Chapter 1

General introduction
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Cancer

Cancer is a prevalent and burdensome disease. The number of people living with cancer in the Netherlands was over 300,000 in 2013 and the prevalence increases with approximately twenty percent per five years (3). At diagnosis, the cancer is staged based on the size of the tumor (T), the presence of lymph node metastases (N) and distant metastases (M). Between 30 to 75 percent of patients (dependent on tumor type and available screening programs) are diagnosed with synchronic lymph node or distant metastases: stage III or IV disease, also referred to as ‘advanced cancer’. Furthermore, a number of patients will eventually develop metastatic disease after their primary diagnosis (3). Treatment of patients with advanced cancer is mainly focused on prolonging life with specific focus on reduction of symptoms and improvement or maintenance of quality of life. Improvement of quality of life can be achieved by reducing tumor burden and alleviating symptoms (4). Treatment to reduce tumor burden may consist of palliative surgery, hormonal treatment, chemotherapy, radiotherapy or treatment with biological agents (5). Alleviating symptoms can be reached by reducing tumor burden or directly treating symptoms with medication, for example medication to reduce nausea, or with other strategies, such as a celiac plexus block to reduce pain (4;6). Despite efforts to reduce symptoms, patients with advanced cancer still suffer from multiple symptoms, ranging from 4 to 11 symptoms at the same time (7-9). The most prevalent symptoms are pain, fatigue, weakness, insomnia and appetite loss (anorexia). Many symptoms are nutrition-related, such as involuntary weight loss, anorexia, taste alterations and nausea/vomiting (7). These nutrition-related symptoms have been described to have a negative effect on quality of life of patients with advanced cancer (10-12).

Metabolic alterations in cancer

As a consequence of the presence of a malignant tumor, substantial metabolic alterations take place in cancer patients with direct or indirect effects on body weight, body composition and appetite (13). The tumor itself secretes substances such as proteolysis-inducing factor (PIF), activin A, zinc-alpha2-glycoprotein (ZAG) and parathyroid hormone-related protein (PTHrP). Elevated levels of PIF and activin A have been detected in respectively urine and serum of patients with cancer and weight loss (14;15). PIF and activin A are known to promote protein degradation and inhibit protein synthesis, leading to loss of muscle mass (13;16). ZAG, a lipid
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mobilizing factor, is found in patients with weight loss and mechanistically related to loss of fat tissue (17;18). PTHrP is produced by the tumor and mechanistically related to anorexia and food intake in rats, however clinical relevance in humans remains to be investigated (19).

Furthermore, the systemic inflammatory response of the host in reaction to the presence of a tumor elicits a cascade of reactions leading to anorexia and wasting of muscle mass and fat tissue. Pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) have been related to changes in central neurotransmitters, leading to anorexia (20). TNF-α and IL-1 are also involved in two pathways inducing structural muscle protein breakdown and inhibiting protein synthesis: the nuclear factor-k (NF-kB) pathway and the p38- mitogen-activated protein kinase (MAPK) pathway (21). Furthermore, interleukin-6 (IL-6) causes muscle protein degradation via activation of the STAT3 and the MAPK/ERK cascade (22). TNF-α has also been related to lipolysis in cancer cachexia (13).

A change in the functioning of the hypothalamus has also been suggested in the mechanism of cancer cachexia. The hypothalamus controls energy homeostasis via neurons that secrete appetite inhibiting (anorexigenic) and appetite stimulating (orexigenic) neuropeptides to control food intake. An example of an orexigenic neuropeptide is ghrelin, a 28-amino acid peptide and the natural ligand for the growth hormone secretagogue receptor-1a (23). Ghrelin is produced by endocrine cells of the antrum during periods of fasting; some studies found higher ghrelin levels in patients with weight loss (24-27), however other studies did not (28;29) and ghrelin levels were found to be increased in patients with decreased appetite after chemotherapy (23;24). The clinical relevance of ghrelin in the mechanism of anorexia and weight loss in cancer patients remains to be investigated. Figure 1 displays metabolic alterations in cancer leading to loss of muscle and fat mass and loss of appetite, together referred to as ‘cancer cachexia’.
Cancer cachexia

Cachexia was already recognized by Hippocrates (460-370 B.C.); the word ‘cachexia’ is derived from the Greek words ‘Kakos’ and ‘Hexis’, which means bad condition (30). Cachexia has frequently been described as a “…multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism” (2).

