

The role of geriatric assessment and frailty measurements in predicting surgical risk and survival in elderly patients with colorectal cancer

A prospective observational cohort study

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The role of geriatric assessment and frailty measurements in predicting surgical risk and survival in elderly patients with colorectal cancer

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“Seek simplicity and distrust it”

Alfred North Whitehead (1861-1947)

Summary

Background: Colorectal cancer (CRC) can be considered a disease of the elderly, with a median age of diagnosis of 72 years. Surgery is the main treatment for colorectal cancer. As chronological age does not accurately reflect physiological reserves in the heterogeneous elderly population, it has been suggested that older cancer patients may benefit from a comprehensive geriatric assessment (CGA) before treatment decisions are made. A CGA is a systematic approach aiming to assess physical function, comorbidity, polypharmacy, nutritional status, cognitive function, and emotional status in older patients. Based on a CGA, patients may be divided into three groups: Fit, intermediate, or frail. Few prospective studies have investigated the associations between elements of a CGA and surgical outcomes in elderly patients. Furthermore, the definition of “frailty” derived from a CGA is controversial. In geriatric medicine, frailty is more commonly defined as a cluster of physical impairments (often called the *physical phenotype of frailty* – PF).

Aims: To study the association between a categorization of patients into the groups *fit, intermediate, or frail* based on a pre-operative CGA and the risk of post-operative complications in elderly CRC patients who were electively operated; to identify independent predictors of post-operative complications and survival from a CGA and Eastern Cooperative Oncology Group performance status (ECOG PS); to compare a pre-operative multi-domain frailty measurement based on a CGA to a modified version of PF in older CRC patients, and to analyze the ability of the two measurements to predict post-operative complications and overall survival; to compare levels of inflammatory biomarkers (CRP, IL-6, TNF- α), and D-dimer in older CRC patients classified according to the two frailty definitions.

Methods: Patients ≥ 70 years electively operated for all stages of CRC from 2006 to 2008 in three Norwegian hospitals (Ullevaal University Hospital, Aker University Hospital, and Akershus University Hospital) were consecutively included. A pre-operative CGA, an assessment of self-reported health, measurements of grip strength and gait speed were performed, and blood samples were drawn within 14 days of surgery. CGA-frailty was defined as fulfilling *one or more* of the following criteria: Dependency in personal activities of daily living, severe comorbidity, cognitive dysfunction, depression, malnutrition, or >7 daily medications. PF was defined as the presence of three or more of the following criteria:

Unintentional weight loss, exhaustion, low physical activity, impaired grip strength, and slow gait speed. Outcome measures were post-operative complications (any complication and severe complications) and overall survival.

Results: Patients (182) with a median age of 80 years (range, 70-94 years) were included. For the categorization into the three CGA-groups, 178 patients were available for analyses, while 176 patients were available for the comparison between the two frailty classifications. Twenty-one patients (12%) patients were categorized as fit, 81 (46%) as intermediate, and 76 (43%) as frail. Eighty-three patients experienced severe complications, including three deaths; 7/21 (33%) of fit patients, 29/81 (36%) of intermediate patients, and 47/76 (62%) of frail patients ($p=0.002$). Increasing age and ASA class were not associated with complications. Severe comorbidity was an independent predictor of severe complications (odds ratio [OR] 5.62; 95% CI 2.18 to 14.50) and early mortality (hazard ratio [HR] 2.78; 95% CI 1.50 to 5.17). Dependency in instrumental activities of daily living (IADL) and depression were predictors of any complication (OR 4.02; 95% CI 1.24 to 13.09 and OR 3.68; 95% CI 0.96 to 14.08, respectively) while impaired nutrition predicted early mortality (HR 2.39, 95% CI 1.24 to 4.61). When added to the models, ECOG PS independently predicted both morbidity and early mortality, and ECOG PS was a more powerful predictor than IADL-dependency, depression, and impaired nutrition. The agreement between the two frailty classifications was poor. CGA-frailty was identified in 75 (43%) patients, while PF was identified in 22 (13%) patients. Only CGA-frailty predicted post-operative complications ($p= 0.001$). Both CGA-frailty and PF predicted survival. Levels of CRP and IL-6 were significantly higher in frail compared with non-frail patients within both measures.

Conclusions: CGA can identify frail patients who have a significantly increased risk of developing post-operative complications after elective surgery for CRC. This multi-domain frailty measurement appears to be more useful than frailty identified from a modified version of the physical phenotype of frailty criteria in predicting morbidity, but for long-term outcomes such as overall survival, both measurements are predictive. Severe comorbidity, IADL-dependency, depression, and impaired nutrition seem to be the most important CGA-elements predictive of post-operative complications and overall survival. As ECOG PS predicts all outcomes, a consistent use of ECOG PS in studies of cancer surgery is recommended.

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In parallel with this, the process of completing a clinical research study has been extremely informative. Applying for a grant, planning the study, collecting the data, performing the statistical analyses, and writing the publications have all been valuable lessons in different aspects of medical research. Above all, the PhD process has made me a more critical reader of scientific publications, but I have also become fond of (geriatric) research, which I think is truly exciting because of the complexity! I am very grateful to the Norwegian Cancer Society for sponsoring me with a PhD scholarship.

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List of papers

- I** Kristjansson SR, Nesbakken A, Jordhøy MS, Skovlund E, Audisio RA, Johannessen HO, Bakka A, Wyller TB. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. *Crit Rev Oncol Hematol* 76:208-17, 2010
- II** Kristjansson SR, Jordhøy MS, Nesbakken A, Skovlund E, Bakka A, Johannessen HO, Wyller TB. Which elements of a comprehensive geriatric assessment (CGA) predict post-operative complications and early mortality after colorectal cancer surgery? *Journal of Geriatric Oncology* 1:57-65, 2010
- III** Kristjansson SR, Rønning B, Hurria A, Skovlund E, Jordhøy MS, Nesbakken A, Wyller TB. Frailty as a clinically useful predictor in elderly cancer patients – a comparison of two different approaches. (*Submitted*)
- IV** Rønning B, Wyller TB, Skovlund E, Seljeflot I, Jordhøy M, Nesbakken A, Kristjansson SR. Frailty measures, inflammatory biomarkers, and postoperative complications in older surgical patients. *Age Ageing* 39:758-61, 2010

Abbreviations

ADL	Activities of Daily Living
APACHE	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiologists
CACI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CHS	Cardiovascular Health Study
CSHA	Canadian Study on Health and Aging
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
CRC	Colorectal Cancer
CRP	C-reactive protein
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
ERAS	Enhanced Recovery After Surgery
FT	Fast Track
GDS	Geriatric Depression Scale
IADL	Instrumental Activities of Daily Living
IL-6	Interleukin-6
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
NEADL	Nottingham Extended Activities of Daily Living
PACE	Preoperative Assessment of Cancer in the Elderly
PADL	Personal Activities of Daily Living
PF	Physical Phenotype of Frailty
PI	Principal Investigator
POSSUM	Physiological and Operative Severity Score in Enumeration of Mortality and Morbidity
RCT	Randomized Controlled Trial
TNF-α	Tumor Necrosis Factor-alpha
TUG	Timed Up and Go

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Overture

Colorectal cancer mainly affects elderly patients; in Norway sixty percent of patients are more than 70 years old at diagnosis¹. The resection rate is high even in advanced age for this cancer type, leading to a large number of elderly patients undergoing surgery². Many studies have attempted to link pre-surgical risk factors to post-operative morbidity, but most of these lack information about common risk factors among elderly patients, such as functional status, malnutrition, depression, and dementia. Several review articles have advocated the routine use of a comprehensive geriatric assessment (CGA) in elderly cancer patients in order to shape interventions and clinical decisions in oncology³⁻⁶. A CGA offers a systematic approach aiming to assess physical functioning, comorbidity, polypharmacy, nutritional status, cognition, and emotional status in elderly patients. Due to a lack of clinical studies, it still remains unclear whether the additional information obtained from a CGA adds to a routinely performed pre-operative workup in terms of predicting treatment complications and survival in elderly patients operated for colorectal cancer.

Thus, the aim of this prospective observational cohort study was to examine the relationship between a pre-operative CGA performed in 187 patients aged 70 years and older and two post-operative outcomes: complications within 30 days of surgery and overall survival. We primarily wanted to study an overall categorization into three patient groups (fit, intermediate, or frail) based on the complete CGA. Subsequently we wanted to study which domains of the CGA were the most important predictors of the outcomes.

The term frailty is often used to describe an elderly patient who is at high risk for adverse outcomes such as hospitalization and mortality. It is widely debated within the geriatric literature how to identify such a patient. Particular interest is taken in patients who appear healthy, but have limited reserve capacity and therefore decompensate when they are exposed to stress such as surgery or an infection. As our cohort may be viewed as a group of patients who are exposed to a similar form a stress, a surgical resection of a colon or rectal tumor, we also used our dataset to test the ability of two commonly used frailty-classifications to predict post-operative complications and overall survival.

Based on our dataset and analyses, we believe that we have contributed to the scientific rationale for recommending CGA in elderly cancer patients. This may impact the development of geriatric oncology as a scientific discipline. Surgeons and oncologists treat a large number of elderly patients, but few programs offer specialized training in geriatric surgery or geriatric oncology. By showing that typical geriatric elements, such as functional status, comorbidity, and depression, were more important predictors of surgical outcomes than increasing age and American Society of Anesthesiologists Physical Status Classification, we hope to increase the interest among surgeons to assess such factors in clinical practice and to include them in scientific publications. For geriatricians, we believe that our data regarding the clinical usefulness of two different ways of identifying frailty represent a valuable contribution to the frailty debate.

There are several aspects of surgery in elderly patients with colorectal cancer that will not be discussed in this dissertation. As we have merely concentrated on the pre-operative assessment of the elderly surgical patient, important factors such as pre-operative preparation of the patient for surgery, type of anesthesia, the surgical procedure itself, or implementation of specific post-operative measures have not been covered. Even though survival analyses are included in the publications from our study, we have not yet looked into quality of life after surgery, long-term functional consequences of the surgical treatment, or causes of deaths in our cohort. However, data regarding these long-term aspects have been collected, and will be published on a later occasion.

Introduction

The prevalence of cancer rises with increasing age. In Norway, 60% of colorectal cancers occur after the age of 70¹. When treating cancer in older adults, a number of challenges have to be faced. Firstly, there is little evidence from the medical literature regarding this group of patients^{7,8}. Patients are often excluded from clinical trials due to advanced age and severe comorbidity. Secondly, the elderly population is characterized by a marked variability in the rate of aging, and chronological age does not accurately reflect remaining life expectancy and treatment tolerance⁹. Thirdly, the training of oncologists and surgeons may in some settings focus on choosing the best therapy for physically fit patients. Geriatricians, on the other hand, have limited knowledge about oncology and surgery.

Over the recent years there has been a growing interest in a subspecialty field of oncology; geriatric oncology. One of the major priorities within this field is to develop an assessment tool for oncologists and surgeons who treat elderly cancer patients^{5,10,11}. This tool should be able to capture an older individual's "biological age", independently of his or her chronological age. The perfect assessment tool would identify crucial factors such as remaining life expectancy and treatment tolerance, as well as remediable problems that might influence treatment choices, therapeutic adherence, discharge planning, and rehabilitation.

Cancer and aging

Increasing age is the single most important risk factor for cancer development¹². However, the age-dependent escalation in cancer risk is mostly due to a marked increase in epithelial carcinomas from 40 to 80 years of age. After 80 years, the incidence of cancers level off. A common mechanism for aging and cancer development is the generation and accumulation of cellular damage. Interestingly, other divergent mechanisms that have opposing effects on cancer and aging are also identified, and these mechanisms seem to protect us from cancer but promote aging. Examples are telomere shortening and cellular senescence. These mechanisms prevent excessive cellular proliferation, thereby limiting long-term regeneration and longevity. To date, most of the fundamental questions regarding the relationship between cancer and aging remain unanswered¹³.

Biological age and frailty

As almost all age-related changes lead to reduced function, aging itself increases vulnerability for adverse health events¹⁴. However, the elderly population is characterized by a marked variability in the rate of functional deterioration, both between individuals and within individuals. Thus, as the passage of time is only indirectly related to age, knowing a patient's chronological age is not sufficient to determine the individual's functional or physiological capacity¹⁴. Instead one speaks of *biological age* as an indicator of the rate of aging in an individual human. Various biomarkers have been proposed to determine biological age in humans, and some examples are lung capacity, grip strength, and systolic blood pressure. The concept of *reserve capacity* is frequently discussed in the context of biological age. In order to determine susceptibility in an individual human it may be relevant to understand the compensatory mechanisms that let older individuals maintain their autonomy in daily life despite deteriorations in organ functions¹⁵. For example, a patient may have balance problems due to central nervous system disease. Such a patient potentially needs more muscle strength than is normally needed in order to maintain normal walking to compensate for the balance problems – good strength compensates for the impaired balance¹⁶. But because the patient is already using his or her reserve capacity, there is an increased risk of decompensation (in this case falling) if further stress is experienced, for example if the patient slips on a wet surface while walking. The analogue in the context of elderly patients undergoing surgery for colorectal cancer would be an individual that appears relatively healthy, but is using all his compensatory mechanisms to preserve the autonomy in daily life. When facing a challenging situation such as surgery, the limited reserves may manifest themselves as post-operative complications and prolonged recovery.

In geriatric medicine, physicians often deal with susceptible patients who are at risk for imminent decline in physical and cognitive functioning. A term that is frequently used to describe such patients is *frailty*. Interestingly, a consensus definition of frailty is still lacking, even after a 2007 meeting of a task force on frailty including experts from Europe, Canada, and the US¹⁷. However, frailty in an individual is widely recognized as “an elderly patient who is at heightened vulnerability to adverse health status change because of a multisystem reduction in reserve capacity”¹⁸. This corresponds to a high biological age. Because of the increased risk of adverse outcomes, a frail patient is likely to be a candidate for preventive interventions. The increased susceptibility may lead to fluctuations in health status and

require intensive medical treatment in case of an acute medical situation. Furthermore, a frail patient has an increased risk of complications, toxicity, and side effects of medical interventions. Thus, special attention is needed when treating such a patient with surgery, chemotherapy, or other drugs. It also remains controversial how to *identify* frailty in an individual, as will be discussed below.

Assessment of elderly cancer patients

Comprehensive Geriatric Assessment (CGA)

The heterogeneity of the aging process has practical consequences for the assessment of elderly cancer patients: patients need individualized assessments to approximately determine their biological age. There is no simple way to assess biological age, but an approach frequently used by geriatricians involves a comprehensive geriatric assessment. Although no standardized version of CGA exists, there is general agreement within the literature of the components that comprise a CGA. Areas where older adults often present with problems are systematically assessed. The general composition of a CGA involves functional status, comorbidity, polypharmacy, nutritional status, emotional status, cognitive function and social support.

Functional status is often divided into primary (or personal) activities of daily living (PADL) and instrumental activities of daily living (IADL). PADL-functions are often abbreviated just ADL and constitute basic self-care abilities such as feeding, transferring from bed to chair and bathing/showering. Requiring assistance in ADL, or ADL-dependency, implies that a person needs help from a caregiver on a daily basis in order to survive. IADL describes more advanced activities, such as doing laundry, managing money and driving, and provides an estimate of the person's ability to live an independent life. Requiring assistance with ADLs or IADLs is associated with an increased risk of further functional decline¹⁹, hospitalization¹⁹, and mortality¹⁹⁻²¹. Functional status is not a stable variable, and declines in physical functions that persist over time are associated with poorer overall survival and increased risk of hospitalizations compared with transient declines in physical function²². This highlights the need for repeated measurements of functional status. In the context of a planned surgical procedure, knowledge of the functional status prior to the operation provides a useful benchmark for planning post-operative rehabilitation.

Comorbidity is defined as the presence of one or more disorders in addition to the index disease (in this context cancer is the index disease). Comorbidity may impact on a patient's risk of mortality and morbidity, as well as tolerance to cancer therapy. A comorbidity assessment is therefore necessary to answer the following questions: Is the patient's remaining life-expectancy more likely to be limited by the cancer or another comorbid medical condition²³? Will the comorbid condition(s) affect treatment tolerance? What are the interactions between the comorbid medical conditions and the cancer disease? In general, the severity of comorbidity is associated with survival in cancer patients, independent of cancer stage²⁴. Not surprisingly, it has also been shown that the prognostic importance of overall comorbidity depends on the mortality burden of the index cancer: comorbidities seem to have the greatest prognostic impact among groups with the highest survival rate, and least impact in groups with the lowest survival rate²⁵. If tumor complications are unlikely to occur during the patient's remaining lifetime, cancer treatment may do more harm than good. Drugs that are used in the oncology population, such as steroids, may unmask or exacerbate comorbid illnesses, such as diabetes or glucose intolerance. Furthermore, specific chemotherapeutic drugs may be contraindicated or must be used with caution due to comorbidity. Examples are neurotoxic drugs that may exacerbate underlying neuropathy, or the increased risk of trastuzumab- or anthracycline-associated cardiomyopathy in the presence of hypertension²⁶. In order to study comorbidity statistically, a comorbidity index is useful. Examples of comorbidity indexes used in geriatric oncology are the Charlson's comorbidity index and the Cumulative Illness Rating Scale²⁷.

