Summary

Introduction
Cancer is an increasing prevalent and burdensome disease and not all patients with cancer can be cured. Patients with advanced cancer suffer from many symptoms, caused by the tumor and/or anticancer treatment. Cancer cachexia, which is severe loss of muscle mass and function, is a frequently observed problem in patients with advanced cancer. Patients with cachexia frequently also experience decreased appetite (anorexia), signs of systemic inflammation and fatigue. Cachexia is associated with worse quality of life and shorter survival. Despite the fact that cancer cachexia has since long been recognized, active assessment or management has not become standard of care due to lack of diagnostic criteria until recently. The diagnostic framework launched in 2011 distinguished 3 stages: ‘pre-cachexia’, ‘cachexia’ and ‘refractory cachexia’. After publication of this diagnostic framework, validation with empirical data was awaited.

Furthermore, although numerous studies have shown that weight loss and low muscle mass are associated with worse outcome, it remains unknown how muscle mass develops during anticancer treatment for advanced cancer. Another lack of knowledge can be found in older patients with cancer, as most studies on muscle mass were performed in relatively young patients with cancer. As older patients with cancer may suffer from competing comorbidities and age-related muscle loss, associations between muscle wasting and clinical outcomes may be different from younger patients, but evidence on this topic is scarce. The aim of this thesis was to contribute to the knowledge of diagnosis and clinical consequences of cachexia in patients with advanced cancer.

Diagnosis of cachexia
The prevalence of pre-cachexia was very low (0.5%) in 200 patients with advanced cancer when applying the diagnostic framework (Chapter 2). Using a higher cut-off value for anorexia resulted in an increase of the prevalence of pre-cachexia to 2% but still, very few patients with pre-cachexia were identified using the current diagnostic framework.

In the diagnostic criteria of cachexia, weight loss of 5% or more in 6-12 months was proposed to be used. In a pilot study of 20 patients with advanced cancer, we found that patients with weight loss of 5% or more in 12 months prior to chemotherapy had a significant decrease of fat free mass in the first nine weeks of chemotherapy.
compared to patients with <5% weight loss (Chapter 3). Furthermore, our results suggested an association between ≥5% weight loss and shorter survival. For the assessment of anorexia, experts advised to use the VAS (scale 0-100 mm) or FAACT-A/CS questionnaire (scale 0-48), however validated cut-off values for these two instruments were lacking. We determined cut-off values for these two instruments in 273 patients with advanced cancer using two external criteria: the EORTC-QLQC30 symptom scale of anorexia and the question “Do you experience a decreased appetite?” (Yes/No). The optimal cut-off values we found were ≤37 for the FAACT–A/CS and ≤70 for the VAS for appetite (Chapter 4). The obtained cut-off value of ≤37 for the FAACT–A/CS is substantially higher than the formerly used cut-off value of ≤24 and even higher than the more recently proposed cut-off value of ≤30. Using lower cut-off values to detect anorexia might leave many patients with anorexia undetected and this increases the risk of developing undernutrition.

In the diagnostic framework of cancer cachexia, four different options to determine low muscle mass were proposed. We compared muscle measurements using Computed Tomography (CT) scans, mid-upper arm muscle area (MUAMA) and bio-electrical impedance analysis (BIA) with their accompanying cut-off values to one another in 241 patients with advanced cancer. We found a large disagreement of 85% on presence of low muscle mass between the measurements with a prevalence of low muscle mass of 13% using MUAMA, 59% using CT scans and 93% using BIA (Chapter 6). In turn, the prevalence of cachexia was 37%, 43% and 48%; the majority of patients were already defined cachectic by concurrent weight loss of >5% weight loss in the previous six months, which thus appeared to be the factor with the highest influence on the diagnosis of cachexia. Irrespective of type of muscle measurement, patients with cachexia presented more often with anorexia, inflammation, low muscle strength and fatigue and had lower quality of life. Patients with cachexia had worse overall survival compared to patients without cachexia: HR 2.00 (95% CI 1.42-2.83) with MUAMA, HR 1.64 (95% CI 1.15-2.34) with CT, and HR 1.50 (95% CI 1.05-2.14) with BIA (all p<0.05).

**Consequences of cachexia and potential treatment**

In 103 older patients (≥60 years) with advanced cancer, we found that, although the amount or quality of muscle mass before chemotherapy was not related to clinical outcomes, higher muscle strength before start of chemotherapy was statistically significantly related with prolonged survival (HR 1.75; 1.02-3.00, p<0.05, adjusted for
relevant confounders such as gender, tumor type and treatment line, Chapter 7). Nevertheless, the discriminative value for too low muscle strength was inadequate due to low sensitivity (40%) and poor positive predictive value. Therefore, clinical applicability needs to be investigated in future research.

In 63 patients with metastatic colorectal cancer, we measured muscle mass using CT scans before and during palliative chemotherapy. We detected a significant decrease of muscle area of approximately 6% in three months (95% CI 3.8 to 8.4%, p<0.001). A decrease in muscle area of 9% or more (the lowest tertile of patients) was independently associated with poorer survival in this patient group (HR 4.47; 2.21-9.05, p<0.001, adjusted for relevant confounders, Chapter 8). This finding raises the question whether preservation of muscle mass during treatment can be achieved with interventions and whether this may lead to improvement in clinical outcomes. Therefore, we designed a randomized controlled multicentre trial (Chapter 9). The aim of this study is to determine whether individualized nutritional counselling is effective in preserving muscle mass during chemotherapy and to evaluate whether also positive effects on treatment toxicity, quality of life and survival can be achieved. Recruitment for this study is still ongoing.

Another promising new therapeutic target for cachexia is ghrelin. Ghrelin is involved in regulation of hunger and satiety. Treatment with ghrelin and ghrelin receptor agonists has led to promising results regarding improvements in appetite, food intake, lean body mass and quality of life of patients with cancer cachexia, however no statistical significant effect on physical functioning and survival could be demonstrated. In 40 patients with lung cancer we found that having anorexia was significantly related to higher plasma ghrelin levels compared to patients without anorexia (β: 348.3, p=0.031) but we did not find associations between ghrelin levels and cachexia (β: -163.7, p=0.354) (Chapter 5). In order to prevent severe weight loss and deterioration in physical functioning, treatment with ghrelin (receptor agonists) should therefore be considered for patients with anorexia rather than patients who already suffer from severe weight loss.

**General conclusions and recommendations**

In conclusion, cachexia is a prevalent and clinically relevant problem for patients with advanced cancer. Although the diagnostic framework to detect cancer (pre-) cachexia helps to recognize and standardize diagnosis of cancer cachexia, this still needs refinement. Regular weight measurement remains important for the early recognition of (risk on) cachexia. Furthermore, the assessment of anorexia, muscle
mass and muscle strength seems to be of clinical relevance, however timing, target group of patients, type of measurement and cut-off values for the assessment of these features of cachexia should all be subject of future research. Moreover, the additional value of these measurements in comparison to current assessment of these features by doctors and nurses is of interest.

Although earlier nutritional intervention studies in cachexia showed improvements in food intake and in some cases, improvement in body weight, they failed to show positive effects on quality of life and survival. Future studies should focus on investigating whether earlier interventions (in patients with no or minor weight loss) and multimodal approaches (combining nutritional therapy, exercise and new pharmacological treatments) tailored to the patients' symptoms and needs might help to prevent nutritional and clinical decline.

Together, the findings in this thesis contribute to the knowledge on diagnosis of cancer (pre-)cachexia and present new hypotheses for treatment of (pre-)cachexia.