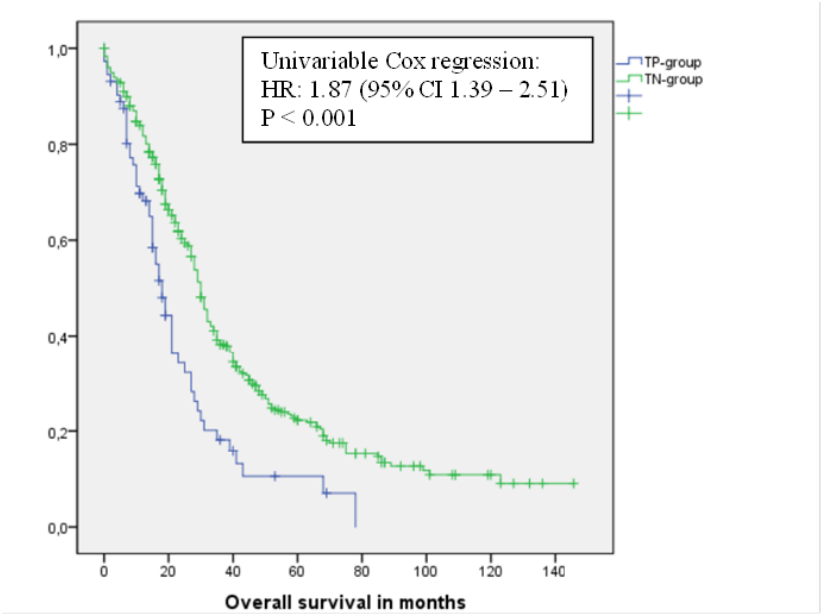
B. Time to next treatment



TP	82	5	2	0	0	0	0	0	Median TNT: 7 months (95% CI 6.1 – 8.0)
TN stage I-III	268	83	34	17	11	5	1	0	Median TNT: 13 months (95% CI 11.5 – 14.5)
TN stage IV de novo	119	29	12	4	2	1	0	0	Median TNT: 14 months (95% CI 9.3 – 18.7)

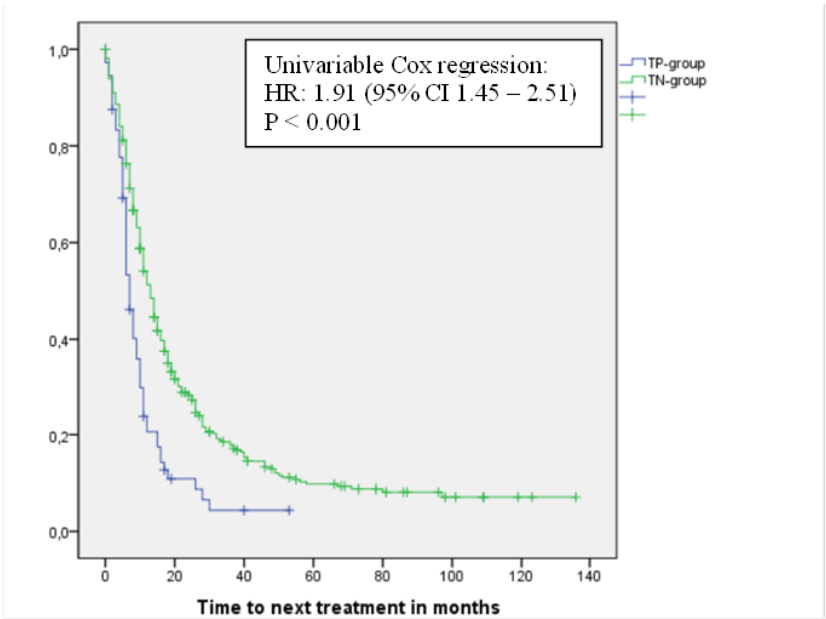
Supplemental figure 2. Survival without the patients treated with first-line lapatinib.

A. Overall survival



TP	73	22	7	3	0	0	0	0	Median OS: 18 months (95% CI 14.5 – 21.5)
TN	377	230	107	52	26	13	7	1	Median OS: 30 months (95% CI 28.0 – 32.0)

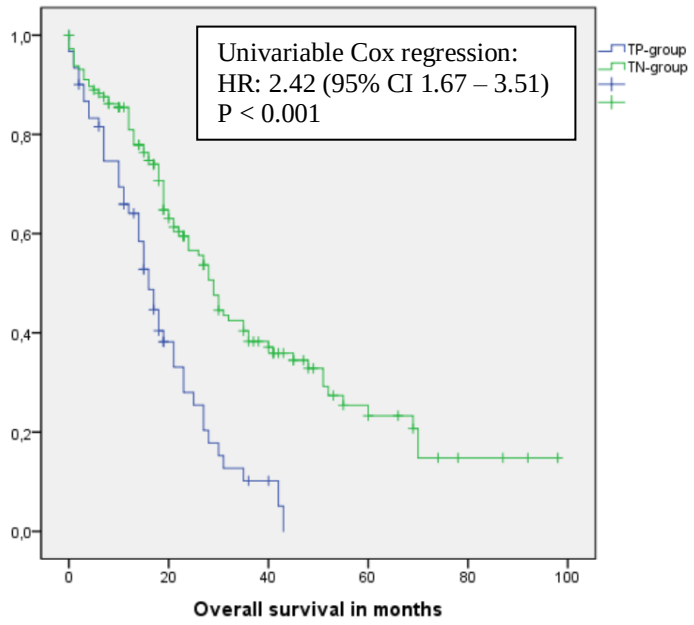
B. Time to next treatment



TP	73	5	2	0	0	0	0	0	Median TNT: 7 months (95% CI 5.8 – 8.2)
TN	377	110	44	21	13	6	2	1	Median TNT: 13 months (95% CI 11.6 – 14.4)

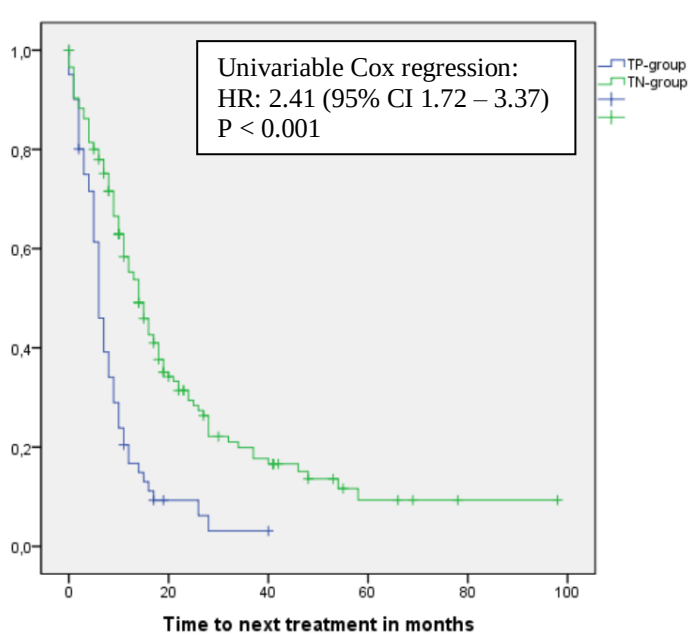
Supplemental figure 3. Survival of patients diagnosed after 1st January 2006

A. Overall survival



TP	61	15	3	0	0	0	Median OS: 16 months (95% CI 13.1 – 18.9)
TN	146	75	33	12	3	0	Median OS: 29 months (95% CI 25.7 – 32.3)

B. Time to next treatment



TP	61	3	1	0	0	0	Median TNT: 6 months (95% CI 4.9 – 7.1)
TN	146	39	16	4	1	0	Median TNT: 14 months (95% CI 11.4 – 16.6)

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Chapter 3

The prevalence and prognostic value of low muscle mass in cancer patients: a review of the literature

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Oncologist 2016 Nov; 21(11):1396-1409

Abstract

In several diseases, a low muscle mass has been revealed as an unfavorable prognostic factor for outcome. Whether or not this holds true in patients with solid malignancies as well has increasingly been explored in the last years. This research field is however severely hampered by a lack of consensus on how to determine muscle mass in cancer patients and on the definition of low muscle mass. Consequently, the prevalence of a low muscle mass widely varies across the several studies. Nevertheless, most studies show that also in patients with solid malignancies a low muscle mass is associated with a poor outcome. In the next years, more effort is needed to get a better insight into the best method to determine the muscle mass, on the exact prognostic value of a low muscle mass in the diverse tumor types and stages, on pathophysiology of a low muscle mass in patients with cancer and on ways to intervene and to improve muscle mass in patients. The review addresses the current literature of the importance of muscle mass in cancer patients and the methods of muscle measurement.

Introduction

Muscle mass starts to decline around the age of 40 years, resulting in a mean loss of 8% per decade until the age of 70 [1]. Above 70 years of age, this decline accelerates to 25-40% muscle mass loss per decade [2,3].

Loss of muscle mass is associated with unfavourable outcomes in chronic diseases such as liver-cirrhosis [4] and cardiovascular disease [5], and is frequently present in patients with rheumatoid arthritis [6], diabetes [7] and HIV/AIDS [8]. In surgical patients, low muscle mass is associated with postoperative complications and can be used to identify risk patients before surgery [9]. Recently, the role of low muscle mass has become of interest in patients with cancer. In different tumor types and treatment settings, patients with a low muscle mass appear to have worse survival compared to patients without a low muscle mass [10-13]. Additionally, patients with low muscle mass are more likely to experience more severe toxicities from systemic anti-tumor agents [14]. Many chemotherapeutic drugs are distributed to the fat-free compartment of the body [15]. Since low muscle mass is associated with a decline of the fat-free compartment, low muscle mass is thought to result in relatively higher drug concentrations with all accompanying toxicities [16]. Consequently, muscle mass could be an important new prognostic factor for survival and treatment tolerability in cancer patients.

In patients with cancer, muscle loss is probably the result of both sarcopenia and processes closely linked to cachexia. Sarcopenia is a geriatric syndrome with multifactorial etiology and consisting of a low muscle mass combined with low muscle strength or impaired physical performance [17]. In older adults, sarcopenia is associated with mortality [18,19] and physical disability [20]. Cachexia is a severe wasting of both fat- and muscle mass and loss of weight, mediated by systemic inflammation in the presence of a severe chronic disease [22]. Several names have been used in the literature to describe muscle status, such as sarcopenia, low muscle mass and muscle loss. In oncological studies, the term sarcopenia is frequently used although most studies do not report impaired muscle function and physical performance, while these parameters are crucial to diagnose sarcopenia [17].

Here, we review the current knowledge on diagnosing low muscle mass, its prevalence and its prognostic value in cancer patients. To make the nomenclature in this review clear, we use the term low muscle mass to describe radiological measured muscle mass (i.e. using radiation techniques). We use the term sarcopenia when describing the combination of radiological measured muscle mass, impaired muscle function and impaired physical performance. As most of the literature on muscle mass and its association with outcome has been generated in studies on elderly, special emphasis is put on the methods used in muscle measurement, which might be useful for studying the clinical relevance of low muscle mass in patients with cancer.

Sarcopenia and aging

The probable mechanism of sarcopenia occurring in elderly is an imbalance in muscle protein turnover [23] without the possibility of pointing out a single factor as the main cause (**table 1)** [17]. Muscle protein synthesis decreases during aging, partly because of age-related endocrine changes such as a reduction of sex hormones and growth factors [24]. Additionally, muscle protein breakdown increases mainly due to age-related low-grade systemic inflammation [25], alongside other factors such as physical inactivity and malnutrition [22]. This low-grade systemic inflammation, also called inflammaging [26], is characterized by elevated pro-inflammatory cytokines and is caused by age-related cell damage [26] and mitochondrial dysfunction, leading to accumulation of oxidative stress [27].

Middle-aged men (40-50 years) have more muscle mass than women of the same age [1]. However, due to faster deterioration of muscle mass and muscle strength in men compared to women, at older age, men experience more absolute muscle loss and larger percent losses of both muscle mass and muscle strength than women [2,3]. A specific subgroup is patients suffering from sarcopenic obesity. Sarcopenic obesity is not just the combination of obesity and low muscle mass, but the result of unfavorable metabolic changes leading to both obesity and low muscle mass [28]. These patients possibly form a particular worse prognostic group for adverse outcomes.

Table 1. Etiological factors of sarcopenia.

Etiological factors of sarcopenia[a]	Mechanisms
Muscle disuse	Physical activity ↓
	Cognition ↓
	Immobility
Endocrinal changes	Testosterone ↓
	Growth hormone ↓
	IGF-1 ↓
	Insulin resistance ↑
Malnutrition	Inadequate food intake
	Impaired adaptation to nutrients by skeletal muscles
	Malabsorption
Low-grade systemic inflammation	Interleukin 1 ↑
	Interleukin 6 ↑
	TNF-α ↑

Based on references [23] and [101]
[a]Sarcopenia could be age-related (primary) or disease-related (secondary)

Diagnosing sarcopenia in geriatrics

Nowadays, deterioration of muscle mass alone is considered insufficient to establish the diagnosis sarcopenia. A prospective cohort study in 2292 community-dwelling elderly showed that muscle strength had a higher association with mortality than muscle mass [29], while there is no linear correlation between muscle loss and reduced muscle strength [17]. Longitudinal studies report dissociations in time between loss of muscle mass and loss of muscle strength [30] with muscle strength deteriorating more rapidly than muscle mass [20].

Therefore, it is recommended by the European Working Group on Sarcopenia in older people (EWGSOP) to include muscle strength and physical performance besides muscle mass to diagnose sarcopenia in the elderly (**fig 1)** [17,20,22,31]. A crucial shortcoming of this recommendation however, is that no advice on how to measure muscle mass and strength has been given, neither which cut-off values to define sarcopenia should be used. Consequently, consensus about a definition of sarcopenia has not been reached yet and various methods and definitions are used [17,32]. Studies comparing the various definitions diagnosing sarcopenia which include muscle mass, muscle strength and physical performance, showed a large variation of 0% to 20% in the prevalence of sarcopenia in different populations [21,33,34].

Cachexia

In contrast to sarcopenia, cachexia is not caused by aging itself, but is a result of metabolic changes due to disease [35]. Cachexia is a combination of weight loss, muscle- and adipose tissue loss, anorexia [35], hyperglycaemia, hyperlipidaemia and anaemia [36] (the 2 most widely used definitions of cachexia are listed in **table 2**). Factors contributing to these metabolic changes and muscle protein degradation are pro-inflammatory cytokines, while in cancer patients, tumour metabolism contributes as well [36].

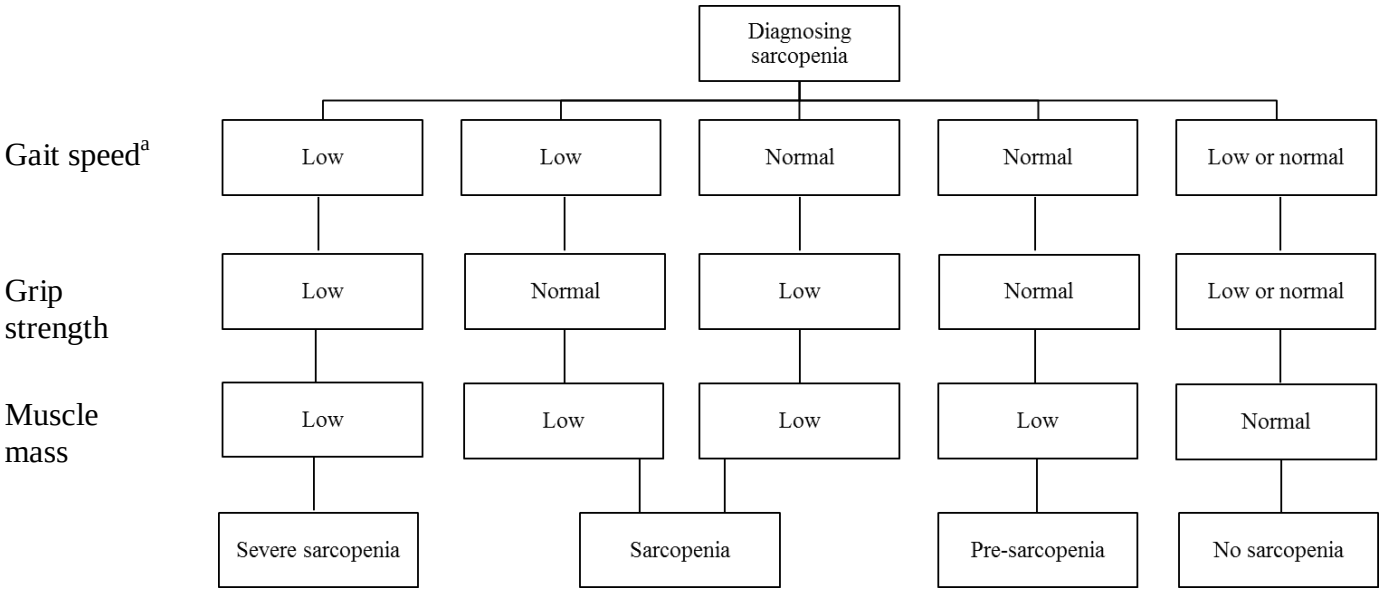
Both sarcopenia and cachexia are featured by the combined loss of muscle mass and muscle function, thus distinguishing these two syndromes in one patient can be difficult or even impossible [22,37]. However, certain clinical features are more pathognomic for cachexia, such as weight loss in a short time-frame in combination with failure of nutrition support [36,38] and abnormal biochemistry. In general, muscle mass measurement only or even the combination with muscle function, is not sufficient to differentiate sarcopenia and cachexia; knowledge regarding metabolic state is essential [37].

Determination of muscle mass in non-cancer patients

Muscle mass is part of the fat-free mass (FFM) of the human body. Total body mass consists of several compartments; i.e. fat mass (FM), water, protein and bone, with the latter three forming the fat-free compartment [39]. Body composition analyses focus on measuring these compartments individually rather than simply measuring total body weight. Distinguishing the measurement of FM and FFM can be important, as alterations in both compartments do not occur synchronically [40]. Furthermore, body mass index [41] and body surface area [42] cannot be relied on to detect total lean body mass or muscle mass, which urges the need to assess these conditions separately.

In geriatric studies, measurement of muscle mass is mostly done by dual energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) [31]. In oncological studies, CT-imaging is most often used. Other options are magnetic resonance (MR)-imaging [32] and ultrasound [43]. CT- and MR-imaging are regarded as gold standards for muscle

mass measurement [31,44]. In a cadaver validation study, muscle measurement was highly accurate using CT- and MRI-imaging (r = 0.99). [45]. An alternative is DEXA, as this has shown high accuracy (r = 0.94) compared to MRI-images [46], although DEXA loses accuracy when assessing body composition in obese patients [47]. Furthermore, a study in advanced cancer patients showed that appendicular skeletal muscle mass obtained from DEXA and muscle cross-sectional area at the L3 level measured by CT showed a moderate correlation (R = 0.70) but with a large difference in agreement after Bland Altman analysis [48]. Use of BIA is discouraged because of less accuracy, [31,49,50], often leading to overestimation of measured muscle mass [51]. In oncological patients, we recommend CT-imaging to measure skeletal muscle, because of the high accuracy and availability.



[a]Low gait speed: ≤0.8 m/s. Normal gait speed: >0.8 m/s.

Figure 1. Sarcopenia in older people (EWGSOP) [17].

Muscle mass measurement using DEXA has been described in two ways, with different cut-off points to define low muscle mass. In the first method, appendicular skeletal muscle mass (ASM), which is the sum of the muscle mass of all limbs [52], is measured and corrected for height. In one study, low muscle mass is defined as ASM two standard deviations below ASM in young adults, aged 30 years (mean), resulting in cut-offs of 7.26 kg/m^2 for men and 5.45 kg/m^2 for women [53] and these cut-off points are frequently used in studies. In other cut-off points commonly used, low muscle mass is defined as the 20th percentile ASM in

community-dwelling elderly, resulting in cut-offs of 7.23 kg/m^2 for men and 5.67 kg/m^2 for women [54], which shows high similarity. In the second method, ASM is corrected for both height and fat mass using linear regression. The residuals of the regression were used to identify the difference between expected muscle mass and true muscle mass. Low muscle mass was defined as the 20th percentile of the distribution of the residuals [54]. However, despite using 20th percentiles as cut-off points in both methods, almost half of the people in a population of community-dwelling elderly were identified as having low muscle mass by one method, but not by the other [54]. This discrepancy clearly stresses the high need for a standardized approach to measure muscle mass.

Table 2. Definitions of cachexia.

Reference	Definition of cachexia
Fearon K et al 2011 [36]	Pre-cachexia • Weight loss ≤5% • Anorexia (reduced food intake) • Metabolic change Cachexia • Weight loss >5% the past 6 months in the absence of starvation or • BMI <20 kg/m^2 and any weight loss >2% or • Low muscle mass[a] and weight loss >2% Refractory cachexia • Variable degree of cachexia • Cancer disease procatabolic and not responsive to cancer treatment • WHO performance score 3 or 4 • Expected survival <3 months
Evans WJ et al 2008 [38]	Cachexia • Weight loss ≥5% in the past 12 months or • BMI <20 kg/m^2 and 3-5 of the following: • Decreased muscle strength • Fatigue • Anorexia • Low muscle mass[a] • Abnormal biochemistry (elevated inflammation parameters, anaemia, hypoalbuminaemia)

[a]Appendicular skeletal muscle index <7.26 kg/m^2 for males and <5.45 kg/m^2 for females

Determination of low muscle mass in cancer patients

Little is known about the pathophysiology of low muscle mass in cancer patients [55]. Etiological factors seen during aging such as physical inactivity and increased levels of pro-inflammatory cytokines also contribute to cancer-related muscle wasting, however, the main cause is probably an increased activity of the ubiquitin-proteasome system (UPS), resulting in an increased muscle protein degradation. This can be present without the other determinants of cachexia, such as weight loss, metabolic changes and loss of muscle- and adipose tissue. Furthermore, cancer treatment frequently lead to, vomiting, inappropriate food intake and lack of physical activity which can also result in the loss of both fat and muscle tissue [56]. In addition, corticosteroids frequently used in cancer patients, stimulate the UPS and cause insulin resistance, both leading to muscle proteolysis [57].

To measure muscle mass in cancer patients, CT-imaging instead of DEXA is mostly used because of its high availability given its frequent use to evaluate tumor growth. However, also in cancer patients DEXA could be a valuable alternative to measure muscle mass. Unfortunately, as holds true for muscle measurement in elderly, consensus for determining muscle mass by CT-scanning is lacking.

Muscle mass has been determined by measuring either the total psoas cross-sectional area (TPA) at the L3-level [58-61], or the total abdominal muscle area (TAMA) at the L3-level [16,42,62,63]. The TAMA measured at the L3-level is highly correlated with the total body muscle mass (Pearson correlation coefficient of 0.924) [64]. The TAMA is corrected for height, resulting in a skeletal muscle index (SMI) (cm^2/m^2). Therefore, muscle mass quantification can be performed easily using only one slice, avoiding analyses of multiple images and larger surfaces being exposed to radiation.
Importantly, the first cut-off points for TAMA measurement using the single slice technique were computed in an obese population [16], but the prevalence of obesity in later studies using these cut-off points varied from 14% [65] to 57% [66]. Several studies established their own cut-off points for both TAMA and TPA, resulting in a large variation of diagnosing low muscle mass **(table 3).** Furthermore, cut-off points for low muscle mass are mostly established by optimum stratification to detect the association with mortality but the sensitivity to detect survival differences is higher in obese patients [62]. However, few studies

report the distribution of muscle loss according to body mass index (BMI)-groups in cancer patients.

Table 3. Cut-off points for low muscle mass associated with mortality.

Study	Number of patients	Definition of sarcopenia	Population
Method 1: Prado CM et al 2008 [16]	250	L3[a] TAMA[b]/height^2 in cm^2/m^2 HU: -29 to +150 Males: <52.4 Females: <38.6	Cancer of the gastro-intestinal and respiratory tract. BMI[c] ≥30
Method 2: Baracos VE et al 2010 [42]	441	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males: <55.4 Females: <38.9	Cancer of the respiratory tract (at diagnosis)
Method 3: Vledder van MG et al 2012 [102]	196	L3 TAMA/height^2 in cm^2/m^2 HU: -30 to +110 Males: <43.75 Females: <41.1	Colorectal cancer with liver metastases (before hepatic surgery)
Method 4: Peng P et al 2012 [58]	557	L3 lowest quartile TPA[d]/height in cm^2/m^2 HU: -30 to +110 Males: <4.92 Females: <3.62	Pancreatic cancer (before curative surgery)
Method 5: Martin L et al 2013 [62]	1473	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males BMI <25: ≤43.0 Males BMI ≥25: ≤53.0 Females BMI <25: ≤41.0 Females BMI ≥25: ≤33.0	Cancer of the gastro-intestinal and respiratory tract
Method 6: Camus V et al 2014 [73]	80	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males: <55.8 Females: <38.9	Elderly patients (mean age 79 years) with DLBCL[e]
Method 7: Smith AB et al 2014 [61]	224	[f]L3 TPA/height^2 in cm^2/m^2 HU: -30 to +110 Males: <65.3 Females: <52.3	Bladder cancer
Method 8: Fujiwara N et al 2015 [68]	1257	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males: <36.2 Females: <29.6	Hepatocellular carcinoma in Asian people
Method 9: Iritani S et al 2015 [77]	217	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males: <36.0 Females: <29.0	Hepatocellular carcinoma in Asian people
Method 10: Amini N et al 2015 [59]	763	L3 lowest quartile TPA/height in cm^2/m^2 HU: -30 to +110	Pancreatic cancer (before surgery)

		Males: <5.64 Females: <4.15	
Method 11: Joglekar S et al 2015[60]	118	L3 lowest quartile TPA/height in cm^2/m^2 HU: -30 to +110 Males: <5.2 Females: <4.0	Pancreatic cancer (before surgery)
Method 12: Nakamura N et al 2015 [91]	207	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males: <47.1 Females: <34.4	DLBCL Asian people
Method 13: Peyton CC et al 2015 [103]	128	L3 lowest quartile TPA/height^2 in cm^2/m^2 HU: -20 to +100 Males: ≤4.27 Females: ≤3.80	Renal cancer
Method 14: Choi Y et al 2015 [104]	484	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males: <42.2 Females: <33.0	Pancreatic cancer (unresectable or metastatic)
Method 15: Harada K et al 2015 [105]	325	L3 lowest tertile TAMA/height^2 in cm^2/m^2 HU: -29 to +150 Males: <44.5 Females: <36.5	Lung cancer
Method 16: Kimura L et al 2015 [106]	134	L3 TAMA/height^2 in cm^2/m^2 HU: -29 to +100 Males: <41.0 Females: <38.0	Lung cancer

[a] L3: Lumbar vertebra 3
[b] TAMA: Total abdominal muscle area (psoas, Para spinal muscles, abdominal wall muscles)
[c] BMI: Body mass index
[d] TPA: Total psoas area (psoas muscle area only)
[e] DLBCL: Diffuse Large B-cell Lymphoma
[f] Muscle mass associated with major postoperative complications instead of mortality

Prevalence of low muscle mass in cancer patients

Several large studies have reported on the prevalence of low muscle mass in cancer patients [42,62,67,68]. Most studies used TAMA and TPA to describe the prevalence of low muscle mass. The prevalence of low muscle mass using TPA seems to be somewhat lower compared to the measurement of TAMA **(table 4)**. However, since there is no standard method for the quantification of muscle mass by CT-imaging, reported prevalence's of low muscle mass are difficult to compare and are highly dependent of the used definition for muscle measurement.

