Frailty, functional status and quality of life in older patients after surgery for colorectal cancer

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SUMMARY

Background: Cancer is a disease mainly occurring in older individuals, which in part could be explained by some common pathogenetic mechanisms in biological aging and carcinogenesis. One of the most commonly occurring cancer types in the Western world is colorectal cancer, where about 60% of patients are ≥70 years old at the time of diagnosis. Older patients are characterized by a high degree of heterogeneity in terms of factors such as comorbidities, physical function and cognitive function. This is often inadequately reflected by their chronological age. Some older patients are further characterized by frailty, defined as a state of reduced biological reserves and increased vulnerability towards stressors. A geriatric assessment (GA) is recommended in the management of older cancer patients, and involves a thorough evaluation of physical function, comorbidity, cognitive function, nutritional status, emotional function, polypharmacy and social support. The GA may be a tool to identify frailty, but frailty could alternatively be identified by the physical frailty phenotype. The main treatment modality in colorectal cancer is surgery. Important treatment outcomes for older patients, in addition to survival and postoperative complications, are physical function and quality of life (QOL). However, little is known about the long-term impact of colorectal cancer treatment on these outcomes in the older population.

Aims:
- To investigate the trajectories of physical function and QOL in frail and non-frail individuals after surgery for colorectal cancer.
- To explore frailty and individual components of GA as possible predictors of poor functional outcome.
- To investigate the possible roles of serum inflammatory biomarkers as prognostic factors in this patient population.

Methods: The study was designed as a follow-up study. Patients were recruited from a previous observational prospective cohort study, were aged 70 years or older at baseline, and had undergone surgical treatment for solid tumors in colon or rectum. Preoperatively, patients were assessed by a GA which formed the basis for a frailty classification, QOL was measured by the European Organization of Research and
Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and preoperative blood samples for determining serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor – alpha (TNF-α) and D-dimer were collected. Finally, data from the preoperative assessment were used to classify patients according to a modified version of the frailty phenotype. Information about postoperative complications was collected retrospectively. The EORTC QLQ-C30 was repeated in most patients three months after surgery. For the current follow-up study, physical function was reassessed by activities of daily living (ADL) and instrumental activities of daily living (IADL) as well as physical performance tests. QOL was reassessed by the EORTC QLQ-C30. In addition, cognitive function was assessed by a battery of cognitive screening tests.

**Results:** A total of 84 patients were included in the follow-up study, representing 69% of those alive and available for inclusion from the original cohort. Median time to follow-up was 22 months (range 16-28). We found that preoperative circulating levels of CRP and IL-6 were higher in frail than non-frail patients, and IL-6 was an independent predictor of postoperative complications. A comparison of the GA-based frailty measure and the modified frailty phenotype revealed poor agreement between the two, and only the former was predictive of postoperative complications. We identified a significant decline in both ADL function and IADL function at follow-up compared to baseline, but no significant change for physical performance measures. Neither frailty nor individual components of a GA were able to predict poorer functional outcome at long-term follow-up. Overall QOL and emotional function improved three months after surgery in both frail and non-frail patients. At the long-term follow-up the scores had decreased, but to values above baseline.

**Conclusions:** In our population of older patients undergoing elective surgery for colorectal cancer, the long-term negative impact on functional status was minor, and the effect on QOL positive. A GA-based frailty definition was superior to a modified frailty phenotype in predicting postoperative complications in these patients. Levels of CRP and IL-6 were higher in frail than non-frail patients with colorectal cancer, and IL-6 seems to carry individual prognostic significance for postoperative complications.
Abbreviations

ADL – Activities of Daily Living
ANOVA – One-way repeated measures analysis of variance
ASA – American Society of Anesthesiologists
ASCO – American Society of Clinical Oncology
BDI – Beck Depression Inventory
CCI – Charlson Comorbidity Index
CGA – Comprehensive Geriatric Assessment
CIRS – Cumulative Illness Rating Scale
CRP – C-reactive Protein
CRT – Chemoradiotherapy
CXCCL-10 – CXC Chemokine Ligand 10
DXA – Dual Energy X-ray Absorptiometry
ECOG PS – Eastern Cooperative Oncology Group Performance Status
ERAS – Enhanced Recovery Program After surgery
EORTC QLQ C30 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
ESPEN – European Society of Parenteral and Enteral Nutrition
FACT-G – Functional Assessment of Cancer Therapy - General
GA – Geriatric Assessment
GDS – Geriatric Depression Scale
GPS – Glasgow Prognostic Score
IADL – Instrumental Activities of Daily Living
IL-6 – Interleukin-6
KPS – Karnofsky Performance Status
MCI – Mild Cognitive Impairment
MI – Myocardial Infarction
MMSE – Mini Mental State Examination
MNA – Mini Nutritional Assessment
NEADL – Nottingham Extended Activities of Daily Living
OTU – Overall Treatment Utility
PACE – Preoperative Assessment of Cancer in the Elderly
PI – Prime Investigator
PRO – Patient Reported Outcome
PROM – Patient Reported Outcome Measure
RCT – Randomized Controlled Trial
SIOG – International Society of Geriatric Oncology
sVCAM – Soluble Vascular Adhesion Molecule
TME – Total Mesorectal Excision
TMT – Trail-making Test
TNF-α – Tumor Necrosis Factor Alpha
TUG – Timed up-and-go
VES-13 – Vulnerable Elders Survey -13
QOL – Quality of Life
List of papers


* =Rostoft S (former name Kristjansson, Siri Rostoft).
INTRODUCTION

1 Approach to the older person with cancer

1.1 Biological aging and cancer

With few exceptions, increasing age is the most important risk factor for cancer. It has been proposed that molecular, cellular and systemic changes associated with normal aging are all involved in this development. For example, free radical generation, genomic instability, mutation rate and oxidative stress all increase with higher age, and are important steps of carcinogenesis (1). Interestingly, in individuals 85 years and older, epidemiological data suggest that the overall incidence of cancer disease decreases (2). It is possible that this phenomenon may, in part, be due to age-related changes that protect against carcinogenesis. Such changes may be decreased telomere length and angiogenesis, and increased apoptosis. The mechanisms behind this are not completely understood (3). However, for many cancer types, such as colorectal cancer, pancreatic cancer, stomach cancer and several soft tissue malignancies, incidence rates continue to increase after 85 years (2). It is hypothesized that for these cancers, continuous exposure to carcinogens through a long life is an important etiological factor.

With increasing age, estimated life expectancy decreases (4). Still, the rate in which the aging process develops differs between individuals - and older people are characterized by a high degree of heterogeneity. From clinical experience, we know that an 85-year-old individual may be much less affected by the aging process than a 75-year-old individual. This has been demonstrated in detail by a prognostic index developed for estimating remaining life expectancy in older individuals in different settings. In this index, elements such as comorbidity and physical function in addition to chronological age determine remaining life expectancy (5). The index is not yet validated to the extent that it can be recommended for use in clinical practice. Still, it seems to be more robust than chronological age in terms of predicting survival in individual patients. Such an index may be considered as an approach to measure biological age - a term often used to highlight that factors other than chronological age influence survival in the elderly population. Biological age is also related to
treatment tolerance, and the individual patient’s ability to overcome acute disease and physiological stress (6). High biological age implies reduced biological reserves, and increased occurrence of age-related diseases such as heart failure, renal failure or dementia. Later in this thesis, the term *frailty*, which is associated with biological age and reduced biological reserves, will be thoroughly discussed.

Cancer treatment, whether surgical or oncological, represents a significant stressor for the organism, and is often associated with considerable complications. Examples include bleeding, pain and wound infection after surgery, and mucositis, neutropenia, neuropathies and cardiac toxicity after chemotherapy. The most serious complication from cancer treatment is death. Older cancer patients, particularly those who are frail, have an increased risk of experiencing treatment complications. However, older patients in general and frail patients in particular are underrepresented in clinical trials, and evidence-based treatment recommendations for this patient group are lacking (7).

### 1.2 Geriatric oncology

In response to the increasing number of older cancer patients as a consequence of the aging of the population in both industrialized and developing countries, and the challenges related to managing these patients, the field of geriatric oncology has emerged over the past decades. The core questions of geriatric oncology have been defined as (8):

1. What is the lethality of the malignancy in the context of competing comorbidities?
2. Is the patient going to live long enough to experience the complications of cancer?
3. Can the patient tolerate cancer treatment?
4. Will the cancer or cancer treatment alter physical and/or cognitive function in such a way as to limit autonomy and require institutionalization?

In geriatric oncology, geriatric principles are applied to clinical oncology in an attempt to answer these questions and to provide the best possible care for older
patients with cancer. The International Society of Geriatric Oncology (SIOG) was founded in 2000, and is focused on promoting education and research in the field, as well as publishing guidelines for clinical practice (9). In the US, the American Society of Clinical Oncology (ASCO) has initiated a geriatric oncology subspecialty, and developed a fellowship program available in several institutions. To date, geriatric oncology has not been approved as a subspecialty in Norway.

1.3 Geriatric assessment

*Definition and implementation*

Geriatric assessment (GA) is a clinical tool used in geriatric medicine that in recent years also has been recommended in the evaluation of older cancer patients (10). Comprehensive Geriatric Assessment (CGA) is a term concurrently used in the literature. However, a CGA by definition is a multidisciplinary evaluation based on which a plan for management and follow-up is created (11). This distinction is not always made in clinical studies, where intervention and plan for follow-up is not necessarily present. For the sake of correctness in the current study, the term GA will be used in this thesis.

A GA involves using validated tools to evaluate domains that are important to generate a holistic impression of the health status of an older individual. These domains generally include physical function, comorbidity, cognitive function, nutritional status, emotional (mental health) status, medications/polypharmacy and social support (11). A Cochrane review from 2011 concluded that implementing GA in older adults admitted to hospital increased patients’ likelihood of being alive and living at home up to 12 months after discharge (12). In a Delphi-study from 2015 on geriatric assessment in oncology, there was agreement that all cancer patients >70 years, and younger patients with age-related issues, should be referred for GA (13). To date, GA has not been standardized across countries and institutions. Both in research and clinical practice, a variety of tools are used to measure the individual components of GA. A recent review concluded that current knowledge is insufficient to recommend one set of tools above another (14). Rather, local traditions and experience should guide the structure of the GA.
Several advantages of implementing GA in standard cancer care have been established (13,15). Firstly, through the broad evaluation that is the hallmark of the GA, health problems that have not previously been recognized may be identified, such as malnutrition, physical impairments or psychiatric problems. These problems are potentially reversible with intervention, like nutritional supplements, exercise/physical therapy or pharmacotherapy/cognitive therapy. Secondly, in patients presenting with cancer, GA may also guide treatment decisions such as intensity (adjustments in doses or regimens) or treatment goals. Thirdly, there is increasing evidence that information retrieved through a GA is independently predictive of overall survival. Finally, geriatric assessment is one possible approach to identifying the clinical syndrome of frailty in older patients – a topic that will be discussed in detail below (14).

**GA; brief review of domains and examples of assessment tools**

How to best implement a GA in oncological practice has recently been discussed (13). O'Donovan and co-authors invited experts from various relevant fields; geriatric oncology, radiation oncology, medical oncology and geriatrics, resulting in a total of 49 experts participating in a four-round Delphi-process. There was consensus that all GA domains are relevant for older cancer patients, but functional status, comorbidities and cognitive function are the most important. In the following section, each GA domain with examples of assessment tools will be presented.

