General discussion

A low muscle mass before treatment and loss of muscle mass during chemotherapy is known to be related to poorer clinical outcomes in cancer patients. The studies described in this thesis evaluate the effect of nutritional counselling on muscle mass and clinical outcomes. Also, information needed for interpretation of muscle mass is provided. Furthermore, nutritional aspects – in particular taste alterations – during treatment with protein kinase inhibitors were studied. The main findings of the studies are discussed in this chapter, as well as methodological considerations and implications for clinical practice and future research.

Main findings and comparison with literature

**Dietary intake in patients with colorectal cancer**

Cancer cachexia is caused by a negative protein and energy balance driven by a reduced food intake and abnormal metabolism.\(^1,2\) It is associated with a reduced quality of life, poorer treatment tolerance and shorter survival.\(^5-12\) Whilst treatment of metabolic changes mainly concerns treatment of the underlying cancer, reduced dietary intake can be targeted by nutritional intervention. Early identification of patients with a reduced dietary intake could provide the opportunity to prevent malnutrition with timely nutritional intervention.\(^13\) In a large cohort (n=1131) of hospitalised patients with colorectal cancer 54% ate less than normal (Chapter 2). Factors associated with a reduced dietary intake were being female, a higher cancer stage, a worse self-reported performance score, a longer duration of hospital stay and unintentional weight loss. In addition, the symptoms having pain, lacking appetite and feeling weak, tired or depressed were significantly associated with reduced dietary intake. Most of these characteristics have previously been identified as nutritional risk factors.\(^9,14-16\) The results in our study were derived from a larger sample and provide a more complete overview of determinants of a low dietary intake in patients with colorectal cancer. Knowledge about these determinants facilitate early recognition of patients at risk of malnutrition and may optimise nutritional treatment. Management of related symptoms may have to be incorporated to achieve an optimal nutritional intake.

*Nutritional intervention during chemotherapy*
Evidence for the effectiveness of nutritional intervention in patients with cancer undergoing systemic treatment is scarce. Guidelines recommend a target energy intake between 25 and 30 kcal/kg body weight and a target protein supply of at least 1.2 g/kg body weight per day, noting that the level of evidence is low and effects of nutritional intervention on clinical outcomes has yet to be determined.\textsuperscript{13,17} Standard practice in patients undergoing systemic cancer treatment comprises referral to a dietitian when indicated, depending on shared-decision-making by patient and the treating oncologist. In Chapter 3 and Chapter 4, we describe a randomized controlled trial in patients with metastatic colorectal cancer evaluating the effect of individualized nutritional counselling on muscle mass during chemotherapy. As secondary outcomes, body weight, quality of life and clinical outcomes were studied. Patients in the intervention group received intensive nutritional counselling, mostly also including prescription of oral nutritional supplements or tube feeding. The dietitian also provided simple physical activity recommendations. Nutritional counselling resulted in higher energy- and protein intake compared to usual care (energy 115 vs 95\% of the intake goal, \textit{p}=0.010; protein 111 vs 90\% of the intake goal, \textit{p}=0.010). Nutritional counselling had no beneficial effect on muscle mass. However, nutritional counselling improved body weight (during the first cycles of chemotherapy), progression free survival and overall survival. A previous pilot study in cachectic patients with different types and stages of cancer (TiCaCo trial, \textit{n}=20) showed similar results. In this pilot study, tight caloric control aimed at equalling total energy expenditure resulted in higher caloric intake (1655 versus 1278 kcal), weight maintenance and improved survival.\textsuperscript{18} Our randomized controlled trial comprises a larger and more homogeneous population regarding type and stage of cancer. Nutritional counselling started at the first cycle of chemotherapy, in order to prevent a deterioration of nutritional status in an early (precachectic) phase, while most previous nutritional intervention studies included more cachectic or even refractory cachectic patients. Although we hypothesized that nutritional counselling would improve outcomes via muscle mass, this was not supported by our results. The beneficial effect of nutritional counselling on survival may be mediated by other factors. Frequent consultations may result in better symptom management or other treatment choices, as also hypothesized to explain the effect of early palliative care on survival.\textsuperscript{19-21} However, for dietetic consultations this explanation is less obvious. Moreover, increased availability of nutrients including amino acids, vitamins, minerals and trace elements may increase anti-tumor response via the immune system.\textsuperscript{22-25} Nonetheless, how nutritional counselling exerts its effects on survival remains elusive. Future trials powered on survival should confirm the beneficial effect of nutritional counseling and will have to investigate the mechanism whereby survival is improved.
No previous studies have evaluated the effect of nutritional counselling on muscle mass in a comparable population. Thus far trials evaluating the effect of dietary counselling and/or high-energy oral nutritional supplements have focussed on body weight and showed no effect of intervention, partially explained by the difficulty of patients achieving the intake goals. The current study shows that intensive nutritional counseling including prescription of oral nutritional supplements when intake from regular foods falls short, results in increased energy and protein intakes and increases body weight. The lack of an effect on muscle mass indicates that increased energy and protein intake may not be sufficient to counteract metabolic changes related to muscle loss in cancer patients. Probably an intervention mainly focussed at adequate energy and protein intake is not sufficient for maintenance of muscle mass, but should by supported by physical exercise.