Furthermore, the level of correlation between TPA and TAMA is unknown, which makes it hard to compare these results with other studies. **Table 4** describes the reported prevalence of low muscle mass and the used definition per cancer type. The prevalence of low muscle mass was highly variable across cancer types, ranging from 5% to 89%.

In cancer patients, low muscle mass more often occurs in patients above 65 years, although is not restricted to the elderly [16]. In patients with tumors of the respiratory and gastro-intestinal tract, 68% of the patients with low muscle mass was above 65 years. Among the group of patients without low muscle mass, 45% was above 65 years [16]. Knowledge about the prognostic value of low muscle mass in different age groups, in the presence of malignancy, is lacking. According to gender, there seems no difference in the prevalence of low muscle mass [68-71]. Compared to women however, susceptibility for muscle loss and adverse outcomes related to low muscle mass in males has been described on multiple occasions in patients with [69,72-74], and without cancer [19,75].

In addition to taking into account gender and BMI, it should be considered to stratify cut-off points for low muscle mass also by ethnicity. It has been reported that the muscle mass of young healthy Chinese men was 17% lower than in Caucasian men [76]. In studies investigating Asian populations, lower cut-off points for low muscle mass are applied [68,77] **(table 3)**.

Adding functional assessments to muscle mass measurements in cancer patients

Importantly, likewise of what has been done in studies in elderly and according to the previously mentioned EWGSOP guidelines, the prognostic value of determining muscle mass can potentially be increased by adding functional tests to muscle mass measurement in cancer patients. Physical performance is mostly described using the ECOG performance score in cancer patients. Although a high ECOG performance score correlated well with impaired physical function according to geriatric assessment, 38% of the patients with low ECOG performance scores were limited in instrumental activities of daily living, which possibly requires additional parameters to assess functional status [78].

However, so far, only two studies among cancer patients combined muscle mass determination and functional assessments (gait speed and handgrip strength) according to the EWGSOP guidelines, and reported that the combination of radiological muscle mass and functional assessments had more predictive power for postoperative complications than radiological muscle mass alone in patients with colorectal cancer [12] and in patients with gastric cancer [83]. Although the EWGSOP guidelines do not recommend devices to determine hand grip strength, the Jamar hand dynamometer (Lafayette Instrument Company, USA) is most widely used and is considered the gold standard to measure hand grip strength [84].

Functional tests actually reflect muscle quality and several mechanisms of muscle quality are reported in the literature, such as decrease in muscle fiber size and number (resulting in reduced gait speed), reduction of muscle fiber contractility (resulting in reduced strength), mitochondrial dysfunction and micro- or macro fatty infiltration of muscle. Further research is warranted to determine whether or not adding functional tests improves the clinical value of muscle mass determination in cancer patients, and to establish the most appropriate way to determine muscle quality.

Association of low muscle mass with chemotherapeutic toxicity and survival

Low muscle mass might be of emerging clinical significance in the oncological field due to its association with clinical end points such as toxicity and cancer-related mortality [85]. A summary of all studies reporting on the prognostic value of low muscle mass for survival and treatment toxicity in cancer patients undergoing chemotherapeutic treatment is listed in **table 5.** The studies are characterized by a variation of muscle measurement methods. The knowledge regarding prognosis will be described per cancer type.

Table 4. Prevalence of low muscle mass in patients with cancer using CT imaging.

Cancer site	Studies	Mean age	Prevalence (%)	Method[a]
Respiratory tract	Prado CM et al 2008 [16]	64	5	Method 1
	Baracos VE et al 2010 [42]	67 (male) 65 (female)	61 31	Method 2
	Stene GB et al 2015 [74]	67	74	Method 1
	Kim E et al 2015 [107]	69	79	Method 2
Respiratory tract metastatic	Kitamura L et al 2015 [1]	66	87 (male) 36 (female)	Method 16
Colorectal	Prado CM et al 2008 [16]	64	25	Method 1
	Lieffers JR et al 2012 [108]	63	39	Method 1
	Huang DD et al 2015 [12]	62	12	Method 9 + impaired hand grip strength[b] or gait speed[c]
	Jung HW et al 2015 [92]	61	25	L4 TPA sex-specific lowest quartile (not specified)
	Reisinger K et al 2015 [109]	51% <70 yrs	48	Method 1
	Broughman JR et al 2015 [110]	77	60 (male) 56 (female)	Method 5 (used different HUs)
Colorectal metastatic	Vledder van, MG et al 2012 [102]	65	19	Method 3
	Thoresen L et al 2012 [111]	64	20	Method 1
	Thoresen L et al 2013 [112]	65	39	Method 1
	Barret M et al 2014 [72]	65	71	Method 2
	Vugt van, JL et al 2015 [71]	61	44	Method 1
Breast	Del Fabbro E et al 2012 [87]	NA[d]	14	Method 1
Breast metastatic	Prado CM et al 2009 [86]	55	27	Method 1
Pancreas (curative)	Dalal S et al 2012[113]	59	37	Method 1
	Peng P et al 2012[58]	66	25	Method 4
	Di Sebastiano et al 2013 [114]	66	48	Method 2
	Amini N et al 2015 [59]	67	25	Method 10
	Cooper AB et al 2015 [99]	63	52	Method 2
	Joglekar S et al 2015 [60]	NA	26	Method 11
Pancreas (palliative)	Tan et al 2009 [98]	56	60	Method 1
	Wesseltoft N et al 2015 [115]	72	89	Method 2
	Choi Y et al 2015 [104]	NA	21	Method 14
Kidney	Antoun S et al 2010 [116]	59	55	Method 2
	Peyton CC et al 2015 [103]	63	25	Method 13
Kidney metastatic	Huillard O et al 2013 [117]	60	53	Method 2
	Cushen S et al 2014 [118]	64	33	Method 2
	Sharma P et al 2015 [119]	61	29	Method 5
Oesophageal[f]	Awad S et al 2012 [94]	63	57	Method 1

	Yip C et al 2014 [65]	63	26	Method 1
	Anandavadivelan et al 2015 [66]	67	43	Method 1
	Tan et al 2015 [70]	66	50	Method 1
	Tamandl D et al 2015 [120]	64	65	Method 2
	Harada K et al 2015 [105]	NA	33	Method 15
Liver	Mir O et al 2012 [121]	63	28	Method 2
	Mir O et al 2012 [100]	64	50	Method 2
	Harimoto N et al 2013 [122]	66	40	Method 3
	Meza-Junco J et al 2013 [69]	58	30	Method 5
	Voron T et al 2014 [123]	62	54	Method 1
	Fujiwara N et al 2015 [68]	69	11	Method 8
	Imai K et al 2015 [124]	67	38	<39.2[g]
	Iritani S et al 2015 [77]	72	11	Method 9
	Nault JC et al 2015 [125]	61	76	[h]L3 TAMA/height^2 in cm^2/m^2 Males: <55.0 Females: <39.0
	Kamachi S et al 2015 [126]	72	67	Method 1
Bladder	Psutka SP et al 2015 [127]	71	70	[h]L3 TAMA/height^2 in cm^2/m^2 Males: <55.0 Females: <39.0
	Smith AB et al 2014 [61]	66	38	Method 7
	Fukushima H et al 2015 [128]	68	60	Method 5
Non-Hodgkin Lymphoma	Camus V et al 2014 [73]	79	55	Method 6
	Nakamura N et al 2015 [91]	67	56	Method 12
Gastric	Tegels JJ et al 2015 [95]	70	58	Method 5

[a] The used sarcopenia-definition refers to the methods mentioned in table 2.
[b] Hand grip strength <26 kg for males or 18 kg for females
[c] Gait speed <0.8 m/s
[d] NA: Not available
[e] HU: Hounsfield unit
[f] All before start of neo-adjuvant chemotherapy
[g] L3 TAMA/height^2 in cm^2/m^2. No specification by gender
[h] Based on the definition of a muscle mass of two standard deviations below healthy adults [36]. It must be noted that muscle mass in that population was measured using dual-energy X-ray (DXA). Reference populations for CT-imaging are currently not available.

Breast cancer

After the introduction of muscle mass measurement using CT imaging, the first study that reported on the association of low muscle mass and oncological outcome was conducted among 55 younger patients with metastatic breast cancer and a mean age of 55 years [86]. All patients received a fixed dose of capecitabine and toxicity was determined after one cycle to avoid the influence of treatment adjustments. Muscle mass was calculated using TAMA-measurement. Patients with low muscle mass had a calculated higher capecitabine dose per kg lean body mass and had a 3-times greater risk of chemotherapeutic toxicity, such as diarrhoea and stomatitis. Moreover, low muscle mass was the only independent predictor of toxicity in a model with age, body surface area and ECOG performance score. In the same study, low muscle mass was associated with a shorter time to tumor progression (62 days vs.105 days). The authors mentioned that chemotherapeutic dose interruption or reduction for toxicity, which was more prevalent in patients with low muscle mass, could be responsible for a shorter time to tumour progression. Alternatively, the low muscle mass before starting treatment itself could be a sign of aggressive or advanced underlying disease [86].

In contrast, patients with localized breast cancer and low muscle mass achieved higher rates of pathological complete response after neo-adjuvant chemotherapeutic treatment compared to those without low muscle mass [87]. An explanation for this finding is unclear, but it is possible that patients with low muscle mass received a higher dose of chemotherapeutic agents per kg lean body mass (LBM), resulting in a better chemotherapeutic efficacy on tumor eradication [87]. The systemic clearance of hydrophilic chemotherapeutic agents correlates well with the LBM [15,88] and in patients with low LBM in relation to their length and weight, a low volume of distribution of chemotherapeutic drugs in proportion to the BSA is reported [14,89,90].

Non-Hodgkin lymphoma

Three studies described the prognosis of patients with non-Hodgkin lymphoma undergoing chemotherapeutic treatment [63,73,91]. Only one study investigated the association between low muscle mass and treatment tolerability. Low muscle mass was a predictive factor of cancellation of chemotherapy compared to normal muscle mass, although the reasons of treatment interruption were not mentioned (40% vs. 16%, $p = 0.02$) [63]. In all studies,

muscle mass was measured before the start of chemotherapy and low muscle mass was associated with a worse overall survival compared to patient with normal muscle masses. In one study, the unfavorable survival effect was only detected in males [63,73,91].

Gastro-intestinal tumors

In colorectal cancer, low muscle mass was associated with a higher incidence of grade 3-4 chemotherapeutic toxicity during both adjuvant [92] and palliative treatment [72,93]. Furthermore, most studies report impaired overall survival in patients with low muscle mass. Two studies showed an association between low muscle mass and mortality due to disease progression in patients with stage III colon cancer receiving adjuvant chemotherapy (HR 1.85, $p=0.022$) [92] and in a large cohort of 1473 patients (HR 1.34, $p<0.001$) [62]. A third study showed that muscle loss larger than 5% during chemotherapy resulted in a two times higher mortality [93]. Remarkably, no association with recurrence-free survival is reported [92,93].

In patients with oesophageal cancer, the association of low muscle mass with a higher incidence of chemotherapeutic toxicity was further confirmed [66,70]. Among obese patients, low muscle mass had a five times higher risk of treatment toxicity compared to obese patients without low muscle mass prior to neo-adjuvant chemotherapy. Risk of toxicity did not reach significance in patients with low muscle mass and normal weight, also indicating that especially obese patients with low muscle mass are the worst prognostic group [66]. Another study containing 47 patients with esophago-gastric cancer reported that 57% was diagnosed with low muscle mass before start of neo-adjuvant chemotherapy and these patients suffered further reduction of muscle mass during chemotherapy. There was no association with reduced completion of chemotherapy or mortality, although this should be interpreted with caution, as the study was not powered to detect differences in clinical outcome [94].
Only one study determined the association between muscle mass and survival in patients with gastric cancer [95]. In this study, involving 152 patients before surgery, low muscle mass was not associated with mortality during hospital admission and 6-month mortality, although other studies have reported a higher incidence of postoperative complications in patients with low muscle mass after gastrectomy [96,97].

Pancreas and hepatocellular cancer

Associations of low muscle mass with treatment toxicity in patients with these types of cancer have not been described yet. In patients with pancreas cancer in palliative setting, impaired overall survival has been reported in obese patients with low muscle mass. Noteworthy, these results mostly could not be extended to patients with low muscle mass and normal weight [98,99] (**table 5)**. In patients with hepatocellular carcinoma, low muscle mass was associated with both overall- and progression free survival [69,100].

Table 5. Prognostic impact of low muscle mass in patients undergoing chemotherapeutic treatment.

Ref	Year	N	Mean age	Type of cancer	Method[a] and cut-offs	Prevalence low muscle mass (%)	Incidence grade 3-4 toxicity[b]	Survival[c]
[14]	2007	62	60	Colon	Total LBM[d] = TAMA – 3.2459 / 3.0583	NA[e]	Present vs. absent Males: dose12.8 – 23 mg/kg Females: dose 12-20.1 mg/kg	NA
[16]	2008	250	63.9	GI[f] + respiratory	At cancer diagnosis	15.2	NA	11.3 vs. 21.6 months (p<0.0001)
[86]	2009	55	54.8	Metastatic breast cancer	After failure of taxanes/anthracyclines	25.5	Toxicity after 1 cycle: 50% vs. 20% (p=0.03)	TTP[g]: 101 days vs. 173 days (p=0.05)
[98]	2009	111	55.9	Pancreas	At diagnosis of distant metastases	55.9	NA	P = NS[h] Sarcopenic obesity vs. other: 55 vs. 148 days (p=0.003) Sarcopenic vs. non-sarcopenic: NS[e]
[56]	2011	24	52.5	Breast cancer	Total LBM = 0.30 x TAMA + 6.06	NA	Mean LBM: 56.2 vs. 41.6 kg (p=0.002)	NA
[94]	2012	47	63.0	Oesophago-gastric	Before and after neo-adjuvant chemotherapy	Before: 57.4 After: 78.7	NA	p = NS 1-year OS: 76.1%

Table 5. Continued.

Ref	Year	N	Mean age	Type of cancer	Method and cut-offs	Prevalence low muscle mass (%)	Incidence grade 3-4 toxicity	Survival
[113]	2012	41	58.9	Pancreas (inoperable)	Before and after chemo radiation	Before: 37.0	NA	Muscle loss <3.8% vs. >3.8%: 10.1 vs. 16.3 months. (p=NS)
[121]	2012	65	64.0	Liver	Before chemotherapy L3 TAMA Males: ≤55.4 Females ≤38.9	50	NA	3.0 vs. 10.0 months (p<0.001) PFS: 2.3 vs. 4.5 months (p=0.0008)
[87]	2012	129	NA	Breast cancer	Before neo-adjuvant chemotherapy	14	NA	pCR[i]: 72% vs. 49% (p=NS)
[62]	2013	1473	64.7	GI/respiratory	At cancer diagnosis. Sex- and BMI specific cut-off points[j]	40.9	NA	13.0 vs. 20.1 months (p<0.001)
[69]	2013	116	58.0	Liver	At cancer diagnosis. Sex- and BMI specific cut-off points[j]	30	NA	16.6 vs. 28.3 months (HR 2.2, p=0.01)
[129]	2013	216	60.0	Liver (local or distant)	L3 TPA lowest quartile Males: ≤477 mm^2/m^2 Females: ≤338 mm^2/m^2	28	NA	90-days mortality: 9.3% vs. 12.7% (p=NS)

Table 5. Continued.

Ref	Year	N	Mean age	Type of cancer	Method and cut-offs	Prevalence low muscle mass (%)	Incidence grade 3-4 toxicity	Survival
[72]	2014	51	65.0	Metastatic colorectal	Before palliative chemotherapy. L3 TAMA Males: <55.4 Females: 38.9	70.6	33.3% vs. 13.3% (p = 0.043)	NA
[73]	2014	80	78.7	DLBC[k]	At diagnosis L3 TAMA Males: ≤55.4 Females ≤38.9	55	NA	Low muscle mass: HR 3.23 (p = 0.0007) PFS[l]: NS
[130]	2014	93	57.0	Varied (Phase I-trial)	<30 days before inclusion. L3 TAMA median Males: <52.1 Females: <41.8	NA	Mean SMI[m] DLT[n]/DIT[o] vs. no DLT/DIT: Males: 44.4 vs. 53.6 (p= 0.01) Females: 40.0 vs. 42.0 (p=NS)	NA
[63]	2014	82	78.0	DLBCL	Before chemotherapy L3 TAMA Males: ≤55.4 Females ≤38.9	55	Cancellation of treatment: 40% vs. 16.2% (p = 0.02)	PFS: 13.0 vs. 32.8 months (HR 2.7, p = 0.0008) 2-years OS: 46% vs. 84% (HR 3.2, p = 0.0002)

Table 5. Continued.

Ref	Year	N	Mean age	Type of cancer	Method and cut-offs	Prevalence low muscle mass (%)	Incidence grade 3-4 toxicity	Survival
[65]	2014	35	63.0	Oesophageal	Before and after neo-adjuvant chemotherapy	Before: 26 After: 43	DLT: NS	Treatment response: NS OS: NS PFS: NS
[74]	2015	35	67.0	Non-small Lung cancer	Before and after palliative chemotherapy	74	NS	7.5 vs. 7.9 months (HR 1.4, p=NS)
[92]	2015	229	61.0	Stage III colon cancer	Before adjuvant chemotherapy L4 TPA lowest quartile	25.3	Lowest vs. highest quartile: 75% vs. 40% (OR 1.67, p =0.0001)	Median not reached (HR 1.85, p = 0.022) PFS: NS
[66]	2015	72	67.0	Oesophageal	Before neo-adjuvant chemotherapy	43	Low muscle mass: OR 2.47 (p = 0.09) Low muscle mass + obese: OR 5.54 (p = 0.04)	NA
[70]	2015	89	65.8	Oesophago-gastric	Before neo-adjuvant chemotherapy	49.4	DLT: 54.4% vs. 28.9% (OR 2.95, p = 0.015)	569 vs. 1013 days (p = 0.04)

Table 5. Continued.

Ref	Year	N	Mean age	Type of cancer	Method and cut-offs	Prevalence low muscle mass (%)	Incidence grade 3-4 toxicity	Survival
[93]	2015	148	NA (73% <70)	Colorectal (inoperable)	Before and after chemotherapy L3 TAMA lowest quartile	NA Muscle loss during therapy: 4.2%	NA	OS: NS PFS: NS ≥5% loss of muscle mass: HR 1.97, p = 0.017
[99]	2015	89	63.0	Pancreas	L3 TAMA Males: ≤55.8 Females ≤38.9	55	NA	16.8 vs. 20.4 months (p = NS) Low muscle mass + obese 12.9 vs. 20.7 months (p = 0.04)
[104]	2015	484	NA	Pancreas	Before palliative chemotherapy L3 TAMA Males: <42.2 Females: <33.9	21.3	NA	Low muscle mass: HR 1.502 (p = 0.002)

Table 5. Continued.

Ref	Year	N	Mean age	Type of cancer	Method and cut-offs	Prevalence low muscle mass (%)	Incidence grade 3-4 toxicity	Survival
[93]	2015	207	67.0	DLBCL	Before chemotherapy L3 TAMA Males: <47.1 Females: <34.4	56	NA	Univariable: 3-yr OS: 70% vs. 85% (p = 0.026) 3-yr PFS: 63% vs. 76% (p = NS) Multivariable: p = NS Multivariable: p = NS
[131]	2015	98	64.8	Pancreas + bile ducts	Before and after chemotherapy. Sex- and BMI specific cut-off points[j]	Before: 61.2 After: 70.4	16.7 vs. 24.3% (p = NS) Completion of treatment: 32% vs. 43% (p = NS)	P = NS
[132]	2015	117	NA	Lung	Before chemotherapy Pectoral muscle lowest quartile. <4.37	25	NA	10.5 vs. 13.5 months (p = NS) PFS: 6.0 vs. 7.5 months (p = 0.009)

Table 5. Continued.

Ref	Year	N	Mean Age	Type of cancer	Method and cut-offs	Prevalence low muscle mass (%)	Incidence grade 3-4 toxicity	Survival
[106]	2015	134	66	Lung	Before, halfway, after and 1 year after chemotherapy L3 TAMA Males: <41 Females: <38	Before: 38.3 Halfway: 48.1 After: 45.7 1 year: 49.4	NA	OS in months: Males: (p = 0.0119) Before: 8.9 vs. 14.8 Females: (p = 0.0155) Before: 19.2 vs. 33.6

[a]Method of muscle measurement is according to Prado CM et al [12] (method 1, table 2), unless listed otherwise
[b]Low muscle mass vs. no low muscle mass, unless listed otherwise.
[c]Overall survival low muscle mass vs. no low muscle mass, unless listed otherwise.
[d]LBM: Lean body mass
[e]NA: Not available
[f]GI: Gastro-intestinal
[g]TTP: Time to tumour progression
[h]NS: Not significant
[i]pCR: Pathologic complete response
[j]Method of muscle measurement is according to Martin L et al [49] (method 5, table 2)
[k]DLBCL: Diffuse Large B-cell Lymphoma
[l]PFS: Progression-free survival
[m]SMI: Skeletal muscle index
[n]DLT: Dose-limiting toxicity
[o]DIT: Dose-interrupting toxicity

Discussion and conclusion

Muscle mass loss occurs during aging and in cancer patients is possibly due to cachexia-associated processes. Accordingly, in cancer patients, low muscle mass is prevalent across all ages, but particularly in the elderly. The number of studies in cancer patients investigating the relation between low muscle mass and clinical outcome rapidly increases and promising results on the use of muscle mass measurement as a prognostic factor have been reported.

There are, however, a few limitations. There is no consensus of a standard approach to measure muscle mass while different cut-off points and devices are used. Furthermore, the current terminology of muscle mass in the literature is confusing. Radiological low muscle mass is part of the sarcopenia-syndrome and is often named sarcopenia. However, sarcopenia is more than low muscle mass alone and consists of a triad of radiological low muscle mass, low muscle strength and impaired physical performance [17]. Unfortunately, there is also no consensus on a definition of sarcopenia. Although low muscle mass seems a good prognostic marker, it is possible that the prognostic value can be improved further by measuring muscle function and physical performance. This needs further investigation. Functional measures such as gait speed and handgrip strength are easy to perform but are not widely available in oncological care yet. Nevertheless, many studies report a prognostic significance on measuring muscle mass and establishing low muscle mass as a prognostic factor could be a valuable addition in estimating treatment risks and survival effects.

In cancer patients, CT-imaging is mostly used to measure muscle mass, but a reference population for this evaluation has never been described. Consequently, the prevalence of low muscle mass and/or sarcopenia and their association with clinical outcomes is highly variable across the different studies and hard to put into perspective. Studies are needed to construct reference populations for muscle mass measurement by CT-imaging, adjusted for age, gender, ethnicity and body mass index. Furthermore, the usage of devices to measure muscle mass, such as DEXA, which are likewise CT-imaging widely available could be explored in cancer patients. DEXA is highly available across cancer patients in particular in postmenopausal hormone receptor positive breast cancer patients treated with endocrine therapy and reference populations for muscle measurement using this device are well described.

To further study the prognostic value of low muscle mass in cancer patients, investigating the pathophysiology of muscle loss and the accompanying functional impairments in cancer patients is crucial. Studies investigating the impact of other well-known etiological factors of low muscle mass, such as low androgen levels, physical inactivity and impaired nutritional intake, or on the effects of anti-tumor agents or co-medication frequently used in cancer patients, such as corticosteroids, on muscle mass in cancer patients are lacking. Better insight into the mechanisms underlying low muscle mass in cancer patients is crucial as this might provide strategies to improve muscle mass and function and thereby potentially improving outcomes. Current treatment strategies to increase the muscle mass in the elderly mainly involve resistance training and stimulation of nutritional intake [101]; another possibility might be the investigation if low androgen levels are involved in low muscle mass in cancer patients and if this can be used as an intervention strategy. However, whether such strategies actually work in cancer patients and if so, what the optimal timing of such strategies should be, remains to be established.

In conclusion, low muscle mass among cancer patients seems an important prognostic factor for outcomes in terms of treatment-induced toxicity and survival, but consensus about a definition of impaired muscle mass and a standardized approach to measure this are urgently warranted. Functional tests need to be measured to use the term sarcopenia, but the added value of these tests in cancer patients are yet to be established. Until a consensus on these items has been reached, reported prevalences of low muscle mass in populations and between cancer sites remain difficult to put into perspective. Consensus about a definition of low muscle mass and knowledge about its prognostic value and the underlying mechanisms are likely to contribute to strategies to come to a more personalized treatment approach and to novel interventions improving outcome.

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Chapter 4

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

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Breast 2016 Oct 27;31:9-15

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.

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 low muscle attenuation (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 [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.

Materials and methods

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.

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 ≥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 ≥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.

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.

Results

Patient characteristics

Initially, 380 patients with metastatic breast cancer undergoing first line palliative chemotherapy were identified. No CT-scan was available in 184 patients, 29 were excluded due to unknown length and weight and 1 patient was excluded because of a second malignancy. Eventually, a group of 166 patients was analyzed with a mean age of 58.8 ± 11.3 years (range 30 – 86), of whom 21% had primary metastatic disease. Median duration of follow-up was 22 months. No patient was lost to follow-up. The median time from the initial breast cancer diagnosis to the diagnosis of distant metastases was 3 years (IQR 0 – 7). The median time from the diagnosis of distant metastases to the start of the first palliative chemotherapy was 1 month (IQR 0 – 7). The median time from CT-scanning to the start of chemotherapeutic treatment was 20 days. Median muscle mass was 38.4 cm^2/m^2 (IQR 34.2 – 42.7). Mean muscle attenuation (MA) was 34.3 HU (IQR 26.3 – 40.5). Median BMI was 26.4 kg/m^2 and 43 patients (25.9%) were classified as obese (BMI ≥30) **(table 1)**

Prevalence of LMM, sarcopenic obesity and LMA.

