Frailty and outcomes in older cancer patients

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GENERAL DISCUSSION

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This thesis addresses current treatment strategies in older cancer patients, as well as the consequences of these decisions for clinical outcomes. In addition, this thesis investigated the value of frailty assessment in different cancer populations and described the implementation of a multidisciplinary team approach in frail older cancer patients.

In this final chapter, reflections on our findings are presented, placed in a broader perspective and recommendations for future research are given. The case presented in box 1 will be referred to throughout the discussion.

Box 1: clinical scenario
A 73-year old women with a history of diabetes mellitus type II, hypertension, chronic obstructive pulmonary disease gold III (COPD), atrial fibrillation, left ventricular ejection fraction of 30% and a transient ischemic attack was referred for a right sided hemicolectomy because of a symptomatic T3N1 colon carcinoma. The surgeon doubted whether she was fit for surgery. In order to obtain more information on her general health status and to aid in preoperative decision making, she was referred for a comprehensive geriatric assessment and multidisciplinary team (MDT) meeting. Geriatric assessment revealed a risk for malnutrition due to recent weight loss, slow gait speed and low grip strength. The patient used nine prescription drugs, including oxazepam twice daily for anxiety. Her physical complaints were abdominal pain and rectal blood loss. She lived alone, since her husband passed away three years ago. She used to play bridge three times a week at the local church. Since three months she spent most of her days inside her house watching television. She was unable to run her household, without the help of her two daughters. Cognitive screening revealed a mild cognitive impairment, which increased the risk of postoperative delirium. Laboratory results revealed a hemoglobin level of 6.4 mmol/l, ferritin 7ug/l and a glucose of 15.1 mmol/l (HbA1c 73 mmol/mol). The patient was very motivated to undergo surgery, but emphasized that independent living (good enough to play bridge and see her friends), without suffering from rectal blood loss and abdominal pain was most important.

Box 1: Continued

At the preoperative MDT meeting the pros and cons of surgery were carefully weighed. The risk of losing functional capacity and independency after surgery was considered high. The prehabilitation program consisted of exercise and respiratory muscle training, nutritional support and treatment with intravenous iron. A pulmonologist and internist were consulted to optimize treatment of COPD and diabetes. Anticoagulants were temporarily discontinued to reduce rectal bleeding and oxazepam use was tapered off by the general practitioner. After 4 weeks, rectal bleeding was largely reduced and the hemoglobin level was increased to 7.4 mmol/l. Her mobility and grip strength had improved and she resumed to play bridge. She gained two kilograms in body weight and her blood glucose curves were acceptable. Oxazepam use was limited to twice weekly, to help her cope with stress. After a reassessment by the MDT, the patient was considered fit for surgery, although the risk of adverse outcome remained high due to multiple chronic diseases. Despite non-pharmacological delirium prevention, surgery was complicated by a mild delirium. She stayed in hospital stay for 7 days after which she was discharged with home care. Her self-reported physical Health Related Quality of Life (HRQL) was better three months after surgery, but her mental HRQL was lower. Six weeks after surgery she played her first game of bridge again.

Anti-cancer treatment in older patients

In an ageing population the number of older patients that are diagnosed with cancer has increased.[1] The ageing of the population has a major impact on oncological care. One of the challenges in treating older cancer patients is their heterogeneity in multiple domains, including overall health, functional status, severity of comorbidities and presence of geriatric syndromes.[2,3] These characteristics increase the risk of adverse outcomes.[4–9] Anti-cancer treatment in older patients aims to improve survival while maintaining health related quality of life and daily functioning. Therefore, a careful consideration of treatment options regarding risks for adverse outcome versus survival gains are essential in order to make the right treatment decision. Risk stratification in older cancer patients is complicated because robust outcome data are currently lacking. Besides, acceptable risk varies greatly between patients.