Although our intervention included simple recommendations to perform moderate intensity physical activity (e.g. walking, cycling or swimming) for at least 30 minutes per day, adherence to these recommendations was low (24% at T1 and 14% at T2). This may have contributed to the lack of an effect of the intervention on muscle mass or strength. In previous studies showing a beneficial effect of physical activity on muscle strength in patients treated for metastatic cancer, physical exercise sessions included resistance and endurance training, were done twice a week and supervised by a physio- or sport therapist. Adherence to the sessions was 69 and 88%. This implicates that more focus on resistance training is needed to affect muscle strength, compared to our recommendations focussed on moderate intensity physical activity. In addition, supervision of physical exercise is important for adherence to exercise intervention.

Cancer cachexia identification

Within the same cohort, 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. Possibly clinical assessment may result in an underestimation of the cachexia prevalence. On the other hand, the cachexia prevalence may be overestimated using the Fearon et al (2011) criteria. Other studies comparing cancer cachexia criteria also found a higher prevalence of cachexia using the Fearon et al (2011) criteria compared to other criteria. No previous studies have evaluated the agreement of clinical assessment by the oncologist with the Fearon et al (2011) criteria. Although the cancer cachexia criteria
Muscle mass measured by CT analysis

The negative protein and energy balance in cancer cachexia result in loss of muscle mass. Muscle mass is one of the main cancer cachexia parameters according to Fearon et al (2011).\(^1\) In patients with cancer muscle mass is often determined using computerized tomography (CT) scans, acquired during routine care for diagnostic purposes. Several studies have defined cut-off values for skeletal muscle index (SMI, i.e. muscle mass adjusted for height) based on optimal stratification with outcomes in patients with cancer. The most commonly used cut-off values for SMI in cancer patients before start of treatment are defined by Prado et al. and by Martin et al., both determined by optimal stratification for survival. Prado et al. defined cut-offs for SMI associated with mortality in obese (BMI \(\geq 30\) kg/m\(^2\)) patients with a solid tumour (n=250). The cut-off was 52.4 cm\(^2\)/m\(^2\) in men and 38.5 cm\(^2\)/m\(^2\) in women, with 15% of the patients having a SMI below this cut-off.\(^34\) Cut-offs defined by Martin et al. were derived from patients with gastro-intestinal or respiratory tract cancer (n=1473), resulting in gender- and BMI specific thresholds (men: 43 cm\(^2\)/m\(^2\) if BMI <25 kg/m\(^2\), 53 cm\(^2\)/m\(^2\) if BMI \(\geq 25\) kg\(^2\) and women: <41 cm\(^2\)/m\(^2\)). The prevalence of a low muscle mass was 31% in men and 53% in women.\(^35\) Although these cut-offs seem to have a prognostic value and indicate that a low muscle mass is common in cancer patients, the cut-offs do not provide any indication of a patient’s muscle mass compared to a healthy reference population. Therefore, we defined percentiles of skeletal muscle measurements derived from a healthy Caucasian population (Chapter 6). When the gender- and BMI specific cut-offs defined by Martin et al. were applied to this healthy population, in which the mean age was 53 ± 11 years old, the prevalence of a low muscle mass was 49% (men 33% and women 59%). This implies that the prevalence of a low muscle mass in patients with cancer (31% in men and 53% in women) is comparable to that of a healthy reference population. However, the American population of Martin et al. may not be comparable to the Dutch population and race specific cut-offs may be required. Our
reference values derived from a healthy population will facilitate interpretation of muscle parameters in disease and indicate what a normal muscle mass is in Caucasian individuals, taking a patient’s gender, body mass index and age into account.