The prevalence of LMM, sarcopenic obesity and LMA was 66.9%, 7.2% and 59.6%, respectively. LMA was especially prevalent in older patients (≥70 years), while age did not differ between the patients with and without LMM and patients with and without sarcopenic obesity. Patients with a higher BMI had more muscle mass on average, but lower MA (Spearman correlation +0.61, $p < 0.001$ and -0.22, $p = 0.009$ respectively). Spearman correlations for muscle mass and MA with age were +0.02 ($p = 0.758$) and -0.54 ($p < 0.001$) respectively. Other patient and tumor characteristics did not significantly influence skeletal muscle measures (**table 1)**. In multivariable logistic regression analyses with age and BMI as independent variables, the associations of LMM with BMI and LMA with age were also statistically significant (OR 0.76, 95% CI 0.69 – 0.84, $p < 0.0001$ and OR 1.11, 95% CI 1.07 – 1.15, $p < 0.0001$) **(supplemental table).**

Overall survival and time to next treatment (TNT)

Median OS for the entire cohort was 18 months (95% CI 15.1 – 20.9 months). At the end of follow-up, 84.3% of the patients had died. Muscle mass on a continuous scale was not associated with OS, while muscle attenuation on a continuous scale showed a marginal association with OS, although this did not reach statistical significance (HR 0.98, 95% CI 0.96 – 1.00, $p = 0.054$) **(table 2)**. When using cut-off points to define patients with LMM, sarcopenic obesity and LMA, LMM and sarcopenic obesity were not associated with OS (median OS 19 vs. 18 months, $p = 0.845$ for LMM and 20 vs. 18 months, $p = 0.481$ for sarcopenic obesity). In contrast, patients with LMA had worse OS than patients with normal MA (median OS 15 vs. 23 months, $p = 0.005$) **(fig. 1A).** Using multivariable Cox-regression, the negative association of LMA with OS was maintained after adjusting for other common prognostic factors **(table 2)**.

Table 1. Differences between patients with LMM and no LMM and with LMA and no LMA.

	LMM[a] N = 111 (%)	No LMM N = 55 (%)	P	LMA[b] N = 99 (%)	No LMA N = 67 (%)	P
Age			0.317			<0.001
• **<50y**	19 (17.1)	10 (18.2)		7 (7.1)	22 (32.8)	
• **50 – 69y**	67 (60.4)	38 (69.1)		63 (63.6)	42 (62.7)	
• **≥70y**	25 (22.5)	7 (12.7)		29 (29.3)	3 (4.5)	
BMI ≥30	12 (10.8)[c]	31 (56.4)	<0.001	24 (24.2)	19 (28.4)	0.591
HR status			0.463			0.480
• **Positive**	77 (70.0)	42 (76.4)		73 (73.7)	46 (68.7)	
• **Negative**	33 (33.0)	13 (23.6)		25 (25.5)	21 (31.3)	
• **Unknown**	1			1		
Her2 status			0.122			0.458
• **Positive**	31 (29.5)	9 (17.6)		21 (23.1)	19 (29.2)	
• **Negative**	74 (70.5)	42 (23.6)		70 (76.9)	46 (70.8)	
• **Unknown**	6	4		8	2	
Primary stage IV	21 (18.9)	14 (25.5)	0.419	18 (18.2)	17 (25.4)	0.333
DFI[d] (years)	3.0 (1.8 – 8.0)	4.0 (2 – 8.5)	0.488	4 (2.0 – 9.0)	3 (1 – 6.3)	0.077
TTT[e] (months)	1 (0 – 6)	1 (0 – 13)	0.826	2 (0 – 12)	1 (0 – 3)	0.015
Metastatic location			0.602			0.787
• **Bone**	24 (21.6)	14 (25.5)		26 (26.3)	12 (17.9)	
• **Visceral**	16 (14.4)	11 (20.0)		15 (15.2)	12 (17.9)	
• **CNS**	3 (2.7)	0		2 (2.0)	1 (1.5)	
• **Skin or lymph node**	10 (9.0)	4 (7.3)		8 (8.1)	6 (9.0)	
• **Multiple**	58 (52.3)	26 (47.3)		48 (48.5)	36 (53.7)	
Number of metastatic sites			0.720			0.905
• **1**	49 (44.1)	27 (49.1)		46 (46.5)	30 (44.8)	
• **2**	41 (36.9)	20 (36.4)		35 (35.4)	26 (38.8)	
• **3**	15 (13.5)	7 (12.7)		13 (13.1)	9 (13.4)	
• **>3**	6 (5.4)	1 (1.8)		5 (5.1)	2 (3.0)	
Previous CTx	55 (49.5)	24 (43.6)	0.512	44 (44.4)	35 (52.2)	0.346
Previous ETx	55 (49.5)	21 (38.2)	0.188	56 (56.6)	34 (50.7)	0.526
First line CTx			0.248			0.355
• **FAC**	27 (24.3)	21 (38.2)		29 (29.3)	19 (28.4)	
• **Paclitaxel**	74 (66.7)	29 (52.7)		58 (58.6)	45 (67.2)	
• **Capecitabine**	9 (8.1)	5 (9.1)		11 (11.1)	3 (4.5)	
• **CMF**	1 (0.9)	0		1 (1.0)	0	
TAMA (cm^2)	97.7 (89.9 – 104)	119.7 (113 – 132.4)	<0.001	93.0 (101.7 –113)	110.8 (97.2 – 125.1)	0.021
SMI (cm^2/m^2)	35.4 (32.5 – 38.4)	44.8 (42.8 – 48.3)	<0.001	37.6 (33.7 – 41.3)	39.5 (34.4 – 44.2)	0.040
MA (HU)	32.8 (25.8 – 41.9)	34.7 (29.3 – 39.8)	0.530	27.5 (24.5 – 32.0)	42.5 (37.9 – 46.6)	<0.001

Continuous variables are described as median (interquartile range). Categorical variables are described as numbers (%).

[a]LMM: SMI <41 cm^2/m^2

[b]LMA: Muscle attenuation <41 HU in patients with BMI <25 and <33 HU in patients with BMI ≥25

[c]Classified as having sarcopenic obesity

[d]DFI: Time between the initial breast cancer diagnosis and the first presentation of distant metastases for the patients not primary presenting with stage IV breast cancer

[e]TTT: Time between the first presentation of distant metastasis and the start of the first line palliative chemotherapy

Abbreviations: BMI: Body mass index; HR: Hormone receptor; DFI: Disease free interval; TTT: Time to palliative treatment; CTx: Chemotherapy; ETx: Endocrine therapy; CNS: Central nervous system; FAC: 5-fluororacil, Adriamycin, cyclophosphamide; CMF: Cyclophosphamide, methotrexate, 5-fluororacil; TAMA: Total abdominal muscle area; SMI: Skeletal muscle index; MA: Muscle attenuation; HU: Hounsfield units.

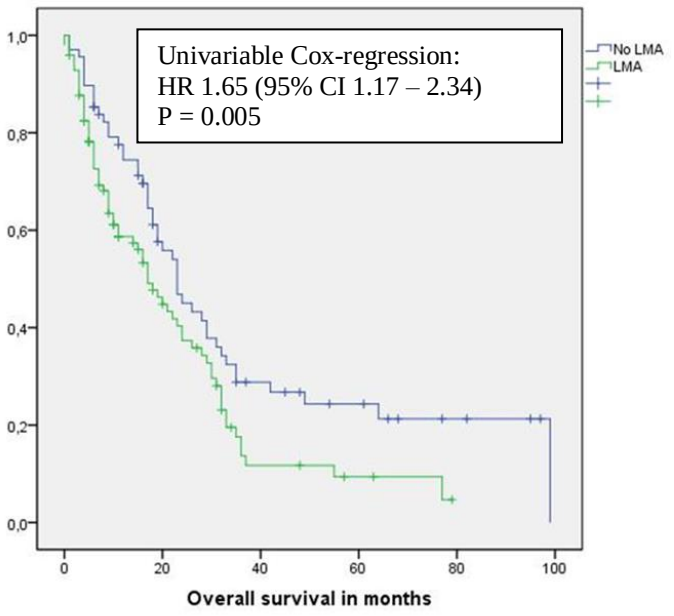
Table 2. Cox proportional hazards models assessing the association with OS.

	Univariable			**Multivariable[a]**		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**P**
Age			0.573			0.215
• **<50 years**	Ref	Ref	Ref	Ref	Ref	Ref
• **50 – 69 years**	0.79	0.51 – 1.24	0.309	0.66	0.41 – 1.09	0.102
• **≥70 years**	0.78	0.45 – 1.37	0.394	0.62	0.33 – 1.17	0.140
Body mass index	0.98	0.95 – 1.01	0.258	0.99	0.96 – 1.02	0.408
Hormone receptor positive	0.75	0.52 – 1.09	0.128	0.47	0.31 – 0.71	<0.001
Her2Neu positive	0.65	0.43 – 0.98	0.037	0.41	0.26 – 0.66	<0.001
Year of diagnosis	1.04	0.98 – 1.11	0.210	1.08	1.01 – 1.15	0.030
Disease free interval (years)[b]	0.98	0.95 – 1.01	0.258	0.96	0.92 – 1.00	0.038
Metastatic location			0.813			0.054
• **Bone**	Ref	Ref	Ref	Ref	Ref	Ref
• **Visceral**	0.85	0.49 – 1.49	0.576	0.56	0.29 – 1.12	0.100
• **CNS[c]**	1.58	0.48 – 5.17	0.453	1.48	0.44 – 4.94	0.527
• **Skin or lymph nodes**	0.79	0.40 – 1.56	0.496	0.57	0.27 – 1.19	0.133
• **Multiple locations**	0.88	0.57 – 1.34	0.535	0.27	0.10 – 0.68	0.006
Number of metastatic sites			0.437			0.012
• **1**	Ref	Ref	Ref	Ref	Ref	Ref
• **2**	1.04	0.72 – 1.51	0.826	2.74	1.21 – 6.20	0.015
• **3**	1.22	0.74 – 2.03	0.441	4.58	1.69 – 12.42	0.003
• **>3**	1.85	0.84 – 4.05	0.126	5.59	1.77 – 17.64	0.003
SMI (cm^2/m^2, continuous)	0.99	0.97 – 1.02	0.536	1.00	0.97 – 1.04	0.987
MA (HU, continuous)	0.99	0.97 – 1.00	0.118	0.98	0.96 – 1.00	0.054
LMM	0.97	0.68 – 1.37	0.845	0.98	0.60 – 1.58	0.923
Sarcopenic obesity	0.78	0.40 – 1.54	0.481	0.87	0.40 – 1.88	0.723
LMA	1.65	1.17 – 2.34	0.005	2.04	1.34 – 3.12	0.001

[a]A multivariable Cox model with all patient characteristics was performed, after which each muscle measurement (below the line) was added to this model in a separate multivariable Cox model.

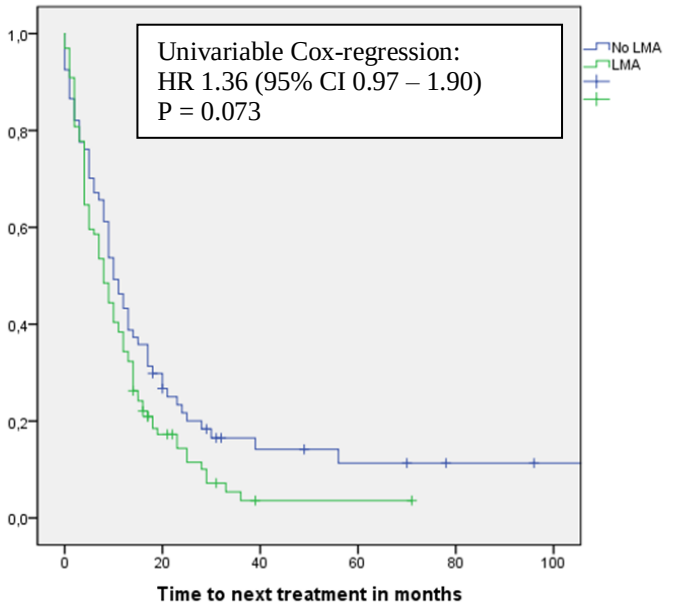
Abbreviations: OS: Overall survival; SMI: Skeletal muscle index; MA: Muscle attenuation; HU: Hounsfield Units; LMM: Low muscle mass; LMA: Low muscle attenuation

a.



No LMA:	67	36	15	10	6	2
LMA:	99	60	7	4	1	0

b.



No LMA:	67	19	6	4	2	1
LMA:	99	14	1	1	0	0

Figure 1. Kaplan Meier curves for OS (a) and TNT (b) between patients with LMM and patients without LMM.

Median TNT for the entire cohort was 9 months (95% CI 7.4 – 10.6 months). The impact of muscle measures on median TNT was comparable to the impact on OS (10 vs. 8 months, p = 0.540 for LMM and 10 vs. 9 months, p = 0.481 for sarcopenic obesity) **(table 3).** Patients with LMA had a median TNT of 8 months compared to 10 months for patients with normal MA, although this was not statistically significant in the univariable Cox regression **(fig 1B)**. However, after adjustment for other factors in the multivariable Cox regression, patients with LMA had shorter TNT than patients with normal MA (HR 1.72, 95% CI 1.14 – 2.62, p = 0.010) **(table 3)**. OS and TNT of the included patients were similar to the excluded patients (**supplemental figure).** No significant violations of the proportional hazards assumption were detected.

Table 3. Cox proportional hazards models assessing the association with TNT.

	Univariable			**Multivariable[a]**		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age			0.173			0.033
• **<50 years**	Ref	Ref	Ref	Ref	Ref	Ref
• **50 – 69 years**	0.66	0.43 – 1.02	0.064	0.53	0.33 – 0.86	0.010
• **≥70 years**	0.68	0.40 – 1.16	0.160	0.56	0.31 – 1.02	0.059
Body mass index	0.98	0.95 – 1.01	0.143	0.98	0.95 – 1.01	0.255
Hormone receptor positive	0.85	0.59 – 1.22	0.368	0.62	0.40 – 0.95	0.027
Her2Neu positive	0.63	0.42 – 0.94	0.024	0.46	0.30 – 0.72	<0.001
Year of diagnosis	0.96	0.91 – 1.02	0.151	0.98	0.92 – 1.04	0.417
Disease free interval (years)[b]	0.98	0.95 – 1.02	0.308	0.97	0.94 – 1.01	0.166
Metastatic location			0.109			0.005
• **Bone**	Ref	Ref	Ref	Ref	Ref	Ref
• **Visceral**	0.79	0.46 – 1.37	0.407	0.56	0.29 – 1.06	0.074
• **CNS[c]**	4.34	1.30 – 14.52	0.017	3.70	1.06 – 12.87	0.040
• **Skin or lymph nodes**	1.15	0.60 – 2.19	0.674	0.97	0.48 – 1.95	0.932
• **Multiple locations**	0.99	0.66 – 1.50	0.966	0.25	0.10 – 0.62	0.003
Number of metastatic sites			0.161			0.001
• **1**	Ref	Ref	Ref	Ref	Ref	Ref
• **2**	1.11	0.77 – 1.59	0.570	3.20	1.44 – 7.12	0.004
• **3**	1.47	0.90 – 2.43	0.127	5.99	2.26 – 15.86	<0.001
• **>3**	2.13	0.97 – 4.66	0.059	6.92	2.25 – 21.34	0.001
SMI (cm^2/m^2, continuous)	1.00	0.98 – 1.03	0.973	1.01	0.97 – 1.04	0.670
MA (HU, continuous)	1.00	0.98 – 1.01	0.531	0.98	0.96 – 1.00	0.107
LMM	0.90	0.64 – 1.27	0.540	0.84	0.52 – 1.37	0.486
Sarcopenic obesity	0.65	0.33 – 1.28	0.211	0.89	0.40 – 1.97	0.774
LMA	1.36	0.97 – 1.90	0.073	1.72	1.14 – 2.62	0.010

[a]A multivariable Cox model with all patient characteristics was performed, after which each muscle measurement (below the line) was added to this model in a separate multivariable Cox model.

Abbreviations: TNT: Time to next treatment; SMI: Skeletal muscle index; MA: Muscle attenuation; HU: Hounsfield Units; LMM: Low muscle mass; LMA: Low muscle attenuation

Discussion

In this study, LMA was a significant prognostic factor for both OS (HR 2.04, 95% CI 1.34 – 3.12, p=0.001) and TNT (HR 1.72, 95% CI 1.14 – 2.62, p = 0.010), whereas LMM and sarcopenic obesity were not. Due to the lack of standardized muscle measurements, we additionally repeated these survival analyses using continuous scales of muscle parameters and found no association between muscle mass and OS and TNT. Unlike the association between LMA and OS, the association between muscle attenuation on a continuous scale and OS was not statistically significant, which suggests a possible non-linear association.

Our study reports on the prognostic value of skeletal muscle measures in the largest cohort of patients with metastatic breast cancer described so far. The association of LMA and OS has only been studied before once in advanced breast cancer patients [9]. In this study, similar to our results, muscle attenuation on a continuous scale was not significantly associated with survival or time to treatment failure. However, only 40 patients were evaluated and no cut-off point was used to identify the patients with LMA and to relate the impact of LMA on OS. Our finding that LMA is a prognostic factor for survival is similar to the results of studies with other cancer types [13,14,16-19]. Similar to our study, two of these studies reported that LMA was significantly associated with poor OS, while LMM was not [13,14], suggesting that LMA is a better prognostic marker for OS than LMM. This is in line with earlier observations in geriatric medicine. In elderly patients without cancer, LMA causes muscle weakness independent of the loss of muscle mass [20], with muscle strength being a better predictor for mortality than muscle mass [21]. This knowledge could be used to determine which muscle measures may be useful in clinical oncological practice.

Generally, results in the literature on the prognostic impact of LMM are mixed. In the current study, we could not show any association between LMM or sarcopenic obesity and OS or TNT, which is in concordance with the most recent study in advanced breast cancer [9] and studies in other tumor types [4,6,8,16,22-25]. This is somewhat in contrast with the only other study among metastatic breast cancer patients by Prado et al, which reported a shorter time to disease progression in patients with LMM compared to patients without LMM [5] and some studies in other tumor types [7,26-29]. Explanations for the discrepancy with our study are probably found in several factors, including differences in cancer type and disease

aggressiveness, age, and disease stage at the time of muscle measurement. Furthermore, different cut-offs to diagnose LMM have been used across studies and these cut-off may not be applicable for all cancer populations. Therefore, the difference in reported outcome is hard to put into perspective. In our study, patients were younger (mean 58.8 years vs. 64-79 years in the studies mentioned above) and all were female. A potential explanation for the different results is that the prognostic value of LMM is lower in younger patients, where prognosis is more dependent on other factors, and in females, which has been reported by studies in patients with [25,28,30] and without cancer [31,32]. In addition, in the study by Prado et al [5], patients had already failed multiple palliative chemotherapeutic lines, while our study was in a population receiving first line chemotherapy. So LMM might be more related to more advanced disease than in patients still responsive to treatment.

Muscle measures have increasingly been recognized over the last years as a prognostic factor for oncological outcomes, such as survival and treatment tolerability, and could be easily obtained in cancer patients using already available CT images. An increasing number of studies investigating interventions targeting low muscle parameters in cancer patients are conducted, such as physical exercise to reverse LMM and thereby improve quality of life in breast cancer [33]. However, implementation of muscle measures in clinical oncological practice to predict outcome and treatment risks is hampered by the lack of a standardized method of measurement, including knowledge of which muscle component (quantity or quality) is best suited as prognostic marker [11]. This study contributes to the literature by comparing different muscle components with outcome and observing that LMA seems a better prognostic factor for survival than LMM in breast cancer.

Especially in older people, LMM is frequently present and associated with mortality and physical disability [34,35]. Furthermore, muscle loss is worsened in the presence of cancer due to cachexia-related processes [36]. However, decreased muscle function (strength) has a stronger association with negative outcomes than LMM [37], and it has been reported that muscle attenuation is negatively correlated with muscle strength. It is therefore likely that muscle quality is more important for muscle function and clinical outcomes than absolute muscle mass [20], which was also supported by the results of this study. Given this, special emphasis in future research should be put on generating prospective data on the prognostic impact of LMM and LMA in elderly patients with advanced breast cancer.

Muscle loss is an important part of syndromes such as sarcopenia and cachexia [38]. Initially, sarcopenia was defined by the decline of muscle mass with aging [39]. Since sarcopenia is a multifactorial syndrome and thus more than solitary LMM [40], the current consensus is to define sarcopenia as the combination of LMM and either low muscle strength or impaired physical performance [41]. Recent studies have reported that sarcopenia is a better prognostic factor for oncological outcomes than solitary LMM [42,43]. Therefore, a distinction should be made in the nomenclature when reporting studies investigating radiologically measured muscle mass or the syndrome sarcopenia, so we used the terms LMM and LMA to indicate the muscle measures in this study.

Several limitations of this study have to be mentioned. Firstly, abdominal CT-images had to be available for muscle measurement, resulting in patients not eligible for the present analysis. It is not possible to avoid this in a population with breast cancer patients as seen in daily practice, as imaging diagnostics such as thoracic X-ray and abdominal ultrasound are sometimes preferred over abdominal CT-imaging to diagnose distant metastases. However, a comparison of the included and excluded patients revealed no differences in outcome, so it is not likely that this had significant impact on our results. A possibility could be the exploration of other devices to measure muscle mass in breast cancer patients, such as dual energy X-ray absorptiometry (DEXA). However, CT is considered the gold standard of muscle measurement, so we feel that this study might provide important information on the prognostic value of muscle measurements for survival in advanced breast cancer using this device. Secondly, the sample size of the patients with sarcopenic obesity was small. Despite the fact that muscle mass was not associated with outcome in this study, patients with sarcopenic obesity are considered a prognostic worse group. The impact of sarcopenic obesity on outcome in advanced breast cancer needs further investigation.

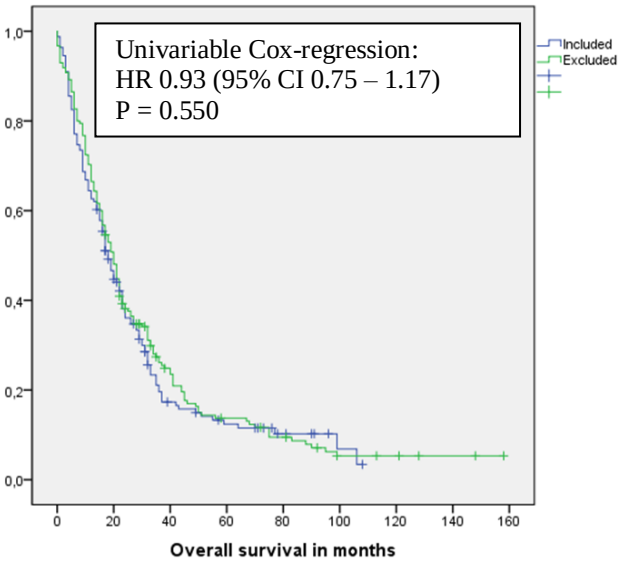
Conclusion

In this cohort of patients with metastatic breast cancer, LMA was a prognostic factor for overall survival and time to clinically relevant disease progression, whereas LMM was not. LMA is potentially an easy to establish prognostic marker in patients with advanced breast cancer, provided that the impact on OS and TNT can be confirmed in other studies. More studies are needed to standardize muscle measurements and to investigate which muscle

parameter is best suited as prognostic marker in different populations and treatment settings. This may eventually result in knowledge on how skeletal muscle measures could be incorporated into treatment decision making, and if possible, to develop strategies to intervene, thereby hopefully improving outcome of patients with advanced breast cancer.

Supplemental figure. Comparison of OS (A) and TNT (B) between included and excluded patients.

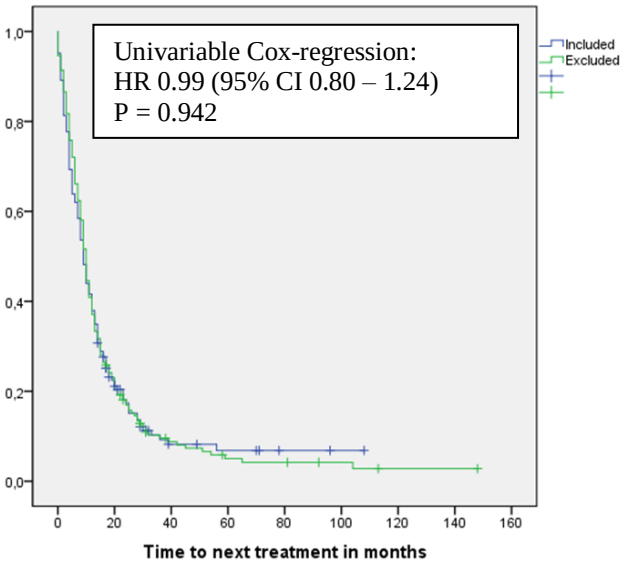
a.



Included patients:	166	73	22	14	7	2	0	0	0
Excluded patients:	185	93	38	20	13	5	4	2	0

Lost to follow up: 29

b.



Included patients:	166	33	7	5	2	1	0	0	0
Excluded patients:	186	42	12	6	5	3	1	1	0

Lost to follow up: 28

Supplemental table. Association of body mass index and age with low muscle mass and low muscle attenuation.

	Low muscle mass[a]			Low muscle attenuation[b]		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (years)	1.01	0.97 – 1.04	0.731	1.11	1.07 – 1.15	<0.001
BMI (kg/m^2)	0.76	0.69 – 0.84	<0.001	0.97	0.91 – 1.03	0.348

Results of multiple logistic regression

[a]SMI < 41 cm^2/m^2

[b]Muscle attenuation <41 HU in patients with BMI <25 and <33 HU in patients with BMI ≥25

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Chapter 5

Changes in body composition and muscle attenuation during taxane-based chemotherapy in patients with metastatic breast cancer

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Breast Cancer Res Treat. 2018 Feb;168(1):95-105.

Abstract

Background: Body composition parameters including low muscle mass, muscle attenuation (which reflects muscle quality), and adipose tissue measurements have emerged as prognostic factors in cancer patients. However, knowledge regarding the possibility of excessive muscle loss during specific systemic therapies is unknown. We describe the changes in body composition and muscle attenuation (MA) during taxane- and anthracyclin-based regimens and its association with overall survival (OS) in metastatic breast cancer patients.

Methods: The lumbar skeletal muscle index (LSMI) was used as marker of muscle mass. LSMI, MA, subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and intramuscular adipose tissue (IMAT) were measured before and after first-line treatment with paclitaxel (n = 73) or 5-fluorouracil-doxorubicin-cyclophosphamide (FAC) (n = 25) using CT-images. Determinants of the change of LSMI and MA were analysed using multiple linear regression. OS was assessed using Cox proportional hazard models.

