Cancer and its treatment

Cancer is one of the leading causes of death worldwide and causes substantial burden on society. The most commonly diagnosed cancers worldwide include prostate, lung and colorectal cancer in men and breast, lung and colorectal cancer in women. Incidence per cancer type varies by country and is affected by differences in the prevalence in risk factors and detection methods. At diagnose, the cancer is staged based on the extent of the primary tumour, the presence and extent of lymph node metastases and the presence of distant metastases. The tumour stage provides an indication of the prognosis and has important treatment implications. Mortality rates mainly depend on the availability of treatment and cancer stage. Especially for metastatic disease (stage IV), cancer related mortality is high and treatment is often aimed at prolongation of survival with a good quality of life. Treatment regimens for metastatic disease often include chemotherapy, which interferes non-selectively with the proliferation of rapidly diving cells. Therefore the cytotoxic effects involve cancer cells as well as non-cancerous cells, resulting in toxicities. For instance, frequently occurring toxicities caused by first-line chemotherapy regimens for colorectal cancer are diarrhea, cytopenia and hand-foot-syndrome. For a selection of cancer types, traditional chemotherapy has been supplanted by targeted agents. Targeted agents interfere with aberrantly activated signalling pathways in cancer cells.

An important class of these anticancer agents are protein kinase inhibitors. Protein kinase inhibitors act by blocking dysregulated kinases involved in cell proliferation, differentiation and apoptosis. Hereby they inhibit kinase activity and downstream signalling. These agents were initially expected to be relatively nontoxic, however frequency and severity of toxicities appeared to be comparable to chemotherapy. Although the nature of toxicity caused by chemotherapy and targeted therapy is different, there is overlap in the type of side effects. Many of these side effects, among which taste alterations, loss of appetite, mucositis, nausea and vomiting, are nutrition-related and are associated with a reduced quality of life. In particular for targeted therapies, which have emerged the last decade as important antitumor agents, the pathobiology of these side effects is unknown and treatment options are limited.

Metabolic alterations in cancer

Cancer cells are rapidly dividing cells consuming large amounts of glucose and amino acids. To meet the requirements for this consumption, protein degradation in skeletal muscle is stimulated. The released amino acids are used by the liver for gluconeogenesis and synthesis of acute-phase proteins and by the tumour for
synthesis of protein and DNA. These metabolic changes are driven by a tumour-induced inflammatory response, mediated by the proinflammatory cytokines interleukin-1-β, interleukin-6, tumor necrosis factor α and interferon-γ. Apart from stimulation of proteolysis, cytokines inhibit growth hormone and insulin-like growth factor, induce insulin resistance and cause anorexia. These compensatory mechanisms to protect the patients’ homeostasis generate energy inefficiency and increased energy expenditure. All together this results in a depletion of physiological reserves of energy and protein. Particularly in metastatic cancer there is an additional burden of tissue with a high metabolic rate causing increases in resting energy expenditure and concurrent with loss of muscle mass.

Dietary intake in patients with cancer

The tumour-induced inflammatory response is associated with symptoms such as loss of appetite, early satiety and a change in the perception of food, which all contribute to anorexia. These tumour-induced symptoms, as well as treatment-related toxicity, may result in a reduced dietary intake in cancer patients. As mentioned above, systemic treatment may cause nutrition-related side effects, which may result in a reduced dietary intake and subsequent malnutrition. Dietary intake seems to be the lowest at the day of chemotherapy and increases stepwise until the next cycle of chemotherapy. Additional factors contributing to reduced dietary intake are possible obstruction in the gastrointestinal tract and psychological factors. Most of these factors have individually been described, yet it is not known to what extent each of these symptoms reduce dietary intake.

Cancer cachexia

The combination of reduced dietary intake and abnormal metabolism results in a negative protein and energy balance. This multifactorial syndrome, defined by an ongoing loss of muscle mass, is referred to as cancer cachexia. Different definitions for cancer cachexia have been proposed, all including weight loss as a main criterion. Additional criteria vary and relate to the aetiology of cachexia (inflammation, reduced dietary intake, anorexia) and the resulting loss of muscle mass. The criteria for cancer cachexia according to Fearon et al (2011) are most frequently used in research and are defined by either weight loss >5% alone, or weight loss >2% in combination with a body mass index <20 kg/m² or with a low skeletal muscle mass, also called sarcopenia. The preferred methods to estimate muscle mass are dual energy X-ray absorptiometry and
computed tomography (CT) cross-sectional image analysis.\textsuperscript{20} Although the traditionally used method was dual energy x-ray absorptiometry, since its validation CT analysis is most commonly used, with cut-offs for sarcopenia based on optimal stratification with survival.\textsuperscript{23-25}