When interpreting SMI in cancer patients and comparing it with healthy controls, the use of contrast enhancement should be considered. The abovementioned studies by Prado et al. and Martin et al. included both contrast enhanced and unenhanced scans, while our normative values in the healthy population were defined including only unenhanced CT scans. We found that the use of a iodinated contrast agent slightly increased skeletal muscle mass measured on CT. Contrast enhancement also affected muscle density (Chapter 7). This is likely to be caused by presence of the iodinated contrast agent in skeletal muscle – either intravascular or interstitial – leading to more radiation absorption by the muscle. Our results of the effect of contrast enhancement on muscle mass and – to a greater extent – on muscle density has recently been confirmed by more recent studies.\textsuperscript{36,37} For reliable evaluation of (change in) muscle mass, contrast acquisition parameters should therefore be similar.

\textit{Taste alterations during treatment with protein kinase inhibitors}

Protein kinase inhibitors constitute a type of targeted agents that induce disease stabilization in a variety of tumour types. In the last decade several protein kinase inhibitors have been approved as standard of care. Due to increased clinical use of these agents, physicians are faced with a new spectrum of toxicity.\textsuperscript{38,39,40,41} Commonly occurring toxicities are oral side effects including taste alterations. In Chapter 8 we describe several hypotheses of the pathobiology of patient-reported taste alterations. Based on their mechanism of action, protein kinase inhibitors may alter taste experience via oral mucositis, distortion of signal transmission for specific taste qualities, distortion of olfactory signal transmission or impaired renewal of receptor cells for taste or smell. The different hypotheses would lead to specific objective changes. Patient-reported and objective changes in taste and smell during treatment with protein kinase inhibitors were evaluated in a pilot study described in Chapter 9. Taste alterations were reported by 61\% of the patients. We found no difference in the change of taste or smell function between patients reporting a decreased taste sensation versus patients reporting no taste alteration, whereas a painful mouth – an indicator of oral mucositis – was related to a patient-reported decreased taste sensation. A previous study showed a similar prevalence, with 7 out of 13 patients (54\%) treated with a tyrosine kinase inhibitor reporting taste alterations.\textsuperscript{42} There are no other studies evaluating patient-reported taste
alterations or no studies objectively measuring taste and smell function during treatment with protein kinase inhibitors. During chemotherapy, studies showed a decrease in objective taste and/or smell function.\(^4\)\(^3\)\(^-\)\(^4\)\(^5\) One study showed no association between objective taste function and oral mucositis.\(^4\)\(^3\) However, the manifestation of protein kinase inhibitor induced toxicities differs from chemotherapeutic toxicities and a different pathobiology is expected.\(^4\)\(^0\),\(^4\)\(^6\),\(^4\)\(^7\) Another study found that patient-reported and objective taste function in patients treated with chemotherapy were not associated.\(^4\)\(^5\) This is in line with our study and may be explained by the fact that the sense of taste is often confused with flavor, a combined sensation resulting from taste, smell, temperature and tactile information.\(^4\)\(^8\) Our studies provide novel insights in the pathobiology of protein kinase inhibitor induced taste alterations and support future research needed for development of treatment modalities.

### Methodological considerations

This thesis includes studies with a diversity of designs. The strengths and limitations of the studies have already been described in each chapter. In this section the most important methodological considerations are summarized.