Results: MA significantly decreased during paclitaxel-treatment (-0.9 HU, p = 0.03). LSMI (p = 0.40), SAT (p = 0.75), VAT (p = 0.84) and IMAT (p = 0.10) remained stable. No significant alterations in body composition parameters during FAC-treatment were observed. Previous (neo-)adjuvant chemotherapy contributed to larger loss of MA during the current treatment. Body composition changes during chemotherapy were not associated with OS.

Conclusions: MA decreased during treatment with paclitaxel, while muscle mass was stable. Body composition changes are not associated with survival in the absence of progressive disease.

Introduction

Low muscle mass (LMM) and low muscle attenuation (LMA) have been associated with physical disability and mortality of otherwise healthy older adults [1,2]. Muscle attenuation (muscle density) reflects the accumulation of adipose tissue in muscles and is therefore considered a marker of muscle quality. Quantitative and qualitative muscle loss are largely age-related [3,4], but also occur in the presence of a chronic disease [5]. In cancer patients, body composition parameters, including LMM, LMA and adipose tissue loss have increasingly been related to unfavourable outcomes [6,7] with LMA being a better prognostic marker than LMM [8-10]. It has also been reported that higher loss of muscle mass over time is associated with impaired survival in cancer patients [11-14], as well as the loss of visceral adipose tissue during chemotherapeutic treatment because in patients with pancreatic cancer [11,15] and ovarian cancer [13].

Studies in patients with metastatic breast cancer showed that LMM resulted in more chemotherapeutic toxicity and a shorter median time to tumour progression [16,17] and that LMA was associated with more hospital admissions [17] and a shorter median overall survival [8]. Currently, it is however unknown whether body composition parameters change during treatment with different systemic agents and whether body composition measures over time have more prognostic power than a single muscle measurement at diagnosis in patients with metastatic breast cancer. Furthermore, the impact of different systemic agents on body composition is relatively unstudied. Therefore, knowledge regarding the possibility of excessive muscle loss during specific systemic therapies and its probable clinical impact is lacking.

In metastatic breast cancer, anthracyclin- or taxane-based chemotherapeutic regimens are often the treatment of choice as palliative chemotherapy. In this study we aimed to describe the changes in body composition and muscle quality during first line palliative anthracyclin- or taxane-based chemotherapy in metastatic breast cancer. To our knowledge, studies regarding this subject are lacking. We hypothesized that patients treated with taxanes experience more muscle loss than patients treated with anthracyclins due to the specific nature of toxicities associated with taxanes, such as the occurrence of neuropathy [18] and myalgia

[19], which might exacerbate any muscle loss. Secondly, we determined the association of muscle- and fat wasting with overall survival.

Methods

Patient inclusion and treatment characteristics

This single-centre, retrospective study involved patients with metastatic breast cancer undergoing first line palliative chemotherapy with taxanes or a anthracyclin-based regimen. Body composition changes during taxane-based therapy were compared with body composition changes during anthracyclin-based therapy. We chose a control group with less muscle-related toxicity and used only anthracyclin-based regimens as control-group due to the less frequent use and large heterogeneity of other cytotoxic regimens. Due to local practice, taxane-based regimens always involved paclitaxel and anthracycline-based regimens consisted of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). Patients diagnosed with breast cancer between 1st January 2000 and 1st March 2016 were identified using the pathology- and radiology-registry at our hospital, after which patients with distant metastases were identified from these databases. Inclusion criteria were first-line palliative chemotherapy with paclitaxel or FAC (intention to complete 6 cycles) and abdominal CT images available within 3 months prior to the start and after the completion of treatment. Exclusion criteria were male gender, a second malignancy (except skin cancer other than melanoma), patients who completed less than 3 cycles of FAC- or paclitaxel –treatment, treatment with other chemotherapeutic regimens than taxanes or FAC and disease progression during the 6 cycles of first line palliative chemotherapy. The latter was done to avoid the impact of progressive disease on muscle wasting [20]. Medical records were searched for patient- characteristics and treatment details. Paclitaxel was administered weekly (6 cycles of 80 mg/m^2 day 1, 8, 15 per 3 weeks) i.e. a total of 18 weeks combined with dexamethasone 8 mg before each dose; addition of trastuzumab was allowed in case of HER2 positive breast cancer. The FAC-regimen consisted of 6 cycles of 5-fluourouracil 500 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks; i.e. a total of 18 weeks. The study was approved by our local institutional review board.

Body composition measurements

Body composition measurements were performed before and after completion of first line palliative chemotherapy and consisted of the measurement of muscle mass and muscle attenuation (MA), which is the density of muscle tissue, with lower muscle density indicating more microscopic fat infiltration of muscle [3]. Total abdominal muscle area (TAMA) corrected for height, resulting in a lumbar skeletal muscle index (LSMI) in cm^2/m^2 was used as parameter of skeletal muscle mass [21]. Adipose measurements included intramuscular adipose tissue (IMAT), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and total abdominal tissue (TAT), which was the sum of IMAT, VAT and SAT. Muscle tissue was identified between -29 and +150 Hounsfield Units (HU) at the L3-level, VAT was identified between -150 and -50 HU and SAT + IMAT between -190 and -90 HU, as previously published [22]. Slice-o-matic software (Slice-o-matic, Tomovision, Canada) [23] was used for all body composition measurements. All body composition measurements were performed by one validated observer after an intraclass correlation coefficient of 0.993 was reached between three observers.

Statistical analyses

Continuous variables were described as mean plus standard deviation (SD) or as median + interquartile range (IQR). Percentages were used to describe categorical variables. Patient characteristics were compared between the paclitaxel-group and FAC-group using the Mann-Whitney U test for continuous variables and the Fisher's exact test or chi-square test for categorical variables. Body composition parameters were measured on a continuous scale before the start of the first chemotherapeutic cycle and after completion of therapy. First, cross-sectional analyses were performed using the Mann-Whitney U test to compare all body composition measurements (LSMI, MA, IMAT, VAT, SAT and TAT) between the two treatment groups before and after treatment. Second, the change of these during chemotherapy was evaluated in each group using the Wilcoxon signed rank test. Simple multiple linear regression analyses were performed to identify possible factors contributing to muscle change during chemotherapy. The change of LSMI and MA during chemotherapy (delta after - before) was used as dependent variable in these models. The independent variables were age, body mass index (BMI), previous chemotherapy (yes/no), previous endocrine therapy (yes/no), paclitaxel treatment and Her2 positivity. The stepwise backward method was

performed to select the independent variables in the multiple linear regression models and only variables with a p-value <0.20 were retained in the final model. Variables that differed significantly between the treatment groups were not considered for removal in the stepwise backward method. Multicollinearity in the multiple linear regression models was assessed by calculating variance inflation factors. Overall survival (OS) was defined as the time from the date of the first chemotherapeutic cycle until the date of death or the end of follow-up (1st September 2016), and was visualized using the Kaplan Meier method. A loss of muscle or fat mass was defined as absolute loss of any degree. Univariable and multivariable Cox proportional hazard regression analyses were performed to determine the association of variables known for their clinical impact and OS. The variables in the multivariable Cox-regression were selected using the stepwise backward method. To determine the amount of selection bias, we compared the patient characteristics and survival between the included and excluded patients. All statistical tests were two-sided and used a significance level of 0.05. The analyses were performed using SPSS version 24.

Results

Patient characteristics

Between 1st January 2000 and 1st March 2016, 723 patients with metastatic breast cancer were identified at our hospital. Patients were excluded in case of other palliative chemotherapy than paclitaxel or FAC (n = 30), no CT-images before (n = 188) or after chemotherapy (n = 62), or progressive disease during the 6 cycles of first-line chemotherapy (n = 33) **(figure 1)**. Eventually, 98 patients were eligible for analysis, of which 73 were treated with paclitaxel and 25 underwent treatment with FAC. The median time between the pre-treatment CT-scan and the start of chemotherapy was 19.5 days (IQR 13 – 32.8 days), with 95% of the patients having CT-imaging less than 60 days before treatment. The post-treatment CT-scan was performed within 30 days after therapy completion. In total, 15 patients (15.3%) received less than 6 cycles of chemotherapy, resulting in a median of 6 cycles of chemotherapy in the entire cohort. Toxicity was the reason of treatment cancellation before completing 6 cycles in 9 patients.

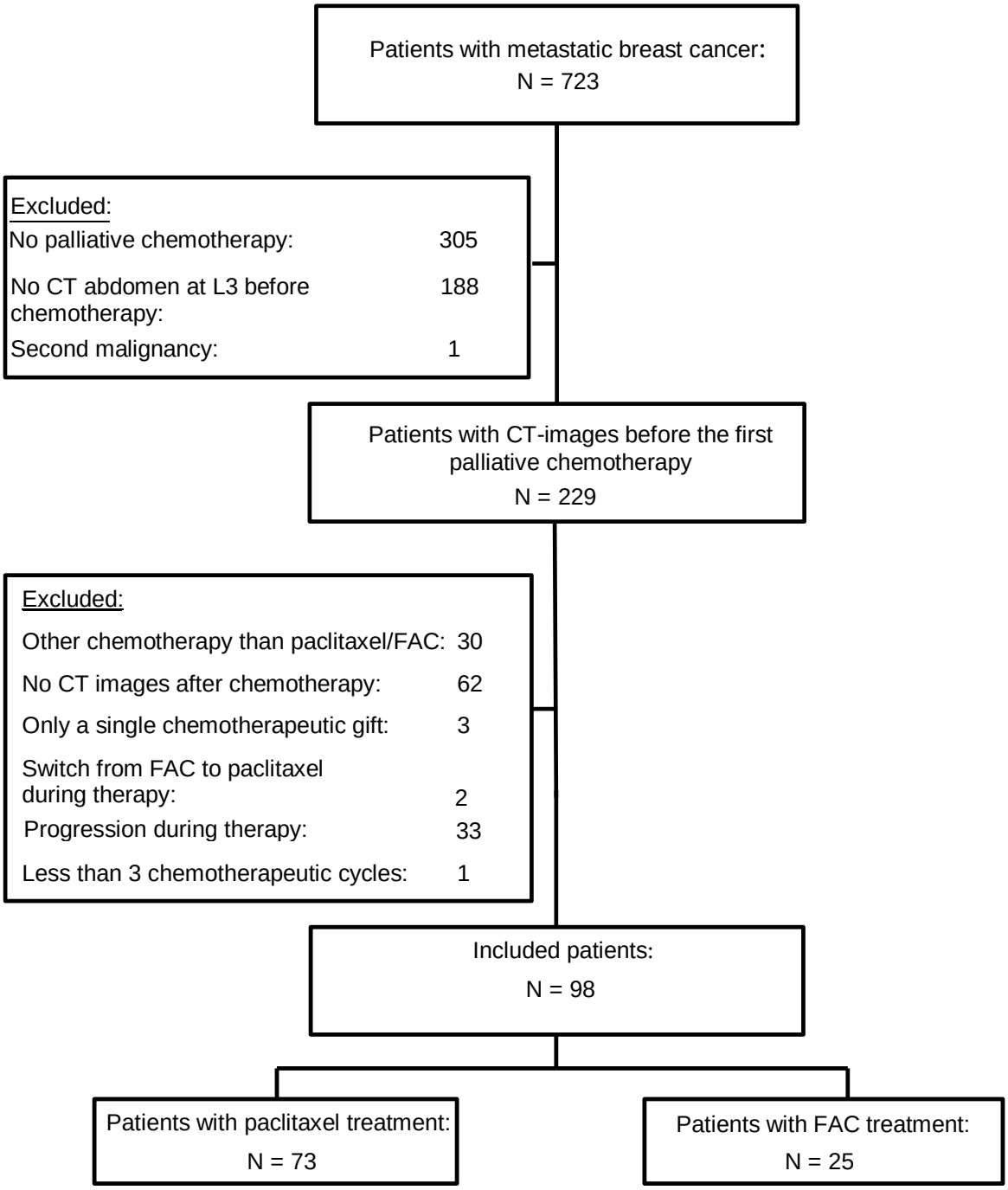


Figure 1. Flow chart of the patient inclusion

Among the other 6 patients, the reasons of treatment cancellation were patient request (n = 2), worsening physical condition without progression or toxicity (n = 1) and a switch to another treatment (n = 4). Prior to treatment start, there were no significant differences in body composition parameters between the two treatment groups (**table 1)**.

Compared with the excluded patients undergoing palliative chemotherapy (n = 319, **supplemental table S1**), included patients had a longer time from the initial breast cancer diagnosis until diagnosis of distant metastases and the sites of the metastases were more often multiple and less likely located solitary in bone. Age, BMI, hormone receptor status, Her2 receptor status, adjuvant chemotherapy and previous palliative endocrine treatment were similar.

Table 1. Patient characteristics.

	FAC (n = 25)	Paclitaxel (n = 73)	p value[a]
Age (years)			0.39
• **Mean (SD)**	56.8 (10.3)	54.5 (10.2)	
• **Range**	39 – 73	31 – 77	
Year of diagnosis[b]			
• **Median (IQR)**	2009 (2006 – 2012)	2011 (2008 – 2013)	0.06
Body mass index			0.70
• **Median (IQR)**	26.8 (23.5 – 30.6)	25.9 (22.9 – 30.6)	
Hormone receptor status			1.00
• **Positive**	19 (76%)	54 (74%)	
• **Negative**	6 (24%)	19 (26%)	
• **Unknown**	0 (0%)	0 (0%)	
Her2Neu status			**0.002**
• **Positive**	2 (8%)	27 (37%)	
• **Negative**	23 (92%)	37 (50.7%)	
• **Unknown**	0%	9 (12.3%)	
Primary stage IV (%)	11 (44%)	16 (21.9%)	**0.04**
Disease free interval (years)[c]			
• **Median (IQR)**	9 (3.5 – 12.5)	4 (2.5 – 10)	0.16
Time to palliative treatment (months)[d]			
• **Median (IQR)**	1.0 (0 – 4.5)	1.0 (0 – 6.0)	0.90
Metastatic location			0.68
• **Bone**	3 (12%)	14 (19.2%)	
• **Visceral**	3 (12%)	12 (16.4%)	
• **Skin or lymph nodes**	3 (12%)	5 (6.8%)	
• **Multiple locations**	16 (64%)	42 (57.5%)	
Number of metastatic sites			0.94
• **1**	9 (36%)	29 (39.7%)	
• **2**	11 (44%)	27 (37%)	
• **3**	4 (16%)	14 (19.2%)	
• **> 3**	1 (4%)	3 (4.1%)	
Previous (neo)adjuvant chemotherapy	4 (16%)	36 (49.3%)	**0.004**
Previous endocrine therapy			0.49
No endocrine therapy	16 (64%)	35 (47.9%)	
(Neo-)adjuvant	3 (12%)	18 (24.7%)	
Palliative	3 (12%)	11 (15.1%)	
Both adjuvant and palliative	3 (12%)	9 (12.3%)	
LSMI baseline[e]	38.4 (34.4 – 45.4)	37.7 (33.3 – 41)	0.11

MA baseline	31.1 (25.2 – 38.1)	31 (25.2 – 40.6)	0.69
SAT baseline (Median + IQR)	181.8 (148.7 – 225.1)[f]	206.9 (147.3 – 237)[g]	0.58
VAT baseline	109 (51.8 – 126)	105.4 (65.1 – 147.2)	0.59
IMAT baseline	17 (11.7 – 22)	14.7 (10.2 – 23.8)	0.61
TAT[h] baseline	314.1 (211.3 – 364)	308.1 (256.9 – 389.5)	0.68

[a]The Fisher's exact test was used for categorical variables with 2 categories and the chi-square test was used for categorical variables with more than 2 categories.
[b]Diagnosis of distant metastases.
[c]DFS: Time between the initial breast cancer diagnosis and the first presentation of distant metastases for patients with M0 presentation of primary breast cancer.
[d]Time to palliative treatment: Time between the first presentation of distant metastasis and the start of the first line palliative chemotherapy.
[e]Before chemotherapy
[f]Missing: n = 4
[g]Missing: n = 11
[h]TAT: Sum of SAT, VAT and IMAT.

Abbreviations: FAC: 5-fluororacil, Adriamycin, cyclophosphamide; IQR: Interquartile range; DFS: Disease-free survival; LSMI: Lumbar skeletal muscle index; MA: Muscle attenuation; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue; IMAT: Intramuscular adipose tissue; TAT: Total adipose tissue

Body composition changes during chemotherapy

In patients treated with 4 or more cycles of paclitaxel, MA significantly decreased during treatment (median -0.9 HU, IQR -4.2 - +1.9 HU, p = 0.03), while all other body composition parameters remained stable. No significant changes in body composition were observed in the patients treated with 4 or more cycles of FAC as well **(table 2, figure 2)**.

Table 2. Changes in body composition during chemotherapy.

Muscle change during chemotherapy, mean (95% CI)				
	FAC	**P[a]**	**Paclitaxel**	**p[g]**
LSMI (cm^2/m^2)	-0.5 (-6.2 - +6.6)	0.28	+0.3 (-3.9 - +6.3)	0.40
MA (HU)	-0.6 (-12.1 - +13.8)	0.44	-1.5 (-12.9 - +6.6)	**0.03**
SAT	-7.4 (-78.4 - +46.2)	0.31	+0.03 (-48.7 - +52.0)	0.75
VAT	-1.6 (-51.4 - +48.6)	0.82	+0.05 (-46.9 - +49.4)	0.84
IMAT	+1.4 (-5.2 - +9.3)	0.15	-0.5 (-11.2 - +8.0)	0.10
TAT	-2.9 (-91.6 - +79.7)	0.71	-0.3 (-100.6 - +88.4)	0.94

[a]The difference in muscle parameters during chemotherapy (after – before) within each treatment group using the Wilcoxon signed rank test.

Abbreviations: FAC: 5-fluororacil, Adriamycin, cyclophosphamide; LSMI: Lumbar skeletal muscle index; MA: Muscle attenuation; HU: Hounsfield Unit; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue; IMAT: Intramuscular adipose tissue; TAT: Total adipose tissue

The results were the same after repeating the analyses with all patients, irrespective of the number of completed cycles **(supplemental table S2 and S3).** Except from the relationship between muscle mass and MA before chemotherapy and muscle change during therapy, multiple linear regression revealed that prior chemotherapy in the (neo-)adjuvant setting significantly contributed to a larger loss of MA during the current treatment, while this was not observed for the change of LSMI.

Table 3a. The effect on change of lumbar skeletal index (LSMI) during chemotherapy.

	Simple linear regression			**Multiple linear regression**		
	Coefficient	**95% CI**	**p**	**Coefficient**	**95% CI**	**P**
Age	-0.02	-0.09 – 0.05	0.65	--	--	--
BMI	0.002	-0.12 – 0.12	0.98	0.22	0.07 – 0.36	**0.004**
Previous Ctx	-0.26	-1.76 – 1.23	0.73	--	--	--
Previous Etx	0.53	-0.95 – 2.01	0.48	1.20	-0.23 – 2.62	0.10
LSMI[a]	-0.14	-0.24 - -0.04	**0.009**	-0.27	-0.40 - -0.14	**<0.001**
Paclitaxel treatment	0.84	-0.84 – 2.52	0.32	-0.32	-1.96 – 1.32	0.70
Her2 positive	-0.06	-1.63 – 1.53	0.95	0.31	-1.28 – 1.89	0.70

Dependent variable: Change of LSMI during chemotherapy.
[a]LSMI: Lumbar skeletal muscle index (cm^2/m^2) before chemotherapy.

Abbreviations: BMI: Body mass index; Ctx: Chemotherapy; Etx: Palliative endocrine therapy; LSMI: Lumbar skeletal index
[a]BMI: Body mass index in kg/m^2
[b]Ctx: Previous chemotherapy.
[c]Htx: Previous endocrine therapy.

Table 3b. The effect on change of muscle attenuation during chemotherapy.

	Simple linear regression			**Multiple linear regression**		
	Coefficient	**95% CI**	**p**	**Coefficient**	**95% CI**	**P**
Age	0.09	-0.02 – 0.19	0.10	--	--	--
BMI	-0.03	-0.21 – 0.15	0.75	--	--	--
Previous Ctx	1.27	-0.98 – 3.51	0.27	2.57	0.23 – 4.90	**0.03**
Previous Etx	-0.17	-2.41 – 2.07	0.88	--	--	--
MA[a]	-0.23	-0.33 – 0.13	**<0.001**	-0.24	-0.35 - -0.13	**<0.001**
Paclitaxel treatment	-0.89	-3.44 – 1.65	0.49	0.93	-1.72 – 3.57	0.49
Her2 positive	-3.04	-5.50 – 0.57	**0.02**	1.32	-1.20 – 3.83	0.30

Dependent variable: Change of LSMI during chemotherapy.
[a]MA: Muscle attenuation (HU) before chemotherapy.

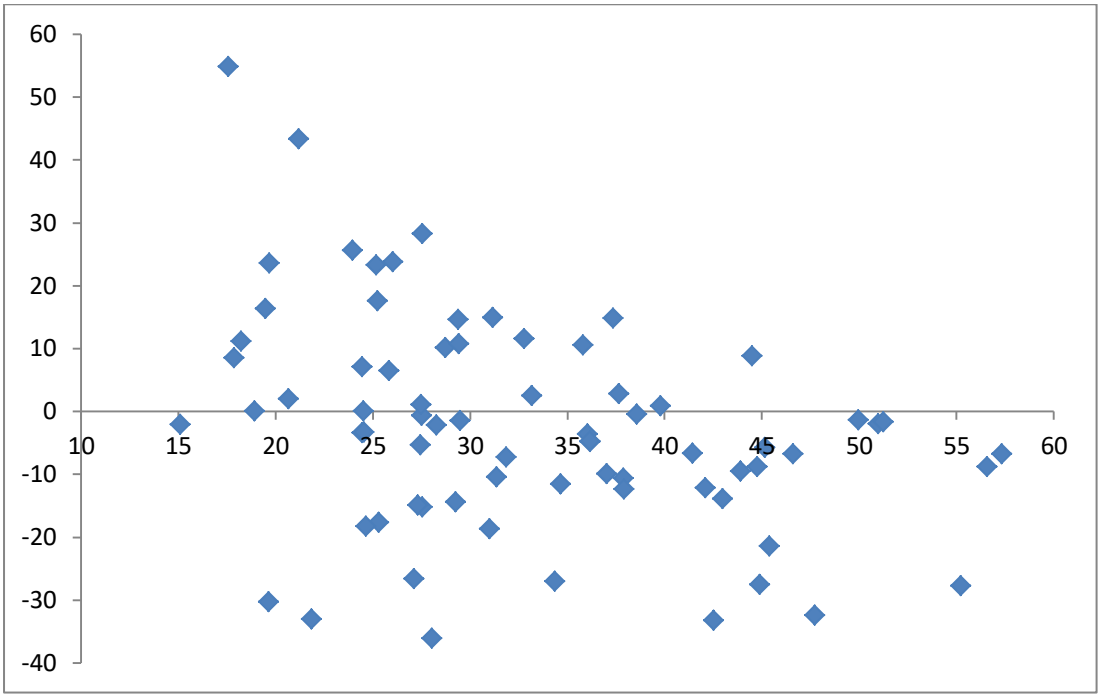
Abbreviations: BMI: Body mass index; Ctx: Chemotherapy; Etx: Palliative endocrine therapy; MA: Muscle attenuation; HU: Hounsfield Unit.

Patients with prior chemotherapy on average had a 2.57 HU higher loss of MA compared to patients without prior chemotherapy (which is 8.3% of the median MA at baseline). A lower BMI was associated with larger loss of muscle mass during chemotherapy, although the amount of extra muscle loss was limited. Each decrease in BMI of 1 kg/m^2 resulted in a 0.22 cm^2/m^2 (<1%) increase of muscle mass loss. Previous endocrine treatment was not associated with larger loss of muscle mass or attenuation **(table 3A and 3B).** No severe collinearity between variables was detected with variation inflation factors between 1.1 and 1.9.

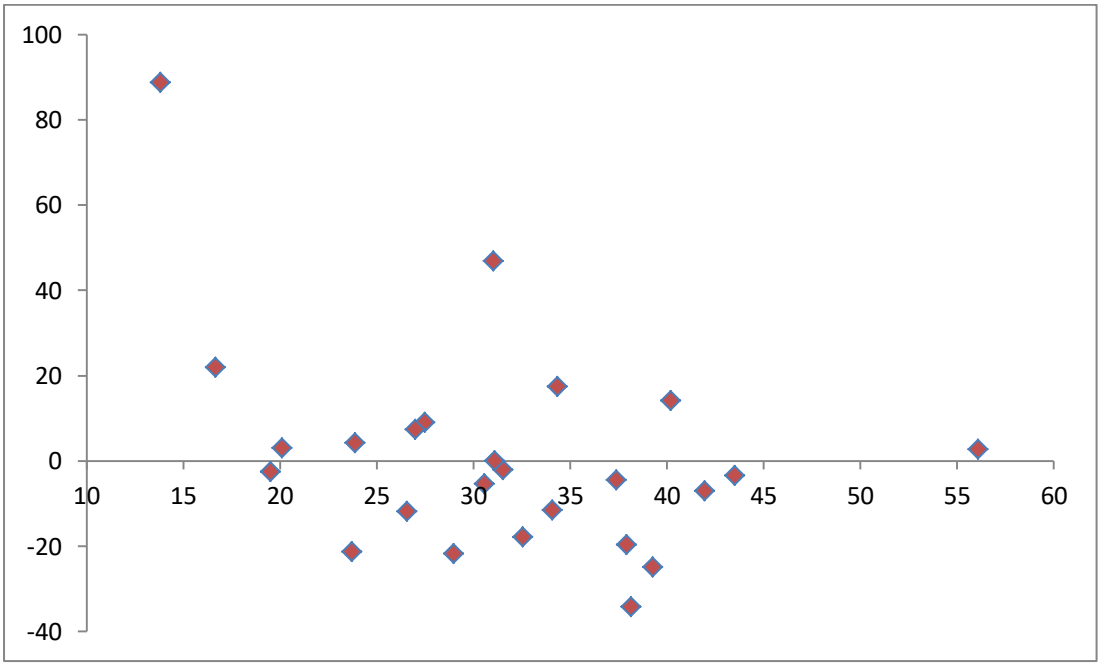
Survival

The median OS in the paclitaxel-group was 21 months and in the FAC-group 22 months (univariable HR for paclitaxel treatment 1.01, 95% CI 0.59 – 1.74, p = 0.96). At the end of follow-up, 68 (69.4%) patients had died. No significant differences in OS were observed between patients who lost muscle mass or muscle attenuation and patients not losing muscle mass or muscle attenuation **(fig 3)**. In the univariable and multivariable Cox-regression, age and de novo stage IV disease were significant predictors of OS. **(table 4)**. Patients with de novo stage IV disease had a longer median OS than patients relapsing after adjuvant treatment (multivariable HR 0.30, 95% CI 0.14 – 0.67, p = 0.003) and these patients were more often allocated to the FAC-group. However, the chemotherapy regimen itself was not predictive of OS (multivariable HR 1.04, 95% CI 0.52 – 2.07, p = 0.92. OS of the excluded patients was worse compared with the included patients **(supplemental figure S1).** No significant violations of the proportional hazards assumption were detected.

a.