- **Functional status/physical function**

Decline in functional ability is expected with increasing age. Activities of daily living (ADL) are basic self-care activities including bathing, dressing and eating, while instrumental activities of daily living (IADL) include more advanced activities that are necessary to lead an independent life at home, such as grocery shopping, cooking, using a telephone and managing personal economy. Dependency in ADL or IADL is often measured using validated questionnaires, which may be answered by the patient/caregiver, or rated by observation in care setting. Commonly used scales for measuring functional ability in ADL are the Katz index and the Barthel index. The
Katz index assesses whether the patient is independent in six activities; bathing, dressing, toileting, transferring, continence and feeding (16). The Barthel index includes ten items, some scored on a two-point scale (dependent/independent) and some on a three- or four-point scale, taking into account the continuum from independent to dependent (17).

Though independent in basic activities of daily living, some older individuals may need assistance in more advanced activities, and to assess this need, more comprehensive scales for activities of daily living are necessary. The Lawton-Brody IADL scale was originally developed for this purpose in 1969 (18). It includes 8 items which are all rated on a three-point scale; "unable to perform", "able to perform with help" and "independent". The items are: using the telephone, shopping, preparing food, housekeeping, laundry, transportation, administrating medications and handling personal economy. An example of a somewhat more extensive IADL scale is the Nottingham Extended Activities of Daily Living scale (NEADL). It was first developed to assess functional independence in the follow-up of stroke patients (19). In addition to the items that are included in the Lawton scale, the NEADL includes leisure activities, and more detailed mobility items.

Physical function may also be measured by objective physical performance tests. The timed Up and go Test (TUG) tests gait and mobility, and involves the patient getting up from a chair, walking three meters and back, and sitting down again at usual pace (20). Measuring gait speed (meters/second) by a walking test, or muscle strength by a handheld dynamometer, are examples of simple screening tests that have been shown to be reliable and valid for assessing muscle mass, strength and physical performance in community-dwelling elderly (21). Another indicator of functional status in older patients is a history of falls. Commonly referred to as a geriatric syndrome, falls are associated not only with injuries and hospitalization, but also with increased risk of nursing home placement (22). In addition to established risk factors for falls such as ADL-dependency, previous falls and cognitive impairment, cancer-related risk factors such as neurotoxic chemotherapy and pain are frequently present in onco-geriatric patients (23).
The relevance of measuring physical function in onco-geriatric patients is demonstrated through findings from several studies. For example, in a study of 280 patients ≥70 years undergoing surgery for solid tumors, increased time to complete TUG was an independent predictor of major postoperative complications (24). A different study, including patients ≥65 years with various types of cancer receiving chemotherapy, found that a history of falls and having reduced mobility were associated with increased risk of experiencing chemotherapy toxicity (25). In addition, several studies have identified associations between reduced physical function and risk of mortality in older cancer patients. One of these, a relatively large study of 993 older patients with hematological or solid malignancies, found that ADL-dependency and TUG were both associated with 1-year mortality (26).

- **Comorbidity**

All organ systems are affected by the aging process, and older patients frequently present with established cardiovascular, pulmonary, renal or gastrointestinal disease. Several assessment tools for comorbidity have been developed, and two of the more extensively studied tools will be considered here. The Charlson comorbidity index (CCI) is a weighted comorbidity assessment, originally developed to predict long-term survival in cancer patients (27). It includes 19 selected conditions that are weighted (range 1 to 6 points) based on relative risk of 1-year mortality. An age-adjusted version also exists. The CCI has been validated in several studies. In a large study of acutely hospitalized elderly patients ≥65 years, the authors found that higher CCI-scores were predictive of both short- (3 months) and long-term (1 and 5 years) mortality, also when adjusting for age (28).

Another example of a weighted comorbidity scale is the Cumulative Illness Rating Scale (CIRS), originally developed in 1968 (29). In 1992, a revised edition with increased focus on problems common in geriatric populations was created, and named the Cumulative Illness Rating Scale for Geriatrics, CIRS-G (30). CIRS-G assesses the presence of disease in a total of 14 organ system categories, and the severity of problem in each category on a five-point scale from 0 (no) to 4 (extremely severe/urgent). It is an extensive scale, with a detailed scoring manual, the most
recent version was published in 2008, and is validated for use in older cancer patients, as well as for the prediction of mortality and re-hospitalization in hospitalized patients (31-32).

An important advantage of the CCI is that it is fast and simple to use, whereas the CIRS requires more training. On the other hand, qualitative information on comorbidities in terms of severity rating is included in the CIRS. For example, while the CCI scores one point for a previous myocardial infarction (MI), the CIRS differentiates between a “remote MI” (two points), previous MI within the last five years (three points) and unstable angina pectoris (four points). It seems intuitive that the latter is of greater prognostic relevance than a small MI that occurred over five years ago. In addition, possibly relevant conditions that are considered by the CIRS such as non-malignant hematopoietical disorders and mild renal failure are not included in the CCI (33).

In an oncological setting, a thorough evaluation of comorbid conditions is relevant to optimize management of these conditions, plan cancer treatment and estimate life expectancy. It is not surprising that the presence of significant comorbidities has been shown to be predictive of both chemotherapy toxicity and survival in several studies of older cancer patients (15).

- **Cognitive function**

Cognitive function is a term used to describe a range of intellectual processes, such as memory, reasoning, learning, awareness, language and problem solving (34). Mild cognitive impairment (MCI) is defined as an impairment that is symptomatic, but not severe enough to affect ADL-function. MCI is present in 10 to 20% of individuals ≥65 years (35). Dementia is characterized as an irreversible, progressive decline in cognitive abilities that, in contrast to MCI, is accompanied by dependency in activities of daily living. The diagnosis can generally not be made until symptoms have persisted for at least six months. The prevalence of dementia in individuals ≥60 years is estimated to be between 5 and 7% worldwide, and prevalence of both MCI and dementia increases with age. In Western Europe, the prevalences of dementia in
the age groups 80-84, 85-89 and ≥90 years are estimated to 12.9%, 21.7% and 43.1%, respectively (36). MCI or dementia is present in a significant proportion of older cancer patients. For screening purposes in geriatric oncology, validated tests such as the Mini Mental State Examination (MMSE) and the Clock Drawing Test are commonly used (37-38). When the screening test is positive, referral for further diagnostic testing is warranted in order to make a diagnosis of MCI or dementia.

Patients with reduced cognitive function may have problems with adhering to therapy due to memory impairments, and in severe cases, their ability to understand and consent to treatment and provide informed decisions about their own health care may be limited (39). Awareness of these problems is always important, and perhaps even more so in onco-geriatric patients, where the disease is potentially life-threatening and treatment often associated with significant side effects. The presence of cognitive impairment also carries prognostic value, as it is independently associated with increased risk of treatment-related toxicity and mortality in older cancer patients (40-41). Finally, treatment with chemotherapy is in some cases associated with the development of cognitive impairments, a phenomenon commonly called chemobrain. It is hypothesized that this effect may be accentuated in those who have pre-existing problems, and if further research supports this theory, identifying pre-treatment MCI or dementia could be highly relevant when choosing the appropriate cancer treatment (42).

- Nutritional status

Poor nutritional status is common in the elderly population. Among 4507 individuals with mean age 82.3 years, the prevalence of malnutrition was reported to be 22.8% overall, but considerably higher in hospitals (38.7%) and nursing homes (13.8%) than in the community (5.8%) (43). When assessing nutritional status in the older patient, dietary intake and anthroprometric measures should be taken into account, as well as unintentional weight loss. Several assessment tools for nutritional risk have been developed. Commonly used is the Mini Nutritional Assessment (MNA), which is developed for use in elderly patients, and identifies patient at risk for, or with established malnutrition (44). For screening purposes, a short version of the MNA is
available. The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends the MNA to detect risk of malnutrition in home dwelling elderly (45). The possibility for intervention makes it important to detect malnutrition and potential risk of malnutrition in older cancer patients. Cancer disease may increase the risk of malnutrition, for example through mechanical obstruction due to gastrointestinal tumors, complications from therapy for head and neck cancer, or cachexia as a consequence of systemic malignant disease (46). Together with reduced mobility, a low MNA-score was predictive of early mortality in a previous study including older patients with various forms of cancer treated with chemotherapy (47). In series of older surgical patients, malnourishment has been associated with postoperative complications and delayed recovery – and is thus likely to be associated also with increased operative risk in older patients who are surgically treated for their cancer disease (48). Furthermore, a study on predictors of mortality in older cancer patients identified malnutrition as one of several factors independently predictive of death within one year (26).

- **Emotional function**

Symptoms of depression and anxiety are considered the most important factors in the emotional function domain of the GA. The literature suggests that about 8 to 16% of older adults suffer from clinically significant depressive symptoms (49). Medical conditions such as stroke, Alzheimer’s disease or Parkinson’s disease increase risk of depression, as do critical life events like experiencing loss of a loved one or the development of physical disability (50). A GA should include validated screening instruments to identify patients at risk for depression – such as the Beck Depression Inventory (BDI) or the Geriatric Depression Scale (GDS) (51-52). With a positive screening, further evaluation to identify those in need of treatment is warranted. Like malnutrition, depression and anxiety are conditions that are potentially remediable through appropriate intervention.

In a recent study on depression in older cancer patients receiving chemotherapy, 45% of patients exhibited depressive symptoms at baseline, and independent risk factors for depressive symptoms during chemotherapy were depression at baseline and malnutrition (53). In a meta-analysis of studies including patients of all ages (overall
mean age 55.4 years, range 34-73) with different types of cancer, depression was shown to be predictive of mortality (54). This was also found in a series of 249 patients ≥70 years with cancer (85% of which were colorectal, lung or genitourinary malignancies), where a high GDS-score was independently predictive of mortality (55).

- Polypharmacy

A natural consequence of multimorbidity in older individuals is polypharmacy. Polypharmacy can be defined as taking more medications than clinically indicated – but in clinical studies, a cut-point of number of medications in daily use is more commonly applied. There is no universal agreement of which cut-point is optimal in terms of predicting adverse events, but the commonly used cut-point of 5 or more has been shown to be reasonable in older patients with cancer, in terms of selecting those in need of a medication review (56). Polypharmacy is prevalent in older patients with cancer, and is associated not only with adverse drug reactions and drug-drug interactions, but with other events such as falls, functional decline and increased health service utilization (57-58). Of particular interest in patients with advanced cancer disease are drugs used with preventive intent, such as statins, which may be inappropriate when there is limited remaining life expectancy – and discontinuation of such drugs should be considered (59). On the other hand, there may be strong indications for preventive drugs in fit older patients – stressing the importance of a tailored approach when assessing polypharmacy.

- Social support

Evaluation of social support is important when planning treatment, future care level and living arrangements. Patients who have previously been home-dwelling and independent may, in the trajectory of cancer disease and treatment, find themselves in need of increased support such as receiving home nursing or staying in a nursing home. In other cases, the patient’s ability to receive outpatient treatment might depend upon the presence of a caregiver. For example, in patients with colon cancer, the administration of adjuvant chemotherapy requires between eight and twelve hospital visits over a period of 6 months (60). In Norway, many patients live several
hours away from the nearest oncology centre, leading to practical challenges regarding transportation – which are more easily solved where a social network is present. Patients without family or other sources of social support require particular concern. In a qualitative study of older patients with cancer living alone, the importance of continuity in primary care and having an open discussion with the patient about planning the future was emphasized (61). Furthermore, disparities in cancer diagnosis, treatment and outcome are present both between and within countries in the developed world, and may in part be explained by differences in socioeconomic status, education and health literacy (62). As an example, a US study found that in patients with stage III or IV colorectal cancer, those with low health literacy were less likely to receive chemotherapy than those with higher health literacy (63). Of note, the study included 347 patients, 105 of whom were considered to have low health literacy – and 71% of these were aged 65 years or older. In addition to age, living alone was associated with low health literacy in this study – emphasizing the advantage of a social support system.

