Chapter 10

General discussion
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The aim of this thesis was to contribute to the knowledge of diagnosis and clinical consequences of cachexia in patients with advanced cancer. The studies described in this thesis used measurements of body weight (loss), muscle mass, muscle strength and appetite and investigated associations with quality of life, treatment toxicity and survival in patients with advanced cancer. This final chapter summarizes the main findings of the studies presented in this thesis, and provides interpretations in the light of existing literature. Furthermore, methodological considerations will be discussed and implications for future research and clinical practice will be described.

Main findings and comparison with available literature

Diagnosis of cancer cachexia

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 2011 (1). In 2010 and 2011, international consensus meetings resulted in two publications on the diagnosis of cachexia in patients with cancer (1;2). Cancer cachexia was stated to be a continuum with three stages of clinical relevance: pre-cachexia, cachexia and refractory cachexia. After publication of this diagnostic framework, validation with empirical data was awaited. When applying the diagnostic framework for pre-cachexia in patients with advanced cancer, we found a very low prevalence of 0.5% (Chapter 2). Other studies show higher prevalence rates of pre-cachexia, ranging between 14-23% (3-7), for which several explanations can be found. These studies differed in patient groups (for example, surgical patients (7)), in cut-off values for weight loss (sometimes also patients without weight loss were included (6;7)) and in the type of anorexia assessment (for example, self-reported decrease in food intake (3;4;6)). In order to compare studies to one another and to use in clinical practice, consensus has to be obtained on the definitive diagnostic criteria of pre-cachexia, with consensus on cut-off values for weight loss and type of anorexia assessment. However, first the clinical relevance of the pre-cachexia stage has to be confirmed in future studies, as we have shown that the present framework identifies only few patients with pre-cachexia (Chapter 2). For the diagnosis of the cachectic stage, weight loss of 5% or more was proposed to be used as a diagnostic criterion (8). We have found that using this criterion, patients with weight loss of 5% or more prior to chemotherapy had a statistical significant loss of fat free mass in the first nine weeks of chemotherapy compared
to patients with <5% weight loss (Chapter 3). Furthermore, we also found an association between ≥5% weight loss and shorter survival. Studies on the best cut-off value for weight loss in the diagnostic criteria of cancer cachexia are conflicting. Whereas some studies also show ≥5% weight loss to be associated with adverse nutritional and clinical outcomes (9;10), some older and newer studies show that even a smaller amount of weight loss (e.g. 2%) is associated with poorer clinical outcome (11-13). These smaller amounts of weight loss are being suggested as the pre-cachectic stage.

Independent of the amount of weight loss, patients with inflammation or anorexia have a worse prognosis compared to patients without inflammation or anorexia (3;5). Therefore, the diagnosis of cachexia might be more complex due to the possible existence of ‘phenotypes’ (1;5, Figure 1). This has to be taken into account when refinement of the diagnostic criteria of (stages of) cachexia is being considered.

For the assessment of anorexia, experts advised to use the VAS or FAACT-A/CS, however validated cut-off values for these two instruments were lacking (2;14). We found that, using two external criteria, the optimal cut-off value to assess anorexia is ≤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 earlier used cut-off value of ≤24 (2) and even higher than the more recently proposed cut-off value of ≤30 (15). For the VAS for appetite, a proposed cut-off value from an earlier study of <70 (16) corresponds with the findings in our study, which implies that the cut-off value of <50 (6) might leave many patients with a lack of appetite undetected. As anorexia may precede significant weight loss, early detection of a (beginning) lack of appetite is important. For clinical practice, the VAS is more practical to use than the FAACT-A/CS as the latter is more time consuming, however efforts have been made to shorten this questionnaire (17). For refinement of the diagnostic criteria of (pre-)cachexia, consensus should be obtained on the best method to assess anorexia in patients with cancer; therefore future studies are warranted to investigate which one is the best to use.