In the past years, the development of a patient-centered treatment plan, including frailty characteristics, to optimize shared decision making and reduce adverse outcomes has gained interest.[10–12] Concurrently, different treatment strategies have been developed

to make cancer treatment more appropriate for the older population. If a treatment that is less harmful is preferred, it does not always mean that there are no treatment options. For instance, endoscopic resection of early stage tumors in colorectal cancer (CRC) patients, short-course radiotherapy with delayed or no surgery in rectal cancer patients, offering monotherapy chemotherapy instead of combination chemotherapy and bladder-sparing approaches such as (chemo)radiation in older bladder cancer patients.[4,13–15] The oncologic effect might not be as strong as the standard treatment, but the risk of adverse events will be less pronounced. An illustration of treatment changes in Dutch cancer patients is shown in **Chapter 2**. This population-based study in Dutch CRC patients aged 70 years and older showed that non-surgical treatment was more often performed over time. In 2014, 3.7% of colon cancer patients had non-surgical treatment compared to 4.8% in 2018. Similar results were shown in rectal cancer patients (17.1% vs 20.2%).

Furthermore, survival benefits were reported for rectal cancer patients treated with (chemo)radiotherapy compared to the no-treatment group, which implies that less invasive and harmful treatment options should be considered in frail older CRC patients. Current treatment decisions are often based on clinical judgement, because the evidence for evidence based medicine of anti-cancer treatment in older patients is lacking.[16] Consequently, treatment decisions vary between clinicians, resulting in a risk of over- or under treatment.[17] The results in **chapter 3** support the hypotheses of the possible risk of under treatment in Dutch older rectal cancer patients.[18] Although neoadjuvant chemoradiotherapy was well tolerated, a small proportion (9%) of patients was received this treatment.

Furthermore, treatment decision are often more complicated in older patients, because of a limited life expectancy, multiple comorbidities, geriatric impairments and a large variety in treatment goals (e.g. longevity, disability-free survival, satisfactory health related quality of life). Therefore, treatment decisions in geriatric oncology cannot depend on the clinical judgment of a single physician.[19,20] This is supported by our findings in **chapter 4**.[21] Half of the older patients who were examined by an experienced physician (oncologist/oncological surgeon) and considered fit for palliative chemotherapy, experienced grade 3 toxicity and/or needed treatment modifications. Apparently, clinical judgement by a single physician is not always sufficient to predict adverse outcomes in older patients. Understanding the influence of frailty on adverse outcomes in patients undergoing anti-cancer treatment is therefore essential in order to improve treatment decisions.

Frailty

Frailty is an age-related clinical syndrome that is commonly defined as a state of reduced functional capacity and occurs as a consequence of the cumulative decline in many physiological systems over a lifetime.[22] Frail patients are vulnerable for external stressors such as anti-cancer treatment (e.g. surgery, chemotherapy, radiotherapy). As older age and comorbidities are often associated with frailty, it seems reasonable to take frailty characteristics into account to improve treatment decisions in the growing cohort of older cancer patients.[23]

In this thesis frailty was evaluated in different older cancer populations. Geriatric impairments were highly prevalent in older Dutch cancer patients and were associated with adverse outcomes. One or more geriatric impairments were present in 71% of patients undergoing palliative chemotherapy **(Chapter 4)** and 45% of non-metastatic colorectal cancer (CRC) patients **(Chapter 5)**.[21,24] The incidence of one or more geriatric impairments was the highest (82.5%) in patients undergoing radical cystectomy **(Chapter 6)**.[25] In all of these studies frailty was associated with adverse outcome, including postoperative complications, worse survival and a clinically relevant deterioration in health related quality of life **(Chapter 4, 5, 6, 7)**.

These findings stress the importance to screen for geriatric impairments and incorporate frailty characteristics in anti-cancer treatment decision making. However, the implementation of frailty into routine oncologic care has been hampered. Frequently used arguments against use of a (comprehensive) geriatric assessment are that it is time and resource consuming. Besides that, the lack of consensus on the best instrument to diagnose frailty is another barrier. This thesis aimed to construct a comprehensive frailty model to aid decision making in Dutch older cancer patients. However, in our studies the associations between individual frailty characteristics and adverse outcomes were not uniform.