1.4 Other assessment tools for older cancer patients

The Eastern Cooperative Oncology Group performance status (ECOG PS), published in 1982, is a widely used tool for assessing physical function in cancer patients, both for clinical and research purposes (64). The ECOG PS grades physical performance on a scale from 0 to 5, as shown in table 1.

ECOG PS is validated in several studies in terms of predicting treatment tolerance and survival. However, in older cancer patients, several relevant factors that may affect these outcomes are not considered in ECOG PS. A clinical study of 363 cancer patients with mean age 72 years aimed to compare the properties of GA with ECOG PS. A considerable percentage of patients with PS <2 had physical impairments in ADL or IADL, and there was no association between higher grade PS and comorbidities (65). It was concluded that GA adds important information to ECOG PS, strengthening the recommendation of implementing GA in care of older cancer patients.

The Karnofsky Performance status (KPS) is another example of an assessment tool for cancer patients. It was developed in 1948 and has since been commonly used in
clinical practice (66). The scale ranges from 0 to 100, where a higher score reflects better performance status and indicates lesser risk of treatment tolerance and better prognosis. In terms of content, KPS is fairly similar to ECOG PS, and it has equal limitations when compared to GA. In a study investigating predictors of chemotherapy toxicity in patients $\geq 65$ years with various cancer types, there was no association between KPS-score and incidence of toxicity (25).

Table 1. ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any selfcare; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

For patients who receive surgical treatment, several surgical risk assessment tools are available. The American Society of Anesthesiologist physical status class (ASA class) was not originally developed to determine risk of surgery, but to stratify the patient’s systemic illness (67). It is widely used in the preoperative setting, regardless of type of surgery. It is based on comorbidity, smoking status, severity of current disease – and, in Norway – age, as to date patients $>80$ years are assigned ASA class 2 or higher. Thus, it does not take into account the high degree of heterogeneity that is seen in octogenarians and nonagenarians.

With the exception of ASA-classification, a standardized preoperative assessment is rarely part of routine care for elective surgical patients, though several scoring
systems have been proposed over the past decades. For older surgical cancer patients, the Preoperative Assessment of Cancer in the Elderly (PACE) has been developed (68). PACE incorporates items from a GA (physical dependence in ADL/IADL, comorbidities, cognitive function, mental health status) together with ASA-classification, ECOG-PS and the Brief Fatigue Inventory – an assessment scale for cancer-related fatigue (69). The validity of PACE has been investigated in a prospective multicenter study conducted by Audisio and co-authors (70). 460 patients with mean age 79.6 years and undergoing surgery for various solid tumors were included. IADL-dependency, moderate/severe fatigue and ECOG PS >1 was associated with the occurrence of any (within 30-days) postoperative complication, while only ASA-class ≥2 was associated with occurrence of a severe complication. In multivariate analyses, IADL-dependency and fatigue remained predictive of any complication. Dependency in ADL and IADL as well as an ECOG PS score >1 were predictive of prolonged hospital stay, while in the multivariate analysis only ADL-dependency remained predictive. The study recommended PACE for routine use in onco-geriatric surgical patients.

In 2015, Huisman and co-authors investigated the predictive ability of screening tools for postoperative complications in older surgical cancer patients (71). The study included 328 patients with solid tumors, median age 76 years. In this study, a scoring system comprising TUG, ASA-class, impaired nutritional status, gender and type of surgery was found predictive of major postoperative complications.

1.5 Quality of life

Cancer, being a potentially life-threatening disease, may lead to considerable psychological stress, concern and fear in patients upon receiving the diagnosis. Furthermore, the treatment is often prolonged, and may be associated with severe discomfort both in the short and the long term. Thus, clinical trials in oncology frequently focus on patient’s own perceived health-related quality of life (QOL) at time of diagnosis, during treatment and at controls, recognizing that the impact of cancer disease is not limited to outcomes such as survival, recurrence and complications.
QOL-measurements should be able to quantify both the negative and the positive impact of treatment on the patient’s general well-being, which is particularly important in cases where treatment is not curative. Another important point is that two patients with identical clinical characteristics and symptoms may have different experiences in terms of how their lives are affected by the health problems (72). While one patient experiences side effects of chemotherapy as intolerable, another patient could experience the same side effects as acceptable.

A QOL-instrument that has been widely used in cancer trials is the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (73). This 30-item questionnaire was developed specifically for cancer patients, and multiple disease-specific modules have subsequently been created, including a module for elderly cancer patients. The questionnaire has been extensively implemented in clinical trials, and is translated into multiple languages. It includes both functional domains (such as physical function, cognitive function and emotional function) and assessment of commonly occurring cancer-related symptoms, like pain, fatigue, appetite loss and insomnia. Another questionnaire developed for the same purpose is the Functional Assessment of Cancer Therapy – General (FACT-G) (74). The FACT-G includes 27 items that are grouped into 4 scales; physical-, social-, emotional- and functional well-being. FACT-G has been more extensively studied in the United States, while EORTC QLQ-C30 is commonly used in European studies. A paper comparing the two questionnaires concluded that while no scale was superior to the other, they differ in terms of structure, tone and in particular assessment of the social domain – thus, the research question should guide what questionnaire to use (75).

It should be noted that several other questionnaires for measuring QOL in both general populations and in cancer patients have been developed, but a complete review is beyond the scope of this thesis. One may argue that the value of measuring QOL in itself is more important than the instrument used.

QOL is an example of a patient reported outcome (PRO). PROs, or patient reported outcome measures (PROMs), are subjective reports on a patient’s health condition that comes directly from the patient, without interpretation by a clinician or anyone
else. A recent review examining the level of association between PROMs (such as pain, fatigue, general health) and functional performance measures (primarily assessed by clinicians) found that the concordance between the two varied from low to moderate, indicating that PROMs provide information about patient symptoms and experiences that are not always captured by the clinician (76). Physical function may also be assessed as a patient reported outcome. For example, while the gold standard for evaluating ADL- or IADL-dependency is by observation, it is easier and less time-consuming to administer as a self-reported questionnaire (77). It is, however, important to be aware of the risk of reporting bias, as older individuals may tend to overestimate their own functional abilities – this may be particularly relevant in patients with dementia (78). Still, it has been suggested that an increased use of PROMs will facilitate patient-centered care and better quality (79).

2 Frailty

2.1 Definition and pathophysiology

Frailty is commonly defined as a geriatric syndrome characterized by increased vulnerability due to an acceleration of the decrease in biological reserves that is seen in normal aging (80). One could also say that frail patients have a high biological age. Frailty is associated with, but remains distinct from, increasing age and multimorbidity. Frail individuals are at higher risk than their non-frail counterparts of experiencing adverse health events such as functional decline, hospital admission and death. Though the pathophysiological mechanisms that lead to frailty are not completely understood, a review from 2009 concluded that inappropriate activation of inflammatory and coagulatory pathways is central in the process (81). Low-grade activation of inflammatory pathways is also seen in normal aging, and in the best-case scenario, it is associated with longevity as it is also demonstrated in healthy centenarians (82). Thus, it is hypothesized that in frail individuals, some degree of dysregulation of inflammation is present. As in other disease processes, genetic and environmental factors also play important roles. It is hypothesized that frailty develops as a continuum, with a gradual loss of function across organ systems and impairment of homeostatic mechanisms. As a consequence, some individuals may be
considered "pre-frail", that is, affected by the mechanisms of frailty development but still able to mobilize adequate physiological resources in response to external stressors (83). Figure 1 shows a hypothesized schematic representation of the pathophysiology of frailty, courtesy of Clegg and co-authors (80).

**Figure 1: Pathophysiology of frailty**

![Pathophysiology of frailty diagram](image)

*Sarcopenia* is loss of muscle mass and function that is associated with aging (84). While some researchers have proposed that sarcopenia causes frailty, others have argued that sarcopenia is a clinical manifestation of frailty (85). An expert consensus statement from 2013 suggests that while sarcopenia may be a component of frailty, the frailty syndrome is more multifaceted than sarcopenia alone (86). This is illustrated in figure 1 above, where skeletal muscle is only one of several organs
affected by reduced physiological reserve in the proposed pathophysiology of frailty. It is, however, clear that the two share important characteristics and etiological mechanisms, and frequently overlap. Like frailty, sarcopenia alone is associated with adverse health outcomes, including disability and death. Sarcopenia can be measured in several ways. Imaging techniques that estimate muscle mass may be used – CT/MRI being the gold standard, dual energy X-ray absorptiometry (DXA) is an alternative involving less radiation. It is recommended that clinicians and researchers begin with measurement of gait speed, and where this is low (≤0.8 meters/second), imaging for determining muscle mass is indicated. With gait speed >0.8 meters/second, measurement of grip strength should be performed – and if this is normal, sarcopenia is most likely not present (87).

2.2 Clinical approach to frailty

In addition to GA, several ways to identify frailty have been suggested, and none of these have been proven superior in general older populations. Rather, current evidence suggests that the clinical setting or research question should guide the choice of frailty assessment tool (88). The two most common approaches to identifying frailty in clinical practice will be presented here.

*Frailty phenotype*

In 2001, Linda P. Fried and co-authors published a paper presenting an operational definition of the frailty syndrome (89). To create this definition, data from a large, prospective observational study, the Cardiovascular Health Study (CHS), were employed. Patients with a history of Parkinson's disease or stroke, an MMSE-score <18 and those treated with antidepressants, levodopa or cholinesterase inhibitors were excluded from the cohort. According to the resulting phenotype of frailty, frailty is present when 3 or more of the 5 following criteria are fulfilled: unintentional weight loss, reduced grip strength, self-reported exhaustion, slow gait speed and reduced physical activity. An intermediate, or pre-frail state was defined as fulfilling 1-2 of these criteria. The frailty phenotype is relatively quick and easy to measure, and it is validated in terms of identifying individuals at risk for falls, hospitalization, disability and death. However, a common objection against the frailty phenotype is that it is
more suitable for research than for clinical purposes. While clearly being able to identify at-risk individuals, the frailty phenotype does not suggest problem areas that may be available for intervention, and it does not take into account common geriatric problems related to frailty, such as cognitive impairment or dependency in activities of daily living (88). Its relevance in geriatric oncology is therefore uncertain.

Frailty index

The frailty index was developed and proposed by Rockwood and co-authors in 2001, and several modifications have since been created. A frailty index is calculated based on the presence of numerous pre-defined ”deficits” – namely symptoms, diseases or disabilities – and an increasing frailty index indicate increased vulnerability and likelihood that frailty is present (90). An advantage of the frailty index is that it does not use cut-points like the frailty phenotype, reducing risk of misclassification due to threshold values (88). Recognizing the relevance of information retrieved through a GA in the setting of defining frailty, a paper from 2005 described a frailty index based on deficits identified through a geriatric assessment (FI-CGA). The FI-CGA measure was associated with higher risk of death and institutionalization in a geriatric population (91). To date, the use of a frailty index has not been routinely implemented in clinical practice, but like the frailty phenotype, is used to define frailty in several original papers.

