Summary

Introduction

Cancer is one of the leading causes of death worldwide and causes substantial burden on society. 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. For a selection of cancer types traditional chemotherapy has been supplanted by targeted agents, among which protein kinase inhibitors. Protein kinase inhibitors interfere with aberrantly activated signalling pathways in cancer cells. Although the mechanism of action of 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 may impair nutritional intake. This puts patients treated with these therapies at risk of a low muscle mass. During systemic treatment, muscle mass can easily and reliably be estimated using CT-scans. Previous studies using this method showed that a low muscle mass before start of treatment and further loss of muscle mass during treatment is related more toxicity and shorter survival. However, it is unknown whether loss of muscle mass can be prevented by nutritional counselling.

The aim of this theses was to contribute to the knowledge of the effect of nutritional counselling on muscle mass, to provide reference values for the interpretation of muscle parameters measured on CT-scan and to describe potential causes for taste alterations caused by targeted therapies.

Nutritional status and nutritional counselling during chemotherapy

A reduced dietary intake was reported by 54% of 1131 hospitalised patients with colorectal cancer (Chapter 2). Determinants for reduced dietary intake were being female, higher cancer stage, worse performance status, duration since hospital admission >4 days and unintentional weight loss. Furthermore, symptoms of pain, weakness, depression, tiredness and lack of appetite were associated with a reduced dietary intake.

In patients treated with chemotherapy for metastatic colorectal cancer (n=105), the effect of intensive nutritional counselling supported by encouragement of physical activity was studied (Chapter 3 and Chapter 4). Patients in the nutritional counselling group had a higher protein and energy intake relative to the intake goals compared
to patients in the usual care group (protein 111 vs 90%, p=0.010 and energy 115 vs 95%, p=0.010), but no differences in physical activity were observed. Nutritional counselling did not have an effect on muscle mass measured on CT scan. However, nutritional counselling increased body weight (during the first cycles of chemotherapy; B coefficient 1.7, p=0.045), progression free survival (median 9.6 vs 7.6 months, log rank p=0.039) and overall survival (21.7 vs 16.0 months, log rank p=0.046). Based on these results, the beneficial effect of nutritional counselling on outcomes does not seem to be mediated by muscle mass. How nutritional counselling may improve survival remains elusive.

Within a subsample of the same cohort (n=69), we determined the prevalence of cancer cachexia according to criteria defined by Fearon et al in 2011 (either weight loss >5% alone, or weight loss >2% in combination with a body mass index <20 kg/m² or with sarcopenia) and according to clinical assessment by the oncologist (Chapter 5). The prevalence of cachexia was 52% based on the Fearon et al (2011) criteria and 9% according to clinical assessment, with slight agreement between the two methods. Patients who were cachectic based on clinical assessment (n=6) had a shorter progression free survival compared to non-cachectic patients (HR 3.310, p=0.016). No other associations with clinical outcomes were observed. Our findings indicate further improvement of the cancer cachexia definition is needed, which should preferably be easily assessable and focused on identifying patients who may benefit from nutritional intervention.

**Muscle mass measured by CT analysis**

Muscle mass can reliably be evaluated using CT-scans. Especially if CT scans are acquired during routine care, as is the case during systemic anti-cancer treatment, this is an easily applicable method. Muscle mass and muscle density can be interpreted by comparison with sex-specific values in healthy controls, which we provided based on a cohort of 420 healthy Caucasian individuals (Chapter 6). Because age was negatively correlated with muscle mass and muscle density and because body mass index was positively correlated with muscle mass and negatively correlated with muscle density, age- and BMI specific values were also provided.

We also studied the effect of intravenous contrast enhancement on CT-derived muscle mass and muscle density in 41 individuals in whom an unenhanced and contrast-enhanced CT scan had been made sequentially (Chapter 7). Agreement between unenhanced and contrast-enhanced scans was excellent for muscle mass (different tube voltage, ICC 0.952; same tube voltage, 0.997) and poor (different tube voltage, ICC 0.207) or good (same tube voltage, ICC 0.682) for muscle density. Because contrast-enhancement slightly influenced muscle mass and into
a greater extent muscle density, contrast acquisition parameters should be similar in order to reliably evaluate (change in) muscle mass and -density.

*Taste alterations during treatment with protein kinase inhibitors*

The pathobiology of patient-reported taste alterations during treatment with protein kinase inhibitors is unknown. Potential mechanisms in which protein kinase inhibitors cause taste alterations are via oral mucositis, by distortion of signal transmission for taste or smell or by impaired renewal of receptor cells for taste or smell *(Chapter 8)*. The different hypotheses would lead to specific objective changes. In a pilot study in 18 patients *(Chapter 9)*, 61% reported taste alterations since start of treatment. Patient-reported decreased taste sensations were not related to objective changes in taste are smell function, whereas a painful mouth – an indicator of oral mucositis – was related to a patient-reported decreased taste sensation. These studies provide novel insights in the pathobiology of protein kinase inhibitor induced taste alterations and support future research needed for development of treatment modalities.

*General conclusions and recommendations*

A low muscle mass in patients with metastatic cancer is prevalent and is associated with adverse outcomes. During chemotherapy, loss of muscle mass was not attenuated by intensive nutritional counselling. However, nutritional counselling improved body weight, progression free survival and overall survival. This effect should be confirmed in future clinical trials, which should preferably be powered on survival. It should also be studied how nutritional counselling exerts its effects on survival and whether nutritional counselling of all patients undergoing chemotherapy is indicated, or if nutritional counselling is effective in only a subgroup of patients. Also the effect of multimodal treatment including supervised physical exercise has to be evaluated. During treatment with protein kinase inhibitors, patient-reported taste alterations are a prevalent side effect. These seemed to be related to oral mucositis. Future studies are needed to confirm this and to develop potential interventions to reduce or prevent this toxicity. It should also be studied whether these taste alterations impair dietary intake and thereby result in loss of muscle mass.

Altogether, this thesis contributes to the knowledge about nutrition-related symptoms and about the effect of nutritional counselling in patients with metastatic cancer. Based on the results, implications for future research are provided, in order to optimize nutritional treatment and improve clinical outcomes in these patients.