

# Ovarian cancer cachexia

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## **Impact paragraph**

## Introduction and results

Ovarian cancer is a highly lethal malignancy. Around 1300 women are diagnosed with ovarian cancer on a yearly basis in the Netherlands, with an approximate mortality of around 1000. Treatment consists of surgery supplemented with chemotherapy. Although there have been some improvements in survival rates, chances for cure remain slim. Five-year survival is estimated at 20-60% for advanced stage ovarian cancer. Therefore, the search for therapeutic targets remains ongoing. The patients' metabolic phenotype has recently gained considerable attention in this context. It was recently seen that ovarian cancer patients who lost skeletal muscle during chemotherapy experience shorter overall survival. Although these are intriguing results, the potential causality between diminishing skeletal muscle tissue and worse overall survival has yet to be determined. Additionally, guidelines or protocols for determining skeletal muscle mass and quality based on radiological imaging were lacking.

This dissertation focuses on body composition measurements and on unravelling skeletal muscle pathophysiology in ovarian cancer patients. The aim of this dissertation was to gain more insight into the association between skeletal muscle measurements and outcome in ovarian cancer patients undergoing surgery and/or chemotherapy. Patients undergoing primary debulking surgery with low baseline skeletal muscle mass as seen on CT-scan experienced worse overall survival when compared to patients with normal skeletal muscle mass. Although previous results showed a clear survival disadvantage for ovarian cancer patients losing skeletal muscle during neoadjuvant chemotherapy, these results were not reproducible in the largest validation cohort to date. However, an interesting association between diminishing skeletal muscle mass and adverse events was detected. A review and meta-analysis confirmed the association between low skeletal muscle index and ovarian cancer survival. However, the validity of this conclusion was hampered by the heterogeneity in used measurement protocols and cut-offs for body composition precluded drawing definitive conclusions. Evidence produced in this thesis provided a sound method for calculating skeletal muscle using CT-scanning. Efforts were made to elucidate mechanisms underlying skeletal muscle tissue loss and ovarian cancer outcome. Cultured skeletal muscle cells were exposed to ascites derived from ovarian cancer patients. Cells exposed to ascites derived from cachectic patients had a lower capacity for protein synthesis. CT-scans were supplemented with extensive physical screening to distinguish cachectic from non-cachectic patients. Data extracted from the physical fitness screening revealed several intriguing correlations between radiological imaging and experimental outcomes. These results underline the importance of complementing radiological imaging with screening for physical fitness.

## Scientific impact

Based on data provided in this thesis, it was proposed to use total skeletal muscle area at the third lumbar vertebra on CT-scans to assess skeletal muscle in ovarian cancer patients. These results were highly cited (73 times) since their publication. This method of assessment has since been widely accepted as a valid way of estimating skeletal muscle mass in (ovarian) cancer patients. Other results of this thesis contributed to determining the relationships between skeletal muscle mass and ovarian cancer survival. It was proposed to use changes in skeletal muscle mass during neo-adjuvant chemotherapy to distinguish sarcopenic from non-sarcopenic patients instead of single measurements in time with a clearly defined cut-off. Although a prospective validation study failed to reproduce a relationship between overall survival and skeletal muscle, a strong correlation between skeletal muscle mass and chemotherapy related toxicity was observed. Based on the observed correlation between skeletal muscle mass and toxicity a future trial should investigate the dosing of chemotherapy based on body composition and its potential impact on the prevention of dose limiting toxicities, thereby translating scientific results to clinical practice. Additionally, skeletal muscle protein synthesis in cultured skeletal muscle cells was negatively affected by exposure to ascites from ovarian cancer patients, introducing a new and accessible tool in translational cachexia research. This approach will shed new light on how skeletal muscle aberrations may originate in cancer patients, since the known genes in skeletal muscle catabolism were not affected by factors in ascites. All the results of this thesis were presented at international conferences and were published in internationally peer reviewed journals.

## Societal impact

Cancer cachexia is a severe and debilitating condition which severely impacts quality of life, survival, treatment efficacy, and psychosocial symptoms and distress. This thesis has revealed relationships between low skeletal muscle mass and impaired outcome in ovarian cancer patients. These outcomes are highly relevant to ovarian cancer patients and their physicians. Body composition analyses could serve as a tool for identifying patients at risk of adverse outcomes in the future work-up of ovarian cancer patients. Body composition measurements could be used for calculating dose administration for systemic cytotoxic therapy and for better shared decision-making for therapy. They could additionally serve as a gateway to improve peri-operative intervention programs, the likes of which have already been implemented in several healthcare institutions. Special attention should be directed at the psychosocial impact of cachexia in ovarian cancer patients. Although very prevalent in cancer patients in general, cachectic patients are even more affected by the psychological and physical aspects of their disease. In conclusion, body composition measurements are not only useful in the context of developing anti-tumor treatment strategies but also have an important role in defining patients at risk of developing adverse psychosocial symptoms and low quality of life related

to their disease. Hence, this thesis also serves to raise awareness about cancer cachexia and its debilitating effects on ovarian cancer patients.

Cancer cachexia also has a profound societal impact. Recent analyses have shown that (cancer) cachexia carries a heavy burden on healthcare costs and hospitalization. Length of stay for cachectic patients was twice as high in comparison to non-cachectic patients, and costs of hospitalization were increased with 4600 euros per hospitalization. In this age of ever-increasing healthcare expenditure, reduction of costs requires special attention. Intervention programs might aid in reducing length of stay and decrease healthcare expenditure for cachectic patients. The methods described in this thesis will aid in distinguishing patients eligible for intervention programs.

## **Activity**

The results of this thesis provided a blueprint for a prospective study evaluating skeletal muscle fluctuations and adverse events in ovarian cancer patients receiving chemotherapy, thereby reaching out to healthcare professionals and patients alike. Efforts have been put into raising awareness and attention to the issue of cancer cachexia. The need for awareness and the effect of intervention studies was addressed in the recent 'kankerkachexie, het belang van het behoud van functie' symposium, where results of this thesis were also presented. Physicians, physician assistants, movement scientists, physiotherapists, and other paramedical staff participated in the symposium. A multidisciplinary approach of addressing cancer cachexia seems to be the way forward. Preservation and maintaining physical functioning, sensory functioning, and personalized medicine in oncologic patients were also embraced by the MUMC+ future perspectives which were addressed in the 'Gezond leven 2025' article. Since the inception of the "Journal of Cachexia, Sarcopenia, and Muscle" in 2010, which focuses on wasting diseases, the number of publications on (cancer) cachexia rose significantly. Its annual conference gained the topic of wasting diseases in oncology significant attention. Results from this thesis were presented on a yearly basis at this conference. However, translation of pre-clinical results to clinical intervention trials is still lacking, a statement which was also expressed by the society on "Cachexia, Sarcopenia, and Wasting Disorders". The PRIMs protocol presented in this thesis is a step in the right direction. However, more efforts could be made towards the inception of new trials and communication towards patients and patient organizations. Much is potentially to be gained in terms of healthcare expenditure, quality of life, psychosocial functioning, and survival of cancer patients. Therefore, the issue of wasting disease in oncology will hopefully gain more attention from patient organizations and healthcare providers as well as insurance companies. Researchers should meanwhile continue addressing the relevance of cancer cachexia.