GA – screening methods

It is established that for clinicians treating older cancer patients, an approach based on GA is the gold standard for patient assessment (14). However, a common objection towards implementing GA in oncological practice is that it is too time consuming to be feasible in a busy practice. Thus, the possibility of a frailty screening tool, detecting individuals at risk of frailty and in need of a complete geriatric assessment has been the focus of many researchers (92). Examples of such tools are the Vulnerable Elders Survey-13 (VES-13) and the G8 screening tool (93-94). The question of whether or not such screening tools perform well enough in terms of sensitivity for detecting vulnerable patients remains to be answered (95).
Dysregulation of inflammatory pathways are thought to be important in the pathophysiology of frailty, and a pro-inflammatory state is also present in normal aging. The latter is described by the term "inflammaging".

Immunosenescence, a term describing the gradual loss of immunocompetence, is mainly caused by a shift in distribution of T-cells. With involution of the thymus that occurs with age, there is a decrease in naive T-lymphocytes that are important in initiation of both cellular and humoral immune-responses (96). Consequently, there is a relative increase in memory and regulatory T-cells, which are partly responsible for the increased secretion of pro-inflammatory cytokines that is seen in inflammaging.

Pro-inflammatory cytokines such as C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) can be measured in serum. In recent years, these cytokines, in this setting commonly referred to as biomarkers, have been subject to much research in terms of their relation to age-related disease/frailty and their possible role as predictors of adverse health outcomes. Elevated levels of CRP, IL-6 and TNF-α are associated with a higher risk of all-cause mortality, and some studies have shown that frail individuals have higher serum levels of the same biomarkers than non-frail controls (97). Furthermore, TNF-α has been shown to be independently predictive of decreased muscle strength in older individuals (98-99). Thus, it seems that the pro-inflammatory state seen in aging and frailty in particular is directly involved in muscle catabolism that in time may lead to functional impairments.

Other possible laboratory biomarkers of aging and frailty have been proposed. CXC chemokine ligand 10 (CXCL10) is produced by monocytes, and is a potent proinflammatory mediator. In addition to higher circulating levels with age, CXCL10 has been shown to be significantly upregulated in frail compared to non-frail individuals (100). Inflammatory pathways are in many ways linked to the activation of coagulation, and D-dimer and soluble vascular cell adhesion molecule (sVCAM)
are examples of biomarkers that increase with activation of coagulatory pathways. In a study of community-dwelling older individuals, D-dimer and sVCAM were independently related to 4-year mortality, as was IL-6 (101). On the cellular level, telomeres are proteins at the end of chromosomes that grow shorter with each cell division. Decreased telomere length is associated with higher age, and has been associated with mortality and disability in older individuals (102-103). As telomeres are progressively shortened, they eventually become dysfunctional. Dysfunctional telomeres secrete markers that may be measured in serum, and a preclinical study found such markers to be able to distinguish old from young adults, as well as healthy older adults from older adults with age-related comorbidity (104). Interestingly, genetically regulated variations in telomere maintenance may lead to increased or lower risk and progression of cancer (105).

Measuring IL-6, TNF-α, CXCCL-10, sVCAM, telomere length and markers associated with telomere dysfunction is not readily available in clinical practice, in contrast to CRP and D-dimer. Furthermore, in older patients with cancer, activation of inflammatory and coagulatory pathways may also reflect the cancer disease in itself, and the role of biomarkers in terms of assessing frailty in this setting is more complicated. However, several examples of prognostic value of biomarkers in cancer patients exist. A review from 2011 concluded that higher CRP-levels were associated with poor prognosis in patients with different cancer diagnoses, including endometrial, cervical, colorectal and pancreatic cancer (106). Similarly, IL-6 is associated with poor prognosis in patients with breast and colorectal cancer (107-108). Increased levels of IL-6 and other inflammatory cytokines have also been associated with cancer-related fatigue (109).

The Glasgow Prognostic Score (GPS), developed by Forrest and co-authors, is a risk score system based on the systemic inflammatory response measured by high CRP levels combined with levels of serum albumin (110). The GPS was originally found predictive of survival in patients with inoperable non-small-cell lung cancer, with comparable prognostic value to the combination of cancer stage and performance status. In patients with colorectal cancer, Ishizuka and co-authors have shown that the GPS is a predictor of mortality both after curative surgery and treatment with palliative chemotherapy (111-112).
In summary, inflammatory biomarkers seem to have predictive properties for adverse health outcomes in older individuals in general – and older cancer patients in particular. However, to date, the role of such biomarkers in clinical practice is not clarified – except for the common use of CRP as a measure of acute-phase response and D-dimer as a measure of coagulation in venous thromboembolic disease.

4 Colorectal cancer – general aspects

4.1 Epidemiology
The incidence of colorectal cancer is increasing worldwide. In Norway, it is one of the most common forms of cancer in both sexes. For women ≥70 years, recent epidemiological data show that colon cancer is in fact slightly more common than breast cancer (113). Most new cases occur in older individuals, and approximately 60% of patients are ≥70 years old when they are diagnosed. Colorectal cancer is also the second most common cause of cancer death in Europe (114). Fortunately, survival from colorectal cancer has been increasing over the past decades. From the period 2004-2008 to 2009-2013, 5-year relative survival from colon cancer in Norway has increased from 61% to 63% in women, and from 58% to 60% in men. For rectal cancer, the corresponding figures are 66% to 67%, and 62% to 67%, in women and men, respectively (113).

4.2 Treatment

A complete review of the various surgical and oncological regimes that are used in the treatment of colorectal cancer is beyond the scope of this thesis, but a brief outline will follow – based on current Norwegian treatment guidelines (60). Surgery is the main treatment modality in colorectal cancer, may be performed with curative or palliative intent, and is generally performed in all patients regardless of age. The common surgical approach for colon cancer is resection of the affected bowel with a tumor-free margin of at least 5 centimeters, and resection of regional lymph nodes. Assessment of resected lymph nodes is important for proper staging of the disease, and thus to guide further oncological therapy. Adjuvant chemotherapy is
recommended for stage III disease, but for patients aged ≥75 years, chemotherapy is offered after an individual assessment of general condition, comorbidities and functional status.

Total mesorectal excision (TME) is the current recommended approach for patients with rectal cancer. In TME, the tumor is resected in toto together with associated lymphatic tissue. For high rectal tumors, a partial mesorectal excision may be acceptable, provided that the distal tumor-free margin is at least 5 centimeters. Neoadjuvant chemoradiotherapy is offered to selected patients with rectal cancer, the most important indication being tumor stage T3/T4 (tumor that invades through the muscularis propria or penetrates to visceral peritoneum). Finally, postoperative chemoradiotherapy is standard for some patients, the main indication being inadequate radicality.

Open surgery and laparoscopic procedures are considered equal in terms of oncological outcome. However, the latter is associated with shorter stay in hospital and faster convalescence (60). In Norway, an increasing amount of procedures are performed by laparoscopy. In 2014, 39% of colon cancers and 50% of rectal cancers were laparoscopically treated, an increase from respectively 21% and 8% in 2008 (115).

4.3 Survival and treatment of older patients with colorectal cancer

Survival

While survival from colorectal cancer in general is improving, recent European data show poorer survival for patients of higher age (>64 years for colon cancer and >74 years for rectal cancer) (116). Interestingly, for older colorectal cancer patients who survive the first year after treatment, cancer related survival rates are comparable to those seen in younger patients. Thus, the age-related difference in survival is mainly attributed to early mortality (117). In a review article from 2000 concerning outcome after surgery for colorectal cancer in elderly patients, the authors found that disease stage at diagnosis as well as proportion of patients undergoing emergency surgery, both increased with age (118). The rate of emergency surgery in patients 85 years and
older was twice as high (29%) as in patients <65 years (11%). This is important, as emergency surgery is associated with higher peri- and postoperative mortality rates as well as more frequent occurrence of postoperative complications (119-120). In addition to emergency surgery, malnutrition, frailty and social isolation are among factors associated with increased mortality after colorectal cancer treatment (121-123). A recent study concluded that colorectal cancer patients receiving treatment nonadherent to guidelines had higher risk of death especially in the first year after diagnosis – and higher age was a predictor of receiving nonadherent treatment (124). While guideline treatment is not always appropriate for frail patients, these data indicate that undertreatment due to fear of complications and toxicity may be a pitfall in terms of improving survival for older patients with colorectal cancer.

Surgery

Being associated with improved survival and fewer complications, elective procedures are highly preferable. It is not surprising that an older patient with reduced biological reserves presenting with a surgical emergency such as a bowel obstruction is more vulnerable to the significant stress of surgery than an equally frail, but stable counterpart. With planned procedures, there is time to implement rehabilitation measures, for example by correcting malnourishment or optimizing treatment of concurrent medical conditions (125). The use of an Enhanced Recovery Program After Surgery - protocol (ERAS) in the surgical management of older patients with colorectal cancer may also improve outcome (126). ERAS is an evidence-based approach, involving several pre-, peri- and postoperative measures, aiming to reduce hospitalization time and occurrence of postoperative morbidity/mortality. Examples of measures included in ERAS are avoiding bowel preparation, using short-acting anesthetic agents, early mobilization and oral nutrition (127). While patient age is not a factor in determining surgical approach (open versus laparoscopic), the advantages of laparoscopic procedures make them highly relevant for older patients (128). However, the advantages of laparoscopy are dependent on surgical experience, and in general, oncological outcome is comparable to open surgery (60).

The implementation of TME in treatment of rectal cancer has improved overall survival, although some controversies regarding its implementation in older patients
exist. Data from the Netherlands failed to demonstrate a survival benefit in patients ≥75 years operated with TME – who rather experienced higher 30-days and 6-months mortality risks, as well as higher risk of postoperative complications compared to younger patients (129). In contrast to this, data from Norway show improved survival also in patients >75 years after the implementation of TME in the early 1990s (130). Simultaneously, several local surgical centers discontinued rectal cancer surgery, emphasizing the importance of volume and surgical expertise in this context.

Preoperative anal sphincter function is an important aspect to consider in older patients with rectal cancer. A study of nursing home residents undergoing surgery for rectal cancer reported high rates of fecal incontinence (37%) after six months (131). Baseline fecal incontinence was strongly associated with incontinence after surgery. A review from 2012 concluded that, while higher age should not be a contraindication to radical surgery with curative intent, frailty status should be considered when choosing surgical approach (132). In addition, preoperative sphincter function should be evaluated, and sphincter-preserving surgery should be reserved for patients with acceptable sphincter function. Preoperative physical function was not considered in this review, but comorbidity and ASA-class were.

An example of a serious complication associated with colorectal cancer surgery is anastomotic leak. It is defined as a defect in surgically joined intestinal wall that leads to a communication between the intra- and extraluminal compartments (133). Reported prevalence of anastomotic leak varies from 1% up to 19%. Risk factors for anastomotic leak that are commonly present in older patients include ASA classification >2 and comorbid conditions including diabetes, pulmonary disease, vascular disease, and frailty (134-135). Other complications that have been shown to occur more frequently in older than younger patients include ileus, peritonitis, wound infections, and systemic complications affecting other organ systems (cardiovascular/renal/respiratory) (136). Postoperative delirium is a common complication in the older patient population. It is defined as an acquired cognitive dysfunction accompanied by fluctuating disturbances in attention and awareness that represents a decline from baseline status – and surgery is only one of many possible triggers. Postoperative delirium may occur after any surgical procedure, including
cancer surgery, and is associated with higher risk of both long- and short-term adverse outcomes, including functional dependency, cognitive decline, and shortened survival (137).