Of the physical frailty tests, the Timed to Get Up en Go test (TUGT) was associated with treatment modifications and grade 3 toxicities in older patients treated with palliative treatment **(Chapter 4).** Polypharmacy showed the strongest predictor in bladder cancer patients **(Chapter 6).**

And most important determinants for a decreased HRQL in CRC patients were comorbidity, impaired daily functioning and dependent living **(Chapter 7).**

There are several explanations for these different findings. First, frailty is not only dependent of an age-related decline. The cancer related burden of disease may induce 'cancer-related frailty'. As shown in box 1, the patient suffered from a bleeding

tumor resulting in anemia. This reduced gait speed, mobility and muscle strength. Consequently, the type of cancer and the cancer related symptoms likely affect the association between frailty characteristics and outcome. Another explanation could be that our selection of frailty questionnaires and tests may not reflect the full frailty status of the patient. Also the differences in anti-cancer treatment may influence the association between frailty and adverse outcomes. Finally, adverse outcomes such as complications, deterioration in HRQL and chemotherapy intolerance depend not only on frailty related factors.

Although the results are heterogeneous, frailty tests predict adverse outcomes **(Chapter 4, 5, 6, 7)**. This indicates that frailty screening and decision making in older patients demand a personalized approach. We advocate the implementation of a quick frailty screening in older cancer patients. Several two-stepped models have been described in literature, in which all patients undergo short simple frailty screening, and only those with abnormal test scores undergo a complete comprehensive geriatric assessment. For example, the G8 (Geriatric 8) and the 6-CIT (6 item Cognitive Impairment Test) have a good sensitivity for detecting geriatric impairments and for identifying the patients who will benefit from a complete comprehensive geriatric assessment.[26,27] This was confirmed in **Chapter 5**. Such frailty screening can categorise patients into 'non-frail' patients in with low chances of adverse events and 'frail' patients who have a higher risk. Subsequently, a complete risk profile including comorbidities, frailty characteristics and expectations/priorities of the frail patients should be constructed. Results of the complete risk profile should discussed in a MDT meeting. Similar to other medical specialties, a collaborative approach of multiple specialties in a MDT seems suitable in these complex patients.

The outcomes of de MDT meeting should be discussed with the patient and care-givers. In addition to improving risk assessment for adverse outcomes, frailty screening has the ability to facilitate targeted prehabilitation.

Prehabilitation

Prehabilitation, defined as a multimodal approach to enhance a patient's condition prior to treatment has gained interest over the past years. The objectives of prehabilitation are: to reduce adverse outcomes, to enhance and speed up recovery and to improve health related quality of life (HRQL). Prehabilitation is so intuitive that a layman might wonder why prehabilitation programs are scarcely present in daily practice. The answer to this question is twofold: there is a lack of evidence for behavioral interventions and it requires a multi-disciplinary collaboration which is often experienced as a logistical challenge.

The goal of anti-cancer treatment in older patients is to prolong life while maintaining their level of daily functioning and HRQL. However, the ability to endure anti-cancer treatment requires substantial physical and psychological resilience of the human body. Considering that frailty is a risk factor for adverse outcome, it seems reasonable to focus on prehabilitation in order to reduce adverse outcomes **(Chapter 5)**. Improving baseline functioning may even make oncological treatment feasible that appeared too risk full. Furthermore, anti-cancer treatment often comprises of different treatment steps. This is why prehabilitation during the complete treatment course to retain fitness is essential. For example, neoadjuvant chemoradiotherapy in rectal cancer patients may reduce physical fitness, which potentially results in the transition of a patient from low to high risk for postoperative complications.