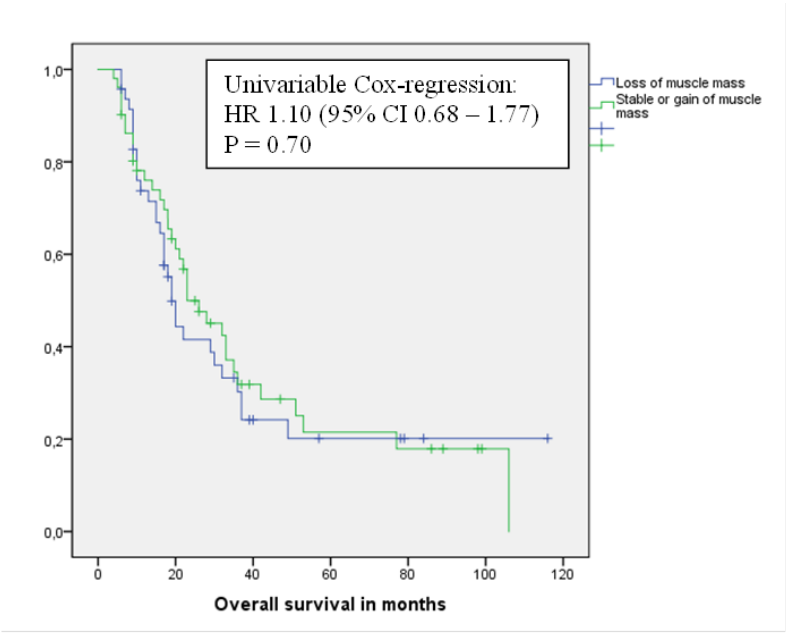
b.



X-axis: Muscle attenuation (HU) before treatment.
Y-axis: Change of muscle attenuation (HU) as percentage of the muscle attenuation before treatment.

Figure 2. Muscle attenuation before and after paclitaxel-treatment (a) and FAC-treatment (b) per patient.

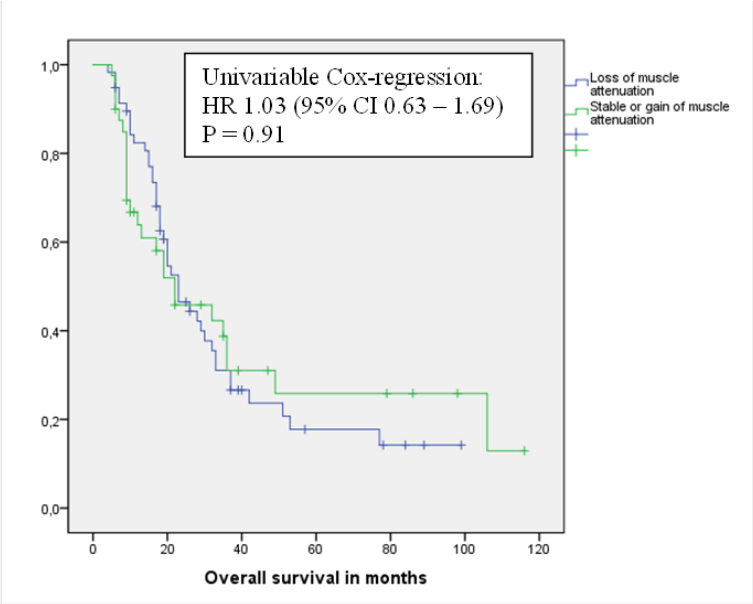
a.



Loss	47	18	7	4	2	1	0
Stable/gain	51	29	10	6	5	1	0

Figure 3a. Kaplan Meier curve for overall survival between patients treated with loss of muscle mass and stable or gain of muscle mass.

b.



Loss	58	30	10	5	3	0	0
Stable/gain	40	17	7	5	4	2	

Figure 3B. Kaplan Meier curve for overall survival between patients with loss of muscle attenuation and stable or gain of muscle attenuation.

Table 4. Cox proportional hazards model assessing the association with overall survival.

	Univariable			Multivariable[a]		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**P**
Age	1.05	1.02 – 1.07	**0.001**	1.04	1.01 – 1.08	**0.01**
Year of diagnosis	1.03	0.95 – 1.12	0.43	1.08	0.97 – 1.19	0.17
DFS[b]	0.98	0.94 – 1.03	0.44	0.91	0.84 – 0.98	**0.01**
ER/PR positive[c]	0.68	0.41 – 1.15	0.15	0.59	0.31 – 1.12	0.11
Her2 positive[d]	0.75	0.44 – 1.30	0.31	0.58	0.29 – 1.17	0.13
Number of metastases			0.11			0.07
• **1**	Ref	Ref	Ref	Ref	Ref	Ref
• **2**	1.77	1.00 – 3.14	0.05	2.16	1.11 – 4.21	**0.02**
• **3**	2.04	1.03 – 4.06	0.04	2.74	1.20 – 6.25	**0.02**
• **>3**	2.30	0.78 – 6.75	0.13	2.09	0.59 – 7.38	0.25
Metastatic location			0.42	-	-	-
• **Bone**	Ref	Ref	Ref	-	-	-
• **Visceral**	0.79	0.31 – 1.99	0.61	-	-	-
• **Skin or lymph nodes**	0.75	0.26 – 2.16	0.60	-	-	-
• **Multiple**	1.27	0.62 – 2.61	0.52	-	-	-
Denovo stage IV	0.74	0.42 – 1.28	0.28	0.30	0.14 – 0.67	**0.003**
Paclitaxel treatment	1.01	0.59 – 1.74	0.96	1.04	0.52 – 2.07	0.92
Baseline LSMI	0.99	0.95 – 1.02	0.47	0.98	0.94 – 1.03	0.42
Baseline MA	0.99	0.96 – 1.01	0.26	1.04	1.00 – 1.09	0.06
Loss of LSMI	1.10	0.68 – 1.77	0.70	0.65	0.36 – 1.20	0.17
Loss of MA	1.03	0.63 – 1.69	0.91	1.22	0.67 – 2.20	0.52
Loss of SAT	1.73	1.00 – 3.01	0.05	0.83	0.39 – 1.76	0.62
Loss of VAT	1.15	0.71 – 1.82	0.56	1.00	0.52 – 1.92	0.99
Loss of IMAT	0.81	0.41 – 1.35	0.42	0.53	0.27 – 1.03	0.06
Loss of TAT	1.15	0.68 – 1.96	0.60	0.58	0.31 – 1.10	0.10

[a]A multivariable Cox model with all patient characteristics was performed, after which each body composition parameter (below the line) was added to this model in a separate multivariable Cox model.
[b]DFS: Time between initial breast cancer diagnosis and diagnosis of distant metastases).
[c]Reference category: ER/PR negative patients (either Her2 positive or Her2 negative)
[d]Reference category: Her2 negative patients (either ER/PR positive or ER/PR negative)

Abbreviations: HR: Hazard ratio; CI: Confidence interval; DFS: Disease-free survival; ER: Estrogen receptor; PR: Progesterone receptor; LSMI: Lumbar skeletal muscle index; MA: Muscle attenuation; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue; IMAT: Intramuscular adipose tissue; TAT: Total adipose tissue

Discussion

This study shows that median muscle attenuation significantly decreased during treatment with paclitaxel (-0.9 HU, p = 0.03). In contrast, in patients treated with anthracyclin-based chemotherapy, the change of median MA was not statistically significant. The amount of

muscle mass and adipose tissue remained stable during treatment in both groups. Previous chemotherapy in the (neo-) adjuvant setting was positively correlated with an 8% increase of the loss of muscle attenuation during the current treatment. In this patient cohort, OS was not affected by body composition changes during chemotherapy.

Only three studies so far have reported results regarding longitudinal changes of MA during chemotherapy. Similar to our study, an absolute loss of MA in these studies was observed of -1.1, -2.4 HU [14,24] and -8.1 HU [25], although the smaller losses of MA did not reach statistical significance. In the study with a mean decrease of -8.1 HU involving pancreatic cancer patients treated with 5-fluorouracil and gemcitabine, patients with larger loss of MA during treatment had shorter OS than patients with small alterations in MA (19.3 vs. 35.3 months, $p = 0.03$), irrespective of MA at baseline [25]. We did not observe an association between decrease in MA and OS in our study, possibly suggesting that a mean decrease of 1.5 HU is too small to be clinically relevant. However, it must be noted that we excluded patients with progressive disease during the current treatment to avoid the impact of progressive cancer on body composition, as we aimed to study possible treatment-specific effects on body composition. Nevertheless, other clinical factors might be of influence as well, such as decreased physical activity and nutritional intake. The true impact of specific systemic therapies on muscle remains difficult without reference populations for muscle measurements in healthy people using CT-imaging, so studies on this are urgently warranted.

MA is a marker of microscopic fatty infiltration of muscle, and associated with systemic inflammation and poor functional status, similar to cancer cachexia [24]. Therefore, patients with MA decrease during treatment could possibly represent frail patients with higher risk of treatment complications and chemotherapeutic toxicity during successive chemotherapeutic regimens [25]. This is supported by the observation in our study that previous chemotherapy in the adjuvant setting was associated with larger decrease of MA during the current treatment. Explanations for the loss of MA during paclitaxel remain speculative, but might be found in several factors, including less physical activity, alterations in muscle composition due to taxane-related myalgia and neuropathy, exposure to (adjuvant) chemotherapy in the past and the impact of routine administration of co-medication, such as corticosteroids. In our study, dexamethasone was administered in all paclitaxel-regimens. However, it has been reported that short-term administration of corticosteroids does not result in corticosteroid-induced myopathy [26,27]. As a result, it is not likely that the dexamethasone administration

in the patients treated with paclitaxel have caused the decrease of median MA. Several studies have reported that low MA is a negative prognostic factor for overall survival [9,10,25,28-30], including a previous study in metastatic breast cancer [8], clearly indicating that having a low MA to start with has different prognostic consequences than diminishing MA during treatment with normal MA at baseline.

Mixed results are reported about the association between the loss of muscle mass during therapy and overall survival [7,13,31]. Overall, studies are hard to compare due to the use of different cut-off points of muscle loss to categorize patients. An association between muscle mass loss and an impaired OS has been reported in patients with colorectal cancer (≥5% loss HR 1.97, $p = 0.017$ [12] and ≥9% loss HR 4.47, $p < 0.01$ [14]) and pancreatic cancer (loss ≥3.8% HR 2.08, $p = 0.027$) [11]. We did not detect any survival differences when comparing patients with loss of muscle mass versus those without. However, these results are hard to compare to the abovementioned studies, as no other studies have been conducted investigating the course and prognostic impact of muscle mass change during chemotherapy in patients with (metastatic) breast cancer.

In this study, the loss of adipose tissue was not associated with OS, which is in concordance with a study in oesophageal cancer [32]. In contrast, studies in ovarian cancer [13] and pancreatic cancer [7,11] reported a negative association between the loss of VAT and OS. However, these results are difficult to compare with our study as half of the patients had ascites [13], which complicates VAT measurement. Higher VAT measurements due to diminished ascites as a result of a chemotherapeutic response might have influenced the survival analyses. The prognostic impact of adipose tissue measurements, especially VAT, needs further investigation in patients with metastatic breast cancer.

To our knowledge, this is the first study investigating longitudinal body composition changes during chemotherapy, in patients with metastatic breast cancer. Knowledge regarding changes in body composition during chemotherapy might be important for clinical decision-making because of several reasons. Since increased fat infiltration of muscle represent negative metabolic changes, comparable with the metabolic changes occurring in cancer cachexia [3,33], patients with loss of MA might be at increased risk for negative clinical outcomes and might have lower quality of life due to worse physical function. Furthermore, it has been reported that muscle and adipose tissue measurements show higher association with

chemotherapeutic pharmacokinetics than body surface area [34]. It could be hypothesized that patients with decreasing fat mass might experience more chemotherapeutic toxicity from the lipophilic paclitaxel, as a lower volume of distribution to adipose tissue occurs, resulting in higher systemic drug levels.

This study has several limitations. Firstly, this was a single-centre retrospective study. Secondly, CT-imaging of the abdomen at L3 level was required for muscle measurement, which led to the exclusion of a large number of patients without available CT-images. The lack of CT-images was mostly due to other imaging diagnostics preferred at our centre, such as thoracic X-ray and ultrasound, to diagnose the presence of distant metastases, which is common in clinical breast cancer care. Another frequent reason to omit abdominal CT-imaging is that metastatic lesions are not located in the abdomen. To avoid this, other devices and/or other locations to measure muscle mass in breast cancer patients should be explored. Nevertheless, as studies investigating muscle parameters in breast cancer are scarce, we chose to measure muscle at the L3-level using CT-imaging, as this is regarded the gold standard. To determine the amount of selection bias, we compared the results of the included and excluded patients. OS of the excluded patients was worse, but this is likely due to the fact that patients not able to complete all cycles of first-choice palliative chemotherapy (i.e. regimens involving anthracyclins and/or taxanes) have a worse prognosis, as well as patients treated with other agents than anthracyclins or taxanes. Therefore, results cannot be generalized to the entire population. Furthermore, this might have affected the observation that changes in body composition were not associated with survival. However, the aim of this study was to evaluate the possibility of excessive muscle wasting during chemotherapy in the absence of progressive disease and we were able to investigate this in a group of patients receiving the same type of cytotoxic agents and the same number of cycles. Thirdly, the number of the patients in the FAC-group was small and a type II statistical error could not be ruled out. However, our main interest was the change of muscle mass and muscle attenuation during a treatment with muscle-affecting toxicity compared to a treatment regimen without muscle-affecting toxicity. We assumed that this would provide a better comparison of body composition changes due to systemic therapy than choosing a reference group without treatment at all.

Conclusion

In conclusion, the quality of the muscle significantly decreased during treatment with paclitaxel in our patient cohort, while the amount of muscle mass and adipose tissue remained stable. In addition, muscle changes in the absence of progressive disease in metastatic breast cancer seem not clinically relevant, which could be useful knowledge when exploring future possibilities of selecting patients for interventions optimizing muscle mass and attenuation. Prospective studies with a larger number of patients are required to confirm the results of this study and to investigate the correlation between body composition alterations over time and survival.

Supplemental Table 1. Comparison patient characteristics of included and excluded patients.

	Included (n = 98)	Excluded (n = 319)	p value
Age (years)			0.07
• **Median (IQR)**	56 (48 – 63)	52 (45 – 61)	
• **Unknown**	0	6	
Year of diagnosis[b]			
• **Median (IQR)**	2011 (2008 – 2013)	2007 (2005 – 2011)	**<0.001**
• **Unknown**	0	4	
Body mass index			0.40
• **Median (IQR)**[c]	26.9 (23.2 – 30.5)	25.7 (22.8 – 29.6)	
• **Unknown**	0	90	
Hormone receptor status			0.06
• **Positive**	73 (74.5%)	190 (63.8%)	
• **Negative**	25 (25.5%)	108 (36.2%)	
• **Unknown**	0	21	
Her2Neu status			0.90
• **Positive**	26 (40.6%)	90 (31.7%)	
• **Negative**	38 (59.4%)	194 (68.3%)	
• **Unknown**	7	35	
Primary stage IV (%)	20 (28.2%)	83 (26.1%)	0.79
• **Unknown**	0	1	
Disease free interval (years)[d]			
• **Median (IQR)**	5.0 (3 - 10)	2.0 (1 – 6)	**<0.001**
Time to palliative treatment (months)[e]			0.38
• **Median (IQR)**	1.0 (0 – 6)	1.0 (0 – 7)	
Metastatic location			**0.004**
• **Bone**	10 (14.1%)	99 (31.5%)	
• **Visceral**	11 (15.5%)	44 (14.0%)	
• **CNS**	0	10 (31.8)	
• **Skin or lymph nodes**	8 (11.3%)	36 (11.5%)	
• **Multiple locations**	42 (59.2%)	125 (39.8%)	
• **Unknown**	0	5	
Number of metastatic sites			**0.005**
• **1**	28 (39.4%)	184 (58.6%)	
• **2**	30 (42.3%)	85 (27.1%)	
• **3**	10 (14.1%)	32 (10.2%)	
• **> 3**	3 (4.2%)	13 (4.1%)	
• **Unknown**	0	5	
Previous chemotherapy	26 (36.6%)	152 (47.9%)	0.20
• **Unknown**	0	2	
Previous palliative endocrine therapy	33 (46.5%)	42 (36.5%)	0.22
• **Unknown**	0	204	

[a]FAC: 5-fluororacil, Adriamycin, cyclophosphamide.
[b]Diagnosis of distant metastases.
[c]IQR: Interquartile range.
[d]DFS: Time between the initial breast cancer diagnosis and the first presentation of distant metastases for patients with M0 presentation of primary breast cancer.
[e]Time to palliative treatment: Time between the first presentation of distant metastasis and the start of the first line palliative chemotherapy

Supplemental Table 2. Patient characteristics of all patients.

	FAC (n = 35)	Paclitaxel (n = 100)	p value
Age (years)			
• **Median (IQR)**	55 (46 – 62)	53 (45 – 61)	0.25
Year of diagnosis[a]			
• **Median (IQR)**	2009 (2007 – 2012)	2011 (2008 – 2013)	0.03
Body mass index			
• **Median (IQR)**	26.7 (23.6 – 30.9)	25.9 (22.5 – 29.8)	0.59
Hormone receptor status			1.00
• **Positive**	25 (71.4%)	71 (71%)	
• **Negative**	10 (28.6%)	29 (29%)	
• **Unknown**	0	0	
Her2Neu status			**0.001**
• **Positive**	2 (5.7%)	33 (33%)	
• **Negative**	32 (91.4%)	57 (57%)	
• **Unknown**	1 (2.9%)	10 (10%)	
Primary stage IV (%)	13 (37.1%)	20 (20%)	**0.07**
Disease free interval (years)[b]			
• **Median (IQR)**	7.5 (2 – 10.5)	3 (2 – 8.8)	0.11
Time to palliative treatment (months)[c]			
• **Median (IQR)**	1 (0-6)	1 (0 – 7)	0.66
Metastatic location			0.73
• **Bone**	6 (17.1%)	21 (21%)	
• **Visceral**	6 (17.1%)	17 (17%)	
• **Brain**	0 (0%)	1 (1%)	
• **Skin or lymph nodes**	4 (11.4%)	6 (6%)	
• **Multiple locations**	19 (54.3%)	55 (55%)	
Number of metastatic sites			0.86
• **1**	14 (40%)	43 (43%)	
• **2**	14 (40%)	35 (35%)	
• **3**	6 (17.1%)	16 (16%)	
• **> 3**	1 (2.9%)	6 (6%)	
Previous (neo)adjuvant chemotherapy	9 (25.7%)	56 (56%)	**0.003**
Previous endocrine therapy			0.31
No endocrine therapy	19 (54.3%)	42 (42%)	
(Neo-)adjuvant	7 (20.0%)	25 (25%)	
Palliative	5 (14.3%)	13 (13%)	
Both adjuvant and palliative	4 (11.4%)	17 (17%)	
Unknown	0	3 (3%)	
LSMI baseline[d]	38.4 (35.2 – 44.2)	37.8 (32.8 – 41.0)	0.06
MA baseline	31.5 (26.6 – 38.2)	31.0 (25.2 – 41.0)	0.81
SAT baseline (Median + IQR)	191.4 (150.5 – 230.3)	203.5 (150.6 – 250.2)	0.69
VAT baseline	109 (53.9 – 126.2)	101.0 (61.2 – 144.1)	0.89
IMAT baseline	16.6 (10.0 – 21.8)	14.6 (9.6 – 22.2)	0.83
TAT[g] **baseline**	317.9 (211.4 – 364.9)	308.1 (249.3 – 393.1)	0.75

[a]Diagnosis of distant metastases.
[b]DFS: Time between the initial breast cancer diagnosis and the first presentation of distant metastases for patients with M0 presentation of primary breast cancer.

[c]Time to palliative treatment: Time between the first presentation of distant metastasis and the start of the first line palliative chemotherapy.
[d]Before chemotherapy
[e]Missing: n = 4
[f]Missing: n = 11
[g]TAT: Sum of SAT, VAT and IMAT.

Abbreviations: FAC: 5-fluororacil, Adriamycin, cyclophosphamide; IQR: Interquartile range; DFS: Disease-free survival; LSMI: Lumbar skeletal muscle index; MA: Muscle attenuation; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue; IMAT: Intramuscular adipose tissue; TAT: Total adipose tissue

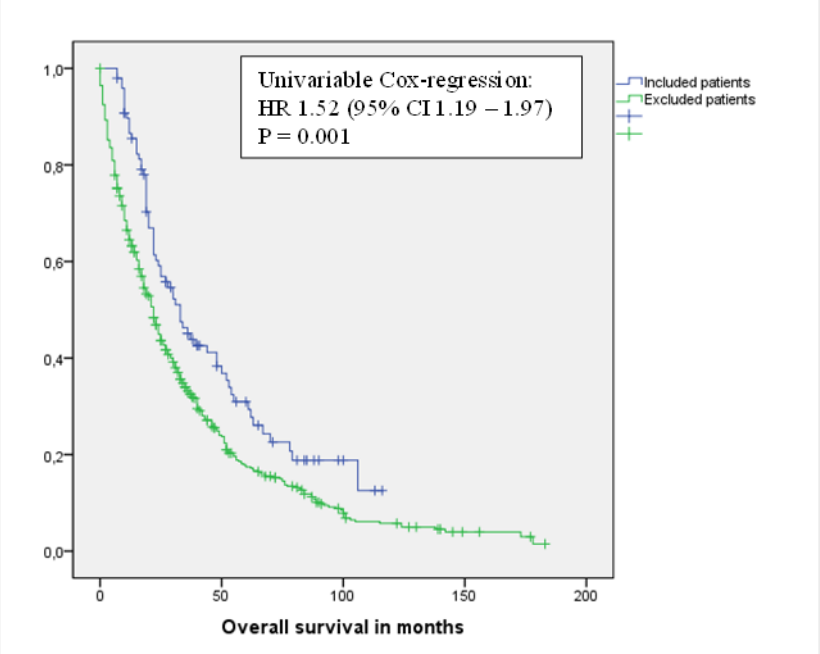
Supplemental table 3. Changes in body composition during chemotherapy of all patients.

Muscle change during chemotherapy, median (IQR)				
	FAC	**p[a]**	**Paclitaxel**	**p[a]**
LSMI (cm^2/m^2)	-1.1 (-2.9 - +0.9)	0.05	-0.4 (-2.3 – +1.4)	0.49
MA (HU)	-0.5 (5.1 – +2.5)	0.56	-0.8 (-4.6 - +2.3)	**0.02**
SAT	-17.3 (-35.5 - +5.1)	**0.02**	-8.2 (-26.6 - +16.2)	0.29
VAT	-1.0 (-18.0 - +10.3)	0.41	-0.6 (-19.3 - +11.1)	0.52
IMAT	+0.2 (-2.3 - +3.3)	0.34	+0.9 (-2.0 - +3.2)	**0.04**
TAT	-20.0 (-43.0 - +23.9)	0.12	-3.9 (-41.3 - +28.6)	0.57

[a]The difference in muscle parameters during chemotherapy (after – before) within each treatment group using the Wilcoxon signed rank test.

Abbreviations: FAC: 5-fluororacil, Adriamycin, cyclophosphamide; IQR: Interquartile range; LSMI: Lumbar skeletal muscle index; MA: Muscle attenuation; HU: Hounsfield Unit; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue; IMAT: Intramuscular adipose tissue; TAT: Total adipose tissue

Supplemental figure. Kaplan Meier curve for overall survival between included and excluded patients.



Included patients	98	26	26	0	0
Excluded patients	561	105	26	5	0

Overall survival has been calculated from the date of diagnosis of distant metastases until the date of death or the end of follow-up.

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Chapter 6

Severe sarcopenia might be associated with a decline of physical independence in older patients undergoing chemotherapeutic treatment

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Abstract

Background: Assessing physical reserve in older cancer patients before treatment-decision making remains challenging. The maintenance of physical independence during therapy is sometimes just as important for these patients as oncological outcomes. Recently, sarcopenia has been recognized as a possible important prognostic factor for outcome in cancer patients. We investigated the association between different levels of sarcopenia and the decline of physical independence during chemotherapy in older cancer patients (≥ 65 years).

Methods: Sarcopenia was divided into presarcopenia, sarcopenia and severe sarcopenia according to an international consensus and were related to physical independence determined by measuring instrumental activities of daily living (IADL), using binary logistic regression models. CT-based muscle mass is necessary to diagnose sarcopenia and was related to 5 functional tests, in order to investigate whether these easy to perform tests could replace the more invasive CT-based muscle measurement.

Results: A total of 131 patients were included (median age 72 years). The prevalence of presarcopenia, sarcopenia and severe sarcopenia was 47.7%, 18.5% and 7.7%, respectively. Compared to no sarcopenia, only severe sarcopenia seemed associated with a decline of physical independence after chemotherapy (OR 5.95, 95% CI 0.76 – 46.48). Muscle mass was only significantly associated with muscle strength, but not with tests measuring physical function.

Conclusion: The level of sarcopenia might be a useful tool in addition to routine oncological assessment to identify older cancer patients with increased risk of physical decline after chemotherapy.

Introduction

Sarcopenia, initially defined as a low muscle mass (less than 2 standard deviations below the mean of a young reference group) according to the definition of Baumgartner et al [1], has been related to physical disability [2, 3] and mortality [4] in older adults. In the presence of cancer, low skeletal muscle mass has emerged as a novel negative prognostic factor for survival as well as for treatment tolerability [5, 6]. In oncological research, increased attention is paid to the prognostic value of CT-based low muscle mass, which on some occasions is easy to perform using already available routine staging CT-scans.

However, evidence in the literature suggests that there is no linear correlation between the loss of muscle mass and the loss of the clinically more relevant muscle strength [2, 7, 8], with muscle strength being more prognostic for mortality than muscle mass [9], and suggesting that the geriatric syndrome sarcopenia is more than muscle loss alone. Studies in elderly people have revealed that changes in muscle mass only explained 5% of the variability of muscle strength decline [10, 11]. Therefore, it is currently recommended to redefine sarcopenia as the loss of muscle mass in combination with the loss of muscle strength and/or impaired physical performance [7]. In the European consensus on the definition of sarcopenia, several levels of sarcopenia are identified, i.e. presarcopenia (solitary low muscle mass), sarcopenia (low muscle mass + low muscle strength or slow walking speed) and severe sarcopenia (low muscle mass + both low muscle strength and slow walking speed) [7].