Tumors in colon and rectum frequently metastasize to the liver. Due to improvements in surgical techniques and more effective chemotherapy, an increasing proportion of patients with liver metastases are considered candidates for liver resection with potentially curative intent (60). Several authors have reported that surgical treatment of liver metastases may be performed in selected fit older patients with acceptable risk and survival benefit comparable to younger patients (138-139). Thus, higher age should not be considered a contraindication to resection of liver metastases, but careful preoperative assessment to identify those who are likely to benefit from this treatment is warranted (140).

**Chemotherapy**

While surgery is well established in the treatment of older patients with colon cancer, the role of adjuvant chemotherapy is not fully clarified. This is partly related to the fact that older, and particularly frail, patients are underrepresented in clinical chemotherapy trials. While studies have shown that age is not necessarily associated with higher risk of adverse events in currently used chemotherapy regimens, higher age may lead to reduced tolerance to adverse events (141-142). SIOG guidelines state that clinical judgement and individual risk assessment should guide the decision of whether or not to offer adjuvant chemotherapy to older patients (140). This is reflected in current Norwegian treatment guidelines, where the choice of whether or not to offer adjuvant chemotherapy to patients ≥75 years is based on evaluation of general condition, functional status and comorbidities (60).

**Chemoradiotherapy**

For patients with rectal cancer presenting with intermediate or locally advanced disease, neoadjuvant chemoradiotherapy is standard part of management. A review from 2007 concluded that neoadjuvant CRT, alternatively radiotherapy alone, improves local control with acceptable toxicity in older patients who are able to
tolerate surgery (143). Norwegian guidelines state that for patients aged ≥75 years with reduced physical function, significant comorbidities or poor general condition, a shorter course of preoperative radiation without chemotherapy should be considered as neoadjuvant treatment (60).

With increasing age, the likelihood of receiving neoadjuvant treatment with subsequent radical surgery decreases (144). In addition, higher age is associated with increased likelihood of deviation from planned treatment. In a US study from 2011, the medical records of patients ≥75 years receiving CRT for rectal cancer were retrospectively reviewed. 25% required a break from radiotherapy, and 33% required dose reduction, break from, or discontinuation of chemotherapy (145). Interestingly, the authors found that toxicity rates were not higher than in previously reported clinical trials of CRT, though deviation rates were higher – suggesting that clinicians may have a (possibly appropriate) lower threshold for adjusting therapy in older than in younger patients. It should be mentioned that the study was fairly small, including only 36 patients that were probably highly selected.

**Palliative treatment**

When curative treatment is not possible, life-prolonging treatment and/or palliative treatment, that is, treatment aimed to relieve symptoms and increase QOL, should be implemented. Chemotherapy is the most important life-prolonging treatment modality. The administration of chemotherapy in this setting should be carefully weighed against treatment toxicity. However, evidence exists showing that older patients benefit from palliative chemotherapy to the same extent as younger patients, and age alone should not be considered a contraindication (146). These results, however, are based on retrospective data, and do not take into account data on functional status besides ECOG PS. Thus, it is uncertain if they can be expanded to a frail and disabled older population.

The fact that older and frail patients are underrepresented in clinical trials does not mean that conducting a clinical trial with this patient population is impossible. This has been demonstrated by the authors of the FOCUS2 (Fluorouracil, Oxaliplatin,
CPT11 [ironotecan]: Use and Sequencing) –trial. In FOCUS2, patients with advanced colorectal cancer who were not candidates for standard chemotherapy treatment were randomized to receive one of four chemotherapy regimens, starting at 80% of standard dose (147). The main research questions in this trial were (1): does oxaliplatin improve progression-free survival, (2): does substituting fluorouracil with capecitabine improve quality of life, and (3): overall treatment utility (OTU) – roughly defined as whether or not patient and clinician found that the treatment had been worthwhile. Interestingly, the authors found that using orally administered capecitabine rather than fluorouracil did not improve QOL in this patient population. More importantly, the novel outcome measure OTU, comprising both patient-reported and objective factors was implemented, and a predictive model for OTU including symptom burden, presence of metastasis, treatment, age and performance status was created. The model needs validation, but the possibility of a method to predict outcome of chemotherapy in patients where the benefit of treatment is uncertain is undoubtedly intriguing.

Biological agents targeting angiogenesis are in some cases used in combination with life-prolonging chemotherapy. Studies have shown that combination regimes increase progression-free survival also in elderly patients (148-149). However, limited data exist, and while these drugs may be feasible in the treatment of older colorectal patients, adding biological agents increase risk of treatment toxicity and adverse events. This must be weighed against potential benefits (140).

Symptoms related to gastrointestinal obstruction may be subject to palliative treatment. Surgical procedures to reduce tumor volume may be indicated; alternatively, endoscopically placed self-expanding metallic stents (SEMS) can be used. In a review comparing surgical intervention to SEMS in obstructive unresectable colorectal cancer concluded that SEMS, though associated with complications such as perforation and stent migration, was superior to surgery in terms of long-term survival and possibly QOL (150). Another minimally invasive method to relieve obstruction that is considered safe and effective is percutaneous gastrostomy (151).
Symptoms that may be subject to palliative treatment in rectal cancer are pain, fistulations, bleeding and fecal or micturation problems. Radiotherapy may be directed to reduce tumor volume, and thus relieve symptoms. Symptoms related to obstruction may be relieved by the implantation of the previously mentioned SEMS.

5 Functional outcomes and quality of life in older patients with colorectal cancer

A paper from 2002 examining treatment preferences in patients >60 years with limited life expectancy due to cancer, heart failure or chronic obstructive pulmonary disease, found that a majority of patients would refuse low-burden treatment if the outcome was survival with severe physical or cognitive impairment (152). This finding suggests that many older patients prioritize functional outcomes over survival. A similar example is found in patients with rectal cancer, who may accept a higher local recurrence rate to avoid a permanent stoma (128). Thus, knowledge about treatment outcomes other than survival and early complications is important. Though examples are not abundant, there are some previous studies investigating physical function and QOL after treatment for colorectal cancer in older patients.

In a paper from 2004, Lawrence and co-authors investigated the course of functional recovery in patients >60 years within 6 months after major abdominal surgery (153). They found that 6 months after surgery, ADL- and IADL-scores were lower than preoperatively in 9% and 19% of patients, respectively. Performance-based measures were also investigated, and at 6 months postoperatively, 39% of patients had not regained preoperative gait speed (measured by TUG), 58% had poorer functional reach and 52% poorer grip strength than preoperatively. In this study, predictors of poorer recovery were serious postoperative complications and preoperative depression, while better preoperative performance status was associated with better recovery. Age was not significantly associated with poorer recovery in multivariate analyses. The study was not limited to patients with colorectal cancer.
A Japanese study from 2007, including patients ≥75 years with gastric or colorectal cancer, measured ADL-function and QOL at one, three and six months after elective surgery (154). In this material, 24% of patients exhibited a decline in ADL-function one month postoperatively, however, for most patients this decline was transient, as only 3% of patients had worse ADL-scores after 6 months compared to preoperatively. A similar trajectory was found for QOL, as patients scored lower at one month after surgery, with a subsequent increase to values similar to, or higher than, preoperatively after three and six months.

In 2012, Finlayson and co-authors examined functional status in nursing home residents after surgery for colon cancer (155). In this retrospective cohort study including 6822 patients >65 years, a 28-point ADL-scale (Minimum Data Set Activity of Daily Living) was assessed before and after surgery. The authors found an average decrease in ADL-scores of 3.9 points one year after surgery compared to preoperatively, and about half of those who were alive after one year had not regained baseline ADL-function. In a study of 299 cancer patients ≥70 years receiving first-line chemotherapy for their disease (77 of which had colon cancer), 50 patients (17%) experienced functional decline in ADL between the first and second treatment cycle (156). Increased risk of functional decline was present in patients with baseline high GDS-scores and low IADL-scores.

A recently published review concerning physical capacity changes after colorectal cancer treatment concluded that there seems to be a permanent loss in physical function at one year after treatment, especially in elderly patients, with some studies reporting up to a 61% decline in self-care capacity (157).

A case-control study from 2006 compared different QOL domains in 29 patients ≥80 years to patients ≤70 years who had been treated for colorectal cancer within 5 years (158). The authors found similar scores for the two groups, with the exception of physical functioning, functional role, micturition and stoma-related problems – where older patients exhibited poorer scores. In another study comparing QOL measured by the EORTC QLQ-C30 in patients older than and younger than 70 years after laparoscopic colectomy for colorectal cancer, older patients exhibited lower scores in
most domains one month postoperatively (159). After 6 months, differences were still present for role functioning, cognitive functioning and sleep disturbances, with older patients reporting lower scores – while scores for the other domains had improved.

In summary, the evidence is somewhat conflicting regarding the trajectories of physical functioning and QOL in older colorectal cancer patients. While most authors report some degree of negative development in physical functional measures after treatment, the magnitude of these changes are highly variable in existing studies. In addition, most studies are fairly small, and time to follow-up is generally limited. In particular, little is known of these outcomes in the subgroup of frail patients. An important question is whether or not the increased vulnerability that is inherent in the frailty syndrome makes these patients more susceptible to functional decline after cancer treatment, which for frail patients with colorectal cancer is limited to surgery in most cases.
OBJECTIVES OF THE STUDY

The main goal of the present study is to describe the long-term trajectory after surgery for colorectal cancer in older patients. More precisely, our objectives are:

A. To describe physical function, cognitive function and quality of life at long-term follow-up.

B. To investigate the possible predictive role of different frailty definitions and information retrieved through a preoperative geriatric assessment on physical function, cognitive function and quality of life.

C. To examine the role of biomarkers in the setting of elective surgery for older patients with colorectal cancer, and their possible relation to frailty and functional decline.
MATERIAL AND METHODS

Study design and ethical considerations

This study was designed as a planned follow-up of a prospective observational cohort study investigating the role of geriatric assessment and frailty in predicting surgical risk and survival in elderly patients with colorectal cancer (160). Eligible participants for the original study were aged ≥70 years, and scheduled for elective surgery of solid tumors in colon or rectum at either one of three hospitals in Oslo; Ullevål, Aker or Akershus University Hospital. When fulfilling these criteria, the only exclusion criterion was not being able to provide a written informed consent. For the follow-up study, participants were consecutively contacted by mail and telephone by the prime investigator (PI), author of this thesis, requesting permission to perform a home-visit. Inclusion began approximately one year after the last participant was enrolled in the original study.

The original study and the current follow-up were both approved by the Regional Committee for Medical and Health Research Ethics in East Norway. Due to the collection of material for a biobank in the original study, approval from the Data Protection Officer at Ullevaal University Hospital was also obtained. All study participants provided written informed consents both at baseline, and again at follow-up. Participants were thoroughly informed in writing and orally of the contents and purpose of the studies, and of their right to withdraw from participation at any time, without consequences for their medical care. The studies did not involve invasive procedures, except for the collection of blood samples for the biobank, which was coordinated with routine preoperative testing, and thus did not represent any increased risk. As the investigations performed in the follow-up study were conducted at a home-visit, the practical burden of participation was minimized. When performing the home-visits, the PI did not find any participants in unsatisfactory living conditions, lack of basic care or any other similar issues that would have warranted intervention.
Baseline data collected in the original study

The PI of the original study, a medical doctor with training in geriatrics, performed a preoperative geriatric assessment in all included participants. The GA included the following domains, assessment tools and cut-off values – thoroughly described in a previous paper (135):

- **Functioning in activities of daily living (ADL)**, measured by the Barthel index and the NEADL-scale. Patients were categorized as independent in ADL if they scored 19-20 points on the Barthel scale, and independent in instrumental ADL if they scored 44 points or above on the NEADL-scale.