Nutritional status is part of a CGA because nutritional problems are frequent in elderly patients, and weight loss of 4-5% is associated with an increased risk of mortality^{28,29}. The prevalence of malnutrition varies depending on which assessment tool is utilized, and differs between populations. In two studies from Norway, 39% of surgical patients were either moderately or severely malnourished³⁰, and about 70% of patients older than 70 years admitted to the medical department were at risk for malnutrition³¹. Weight loss and malnutrition have been reported as risk factors for post-operative complications in patients with gastrointestinal cancer^{32,33}. Furthermore, weight loss prior to diagnosis or treatment of gastrointestinal cancer has been associated with poor outcomes, including an association between weight loss and poorer quality of life³⁴.

The risk of depression increases with increasing age. The prevalence of depression in patients older than 60 years was reported to be 19% in a Norwegian study³⁵. Self-reported depression in patients over the age of 80 years was 20% in another population-based Norwegian study³⁶. In older age, depression is associated with functional decline, increased need for informal caregiving, and increased use of health care resources³⁷⁻³⁹. It is possible that patients with cancer are at an increased risk for depression, given the life-threatening nature of the diagnosis, related symptomatology, and the need for aggressive treatment. Furthermore, depression may interfere with the motivation to receive treatment for cancer. It has to our knowledge not yet been established how to optimally deal with depression in elderly patients in the context of a cancer diagnosis and the subsequent treatment such as surgery and chemotherapy.

The prevalence of cognitive impairment and dementia increases with age. Cognitive impairment is associated with an increased risk for functional decline and an increased risk of mortality⁴⁰⁻⁴². In cancer patients, cognitive performance may be affected by fatigue, symptoms, depression, and pain. Cognitive problems are frequently not recognized, and formal testing may be required. The presence of cognitive impairment may lead to a delay in the diagnosis of cancer, as well as affect the delivery of care. In a study of older patients with colon cancer and dementia, Gupta and colleagues found that patients with dementia were twice as likely to have colon cancer reported after death (the data were derived from autopsy or the death certificate)⁴³. When cancer was diagnosed while the patients were alive, it was found that patients with dementia were less likely to obtain a pathological diagnosis and undergo surgical resection. Whether cancer and/or cancer treatment impacts on cognitive function in cancer survivors is not clear. In one study of patients aged 55 years and older who had survived cancer for four or more years, no difference in self-reported cognitive function was found⁴⁴. Another prospective longitudinal study that included comprehensive neuropsychological assessment of cognitive function also failed to find increased risk of developing dementia in patients with a history of cancer compared with cancer-free participants⁴⁵. Conflicting results were found in a study of twins aged 65 years and older from the Swedish twin registry⁴⁶. This study identified twin pairs where one twin was a cancer survivor, while the other had no history of cancer. The cancer survivor twin was more likely to have cognitive dysfunction than the unaffected twin. Cognitive function was measured by a

telephone mental screening interview or informant report in this study. In conclusion, the association between cancer and development of cognitive dysfunction is complex and depends on a variety of factors such as treatment modalities (surgery, radiation therapy, medical anticancer therapy), type and combination of cancer drugs, comorbidities, and diet. Nevertheless, an assessment of cognitive function is needed prior to prescription of cancer therapy in order to ensure that the patient can provide informed consent and understands the risks, benefits, and alternatives of the therapy. It is also vital to know whether the patient realizes the side effects of therapy, and when to seek help. Another question is whether the patient is able to comply with the drug regimen, or if additional care is needed. In the surgical setting, pre-operative cognitive impairment is associated with an increased risk of post-operative delirium, which may be prevented⁴⁷.

Loneliness and social isolation are associated with increased mortality and morbidity in the elderly^{48,49}. It has been shown that the presence of social support impacts the treatment received for cancer. In a study of patients with stage III colon cancer from 2009, it was found that divorced/widowed marital status was associated with lower chemotherapy use⁵⁰. Assessment of social support is also vital for treatment planning.

In clinical geriatrics, the CGA is frequently carried out in the presence of a multidisciplinary team. The team usually includes some or all of the following specialists: a geriatrician, a geriatric nurse, a physiotherapist, an occupational therapist, a dietician, a social worker, and a pharmacist. The CGA-assessment may be carried out with or without the use of standardized tools for the various domains. In the Department of Geriatric Medicine at Oslo University Hospital, for example, ADL-functions are usually scored, while comorbidities are recorded from the routinely performed clinical examination without the use of a formal scoring tool. Nutritional status beyond body mass index and depression are not systematically assessed. The use of standardized tools in clinical practice seems to be more established in oncology departments, and oncologists often ask for a copy of “the CGA” scoring sheet, which does not exist.

Categorization into groups fit, intermediate, and frail based on CGA

One of the first authors to suggest the use of CGA in older adults with cancer was oncologist and geriatrician Lodovico Balducci at Moffitt Cancer Center & Research Institute in Florida,

USA. Balducci outlined three treatment groups of elderly cancer patients that could be identified from the CGA – fit elderly, intermediate elderly, and frail elderly. He suggested that the fit elderly should receive treatment similar to younger patients, while frail elderly should be offered palliative care. The intermediate patients would need an individualized approach⁵¹. Balducci’s criteria for defining the frail elderly were based on the criteria originally presented by Winograd in 1991⁵². The Winograd criteria were: impairment of single ADL, imbalance/dizziness, impaired mobility, chronic disability, weight loss, falls during last three months, confusion, vision or hearing impairment, depression, malnutrition, mild or moderate dementia, urinary incontinence, social or family problems, polypharmacy, and prolonged bed rest. In several review articles about the use of CGA in geriatric oncology, a categorization of patients into the three fitness groups (fit, intermediate, and frail) has been advocated⁵³⁻⁵⁵, and intuitively this method seems reasonable. Unfortunately, research data supporting this approach in elderly cancer patients are scarce. Furthermore, as mentioned above, the expression “frailty” is heavily debated, and there is still no clear and universally accepted definition of this term¹⁷. Nevertheless, the Balducci criteria for defining frailty are frequently cited in the context of geriatric oncology.

The physical phenotype of frailty criteria

Within the geriatric and biogerontological literature, a definition of frailty as an entity separate from comorbidity and disability, as suggested by Fried and colleagues, is more commonly used than the multi-dimensional Balducci definition, especially in the US⁵⁶. This physical phenotype of frailty is identified when fulfilling at least three of the following five criteria: unintentional weight loss, exhaustion, slow walking speed, low physical activity, and weakness. Clusters of physical impairments form the basis of frailty within this construct. The physical phenotype of frailty has been validated in several population-based studies as identifying those at high risk for disability, falls, hospitalizations, hip fracture, and mortality⁵⁷⁻⁶⁰. The physical frailty phenotype has rarely been discussed in geriatric oncology publications or during the annual geriatric oncology meetings organized by the International Society for Geriatric Oncology (personal experience). When our study was initiated, there were to our knowledge no studies that had investigated whether the physical phenotype of frailty was able to predict short-term outcomes, such as post-operative complications after elective surgery, in a homogeneous cohort of elderly cancer patients.

Laboratory biomarkers of frailty

Interesting data have shown associations between various biomarkers in blood in elderly people and negative outcomes such as mortality, disability, and frailty. The term “inflammaging” is frequently used to describe physiological and molecular changes consistent with the aging process that are associated with chronic activation of inflammatory pathways. In a population-based study by Cohen and colleagues, markers of inflammation (interleukin-6 – IL 6) and coagulation (D-dimer) were associated with mortality and functional decline⁶¹. In another prospective longitudinal study of healthy non-disabled older adults, higher levels of C-reactive protein (CRP) and IL-6 were associated with an increased risk of death⁶². An association between higher plasma levels of tumor necrosis factor- α (TNF- α) and death in community-dwelling subjects aged 72-92 years and in centenarians has also been found^{63,64}. Chronic exposure to inflammatory mediators may lead to the alterations in multiple physiological systems associated with the physical frailty phenotype in the elderly^{65,66}. Hubbard and colleagues have shown that inflammatory activity is higher in frail than in non-frail patients across different frailty measures⁶⁷, and higher levels of CRP were associated with the physical phenotype of frailty in 4735 community-dwelling adults aged 65 years and older that were participating in the Cardiovascular Health Study⁶⁶. The association between biomarkers and frailty do not provide insight regarding causality, but biomarkers may add to the validity of the clinical diagnosis of frailty. Furthermore, if measurements of individual inflammatory biomarkers become easier and cheaper, and more specificity is assigned to the markers, perhaps serum inflammatory markers may turn out to be useful clinical tools that can help identify vulnerability in elderly patients and guide therapeutic interventions. The importance of elevated levels of biomarkers such as CRP, IL-6, and D-dimer has also been described in the oncology literature. Inflammation is linked to cancer in some way, and possible mechanisms include the production of reactive oxygen species in chronic inflammation. Such reactive oxygen species may cause DNA damage, activation of growth factors, and inhibition of apoptosis⁶⁸. In a study of patients with advanced non-small-cell lung cancer, higher IL-6 levels were associated with poorer overall survival and poorer performance status⁶⁹. Baseline D-dimer levels have been found to predict overall survival and disease progression among patients with metastatic colon cancer⁷⁰. In the surgical literature, IL-6 has gained some attention because IL-6 levels seem to be associated with the degree of operative stress, and cytokine production may play a role in post-trauma events⁷¹. In our

study, we collected blood samples pre-operatively in order to study the association between biomarkers and the two measurements of frailty and between biomarkers of inflammation and the occurrence of post-operative complications.

Previous research on CGA and frailty in clinical geriatric oncology

Even though a large number of review articles recommend CGA in elderly cancer patients^{5,72-77}, dedicated clinical studies providing data showing that CGA is useful are relatively scarce. This is the main reason why we chose to perform a rigorous study testing whether a CGA-based classification of elderly patients actually predicted a short-term outcome such as post-operative complications.

Outside of oncology, CGA is an established tool to plan the management of frail, older individuals with complex medical needs^{15,78}. A recent systematic review and meta-analysis found that inpatient rehabilitation specifically designed for geriatric patients had the potential to improve outcomes related to function, admission to nursing homes, and mortality⁷⁹. Inside oncology, only a few studies have studied the impact of CGA. In a pilot study that included a small cohort of elderly patients with early breast cancer, Extermann and colleagues identified on average six initial problems detected by CGA and three new problems during follow-up⁸⁰. They found that 87% of the problems, such as pharmacological, psychosocial, and nutritional risks, could be successfully addressed. Another prospective study of CGA in cancer patients found that in patients with a good Eastern Cooperative Oncology Group performance status (ECOG PS), about 10% had limitations in ADL, while about one third had limitations in IADL⁸¹. CGA has also been shown to provide information regarding survival in cancer patients, but the completeness of the CGA assessments varied between the studies. In a study of 566 patients aged 70-84 with stage IIIB or IV non-small-cell-lung cancer treated with chemotherapy, IADL score and performance status, but not ADL score and comorbidity, predicted survival⁸². Both ADL and IADL measurements predicted survival in a cohort of 252 patients aged 65-94 with various cancers⁸³. Performance status was not found to be a predictor of survival in a study of 155 patients aged 70-90 years with advanced ovarian cancer⁸⁴. In the latter study, the presence of depressive symptoms (assessed merely by the judgment of the treating physician) was a significant predictor of mortality. A randomized

controlled trial of post-operative CGA in older post-surgical cancer patients with home visits performed by a nurse, demonstrated a survival benefit only in the patients with cancer in an advanced stage (hazard ratio 2.04, 95% confidence interval 1.33 to 3.12)⁸⁵. In a secondary subset analysis of a randomized trial studying the benefits of treating frail older hospitalized adults in geriatric inpatient units compared to usual care, or geriatric outpatient units compared to usual care, Rao and colleagues found geriatric inpatient care in frail cancer patients to improve bodily pain, emotional limitation, and mental health (based on scores from self-reported quality of life questionnaires), but no survival benefit⁸⁶. That study was based on data from Veteran Administration units in the US, and thus includes more than 90% men.

Previous research regarding surgery in elderly patients with colorectal cancer

Colorectal cancer surgery in the elderly has been addressed in a number of surgical publications in the last ten years^{71,87-123}. Already in 1980, Boyd and colleagues elegantly showed that mortality rates after colon resection (70% of the patients had colon cancer) compared by decades of age correlated with the number of pre-existing conditions, and not with age as an isolated factor¹²⁴. They concluded that a careful pre-operative assessment, correction of pre-existing pulmonary and nutritional deficiencies, and avoidance of emergency procedures might improve morbidity and mortality rates associated with colon resections in elderly patients. The exact same statement seems to hold true today. A large systematic review published in 2000 looked at how the outcomes of surgery for colorectal cancer differed between elderly and younger patients¹²⁵. The cohort consisted of 34 194 patients, and was divided into the following age groups: aged less than 65 years, aged 65-74 years, aged 75-84 years, and aged 85+ years. Post-operative morbidity and mortality were found to increase with age. The authors proposed that this could be attributed to the following factors being more common with advancing age: comorbidity, the rate of emergency operations, and the rate of advanced cancer stages. They also found that elderly patients were less likely to undergo curative surgery. Overall survival was poorer for the older patients, but the differences in cancer-specific survival were less noticeable.

When studying the surgical literature regarding the impact of increasing age on surgical outcomes, methodological differences complicate a direct comparison between published studies. Some of these methodological issues will be discussed below.

Differences in recording and presentation of pre-operative patient variables (age, comorbidity, functional status, nutritional status, cognitive function)

There is no consistent definition of what constitutes the *elderly*. The most commonly used cut-offs when comparing a younger to an older population are 70, 75, or 80 years. Thus, the term “elderly” always needs to be specified.

The influence of comorbidity on treatment and outcomes in older cancer patients is not well understood, except that comorbidity influences survival¹²⁶⁻¹²⁸. Some studies indicate that a few specific diseases matter¹²⁹, but the overall burden of disease may be as important. Unfortunately, specific comorbidities and the severity of comorbidities are often not registered pre-operatively in surgical publications. Instead, American Society of Anesthesiologists physical status class (ASA class) is employed as a sole measure of comorbidity. ASA class distinguishes between no systemic disease, mild systemic disease, and severe systemic disease. I searched MEDLINE for English-language articles published in the last 10 years until October 1, 2010, that reported the results of studies about age and colorectal cancer surgery. I used the search terms: *age, colorectal cancer, surgery, and surgical outcome*. From the articles identified, I selected those for which the abstract indicated that the reported analysis investigated the impact of age on surgical outcomes. I found that 19 of 38 studies on age and the outcome after surgery for colorectal cancer included information about comorbidity beyond ASA class^{87,89,94-99,104,108,111,114,115,119,122-124,130,131}. Of these, only six included a comorbidity index^{94,97,99,122,123,130}. Zingmond and colleagues studied predictors of serious medical and surgical complications after colorectal resections in 56 621 patients identified from the California hospital discharge database⁹⁴. Independent predictors with the highest impact on developing serious medical complications were greater age, higher Charlson comorbidity index (CACI)¹³² score, and emergency surgery, while independent predictors of serious surgical complications were tumor location, greater age, and higher CACI score. Ouellette and colleagues evaluated CACI as a predictor of morbidity and mortality in 239 patients with colorectal carcinoma⁹⁷. They found that CACI correlated with a longer length of stay, peri-operative mortality, and overall mortality.

However, in their study, CACI did not predict which patients would have minor versus serious complications. In a retrospective registry study by Rabeneck and colleagues, 30-day mortality in elderly patients following surgery for colorectal carcinoma in the veteran affairs health care system was studied⁹⁹. Unfortunately, emergency versus elective procedures were not included in the multivariate analyses in that study. They found that predictors of 30-day mortality after rectal and colon cancer resections were age > 65 years, comorbidity (measured by the Deyo index¹³³), and marital status. A study by Rutten and colleagues about total mesorectal excision and age used comorbidity data to show that comorbidity increased with increasing age up to 85-89 years, but they did not study the impact of comorbidity on post-operative morbidity or mortality¹²⁰. Tan and colleagues studied a population of 121 octogenarians undergoing colorectal cancer surgery. In multivariate analyses, ASA class III and CACI scores ≥ 5 were independent predictors of morbidity. Of note, only 13 (12.4%) of their patients were ASA class III, and the majority of their octogenarians were actually ASA class I. In the Preoperative Assessment of Cancer Patients (PACE) study, the association of geriatric domains (ADL, cognition, depression, and comorbidity), performance status, and fatigue with surgical outcomes in a heterogeneous sample of 460 cancer patients was studied¹²². The majority of the patients in PACE had breast cancer (47%), while 31% had colorectal cancer. PACE did not include nutritional data. Independent predictors of surgical morbidity were fatigue and dependence in IADL. Comorbidity, measured by Satariano's index of comorbidities¹³⁴, was not an independent predictor of post-operative morbidity in PACE. The 13 remaining publications that registered comorbidity beyond ASA class used a variety of comorbidity lists, and registered from five to eight individual diseases such as for example cardiovascular disease, pulmonary disease, or diabetes. Furthermore, some studies included the absolute number of comorbidities in their analyses, while others looked at the predictive value of specific diseases for the outcome in question. As a consequence, the general impact of comorbidity on surgical outcomes is difficult to establish. Comorbidity increases with increasing age, and studies of independent risk factors for surgical morbidity in the elderly should include a standardized comorbidity assessment in order to untangle age from comorbidity. In fact, in the above mentioned systematic review from the Colorectal Cancer Collaborative Group, it was not possible to study the impact of comorbidity because too few studies had included such data¹²⁵. However, it is still unclear how to optimally assess comorbidity in the surgical setting. Interpretation of comorbidity data is also influenced by how comprehensively comorbidities are registered. For example, comorbidity data that are

extracted from medical charts, administrative claim data, or registry data will usually be far less complete than data based on additional consulting with the primary care physician, the patient, and caregivers. In a study by Puig-La Calle and colleagues on rectal cancer resection in the elderly, 32% of patients younger than 75 years had hypertension, while only 31% of patients older than 75 years had hypertension. This seems counter-intuitive. If their elderly group was very selected and included mostly fit patients, it could explain the findings. An alternative explanation may be that hypertension was under-diagnosed in the elderly. The diagnosis of hypertension in the study was established through “chart review and telephone interview, when possible”. In the discussion, the authors point out that there is a correlation between a history of hypertension in elderly patients and post-operative urinary retention, and they discuss possible mechanisms. However, the validity of the hypertension data is not questioned in the discussion.