Irrespective of oncological outcomes, the physical status of an individual patient and maintaining the level of physical independence remains one of the key challenges in the treatment of the older cancer patient. Currently, the most commonly used parameters in oncological care to assess physical function of patients are the ECOG or WHO performance scores. These scores, however, have a low sensitivity to detect the heterogeneous distribution of physical reserve that characterizes older cancer patients [12, 13].

Therefore, the purpose of this study was to determine the association between the different levels of sarcopenia before chemotherapeutic treatment and the maintenance of physical independence after chemotherapy. Muscle mass measurement is the common component

between all levels of sarcopenia, but requires imaging diagnostics (CT-imaging in this study), and furthermore, there is no uniform definition of low muscle mass yet, which hampers muscle mass measurement in routine clinical care. The second aim of this study was therefore, to correlate CT-based muscle mass to easy to perform functional tests, in order to investigate the possibility of replacing CT-based muscle mass with tests requiring lower costs and less patient burden.

Methods

Study design

In this single center prospective cohort study, patients diagnosed with cancer above 65 years of age underwent individual tests assessing physical status (as part of a comprehensive geriatric assessment) before, halfway and after completion of chemotherapeutic treatment between October 2013 and May 2016. Exclusion criteria were chemotherapeutic treatment less than 3 months prior to inclusion and the absence of abdominal CT-images. Muscle measurements were obtained using abdominal CT-images acquired during routine care and correlated to the functional tests, which included walking speed, the five-times-sit-to-stand test (FTSTS), handgrip strength, the steep ramp test and the Timed Up and Go (TUG). The time between CT-imaging and geriatric assessment had to be less than 3 months. The levels of sarcopenia were categorized into presarcopenia, sarcopenia and severe sarcopenia, according to the recommendation of the European Working Group on Sarcopenia in Older People [7] and were related to diminished physical independence after completion of therapy. Physical independence was determined by the measurement of instrumental activities of daily living (IADLs) according to the scale of Lawton and Brody [14] **(Appendix A)**. IADLs included grocery shopping, meal preparation, telephone use, household and independence in travelling, medication management and financial management. A score of 0 points on the IADL-scale of Lawton and Brody was considered being fully IADL-dependent and a score of 8 points was considered full IADL-independence. A clinically significant decline in IADL-independence was defined as either a decline of ≥3 points immediately after completion of chemotherapy or a decline of ≥2 points 1 year after the completion of chemotherapy, compared to baseline. The study was approved by the central review board (METC 2015_08, NL47633.101.15). All patients provided written informed consent prior to inclusion.

Muscle measurements and definitions

All muscle measurements were performed at one transversal CT-image (slice thickness 3 mm, Brilliance 64 CT or Brilliance 40 CT, Philips, Best, the Netherlands) at the L3-level using slice-o-matic software (Slice-o-matic, Tomovision, Canada) [15]. Total abdominal muscle area (TAMA) in cm^2 was used as parameter for muscle mass, as TAMA at L3 is representative of total body muscle mass [16]. TAMA was corrected for height according to the formula TAMA/height^2, resulting in a skeletal muscle index (SMI) in cm^2/m^2. Presarcopenia was defined as solitary low muscle mass (LMM) according to previously published cut-off points [17]. In patients with a body mass index (BMI) <25 kg/m^2, LMM was defined as a SMI <43 cm^2/m^2 (males) or a SMI <41 cm^2/m^2 (females). In patients with a BMI ≥25 kg/m^2, LMM was defined as a SMI <53 cm^2/m^2 (males) or a SMI <41 cm^2/m^2 (females). Sarcopenia was defined as LMM plus either a walking speed ≤0.80 m/s or a low handgrip strength (<26 kg for males and <16 kg for females, which was based on a pooled sample of 9 studies involving 26,625 community-dwelling elderly) [18]. Severe sarcopenia was defined as LMM and both slow walking speed and low handgrip strength. HU-thresholds to identify muscle tissue were set between -29 and +150 HU, as previously published [19].

Functional tests assessing physical status

Functional tests reflecting muscle strength (FTSTS, grip strength and the steep ramp test) and physical function (walking speed and TUG) were obtained from the geriatric assessment and related to CT-based muscle mass on a continuous scale.

1. FTSTS: The five-times-sit-to-stand test (FTSTS) [20] was used as assessment for lower extremity strength [21]. Patients were instructed to sit on a chair standing against the wall with their arms crossed over their chest. The performance of the test was demonstrated, after which the patient had to rise five times from the chair to a full stand as fast as possible. The time to complete this from the moment that the investigator stated “go” until the return to seated position for the fifth time was recorded in seconds.

2. Grip strength: Hand grip strength was measured using a Jamar hand dynamometer (Lafayette Instrument Co., Lafayette, IN, http://www.lafayetteinstrument.com), which measures handgrip force in kilograms (kg) per square inch. Measurements were performed alternately two times for both hands, after which average grip strength for each hand was calculated. The highest average was used for the analysis.

3. Steep ramp test: A steep ramp test was performed to determine short maximal exercise capacity [22]. Patients were instructed to cycle on a cycle ergometer with a pedal frequency between 70 and 90 rounds per minute (rpm), starting at 0 watt (W). After 10 seconds of cycling at 0W, the workload was increased by 25W every 10 seconds until exhaustion or when the pedal frequency dropped below 60 rpm. The maximal workload in W per kg body weight was recorded alongside the cycle time and heart rate at the end of the test.
4. Walking speed: Walking speed in meters per second (m/s) was determined over an 8 m-course at usual pace.
5. TUG: The timed up and go (TUG) was used as assessment for functional mobility [23]. The patient was instructed to rise from a seating position (approximately 46 cm height), walk over a 3 m-course at usual pace, turn around, walk back and sit down again. The time to complete this assessment differs according to age.

Statistical analyses

Continuous variables were described as median + interquartile range (IQR) and categorical variables as percentages. Comparisons between males and females were performed using Mann-Whitney U tests for continuous variables, Fisher exact tests for categorical variables with 2 categories and chi-square tests for categorical variables with more than 2 categories. To assess the impact of the heterogeneity in tumor type and disease stage in this cohort on the results of our analysis, the following parameters were compared between the patients with severe sarcopenia and all other patients: age, body mass index (BMI), gender, WHO score, tumor type, disease stage, treatment purpose (curative or palliative), IADL limitations before chemotherapy, ADL limitations before chemotherapy, nutritional status, cognition and response to chemotherapy. We divided “tumor type” into the following categories: aggressive hematological malignancies, indolent hematological malignancies, non-metastatic solid malignancies and metastatic solid malignancies. Univariable and multivariable binary logistic regression models were used to determine associations between levels of sarcopenia and the decline of physical independence after chemotherapy. The dependent variable in these models was the decline of physical independence (yes/no). The independent variables were age, gender, impaired cognition (Mini Mental State Evaluation ≤24 vs. >24), tumor type, treatment purpose, response to chemotherapy, IADL at baseline and the level of sarcopenia before treatment. It must be noted that the prognostic impact of disease stage differs considerably between solid and hematological malignancies. Therefore, the prognostic impact of disease

stage might be better addressed using the purpose of treatment (curative or palliative) as variable, than the actual disease stage itself. The level of sarcopenia was categorized into no sarcopenia, presarcopenia, sarcopenia and severe sarcopenia. Interaction effects between sarcopenia levels/tumor type and sarcopenia/disease stage were assessed by adding these interaction terms separately to the multivariable logistic regression model, and testing their significance with a likelihood-ratio test. A Hosmer-Lemeshow test was performed to evaluate the goodness-of-fit of the multivariate binary logistic regression model.

Spearman's rank correlation was used to determine univariate associations between functional tests and muscle parameters on a continuous scale in the entire cohort; for this analysis the first available measurement of functional tests was used for each patient. Linear mixed models were used to determine multivariate associations between the repeated measurements of functional tests and muscle parameters on a continuous scale. This statistical method accounts for missing observations in the dependent variable. The dependent variables in the linear mixed models were the functional tests, with a separate linear mixed model for each functional test. The independent variables were age, gender, body mass index (BMI), the time of assessment, treatment purpose (palliative vs. curative intent), tumor type (non-hematological vs. hematological) and muscle mass (SMI in cm^2/m^2). The time of assessment was categorized into assessment before, during, after and 1 year after chemotherapeutic treatment. A random intercept was included in the linear mixed models to account for the within-subject correlations. All analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA) with a two-sided significance level of 0.05.

Results

Patient characteristics

In total, 142 patients underwent geriatric assessment between October 2013 and May 2016 with a total of 247 abdominal CT-images available for muscle measurements. Of these, 36 CT-images were excluded because of no accompanying geriatric assessment and 5 because of technical reasons regarding the Slice-o-matic preventing the assessment of muscle mass and attenuation. Eventually, 206 combinations of CT-imaging and functional measures, derived from 131 individual patients were included in the analysis. The median time between the CT scan and the measurement of geriatric parameters was 21.5 days (range 0 – 90, IQR 8 – 44).

The median age in the entire cohort was 72 years (IQR 69 – 78) and 73 (55.7%) were male **(table 1)**. Compared to females, males had significantly more muscle mass (median 45.3 cm^2/m^2 vs. 36.7 cm^2/m^2, $p < 0.001$) and greater grip strength (median 32.0 vs. 18.5 kg, $p < 0.001$). Other functional measures were similar between males and females **(table 2)**.

Table 1. Patient characteristics (n = 131)

Variable	N (%)
Age	
• **<75 years**	78 (59.5)
• **≥75 years**	53 (40.5)
Gender	
• **Male**	73 (55.7)
• **Female**	58 (44.3)
BMI, median (IQR)	26.3 (23.4 – 29.0)
WHO performance score	
• **0**	29 (29.0)
• **1**	59 (59.0)
• **2**	11 (11.0)
• **3**	1 (1.0)
• **Unknown**	31
Tumor type[a]	
• **Aggressive haematological malignancies**	29 (22.1%)
• **Indolent haematological malignancies**	34 (26.0%)
• **Non-metastatic solid malignancies**	41 (31.3%)
• **Metastatic solid malignancies**	27 (20.6%)
Disease stage	
• **Stage I**	6 (4.6)
• **Stage II**	19 (14.6)
• **Stage III**	46 (35.3)
• **Stage IV**	59 (45.4)
• **Unknown**	1
Treatment purpose	
• **Curative**	69 (52.7)
• **Palliative**	62 (47.3)
IADL limitations[b]	
• **Yes**	44 (36.1)
• **No**	78 (63.9)
• **Unknown**	9
ADL limitations[b]	
• **Yes**	40 (30.5)
• **No**	91 (69.5)
Nutritional status	
• **Malnourished (MNA <17)**	6 (4.6)
Cognition	
• **Impaired (MMSE ≤ 24)**	15 (11.5)

Abbreviations: BMI: Body mass index; WHO: World Health Organization; IADL: Instrumental activities of daily living; ADL: Activities of daily living; MNA: Minimal nutritional assessment; MMSE: Mini mental state examination

Association between sarcopenia levels and decline of physical independence

The prevalence of presarcopenia, sarcopenia and severe sarcopenia were 47.7% (n = 62), 18.5% (n = 24) and 7.7% (n = 10), respectively. Compared to men, slightly more women had severe sarcopenia, but this difference was not statistically significant (p = 0.34). The patients with severe sarcopenia were older and more often malnourished (MNA <17). Strikingly, 9 of the 10 patients with severe sarcopenia were diagnosed with a hematological malignancy, equally distributed between aggressive and indolent tumors. Of the 27 patients with metastases of solid tumors, no patients were classified as severely sarcopenic **(table 3)**.

Table 2. Muscle parameters and functional measures according to gender.

	Male (n = 73)	Female (n = 58)	p
Muscle mass (cm^2/m^2)	45.3 (41.6 – 50.4)	36.7 (33.4 – 41.9)	<0.001
Sarcopenia level			0.35
• **Normal**	19 (26.0)	15 (26.3)	
• **Presarcopenia**	36 (49.3)	26 (45.6)	
• **Sarcopenia**	15 (20.5)	9 (15.8)	
• **Severe sarcopenia**	3 (4.1)	7 (12.3)	
Walking speed (m/s)	1.0 (0.8 – 1.2)	1.0 (0.8 – 1.2)	0.63
FTSTS (seconds)	13.3 (11.2 – 16.6)	13.9 (11.1 – 19.3)	0.63
Hand grip strength (kg)	32.0 (27.5 – 38)	18.5 (13.5 – 21.0)	<0.001
Steep ramp test (W/kg)	2.2 (1.7 – 2.6)	2.0 (1.2 – 2.3)	0.04
Timed up and go (seconds)	8.8 (7.8 – 10.6)	9.5 (8.2 – 11.4)	0.25

[a]The levels of sarcopenia are described as numbers (%), the other measures as median + interquartile range

Abbreviations: m/s: Meters per second; FTSTS: Five-times-sit-to-stand test; W/kg: Watt per kilogram

Before chemotherapeutic treatment, 63.9% of the patients were fully physically independent (IADL-score of 8), which decreased to 56.3% after completion of chemotherapy. A clinically significant decline of physical independence (i.e. an IADL-decline of ≤2 points immediately after chemotherapy or ≤3 points 1 year after chemotherapy) was observed in 15 patients (11.5%). The course of physical independence during therapy could not be observed in a fair number of patients (n = 38, 29%) because these patients did not return for follow-up geriatric assessment (GA). The main reasons for this were physical decline, causing follow-up GA to be a too large burden (23.7%) and progressive disease, resulting in another line of chemotherapeutic treatment, death or best supportive care (28.9%). In the analysis, these patients were therefore incorporated into the group of patients having clinically significant decline of physical independence.

Table 3. Characteristics of patients with severe sarcopenia.

	Severe sarcopenia (n = 10)	Normal muscle mass or non-severe sarcopenia (n = 121)	P
Age, median (IQR)	80.5 (72.5 – 82.3)	72 (69 – 77)	0.02
BMI, median (IQR)	26.3 (20.8 – 30.5)	26.3 (23.4 – 28.8)	0.82
Gender			<0.001
• **Male**	3 (30.0)	70 (57.9)	
• **Female**	7 (70.0)	51 (42.1)	
WHO performance score			<0.001
• **0**	2 (20.0)	29 (24.0)	
• **1**	2 (20.0)	57 (47.1)	
• **2**	6 (60.0)	6 (5.0)	
• **3**	0	1 (0.8)	
Tumor type			0.02
• **Aggressive haematological malignancies**	5 (50.0)	24 (19.8)	
• **Indolent haematological malignancies**	4 (40.0)	30 (24.8)	
• **Non-metastatic solid malignancies**	1 (10.0)	40 (33.1)	
• **Metastatic solid malignancies**	0	27 (22.3)	
Disease stage			0.98
• **I**	1 (10.0)	5 (4.2)	
• **II**	1 (10.0)	18 (15.0)	
• **III**	3 (30.0)	43 (35.8)	
• **IV**	5 (50.0)	54 (45.0)	
• **Unknown**	0	1	
Treatment purpose			0.75
• **Curative**	6 (60.0)	63 (52.1)	
• **Palliative**	4 (40.0)	58 (47.9)	
Disease response			0.02
• **Complete remission**	0	33 (27.5)	
• **Partial remission or stable disease**	5 (50.0)	42 (35.0)	
• **Refractory or progressive disease**	4 (40.0)	15 (12.5)	
• **Deceased**[a]	0	3 (2.5)	
• **Unconfirmed complete remission**[b]	0	27 (22.5)	
• **Unknown**	1	1	
IADL limitations	6 (60.0)	38 (33.6)	0.14
ADL limitations	9 (90.0)	31 (25.6)	<0.001
MNA <17	2 (20.0)	4 (3.3)	0.02
MMSE ≤24	2 (22.2)	13 (10.7)	0.28

[a]Deceased during chemotherapy, no response monitoring

[b]Complete remission not confirmed after adjuvant chemotherapy for a solid malignancy, but no evidence of disease. After such treatments, imaging diagnostics to confirm response are not regularly conducted in our centre.

Abbreviations: ADL: Activities of daily living; BMI: Body mass index; IADL: Instrumental activities of daily living; IQR: Interquartile range; MMSE: Mini mental state examination; MNA: Minimal nutritional assessment

In the univariable logistic regression models, with decline of physical independence as dependent variable, the only parameter associated with decline of physical independence during chemotherapy was refractory or progressive disease after completion of treatment (univariable OR 7.54, 95% CI 1.95 – 29.14, p = 0.003) with complete remission used as reference category. Complete or partial disease response, tumor type, palliative treatment purpose, and physical function at baseline and the presence of distant metastases of a solid malignancy were not significantly associated with a decline of physical independence after chemotherapy.

Table 4. Associations between sarcopenia and decline of physical independence.

	Univariable			**Multivariable[a]**		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	1.07	1.00 – 1.15	0.05	1.07	0.99 – 1.16	0.10
Impaired cognition[b]	3.36	0.99 – 11.43	0.05	3.67	0.84 – 15.96	0.08
IADL baseline[c]	0.88	0.67 – 1.16	0.37	-	-	-
Tumor type			0.79	-	-	-
• **Solid metastatic**	Ref	Ref	Ref			
• **Solid non-metastatic**	1.71	0.54 – 5.50	0.36			
• **Haematological aggressive**	1.26	0.37 – 4.36	0.71			
• **Haematological indolent**	1.65	0.51 – 5.38	0.42			
Palliative treatment[d]	1.00	0.46 – 2.18	0.99	-	-	-
Response			0.03	-	-	-
• **Complete remission**	Ref	Ref	Ref			
• **Partial remission**	2.15	0.67 – 6.90	0.20			
• **Refractory or progression**	7.54	1.95 – 29.14	0.003			
• **Deceased**	9.60	0.72 – 153.15	0.09			
• **Unconfirmed complete remission[e]**	1.80	0.47 – 6.91	0.39			
Sarcopenia level			0.23			0.28
• **Normal**	Ref	Ref	Ref	Ref	Ref	Ref
• **Presarcopenia**	1.82	0.63 – 5.24	0.27	2.90	0.82 – 10.18	0.10
• **Sarcopenia**	2.56	0.72 – 9.08	0.15	2.59	0.53 – 12.52	0.24
• **Severe sarcopenia**	4.79	0.98 – 23.56	0.05	5.95	0.76 – 46.48	0.09

[a]The multivariable logistic regression analysis was performed with age, impaired cognition, and sarcopenia level as independent variables.
[b]MMSE ≤24
[c]According to the scale of Lawton and Brody (score 0-8, with 8 fully physically independent)
[d]Versus curative treatment (curative = reference category)
[e]Complete remission not confirmed after adjuvant chemotherapy for a solid malignancy. After such treatments, imaging diagnostics to confirm response are not regularly conducted in our centre.

Abbreviations: BMI: body mass index; MMSE: Mini mental state examination; IADL: Instrumental activities of daily living

Presarcopenia (solitary low muscle mass) and sarcopenia before chemotherapeutic treatment did not result in a clinically significant decline of physical independence after chemotherapy, compared to patients without sarcopenia (OR 1.82, 95% CI 0.63 – 5.24, p = 0.27 and OR 2.56, 95% CI 0.72 – 9.08, p = 0.15, respectively) **(table 4)**. Severe sarcopenia seemed to be predictive of a decline of physical independence, with high ORs in both the univariable and multivariable regression models, although statistical significance was not reached (OR 4.79, 95% CI 0.98 – 23.56, p = 0.05 and OR 5.95, 95% CI 0.76 – 46.48, p = 0.09, respectively) **(table 4)**. The interaction effects between sarcopenia level and tumor type and between sarcopenia level and disease stage were both statistically not significant (p = 0.26 and p = 0.08, respectively), suggesting that the association between sarcopenia levels and the decline of physical independence was not influenced by tumor type or disease stage.

Table 5. Associations between CT-based muscle mass and functional tests.[a]

	Muscle mass (continuous scale)		
	Coefficient	**95% CI**	**p**
Walking speed[b]	-0.001	-0.01 – 0.01	0.74
FTSTS[b]	-0.31	-0.51 - -0.11	0.002
Hand grip strength[b]	0.04	-0.10 – 0.19	0.56
Steep ramp test[b]	0.02	0.002 – 0.04	0.03
Timed up and go[b]	0.002	-0.17 – 0.18	0.98

[a]A total of 206 measurements were analyzed, derived from 131 individual patients: before chemotherapy: 124; halfway chemotherapy: 41; after chemotherapy: 35; 1 year after the start of chemotherapy: 6.
[b]Linear mixed models corrected for age, BMI, gender, tumor type (non-haematological vs. haematological), treatment purpose (palliative vs. curative) time of assessment and muscle mass, with the functional tests as dependent variables.

Correlation between CT-based muscle mass and physical function (walking speed and TUG).

Overall, the amount of muscle mass on CT-images showed no correlation with the functional tests reflecting physical function (i.e. walking speed and the TUG) using Spearman's rank correlation (walking speed rho = +0.05, p = 0.48, TUG rho = -0.04, p = 0.55). In the linear mixed models, the associations between both walking speed and the TUG and muscle mass were not statistically significant **(table 5)**.

Correlation between CT-based muscle mass and muscle strength (FTSTS, handgrip strength and steep ramp test).

In contrast, muscle mass on a continuous scale was significantly associated with functional tests reflecting muscle strength, demonstrated by Spearman's rank correlation coefficients of -0.20 ($p = 0.004$), +0.51 ($p < 0.001$) and +0.19 ($p = 0.01$) for the FTSTS, grip strength and the steep ramp test, respectively. After correction for age, BMI, gender, tumor type and treatment purpose, and the time of assessment using linear mixed models, the FTSTS and the steep ramp test in Watt/kg were still significantly associated with the amount of muscle mass on CT (coefficient -0.31, 95% CI -0.51 - -0.11, $p = 0.002$ and coefficient +0.02, 95% CI 0.002 – 0.04, $p = 0.03$ respectively). **(table 5)**.

Discussion

In this study, the level of sarcopenia seemed positively correlated with the level of physical dependence according to the IADL-scale of Lawton and Brody. High ORs for the decline of physical independence were observed in the relatively small group of patients with severe sarcopenia ($n = 10$), indicating that these patients were at risk for a clinically significant decline of physical independence after treatment, irrespective of the etiology of this decline. These results need to be confirmed in a larger study cohort since statistical significance was not reached yet. The only statistically significant predictor of physical decline in this study was refractory or progressive disease during chemotherapy. However, treatment response is not available at the start of treatment, so cannot be used to estimate the risk of decline of physical independence prior to the start of therapy. Therefore, we believe that other parameters, including pre-treatment sarcopenia levels, deserve further research as prognostic markers for physical decline. Notably, 40% of the patients with severe sarcopenia were classified as having a WHO performance score of 0 or 1 by their treating physician (data not shown), i.e. were considered physically fit for chemotherapeutic treatment. This indicates that assessing the level of sarcopenia might be a useful tool to identify patients at risk of physical dysfunction after chemotherapy in older cancer patients in addition to the routine oncological assessment.

In oncological research, CT-based muscle measurements as prognostic markers for clinical outcomes are a field of increasing interest. Low muscle mass (LMM), i.e. presarcopenia, has been related to poor oncological outcomes in terms of survival [5] and chemotherapeutic toxicity [24]. Studies investigating the association of CT-based muscle measurements with patient reported outcomes, such as physical dependence, are scarce while these outcomes are particularly important in older cancer patients. Furthermore, in most oncological studies, no distinction is made between solitary LMM (presarcopenia) and the syndrome sarcopenia. The necessity of this in oncological research is intensively debated. Solitary LMM is frequently called sarcopenia in the oncological literature, which in fact is a misnomer. Our study revealed that the majority of patients with LMM on CT (n = 97) did not meet the diagnostic criteria for sarcopenia (only n = 34) and that patients with presarcopenia only did not have an increased risk of physical decline during treatment. This is supported by recent studies in colorectal and gastric cancer, reporting that sarcopenia has a stronger prognostic impact than LMM alone [6, 25], further underlining the importance to distinguish LMM from sarcopenia.

Muscle mass measurement is the key component in diagnosing sarcopenia, but the method of muscle measurement is contentious and there is no consensus on how to define muscle mass. Furthermore, CT-based muscle measurement might not always be available. Therefore, we related CT-based muscle mass on a continuous scale with easy to perform functional tests. CT-based muscle mass showed a significant correlation with functional tests measuring muscle strength (the FTSTS and the steep ramp test), but not with functional tests measuring physical function (walking speed and the TUG). The associations were not linear, indicating that low muscle mass (presarcopenia) and decreased physical reserve are two different entities. The observation that CT-based muscle mass did not show a linear association with muscle strength and physical function is in line with other observations in the literature. Studies in community-dwelling elderly revealed that changes in muscle mass only explained 5% of the variability of muscle strength decline and that muscle quality seemed to have a slightly stronger correlation with physical function than muscle mass [10, 26, 27].

In this study, severe sarcopenia was almost exclusively present in the patients with hematological malignancies. The higher incidence of severe sarcopenia in patients with hematological tumors might be explained by the fact that a) untreated hematological malignancies often cause rapid deterioration of physical performance with possible excessive muscle loss and b) patients with few physical reserve more often nevertheless proceed to

intensive cytotoxic treatment when compared to patients with solid tumors due to the aggressiveness and nature of hematological malignancies. The number of patients with metastatic solid tumors was too small to draw robust conclusions about the impact of severe sarcopenia on the physical independence of these patients. Further research is needed to determine the incidence of (severe) sarcopenia in advanced cancer patients and a possible association with clinical outcomes.

Our study has several limitations. First, both abdominal CT-images combined with functional tests had to be available for the analysis, which resulted into the exclusion of 36 measurements with available CT but without functional tests, mainly because of a poor clinical condition preventing further treatment or patients refusing undergoing functional tests because of a poor clinical condition. Therefore, a positive selection for patients with good physical performance could have occurred. Second, we included a diverse group of patients with various tumor types and cytotoxic regimens, which had substantial heterogeneity. Therefore, it was not possible to relate the CT-based muscle measurements and functional tests to treatment endpoints, such as dose-limiting or dose-interrupting chemotherapeutic toxicity, and progression free survival. However, this is the first study investigating the association of all levels of sarcopenia according to the current international consensus with a clinical endpoint specifically important in older cancer patients and to describe the overlap between solitary LMM and the syndrome sarcopenia. Our aim was to investigate a possible association between sarcopenia and physical independence in a broad population without excluding specific tumor or treatment groups, in order to provide information about a population as seen as in the general oncological practice. The results should be interpreted in that way, with this study providing a platform for further studies investigating the exact prognostic impact of sarcopenia levels on physical function in well-defined tumor types and treatment settings. Third, we found high ORs for the association between severe sarcopenia and the decline of physical independence, suggesting that severe sarcopenia is a negative prognostic marker for outcome. However, the results were not statistically significant, possibly because of limited power to detect significant outcomes. Furthermore, due to small patient numbers, we were not able to conduct a subgroup analysis of the patients with hematological malignancies only. Therefore, definitive conclusions about the prognostic impact of sarcopenia, especially in hematological malignancies, cannot be drawn, but need to be reassessed in further studies with larger patient numbers. When confirmed in further studies, it is an easy to evaluate marker, which can be used during treatment decision making and patient counseling before treatment.