- **Comorbidity**, measured by the Cumulative Illness Rating Scale. Mild comorbidity was defined as having no comorbidity higher than grade 2 and less than three grade 2 comorbidities. Moderate comorbidity was defined as having no more than two grade 3 comorbidities and no grade 4 comorbidity. Severe comorbidity was defined as at least three grade 3 comorbidities or any grade 4 comorbidity.

- **Cognitive function**, measured by the Mini Mental State Examination. A score of 27 points or more was defined as good cognitive function, a score between 24 and 26 as moderately impaired cognitive function, and a score of 23 or lower as cognitive dysfunction.

- **Nutritional status**, measured by the Mini Nutritional Assessment. Malnutrition was defined as a score of <17, and risk of malnutrition as a score of 17-23.5 points.

- **Depression**, measured by the Geriatric Depression Scale. A score of 14 points or more was defined as depression.

- **Polypharmacy**, measured by the number of systemic drugs used on a daily basis. Cut-off for polypharmacy was set at >7 daily medications.

In addition, some patients were tested by objective functional measures: the Timed up-and-go and grip strength. The EORTC QLQ-C30 was used as a measure of preoperative QOL and self-perceived health status. ASA-classification and ECOG-PS were also obtained.
Preoperative blood samples for analyses of selected biomarkers were collected when practically possible. Serum preparation was performed by centrifugation according to hospital laboratory guidelines; 3400-3700 rpm for 10-12 minutes. Serum was transported on ice before storage at -70°C Celsius. D-dimer analyses were performed with the STA Liatest® D-Di (Diagnostica Stago, Asniéres, France). CRP levels were determined by an enzyme-linked immunosorbent assay (DRG Instruments GmbH, Germany), detection limit was 0.1 g/L, coefficient of variation (CV) <5%. Levels of IL-6 and TNF-α were measured using enzyme-linked immuno assays with commercially available kits (R&D Systems Europe, Abingdon, Oxon UK), CV in our collaborating lab 10.5% and 8.5%, respectively.

After surgery, information on postoperative complications was collected from hospital records. Complications were classified by severity, from grade I to grade IV, using a grading system created by Clavien and co-authors (161). According to this system, a grade I (minor) complication is an event that only requires simple symptomatic medication, for example antipyretics in a febrile patient. Grade II and III complications are defined as potentially life-threatening events, or events leading to hospitalization longer than twice the median expected stay for the procedure. The distinction between grade II and III complications is made by the presence of sequelae in the latter. A grade IV complication is a lethal event.

Three months after surgery, the PI contacted the patients again by phone, and in participants who answered, the EORTC QLQ-C30 was performed as a telephone-based interview.

**Baseline frailty classification**

Based on the geriatric assessment, patients were classified as frail if one or more of the following criteria were present:

- Dependency in ADL
- Severe comorbidity
- Cognitive dysfunction
- Malnutrition
- Depression
- Polypharmacy (>7 medications on a daily basis)

To be classified as fit, the patient had to be independent in ADL and IADL, have mild comorbidity, good cognitive function (MMSE score >26), have MNA score >23.5, no depression and use <5 daily medications. Patients were classified as intermediate if they did not fulfil the criteria to be fit, and did not meet any frailty criteria.

In addition to the frailty classification based on a GA, a modified frailty phenotype classification was created, based on the frailty phenotype developed by Fried and co-authors (89). The following modifications to the original criteria were applied:

- **Weight loss.** This was defined as a self-reported weight loss of 3 kilograms or more during the last three months – data collected from the MNA.

- **Grip strength.** Low grip-strength was defined by the previously published cut-off values from the Cardiovascular Health Study (89). That cohort consisted of community-dwelling individuals ≥65 years, and cut-off was set at the lowest 20% by gender and body mass index.

- **Gait speed.** A time to complete TUG of 19 seconds or more was defined as slow gait, based on distribution values from the population-based Canadian Study of Health and Aging (162).

- **Exhaustion and low physical activity.** For these criteria, patients' answers to selected questions in the EORTC QLQ-C30 were used. If patients answered ”quite a bit” or ”very much” to questions 12 ("have you felt weak") or 18 ("were you tired"), they were considered to have a positive frailty criterion for exhaustion. The low physical activity criterion was positive in patients who answered ”quite a bit” or ”very much” to question 4 – "do you need to stay in bed or a chair during the day”.

Patients who fulfilled three or more of the modified criteria were considered frail, patients without any criteria were considered fit. If one or two criteria were present, patients were considered pre-frail/intermediate.
Follow-up data collection

At the follow-up home visit, physical function was measured by the Barthel index, the NEADL-scale, TUG and grip strength. For the measurement of grip strength, a Jamar® handheld dynamometer was used. The best value out of three attempts using the dominant hand was noted. Nutritional status and emotional status were assessed by the Mini Nutritional Assessment and the Geriatric Depression Scale.

Cognitive function was assessed by a broader battery of tests than preoperatively. The Clock-Drawing Test, where the test subject is asked to draw a circle with digits and hands to construct a clock was applied. It provides a simple assessment of executive function, visuospatial functioning and logical reasoning (38). Different scoring systems have been proposed for this test. In this study we chose a 5-point scale, in accordance with the tradition of the memory clinic at Oslo University Hospital. In this scale, scores of 4 and 5 points represent normal performance, while a score of three or less is considered abnormal (163). In addition, the Trail-Making Test battery part A (TMT-A) was used to assess cognitive flexibility and working memory (164). For this test, the subject uses a pencil to draw a connecting line between numbers 1-25. Test score equals the time required to perform this task. Normative data by age group are available, and a time required to complete the task $\geq 2$ standard deviations from mean for age group is considered abnormal (165).

For information on health-related QOL at follow-up, the EORTC QLQ-C30 was used. It was conducted as a structured interview, to be able to include participants with reduced vision and reading abilities.
**Statistical methods**

The distribution of most variables at follow-up was skewed – thus, non-parametric statistical methods were mainly applied. Analyses were performed using SPSS Statistics software (Chicago, IL).

In paper I, we wanted to examine whether or not there was a difference in serum levels of selected inflammatory biomarkers between frail, intermediate and fit patients – classified by a GA and by the modified frailty phenotype. Firstly, comparisons across all three groups for each frailty measure were made by the Kruskal-Wallis test. Secondly, Mann-Whitney U tests were used to compare paired groups. For the secondary analyses, Bonferroni correction was applied due to multiple comparisons, and the statistical level of significance was set to 2.5%. In the same paper, we investigated the possibly predictive role of inflammatory biomarkers for postoperative complications. To achieve this, we first grouped levels of biomarkers into quartiles or tertiles, and used chi-square tests to examine their association to both severe complications and to any complication. Based on trend analyses, cut-off points for individual biomarkers were created, and included in crude and adjusted logistic regression models.

In paper II, we tested level of agreement between the GA-based frailty measure and the modified frailty phenotype using the Kappa Measure of Agreement. The outcome variables of interest were the same as in paper I; ”any” versus ”no” complication and ”severe” versus ”any” complications. We compared the associations between these outcomes and GA-based frailty categories and modified frailty phenotype categories using chi-square tests for trend. Furthermore, chi-square tests were used to explore bivariate association between individual modified frailty phenotype criteria and occurrence of severe complications. A multivariate logistic regression model including frailty phenotype criteria with a p-value of less than 0.10 as well as GA-elements previously shown to be associated with severe complications was created. The model also included tumor location, which, in our material was a strong independent predictor of severe complications (patients operated for rectal cancer had more complications). Independent predictors of severe complications were identified using this model by a backward stepwise approach. Finally, paper II included survival
analyses, comparing age groups, cancer stage, GA-classification and classification according to the modified frailty phenotype. Survival curves were estimated by the Kaplan-Meier method and compared by log rank tests. Cancer stage was also entered into Cox proportional hazards models with both GA-category and the modified frailty phenotype category. For this model, GA-category was dichotomized into frail versus non-frail, as the proportionality assumption was not fulfilled.

In paper III, we used the Wilcoxon signed rank test to determine significant changes in physical function measures (ADL-score, NEADL-score, TUG-score and grip strength) from baseline to follow-up. Next, we investigated the predictive role of a priori determined variables (GA-category, individual GA-items, preoperative levels of biomarkers and occurrence of postoperative complication) for poorer physical function at follow-up. No homogeneous relationship between our explanatory variables and physical function measures at follow-up was identified in exploratory analyses. Thus, our explanatory variables had to be dichotomized and implemented in logistic regression models. The dichotomization of explanatory variables was based on cut-off values from previously published papers by our group. Our outcome variables were dichotomized as follows:

- No reduction in Barthel score versus 1-point reduction or more (representing loss of independence in at least one item).
- No reduction in NEADL-score versus 4-point reduction or more (representing loss of independence in at least one item).
- Increased time needed to complete TUG of one second or more at follow-up versus same or shorter time than preoperatively.
- Any reduction in grip strength versus no reduction.

In paper IV, we compared scores from selected EORTC QLQ-C30 scales at three time points; preoperatively, three months after surgery and at follow-up. This was done for the entire cohort and for frail and non-frail patients (based on GA), individually. One-way repeated measures analyses of variance (ANOVA) were used for this purpose. The assumption of sphericity was checked by Mauchly’s test, and
Huyn-Feldt correction applied as appropriate. Post-hoc tests using the Bonferroni corrections were performed where a statistically significant effect of time was present.
MAIN RESULTS

A total of 182 patients were included in the original study. At follow-up, 47 (26%) of them had died, 38 (21%) did not want to participate, while 11 (6%) were lost due to practical causes – geographical considerations being the main issue, as some patients had moved to other parts of the country or lived abroad at follow-up. Another two patients were excluded as they were not able to consent. A total of 84 patients were included, representing 69% of those who were still alive and available for inclusion. The main results from the four scientific papers included in this thesis will be presented here.

Paper I. Preoperative inflammatory biomarkers – differences between frail and non-frail patients, and prediction of postoperative complications

We found that patients classified as frail according to a GA and to a modified frailty phenotype had significantly higher preoperative circulating levels of CRP and IL-6 than their non-frail counterparts. Levels of TNF-α were also higher in frail patients within GA-categories. In addition, we found that IL-6 was an independent predictor of severe complications, also when adjusting for tumor location and frailty based on a GA.

Paper II. Comparison of two approaches to frailty in older patients with colorectal cancer

When comparing a GA-based frailty measure to a modified frailty phenotype measure, we found poor agreement between the two in terms of which patients were classified as frail. In this paper, we further found that GA-based frailty was predictive of both any and severe postoperative complications, while the frailty phenotype was not. Both frailty measures however, were able to predict overall survival.
Paper III. Long-term physical function in older patients after surgery for colorectal cancer

In this paper, we found a statistically significant decline in both ADL and IADL function at follow-up compared to baseline. A significant change for the physical performance measures TUG and grip strength was not identified. When exploring predefined frailty indicators as possible predictors for poorer physical function at follow-up, we were only able to identify an association between postoperative complications and grip strength at follow-up.