The prevalence of cancer cachexia depends on tumor type and method used to define cachexia but is estimated to be 50-80 percent in advanced cancer (31). The prevalence of severe weight loss does not seem to have changed the past 30 years but because prevalence of overweight and obesity increased, the diagnosis of cachexia may nowadays be more difficult as it is less visible (32). Despite the fact that cancer cachexia has been recognized as an adverse effect of cancer for a long time, active assessment or management has not become standard of care due to lack of diagnostic criteria (2). In the past years, efforts have been made to create a diagnostic framework to increase detection of cancer cachexia. In 2008, Evans and colleagues presented a general framework to diagnose cachexia within all chronic diseases with a key component of at least 5% loss of body weight during the previous twelve months or less. Other diagnostic criteria for cachexia included...
decreased muscle strength, fatigue, anorexia, low muscle mass and biochemical abnormalities (33). The authors suggested to classify the degree of cachexia as mild, moderate or severe depending on the severity of weight loss (33). 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 (Figure 2).

In pre-cachexia, early clinical and metabolic signs can precede substantial involuntary weight loss. The risk of progression to cachexia and refractory cachexia varies and depends on factors such as cancer type and stage, the presence of systemic inflammation, low food intake and lack of response to anticancer therapy. In refractory cachexia, cancer is not responsive to anticancer treatment. This stage is associated with low performance status (WHO score 3 or 4) and a life expectancy shorter than 3 months (2). Panel 1 shows the classification of the cachexia stages.

For inflammation, elevated serum levels of inflammatory markers such as C-reactive protein were advised to use. For anorexia, a score of ≤24 on the anorexia/cachexia subscale (A/CS) of the Functional Assessment of Anorexia and Cachexia Therapy (FAACT) questionnaire was advised (1). Alternative measures for anorexia included a visual analogue scale (VAS) for appetite or measurement of food intake (1). For the VAS and FAACT-A/CS, cut-off values to detect anorexia need validation with empirical data.

The prognostic value of the pre-cachectic stage was assessed by Blum and colleagues. They defined pre-cachexia by: weight loss >1 kg but <5% of usual body weight in the past 6 months (34). They found that, by using these criteria, survival rates were not different from those of patients without cachexia. The authors stated that ‘the pre-cachexia stage might be better defined by additional factors representing the cachexia domain, for instance CRP and appetite loss’ (34). Unknown is whether
addition of these factors to the diagnostic framework of pre-cachexia will improve
the diagnosis of pre-cachexia.

Panel 1: Classification of cachexia stages

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<th>Pre-cachexia (1)</th>
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<tr>
<td>- Unintentional weight loss ≤5% of usual body weight during the last 6 months AND</td>
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<td>- Chronic or recurrent systemic inflammatory response AND</td>
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<td>- Anorexia or anorexia-related symptoms</td>
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<tr>
<th>Cachexia (2)</th>
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<tr>
<td>- Unintentional weight loss &gt;5% over the past 6 months OR</td>
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<tr>
<td>- BMI &lt;20 and any degree of weight loss &gt;2% OR</td>
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<tr>
<td>- Low muscle mass and any degree of weight loss &gt;2%</td>
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Other features such as inflammation or decreased food intake may also be present

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<th>Refractory cachexia (2)</th>
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<tr>
<td>- Variable degree of BMI and amount of weight loss and presence of other features</td>
</tr>
<tr>
<td>- Cancer not responsive to treatment</td>
</tr>
<tr>
<td>- Low performance score</td>
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<td>- &lt;3 months expected survival</td>
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The cut-off value for weight loss used to define the cachectic stage, ≥5% in the
past year (33), is stricter than the cut-off value in the screening tool for malnutrition
currently used in Dutch hospitals (35). Unknown is whether ≥5% weight loss in the
past year identifies patients at risk for further deterioration in nutritional and clinical
status.

Although assessment of systemic inflammation and food intake was also advised in
the cachectic stage, consensus on the role for these features and the methods to
measure these items was not reached (2).