Interestingly, only eight of the 38 studies mentioned above included data regarding the functional status of the patients pre-operatively^{71,92,97,102,108,114,122,123}. Two studies used the Karnofsky Performance Status Scale, while two other studies used the Eastern Cooperative Oncology Group Performance Status (ECOG PS). The remaining four studies included information about form of residence or activities of daily living. Functional status was found to be an independent predictor of post-operative mortality in three studies^{71,97,114}, while two other studies did not include functional status in the multivariable models^{92,108}, and one study did not explain how multivariate analyses were performed¹⁰². In a study from Japan, only three of 121 octogenarians were ADL dependent, and ADL dependency was not found to predict morbidity in bivariate analysis¹²³. In PACE, ECOG PS was a significant predictor of post-operative complications in bivariate analysis, but not in multivariate analysis when fatigue and IADL were included in the model¹²². However, it seems that functional status is a valuable pre-operative predictor in elderly patients undergoing surgery, and this variable should be included in surgical publications.

Nutritional risk is associated with increased post-operative morbidity and mortality after elective surgery¹³⁵. Seven of the 38 studies on age and colorectal cancer surgery included some form of pre-operative nutritional information: two studies recorded weight loss^{102,115}, while five included body mass index^{89,110,111,123,131}. Nutritional status is of particular interest pre-operatively in elderly patients for at least three reasons: malnutrition is frequent in the

elderly, weight loss may be related to frailty, and nutritional status may be improved by peri-operative interventions.

The risk of cognitive dysfunction increases with increasing age, and it has been shown that the risk of post-operative delirium is strongly related to pre-operative cognitive dysfunction. Only PACE of the studies mentioned above included information about cognition, through the Mini Mental State Examination (MMSE)¹²². Cognitive dysfunction was not found to be a predictor of post-operative morbidity in PACE, however, PACE did not include post-operative delirium in their thirty-day morbidity checklist.

Differences in recording and scoring of post-operative complications after surgery for colorectal cancer

Estimates of morbidity after colorectal cancer procedures are commonly reported around 20% to 30%. The methods for registering complications grossly influence the reported rate¹³⁶. Additionally, a common complication in elderly surgical patients such as post-operative delirium is frequently not recognized in clinical practice, and in many cases not even considered in surgical publications. Morbidity is higher in emergency surgery, and series of elective procedures are not directly comparable to mixed series including both elective and emergency procedures. In summary, reported complication rates are not necessarily comparable between studies.

There seems to be a lack of consensus on how to define and grade the severity of post-operative complications. It is obviously a difference between getting a post-operative lower urinary tract infection and an anastomotic leakage. Post-operative complications are often presented as minor or major, without a clear definition of the difference, for example in PACE¹²². Several publications make a distinction between surgical and medical complications without clearly defining the difference. Post-operative complications, surgical or medical, increase lengths of stay, costs, disrupts quality of life, and may lead to an increased long-term mortality^{120,137}. A standardized scoring system for post-operative complications similar to the Common Toxicity Criteria used in studies of adverse effects of chemotherapy would make it easier to compare results from surgical studies. One such classification system for post-operative morbidity was presented by Clavien and colleagues in 1992¹³⁸. This system uses a broad definition of complications: “any event requiring treatment measures not routinely

applied post-operatively”. Scoring is based on a pragmatic approach, relying mostly on the therapy used to treat the complication. Thus, it is a practical grading system for post-operative complications. Clavien and colleagues specifically stated that their aim was to “define relevant terms and propose a system of classifications of complications based on severity that can act as a standard reporting guide”. Even though the authors used elective cases of cholecystectomies to illustrate the relevance of their classification, the scoring system was never designed solely for post-cholecystectomy complications. On the contrary, the authors’ main purpose was to create a system for standardized reporting of complications, and they state that they have “proposed a *general classification of complications* and applied this classification specifically to cholecystectomy”. This is further illustrated by the fact that Clavien’s classification system has been used in other studies of post-operative morbidity in gastrointestinal surgery, such as in patients with colorectal carcinoma⁹⁷, and in elderly patients undergoing liver resections¹³⁹.

Differences in peri-operative care

The outcomes after colorectal cancer surgery are highly influenced by the peri-operative care provided for each patient. For example, it has been demonstrated that an enhanced recovery after surgery program (ERAS) for elective bowel surgery may reduce morbidity, lead to a faster recovery, and shorten hospital stay^{140,141}. This accelerated multimodal rehabilitation program includes, among other factors, optimal pain relief, stress reduction with regional anesthesia, early enteral nutrition, and early mobilization. Another strategy that was recently shown to substantially improve surgical quality was the implementation of surgical checklists during different phases of pre-operative, intra-operative, and post-operative care¹⁴². In the western health region of Norway, an ongoing research project is evaluating the effect of implementing the Surgical Safety Checklist recommended by the World Health Organization. Exploring potential differences in peri-operative care between hospitals was not within the scope of our study, nevertheless, some of the literature regarding peri-operative care will be discussed below.

Peri-operative care and the evidence in older colorectal cancer patients

Approximately 40% of colorectal cancer patients are 75 years and older, while approximately 24% are aged 65-74 years. In other words, the majority of patients, about 64%, is 65 years and older. However, in surgical studies dealing with elements of peri-operative care in

patients with colorectal cancer, it is surprisingly rarely discussed that the clinical applicability of results from trials is largely dependent on whether the study participants represent the population in interest. On rare occasions, the importance of age, comorbidity, cognitive function, polypharmacy, and functional status are mentioned. As discussed earlier, it is well known from other fields of medicine that older cancer patients are underrepresented in clinical trials^{143,144}, and this seems to hold true for many surgical publications as well. It may be argued that there is no reason to believe that the results of clinical trials in surgical patients would differ if the study population was older and reflecting the actual age and fitness level of the patient population, but this question remains largely unanswered. Within the oncology field, there may be changes in the biological behavior of tumor and responsiveness to treatment with age, and as discussed earlier little is known about how cancer treatments interact with the vulnerability of aging people. From a physiological perspective, it is well known that the aging process leads to several important changes that limit a person's reserve capacity, especially when the body is subject to stress such as surgery. An interesting example relevant in this setting is the question about whether the implementation of TME in curative rectal cancer surgery has been beneficial to the patients aged 75 years or older. TME is the standard of care for resectional treatment of rectal cancer, and was established in Norway in 1994. Population-based registries in the Netherlands and Norway have been used to study the effects of implementing this technique in the general patient population. Based on cancer registry data, Rutten and colleagues have concluded that the implementation of TME in the Netherlands did not improve 5-year survival in patients 75 years or older, and the 6-month mortality in this patient group after TME surgery remained substantial at 14%¹³⁰. The authors state that this example illustrates the importance of being careful when extrapolating results from studies done in younger surgical patients to older patients¹²⁰. In contrast, in a Norwegian study by Nedrebo and colleagues¹⁴⁵, relative survival for rectal cancer was significantly improved also for patients older than 75 years between the early (1994-1996) and late (2001-2003) time periods that were studied. These two studies are not directly comparable, as Rutten and colleagues look at overall survival, while Nedrebo and colleagues calculated relative survival. The two studies reach opposite conclusions, and illustrate the complexity of decision making in older patients where the "hard" evidence is scarce.

Multimodal peri-operative interventions

A general goal in surgery is to use the minimal anesthesiological time necessary and to minimize the surgical trauma. Re-establishing natural functions, such as eating and moving around as soon as possible after surgery, is beneficial for surgical outcomes. As this is a multidisciplinary issue, it should be the focus of all healthcare professionals dealing with the surgical patient as well as the patient himself. In older patients, where comorbidities and reduced functional reserves make patients especially prone to the negative effects of bedrest and the surgical trauma, a multidisciplinary approach to a speedy recovery may be even more important. As an example, a multicomponent intervention effectively reduced the prevalence of post-operative delirium in older surgical patients with hip fracture^{47,146}. On the other hand, patient factors may make early mobilization and a quick recovery more challenging in older adults.

When studying elements that may improve the peri-operative course, addressing single factors in isolation may be less interesting than addressing a variety of factors simultaneously. Logically, optimizing all aspects of peri-operative care at the same time using a multimodal approach may be the most efficient way to organize care. For colonic surgery, this has been implemented and tested through the enhanced recovery after surgery (ERAS) program, also called fast-track (FT) surgery^{141,147}. The aim of this program is to enhance post-operative recovery and to avoid obstacles to early hospital discharge, for example post-operative complications, the need for parenteral analgetics, and delayed patient mobilization. Main elements of this program are pre-operative counseling, no bowel preparation, no premedication, no pre-operative fasting, tailored anesthesia, avoidance of fluid overload, no routine use of nasogastric tubes, and early post-operative feeding and mobilization. A metaanalysis from 2006 included randomized or clinical controlled trials that compared two prospectively included groups receiving either FT surgical care or traditional care (TC) for benign or malignant colonic resections¹⁴⁸. Six studies were included in this metaanalysis; three randomized and three controlled clinical trials. The metaanalysis supported the FT approach to colonic surgery because it was associated with fewer post-operative complications and a shorter length of stay. The three randomized trials (RCT) in the metaanalysis included patients with a mean age ranging from 42 to 68 years¹⁴⁹⁻¹⁵¹. Two of the controlled trials had a mean age of included patients of 60-65 years (14, 15), while one study by Basse and colleagues included two groups of patients with mean ages of 72 and 74 years,

respectively¹⁵². The study by Basse included a total of 260 patients, and data regarding the control group (TC) were collected retrospectively and from a different hospital than data regarding the FT group. Comorbidity seemed to be more common in the FT group, and a possible explanation was that data from the FT group, as opposed to those from the TC group, were collected prospectively. However, this may not entirely explain the differences, since ASA class was also higher in the FT group. The rate of medical complications was lower in the FT group, especially cardiopulmonary complications. On the other hand, the rate of readmissions was higher in the FT group (20% compared to 12%), with 6 of the 27 readmissions being due to social factors. In an observational study of 60 patients with a median age of 74 years, a similar clinical pathway to enhance recovery after colonic resection successfully reduced length of stay¹⁴⁷. In that study, 16 patients were older than 80 years, 18 had impaired mobility, and comorbidity was reported as frequently occurring, indicating that even frail patients may benefit from a FT program. However, as the authors note, for such an early discharge to be possible, it is vital that patients are able to contact the hospital immediately if there are signs of post-operative complications. In older patients, where cognitive dysfunction is relatively common, this early discharge approach calls for a cognitive screening pre-operatively. The use of a FT post-operative management protocol in patients undergoing colonic and rectal surgery was also addressed by Delaney and colleagues¹⁵³. The median age of included patients in their study was only 44.5 years (range, 13-70), while 40 of the 58 patients were classified as “with comorbidity”. The authors concluded that patients with a high level of comorbidity benefit from a FT program.

In conclusion, there are limited data indicating that a FT multimodal approach to colonic surgery in older patients may be beneficial. To my knowledge, the importance of functional status, comorbidity, cognitive function, social support, and emotional status on feasibility and outcome in older patients undergoing colonic resections in a fast track program remain largely unknown, and further studies addressing these issues are warranted.

Peri-operative factors influencing post-operative outcome in older patients

Surgical checklists

A recent publication studied the effects on patient outcomes of a comprehensive, multidisciplinary surgical safety checklist¹⁴². Included items were for example pre-operative nutritional screening, medication use both before surgery and at discharge, and instructions to

patients concerning dietary factors. Interestingly, the checklist used in the study also included delirium screening and prevention. The implementation of checklists resulted in a significant reduction in post-operative complications. Even though this was studied in adults undergoing general surgery, it is relevant in this setting because it shows the importance of organizational routines on surgical outcomes.

Patient information

It has been suggested that standardized pre-operative information and counseling to the patient impacts the peri-operative course¹⁴⁰. The evidence is limited, and to my knowledge it has not been studied in older patients^{154,155}. The recommendation by the ERAS group is to present the patient with information about pain, pain treatment, his or her role in the post-operative process with an emphasis on the benefits of early mobilization, and the expected length of stay¹⁴⁰. Older patients in particular may have unrealistic expectations about the hospital stay after surgery, as the length of stay after a surgical procedure frequently exceeded two weeks 30-40 years ago. In patients with cognitive dysfunction, pre-operative counseling may pose a challenge, but it is not unreasonable to hypothesize that informing caregivers of the importance of early mobilization and expected length of stay will be beneficial.

Pre-operative bowel preparation

Pre-operative bowel preparation may lead to disturbances in the fluid- and electrolyte balance and dehydration¹⁴⁰. Based on available evidence, it is not indicated for elective colon cancer surgery except when intra-operative colonoscopy is needed^{156,157}. Two randomized trials have studied this; one of them included patients with a mean age of 69 years¹⁵⁶, while the other trial did not present the age of the included patients¹⁵⁷. For lower resections, the findings from studies are inconsistent, and further trials are needed to establish the optimal approach for bowel preparation in patients undergoing lower resections¹⁴⁰.

Pre-operative fasting and carbohydrate load

Fasting before surgery deprives patients of nutrition and hydration. A Cochrane review from 2003 concludes that there is no evidence to support that a shortened fasting period for fluids leads to more aspiration, regurgitation, or related morbidity than longer fasting periods¹⁵⁸. However, the authors also state that elderly patients are more likely to regurgitate under anesthesia (possible causes are reduced tone of the lower esophageal sphincter, a greater

incidence of hiatal hernias, and increased gastrointestinal reflux), and more research is needed to establish whether these patients can also safely drink up to a few hours before surgery. The general recommendation is that the pre-operative fasting period does not need to exceed two hours for clear liquids and six hours for solid food¹⁴⁰. It has also been suggested that a pre-operative carbohydrate load may be beneficial in order to avoid for example muscle loss after surgery. This may be particularly important for older patients, specifically frail older adults, because they already have a limited muscle mass. One of the randomized trials studying the effect of an oral carbohydrate-containing fluid load found that it was safe and potentially attenuated depletion of muscle-mass¹⁵⁹. However, the mean ages of included subjects in the two study groups were only 52 and 53 years, respectively. Another randomized trial of pre-operative carbohydrate loading assessed effects on grip strength, gastrointestinal function, and hospital stay¹⁶⁰. That study included patients with a mean age of less than 60 years. The results showed a shorter hospital stay for the group receiving carbohydrates. Relevant in the context of frailty, the fasted group had a statistically significant reduction in post-operative grip strength as opposed to the carbohydrate group and yet another group receiving pre-operative oral water compared to pre-operative levels. However, the grip-strength results were difficult to interpret because they showed considerable fluctuations throughout the post-operative course¹⁶⁰.

Premedication, prophylactic antibiotics, and prevention of post-operative nausea

Premedication that does not cause post-operative drowsiness is recommended, as drowsiness may increase the risk of post-operative delirium and hamper early mobilization¹⁶¹. For colonic and rectal procedures it is recommended to administer pre-operative prophylactic antibiotics against both aerobic and anaerobic microbes one hour before surgery. This reduces the rate of post-operative surgical site infections and sepsis¹⁶². If the procedure lasts more than three hours, a subsequent dose should be administered¹⁶¹. It has also been suggested to provide the patient with medication to prevent post-operative nausea, such as dexamethasone or serotonin antagonists. The risk of developing post-operative nausea varies between patients, and risk factors include being female, history of motion sickness, post-operative administration of opioids, and having a nonsmoking status¹⁶³. In a randomized trial of prevention of post-operative nausea and vomiting by metoclopramide combined with dexamethasone, it was found that early post-operative nausea and vomiting was less frequent in patients aged 50 or more, but late episodes were more frequent, as were adverse reactions¹⁶⁴.