In the consensus diagnostic criteria of cancer cachexia, different options to determine low muscle mass were proposed. When comparing three different muscle measurements with their accompanying cut-off values, we found a large disagreement on presence of low muscle mass (Chapter 6). However, since the majority of patients with low muscle mass also had lost >5% of their body weight in the previous six months, the disagreement between muscle measurements affected the diagnostic criteria of cancer cachexia only marginally. Two other studies also
showed that the prevalence of low muscle mass was dependent on type of muscle measurement and chosen cut-off value (18;19), however our study was the first to show the impact of these differences on the diagnosis of cancer cachexia. For the determination of (low) muscle mass, cut-off values for muscle measurements need to be brought into agreement to one another. We found a prevalence of cachexia between 37-48% (dependent on type of muscle measurement used, Chapter 6), which can be regarded as clinically relevant although it is lower than for example the prevalence of 50-80% found by von Haehling and colleagues (20). This may be explained by the fact that we only included patients starting anticancer treatment. We expect the prevalence of cachexia to be higher in patients who are not offered anticancer treatment as a poor nutritional status may be a reason to refrain from anticancer treatment.

**Consequences of cachexia**

Cachexia is associated with poorer clinical outcomes and the last decade, muscle wasting was found to be the most important contributor to the adverse effects of cachexia in patients with cancer (1). However, studies were mostly performed in relatively young patients with cancer or included only one measure of muscle mass (cross-sectional study design). We found in older patients with cancer that, although the amount or quality of muscle mass before start of chemotherapy was not related to clinical outcomes, higher muscle strength before start of chemotherapy was significantly associated with prolonged survival (Chapter 7). Other studies in younger patients with cancer (21), in elderly hospitalized patients (22) and in healthy older adults (23;24) support the association between muscle strength and survival. Nevertheless, the discriminative value of low muscle strength as single predictor for survival was inadequate due to low sensitivity (40%) and poor positive predictive value. Therefore, future studies should investigate the additional role for muscle strength measurements in the combined assessment of older patients with advanced cancer who are screened on fitness for anticancer treatment.

Furthermore, we found a significant decrease of muscle area of approximately 6% in patients with metastatic colorectal cancer during three months of palliative chemotherapy. A decrease in muscle during chemotherapy was associated with poorer survival in this patient group (Chapter 8). Studies in patients with other types of advanced cancer revealed similar results on loss of muscle mass, for example in renal cell carcinoma during treatment with Sorafenib (25), in cholangiocarcinoma during standard chemotherapy treatment (26) and in lung
cancer during palliative chemotherapy (27). On the other hand, treatment with Selumetinib for cholangiocarcinoma was associated with skeletal muscle anabolism (26). Similar to our results, changes in muscle during treatment, but not baseline muscle mass, was related to poorer outcome in patients with lung cancer (27). These findings raise the question whether preservation of muscle mass during treatment can be achieved with interventions and whether this may also 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 for metastatic colorectal cancer and to evaluate whether also positive effects on treatment toxicity quality of life and survival can be achieved. Recruitment of participants is currently ongoing.

Furthermore, one of the promising new therapeutic targets for cachexia is ghrelin. 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 hand grip strength and survival could be demonstrated (28;29). We found that patients with NSCLC and anorexia had significantly higher plasma ghrelin levels compared to patients without anorexia but we did not find associations between ghrelin levels and cachexia (Chapter 5). These results support the hypothesis that the association between ghrelin levels and cachexia may be mediated through anorexia (30). In order to prevent severe weight loss and deterioration in physical functioning, treatment with ghrelin (receptor agonists) should be considered for patients with anorexia rather than patients who already suffer from severe weight loss. Future studies should investigate whether intervening earlier (before weight loss occurs) may improve clinical outcomes such as muscle strength and survival.

Methodological considerations
The strengths and limitations of the research described in this thesis have already been described in each chapter. This section provides an overview of the most important methodological considerations.