To determine muscle mass, four options to measure muscle mass were advised:
mid upper arm muscle area by anthropometry (men <32 cm², women <18 cm²);
appendicular skeletal muscle index determined by dual energy x-ray absorptiometry
(men <7.26 kg/m²; women <5.45 kg/m²); lumbar skeletal muscle index determined
by CT imaging (men <55 cm²/m²; women <39 cm²/m²); whole body fat-free mass
index without bone determined by bioelectrical impedance (men <14.6 kg/m²);
women <11.4 kg/m²) (2). Authors advised to use a direct measure of muscularity in the presence of fluid retention, a large tumor mass, or overweight/obesity (2). Unknown is whether the choice for type of muscle measurements affects the detection of low muscle mass and cachexia.

Consequences of cancer cachexia

We have known for a long time, that weight loss in cancer is associated with shorter survival, reduced response to anticancer treatment, increased adverse events from treatment and poorer quality of life (36-38). Muscle wasting is regarded the most important contributor to the adverse effects of weight loss in patients with cancer (2). Patients with advanced cancer and low muscle mass experience more toxicity of chemotherapy (39-42), more complications of surgery and longer length of hospital stay (43-46), have lower quality of life scores (12) and shorter survival (47-49) compared to patients with normal muscle mass. Furthermore, anorexia has been associated with negative outcomes such as decreased quality of life, diminished social, emotional and physical functioning (50;51). Anorexia also affects clinical outcomes by contributing to muscle wasting via reduced food intake (52-54).

Reversing muscle loss in patients with cancer is difficult, because cachexia is mainly caused by tumor activity and released cytokines. Nevertheless, newer studies suggest the possibility of muscle anabolism in patients (55;56). The best chance for successful interventions is during active anticancer treatment, when the tumor and its metabolic effects are being targeted. Longitudinal studies on changes in muscle mass during treatment for advanced cancer are scarce. Most studies measured muscle mass at one time point, for example before start of treatment (12;39-49;57), or over time, but not during active anticancer treatment (58;59). Furthermore, studies on consequences of muscle wasting were mostly performed in relatively young patients with cancer; as in trials on anticancer treatment, patients above 70 years were often excluded, or older patients were underrepresented based on strict exclusion criteria regarding comorbidities (60). As older patients may present with comorbidity and age-related muscle loss simultaneously, associations between muscle measures and clinically relevant outcomes may be different. Thus, it is unknown whether muscle wasting is associated with treatment toxicity and survival in older patients with advanced cancer.
Aims and outline of this thesis
Cancer cachexia is a major issue for patients with advanced cancer due to its high prevalence and significant impact on patients' physical performance. Despite the fact that cancer cachexia has since long been recognized as negative consequence of cancer, active assessment or management has not become standard of supportive care due to lack of validated diagnostic criteria. Furthermore, although we know that weight loss and low muscle mass are associated with worse outcome, unknown is how muscle mass develops during anticancer treatment for advanced cancer. The major aim of this thesis is to contribute to the knowledge of diagnosis and clinical consequences of cachexia in patients with advanced cancer.

Chapter 2 describes the relevance of diagnostic criteria of ‘pre-cachexia’.
Chapter 3 describes a pilot study on the association between the cut-off value of ≥5% weight loss in the past year on changes in body composition during palliative chemotherapy for advanced cancer.
Chapter 4 describes cut-off values for the FAACT – A/CS and the VAS for appetite in the diagnosis of cancer anorexia.
In chapter 5 we studied associations between ghrelin levels and anorexia and cachexia in patients with non-small cell lung cancer (NSCLC).
Chapter 6 describes the influence of different types of muscle mass measurements on the diagnosis of low muscle mass and cancer cachexia.
Chapter 7 shows the association between muscle measures, toxicity and survival in older patients with advanced cancer.
In chapter 8 we studied changes in muscle mass during palliative chemotherapy in patients with metastatic colorectal cancer and the consequences for treatment toxicity and survival.
Chapter 9 describes the design of a randomized controlled trial on the effect of individualized nutritional counseling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy.
In chapter 10 the main findings of the studies are summarized and discussed in context of clinical implications. Also, recommendations for further research are provided.
References