Anesthesia

According to Norwegian guidelines, the optimal anesthetic protocol for colorectal procedures is yet to be decided¹⁶¹. As long-acting, intravenously administered opioids may interfere with the goals of early mobilization, it seems more optimal to use short-acting agents¹⁴⁰. For the same reason, premedication such as hypnotics, long-acting sedatives, and opioids should be avoided. The use of intraoperative epidural analgesia may be beneficial because it might decrease the need for general anesthetic agents. The aging process affects the pharmacokinetics and pharmacodynamics of many drugs, including drugs used in anesthesia. This is true for both inhaled anesthetics, where minimum alveolar concentration (MAC) that prevents movement in response to noxious stimulation decreases with age, and for injectable anesthetic and sedative drugs¹⁶⁵. A discussion of the mechanisms responsible for these changes is beyond the scope of this thesis.

Nasogastric decompression

Nasogastric decompression is not recommended as a routine measure for colorectal surgery. Extensive evidence suggests that patients who do not receive routine nasogastric tubes have an earlier return of bowel function as well as fewer pulmonary complications¹⁶⁶. Thus, a selective use of nasogastric decompression is recommended.

Peri-operative fluids

Overhydration of patients undergoing bowel surgery may cause intestinal paralysis, edema, diminished tissue oxygenation, and potentially weakened strength of the anastomosis¹⁴⁰. Thus, it has been suggested that more restrictive regimens for fluids are beneficial. The evidence suggests regimens that maintain body weight, but hypovolemia should be avoided¹⁶⁷. Epidural and spinal anesthesia may cause hypotension due to a blockage of the sympathetic nervous system leading to vasodilatation, even if the blood volume remains unchanged¹⁶⁸. Consequently, this may be better treated with vasopressors than with excessive fluids, especially in patients with cardiopulmonary disease. In an RCT studying the effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection it was concluded that a positive salt and water balance sufficient to cause a 3 kg weight gain after surgery delayed return of gastrointestinal function and prolonged hospital stay¹⁶⁷. The mean ages of patients in the two study groups were 59 and 62 years, respectively. However,

another RCT studying 32 patients receiving liberal versus restrictive fluid regimen in a FT program found that morbidity tended to be increased in patients receiving the restrictive regimen¹⁶⁸. The mean ages of the patients in the latter study were 74 and 77 years, respectively. From a physiological point of view, alterations in the cardiovascular system are likely to make older patients more sensitive to fluid shifts, and elderly-specific trials regarding peri-operative fluid therapy are desirable. Blood vessel distensibility is decreased in older individuals, and population-based data show that the majority of older adults suffer from hypertension¹⁴. Furthermore, a genuine age-related change in the heart is an approximately 30% increase in the thickness of the left ventricular wall, and the left ventricle may be stiff due to increased collagen content with age¹⁴. Thus, the heart is dependent on adequate preload to maintain cardiac output. As baroreflexes are frequently blunted with increasing age, the response to hypovolemia may be inadequate in older patients¹⁶⁵. It is well known that older adults have an increased risk of orthostatic hypotension with drug therapy.

The use of urinary catheters

A recent meta-analysis comparing suprapubic and transurethral catheterization for bladder drainage after abdominal surgery found that the suprapubic route lead to fewer urinary tract infections and was more acceptable to patients¹⁶⁹. Especially in rectal cancer surgery, which usually requires a prolonged use of a urinary catheter, a suprapubic catheter allows for greater mobility. For colonic resections, the catheterization period is shorter. An uncontrolled study including 100 patients with a median age of 72 years undergoing colonic resection who received thoracic epidural analgesia, found that removing the urinary catheter on the first post-operative morning resulted in low incidences of urinary retention and urinary tract infections¹⁴⁷.

Post-operative ileus

A Cochrane review from 2000 found that gastrointestinal paralysis was reduced when epidural local anesthetics were used instead of opioid-based analgesic regimens in patients undergoing laparotomy¹⁷⁰. It remains unclear whether the ileus-reducing effect of epidural local anesthetics is due to the effect of using epidural analgesia per se, or due to the concurrent avoidance of gastric tubes and early institution of oral nutrition¹⁵². The combined positive effect of continuous epidural analgesia, early mobilization and oral nutrition, cisapride (gastroprokinetic agent) and laxative treatment with magnesium was demonstrated

in a small study that included patients with a mean age of about 72 years undergoing colonic resection¹⁷¹. In that study, normal gastrointestinal transit was established within 48 hours post-operatively, instead of the more commonly experienced two to five days.

Post-operative pain management

Post-operative pain management is essential for early mobilization. A recent meta-analysis compared the effects of epidural analgesia to systemic opioid analgesia after colorectal surgery¹⁷². The authors found that epidural analgesia significantly reduced post-operative pain and the duration of ileus, but on the other hand it was associated with pruritus, urinary retention, and arterial hypotension. The mean ages of the patients included in the randomized trials comprising the meta-analysis were not reported. Paracetamol is also recommended for post-operative pain management, and studies suggest that non-steroid anti-inflammatory drugs (NSAIDs) reduce the need for opioids¹⁴⁰. However, due to the side effect profile of NSAIDs, caution is required when using NSAIDs in older patients.

Oral nutrition

Post-operative feeding should start as soon as possible after surgery. There is apparently no increased risk of anastomotic leak, and early continuation of feeding reduces length of stay and may also reduce the rate of post-operative complications¹⁴⁰. In a study from 2001 investigating whether an early feeding protocol in older (70+ years) patients undergoing elective open colonic resection would result in early discharge and low morbidity, it was found that close to 90% of patients tolerated early feeding¹⁷³. Comorbidity was not reported beyond ASA class in that study, but functional status was recorded. Only one of the 87 included patients was dependent in ADL, suggesting a highly selected older study cohort. Beattie and colleagues showed that malnourished patients, as defined by a body mass index \leq 20, anthropometric measurements \leq 15th percentile on admission or on resumption of the oral diet, and/or a weight loss of 5% or more from admission until oral intake was resumed, profited from post-operative oral nutritional supplements for eight weeks in terms of recovery of nutritional status, protein economy, and quality of life¹⁷⁴. The mean ages of the subjects in that study were 54 years in the treatment group and 62 years in the control group.

Early mobilization

Early mobilization is a key principle in geriatric medicine as well as in post-operative surgical care. Prolonged bedrest has a negative impact on several bodily functions, and may among other things lead to muscle loss, bone loss, insulin resistance, decrease in cardiac output, baroreceptor desensitization and orthostatic hypotension, atelectasis, and pulmonary dysfunction, and thereby increase the risk of pneumonia, pressure ulcers, thromboembolism, and falls. Early mobilization may be obtained through specific treatment measures such as optimal pain relief, minimal use of immobilizing equipment (urethral catheters, physical restraints), and through specific actions to encourage ambulation. Examples are preplanned structured mobility schedules, removal of television in the hospital rooms, designated dining rooms in the wards to prevent meal intake in bed, a uniform focus on ambulation from all members of the health care team, and continuous information to caregivers and patients about the importance of ambulation. If ambulation is not possible, range of motion exercises and the maintenance of an upright posture should be emphasized.

Intra-operative variables influencing surgical outcomes

Laparoscopy assisted versus open surgery

Several short-term outcomes, such as blood loss, wound complications, post-operative pain, and length of stay, have been improved when performing laparoscopic surgery. A systematic review published in 2006 concluded that laparoscopic resection for colon and rectosigmoid cancer is feasible, safe and has many short-term benefits¹⁷⁵. However, the age of patients included in the studies that comprise the review is not discussed. In the COLOR trial, where 1082 patients with colon cancer were randomized to open versus laparoscopic surgery, the mean age in the two study groups was 71 years¹⁷⁶. In that study, patients assigned to laparoscopic resection had less blood loss, earlier recovery of bowel function, and a shorter hospital stay. Morbidity and mortality did not differ between the two groups. The authors specifically emphasized that elderly patients were not excluded from the study. Yamamoto and colleagues investigated the effect of laparoscopic colonic surgery in a small sample of octogenarians, and found that there were no significant differences between the older group and a group of patients aged 60 years and younger in terms of the incidence of complications, the interval before resumption of liquid or solid food intake, or length of hospitalization¹⁷⁷. Similarly, Sklow and colleagues found that patients older than 75 years who underwent colectomy for colorectal cancer improved more rapidly in their bowel function after

laparoscopic than after open surgery, as did younger patients¹⁷⁸. There were no differences in independence at discharge according to type of surgery. The study by Sklow and colleagues was a retrospective review, while the study by Yamamoto and colleagues was a matched case-control study. Stewart and colleagues prospectively evaluated patients 80 years or more undergoing elective laparoscopic or open colorectal procedures between 1992 and 1997, and found that laparoscopically assisted colorectal surgery was safe and associated with a low incidence of complications, short hospitalization, and a rapid return to pre-operative activity levels¹⁷⁹. Major intercurrent disease was found in 63 of 77 patients, indicating a representative patient cohort. It has, however, been questioned whether the favorable results of laparoscopic surgery compared to open resections are due to improved organization of peri-operative care rather than the procedure itself¹⁵². In conclusion, laparoscopic surgery now seems to be an acceptable alternative to open surgery for colon cancer, but more data are warranted. When patients are operated within a FT program, the benefits from laparoscopic surgery, especially the decreased length of stay, seem less clear. A randomized controlled trial is underway to compare laparoscopic versus open colonic surgery within a FT setting, and hopefully this study has included a representative cohort of patients with respect to age¹⁸⁰.

For rectal cancer, it is less clear whether laparoscopic surgery provides advantages compared to open surgery¹⁶¹.

Surgery for colon versus rectal cancer

In Norwegian guidelines, rectum is defined as bowel 15 cm or less from the anal verge, measured from the lower tumor border by rigid proctoscopy. Patients with rectal cancer are treated by a different surgical protocol than patients with colon cancer. The multidisciplinary team is crucial in deciding treatment plans for rectal cancer patients, including whether multimodal therapy is necessary. The main goals of treatment are to prevent local recurrence and secure long-term survival with a minimum of side effects. Rectal cancer rarely requires emergency surgery, but is associated with more frequent complications than cancer surgery in other parts of the large bowel^{94,181-186}. Usually, the risks of anastomotic leak, delayed perineal wound closure, and other post-operative complications are higher in rectal cancer surgery, and pre-operative use of chemoradiation increases the risks further¹⁸⁶. Anastomotic leak, in addition to impacting the immediate post-operative mortality and possibly the risk of local recurrence, has been associated with a significantly worse long-term survival in patients

undergoing curative resection for colorectal cancer¹⁸⁷. Patients with rectal cancer are a heterogeneous group because of differences in tumor size, tumor location, lymph node involvement, and the varying use of neoadjuvant treatment. The Norwegian National Rectal Cancer Registry was established in 1993, and data regarding all patients over 65 years operated between November 1993 and December 2001 have been published¹⁸⁸. The age groups 65-74, 75-79, 80-84, and 85 and older were compared. The rates of local treatment and palliative treatment increased with increasing age, regardless of tumor stage. In the younger group, 77% received curative resection, compared to 47% in the oldest group. The paper does not contain information about comorbidity or functional status. In patients treated for cure, the use of both pre-operative and post-operative radiation therapy decreased with age. The rate of post-operative mortality was 8% for the oldest group compared to 3% for the youngest group ($p < 0.001$). Relative five-year survival was lower in the oldest group compared to the youngest group, but there was no consistent age-related trend: The relative five-year survival in patients treated for cure were 77%, 70%, 72%, and 65% for the four groups, respectively.

Existing pre-operative risk assessments of surgical patients

In Norway, the anesthesiologist assigns the patient to an American Society of Anesthesiologist physical status class (ASA class) pre-operatively. ASA class is related to outcomes after surgery, but does not incorporate type of operation. In the Norwegian translation of the ASA classification that is published by the Norwegian Society of Anesthesiologist, patients aged over 80 years are automatically assigned to ASA class II or higher, regardless of physical status. In a study of octogenarians undergoing colorectal surgery from Japan, however, 51/121 patients were classified as ASA class I¹²³. Thus, the association between ASA and surgical outcomes in the elderly may be difficult to compare between studies. Furthermore, surgical studies often include a mix of emergency and elective procedures, which further complicates a direct comparison of study outcomes. Tan and colleagues found in their study of octogenarians from Japan that ASA class (≥ 3 versus < 3) was an independent predictor of morbidity¹²³, while a French study (all ages) did not find that ASA class independently predicted morbidity¹⁸⁹. In a large study of surgical risk factors and morbidity in elderly patients (major general, general thoracic, and vascular surgical procedures), Turrentine and colleagues found that ASA class was an independent predictor of collective post-operative morbidities in the 60- to 79-year age group, but not in the 80- to 103-year age group¹⁹⁰. In the older group, the most frequent predictors of collective post-

operative morbidities were pre-operative transfusion, emergency operation, weight loss, operative duration, and chronic obstructive pulmonary disease.

The APACHE (Acute Physiology and Chronic Health Evaluation) II index and POSSUM (Physiological and Operative Severity Score in Enumeration of Mortality and Morbidity) are examples of surgical assessment scales. The APACHE II includes twelve physiological indicators (heart rate; respiratory rate; mean arterial blood pressure; temperature; oxygenation; arterial pH; serum sodium concentration; serum potassium concentration; packed-cell volume; white-blood-cell count; serum creatinine concentration; score on the Glasgow coma scale), as well as age and the presence or absence of severe chronic health problems. The tool is usually used in the intensive care setting. APACHE II provides limited information pre-operatively regarding the suitability of an elderly patient to undergo cancer treatment, but may be more relevant in the immediate post-operative period. POSSUM was developed as a surgical audit tool in 1991, and has been shown to predict morbidity and post-operative mortality in general surgery. The scale includes 12 physiological parameters (age, cardiac history, respiratory history, blood pressure, pulse rate, Glasgow coma scale, hemoglobin level, white cell count, urea concentration, sodium level, potassium level, and electrocardiography) as well as six operative parameters (operative severity, multiple procedures, total blood loss, peritoneal soiling, presence of malignancy, and mode of surgery). POSSUM has been shown to overestimate post-operative morbidity and mortality in younger patients, and to underestimate mortality in older patients^{110,118,123,191}. Colorectal-POSSUM (CR-POSSUM) was developed in 2004, and is specific to colorectal surgery¹⁹². It was shown to perform better than POSSUM in a cohort of patients undergoing surgery for complicated diverticular disease¹⁹¹. Since it uses operative variables, CR-POSSUM cannot be used as a pre-operative decision making tool. Another mathematical model for prediction of operative mortality in colorectal cancer is the colorectal cancer model of the Association of Coloproctology of Great Britain and Ireland (ACPGBI)¹⁹³. This tool can be accessed online (<http://www.riskprediction.org.uk/index-crc.php>), and it includes patient age, cancer resection status, ASA class, cancer stage, and operative urgency.

Aims of the present study

The aims of the present study were to investigate whether a comprehensive geriatric assessment could predict short-term and long-term outcomes after elective colorectal surgery in elderly patients. Furthermore, we wanted to explore two different methods of identifying frailty in the context of colorectal cancer surgery in the elderly. More specifically, the aims were:

- a. To prospectively study a pre-operative categorization of elderly patients with colorectal cancer into three groups fit, intermediate, and frail, based on a CGA, and to analyze the ability of this classification to predict post-operative complications
- b. To prospectively analyze the predictive ability of the elements of a pre-operative CGA, both for post-operative complications and overall survival
- c. To compare two different approaches to identifying frailty in elderly patients with colorectal cancer, a multi-modal CGA-based frailty measure and a modified version of the physical phenotype of frailty, and to analyze their predictive ability for post-operative complications and overall survival
- d. To study the associations of proposed biomarkers of frailty with frailty defined from a CGA and from a modified version of the physical phenotype of frailty

Patients and methods

All studies were conducted in different subsamples of 182 patients who were consecutively admitted to Ullevaal, Aker and Akershus University Hospitals from November 2006 through June 2008. Patients were identified from the routinely scheduled surgical programs at each hospital. At Ullevaal and Akershus University Hospitals, the patients were admitted to the hospital the day before surgery, and the assessment took place that day. At Aker, most of the patients were assessed after their outpatient pre-operative work-up, in most cases conducted one week prior to surgery. Patients operated at Aker University Hospital were most frequently admitted for same-day surgery. In Norway, all operations for colorectal cancer are performed in public hospitals, and patients are generally operated in the hospital that serves the patient's residential area. All patients provided a written informed consent. The decision regarding whether a patient was eligible to provide consent was based on the judgment of the principal investigator (PI), a medical doctor with training in geriatrics.

Two hundred ninety-six patients were scheduled for elective surgery for colorectal cancer in the three hospitals during the recruitment period. Of these, 101 were lost for independent logistical reasons. The most common reason was that the PI was not informed about the patients. Other reasons were changes in the operative schedule that were not communicated to the PI in a timely manner, unavailability of the PI due to mandatory PhD-courses or vacation, or that patients were scheduled for pre-operative work-up at two hospitals at the same time. Of the 195 patients assessed for eligibility, 10 were excluded pre-surgery. Five were not able to provide a written informed consent, three refused to participate, while two were deemed unfit for surgery. Of the 185 patients included in the study, three were excluded post-surgery. One did not undergo a resection, while the other two were re-operated for other reasons than complications. A flow chart is presented in paper I (Figure 1).