We performed a large observational study in 302 patients with advanced cancer (results of (parts of) these data can be found in chapters 2, 4, 5, 6, 7 and 8) and a small pilot study in 20 patients (Chapter 3) at the VU University Medical Center (VUmc). As the VUmc is a university hospital, patients may suffer from more (complex) comorbidities compared to patients treated in a general hospital. Furthermore,
the large observational study concerned patients with lung, prostate, breast and colon/rectal cancer, but not other cancer types. These two factors may influence the generalisability of our results to all patients with advanced cancer. For example, patients treated in a general hospital are on average older and tumours are less complex which are important factors influencing cancer cachexia.

An overall limitation is the selection of patients who were planned to receive palliative chemotherapy. These patients may have been the ones with better nutritional status as a poor nutritional status may be a reason to refrain from palliative chemotherapy. As only 4% of the invited patients decided not to participate in the study, our sample may be a good representation of patients receiving palliative chemotherapy in a university hospital.

During the study, muscle mass measurements on CT scan became available in our centre. This is regarded an accurate method of muscle mass measurement and now regarded a gold standard. For the subgroup of patients with lung cancer however, measurements were performed at T4 level (instead of the validated L3 level), as only thoracic CT scans were available. Muscle mass measurements at T4 level have to be validated and therefore, interpretation of the measurements at T4 needs caution.

**Implications for future research and clinical practice**

The findings of our research have implications for both future research and clinical practice.

Although efforts have been made (by us) to refine and validate the diagnostic framework of cancer cachexia, it is not ready for use in clinical practice yet. Figure 1 shows an algorithm also including management of cancer cachexia (1). Before this algorithm can be used, a number of issues still need to be addressed.

**Diagnosis of pre-cachexia and cachexia**

Although experts advised to measure muscle mass in the diagnosis of cancer cachexia, we have shown that the currently advised measures of muscle mass are not interchangeable to one another as a large disagreement in presence of low muscle mass occurred when comparing three methods. However, the majority of patients with cachexia will already be detected with the weight loss criterion alone. For clinical practice, weight loss and body mass index could form the basis for screening on (risk of) cachexia. For example, a simple grading system with BMI-adjusted weight loss categories, as recently proposed, can help define the severity of weight loss (e.g. grade 0/1/II/III/IV) (13).
After defining the severity of weight loss, assessment of other features of cachexia is advised. We have shown the clinical relevance of assessing anorexia (Chapter 5), muscle strength (Chapter 7) and muscle mass (Chapter 8), however the timing, patient category, 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 judgement by doctors and nurses after the physical examination of the patient is of interest.

Management of pre-cachexia and cachexia

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 (31). The studies may not have been powered enough to find a significant effect but also inclusion of patients with already
very severe weight loss or refractory cachexia may be an explanation (31). Perhaps selecting patients with only minor weight loss for intervention trials may help assessing whether severe weight loss and deterioration in muscle mass and physical functioning can be prevented. Also, most previous intervention studies included a single strategy to treat cachexia but as the pathophysiology is multifactorial, a multimodal approach with integration of nutritional counselling, exercise therapy and new pharmacological treatments may be more promising (32). Interventions should be timed during active anticancer treatment and include clinically relevant endpoints such as quality of life, physical functioning and survival. Interventions can be based on current knowledge of problems in specific patient groups, for example, muscle loss during chemotherapy for metastatic colorectal cancer such as the randomized controlled trial we describe in Chapter 9 of this thesis. Or interventions can be based on presence of a symptom such as anorexia as we suggest in Chapter 5. Altogether, a multimodal treatment, tailored to the patients’ symptoms and needs, might be the future in cancer cachexia treatment (33).

**Conclusions**

In conclusion, cachexia is a prevalent and clinically relevant issue for patients with advanced cancer as it affects approximately 40% of patients. Although the diagnostic framework to detect cancer (pre-)cachexia helps to recognize and standardize diagnosis of cancer cachexia, this still needs refinement. Nevertheless, regular measurement of body weight remains important for the early recognition of (risk on) cachexia. Furthermore, the assessment of anorexia, muscle mass and muscle strength all seem to be of clinical relevance, however timing and methods of assessment still need attention in future research. Moreover, future studies should focus on investigating whether earlier interventions (in patients with no or minor weight loss) 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.
References