Prehabilitation also provides an opportunity for patients to be involved in their health journey. Prehabilitation can shift the classic 'waiting period' to a time frame in which patients improve their health, and thus increase their chances on improved outcome. In the clinical example shown in box 1, the patient was motivated to improve her physical condition, not only to prevent postoperative complications but also to increase her activity level. In most studies, the time interval for prehabilitation is 4 to 8 weeks, with shorter time periods for patients with high burden of disease.

Short preoperative timeframes can be a problem. However, fitness improvements can be made in as little as 2 to 4 weeks.[28] As shown in box 1, after 4 weeks the patient experienced a better physical condition. As a results, she was able to walk to church and resume playing Bridge. This example illustrates that an personalised prehabilitation program targets the physical, mental and social domains.

In recent years, research on prehabilitation has received considerable attention which has resulted in a wide range of mixed results.[29–32] Prior studies focused on single modal programs often on nutritional status or exercise training. Most studies concluded an improvement in physical and nutritional status, but demonstrated no significant effect on the reduction of adverse outcomes.[33,34] However, considering the multifactorial origins of a patient's vulnerability, a multimodal approach combining nutritional support, exercise training, physiological support, smoking cessations and anemia correction, might be more effective. In this respect, a multidisciplinary team (MDT) approach, as shown in **Chapter 5**, is more likely to deliver a tailored prehabilitation program than an individual physician. **Chapter 5** demonstrates that MDT care, that includes a prehabilitation program, can lead to similar rates of postoperative complications in frail and non-frail CRC patients.

Health Related Quality of Life

Prolonging survival is usually considered the main goal of anti-cancer treatment. However, maintaining or even improving quality of life can be equally important. Especially in older patients who have worse life expectancy in comparison with younger patients and may be less willing to exchange current quality of life for longevity. Change in health related quality of life (HRQL) should ideally be discussed, in addition to survival and risk of complications, when considering anti-cancer treatment options.[35]

Studies on change in postoperative HRQL in surgical cancer patients show that most patients benefit from surgery, but a significant number of patients experience a decrease in HRQL after surgery.[36–39] **Chapter 7** reported the short term outcomes (3 months follow up) of the multicentre prospective AGE-CRC (Advanced Geriatric Evaluation-ColoRectal Cancer) study. Ultimately, this study aimed to identify determinants for a decreased HRQL at one year after CRC diagnosis. Our findings confirmed that three months after CRC diagnosis, a significant proportion of older patients experienced a decreased HRQL. Patients with a non-surgical approach and those who experienced severe postoperative complications were prone to experience a deterioration of short term HRQL. Most important determinants of decreased HRQL were comorbidity, impaired daily functioning and dependent living at time of CRC diagnosis.

An important finding is that most preoperative determinants, including frailty, were poorly associated with a deterioration in HRQL (**Chapter 7).** The causes of a deterioration of HRQL are multifactorial and can vary over time, which makes HRQL a complex outcome measurement. This makes prediction of deterioration in HRQL challenging. Patient reported outcome measures (PROMs) are susceptible to subjectivity. Survivors of cancer have often described the period after treatment as more difficult than treatment itself. It brought feelings of uncertainty about the future and fear of cancer recurrence, while others experienced more positive feelings by resuming normal life.[40] Furthermore, cognitive disorders can lead to difficulty with understanding HRQL questionnaires, comorbidity and frailty may have a larger impact on HRQL than cancer itself.

In addition, adjuvant chemotherapy or changes in social environment (e.g. loss of a partner or family member) can negatively impact HRQL. Also, a patient's perception of their internal standards, values and conceptualization of HRQL may be reframed over time.[41,42] This concept is known as a response shift. For example, a patient may initially experience a worse mental HRQL after surgery. But, over time, the patient adapts and grows accustomed to the new circumstances and HRQL recovers to baseline. These variations in HRQL between and within patients, make predictions difficult and could partly explain the lack of associations with preoperative determinants.

Despite the difficulties in predicting HRQL, nowadays it is essential to implement such measurements not only in clinical trials, but also in the perioperative practice. HRQL assesses the impact of an intervention on a patient's life, rather than just their body or a single organ; information which is very relevant when counselling a patient on expected recovery.