Data regarding overall survival were obtained from the National Registry of Norway.

Assessment tools

Comprehensive Geriatric Assessment

The principal investigator performed a comprehensive geriatric assessment in all the study participants. All patients were interviewed, and the geriatric assessment forms were completed during the interview based on self-report. The interview and examination were in most cases carried out when only the patient was present. If permitted by the patient, caregivers were invited to join the interview. Thus, no multidisciplinary team was involved in the CGA assessments in this study, and no forms were self-administered.

Table 1 presents an overview of the domains included in the comprehensive geriatric assessment and the tools that were used. The tools are described in more detail in the text below.

Table 1. Elements of CGA, tools utilized in the study, and cut-off scores for the various elements

CGA-element	Tool	Cut-off scores	Range
Personal ADL	Barthel index		0-20
	Independent	19-20	
	Dependent	0-18*	
Instrumental ADL	Nottingham extended ADL scale		0-66
	Independent	44-66	
	Dependent	0-43	
Comorbidity	Cumulative Illness Rating Scale		14 organ
	Mild	See text	systems,
	Moderate		severity grade
	Severe		0 to 4
Polypharmacy	Number of drugs in daily use		0 to 14
	0-4	0-4	
	5-7	5-7	
	8 or more	8 or more	
Nutritional status	Mini Nutritional Assessment		0-30
	Normal	24-30	
	At risk	17-23.5	
	Malnutrition	0-16.5	
Cognitive Function	Mini Mental State Examination		0-30
	Good	27-30	
	Moderately Impaired	24-26	
	Cognitive Dysfunction	0-23	
Depression	Geriatric Depression Scale		0-30
	No depression	0-13	
	Depression	14-30	

Abbreviations: CGA; comprehensive geriatric assessment, ADL; activities of daily living

*In this study, patients with fecal incontinence due to rectal cancer were classified as independent if this was their only personal ADL limitation

The Barthel ADL index. The Barthel index includes 10 items assessing basic self-care abilities such as fecal continence, feeding, transferring from bed to chair and bathing/showering¹⁹⁴. This index is well proven and widely used for the assessment of basic ADL functions. The index was used as a questionnaire for the retrospective assessment of ADL during the last two weeks. It has been suggested that the factor structure of the Barthel index depends upon the category of patients being studied. Among geriatric patients, two factors have been identified – one related to mobility, and the other related to bodily functions¹⁹⁵. Among stroke patients, on the other hand, it seems that the Barthel index is unidimensional. The internal consistency of the Barthel ADL index in our study sample was measured by the Cronbach's alpha coefficient. We found that the Cronbach alpha coefficient was 0.84, suggesting good internal consistency reliability for the scale with our sample.

The Nottingham Extended ADL (NEADL) scale. The NEADL provides more comprehensive information about the patients' ability to perform more complex activities than basic ADL functions. The scale consists of four subsections - mobility, kitchen, domestic and leisure activities, but according to previous research it may also be appropriate to add the subscales to provide an overall score¹⁹⁶. NEADL was applied as an interview with the patients, and, in some cases, their caregivers provided supplemental information. In the current study, the Cronbach alpha coefficient was .89, suggesting very good internal consistency reliability for the NEADL scale in our cohort.

The Cumulative Illness Rating Scale (CIRS). This comorbidity index allows scoring of the number of comorbidities, a measure of chronic medical illness burden, as well as the severity of comorbidity. CIRS has been extensively used in clinical series, and correlates with mortality, hospitalization rates and duration, hospital re-admission, medication usage, and functional disability in geriatric populations¹⁹⁷⁻²⁰⁰. It has been validated in older cancer patients²⁰¹. The detailed manual for the scoring of CIRS was revised and published in 2008, and this manual was used for CIRS scoring in our study²⁰⁰. The CIRS assesses 14 organ systems, and comorbidity in each organ system is scored on a five-point scale ranging from 0 (no problem) to grade 4 (extremely severe/immediate treatment required/end organ failure/severely impaired function). Overall comorbidity was classified in the following way: *mild/no comorbidity* when there was no comorbidity higher than grade 2 and less than three grade 2 comorbidities, *moderate comorbidity* when there were a maximum of two grade 3

comorbidities and no grade 4 comorbidity, or *severe comorbidity* when there were at least three grade 3 comorbidities or any grade 4 comorbidity^{54,202}.

Polypharmacy. Polypharmacy is commonly included in a CGA, but how to classify polypharmacy in the context of frailty is not well established in the literature. In a Swedish study of individuals 65 years and older, 39% used five or more prescription drugs²⁰³. In our study, we simply counted the number of systemic drugs that the patients used on a daily basis. However, we did not study details regarding types of medications, possible interactions, or possible inappropriate drugs.

The Mini Nutritional Assessment (MNA). MNA was developed to identify elderly at risk of malnutrition. The prevalence of malnutrition as measured by MNA varies greatly between different settings, but the mean rate is as high as 20% in hospitalized patients²⁰⁴. The MNA consists of a two-step procedure for screening followed by a full assessment. The screening part includes questions about food intake, weight loss, mobility, acute stress/disease, cognitive function, and body mass index. Because several of our patients had experienced weight loss, and all had suffered psychological stress or acute disease in the past three months (diagnosed with cancer), we completed the full MNA in almost all the patients. In hospitalized patients, low MNA scores are predictive of adverse outcomes including longer lengths of stay, more frequent discharge to nursing homes, and increased mortality²⁰⁴.

The Mini Mental State Examination (MMSE). The MMSE is the most widely used screening test for cognitive impairment in general and in the assessment of older adults with cancer²⁰⁵. It includes 20 items testing a variety of cognitive functions, including memory, orientation, abstraction, and visuospatial ability. MMSE has low sensitivity to impairments in abstraction, executive function, and visual perception, and is highly dependent on good language function.

The Geriatric Depression Scale (GDS). The GDS was the first screening instrument for depression designed for use in older adults. The scale consists of 30 questions answered by *yes* or *no*. The sensitivity and specificity of GDS varies according to which cut-off is used for depression. A score of 14 or higher has been found to indicate depression with a sensitivity of 80% and a specificity of 100%²⁰⁶. The GDS has well-established internal consistency, and high Cronbach's alpha reliabilities have been reported, such as .94²⁰⁶ and .87²⁰⁷. Salamero and

colleagues have argued that the scale should be considered unidimensional²⁰⁷, while Adams and colleagues presented a five-factor measurement model estimated with confirmatory factor analysis methods that showed good overall fit using 26 items of the GDS²⁰⁸. The five factors were dysphoric mood factor, withdrawal/apathy/vigor, hopelessness, worry, and cognitive impairment²⁰⁸. In the current study, where GDS was considered unidimensional, the Cronbach alpha coefficient was .87 for the scale, suggesting good internal consistency reliability in our sample. In my experience, the GDS may be too intrusive in the pre-operative evaluation of cancer patients. Before initiating the study, we decided not to use a minimum GDS score for placement in the fit category in our categorization (see Table 2). Even if a GDS score of 14 or higher clearly indicates depression, there are no indications that a certain level of “happiness” is required to be classified as fit. In this respect we treated emotional status differently from for example comorbidity and nutritional status.

Categorization of patients into groups fit, intermediate, and frail based on the CGA

The categorization of patients into the three fitness groups is thoroughly described in paper I. Table 2 displays the classification criteria for each group.

Table 2. Categorization of patients based on CGA		
Tool	Fit*	Frail*
	<i>All of the following criteria</i>	<i>One or more of the following criteria</i>
Barthel	>18	<19
NEADL	>43	
CIRS	Mild comorbidity	Severe comorbidity
No of drugs	<5	>7
MNA	>23.5	<17
MMSE	>26	<24
GDS		>13

Abbreviations: CGA; comprehensive geriatric assessment, NEADL; Nottingham Extended Activities of Daily Living Scale, CIRS; cumulative illness rating scale, MNA; mini nutritional assessment, MMSE; mini mental state examination, GDS; geriatric depression scale

*Patients who were neither fit nor frail were classified as intermediate

Pre-operative assessment by the anesthesiologist

American Society of Anesthesiologists Physical Classification System (ASA classification).

Anesthesiologists routinely assign patients to an ASA category before surgery in Norway.

ASA consists of the following six categories:

1. A normal healthy patient
2. A patient with mild systemic disease
3. A patient with severe systemic disease
4. A patient with severe systemic disease that is a constant threat to life
5. A moribund patient who is not expected to survive without the operation

6. A declared brain-dead patient whose organs are being removed for donor purposes. The Norwegian Anesthesiology Society has published a Norwegian version on their webpage (http://www.nafweb.no/index.php?option=com_content&view=article&id=62:asa-klassifikasjon&catid=38&Itemid=27, accessed Oct 26, 2010). In their translation, an age criterion has been added: A patient needs to be younger than 80 years to be assigned to ASA class 1. The ASA class was recorded from the hospital records. Data were missing in 16 patients.

Surgeon's clinical judgment

At Ullevaal University Hospital, we asked the surgeon who examined the patient the day before surgery to assign the patient to either one of the categories *fit*, *intermediate*, or *frail* based on their clinical judgment. This was recorded on a scoring sheet that was delivered to the principal investigator. The principal investigator did not discuss the patients with the surgeon, with a few exceptions that are noted under ethical considerations.

Peri-operative routines

Table 3 describes the peri-operative routines for elective colorectal cancer surgery at the three participating hospitals in the study.

Table 3. Peri-operative routines for elective colorectal resections at the three study hospitals

Item	Aker	Ahus	UUS
Multidisciplinary team	Surgeon, oncologist, radiologist, pathologist (not always)	Same	Same
Oncological treatment	Decided at UUS	Same, a few patients also treated at Radiumhospitalet	Decided at UUS
Number of procedures (cancer) per year	Colon 70 Rectum 30	Colon 120 Rectum 40	Colon 80 Rectum 50
Standardized written pre-admission information	No	No	No
Pre-operative bowel preparation	Colon open surgery: No preparation Colon laparoscopic: Oral preparation Rectal surgery: Oral preparation	Same	Right colon surgery: No preparation Rectosigmoid surgery: Oral preparation
Preoperative fasting	Carbohydrate liquid until day of surgery	Clear liquids until day of surgery	Clear liquids until day of surgery
Antimicrobial prophylaxis	Doxilyn 200 mg iv Metronidazole 1500 mg iv	Doxycyclin 400 mg iv Metronidazol 1500 mg iv	Doxycyclin 400 mg iv Metronidazol 1500 mg iv
Use of edidural	Yes, standard	Same	Same
Nasogastric intubation	Used during procedure, not routinely used post-operatively	Same	Same
Fluids post-operatively	Patients can start drinking the day after surgery. Intravenous fluids, and in some cases nutritional supplement	Same	Patients start drinking at the day of surgery. Intravenous fluids, and in some cases nutritional supplement
Urinary drainage	Colon: Urethral catheter until epidural is removed Rectum: Urethral catheter until day 5 p.o.	Colon: Same Rectum: 3-5 days, follows the use of epidural, but in some cases 5 days is decided pre-operatively	Colon: Same Rectum: 3-5 days, follows the use of epidural, but in some cases 5 days is decided pre-operatively
Prevention of post-operative ileus	No specific measures	Same	Same
Post-operative analgesia	Epidural catheter, Paracetamol and opioids when necessary	Same	Same
Post-operative nutrition	Patients may try eating from day 1	Same	Patients encouraged to eat from day 1
Post-operative mobilization	Get out of bed and walk around day 1. Physiotherapy on demand	Same	Same

Post-operative complications

Clavien's morbidity grading system for post-operative complications: In this grading system, intended to be a standard reporting guide for morbidity, post-operative complications are broadly defined as “any event occurring within 30 days of surgery requiring treatment measures that are not routinely applied post-operatively for colorectal cancer”¹³⁸. Post-operative complications were classified according to severity. A grade I complication was a minor event that did not require treatment other than simple symptomatic drugs (for fever, pain or nausea). Lower urinary tract infection and urine retention were also included in this group. Another important criterion for a grade I complication was that it did not lead to a hospital stay “longer than twice the median stay for the procedure”. A grade II complication was a potentially life-threatening event, or an event that led to prolonged hospitalization beyond that of a grade I complication. Examples of grade II complications are pneumonia, wound infection requiring systemic antibiotics, and delirium. A further sub classification was based on intervention characteristics; grade IIa required only medical therapy, such as parenteral nutrition or blood transfusion, whereas grade IIb was resolved by invasive procedures. A grade III complication was also a potentially life-threatening event, further recognized by the development of lasting disability. Examples are myocardial infarction and cerebrovascular events leading to residual disability. Finally, a grade IV complication denoted the death of a patient due to a complication. The Clavien classification system has also been used in other studies of gastrointestinal surgery^{97,139}. Because it is a highly comprehensive system, it is suitable for use in older patients, where even small events may lead to prolonged bedrest and functional decline.

Paper I

In this prospective observational cohort study, patients were assessed by a comprehensive geriatric assessment and subsequently categorized into three groups: fit, intermediate, or frail. The cut-off criteria for the three groups were defined apriori. In this paper, four patients were excluded from further analysis because they did not have complete data for a CGA-categorization.

After three months, 159 patients were available for analysis of living conditions. The patients who were alive (n=152) were interviewed by telephone, or responded by mail (n=6). The

telephone interview consisted of questions about whether the patient lived at home, and the The European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire C-30 was filled out. However, the quality of life results have not yet been analyzed. The 19 patients who were not assessed did not respond by telephone or by mail about their living conditions.

Paper II

This paper describes 182 patients who were assessed pre-surgery. The tools are the same as for paper I, but no categorization of patients was performed. In this paper, the predictive ability of elements of CGA was compared to Eastern Cooperative Oncology Group performance status (ECOG PS).

European Cooperative Oncology Group Performance Status (ECOG PS). This scale is used by oncologists to assess how the cancer disease affects the daily living abilities of the patient, how the disease is progressing, and to determine appropriate treatment and prognosis²⁰⁹. It is a scale based on five levels: 0; fully active, 1; restricted in physically strenuous activity but ambulatory and able to carry out work of light sedentary nature, 2; ambulatory and capable of all self-care, in bed less than 50% of the time, 3; capable of only limited self-care, in bed more than 50% of the time, 4; completely disabled, 100% bedridden. As surgeons in the three hospitals involved do not routinely use ECOG PS, the PI scored ECOG PS in our study.

Paper III

In addition to the CGA measurements, this paper included physical measurements such as grip-strength and gait speed, as well as an assessment of self-reported health; the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C30).

Modified physical phenotype of frailty measurements

1) Grip strength

Grip-strength. Grip strength was measured by a handheld Jamar dynamometer. The patients were asked to provide three tests with their dominant hand. The best score was recorded. Grip strength is one of the indicators in the physical phenotype of frailty. Cut-offs were calculated

from a cohort of more than 5000 community-dwelling individuals aged 65 years and older who participated in the Cardiovascular Health Study⁵⁶. The lowest 20% according to gender and body mass index had a positive frailty criterion.

2) Gait speed

The Timed Up and Go (TUG) test. TUG measures, in seconds, the time taken by an individual to stand up from a chair, walk a distance of 3 meters, turn, walk back to the chair, and sit down again. We defined a time of 19 seconds or more as slowness, based on the time distributions in the Canadian Study of Health and Aging (CHSA)²¹⁰. CHSA is one of the largest population-based studies to include the TUG. A cut-off of 19 seconds approximately identified the slowest quintile among the non-institutionalized participants in the CHSA.

3) Low activity and exhaustion

The European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire C-30 (QLQ C30). This core quality of life questionnaire is designed to measure cancer patients' physical, psychological, and social functions²¹¹. The QLQ C30 is built by a modular approach to measuring quality of life, and it is composed of multi-item scales and single items. Five functional scales are incorporated: Physical, role, cognitive, emotional, and social, as well as three symptom scales: Fatigue, pain, and nausea and vomiting. In addition, there are two global health and quality of life scales. Furthermore, there are single items measuring symptoms such as dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea, and there is a question about perceived financial impact of the disease and treatment. Most of the questions are answered on a scale from one to four, where three equals "quite a bit" and four equals "very much". The QLQ C30 is a widely used measure of quality of life in cancer patients, and have been shown to exhibit satisfactory to excellent psychometric properties²¹¹. In our study, we have not yet analyzed the results of the quality of life data derived from QLQ C30. However, in order to operationalize a modified version of the physical phenotype of frailty from our dataset, we extracted three questions from QLQ C30. The original criteria for the physical phenotype of frailty proposed by Fried and colleagues used two extracted questions from the Center for Epidemiological Studies-Depression scale questionnaire (CES-D Depression Scale) to categorize patients as frail by the exhaustion criterion⁵⁶. In our dataset, if a patient scored three or four on either "have you felt weak?" (question 12) or "were you tired?" (question 18), they were considered to have a

positive frailty criterion for exhaustion. Both items are from the fatigue subscale of the QLQ C30. In order to categorize patients as frail by the low activity criterion in the study by Fried and colleagues, the authors used number of kilocalories of physical activity per week based on the short version of the Minnesota Leisure Time Activity questionnaire. In our study, patients were considered to have a positive frailty criterion for low activity if they reported “quite a bit” or “very much” when asked “do you need to stay in bed or a chair during the day” (question 4). This question is from the physical functioning scale of QLQ C30.