Conclusion

This study showed that severe sarcopenia seems a promising new marker to identify patients at risk for physical decline after chemotherapy, although further studies with larger patient numbers are needed to definitely confirm this. Furthermore, functional tests measuring muscle strength show some correlation with CT-based muscle mass, but not with tests measuring physical function, indicating that low muscle mass and decreased physical reserve are two different entities. In future oncological studies on this subject, more attention could be paid to the syndrome sarcopenia (impaired muscle function alongside low muscle mass), rather than measuring muscle mass only.

Appendix A

Instrumental Activities of Daily Living (IADL)

Instructions: Circle the scoring point for the statement that most closely corresponds to the patient's current functional ability for each task. The examiner should complete the scale based on information about the patient from the patient him-/herself, informants (such as the patient's family member or other caregiver), and recent records.

A. Ability to use telephone	Score
1. Operates telephone on own initiative; looks up and dials numbers, etc.	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone at all	0

B. Shopping	
1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip	0
4. Completely unable to shop	0

C. Food preparation	
1. Plans, prepares, and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats and serves prepared meals, or prepares meals but does not maintain adequate diet	0
4. Needs to have meals prepared and served	0

D. Housekeeping	
1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")	1
2. Performs light daily tasks such as dishwashing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
4. Needs help with all home maintenance tasks	1
5. Does not participate in any housekeeping tasks	0

E. Laundry	Score
1. Does personal laundry completely	1
2. Launders small items; rinses stockings, etc.	1
3. All laundry must be done by others	0

F. Mode of transportation	
1. Travels independently on public transportation or drives own car	1
2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Travels on public transportation when assisted or accompanied by another	1
4. Travel limited to taxi or automobile with assistance of another	0
5. Does not travel at all	0

G. Responsibility for own medications	
1. Is responsible for taking medication in correct dosages at correct time	1
2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Is not capable of dispensing own medication	0

H. Ability to handle finances	
1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income	1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Incapable of handling money	0

(Lawton & Brody, 1969)

Scoring: The patient receives a score of 1 for each item labeled A – H if his or her competence is rated at some minimal level or higher. Add the total points circled for A – H. The total score may range from 0 – 8. A lower score indicates a higher level of dependence.

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Chapter 7

Discussion and summary

General discussion and summary

This thesis reported on potential clinical factors influencing treatment decision-making and clinical outcomes in cancer patients, with special emphasis on patients with metastatic breast cancer (MBC). In patients with Her2 positive MBC, an important prognostic factor is the response to Her2-targeted therapy. The current standard of care of first-line Her2-targeted therapy in Her2 positive MBC involves dual Her2 blockade with trastuzumab and pertuzumab in combination with a taxane [1], while single Her2 blockade is still conducted in further treatment lines and in many countries where pertuzumab is not available. Generally, Her2-targeted therapy is administered until unacceptable toxicity or disease progression [2], although there is no evidence on the optimal treatment duration [3]. Furthermore, it is unclear whether all patients derive reasonable benefit from Her2-targeted therapies. An attempt to provide a possible answer to this question is provided in **chapter 2**. The remainder of the thesis focused on the utility of body composition parameters in oncological care. General overviews of the current state of the art regarding body composition measurements in oncological care and the evidence on its prognostic impact in solid malignancies is provided in **chapter 3.** In **chapter 4 and 5**, this was specifically addressed in MBC-patients. The position of body composition measurements among other tests assessing physical fitness before systemic treatment is studied in **chapter 6**.

Response to Her2-targeted therapy in metastatic breast cancer.

In **chapter 2**, we revealed that first-line trastuzumab-containing treatment regimens are less effective in patients who have been pretreated with adjuvant trastuzumab, with a median overall survival (OS) almost twice as short (17 vs. 30 months, adjusted HR 1.84, p = 0.01). Similar results were observed for time to next treatment (7 vs. 13 months, adjusted HR 1.65, p = 0.03). Subgroup analyses addressing potential selection bias and multivariate analyses addressing possible confounders, including age, disease-free interval, brain- and visceral metastases, hormone receptor status and response to taxanes, revealed that this survival difference was most likely due to trastuzumab resistance in the patients with failure of adjuvant trastuzumab.

In the studies performed on HER2-positive MBC, which form the basis of the current standard treatment approaches, this group of patients was underrepresented, as these studies were mostly done in patients without previous Her2-targeted therapy. A recent study reviewing survival data of randomized trials revealed that the number of patients treated with adjuvant trastuzumab in these trials was less than 5% [5]. Median progression-free survival (PFS) (10.9 months) and OS (33.3 months) of these trial-patients are comparable with PFS and OS of our patients without previous trastuzumab treatment [5]. Clearly, the current population of Her2-positive MBC-patients, most treated with trastuzumab in the adjuvant setting, might represent a selection of patients with resistance against Her2-targeted therapy, either primary or acquired during adjuvant treatment. These results are concerning, as patient cohorts with trastuzumab-naïve patients in the first-line setting have been largely disappeared in the current daily practice.

Recognizing patients with trastuzumab resistance in advance is an unsolved clinical challenge. Trastuzumab has multiple mechanisms of action and therefore also multiple mechanisms of resistance, including restored Her2-mediated DNA repair, bypass of the Her2 signaling pathway and less antibody dependent cell cytotoxicity (ADCC) activity [6]. The driving resistance mechanism seems at least partly dependent of the choice of previous systemic therapy and is therefore most likely different between patients and time periods. Accordingly, it has been reported that trastuzumab resistance after (neo)adjuvant trastuzumab treatment, concomitantly administered with chemotherapy, is mostly due to the inhibition of Her2-mediated DNA repair [6], while enhancement of ADCC, which is a different resistance mechanism, has been reported after dual Her2-blockade in vitro and in mice [7]. This might be of particular clinical relevance, since the current standard first-line therapy for Her2 positive MBC is dual Her2-blockade with trastuzumab and pertuzumab in combination with a taxane. In summary, our study revealed possible trastuzumab resistance in Her2 positive MBC patients receiving first-line single Her2-blockade with trastuzumab. Further research is warranted on the influence of trastuzumab resistance on first-line dual Her2-blockade, which is applicable to the future population of Her2 positive MBC patients.

Body composition measurements as prognostic markers in metastatic breast cancer

Body composition analyses include measurements of fat mass and fat-free mass (including skeletal muscle), thereby differentiating total body weight into individual compartments. This

seems clinically relevant since metabolic activity differs between compartments and alterations in individual compartments do not occur synchronically [8, 9]. The use of body composition analyses is increasingly studied in cancer patients with muscle mass being the most studied body composition parameter. In **chapter 3,** the literature on low muscle mass (LMM) as a prognostic marker for survival and chemotherapeutic toxicity in various solid and hematological malignancies is reviewed, confirming LMM as a potentially important prognostic maker.

Evidence on the clinical relevance of body composition parameters in breast cancer patients is, however, extremely limited. This gap in the literature was addressed in **chapter 4 and 5** of this thesis. In **chapter 4**, LMM prior to first-line chemotherapy in MBC patients was not associated with overall survival (OS) and time to next treatment (TNT). Strikingly, however, the quality of muscle proved to be a better predictor of outcome than quantitative muscle mass. Muscle quality can be determined by measuring muscle attenuation (density) using CT-imaging, with low muscle attenuation (LMA) reflecting the accumulation of microscopic adipose tissue in muscle [10]. Our study showed that LMA was associated with both OS (adjusted HR 2.04, p = 0.001) and TNT (adjusted HR 1.72, p = 0.01), independently of age, tumor biology and metastatic locations.

In concordance with the literature, LMA being a better prognostic marker than LMM is reported in patients with other tumor types [11, 12] and in older people without cancer [13, 14]. The decrease of muscle mass and muscle quality, especially present in older people [15, 16], is mainly due to age-related endocrine changes, age-related systemic inflammation, physical inactivity and malnutrition [17]. Furthermore, muscle quality deteriorates more rapidly than muscle mass [18] and is associated with older age and obesity (**chapter 3**). In the presence of cancer, muscle wasting is even further accelerated due to cachexia-related processes [19]. In conclusion, LMA is a potentially easy to establish radiological prognostic marker in MBC patients undergoing chemotherapy. Future research is needed to investigate the impact of LMA on survival a) across different disease stages, b) in older patients with MBC, c) during the exploration of other imaging diagnostics measuring muscle than CT and d) when conducting interventions optimizing muscle status.

A study in patients with ovarian cancer showed that body composition measures over time have more prognostic power than a single measurement at diagnosis [20]. Furthermore, the

possibility of excessive muscle loss during specific systemic treatments and its possible clinical impact is unknown. These issues were addressed in **chapter 5**, in order to further explore the prognostic value of LMM and LMA in MBC patients. In this chapter, other known body composition parameters (subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and macroscopic intramuscular adipose tissue (IMAT)) were evaluated as well. Changes in body composition during first-line chemotherapy with FAC and paclitaxel were determined and related to OS.

The main finding of **chapter 5** was that muscle attenuation (MA) significantly decreased during treatment with paclitaxel, while muscle mass and adipose tissue remained stable. The decrease of MA was associated with previous chemotherapy in the adjuvant setting. No changes in body composition were observed during FAC-treatment. OS was not affected by the decrease of MA. Importantly, patients with progressive disease during chemotherapy were excluded to avoid its impact on muscle wasting, so the results are only applicable in patients with controlled disease.

Since OS was not affected by muscle wasting during chemotherapy in our study, our observations are contradicted to the study in patients with ovarian cancer. Possible explanations for this include the difference in tumor type and the fact that the patients in our study were younger, which can cause less prognostic impact of muscle parameters. Nevertheless, the results should be interpreted with caution. Firstly, the number of patients treated with FAC was small, so the power to detect body composition changes during FAC is limited. Further research is warranted to establish body composition alterations during FAC. Secondly, we attempted to investigate the impact of specific cytotoxic agents on body composition parameters, but this remains difficult since other clinical factors are also influencing body composition, such as decreased physical activity and nutritional intake. To determine the true impact of specific systemic treatment regimens on body composition, reference populations without cancer are needed.

However, **chapter 5** shows some results valuable for hypothesis generation on this subject. Paclitaxel could possibly induce more muscle wasting (mass or attenuation) due to the specific nature of taxane-toxicity, such as neuropathy and myalgia and as a consequence: less physical activity and hypothetically, microscopic changes in muscle. Chemotherapy in the past was associated with the decrease of MA after adjustment of other clinical factors,

including MA at baseline. Almost all these previous regimens were taxane-based, supporting the hypothesis that MA is influenced by paclitaxel treatment. This is particularly relevant as decreases in MA are associated with systemic inflammation (comparable with the metabolic changes observed in cancer cachexia) and poor functional status [21]. Therefore, patients with MA decrease might represent frail patients with higher risk of treatment complications during successive chemotherapeutic regimens [22]. Longitudinal prospective studies are needed to investigate a) the impact of individual cytotoxic agents on body composition and b) the correlation of body composition changes during chemotherapy with survival and toxicity.

The road to the implementation of body composition measurements in oncological care

Increasing evidence suggests that body composition measurements should be considered in routine clinical care [23, 24]. However, this is hampered by several problems in the research field of body composition analyses. Besides describing the prognostic impact of low muscle mass in cancer, **chapter 3** further describes potential flaws in the methods of muscle measurement and is summarized below.

Firstly, there is a lack of consensus on the definition of low muscle mass and on a standard approach to measure muscle mass in cancer patients. In almost all oncological studies on this subject, sarcopenia is the used term to describe radiological low muscle mass, a term derived from the literature on geriatric medicine and which is in concordance with the first proposed definition of sarcopenia [25]. However, the relationship between solitary muscle mass loss and physical decline and adverse outcomes is inconsistent in older people, i.e. sarcopenia is a complex geriatric syndrome with multifactorial etiology [26]. The syndrome “sarcopenia” has therefore been redefined to the combination of low muscle mass and either low muscle strength, or impaired physical performance [27]. The distinguishement of low muscle mass and sarcopenia proved also to be relevant in oncological care, as the prognostic impact of sarcopenia on survival was higher than the prognostic impact of solitary LMM in both colorectal and gastric cancer [28, 29]. Functional tests measuring muscle strength and physical performance are not widely available in oncological care, so more research is needed on the relevance of adding functional tests to muscle measurement in cancer patients. Recognized tests for determining muscle strength and physical performance respectively are hand grip strength measured by a Jamar hand dynamometer (Lafayette Instrument Co. Lafayette, IN, http://www.lafayetteinstrument.com) and walking speed at usual pace in meters

per second [27]. Recommended cut-offs for low handgrip strength and low walking speed are <26 kg in males and <16 kg in females [30] and a walking speed ≤0.80 m/s [27]. However, the first step in oncological care is getting the nomenclature of muscle wasting right and recognizing that radiological LMM and sarcopenia are two different entitities.

Secondly, the definition of LMM is unclear in terms of reference values to diagnose LMM. In geriatric medicine, a widely used definition of LMM is muscle mass below two standard deviations below muscle mass in young adults [25], which is usually measured using other imaging diagnostics than in oncological care. CT-imaging is considered the gold standard of muscle measurement after cadaver validation and most widely used in oncological care due to high availability but no such reference populations are described for muscle measurement using CT-imaging. These populations are needed to put the reported prevalence and prognostic impact of LMM across different oncological studies into perspective and to unravel the impact of individual cytotoxic drugs, targeted therapies, and impairments because of treatment toxicity on muscle. Future studies constructing reference populations for CT-based muscle measurements should also adjust these populations for age, gender, race and body mass index, as all these parameters influence muscle. Lower muscle mass is particular described in older patients [31], patients with lower BMI [32], males [33] and Asian patients (compared to caucasian ethnicity) [34]. In the absence of proper reference populations, current widely used cut-off points for LMM and LMA are corrected for height and weight and proposed by a large study in patients with different solid malignancies after optimum stratification for overall survival **(table 1**)[32].

Table 1. Reference values for muscle parameters.

	Low muscle mass	**Low muscle attenuation**
Body mass index <30 kg/m^2	Males: <53 cm^2/m^2 Females: <41 cm^2/m^2	<41 Hounsfield Units
Body mass index ≥30 kg/m^2	Males: <43 cm^2/m^2 Females: <41 cm^2/m^2	<33 Hounsfield Units

Thirdly, other body composition parameters than muscle mass are understudied in the oncological research field. Studies on muscle quality (attenuation), subcutenaous adipose tissue and visceral adipose tissue are scarce. These parameters are, however, also of clinical importance because of the possible association between muscle quality and physical function

[35, 36] and the possible association of body composition alterations and chemotherapeutic pharmacokinetics. It has been described that the systemic clearance of hydrophilic chemotherapeutic drugs correlate well with the fat-free mass [37, 38], so in patients with LMM in relation to their length and weight, a lower volume of distribution of chemotherapeutic drugs is observed, resulting in higher systemic drug levels and consequently, more chemotherapeutic toxicity [39-41]. Vice versa, it could be hypothesized that low visceral/subcuteneous adipose tissue might be associated with toxicity of lipophilic drugs, such as paclitaxel.

A first step towards recognizing which muscle parameters and functional tests could be of clinical utility is provided in **chapter 6**. In this chapter, the association between different levels of sarcopenia and a decline of physical independence and the concordance between muscle parameters and functional tests were studied in elderly patients with different cancer types. Elderly patients were specifically included as these patients might derive the most clinical benefit of body composition-based treatment decisions and because adequate parameters to assess physical function are warranted in this population. Severe sarcopenia seemed positively correlated with the level of physical independence according to the scale of Lawton and Brody, while 40% of these patients were classified as having a WHO-performance score of 0 or 1 according to their treating physician. This indicates that sarcopenia levels might serve as an additional clinical marker to assess treatment risks in older cancer patients. Further research is needed on the clinical consequences of pre-treatment severe sarcopenia in individual tumor types. Functional tests measuring muscle strength showed a significant correlation with CT-based muscle mass, while functional tests measuring physical performance did not. In contrast, all functional tests showed significant correlations with muscle attenuation, supporting the hypothesis that muscle quality is more representative for physical function than muscle quantity. The statement that sarcopenia and low muscle mass are two different entities was also confirmed in this study, as 75% of the patients were considered as having LMM, while only half of the patients fulfilled the diagnostic criteria of sarcopenia. However, functional tests were insufficiently able to detect patients with LMM or LMA and could therefore not substitute CT-based muscle measurements.

Conclusion

Body composition analyses are potential prognostic factors for survival in cancer patients, with muscle quality better than muscle quantity. The studies in this thesis are among the first confirming this in metastatic breast cancer as well. More specifically for metastatic breast cancer, patients with Her2 positive disease derive less clinical benefit from first-line trastuzumab-based therapy after failure of trastuzumab in the adjuvant setting. General recommendations derived from this thesis for further research on both topics include:

1. The influence of trastuzumab resistance on first-line dual Her2-blockade.
2. The exploration of other body composition parameters than muscle mass, i.e. muscle attenuation, subcutaneous adipose tissue, visceral adipose tissue and intramuscular adipose tissue in cancer patients.
3. The additional prognostic value of functional tests besides muscle measurements.
4. The impact of individual cytotoxic agents on body composition.
5. Possible pharmacokinetic effects of cytotoxic agents due to body composition changes and their relation with treatment toxicity.

To work towards the possible use of body composition parameters in oncological care, studies are needed to investigate the association of abnormal CT-based body composition measurements, derived from reference populations, and clinical endpoints including survival and treatment toxicity. In older cancer patients, geriatric endpoints such as the maintenance of physical independence or the ability to complete the treatment as planned are often just as important as oncological endpoints. From there, intervention trials are needed to study the clinical impact of optimizing muscle status.

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Chapter 8

Nederlandse samenvatting

Dankwoord

Curriculum vitae

PhD portfolio

Inleiding

Er is een grote verscheidenheid aan klinische factoren die de behandeling en prognose van patiënten met kanker beïnvloedt. Dit proefschrift onderzoekt enkele van deze factoren, waarbij het focus ligt op patiënten met uitgezaaide borstkanker. Bij patiënten met Her2 positieve uitgezaaide borstkanker, is de respons op anti-Her2 therapie een belangrijke voorspeller voor een langere overleving. De huidige standaard eerstelijns behandeling bestaat uit blokkade van de Her2-receptor, met twee verschillende middelen (trastuzumab en pertuzumab) in combinatie met chemotherapie (meestal een taxaan-bevattend schema). In vervolgbehandelingslijnen en in veel landen waar pertuzumab (nog) niet beschikbaar is, berust de Her2-doelgerichte behandeling nog steeds op blokkade van de Her2-receptor door maar één middel, namelijk trastuzumab. Het is echter niet bekend of iedereen wel evenveel baat heeft bij deze therapie. In **hoofdstuk 2** wordt getracht een antwoord te geven op deze vraag. De rest van het proefschrift gaat over de toepasbaarheid van het bepalen van lichaamssamenstelling in de oncologische zorg, aangezien steeds duidelijker wordt dat de lichaamssamenstelling een belangrijke invloed heeft op de prognose van patiënten met kanker en het optreden van bijwerkingen tijdens chemotherapie. De huidige stand van zaken met betrekking tot het gebruik van deze parameters in de oncologie en de invloed op de prognose wordt beschreven in **hoofdstuk 3.** In **hoofdstuk 4 en 5** wordt dit specifiek verder onderzocht bij patiënten met uitgezaaide borstkanker. Verder zou de prognostische waarde van veranderingen in lichaamssamenstelling vooral groot kunnen zijn bij patiënten op leeftijd. Dit wordt onderzocht in **hoofdstuk 6.** Het gekozen eindpunt in dit hoofdstuk is vooral voor de oudere patiënt van belang, namelijk het behoud van zelfstandig functioneren. Verder wordt in **hoofdstuk 6** bekeken hoe goed metingen van lichaamssamenstelling overeenkomen met testen die veel gebruikt worden om het lichamelijk functioneren van een patiënt in kaart te brengen.

Respons op Her2 doelgerichte therapie vanwege uitgezaaide borstkanker.

Uit **hoofdstuk 2** blijkt dat eerstelijns behandelingsschema's met trastuzumab minder effectief zijn bij patiënten die in het verleden al eerder met trastuzumab zijn behandeld (in dit geval als onderdeel van de adjuvante therapie). Deze patiënten hadden een bijna tweemaal zo korte overleving vergeleken met patiënten die nog nooit eerder behandeld waren met trastuzumab

(17 vs. 30 maanden). Vergelijkbare resultaten werden gezien voor de tijd tot het nodig was om een vervolgbehandeling te starten (7 vs. 13 maanden). Subgroep analyses en correcties voor andere klinische factoren lieten zien dat dit overlevingsverschil onafhankelijk bleek van leeftijd, de tijd tussen de primaire diagnose en het ontstaan van uitzaaiingen, de locatie van de uitzaaiingen, de oestrogeenexpressie en de respons op chemotherapie. De verminderde effectiviteit van eerstelijns trastuzumab is het meest waarschijnlijk het gevolg van resistentie tegen trastuzumab.

Patiënten met een uitgezaaid mammacarcinoom die eerder trastuzumab hebben gehad als adjuvante behandeling hebben een slechtere uitkomst op trastuzumab-bevattende chemotherapie. Dit is erg belangrijk omdat deze patiënten ondervertegenwoordigd zijn (maar 5% van het totaal) in oorspronkelijke klinische studies die de effectiviteit van palliatieve Her2-doelgerichte therapie onderzochten. De belangrijkste reden hiervoor is dat veel van deze onderzoeken zijn uitgevoerd bij patiënten die nog nooit eerder Her2 doelgerichte therapie hebben gehad. De mediane progressie-vrije en totale overleving van deze patiënten is vergelijkbaar met die van de patiënten uit onze studie die nog nooit eerder trastuzumab hebben gehad. De huidige populatie patiënten met uitgezaaide borstkanker heeft echter meestal in de adjuvante setting trastuzumab gehad, en daardoor kan er hier sprake zijn van een selectie van patiënten met resistentie tegen trastuzumab, zoals onze studie suggereert.

Het vooraf herkennen van patiënten met trastuzumab resistentie is een onopgelost probleem. Trastuzumab heeft verschillende werkingsmechanismen en daardoor zijn er ook verschillende mechanismen van resistentie beschreven, zoals: een herstel van Her2-gemedieerde DNA-reparatie, omzeiling van de Her2-signaalroute en een verminderd celdodend vermogen van antilichamen. Het resistentiemechanisme lijkt gedeeltelijk afhankelijk van de voorgaande systemische therapie en kan dus verschillend zijn tussen patiënten en tijdsperiodes. In vitro en in muizen is aangetoond dat het resistentiemechanisme na Her2-blokkade met één middel verschilt van het resistentiemechanisme na Her2-blokkade met twee middelen. Dit kan klinisch relevant zijn, aangezien de huidige eerstelijns Her2-doelgerichte therapie met twee middelen wordt uitgevoerd en dus weer anders is dan voorheen. Samenvattend liet onze studie mogelijke trastuzumabresistentie zien in patiënten met eerstelijns Her2-doelgerichte therapie. Er is meer onderzoek nodig om de invloed van trastzumabresistentie op duale Her2-blokkade in kaart te brengen, wat belangrijk zal zijn voor de toekomstige populatie patiënten met Her2-positieve uitgezaaide borstkanker.

De prognostische relevantie van lichaamssamenstelling bij uitgezaaide borstkanker.

Het bepalen van de lichaamssamenstelling bevat het meten van de hoeveelheid vetmassa en vetvrije massa (skeletspierweefsel valt ook onder dit laatste), waardoor het totale lichaamsgewicht onderverdeeld kan worden in verschillende lichaamscompartimenten. Dit lijkt klinisch relevant, aangezien de metabolische activiteit verschilt tussen deze compartimenten en veranderingen in de hoeveelheid vet- en vetvrije massa niet synchroon optreden. Het gebruik van parameters voor lichaamssamenstelling wordt steeds meer onderzocht in patiënten met kanker, waarbij de hoeveelheid spiermassa de meest onderzochte parameter is. **Hoofdstuk 3** bevat een overzicht van alle literatuur over de prognostische waarde van een lage spiermassa voor overleving en chemotherapeutische toxiciteit in verschillende solide en hematologische maligniteiten. Hierbij werd bevestigd dat een lage spiermassa invloed heeft op de prognose van deze patiënten.

Anderzijds is er zeer weinig bewijs voor de klinische relevantie van de lichaamssamenstelling bij patiënten met borstkanker. Dit hiaat in de literatuur wordt beschreven in **hoofdstuk 4 en 5** van dit proefschrift. In **hoofdstuk 4** wordt getoond dat een lage spiermassa voorafgaand aan eerstelijns palliatieve chemotherapie niet geassocieerd is met de totale overleving en de tijd tot aan de volgende systemische behandeling bij patiënten met uitgezaaide borstkanker. Echter was de spierkwaliteit wel van belang en deze blijkt een duidelijkere relatie te hebben met prognose dan spierkwantiteit. De spierkwaliteit kan bepaald worden door het meten van de spierdichtheid met behulp van CT-beelden, waarbij een lage spierdensiteit een toename van intramusculair microscopisch vet vertegenwoordigt. De studie in **hoofdstuk 4** laat zien dat een lage spierdensiteit geassocieerd was met zowel totale overleving (HR 2.04, $p = 0.001$) als de tijd tot aan de volgende noodzakelijke systemische behandeling (HR 1.72, $p = 0.01$). Dit was onafhankelijk van leeftijd, tumorbiologie en locaties van uitzaaiingen.

De observatie dat een lage spierkwaliteit een betere prognostische marker is dan een lage spiermassa is in overeenstemming met de literatuur over patiënten met andere soorten kanker en oudere mensen zonder kanker. De afname van de spiermassa en spierkwaliteit is vooral aanwezig in ouderen, en is vooral het gevolg van leeftijd gerelateerde endocrinologische veranderingen, leeftijd gerelateerde systemische inflammatie, verminderde fysieke activiteit en ondervoeding. Daarnaast neemt de spierkwaliteit sneller af dan de spiermassa en is de spierkwaliteit lager in obese patiënten. In de aanwezigheid van een maligniteit wordt het

spierverlies zelfs versneld door cachexie-gerelateerde processen. Concluderend is een lage spierdensiteit een makkelijk te meten radiologische marker, die belangrijk kan zijn voor de prognose van patiënten met uitgezaaide borstkanker die chemotherapie krijgen. Er zijn meer studies nodig om de impact van een lage spierdensiteit op de overleving te bepalen:

- In verschillende ziektestadia
- In oudere patiënten met borstkanker
- Als de metingen met andere beeldvormende diagnostiek dan CT wordt gedaan
- Als er interventies worden gedaan om de spierstatus te optimaliseren.