Multidisciplinary team approach
Currently, most decisions regarding a treatment of cancer are first discussed in an oncological multidisciplinary team (MDT) meeting with the focus on the cancer diagnosis, rather than taking patients related factors such as frailty into account. Large differences in overall health and functional status, severity of comorbidities and presence of geriatric syndromes, raise the question of how to incorporate frailty screening and assessment in an oncological MDT meeting.

The increasing complexity of the management of older cancer patients and concerns of adverse outcomes demands accurate risk assessment.[43] Due to the absence of high-quality outcome data in frail patients, clinical consensus in the form of a MDT approach (experienced based medicine) may be the best available advice to guide patient selection for anti-cancer treatment **(Chapter 5)**. Older patients often suffer from multiple chronic diseases which demands a broader multidisciplinary approach. Similar to other medical specialties, a collaborative approach of multiple specialties in a MDT seemed suitable in these complex patients.

A MDT approach based on a geriatric assessment and patient preference can be beneficial in the development of a patient-centered treatment plan which is described in **chapter 5** of this thesis. **Chapter 5** showed that the implementation of such preoperative MDT care for frail patients with CRC improves risk stratification and prehabilitation, resulted in comparable short term outcomes for frail and non-frail patients.

Facilitators and barriers to the implementation of MDT care
With these goals in mind, a weekly MDT meeting in the St. Antonius Hospital for high risk surgical patients was set up in 2016. Prior to MDT meetings a comprehensive geriatric assessment is performed in patients to be discussed. The assessment includes tests or questionnaires in four domains **(Table 1, Chapter 5)**. During MDT meetings a team of dedicated (para)medical specialists including a medical and surgical oncologist, anesthesiologist, geriatrician, pharmacologist, physiotherapist, dietician and nurse specialist interpret pretreatment risk factors and construct a patient's tailored plan. The geriatric assessment can identify potentially modifiable risk factors. During the MDT meeting the following topics were addressed: indication of treatment, possible

less invasive treatment options, severity of comorbidities and frailty, burden of disease, expected prognosis with and without treatment, patient motivation, possibilities and time frame of prehabilitation. After the MDT meeting the treatment plan is discussed with the patient and care-givers by the treating specialist and nurse according to shared decision making principles.

Several benefits of MDT care for complex cancer patients are described above. Additional lessons can be learned from our experience. First, the implementation of a MDT approach demands a significant effort from every specialty. Time, preparation and attendance at MDT meetings is necessary in order to make optimal treatment decisions in complex cases. Second, accurate selection of high-risk patients to be discussed in MDT meetings is essential. Inappropriate referral may delay treatment in healthy patients in whom MDT involvement is redundant.

To limit the strain on available resources and prevent an unnecessary increase in patient burden, MDT care should be targeted at complex patients at high risk for adverse outcome. For example, the patient from the clinical example had multiple comorbidities and several impairments in frailty characteristics. As a result of the MDT meeting, her surgery was postponed and a prehabilitation program was considered and discussed with the patient. Her physical condition, nutritional status, anemia, COPD, diabetes mellitus and polypharmacy were optimised. The postsurgical course was only complicated by a mild delirium.

Anti-cancer treatment might be postponed when a prehabilitation program is advised. Ideally, patients must start their anti-cancer treatment within short time after diagnosis, because delaying this treatment can have major consequences such as the increase cancer related symptoms or the risk of tumor progression.

Last, to limit the increasing workload of physicians, standardized frailty screening tests as preparation for the MDT can be done by trained nurses. Although for a group of older patients with complex multi-morbidity, cognitive disorders or comprehensive geriatric syndromes a full comprehensive geriatric assessment by a geriatrician should be performed.