4) Weight loss

MNA includes a question about weight loss. If a patient reported a weight loss greater than 3 kg during the last three months (screening question B from MNA), this was considered a positive weight loss criterion.

Paper IV

This paper utilizes all the CGA tools as well as the tools used in paper III. In addition, blood samples were analyzed. Blood samples were collected for routine pre-operative testing and additional blood was drawn for serum preparation, by centrifugation according to guidelines at the individual hospital laboratories (3400-3700 rpm for 10-12 minutes). The D-dimer analyses were performed at the respective hospital laboratories, with the STA Liatest® D-Di (Diagnostica Stago, Asnières, France). D-dimer was analyzed with the routine pre-operative blood samples. Serum was kept on ice during transport to be stored at -70° C. All the stored blood samples were analyzed at the same time in the laboratory at the Center for Clinical Heart Research, Ullevaal University Hospital. CRP levels were determined using an enzyme linked immunosorbent assay (DRG Instruments GmbH, Germany), detection limit 0.1 mg/L, coefficient of variation (CV) <5%. The remaining biomarkers were measured using enzyme-linked immuno assays with commercially available kits (R&D Systems Europe, Abingdon, Oxon, UK): IGF-1 (CV (in our lab) 8%), IL-6 (CV 10.5%), TNF-a (CV 8,5%) and MCP-1 (CV 9%).

Statistical considerations

Variable characteristics

Most of the variables in the study were categorized. The categories were decided apriori, based on the literature when available, or clinical experience (cut-offs for polypharmacy and IADL scores). Variables were either dichotomized or divided into three groups. For bivariate analyses, Chi-square-tests for trend or Pearson's chi-square were used as appropriate. Outcome variables were either post-operative complications within 30 days of surgery, or survival. The post-operative complications were further divided into two separate outcomes: "any complication" versus "no complication", and "severe complications" (grade II or higher according to the Clavien classification) versus "no/mild complications". Logistic regression models were used for the dichotomized outcomes, while Cox regression models were used to investigate predictors of mortality.

In paper III, the agreement between the two measures of frailty was tested with the Kappa Measure of Agreement.

In paper IV, non-parametric methods were used due to skewed distribution of biomarkers. To examine differences in levels of the various biomarkers within each frailty-measure, the Kruskal-Wallis test was used. When overall significant differences ($p < 0.05$) were found, we performed Mann-Whitney U tests between group pairs, adjusting the statistical level of significance to 2.5% using Bonferroni correction. We grouped levels of individual biomarkers into quartiles or tertiles, and examined their association to post-operative complications by chi-square tests. Trend analyses were performed to identify cut-off points. CRP-levels were dichotomized into values below the 25th percentile versus higher levels, and IL-6 in values below the 66.66th percentile versus higher levels. The dichotomized variables were subsequently included in crude and adjusted logistic regression models to examine their relative predictive value for post-operative complications.

Challenges in the multivariate analyses

The cut-offs of the variables influence the result of the multivariate analyses. We chose to adhere to our apriori defined categories when we analyzed the data in subsequent papers. In logistic regression analyses, the more variables you include in the model, the less power you

get in each test for significant effects on each variable. In addition to creating smaller subgroups within the dataset, logistic regression is also vulnerable to multicollinearity. To test for this in our multivariate models, we performed a linear regression analysis using the same outcome and predictors. There were no cases of tolerance values below .1 or Variance Inflation Factors values greater than 10, and this indicates that there are no multicollinearity issues in the data. ECOG PS and the three CGA categories were highly correlated, and could not be introduced into the same multivariable models.

Missing values

In clinical studies, one often has to deal with missing data. A few patients got tired during the CGA assessment, and we were not able to complete the assessment. In other cases, patients had to leave to complete pre-operative x-rays or speak to medical doctors involved in their cancer care. These data were considered as “missing” in the proper sense of the word, and we excluded such cases from all analyses. However, when variables with missing data became non-significant in the multivariate modeling, the whole cohort was included in the final calculations. There were no missing data for the outcome variables in the study.

In the CGA categorization, patients who fulfilled at least one frailty criterion were assigned to this group even if they did not complete all the assessments, because one criterion was enough to place them in the frail category.

For classification of the physical frailty phenotype the patients were required to have assessment data in at least three of the five domains. This was in accordance with the original publication by Fried and colleagues⁵⁶.

Ethical considerations

The Regional Committee for Medical and Health Research Ethics in East Norway as well as the Privacy Protection Representative at Ullevaal University Hospital approved the study. The inclusion in the study did not involve treatment leading to an increased risk of complications, and the comprehensive geriatric assessment did not have any consequences for treatment decisions. Extra blood was drawn, but only when it could be done in relation to the routinely performed pre-operative blood sampling. Ethical aspects included that the patients were subject to extra investigations that they may have found challenging, and that sensitive information was obtained and stored. Patients were in a sensitive phase, as they had only just learned about the cancer diagnosis. The inclusion was based on a written informed consent, and the patients were told that they might withdraw from the study at any time. The PI determined whether the patient was able to provide a written informed consent prior to the data collection. This was done by talking to the patient about their situation and describing the study. Patients who to the best of the PI's knowledge seemed to understand the information were asked to sign the consent form. This decision was not changed even if the patient scored low on the MMSE later on. The data collection was terminated if the patient got tired or expressed distress when answering the questions, but this only happened on a few occasions.

In two cases, the study provided crucial pre-operative information that would otherwise have been overseen. One patient with enlarged axillary glands on the preoperative CT scan (originally interpreted as metastases of the colon cancer) revealed during the CGA interview that she had been diagnosed with sarcoidosis many years earlier. The treating surgeon was informed. Another patient had extremely high values of D-dimer (analyzed solely for the purpose of the study) the day before surgery, and was found to have a lung embolus; surgery for the rectal cancer was subsequently postponed. On one occasion, the PI phoned the treating surgeon when a patient with myelodysplasia and low counts of neutrophil granulocytes experienced fever post-operatively. Three patients were referred to psychiatric follow-up due to high scores on GDS, and one patient was referred to a dietician because of malnutrition. Not all patients with depression or malnutrition were referred to follow-up, either because they already had received such care or because they preferred their primary physician to pursue these issues.

Main results

This chapter describes the main results from the four papers briefly. More details are provided in the original papers.

CGA as a predictor of post-operative complications and survival (papers I, II, and III)

CGA predicted post-operative complications and survival in elderly patients electively operated for colorectal cancer. Increasing age and ASA score were not related to post-operative complications. When the complete CGA was used as a basis for categorizing patients into three groups of fit, intermediate, and frail patients, the frail group had significantly higher rates of severe post-operative complications (OR 3.13, 95% CI 1.65 to 5.92). When studying the occurrence of individual complications, frail patients had higher relative risks for developing pulmonary and cardiac complications as well as anastomotic leakage and delirium. The relative risks of readmission and reoperation were also significantly higher in the frail patients. Survival was also significantly reduced in frail patients compared to the non-frail, even when correcting for tumor stage.

In paper II we omitted the categorizations and looked at the individual elements of CGA. We showed that severe comorbidity, dependency in IADL, depression, and malnutrition were the CGA-elements that independently predicted post-operative outcomes. However, when ECOG PS was added to the models, elements from CGA no longer contributed to the predictive model. The only exception was the presence of severe comorbidity; this CGA-element added to the predictive model of severe complications also after including ECOG PS. Severe comorbidity was also borderline significant as a predictor of survival along with ECOG PS.

Frailty as a clinically useful predictor of post-operative outcomes – comparing two approaches (paper III)

This study of older adults with colorectal cancer demonstrated poor agreement between two definitions of frailty – one based on multi-dimensional geriatric assessment criteria and the other based on the physical phenotype of frailty criteria (PF). The two classifications were

quite consistent in terms of the cases classified as non-frail; however, there was inconsistency between the cases each method considered frail. Interestingly, only one of the frailty classifications was able to predict post-operative complications. The use of a frailty measure as a result of CGA was a much better predictor of 30-day morbidity than the modified physical frailty phenotype. The frailty identified by the physical frailty phenotype was neither a significant predictor of any post-operative complication nor of the severity of complications, whereas the CGA-based frailty measure predicted post-operative complications as well as severe complications. Both frailty classifications were predictive of overall survival. It seems that excluding comorbidity from the physical phenotype of frailty makes this classification less useful as a predictor of short-term outcomes.

Pre-operative levels of biomarkers in elderly patients with cancer and their relation to frailty status (paper IV)

When comparing levels of biomarkers between patients classified according to a modified version of the physical frailty phenotype and a CGA, we found overall differences in levels of CRP, IL-6, TNF- α and D-dimer: levels of all these markers were significantly higher in frail patients within both measures. IL-6 remained an independent predictor of severe post-operative complications even after adjusting for frailty-status.

Discussion

Decision making in elderly patients

Treatment decisions in older adults with colorectal cancer are not based solely on the surgical risk. Colorectal cancer is a deadly disease. Furthermore, the tumor itself represents a threat to the patient's health, functional status, and quality of life. For example, the tumor may cause obstruction, bleeding, distant metastases, or local invasion, resulting in medical emergency, pain, suffering, fatigue, or discomfort. Thus, removal of the tumor is often indicated, even in advanced age. However, for patients with a stage IV colorectal cancer, surgical removal of the primary tumor is controversial. According to guidelines from the National Comprehensive Cancer Network in the US, surgery is indicated if the patient is symptomatic, at risk of impeding obstruction, or has metastatic sites possibly open to curative resection⁹⁶. In a US study of patients ≥ 65 years with stage IV disease, 72% underwent surgery⁹⁶. Epidemiological data show a high resection rate of colon cancer in elderly patients², while data from the Norwegian Rectal Cancer Project demonstrate that surgical treatment of rectal cancer becomes less common with increasing age¹⁸⁸. In a Norwegian study of colorectal cancer in patients over 80 years from 1998, the resectability rate for patients < 80 years was 93% and the rate of curative resection was 75%, while in patients aged 80 and over the corresponding rates were 81% and 59%²¹². All treatment decisions are based on an evaluation of risks versus benefits. In older adults, this is often less straightforward than in younger people. An important first step is to determine remaining life expectancy, which again depends on chronological age, comorbidity, and functional status⁹. There may be "competing risks"; a scenario where the patient has two or more diseases that are life-threatening²³. The next step would be to evaluate whether the disease may influence the patients' health, functional level, and/or quality of life within his or her remaining lifetime. A small intestinal tumor that constantly bleeds and causes anemia, may dramatically limit functional status and well-being. A large tumor that may cause obstruction increases the risk of emergency surgery. Emergency surgery carries a much higher risk than elective surgery, and this is even more pronounced in the elderly. These factors necessitate thorough information to the patient; the risks of surgery on one hand, compared to the risk of not having surgery on the other hand. Experiences from clinical work sometimes leave the impression that health personnel without special knowledge of oncology want to "protect" the older adult from what they conceive as "harmful treatment", such as surgery, without knowledge of the risks of not being operated. It has been

documented that both caregivers and health professionals actually under-estimate the older patient's willingness to undergo treatment²¹³. It has also been shown that older adults accept chemotherapy treatment in a similar fashion than younger patients²¹⁴. However, in the same study, the older patients were less willing to trade survival for current quality of life when treatment was presumed.

Pre-operative risk assessment – scales versus clinical judgment

There are several ways to measure pre-operative risk. In Norway, anesthesiologists routinely assign patients to an ASA class pre-operatively. More specific risk models such as POSSUM and APACHE II have been developed, as discussed previously. In our cohort, we found that a classification based on CGA predicted the occurrence of post-operative complications, whereas increasing age and ASA classification did not. The vast majority of our patients were classified as ASA II or III, and the two categories were not able to differentiate between patients who experienced complications and patients who did not. The multivariate analyses of CGA-elements identified severe comorbidity, IADL-dependency, and depression as independent predictors of morbidity. Table 4 displays a comparison between a categorization based on CGA (into fit, intermediate, or frail) and the model derived from the multivariate analysis of elements of CGA and their ability to predict severe complications.

Table 4. Comparison of CGA categorization and elements of CGA for prediction of severe complications					
	PAC	Sensitivity	Specificity	PPV	NPV
CGA categorization	66.3%	77.1%	56.8%	61%	74%
Elements of CGA	66.5%	53.6%	77.6%	66%	68%
Abbreviations: CGA; comprehensive geriatric assessment, PAC; percentage accuracy in classification; PPV; positive predictive value, NPV; negative predictive value					

After a stepwise backward logistic regression analysis with elements of CGA, the percentage accuracy in classification of severe complications was 66.5%. The sensitivity was 53.6%,

while the specificity was 77.6%. The positive predictive value (the percentage of cases predicted by the model to have severe complications that was actually observed to have severe complications) was 66%, while the negative predictive value was 68%. When using the categorization based on a complete CGA in the multivariate analyses, the percentage accuracy in classification was 66.3%. The sensitivity was 77.1%, while the specificity was 56.8%. The positive predictive value was 61%, while the negative predictive value was 74%. These data are derived from the classification tables of the multivariate analyses.

Interestingly, our data indicate that the surgeon’s judgment can predict morbidity in a manner comparable to a CGA-classification. We asked the surgeons at Ullevaal University Hospital to report whether they considered the patient to be fit, intermediate or frail after they did their pre-operative assessment. The reason why we did this was because we expected CGA to be a much better predictor. Given that the surgeons evaluated only 49 of the 182 patients, this dataset is less robust. Surgeons’ judgment turned out to be a good predictor of severe complications. The overall percentage accuracy in classification for the surgeons’ judgment was 72%, sensitivity was 65.2%, and specificity was 77.8%. Positive predictive value of the surgeons’ judgment was 71%. When CGA classification was used in the same patient sample, the overall accuracy in classification was 69.4%, sensitivity was 65.2%, and specificity was 73.1%. The positive predictive value was 68%. Of the 29 patients that were classified as “fit” by the surgeons, 15 were intermediate and 8 were frail according to CGA. Only 6 patients were classified as fit by both the surgeons and the CGA assessment. A comparison between the two classifications is displayed in Table 5.

Table 5. Crosstabulation of CGA category and surgeons’ judgment					
		Surgeons’ judgment			Total
		Fit	Intermediate	Frail	
CGA category	Fit	6	0	0	6
	Intermediate	15	6	0	21
	Frail	8	9	5	22
Total		29	15	5	49

This observation needs validation in a separate cohort, but may have practical implications. Other authors have found that clinical judgment is a valuable predictor of risk, and in some

cases even superior to standardized scoring tools. For example, Mary Charlson found that the residents' scoring of disease severity was a more accurate predictor of mortality than the Charlson comorbidity index²¹⁵. Furthermore, Christensen et al found that perceived age predicts survival among people aged 70 and older, even after adjustment for chronological age, sex, and other biomarkers of aging²¹⁶. In that paper, the authors ask why there has been so little research on the reliability and validity of perceived age given that it is so widely used and formally registered in patients' notes in many settings. It may be that perceived age, and the use of clinical judgment, is deemed as less scientific because of their diffuse and subjective nature. However, in my opinion, the sensitivity and specificity of short screening tools should be tested against clinical judgment – to investigate whether the formal tools add predictive value. Within geriatric oncology, for example, a number of short screening tools have been proposed in order to identify patients who will benefit from a complete CGA²¹⁷. However, it may be that the judgment of the surgeons or oncologists is equally sensitive *if they are asked to consider the need for a CGA*. This conception is often met with reluctance and even anger, because it is interpreted as a step backwards for geriatric oncology, leaving patients with the rule of thumb approach instead of evidence-based medicine. In my opinion, this is a misunderstanding that probably reflects the misconception of judgment as an unscientific approach. My own experience with this clinical research study has made me aware of some of the limitations of a purely quantitative approach. It is likely that the development and use of a screening tool is not as straightforward as it seems, considering all the choices that have to be made along the way to develop the tool, for example regarding scoring, cut-off values, which items to include, and what outcome measures to study. Furthermore, the systems for scoring are fixed, and in practical medicine there will often be surrounding factors that make the sum score seem misleading. As an argument opposing the usefulness of judgment as a predictor of risk, a study from British Journal of Urology found that doctors (urologists and oncologists) were poor at predicting 10-year survival when presented with patient case scenarios²¹⁸. The authors conclude that many patients may be denied treatment after a (wrongly) pessimistic assessment of life expectancy. An important limitation with that study, however, is that the doctors did not meet the patients. The value of clinical judgment does not only lie in the facts about the patients, but according to Christensen's results it is more likely to be based on the actual perception of the patient. This detail has important implications, as "paper representations" of real patients are frequently used in multidisciplinary meetings where treatment plans are formed. In conclusion, including

judgment as an addition to established assessment tools is more likely to contribute to science than to undermine it.