Een studie in patiënten met eierstokkanker toonde aan dat longitudinale lichaamssamenstellings-metingen mogelijk meer prognostische waarde hebben dan een enkele meting bij diagnose. Daarnaast is het onbekend of er fors spierverlies als gevolg van individuele chemotherapeutica optreedt en wat de klinische impact hiervan is. Deze vragen werden bestudeerd in **hoofdstuk 5**. In deze studie werden er behalve spiermassa en spierkwaliteit ook andere lichaamscompartimenten bepaald, te weten: subcutaan vet, visceraal vet en macroscopisch intramusculair vet. De veranderingen in lichaamssamenstelling tijdens eerstelijns behandeling met 5-fluorouracil/adriamycine/cyclofosfamide (FAC) en paclitaxel vanwege uitgezaaide borstkanker werden retrospectief bepaald en gerelateerd aan de totale overleving.

De belangrijkste bevinding van de studie in **hoofdstuk 5** was dat spierdensiteit significant afnam tijdens behandeling met paclitaxel, terwijl de spiermassa en de vetmassa stabiel bleven. De afname van de spierkwaliteit was geassocieerd met chemotherapie in het verleden (adjuvant). Er werden geen veranderingen in lichaamssamenstelling waargenomen tijdens behandeling met FAC. De afname van de spierkwaliteit had deze keer geen invloed op de totale overleving. Het is daarbij belangrijk om te noemen dat patiënten met progressieve ziekte tijdens de behandeling zijn geëxcludeerd om de impact van progressieve kanker op spierverlies te vermijden in de analyses. De resultaten zijn dus alleen van toepassing op patiënten waarbij de ziekte tijdens chemotherapie onder controle is.

In onze studie werd gezien dat de totale overleving niet werd beïnvloed door spierverlies tijdens chemotherapie. Dit is niet in overeenstemming met de studie bij de patiënten met eierstokkanker. Mogelijke verklaringen hiervoor zijn het verschil in tumortype en het feit dat de patiënten in onze studie jonger waren, wat kan resulteren in een minder prognostisch effect

van spierparameters. Desondanks moeten onze resultaten voorzichtig worden geïnterpreteerd. Ten eerste was het aantal patiënten dat behandeld werd met een FAC-schema klein, dus de power om verschillen in lichaamssamenstelling tijdens FAC te detecteren was beperkt. Meer onderzoek is hiervoor nodig. Ten tweede was ons doel om de impact van specifieke cytostatica op de lichaamssamenstelling in kaart te brengen, maar dit blijft lastig als er ook andere factoren zijn die de lichaamssamenstelling beïnvloeden en die we niet meten, zoals verminderde fysieke activiteit door chemotherapie en voedselintake. Er zijn goede controlegroepen nodig met patiënten zonder kanker om de echte impact van cytostatica op de lichaamssamenstelling te bepalen.

Toch laat **hoofdstuk 5** enkele waardevolle resultaten zien die hypothese-genererend zijn. Er kan mogelijk meer spierverlies (zowel kwantiteit als kwaliteit) tijdens behandeling met paclitaxel optreden, omdat dit middel specifieke spier-beïnvloedende toxiciteit geeft, zoals neuropathie en spierpijnen, met als gevolg minder fysieke activiteit en theoretisch gezien, microscopische veranderingen in de spier zelf. Chemotherapie in het verleden was geassocieerd met de afname van de spierkwaliteit na correctie voor andere factoren. Deze voorgaande chemotherapie was meestal een taxaan-schema, wat de theorie dat de spierkwaliteit wordt beïnvloed door paclitaxel versterkt. Dit is vooral klinisch relevant aangezien een afname van de spierkwaliteit geassocieerd is met systemische inflammatie (vergelijkbaar met de systemische inflammatie bij kanker cachexie) en slechte lichamelijke functie. Daarom kan een dalende spierkwaliteit een teken zijn van kwetsbaarheid bij patiënten met een hoger risico op complicaties tijdens opeenvolgende lijnen chemotherapie. Er zijn longitudinale prospectieve studies nodig om:

- De impact van individuele cytostatische middelen op de lichaamssamenstelling te bepalen.
- De correlatie tussen veranderingen in lichaamssamenstelling en overleving of toxiciteit te bepalen.

De weg naar het opnemen van de bepaling van lichaamssamenstelling in de oncologische zorg

Er is toenemend bewijs dat het bepalen van de lichaamssamenstelling mogelijk opgenomen zou moeten worden in de standaard zorg. Dit wordt echter bemoeilijkt door verschillende problemen bij het wetenschappelijk onderzoek in dit veld. Naast het beschrijven van de prognostische waarde van een lage spiermassa bij patiënten met kanker laat **hoofdstuk 3**

verder zien wat de knelpunten zijn in het huidige onderzoek naar het meten van lichaamscompartimenten.

Ten eerste is er geen consensus over een definitie van een lage spiermassa en er is ook geen standaardmethode om dit te meten bij patiënten met kanker. In bijna alle oncologische studies wordt de term “sarcopenie” gebruikt om een lage spiermassa aan te geven. Deze term is afkomstig uit de geriatrische literatuur en de eerste definitie van sarcopenie was inderdaad enkel een lage spiermassa. Er is echter bij ouderen geen lineaire relatie tussen een lage spiermassa en een verminderd lichamelijk functioneren. Daarom wordt sarcopenie beschouwd als een complex geriatrisch syndroom met verschillende oorzaken. Er is om die reden nu een nieuwe definitie van sarcopenie, te weten: een lage spiermassa in combinatie met een lage spierkracht en/of verminderd lichamelijk functioneren. Het onderscheid tussen een lage spiermassa en sarcopenie is ook klinisch van belang in de oncologie, aangezien studies hebben aangetoond dat de prognostische impact van sarcopenie veel groter was dan de prognostische impact van enkel een lage spiermassa. Veelgebruikte geriatrische testen om een verminderd lichamelijk functioneren in kaart te brengen zijn echter niet veel voorhanden in de oncologische zorg, dus er zijn meer studies nodig om het toevoegen van deze testen aan de standaard oncologische zorg te onderzoeken. Erkende testen voor een lage spierkracht en een verminderd lichamelijk functioneren zijn respectievelijk: de spierkracht van de hand meten met een Jamar hand dynamometer en het bepalen van de loopsnelheid in meter per seconde. Maar de eerste stap in de oncologie zou moeten zijn de nomenclatuur van spierverlies-fenomenen helder te hebben en te herkennen dat sarcopenie en spierverlies twee verschillende entiteiten zijn, die slechts deels met elkaar overlappen.

Ten tweede is de definitie van een lage spiermassa ook onduidelijk, aangezien goede referentiewaardes voor een lage spiermassa niet beschikbaar zijn. Een veelgebruikte definitie in de geriatrische literatuur is een spiermassa die meer dan twee standaarddeviaties ligt onder de gemiddelde spiermassa van een jongvolwassene. Meestal zijn deze metingen met andere apparatuur gedaan dan CT. CT-beeldvorming wordt echter gezien als de gouden standaard voor spiermetingen, vanwege validatie in kadavers en wordt het meest gebruikt in de oncologie. Er zijn echter geen referentiepopulaties beschikbaar voor deze methode. Deze referentiepopulaties zijn wel nodig om de prevalentie van een lage spiermassa en de prognostische waarde in verschillende oncologische studies te interpreteren en om de impact van cytostatica, doelgerichte therapie en de klinische gevolgen van spierverlies in kaart te

brengen. Toekomstige studies moeten zich richten op het beschrijven van referentiepopulaties voor spiermetingen met behulp van CT-beeldvorming. Deze spiermetingen moeten in verschillende leeftijds- en BMI-groepen en per ras en geslacht bepaald worden, aangezien al deze parameters de hoeveelheid spiermassa bepalen. Zolang zulke referentiepopulaties nog niet beschikbaar zijn, zijn eerder bepaalde afkappunten voor een lage spiermassa een goed alternatief, zoals de afkappunten die bepaald zijn in een studie met meer dan 1000 patiënten met solide maligniteiten.

Ten derde is er nog relatief weinig aandacht in de oncologische literatuur voor andere metingen van lichaamssamenstelling dan spiermassa. Er zijn weinig studies naar de kwaliteit van de spier en naar de metingen van diverse vetcompartimenten (subcutaan, visceraal en intramusculair). Deze parameters zijn echter ook belangrijk vanwege hun mogelijke associatie met lichamelijk functioneren en de mogelijke interacties met de farmacokinetiek van chemotherapeutische middelen. In de literatuur is herhaaldelijk beschreven dat de systemische klaring van hydrofiele cytostatica een sterke correlatie heeft met de hoeveelheid vetvrije massa. Daarom hebben patiënten met een relatief lage spiermassa een lager distributievolume van deze middelen, resulterend in hogere plasmaspiegels en daardoor mogelijk meer toxiciteit. Andersom zou dit ook kunnen gelden voor een mogelijke relatie tussen een relatief lage vetmassa en plasmaspiegels van lipofiele cytostatica, zoals paclitaxel.

Een eerste stap in de richting van de implementatie van lichaamssamenstellingsmetingen in de oncologische zorg zou een inventarisatie kunnen zijn van welke spiermetingen en functionele testen gebruikt kunnen worden in de praktijk. Dit wordt beschreven in **hoofdstuk 6**. In dit hoofdstuk worden de overeenkomsten tussen spiermassa en spierkwaliteit en functionele testen in oudere patiënten met kanker onderzocht. Ook wordt de relatie tussen verschillende gradaties van sarcopenie en verlies van zelfstandigheid bestudeerd. Ouderen zijn specifiek geïncludeerd omdat deze patiënten waarschijnlijk het meeste voordeel hebben van beslissingen op basis van de lichaamssamenstelling. Een tweede reden is dat er meer duidelijkheid nodig is over testen die nauwkeurig het lichamelijk functioneren van ouderen met kanker kunnen beschrijven. Testen die de spierkracht meten lieten een significante correlatie zien met de spiermassa, terwijl dit niet gold voor testen die de mobiliteit in kaart brengen. Daarentegen lieten alle functionele testen een significante correlatie zien met de spierkwaliteit. Dit steunt opnieuw de theorie dat de spierkwaliteit meer zegt over het lichamelijk functioneren dan de spierkwantiteit. De stelling dat sarcopenie en een lage

spiermassa niet hetzelfde zijn werd opnieuw bevestigd in deze studie, aangezien 75% van de patiënten een lage spiermassa had volgens de afkappunten in de literatuur, maar minder dan de helft ook echt sarcopenie had volgens de meest recente criteria. Toch waren functionele testen niet goed in staat om patiënten met een lage spiermassa of kwaliteit te identificeren en daarom kunnen zij CT-gebaseerde spiermetingen niet vervangen. Patiënten met ernstige sarcopenie leken na chemotherapie vaker zo lichamelijk achteruit te zijn gegaan dat er langdurig meer zorg voor de dagelijkse activiteiten nodig was. Van belang is dat 40% van deze patiënten met ernstige sarcopenie "fit" genoeg werd beschouwd voor chemotherapie door de behandelend arts. In toekomstige studies moet daarom eerder aandacht besteed worden aan het (geriatrische) syndroom sarcopenie dan aan individuele spiermetingen.

Conclusie

De metingen van de verschillende lichaamscompartimenten (vet en vetvrij) zijn mogelijk belangrijke prognostische factoren voor de overleving van patiënten met kanker, waarbij de spierkwaliteit beter is dan de spierkwantiteit. De studies in dit proefschrift behoren tot de eerste studies wereldwijd die dit ook bevestigen bij patiënten met uitgezaaide borstkanker. Specifiek voor deze patiënten is het ook belangrijk dat er minder profijt van Her2-doelgerichte therapie is na blootstelling aan trastuzumab in de adjuvante setting. Aan de hand van dit proefschrift zijn de aanbevelingen voor toekomstig onderzoek naar beide onderwerpen als volgt:

- Onderzoek naar de invloed van trastuzumab resistentie op de effectiviteit van duale Her2-blokkade.
- Verder oncologisch onderzoek naar andere lichaamssamenstellingsparameters dan enkel spiermassa, te weten: spierkwaliteit (spierdensiteit), subcutaan vet, visceraal vet en intramusculair vet.
- Onderzoek naar de toegevoegde waarde van functionele testen naast spiermetingen.
- Onderzoek naar de impact van individuele chemotherapeutische middelen op de lichaamssamenstelling.
- Onderzoek naar mogelijke farmacokinetische effecten door veranderingen van lichaamssamenstelling en de relatie met chemotherapeutische toxiciteit.

Om verder te werken naar een mogelijke toekomst voor het bepalen van de lichaamssamenstelling bij patiënten met kanker, zijn er studies nodig die de associatie van een abnormale lichaamssamenstelling (bepaald met behulp van referentiepopulaties) en oncologische uitkomsten onderzoeken. Vervolgens zijn er interventiestudies nodig die de spierstatus optimaliseren, en onderzoeken of de overleving en kwaliteit van leven van patiënten met kanker hierdoor verbeterd kan worden. Het is daarbij van essentieel belang op te merken dat geriatrische studie-eindpunten zoals het behoud van zelfstandigheid of het kunnen doorstaan van een behandeling met acceptabele toxiciteit soms belangrijker zijn voor oudere patiënten met kanker dan de oncologische uitkomsten.

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Promoveren, dat was iets wat vrij onverwacht op mijn pad kwam. Ik was werkzaam als arts-assistent niet in opleiding interne geneeskunde in het Albert Schweitzer ziekenhuis en ik was nietsvermoedend visite aan het lopen op de locatie Zwijndrecht toen ik een telefoontje kreeg van Mark-David Levin met direct de vraag: “Wil jij onderzoek doen, met als doel promoveren?”

Na ampel beraad was ik ineens uit de kliniek en vond ik mijzelf terug achter een computerscherm. Nu aan het eind van deze rit ben ik een aantal mensen dank verschuldigd, aangezien dit proefschrift niet tot stand zou zijn gekomen zonder hen.

Als eerste wil ik mijn promotor noemen, prof. dr. Stefan Sleijfer. Beste Stefan, jij was meteen welwillend om mijn promotor te zijn toen ik in 2014 voor het eerst de Daniël den Hoed kwam binnenzeilen met mijn onderzoek vanuit de periferie. Wat heb je mij ontzettend geholpen met het schrijven van de artikelen en met het brainstormen over de inhoud van het onderzoek. Jouw feedback kwam vaak dezelfde dag of de volgende dag, hoe je het doet is mij een raadsel. Bedankt dat je zoveel tijd voor mij hebt genomen en mij zoveel hebt geleerd over het uitvoeren van wetenschappelijk onderzoek.

Daarnaast mijn copromotor, dr. Agnes Jager. Lieve Agnes, bedankt voor je enorme hulp de afgelopen jaren. Ik heb bewondering voor jouw kennis van de oncologie en de wijze waarop je mij hebt begeleid. Ik heb veel van je geleerd over de klinische overwegingen van een oncoloog en de behandeling van borstkanker. Één van de dingen die ik leuk vond aan jou was dat je vaak een stuk of 20 opmerkingen in mijn artikel zette die aangepakt moesten worden en dan even later vroeg of ik niet van streek was door zoveel kritiek. Zoals ik vaak heb geantwoord: “Nee, in het geheel niet, want je bracht het altijd op een uitzonderlijk vriendelijke manier.” Bedankt voor alles en hopelijk meer samenwerking in de toekomst.

Mark-David, jou ben ik ook veel dank verschuldigd als 2^{e} copromotor en vanwege het feit dat jij degene was die het überhaupt mogelijk heeft gemaakt om mijn onderzoek uit te voeren. Niets was te gek, ik mocht naar alle congressen en cursussen die ik nodig achtte. Jij bent

degene met wie ik het meest te maken had op de werkvloer, bedankt voor alle tijd die je daarin hebt gestoken en de kansen die ik daardoor heb gehad.

Leden van de kleine commissie, prof. dr. J.N.M. IJzermans, prof. dr. J.L.C.M. van Saase en prof. dr. H.M.W. Verheul, hartelijk dank voor jullie bereidheid om mijn proefschrift te beoordelen.

Bij dit onderzoek zijn diverse mensen uit het Albert Schweitzer ziekenhuis nauw betrokken geweest. Marc en Joost, bedankt voor jullie respectievelijk radiologische en statistische ondersteuning van dit onderzoek. Marc, door jou heb ik het genoegen gehad het één en ander op te steken van CT-beeldvorming, iets wat ik niet in mijn eigen klinische omgeving zou hebben geleerd. Joost, jij bent als statisticus verbonden aan het Erasmus MC, maar werkt als statistisch consulent in Dordrecht. Dit schept ontelbare mogelijkheden voor wetenschappelijk onderzoek in het Albert Schweitzer ziekenhuis en jij hebt mij met eindeloos geduld van alles bijgebracht over data-analyse. Deze kennis kan ik mijn leven lang gebruiken.

De afdeling geriatrie wil ik bijzonder bedanken voor hun gastvrijheid en flexibiliteit. Dit geldt zowel voor de geriaters zelf, als voor de verpleegkundigen en poli-assistentes. Jullie hebben al die jaren spreekkamers op jullie polikliniek, verpleegkundigen en tijd beschikbaar gesteld aan mijn onderzoek. Als kersverse onderzoeker was het een warme omgeving om in terecht te komen, bedankt. Marianne en Patricia, jullie komt speciale lof toe voor het includeren van alle patiënten.

Tijdens dit promotie-onderzoek heb ik mooie vriendschappen gemaakt die ik anders niet had gehad. Marieke, als internist-ouderengeneeskunde met interesse voor de oncologie was jij nauw betrokken bij het mogelijk maken en de uitvoer van mijn onderzoek. Maar daarnaast was je ook een maatje. We hebben het ontzettend gezellig gehad op congressen, tijdens het lunchen en aan de telefoon. Bedankt dat je altijd voor me klaar stond en mij telkens jouw motto voorhield: “De aanhouder wint.”

Karlijn, mijn collega-promovendus uit het Albert Schweitzer ziekenhuis. Niet alleen voorkwam jij dat ik tegen mezelf ging praten uit eenzaamheid als onderzoeker, maar ook hebben we zo ontzettend veel lol gehad. Zowel in het ziekenhuis als daarbuiten. We hebben 2.5 jaar lang een kamer gedeeld, 40 uur per week, dat is nogal wat. Ja, dan moet je wel

vrienden worden. Bedankt voor de vele onderzoeks-gerelateerde hilarische momenten die we hebben gehad, onder andere het delen van plaatjes met PhD-comics.

Delal, mijn collega-promovendus uit de Daniel den Hoed kliniek. Wij hebben elkaar leren kennen vanwege het feit dat we dezelfde promotor hebben. Door de jaren heen is dat uitgegroeid tot een vriendschap waarbij we om de paar weken uiteten gaan om even bij te kletsen. En om alle (soms hilarische) verhalen over submissies en reviewers te delen. Echt heel gezellig en motiverend om weer door te gaan. Ook na mijn promotie houden we dat natuurlijk zo, en uiteraard kijk ik uit naar jouw boekje.

Etienne, jou heb ik leren kennen door de vele uren die ik op de polikliniek geriatrie heb doorgebracht. Bedankt voor de gezellige koffie-momenten die mij vooral herinnerden aan het feit dat er ook andere zaken zijn dan onderzoek. Jij kon eventuele onderzoek-stress altijd goed relativeren en dat houdt me bij de les.

Ook andere collega's wil ik bedanken voor hun interesse en medewerking aan mijn onderzoek. Dit kon zowel op inhoudelijk als persoonlijk gebied zijn. Inge, Peter en Crista, jullie zijn gedurende 3 jaar lang een luisterend oor geweest voor mij en ik kon op jullie input rekenen indien nodig. Claire, jij was er iets korter dan 3 jaar, maar zeker niet minder waardevol. Dank hiervoor.

Diverse vrienden in de privésfeer zijn op de achtergrond continu aanwezig en hebben daardoor een speciale plaats in mijn hart. Anne, Romeo, Timothy, Regina en Floor, jullie hebben mij altijd door dik en dun gesteund. Ik mocht praatjes komen oefenen, bordspelletjes komen spelen, komen logeren en alles wat verder nog nodig is om goed te gedijen als promovendus. Lisa, je bent de beste nicht die ik me kan wensen en ookal woon jij in Suriname en ik hier, toch was jij er altijd als het moest. Zoals dat gedurende mijn hele leven is geweest.

Lieve Mike, als mijn bijna-even-oude broer(tje) en cardioloog in opleiding had jij altijd een frisse tegenzin om ook maar iets van mijn artikelen te lezen. Want de oncologie, nee, dat is niet jouw vak. Ookal bleef ik, dat wetende, mijn artikelen met goede moed in jouw mailbox deponeren, om een uur later te appen: "Heb je het al gelezen?". Maar juist dat kan ik alleen bij een broer doen. Wij blijven een team, bedankt dat je er bent.

Lieve mama en papa, jullie zijn de belangrijkste mensen in mijn leven. Zonder jullie was ik nergens. Ik kan niet uitdrukken hoeveel ik van jullie hou en hoe belangrijk jullie zijn geweest voor het goed afronden van mijn promotie-onderzoek. En overigens voor alles wat ik tot nu toe heb mogen bereiken in mijn carrière als arts. Ik zal altijd voor jullie klaarstaan, bedankt voor jullie liefde.

Aan het eind gekomen van mijn dankwoord rest mij te zeggen dat ik hoofdstuk 2 van dit proefschrift opdraag aan mijn lieve zuster Hanna, die tijdens dit promotie-onderzoek veel te jong is gestorven aan het probleem dat ik in dat hoofdstuk heb onderzocht. U wilde erbij zijn als dit boek af was, maar dat kon helaas niet. Tijdens het schrijven van dat hoofdstuk kwam ik erachter wat elke patiënt in die studie en haar familie heeft doorgemaakt. Ik had het liever niet willen weten, en het maakte het soms moeilijk om het hoofdstuk op te schrijven, maar net als u laat ik me niet uit het veld slaan. Tijdens het onderzoek niet en in de toekomst ook niet.

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PhD portfolio

Curriculum vitae

Hánah Nicole Rier was born on 13th April 1987 in Amsterdam. She graduated from secondary school in 2005. Thereafter, she started her study Biomedical Sciences at the University of Amsterdam. After 1 year, she quitted this study and attended the study Medicine at the Erasmus University in Rotterdam. She obtained her medical degree in 2013, after which she worked as a resident internal medicine at the Albert Schweitzer hospital in Dordrecht. She started working on this PhD thesis in January 2014 in collaboration with the Erasmus MC Cancer Institute under the supervision of Dr. M-D. Levin, dr. A Jager en prof. Dr. S. Sleijfer. From January 2017 and onwards, she attended a residence programme at the Albert Schweitzer hospital, in order to specialize in the oncological field.

Hánah Nicole Rier werd geboren op 13 april 1987 te Amsterdam. In 2005 voltooide zij het Voortgezet Wetenschappelijk Onderwijs aan de Purmerendse Scholengemeenschap, locatie Jan van Egmond. Zij startte vervolgens met de studie biomedische wetenschappen aan de universiteit van Amsterdam. Na één jaar staakte zij deze opleiding en startte in 2006 met de studie geneeskunde aan de Erasmus universiteit, waarbij zij het artsexamen aflegde in januari 2013. Aansluitend werkte zij als arts-assistent niet in opleiding tot specialist op de afdeling Interne geneeskunde in het Albert Schweitzer ziekenhuis te Dordrecht. Vanaf januari 2014 werkte zij aan het wetenschappelijk onderzoek, wat heeft geresulteerd in dit proefschrift. Het onderzoek is uitgevoerd vanuit het Albert Schweitzer ziekenhuis in samenwerking met de Daniël den Hoed kliniek onder supervisie van dr. M-D. Levin, dr. A. Jager en prof. dr. S. Sleijfer. Vanaf 1 januari 2017 is zij in opleiding tot internist in het Albert Schweitzer ziekenhuis. Zij hoopt zich te zijner tijd te specialiseren in de oncologie.

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PhD Portfolio

Name PhD student: Hánah Nicole Rier
Institution: Albert Schweitzer hospital and Erasmus MC Cancer Institute
Period: January 2014 – December 2016
Promotor: prof. dr. S. Sleijfer
Copromotores: dr. A. Jager
dr. M-D. Levin

	Workload		
	Year	**Hours**	**ECTS**
1. PhD training			
General courses			
- Good clinical practice	2014	15	0.5
- Scientific writing	2015	28	1.0
- Integrity in Science for PhD students Erasmus MC	2016	10	0.4
Specific courses			
- NIHES: Biostatistics for Clinicians	2016	20	0.7
- NIHES: Advanced analysis of prognosis studies	2016	26	0.9
- NIHES: Clinical trials	2016	20	0.7
Seminars and workshops			
- Jonge Oncologen avond	2016	2.5	0.1
- Symposium Borstkanker Behandeling Beter 2016	2016	7.5	0.3
Presentations			
- 9 presentations at group meetings Asz	2014 – 2016	40	1.4
- 2 Poster presentations SIOG	2015	10	0.4
- Oral presentation Internistendagen	2015	5	0.2
- 2 presentations at Wetenschapslunch Asz	2015 – 2016	5	0.2
- 2 presentations at Wetenschapsdag Asz	2015 – 2016	10	0.4
- 1 presentation at Research Meeting Erasmus MC	2016	10	0.4
International conferences			
- Internistendagen	2014 – 2016	70	2.5
- International Society of Geriatric Oncology (SIOG)	2015 – 2016	50	1.8
- European Cancer Congress (ECCO)	2015	42	1.5
- Sarcopenia, Cachexia and Muscle Wasting: 9th International Conference	2016	17	0.6
2. Teaching			
- Teaching residents Internal medicine *Subject: Treatment patterns in breast cancer and the importance of muscle mass as a prognostic factor*	2015	20	0.8

- Supervising Master's Thesis Danielle Bontekoe *Resulted in a poster presentation at the Wetenschapsdag Asz as second author*	2016	28	1.0
- Supervising Researcher Asz *Subject: The prognostic value of low muscle mass and attenuation in non-Hodgkin Lymphoma*	2015 – 2016	48	1.7

3. Other

- Wetenschapslunch Asz	2014 – 2016	36	1.3
- Local investigator CHARMING study *Subject: The change of geriatric morbidity and muscle status in elderly cancer patients undergoing chemotherapeutic treatment*	2014 - 2016	315	11.3
- Peer reviews for several international journals in the field of Oncology	2016	20	0.7