FUTURE DIRECTIONS

Individualization is critical in the heterogeneous population of the older patients with cancer; one size does not fit all. Clinical consensus in the form of a MDT approach may be the best available advice for optimal cancer care in frail older patients. The findings of this thesis and the clinical experiences with the MDT meetings lead to the following considerations on development of clinical research for these patients and opportunities for clinical improvement.

Frailty characteristics are important when making treatment decisions in older cancer patients. A two-step frailty assessment that consists of a quick screening and more thorough assessment on indication seems logical. Future research should focus on these two-step models. Frailty characteristics should be reported systematically in clinical studies on cancer treatment in older patients. In trial designs frail older patients with multiple comorbidities are often excluded from participation, resulting in a limited generalizability of the results. Therefore, to increase the number of older cancer patients and to avoid selection bias of fit older patients participating in large trials, studies should be conducted differently. For instance, by applying less stringent exclusion criteria, development of specific trials for older patients and making studies more accessible for older patients. An additional practical solution is to do research visits at home as we have done in the AGE-CRC study, so older patients are more willing to participate. Willingness to participate can further be increased by incorporating research activities during routine hospital visits, and by providing follow up by telephone. When studying diseases in older patients, collaboration with other hospitals is essential. To perform studies in older CRC patients participation in the Prospective Dutch Colorectal Cancer Cohort (PLCRC) project will be helpful.[44] In this project systematic registration and collection of data is facilitated.

Offering all patients a 'one-size fits all' intervention fails to take individual needs into account which can lead to low compliance. However, each part of the prehabilitation program (e.g. nutrition or physical activity) needs to be standardized. Subsequently, data of all patients should be systemically collected to contribute to real world evidence.

The lack of evidence for MDT care in frail patients is a restricting factor for its implementation in standard care. Studies comparing MDT care with regular care are needed to assess potential benefits on adverse events and PROMs. A solution to add to evidenced based medicine in MDT care is to use a multi-centre and step-wedge design. Each centre includes a part of the control group, then implements the intervention and includes the intervention group. This reduces bias caused by changes in health care and contamination bias.

The following opportunities for daily clinical practice should be considered; first of all, careful patient selection is necessary for MDT care, otherwise it is too costly and time consuming. Using the G8 and 6-CIT questionnaires for patient selection seems appropriate and resulted in an average referral of two CRC patients a week for MDT care in our centre with 250 CRC surgeries annually.

Second, a complete risk profile of the patients is needed to facilitate a profound discussion during MDT meetings and during shared decision making with the patient. Regardless of the frailty assessment of choice, it is essential to evaluate the somatic problems of the patient, and to obtain information about the other three (physical, mental and social) main geriatric domains. These assessments need to be performed prior to the MDT meeting. Third, patient reported outcomes should be measured before and after anti-cancer treatment. Important outcome measures in older patients such as HRQL can be measured using PROMs. Yet PROMs are not structurally incorporated in clinical practice and the large amount of disease specific questionnaires might counteract compliance in patients with multimorbidity. These outcomes should be measured with validated tools from a perspective that matters to the patients and that is relevant to the intervention.

A solution could be one standard set of PROMs specific for older patients and their disease. It is important that the most sensitive PROM is selected for each disease and double questions are avoided. For instance, the International Consortium for Health Outcomes Measurements (ICHOM) assembled an international working group of health professional and patients representatives to develop a standardized minimum set targeted for clinical use.[45 46] The effect of treatment on HRQL should be discussed and used in counselling patients.

Last, the general practitioner (GP) should be invited to participate in the MDT when their own patient is discussed. In complex cases, the GP can provide information on the patient's personal and social history, which is important to ensure that the MDT treatment proposals are in line with the patient's needs and wishes. In this way, the GP can be involved in drafting the personal treatment plan and may participate in shared decision making, monitoring prehabilitation programs or advanced care planning.

This thesis described several steps to improve treatment decisions and prehabilitation in older cancer patients. It provides new understandings on frailty in older cancer patients. Findings from this thesis could be used to design new studies in older cancer patients and inspire to further improve care for older cancer patient using MDT care.

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