It has been shown that CGA adds information to ECOG PS in older adults with cancer⁸¹, and it is frequently stated that ECOG PS is not sufficient as an assessment of fitness in the elderly. In our study, ECOG PS turned out to be an independent predictor of all outcomes. When estimating pre-operative risk in our patients, ECOG PS alone certainly provided valuable information. For some reason, assessment of functional status as a part of the pre-operative evaluation of elderly patients is not a well-established practice, and as discussed earlier the majority of surgical publications lack information about functional status. The publications that do include measurements of function or performance status frequently find this factor to be an independent predictor of risk^{71,97,114,219-221}. We found that ECOG PS was a more useful measurement of functional status than ADL and IADL for pre-operative risk assessment. In PACE, however, IADL was a stronger predictor than ECOG PS for morbidity¹²². PACE also included a measurement of fatigue in the model, and this could be part of the explanation for the difference in results.

Surprisingly, there were no significant differences in morbidity between the fit and intermediate groups in our study. The criteria for being classified as fit were very strict, and the fit group was the group with the smallest number of patients (n=21). One explanation for the lack of differences in morbidity may be that the number of patients was too small to yield any statistical significance. Another possibility is that patients defined as frail were above some threshold that made them susceptible to complications, while the fit and intermediate both were below this threshold. However, we cannot pinpoint this threshold from our dataset or the design of the study.

The frail group in our study was mixed, as patients may have had one or more frailty criteria. Forty-one patients were frail because of severe comorbidity, out of a total of 76 frail patients, and severe comorbidity was the most frequently occurring frailty criterion. Of the 76 frail patients, there were 43 patients (57%) fulfilling one frailty criterion, 22 patients (29%) fulfilling two frailty criteria, eight patients fulfilling three frailty criteria, one patient fulfilling four frailty criteria and two patients fulfilling five frailty criteria. We have not made subgroup analysis within the frail group.

Advantages of CGA

Even though we found that quicker assessments, such as the surgeon's judgment and ECOG PS, were comparable to a CGA-assessment in pre-operative risk prediction, there are several arguments favoring completing CGA as a pre-operative assessment in older adults. Firstly, CGA may uncover previously unknown medical problems, such as cognitive dysfunction and depression. Secondly, knowledge about social support, ADL-function, and cognition may provide information about adherence to treatment protocol. In some cases, arrangements must be made regarding transportation and emergency contacts. The same type of information is important for adequate discharge planning. I will briefly go through the elements of CGA and their potential contributions to patient management in this setting.

Physical functioning

In our study, requiring assistance in IADL was an independent predictor of experiencing any post-operative complication. In addition, knowledge of pre-operative functional limitations may improve the discharge planning as it can be tailored to specific needs. In order to establish a patient-focused goal for rehabilitation after surgery, which aims to restore functional ability of the patient, knowledge of the functional status prior to the surgical procedure is required.

Comorbidity

Not surprisingly, severe comorbidity was predictive of post-operative complications and survival in our cohort. Assessment of comorbidity is already one of the most important parts of the pre-operative evaluation of patients. Whether the use of designated comorbidity indexes adds to assessing specific comorbidities in the pre-operative setting remains uncertain, and comorbidity indexes are rarely used in clinical practice. However, if measuring the total burden of comorbidity adds information regarding remaining life expectancy, and provides an estimate of physiologic reserves, it may be relevant for decision-making. The cumulative illness rating scale also provides data for comorbidity in individual organ systems, and these data will be explored at a later time.

Polypharmacy

In our cohort, 26% of the patients used five or more drugs. A thorough assessment of the patient's medication list before surgery is important. There may be unnecessary or duplicate drugs, drug interactions, or drugs that carry a high risk of side effects. In addition, the list of medications may alert the surgeon about comorbidities that were not noted in the medical records. We did not find polypharmacy, defined as number of systemic drugs in daily use, to be predictive of any outcomes in our study. However, there was a trend towards more frequently occurring severe post-operative complications in the patients who used five or more drugs (OR 1.73, CI 0.87 to 3.44). Polypharmacy is closely related to comorbidity, and comorbidity appears to be a more sensitive predictor of surgical risk.

Nutritional status

Even though it is frequently seen among elderly hospitalized patients, malnutrition often goes undiagnosed²²². In patients undergoing gastrointestinal surgery, the reported prevalence of malnutrition is up to 50%¹³⁵. Studies have found that nutritional risk is associated with increased post-operative morbidity and mortality, but these studies have been carried out in younger and mixed populations, and the analyses are not corrected for functional status^{135,223,224}. Furthermore, the tools used for nutritional screening varied among the studies. We found that the 9% of our patients that were malnourished tended to have a higher risk of severe complications and any complication (OR 2.77, 95% CI 0.89 to 8.65, and OR 2.49, 95% CI 0.77 to 8.06, respectively). We did not analyze whether malnutrition predicted individual complications. Interestingly, in the survival analyses, having a normal nutritional status as opposed to being at risk for malnutrition or malnourished was associated with better survival (hazard ratio 2.39, 95% CI 1.24 to 4.61). One could speculate that a normal nutritional status is a marker of less frailty, as we found that both frailty measures calculated in our study predicted overall survival. Nutritional status represents an interesting pre-operative risk factor because it is potentially reversible.

Cognitive dysfunction

The need for a pre-operative cognitive assessment in elderly patients undergoing surgery can hardly be disputed. The prevalence of cognitive dysfunction increases with age, and in some cases cognitive dysfunction is undiagnosed. This may easily go unnoticed in a brief pre-

operative counseling if formal cognitive testing is not carried out. Cognitive problems necessitate adjustments of the pre-operative counseling, have implications for choice of treatment, and increases the risk of post-operative delirium, which may be prevented⁴⁷. Even though cognitive dysfunction was not predictive of morbidity in our study, cognitive dysfunction was significantly associated with post-operative delirium ($p < 0.001$, test for trend). Furthermore, the use of a more sensitive measure of cognitive function than MMSE might have given different results.

Depression

There are studies indicating that emotional factors, such as depression, are strongly predictive of surgical outcomes such as functional recovery and pain²²⁵. The mechanisms remain unclear. There may be biological explanations involving the immune system, and a behavioral component such as less interest in post-operative mobilization cannot be entirely ruled out. Treatment of depression pre-operatively might be beneficial, but to our knowledge no scientific evidence support this. Unresolved questions are: What type of treatment, which antidepressant drugs, will the benefit outweigh the increased risk of postponing surgery? In any case, a positive screening for depression pre-operatively should alert the surgeon to arrange for follow-up either in-hospital or after the patient is discharged. Being depressed was significantly associated with experiencing post-operative delirium in our data ($p = 0.01$, Fisher's exact test).

Feasibility in clinical practice

An important question that arises when presenting surgeons with the idea of doing a pre-operative CGA is "how long does it take?". In a hectic clinical practice it is not possible for the surgeon to spend one hour with each elderly patient. A lot of effort has been put into developing screening tools for frailty in order to identify patients in need of a full CGA. Unfortunately, this has been done even though the scientific rationale for CGA is still uncertain. Furthermore, the screening tools that are tested have not been compared to clinical judgment. Practical considerations are important, however, time restrictions, as a sole argument against doing a thorough pre-operative work-up, may not be valid. A frail older adult with colorectal cancer scheduled for surgery may in many cases have functional limitations, several comorbidities, a long list of medications, and cognitive problems.

Spending only 10-20 minutes on a pre-operative evaluation of this patient makes little sense from a clinical point of view. Furthermore, a hastily performed pre-operative evaluation might actually lead to extra work post-operatively, such as complications that could have been avoided (for example delirium), uncontrolled comorbidities, unforeseen problems with rehabilitation and problems when discharging the patient to his home. We found that frail patients had significantly higher rates of readmissions and a longer length of stay, and we hypothesize that a more extensive pre-operative work-up would save time after surgery. This needs to be tested in a randomized controlled trial in frail patients. The enhanced recovery after surgery program, which involves careful peri-operative planning, has already been consistently shown to reduce morbidity, lead to a faster recovery, and shorten hospital stays¹⁴⁰.

Frailty

In the context of cancer treatment such as chemotherapy and surgery, it is pertinent to be able to identify patients with limited reserve capacity. In theory, such treatment will potentially exhaust the patient's reserves and lead to complications and toxicity. If these complications are worse than the cancer disease or even fatal, the treatment was not justified. As mentioned earlier, even though the term frailty is frequently used among health professionals, there is still no universally accepted method to identifying frailty. The multi-domain CGA-based definition in our study identified a group of patients with higher risk of complications, and this definition was more useful than the modified version of the physical phenotype of frailty that disregards comorbidity. Traditionally, within gerontology and geriatrics, natural age-dependent changes in structure or function of organs have been distinguished from age-related pathologies. However, normal age-dependent changes are believed to be associated with the prevalence of age-related pathologies, and diseases in organs along with the aging process will exert synergistic effects on each other. The same is probably true for comorbidity and frailty. Maybe the distinction between frailty and comorbidity is less useful from a practical point of view? A recent surgical study showed that the frailty indicators used in the physical phenotype of frailty are predictive of post-operative complications²²⁶. Interestingly, the standardized definition of frailty (three or more criteria) was not utilized in that study. Instead of using a prior hypothesis for their regression analysis, the authors explored the dataset to find the most optimal cut-off for frailty. They divided the cohort into three new groups, and patients with 0-1 indicators were classified as non-frail, patients with 2-3 indicators were

classified as intermediately frail, and patients with 4-5 indicators were classified as frail. For this reason, the results of this study cannot be directly compared to the results from our study or to other studies that use the established definition of the physical phenotype of frailty.

The correlation between biomarkers of inflammation and coagulation and frailty measures may have some practical consequences. Biochemical markers that increase the validity of clinical assessments are attractive for several reasons: they are objective, easy to obtain, and may be compared across large samples. Furthermore, biomarkers provide a possible link to the pathophysiological process and etiology. Additional data are needed to establish the role of biomarkers in identifying frailty, but our findings support previous findings suggesting an important role of inflammatory pathways^{66,67}. Even though different patients were classified as frail according to the two measurements, the levels of CRP and IL-6 were consistently increased in both models. The same holds true for D-dimer, suggesting that activation of coagulatory pathways may contribute to frailty.

Choice of cut-offs and tools in the study

In this prospective study, the cut-offs for the various elements of CGA were established a priori. As described under methods, the choices were based on the literature where available, or by common practice in Norway. Thus, we did not use exploratory statistics to determine cut-off values. In multivariable analyses, the choice of cut-offs heavily influences the results of the analyses. This is best illustrated by looking at the cumulative illness rating scale (CIRS). As CIRS scores 14 organ systems on a range from 0-4, various scores are obtained:

- total score
- number of categories with disease (score 1-4)
- number of categories with score 2-4
- number of categories with score 3
- number of categories with score 4
- severity index (total score divided by number of categories with score 1-4)

Furthermore, one may group the patients into no/mild comorbidity, intermediate comorbidity, and severe comorbidity based on number of categories with score 2, 3, and 4. This is the approach we used in our study. The total score of CIRS is somewhat unreliable, because the results are easily influenced even if the scorer misses small complaints such as constipation,

mildly reduced hearing, or mild depression. Comorbidities grades 3 or 4 are unlikely to be ignored, making these scores a more robust finding. It is important to decide which scores from CIRS to use before analyzing the data, because the high number of possible combinations may facilitate statistical manipulation. As mentioned above, I think it was unwise to change the criteria for frailty according to the physical phenotype in the study by Makary and colleagues²²⁶. Instead of using an established definition, they explored the dataset to find the best cut-off. Thus, their analysis is data-driven rather than hypothesis-driven. This is a problem when the criteria for a categorization have already been established, because it makes it difficult to compare results across different studies.

Methodological differences make it difficult to compare the results from our study to similar studies. In Preoperative Assessment of Cancer in the Elderly (PACE), for example, comorbidity was not found to predict post-operative morbidity¹²². Audisio and colleagues used Satariano's index of comorbidities¹³⁴. This index was validated in a cohort of women with breast cancer, where it predicted mortality, but of whom only a small percentage was older than 70 years. The index disregards dementia and stroke, while gall bladder disease yields a high score. Thus, in my opinion, this index is less useful for elderly cancer patients, and the choice of index may have influenced the multivariate results from PACE. The use of shorter versions of the CGA tools may also influence the outcome from studies. In PACE, GDS-15 was used instead of GDS-30. The cut-off for depression was set to 4, and they found that 27% of the patients were depressed. This cut-off cannot be directly compared to our cut-off of 14 (we found that 11% of the patients were depressed). In conclusion, when there are several ways to study the data, establishing cut-offs apriori is of paramount importance to ensure that results are based on a prior hypothesis, and not due to extensive search in the data. Furthermore, comparison between studies remains difficult when tools and cut-offs are not standardized. In order to make progress within the field of geriatric oncology, a standardized geriatric assessment tool is highly desirable. This would make it possible to compare treatment outcomes and pool results from studies across different populations.

Relevance of peri-operative care in the interpretation of our results

The main focus of our project was to study the association between elements from a geriatric assessment and risk of post-operative complications and survival in elderly patients operated for colorectal cancer. We did not design this study to investigate peri-operative care of

colorectal cancer patients. As peri-operative care issues influences post-operative morbidity, as extensively discussed in the introduction of this dissertation, the question remains whether differences in peri-operative care may have influenced the results of our study. In order to test the hypothesis that a pre-operative CGA-based categorization of older cancer patients could predict post-operative complications, we chose colorectal cancer patients with the assumption that this patient cohort was relatively homogeneous (as opposed to investigating all types of cancer surgery) with a *relatively* standardized procedure. Studying the influence of peri-operative routines was *not* the scope of the study, as our focus was to study the role of a geriatric assessment and frailty in older patients with colorectal cancer. We assumed that the peri-operative routines were fairly similar in each individual patient and in the three hospitals, and that they would not confound the results in any systematic way.

The treatment of colorectal cancer is fairly standardized in Norway through national guidelines published and updated regularly by the Norwegian Gastrointestinal Cancer Group since the early 1990s. The guidelines were accessible from a book (“Grønnboka”), and later through the organization’s website (www.ngicg.no). Since 1993, when the National Rectal Cancer Registry was established, regular meetings in a reference group with members from many hospitals have contributed to discussion and dissemination of the recommendations. The pre-operative investigations, surgical methods, the use of (neo-)adjuvant treatment and follow-up after curative surgery have therefore been standardized in Norway for many years, and the guidelines are followed in most hospitals.

However, until 2010 there were no guidelines with regards to the principles of peri-operative care presented on pages 31-41. We took steps to minimize institutional differences in peri-operative care, as we chose three University Hospitals in Southern Norway with comparable case-load and surgical experience. When comparing the peri-operative routines at the three hospitals in our study, the differences are small (Table 3). Although peri-operative factors are interesting from a practical surgical point of view, it is likely that the three hospitals in our study have a relatively uniform approach to the surgical treatment and peri-operative care of colorectal cancer patients. Furthermore, the design of this study does not allow for conclusions about the effect of differences in peri-operative care, and is merely hypothesis generating as observational studies always are. Analyses of differences in complication rates between the hospitals also support our approach: Chi-square tests reveal no differences in rate

of complications between the three hospitals ($p=0.97$). The same holds true if the model includes tumor location (Aker university hospital had a higher rate of rectal cancer surgery), type of surgery (Ullevål university hospital had a higher rate of laparoscopic surgery), or fitness level of the patients. Finally, as all the hospitals have established routines for treating colorectal cancer, it is highly unlikely that systematic treatment differences between the three patient categories have influenced the main findings in our study. On the contrary, all the patient in this study were older than 70 years old, creating a unique homogeneous cohort of prospectively studied older adults undergoing this type of surgery.

As discussed in the papers, rectal cancer surgery was associated with a higher rate of complications than colon cancer surgery, entirely in line with the literature. Laparoscopic surgery was associated with a lower number of complications in univariate analyses, but remained insignificant in multivariate models. In a separate analysis, where only colon cancers were included, laparoscopic surgery was not associated with a lower number of complications ($p=0.3$), illustrating that tumor location was a more powerful predictor than type of surgery.

Comparable studies, such as PACE, have looked at the association between CGA-elements and all types of cancer surgery in a joint analysis¹²². In a large study by Alves and colleagues¹⁸⁹, studying risk factors associated with post-operative mortality and morbidity after colorectal resections in 1421 patients, the following two variables related to peri-operative care were univariately associated with post-operative mortality (among a total of 28 variables): no prophylactic antibiotics and no bowel preparation. In comparison, seven pre-operative patients variables (age, BMI, ASA class, underweight, Glasgow Coma Scale score, cardiopulmonary comorbidity, neurologic comorbidity) were univariately associated with the outcome. After multivariable analyses, both of the variables related to peri-operative care were removed from the model, suggesting that these factors were not relevant for predicting post-operative mortality in colorectal resections in this large cohort. For predicting post-operative morbidity, the only factor related to peri-operative care that was significant in univariate analyses was no bowel preparation, and again, this variable disappeared in multivariable analyses, suggesting little impact of such factors in predicting post-operative morbidity after colorectal resections. In contrast, age, cardiopulmonary comorbidity, and neurologic comorbidity retained significance in the multivariate model, thus highlighting the

importance of pre-operative patient factors when constructing models to predict risk of post-operative morbidity.