In patients with cancer, CT analysis has advantages over other methods to estimate muscle mass because CT images are acquired during routine care, making this a convenient method for the patient. Furthermore muscle radiodensity can be evaluated, which is inversely related to muscle fat content.\textsuperscript{26} On the other hand, this relatively new method to estimate muscle mass and muscle density also has disadvantages. The influence of acquisition methods, such as the use of an intravenous contrast agent, on skeletal muscle parameters is unknown. In addition, cut-offs to define sarcopenia remain to be determined. The lack of reference values derived from a healthy population impedes interpretation of muscle parameters.\textsuperscript{25,27-29}

Until now, the Fearon et al (2011) criteria are mainly used in research and a more practical classification for routine clinical use is anticipated.\textsuperscript{20} Possibly cachectic patients may be identified by their clinical presentation, although agreement between clinical assessment and the Fearon et al (2011) criteria is unknown.

**Clinical implications of sarcopenia in patients with metastatic cancer**

CT analysis is increasingly used in research to estimate skeletal muscle mass and associations with outcomes. Sarcopenia is associated with a lower functional status and has shown to be a negative prognostic factor, independent of body mass index.\textsuperscript{23,30} In patients treated with systemic therapy, sarcopenia is linked to more toxicity, dose reduction and delay of treatment.\textsuperscript{31-36} Potentially the increased toxicity in sarcopenic patients is a consequence of a lower volume of distribution of chemotherapy and thus a relative overdose. Alternatively sarcopenic patients could be more susceptible to adverse medical events including treatment toxicity. Sarcopenia is also associated with shorter survival\textsuperscript{23,30,37-39}, which in turn may be explained by increased toxicity and concurrent suboptimal treatment.\textsuperscript{28,35} The shorter survival may also be explained by sarcopenia being associated with other poor prognostic factors, like comorbid conditions or more advanced disease.\textsuperscript{30,40,41} In addition, loss of muscle mass particularly occurs within 90 days of death and is related to tumour progression.\textsuperscript{27,42-44} During chemotherapy patients are at risk of further loss of muscle mass. In patients with metastatic colorectal cancer, loss of muscle mass during chemotherapy is associated with shorter survival, even when adjusted for other important prognostic factors.\textsuperscript{45,46}
**Nutritional intervention to prevent muscle loss during chemotherapy**

Although numerous studies have shown that sarcopenia and loss of muscle mass are negative prognostic factors in patients with metastatic cancer, it remains unknown whether strategies to maintain or increase muscle mass may positively affect outcomes. A prerequisite of treatments expected to have a beneficial effect on the muscle mass is an adequate nutritional intake. Guidelines for cancer patients recommend a protein intake of at least 1 g/kg body weight/day, noting that the evidence on the exact quality and amount of proteins is scarce to moderate.\(^7\) It is not known whether nutritional intervention is effective in maintaining or increasing muscle mass in patients with metastatic cancer during chemotherapy, nor if they result in better clinical outcomes, especially improved survival with a good quality of life, which would be the most important goal of any intervention.

**Aims and outline of this thesis**

Nutrition-related symptoms are common in patients with metastatic undergoing systemic treatment. These symptoms negatively affect quality of life and may cause loss of muscle mass, which in consequence is related to functional status and clinical outcomes. However, it is not known if muscle mass can be influenced in patients with metastatic cancer during chemotherapy. Moreover, lack of reference values hampers interpretation of muscle mass. Furthermore the relatively new targeted therapies lead to a new spectrum of toxicities, among which nutrition related toxicities. These toxicities are poorly understood and may, like chemotherapy, cause loss of muscle mass and impair clinical outcomes. The overall aim of this thesis is to evaluate the effect of nutritional counselling on muscle mass in patients treated for metastatic cancer, to provide supporting data for interpretation of muscle mass measured by CT analysis and to study taste alterations during treatment with protein kinase inhibitors.

**Chapter 2** describes the determinants of reduced dietary intake in hospitalised colorectal cancer patients.

**Chapter 3** and **Chapter 4** describe a randomized controlled trial into the effect of individualized nutritional counseling on muscle mass and treatment outcomes in patients with metastatic colorectal cancer undergoing chemotherapy.

**Chapter 5** compares identification of cancer cachexia by clinical assessment with international consensus criteria for cachexia.
Chapter 6 provides percentiles for skeletal muscle parameters based on computed tomography imaging in a healthy population, in order to facilitate interpretation of muscle parameters in disease.

Chapter 7 describes the agreement between non-contrast and contrast enhanced CT scan measurements of skeletal muscle parameters.

Chapter 8 focusses on targeted agents, in particular protein kinase inhibitors. The mechanism of action of protein kinase inhibitors are described and hypothesis on the pathobiology of patient-reported taste alterations are developed.

Chapter 9 describes a pilot study on both patient-reported and objective taste and smell alterations during treatment with protein kinase inhibitors.

Chapter 10 summarizes and discusses the main findings of the studies and provides suggestions for future research.
References