Paper IV. Long-term quality of life in older patients after surgery for colorectal cancer

Using EORTC QLQ-C30 data, we were able to show that scores for emotional function and overall QOL were improved three months after surgery in both non-frail and frail patients. We also examined physical function, where no significant change was identified. At the long-term follow-up, scores for emotional function and QOL were lower, but not significantly lower compared to values at three months, and still higher than baseline. While frail patients overall exhibited lower scores than non-frail patients, the same trajectories for changes over time were present.

Cognitive function in older patients after surgery for colorectal cancer (not published)

Based on cognitive screening tests, our patient cohort was overall cognitively well-functioning at baseline - only 12 (7%) of patients had a poor MMSE-score defined as <24 points, while 22 (12%) had moderately impaired cognitive function defined as an MMSE-score between 24 and 26 points.

At follow-up, the MMSE was performed in 80 patients. Median MMSE-score was 28 points (minimum 22, maximum 30). Five patients (6%) scored <24 points, 13 patients (16%) scored between 24 and 26 points. 78 patients completed the clock drawing test, and 58 patients (77%) scored 4 or 5 points, which is considered normal. Mean time to complete TMT-A was 70 seconds (range 29-266). 80% of patients performed within
the reference values or less than one standard deviation longer than reference values for their age group. Thus, 20% of patients were considered to have an abnormal TMT-A test score.
DISCUSSION

Long term outcomes after surgery for colorectal cancer in older patients

Some older patients may prioritize functional outcomes, like the ability to live an independent life, over survival. While it should be emphasized that this does not apply to all patients of higher ages, knowledge about cancer treatment outcomes other than survival and early complications is important. Still, little is known about the possible impact of surgery for colorectal cancer on these outcomes in older patients. One of the reasons for this is that functional outcomes are rarely studied. This is an issue receiving increased interest in several other fields, such as cardiovascular medicine, with a recent review highlighting lack of evidence for several common therapies and interventions in patients of higher ages (166). Our main aim for this study was to add evidence to the existing gap in knowledge regarding long-term functional outcomes and health-related QOL after surgery for colorectal cancer in older patients.

In our cohort, we found a slight, but significant long-term decrease in patient-reported ADL and IADL function, but no significant change in the objective physical performance measures TUG and grip strength. The observed discrepancy in changes between these measures is interesting. A possible explanation is that the subjective evaluation of physical function when patients report their own ADL/IADL performance is more sensitive to subtle changes than the objective measures. As a patient-reported outcome, other factors than those who may be observed by the clinician are involved, like increasing effort required to perform a task independently. In addition, ADL and IADL questionnaires are more comprehensive and consider more domains than the physical performance tests, which generally focus on one activity. For example, physical performance tests are not able to identify fecal or urinary incontinence, or problems dressing, which may be significant factors in determining degree of dependency.

The most commonly reported trajectory for physical function after surgery for colorectal cancer, as described in a previous review, is an initial drop in scores with a subsequent increase to values below baseline (157). That review did not exclusively include studies with older patients; mean/median patient age for considered papers
varied between 52 and 83 years. Only three of the included papers had a median/mean patient age >70 years, and one of them was paper III included in this thesis. An important strength of our study is the relatively long time to follow-up of median 22 months (range 16-28 months), which is longer than most other comparable studies. It is possible that a more pronounced reduction in physical function measures was present in our cohort during the first postoperative months. If this is true, some degree of functional improvement must have taken place during the months until follow-up, as is also reported by other authors. The fact that such an improvement may be seen even in relatively old and partly frail patients is important, indicating that physical function is not necessarily adversely affected after surgery for colorectal cancer. Lawrence et al have previously reported that in a population of patients >60 years undergoing abdominal surgery, the percentage of patients who had not recovered six months after surgery in terms of gait speed and grip strength was 39% and 52%, respectively (153). This could illustrate that time to potential functional recovery is protracted in older patients.

In a study of nursing home residents undergoing surgery for colon cancer, a more pronounced decrease in ADL-function was present at follow-up than in our cohort (155). The study did not consider preoperative frailty as a factor. Still, it seems intuitive that nursing home residents, who are mostly frail, are more susceptible to functional loss after a stressful event such as major surgery. Of note, 97% of our cohort was home dwelling before surgery. In a smaller study including 47 patients with a mean age of 81.9 years undergoing colorectal resections, the authors found that as many as 94% had an unchanged Barthel score post-operatively (167). In that cohort, both preoperative frailty (which was based on the frailty phenotype criteria) and comorbidity were associated with failure of functional recovery.

We also assessed health-related QOL and emotional function by the EORTC QLQ-C30, and found that scores improved three months after surgery compared to baseline in both frail and non-frail patients. While scores subsequently decreased at long-term follow-up, they remained somewhat higher than the baseline values. For the physical function domain of the EORTC QLQ-C30, no significant changes over time were identified. This was somewhat surprising, as there was a drop in self-reported ADL and IADL function at long-term follow-up. An explanation could be that the changes
defined as clinically significant for the ADL and IADL scales when using the patients own baseline score as reference, were too subtle to be detected by the EORTC QLQ-C30 questionnaire.

An important finding in our study of QOL-domains was that the trajectory of scores – most importantly the clinically and statistically significant improvement in QOL after treatment – were similar in non-frail and frail patients. As frail patients are characterized by reduced biological reserves, and thus are more susceptible to adverse treatment outcomes such as postoperative complications, it was surprising that no negative effect on long-term QOL was identified. Response shift may be a relevant factor to consider in this context. Response shift is a phenomenon that occurs when the individual adjusts his or her internal standards in a way that alters expectations, and may accompany changes in health status that are often seen in increasing age (168). This may explain why one patient with obvious functional limitations and significant comorbidities may characterize her overall health status and QOL as “excellent” – whereas another patient with similar challenges but different values or standards could experience poor general health and QOL. Response shift is difficult to measure. Still, the possible impact it may have had on the data in our cohort does not undermine the significance of the observed improvement in QOL-scores, as our main interest was the patients’ own subjective experience. Other authors have also reported some improvement in QOL-scores in geriatric populations after surgery for colorectal cancer, but we have not found other studies that investigated this outcome in the subgroup of frail patients.

Assessing surgical risk in older patients with colorectal cancer

With the improvement in surgical and anesthesiological techniques that have developed over the past decades, surgery is now routinely performed in patients of high age – in contrast to about 70 years ago, when operating on individuals older than 50 years was controversial (169). For life-threatening diseases such as colorectal cancer, surgery improves survival and reduces risk of complications related to the tumor, like obstruction or bleeding. Thus, there is no doubt that surgical treatment of colorectal cancer is indicated also in older and frail patients. It is, however, known that the risk of mortality and postoperative complications is generally higher in older
than in younger age groups. Being able to estimate surgical risk is of value for clinicians and patients. For the clinician, assessing surgical risk may guide intervention against potentially reversible risk factors, such as malnutrition or depression – and increase focus on predictive measures to avoid adverse events. For the patient, reliable information on estimated risk of the procedure and thus knowing what to expect may improve satisfaction with care. Information about risk is also mandatory when obtaining informed consent.

Risk associated with colorectal cancer surgery is not limited to early postoperative outcomes, but does also include possible long-term effects on physical function, cognitive function and QOL. Thus, we wanted to investigate whether or not preoperative variables were able to predict poor functional outcome at the long-term follow-up. Based on the previous findings, we hypothesized that frailty based on a GA, individual GA-elements, individual components of the frailty phenotype, and higher serum levels of inflammatory biomarkers were potential predictive factors. We also included the more traditional risk factors ASA-score, TNM-stage and ECOG PS. In addition, we analyzed the impact of postoperative complications, also a marker of increased vulnerability in this setting. It was surprising that the only significant association was between postoperative complications and reduced grip strength at follow-up. In particular, we expected to find an association between preoperative frailty and poorer functional outcome at follow-up, given the vulnerable state that is inherent in the frailty syndrome. However, some frailty indicators did show a trend towards poorer functional outcome, and we cannot exclude that a true association does exist, but was not evident in our analyses due to the limited sample size. Another possible methodological issue that could have affected our results is inclusion bias. This is discussed in more detail below.

Early postoperative outcomes that have been the focus of many researchers are complications and mortality. This was also investigated in our cohort, where being frail based on a GA was strongly predictive of postoperative complications and early and 5-year mortality (122,135). Individual GA-elements associated with the occurrence of postoperative complications were severe comorbidity, IADL-dependency, depression and malnutrition (170). When adding ECOG PS to the model, however, severe comorbidity was the only GA-element with independent
predictive value. These findings indicate that GA is useful in preoperative assessment of older patients with colorectal cancer in terms of predicting complications and survival, whereas the relevance for predicting other long-term adverse outcomes is questionable.

Age was not predictive of early or late adverse outcome in our cohort – the former is in discordance with reports from other authors, who have found increasing age to be associated with risk of complications in both colon and rectal cancer patients (171-172). These authors have, however, not considered preoperative frailty as an independent factor, and the effect of age found in those studies may well represent the effect of frailty, which occurs with higher frequency in aged subjects. However, in large patient populations, increasing age seems to be an independent predictor of negative outcomes, and our study may have been underpowered to detect such differences.

While a frailty measure based on a GA seems to be predictive of postoperative complications, its implementation in clinical practice may be complicated due to limited time and resources. Thus, the independently predictive value of individual GA-elements is interesting, implying that a full GA may not be necessary if the goal is to assess surgical risk. In a recent literature review on the utility of individual GA-elements in older surgical cancer patients with different types of cancers, based in part on our data, dependency in ADL/IADL, fatigue and cognitive function were found to increase risk of postoperative complications, as was frailty (173). With the exception of nutritional status, the GA-domains predicting complications in our material are components of the previously mentioned and validated surgical risk assessment tool PACE, which also includes ECOG PS, fatigue assessment and ASA-class (68). PACE has been recommended for clinical use in onco-geriatric surgical patients, and may be more intuitive in a surgical practice than a complete GA. An even simpler screening tool developed by Huisman et al, which combined TUG-score, nutritional status, ASA-class, gender and type of surgery, has also been shown to predict adverse early outcome (71). To my knowledge, none of these screening tools have been investigated with respect to their association with long-term outcomes.
Another possible solution to the practical problem of implementing a full GA in clinical practice is using a frailty screening tool. A recent review published by SIOG concluded that to date, no screening tool can be recommended or discouraged in clinical practice, but screening is still recommended to identify patients in need of evaluation by a GA. The tool G8 seems to perform best in terms of sensitivity (95). The G8 includes eight questions, considering age, nutritional status, weight loss, BMI, mobility, psychological state, number of medications and self-perceived health. A recent study from the Netherlands investigated the ability of different screening tools in terms of predicting functional decline and QOL in patients with and without cancer after one year (174). Interestingly, the authors found that abnormal screening tool scores were associated with increased risk of functional decline – but only in patients without cancer, and only in univariate analyses. No association between abnormal screening scores and poorer QOL was identified. It is not unlikely that the prediction of these outcomes is complicated by the heterogeneity, different degrees of comorbidity and unforeseeable life events that characterize older and frail individuals.

It is clear that screening tools cannot replace a complete GA, which remains superior in terms of detecting and managing frail or at-risk individuals. In addition, screening tools need validation in surgical patients. While the optimal tool for risk assessment in older surgical patients with colorectal cancer is not established, current data strongly support that this assessment should include some evaluation of physical function – and it is uncertain if preoperative assessment is useful in predicting long-term adverse outcomes.