We performed a randomized controlled trial to evaluate the effect of nutritional counselling on muscle mass in patients undergoing chemotherapy for metastatic colorectal cancer (Chapter 3 and Chapter 4). A randomized controlled trial is the preferred design for a clinical trial to evaluate effectiveness of an intervention. Ideally such a trial should be double-blinded. Due to the nature of the intervention, only a single blind design was possible. Contradictory to our hypothesis, we did not observe an effect of nutritional counselling on muscle mass measured on a single CT slice at the lumbar level. Although muscle mass assessment at the lumbar level has been validated for total muscle mass,\(^4\)\(^9\),\(^5\)\(^0\) it might not be sensitive enough to detect relatively small changes in muscle mass. In addition, changes in muscle mass may not be proportional throughout the body.

The studies reported in Chapter 8 and Chapter 9 involve a literature review and a pilot study into patient-reported taste alterations induced by protein kinase inhibitors. These studies provide new insight in potential causes of these taste alterations. A limitation of these studies is the inclusion of a variety of protein kinase inhibitors, while
induced taste alterations may be protein kinase inhibitor specific. Furthermore, the number of patients included in the pilot study was limited (n=18). However, this is the first research into the etiology of these taste alterations, providing important information for future research. An overall limitation of observational studies (also Chapter 2, 7) is that no conclusions on causality can be drawn. Based on these observational studies, intervention trials may be needed to confirm causality and to evaluate whether interventions to prevent or treat taste alterations is effective.

**Clinical implications and future perspectives**

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

Our randomised controlled trial shows no effect of nutritional counselling on muscle mass, but suggests nutritional counselling may improve body weight and survival of patients with metastatic colorectal cancer undergoing chemotherapy. How nutritional counselling influences survival remains elusive and should be further studied. Future trials powered on survival are needed to confirm this effect.

Furthermore more multimodal interventions should be studied, including nutritional support to energy and protein intake, anti-inflammatory therapy to counteract the metabolic changes associated with loss of muscle mass and aerobic and resistance exercise to stabilize muscle mass and muscle strength. Physical exercise sessions should preferably be supervised to optimize adherence. In currently ongoing trials the effect of a multimodal intervention including nutritional intervention and supervised physical exercise are being evaluated.

CT slice analysis is the preferred method to evaluate in patients in whom CT scans are performed as part of routine care, which often is the case in cancer patients. For interpretation of skeletal muscle mass estimated by CT slice analysis, this should be compared with the skeletal muscle mass of a healthy reference population. CT scans should preferably be performed with the same contrast enhancement conditions, especially when muscle density is evaluated. Equations to calculate protein requirements based on skeletal muscle mass should be developed in order to adjust protein recommendations to muscle mass. Although CT slice analysis at the lumbar level has been validated for total muscle mass, further studies are needed to evaluate what outcomes are best used as sensitive measures for change in muscle mass.

The studies into taste alterations during treatment with protein kinase inhibitors show a high prevalence of patient-reported taste alterations. During treatment, development of oral mucositis and changes in the
sensitivity for specific taste qualities may alter the taste experience of the patient. Further research in a larger cohort during treatment with the same PKI is needed to study the contributing role of oral mucositis and to further objectify the changes in taste function during treatment with protein kinase inhibitors. Effects of taste alterations induced by these targeted agents should also be studied. For instance, taste alterations may impair dietary intake and thereby result in loss of muscle mass. A low muscle mass in patients treated with protein kinase inhibitors is in its turn related to dose-limiting toxicities. Currently there are no treatment options for patient-reported taste alterations. Management is limited to recommendations including avoiding specific foods and practicing good oral hygiene in order to achieve sufficient dietary intake and prevent malnutrition. Once there is a better understanding of the underlying pathobiology, potential interventions to reduce or prevent this toxicity should be evaluated.

**Conclusion**

Systemic treatment of patients with cancer often has nutrition-related side effects, including taste alterations and a decreased dietary intake. This may result in a loss of muscle mass, which is related to adverse outcomes in patients undergoing chemotherapy. Intensive nutritional counselling aimed at sufficient protein- and energy intake during chemotherapy did not have an effect on muscle mass measured at the lumbar level. However, nutritional counselling did improve body weight, progression free and overall survival. The mechanism behind the effect of nutritional counselling on survival remains elusive and should be further studied. 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.
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