**Inflammatory biomarkers – potential role in frailty and colorectal cancer**

Activation and dysregulation of inflammatory pathways are likely to be involved in the pathogenesis of frailty, and also in the development of cancer. An interesting research question is whether or not biomarkers of inflammation could be useful in the clinic, for example as predictors of adverse health outcomes, as some previous studies have indicated. We found that IL-6 was an independent predictor of severe complications, also when adjusting for frailty. Levels of inflammatory biomarkers were higher in frail than non-frail patients, and it is uncertain whether or not the predictive role of IL-6 in this setting is related to its association with frailty, an
association that has also been found in other studies (97). Furthermore, there is
evidence that higher levels of IL-6 are associated with more advanced disease stage
and the presence of metastases in patients of all ages, and in a recent case-control
study, IL-6 showed a modest positive association to risk of developing colorectal
cancer (175-176). In terms of predicting postoperative complications, however, our
findings are partly supported by a recent article regarding IL-6 and outcome after
major abdominal surgery (177). In this study, preoperative levels of IL-6 were not
associated with postoperative complications, but higher levels on the first
postoperative day were. Mean patient age was 68 years. The most important
difference between this study and ours is the fact that IL-6 on the first postoperative
day is likely to reflect the inflammatory response that is triggered by the stress of
surgery. Our results are thus not directly comparable, but may still be said to support
the association between systemic inflammation and complications.

Higher levels of CRP were also associated with frailty in our material, but were not
found to be independently predictive of either early or late adverse postoperative
outcomes. In combination with hypoalbuminemia, however, higher CRP-levels seem
to carry prognostic significance for cancer patients, as is demonstrated by the
previously mentioned GPS. In a recent cohort of 115 patients with surgically treated
colorectal cancer with a mean age of 61 years, the GPS was found to be
independently predictive of mortality during a mean follow-up time of 20 months
(178). The authors concluded that the GPS should be included in preoperative
assessment in patients with colorectal cancer. An obvious advantage of the GPS is
that both CRP and albumin are already routinely measured in clinical practice, and its
implementation should thus be uncomplicated, in contrast to IL-6, which demands
special lab equipment not readily available in most institutions.

Systemic cancer disease might contribute to the development of frailty through the
mechanisms that lead to cachexia and fatigue – further complicating the relationship
between frailty, cancer and inflammation. In addition, markers of inflammatory
response are highly unspecific, as they are elevated in a wide range of clinical
settings, and have been associated with adverse health outcomes, such as
cardiovascular events, diabetes/insulin resistance and reduced lung function (179-
181). However, the probable negative effect of inflammatory biomarkers on adverse
health outcomes, does not necessarily imply that they cannot play a role in prognostic considerations for older and frail patients with cancer. More research is warranted to clarify the multifaceted relationships between inflammation, aging, cancer, frailty and comorbidities. Finally, regardless of associations that are demonstrated in scientific papers, an important area of uncertainty is whether or not such inflammatory biomarkers are superior to, or mainly supports information retrieved by clinical parameters and standard laboratory evaluation.

**Choice of frailty measure and outcome variables**

This study was a follow-up of a previous observational cohort study. Thus, the choice of frailty measure and assessment tools was made beforehand. A comment on these choices is still warranted. Our main frailty measure was based on a GA. While the frailty phenotype may be a simpler and more practical tool than a frailty measure based on a GA, the latter was a more natural choice given its established role in geriatric oncology. Furthermore, a patient assessment without a review of important elements such as comorbidities, medications and cognitive status is less informative for clinical purposes – though the nutritional and physical criteria included in the frailty phenotype undoubtedly carry important prognostic information.

There is no current evidence supporting the use of one set of assessment tools above another when performing a GA. In the original study, the choice of tools was based on literature review and local traditions. Well-established and validated assessment tools were used. The classification of frail and non-frail patients was defined *a priori*, and the chosen cut-off values for this classification could be debated. The fact that our frailty measure was later shown to be predictive of postoperative complications and survival does, however, support its validity.

In paper II, a modified version of the frailty phenotype was compared to the GA-based frailty measure. The modified frailty phenotype was created by the use of collected data with similar characteristics to the original frailty phenotype criteria. The modified frailty phenotype was not identical to the original version – though I believe that the modification captures the essence of the original frailty phenotype. The most striking difference is that only 17% of patients classified as frail based on a
GA were frail according to the modified frailty phenotype. A likely explanation for this is that the frailty phenotype does not include evaluation of comorbidities, while this was an important reason for being classified as frail by a GA. This is consistent with the findings of a review from 2015 concerning prevalence and outcomes of frailty in older cancer patients (182). The authors found that in studies using a GA-based approach, median frailty prevalence was 43%, while the overall prevalence of frailty in studies using the frailty phenotype was 13%. Thus, the GA-based approach seems to be more sensitive in detecting vulnerability in older cancer patients.

Our main outcomes in this study were physical function and QOL. For the sake of comparison, we chose to measure these domains by the same assessment tools that were used at baseline. In paper III, concerning long-term physical function, we chose to compare each patient’s score at follow-up to the baseline score. By doing this, we were able to detect changes on an individual level, believing this to be a more meaningful outcome for the patient than changes on a group level.

**Limitations of the study**

An important weakness of this study is the limited sample size. In part, this was embedded in the study design, as it was a follow-up study, and only previous participants were eligible for inclusion. Furthermore, a considerable number of patients had died at follow-up, as is expected in a cohort with a mean age of 79.6 years at baseline. While few of the surviving patients were lost to follow-up due to practical causes, the majority of those who were not included denied participation. My general impression was that most patients who were unwilling to participate explained this with “being tired of hospitals and doctors” and “not having the energy”. The possible bias is that patients who were not included at follow-up had poorer physical function and health-related QOL, and that our findings thus overestimate the fitness and well-being of the original cohort at follow-up. Still, the percentage of patients classified as frail preoperatively was fairly similar at baseline (40%) and at follow-up (32%) – indicating that frail patients with presumably lower scores were well represented at follow-up.
The study was also limited by missing data – both at baseline, three-month follow-up and the long-term follow-up. No deleting or imputation of values post-hoc was performed. Patients with missing data were excluded from the analyses where these data were used. The most common cause for missing data at follow-up was that patients were tired, and did not want to complete all the questionnaires and tests involved. Thus, the domain with most complete data at follow-up was the physical dependency domain measured by Barthel Index and NEADL, which was the first part of the assessment. While this was not obvious to me when performing the home visits, it is possible that patients who were unwilling to or unable to complete the assessment would have exhibited lower scores for the remaining examinations. Accordingly, the final results may have overestimated the performance of the entire cohort.

Another weakness of the study was the lack of a control group. Some degree of functional loss and possibly decrease in self-perceived health and QOL may be expected with normal aging. We were not able to control for significant factors of interest in this context, such as increasing comorbidity. Thus, a control group of both frail and non-frail older patients who were not surgically treated for colorectal cancer would have added an interesting dimension to our material. Still, the main purpose of this study was not to determine a direct causal relationship between the surgical procedure and outcome at follow-up. In a population partly defined by multimorbidity and other possibly confounding factors, such an effort would have demanded a much larger number of participants to gain adequate statistical power. Rather, our design was observational, with exploration of the functional trajectories of the cohort, and comparison of outcomes between non-frail and frail patients.

Finally, while our focus was the impact of surgery for colorectal cancer, some patients in our cohort also received oncological treatment. At baseline, 33% of the patients with rectal cancer were treated with preoperative radiation, nine of which also received neoadjuvant chemotherapy. Only two of the patients with stage III colon cancer were treated with adjuvant chemotherapy. We did not specifically analyze the possible effects of oncological treatment on long-term outcomes, mainly because of the limited size of these subgroups.
**Frailty in colorectal cancer patients – clinical considerations**

We have contributed with evidence indicating that older patients – both frail and non-frail – benefit from surgery for colorectal cancer with low risk of functional decline and acceptable QOL more than one year after treatment. While we were unable to identify any association between overall frailty or individual frailty indicators preoperatively and poorer outcomes at long-term follow-up, the association between preoperative frailty and postoperative complications/mortality is established, and is thus highly relevant to consider in the management of older patients with colorectal cancer. Together, these findings indicate that attention should be brought towards possible interventions against frailty, investigating whether or not the frailty syndrome can be reversed.

The hypothesized effects of physical exercise programs and nutritional interventions on physical performance outcomes and frailty scores have been subject to investigation. The most promising intervention seems to be physical activity/training interventions, and while studies are heterogeneous in terms of frailty definitions and intervention content, several authors report improved physical performance and reduced frailty after intervention (183-185).

Studies investigating the effect of nutritional supplementation have shown more mixed results (186-188). In an interesting recent RCT from Singapore, 246 frail or pre-frail individuals were assigned to physical exercise intervention, nutritional intervention, cognitive training, combination intervention or usual care (189). After 12 months, all intervention groups exhibited lower frailty scores than the control group – but the reduction in frailty scores was most pronounced in the group receiving combined intervention. This supports the implementation of multidimensional intervention in practice, though more research is warranted in order to create validated guidelines.

Another intriguing issue is whether or not frailty may be improved by pharmaceutical interventions. Interestingly, some trials have investigated the effect of drugs on sarcopenia, which, as previously mentioned, is a concept closely related to frailty.
Examples include myostatin antagonists (inhibitors of a cascade leading to decreased muscle growth), androgens and modulators of the inflammatory response (190-192).

Importantly, as stated by an expert task force in 2015, further intervention trials targeting sarcopenia and frailty are dependent on clear definitions of these conditions, as well as validated and clinically meaningful functional outcomes (193). Thus, more research is warranted.
Conclusions

- Surgery for colorectal cancer in both frail and non-frail older patients can be performed with acceptable risk of functional decline, as well as with positive long-term effects on QOL.
- A GA-based frailty measure is robust in predicting postoperative complications and survival, but may be less valuable in terms of predicting long-term outcomes other than survival after surgical cancer treatment.
- The frailty phenotype carries prognostic significance and predicts survival in older patients with colorectal cancer, though it was not able to predict other short-term or long-term adverse outcomes in our cohort.
- Inflammatory biomarkers in serum are associated with frailty, and may have a role in predicting adverse outcome after surgery for colorectal cancer in older patients.
- In cognitively well-functioning older patients, the risk of adverse effect of surgery for cognition seems to be low.
Suggestions for further research

With the aging of the population and expected increase in older individuals diagnosed with colorectal cancer, more research on the optimal management of these patients is warranted. While this study focused on the rather undisputed surgical entity of colorectal cancer treatment, the role of chemotherapy and radiation therapy in adjuvant, neoadjuvant and palliative settings should be further explored in randomized controlled trials including older patients, preferably also those with some degree of frailty. In addition to objective outcome measures, investigating PROMs is also necessary, and an increased focus on long-term outcomes other than mortality is warranted.

The advantages of a GA-based approach to the older cancer patient are well established, but how to select individuals in need of a complete GA is not. This is important, as it is not feasible to complete a GA in all patients above a certain age in clinical practice. To further clarify this, I think the authors of future clinical trials should focus on validating existing and promising screening methods such as the G8, rather than developing new ones.

For future studies investigating long-term outcomes in older patients with colorectal cancer, it would be interesting to see results from intervention-based or case-control designs. In particular, studies investigating the possible advantage of a GA-based intervention before and during treatment in frail individuals would add evidence to the optimal management of this patient group. In addition, case-control studies might shed light on the possible relationships between cancer treatment and outcomes that seem to be important to older patients, such as living independently and preserving cognitive function.
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