Practical consequences

The results of our project highlight the need for an individualized assessment of elderly patients prior to surgery for colorectal cancer. Increasing age itself does not appear to increase the surgical risk in elective procedures, at least not in our cohort. Furthermore, the established ASA classification was not sensitive enough to predict outcome in our patient group. The results need to be validated in a different sample of patients. Whether or not CGA-based interventions in frail patients may reduce complication rates need to be tested in a randomized trial. In Norway, there are not sufficient geriatricians to take part in the routinely performed pre-operative assessment of elderly cancer patients. Surgeons are used to operating the elderly, but specific training in geriatric medicine for surgeons is to my knowledge not well established. Such training would be useful in order to improve the surgeons' knowledge about functional status, cognitive function, and clinical aspects of geriatrics such as the occurrence of general symptoms instead of organ-related symptoms, atypical presentations of disease, and geriatric syndromes. Assessment of functional status, nutrition, emotional status, and formal testing of cognitive function could all be done by a nurse prior to the pre-operative counseling. However, surgeons would need to know how to interpret the results of such assessments in order to make them useful.

Weaknesses of the study

One of the main weaknesses of the study is that we did not manage to include all the patients that were scheduled for surgery at the three hospitals during the inclusion period. As the PI did all the assessments, patients were lost when the PI was not available. This happened during PhD courses or vacation. Furthermore, not all patients were reported to the PI from the respective hospitals. In some cases the surgical schedule was changed in the last minute, and patients were already operated when the PI came to assess them. All in all, the patients were lost in a random manner, and it is unlikely that the results are affected in a systematic way. The number of patients that were missed was calculated by counting the number of patients 70 years or older scheduled for elective surgery from the surgical programs at the three hospitals in a retrospective manner. As these patients were not included in the study, and thus

had not signed any consent forms, no information was recorded about these patients. For this reason, we cannot calculate whether or not they were different from the patients who were included in our study. In conclusion, we cannot be entirely sure that our sample is representative for all patients operated at the three hospitals in the designated time, but due to the arguments presented above it is not unlikely that patients were missed in a random manner.

The 19 patients who did not respond by telephone or mail about their living conditions after three months were characterized by a higher number of patients categorized as frail (63% versus 40%), slightly more women (63% versus 57%), and a mean age comparable to the rest of the cohort (81 years compared to 80 years). The only data used from the follow-up at three months were data regarding living conditions, and it is likely that the actual numbers of patients needing nursing home or extended care are slightly under-estimated in paper 1.

The interventions that were carried out for ethical reasons may have had a minor impact on overall survival.

The PI who did the CGA-assessments also did the scoring of ECOG PS, and this may have influenced the results in paper II. An oncologist who has limited time with the patient usually scores ECOG PS, and thus the basis for scoring ECOG PS was much broader in our study than in routine clinical practice.

For the comparisons of the frailty measures, an important weakness was that the physical phenotype of frailty was not measured in the exact same way as in the original publication by Fried and colleagues. However, for subjective measurements such as exhaustion and low activity, we believe that the results are comparable, because the questions from QLQ C30 are quite similar to the described measurements in the original study. Exhaustion was originally based on two questions extracted from the CES-D Depression Scale (“I felt everything I did was an effort” and “I could not get going”). Subjects answering “a moderate amount of the time” or “most of the time” on either of these questions were categorized as frail by the exhaustion criterion. For low activity, the criterion in the original PF definition was based on self-reported low activity from the Minnesota Leisure Time Activity questionnaire. We did not have such a measurement. In a paper by Rockwood and colleagues²¹⁰, two approaches to

measuring frailty were compared in a similar fashion. In that paper, low activity was operationalized as needing assistance with walking or being unable to walk. In our study, patients were considered to have a positive frailty criterion for low activity if they reported “quite a bit” or “very much” when asked “do you need to stay in bed or a chair during the day”, because needing to stay in bed or a chair for a lot of the time during daytime implies low activity. The question was from the physical functioning scale of QLQ C30. For this reason, even though we find that our results are most likely comparable to the other studies, our results must be interpreted with caution. Our classification is in any case an approximation to measuring frailty as clusters of physical impairments, even though there may be some deviations from the original physical phenotypic frailty criteria. Furthermore, the QLQ C30 was not designed to measure exhaustion and low activity by extracting questions from the subscales. We plan to analyze the results from QLQ C30 before surgery, after three months, and at 1-2 year follow-up at a later time, and in order to proceed with those analyses the internal validity of the QLQ C30 questionnaires will need further investigation.

As previously mentioned in the published papers, a weakness regarding recording of post-operative complications was that the information was collected retrospectively. The major sources for these data were medical records. The following complementary approach was used to ensure comprehensive information about morbidity: data were extracted from all available medical records; including charts, doctors’ notes (inpatient and outpatient), nurses’ notes, and discharge papers. In uncertain cases the medical team was consulted, and if there were inconsistencies in the records nursing homes, caregivers, or patients were consulted. Especially for the occurrence of wound infections, it is important to follow the patients after discharge to ensure complete morbidity data: in a study by Weigelt and colleagues, 35% of surgical wound infections first became manifest after discharge²²⁷. Thus, even though registering post-operative complications retrospectively certainly is a limitation of our study, and the optimal approach would have been a prospective registration, it may be argued that we took several steps to minimize the impact of this limitation. In any case, post-operative complications were registered in the same way for all the patients, and the significant differences in complication rates between frail and non-frail patients remain an interesting finding.

Conclusions

- Elderly patients (70 years old and older) electively operated for colorectal cancer experienced a high rate of post-operative complications, but the operative mortality rate was low
- A comprehensive geriatric assessment (CGA) identified a subgroup of frail elderly patients who experienced a significantly higher rate of post-operative complications compared to patients who were non-frail
- Increasing age and ASA class were not predictors of complications in this cohort
- Survival in elderly patients operated for colorectal cancer is influenced by cancer stage and frailty status
- The most important CGA-elements associated with post-operative complications and survival were dependency in instrumental activities of daily living, severe comorbidity, impaired nutrition, and depression
- Eastern Cooperative Oncology Group performance status can predict post-operative complications and survival
- Surgical publications about pre-operative assessment in the elderly should include measurements of physical performance and comorbidity beyond ASA class
- Frailty identified by a multi-dimensional approach such as CGA was a much better predictor of short-term surgical outcomes than frailty identified through clusters of physical impairment (*Fried frailty*)
- Frail older patients with colorectal cancer have higher pre-operative levels of the inflammatory markers CRP and IL-6 than non-frail patients
- IL-6 was an independent predictor of post-operative complications when adjusting for tumor location and frailty status

Suggestions for further research

There are a number of issues that should be further explored. Firstly, studying the impact of colorectal cancer surgery on functional, cognitive, and emotional status, general health, and quality of life will be very interesting. Medical student Benedicte Rønning has collected such data, and we are eagerly awaiting the results of the analyses of her data obtained from home visits to many of our patients. Secondly, given that frail patients experienced significantly more post-operative complications, it would be interesting to randomize frail, elderly patients to interventions based on a CGA versus usual care, and to see if this approach can decrease the rate of complications. Our research group is about to launch a randomized controlled study in frail elderly patients scheduled for elective surgery for colorectal cancer to test this hypothesis. Ideally, this approach should have been integrated with establishing ERAS in the hospitals, but unfortunately this does not seem to be in place to date.

Further research on the role of comorbidity and functional status in relation to surgical outcomes in elderly patients is needed. In addition, it would be interesting to expand on the knowledge of how the occurrence of post-operative complications influences long-term survival. It has been suggested that the occurrence of post-operative complications reduces long-term survival independently of pre-operative patient factors¹³⁷, but an alternative explanation is that data regarding patient factors were not extensive enough.

Interesting data have been published regarding cancer survivorship in elderly patients, and further research on this topic is also likely to improve decision-making, treatment planning, and information to patients.

I would also like to see publications regarding how cancer treatment is delivered to elderly patients in Norway, for example by analyzing registry data.

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Attachments

Scientific papers I - IV

FRAILITY AS A CLINICALLY USEFUL PREDICTOR IN ELDERLY CANCER
PATIENTS – A COMPARISON OF TWO DIFFERENT APPROACHES

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Abbreviated title: Frailty measurements in geriatric oncology

ABSTRACT

Objectives: To compare a pre-operative multi-domain frailty measurement based on a comprehensive geriatric assessment (CGA) to a modified version of the physical phenotype of frailty (PF) in a cohort of older adults with colorectal cancer, and to analyze the ability of the two measurements to predict post-operative complications and survival.

Design: Prospective longitudinal study.

Setting: Three university hospitals in Norway.

Participants: Patients aged 70 or older electively operated for colorectal cancer.

Measurements: A pre-operative CGA, self-reported quality of life, and measurements of grip strength and gait speed were performed. CGA-frailty was defined as fulfilling *one or more* of the following criteria: Dependency in activities of daily living, severe comorbidity, cognitive dysfunction, depression, malnutrition, or > seven daily medications. PF was defined as the presence of three or more of the following criteria: Unintentional weight loss, exhaustion, low physical activity, impaired grip strength, or slow gait speed. Outcome measures were post-operative complications and survival.

Results: One hundred seventy-six patients (median age 80, range 70-94) were included. The agreement between the classifications was poor. CGA-frailty was identified in 75 (43%) patients, while PF was identified in 22 (13%) patients. Only CGA-frailty predicted post-operative complications [P= .001]. Both CGA-frailty and PF predicted survival.

Conclusion: A multi-domain frailty measurement based on a CGA appears to be more useful than frailty identified from a modified version of the physical phenotype of frailty criteria in predicting post-operative complications in older adults operated for colorectal cancer. For long-term outcomes such as overall survival, both measurements are predictive.

Key words: frailty, geriatric assessment, geriatric oncology, colorectal surgery, pre-operative evaluation

INTRODUCTION

Remaining life expectancy and treatment tolerance are important elements to consider when making treatment decisions in elderly cancer patients. Data from epidemiological studies, clinical trials, and studies of the biology of aging support the view that chronological age is not the most important factor in predicting remaining life expectancy and treatment tolerance.¹⁻³ Examples of more useful predictors are functional status, comorbidity, and frailty. The term frailty is widely used in the medical literature, and describes “an elderly patient who is at heightened vulnerability to adverse health status change because of a multisystem reduction in reserve capacity”.⁴ Thus, identifying frailty in cancer patients is important because an increased risk of complications from anti-tumor treatment such as surgery and chemotherapy is very likely. How to recognize frailty, however, remains controversial.

Within geriatric oncology, a widely used definition of frailty is derived from criteria first described by Winograd and later modified by Balducci.^{5,6} Based on a comprehensive geriatric assessment (CGA), a patient is categorized as frail according to this definition when fulfilling any of the following criteria: dependency in activities of daily living (ADL), three or more comorbid illnesses, the presence of geriatric syndromes (for example dementia, malnutrition, depression, delirium, and falls), or age > 85 years. In this multi-component phenotype of frailty, deficits across different health domains, such as clinical, psychological, and functional, are considered to be predictors of treatment tolerance and life expectancy. This classification is comparable to an approach that was used by Jones and colleagues, where a frailty index was constructed from a CGA.⁷ Studies of colorectal surgery have identified single elements from a geriatric assessment, such as functional dependency,⁸

comorbidity,⁹ weight loss¹⁰ and depression,¹¹ as independent predictors of post-operative morbidity. However, only a few surgical studies have performed a comprehensive geriatric assessment pre-operatively.¹² In a study of older adults who underwent elective surgery for colorectal cancer, we found that frailty identified from a CGA, but not increasing age or American Society of Anesthesiologists (ASA) classification, predicted post-operative complications within 30 days of surgery.¹³

Within the geriatric and biogerontological literature, a widely accepted definition of frailty is based on data from more than 5000 community dwelling individuals aged 65 years and older who participated in the Cardiovascular Health Study.¹⁴ The physical phenotype of frailty based on data from this study was defined as fulfilling at least three of the following five criteria: unintentional weight loss, exhaustion, slow walking speed, low physical activity, and weakness. This approach does not include comorbidity and cognition, but highlights the association of frailty with physiological and metabolic changes leading to a loss of functional capacity. A physiologic loss of reserves is identified through clusters of physical impairments. The physical phenotype of frailty predicts incident falls, hospitalizations, worsening mobility, and deaths in large cohorts.^{14,15} It has to our knowledge not been tested whether this physical phenotype of frailty is able to predict short-term outcomes, such as post-operative complications after elective surgery, in a homogeneous cohort of elderly patients.

Thus, the aim of this prospective longitudinal study was to compare a multi-domain frailty classification based on CGA to a frailty classification based on a modified version of the physical frailty phenotype in a cohort of older adults with stage I to IV colorectal cancer who underwent elective colorectal surgery. By comparing the ability of the two classifications to predict post-operative complications and overall

survival, we may get an indication of the most useful approach to identifying susceptible elderly patients at risk for surgical morbidity.

METHODS

Setting and patients

The eligibility criteria for this study included: age 70 years or older, being scheduled for surgery of a suspected or confirmed colorectal cancer in three Norwegian hospitals from November 2006 through June 2008, and ability to provide a written informed consent. The Regional Committee for Medical and Health Research Ethics in East Norway approved the study. The principal investigator, a medical doctor with training in geriatrics, performed the pre-operative assessments 0 to 14 days prior to surgery at the hospitals.

CGA measurements and CGA-classification

Functional dependence in ADL and instrumental ADL (IADL) were assessed using the Barthel Index (BI) and the Nottingham Extended Activities of Daily Living Scale (NEADL).^{16,17} Comorbidity was registered from hospital records, supplied with information from the patient interview, and scored by using the revised Cumulative Illness Rating Scale (CIRS) manual from 2008.^{18,19} The CIRS assesses fourteen organ systems, and comorbidity in each organ system is scored on a five-point scale ranging from grade 0 (no problem) to grade 4 (extremely severe/immediate treatment required/end organ failure/severely impaired function). The Mini Nutritional Assessment (MNA), Mini Mental State Examination (MMSE) and the Geriatric Depression Scale (GDS), were used to assess nutritional, cognitive, and emotional status, respectively.²⁰⁻²² The number of systemic drugs in daily use was recorded from the hospital records. A previous publication provides more detailed descriptions of the tools used in the CGA assessment and the reasoning behind the selected cut-off values.¹³

Based on the pre-operative CGA assessment, patients were categorized into the three groups "fit", "intermediate" and "frail" using a modification of the criteria proposed by Balducci and Extermann.^{6,23} CGA-frailty was defined as fulfilling *one or more* of the following criteria: Dependency in activities of daily living, severe comorbidity, cognitive dysfunction, depression, malnutrition, or > seven daily medications. According to the Balducci-categorization, patients who require assistance with ADL are classified as frail, while independence in both ADL and IADL is required for placement in the fit category. During recent years, cut-off scores for comorbidity and cognition using CIRS and MMSE have been established in the geriatric oncology literature.^{24,25} Comorbidity was classified in the following way: *mild/no comorbidity* when there was no comorbidity higher than grade 2 and less than three grade 2 comorbidities, *moderate comorbidity* when there were a maximum of two grade 3 comorbidities and no grade 4 comorbidity, or *severe comorbidity* when there were three grade 3 comorbidities or any grade 4 comorbidity. Cognitive dysfunction was defined as an MMSE score of 0-23, while cognition was categorized as normal when the score was 27-30. Due to the lack of a standardized definition of geriatric syndromes, we omitted this term as a frailty criterion. Instead we used the scoring from MNA (nutrition) and GDS (depression) and used cut-off criteria proposed by the authors of these tools to categorize the patients.^{21,22} Furthermore, we removed age > 85 years as a classification criterion for frailty. To our knowledge, there is no agreed definition on how to categorize polypharmacy in the context of frailty. Even though the use of five or more prescription drugs is commonly referred to as polypharmacy,²⁶ the prevalence of such drug use was reported to be 39% in a Swedish study of individuals 65 years or older.²⁷ We chose a number slightly higher than five in order to identify patients who were likely to have

severe comorbidity. A comparison of frailty-defining criteria in the two categorizations is presented in Table 1.

Frailty indicators used to operationalize the physical frailty phenotype¹⁴

In order to classify the patients according to the physical frailty phenotype, we used information from the CGA assessment, self-reported quality of life, and physical measurements. Information about weight loss was obtained from MNA; and a loss of greater than 3 kg during the last three months was considered a positive weight loss criterion. Maximal grip strength was measured on the dominant side with a handheld Jamar dynamometer, and the same cut-offs as described by Fried *et al* according to gender and body mass index were used.¹⁴ Subjective exhaustion was based on self-report from the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), a widely used oncology tool measuring self-reported health during the last week.²⁸ When a patient answered either “quite a bit” (score 3) or “very much” (score 4) on either question 12 (“Have you felt weak?”) or question 18 (“Were you tired?”), the exhaustion criterion was considered positive. Slowness was defined as a time of ≥ 19 seconds on the timed up and go (TUG) test. This cut-off was derived from the TUG time distributions in the Canadian Study of Health and Aging (CSHA). CSHA is one of the largest population-based studies to include the TUG.²⁹ In the original physical frailty phenotype definition, slowness was defined as the slowest 20% of the population walking 15 feet. A cutoff of 19 seconds approximately identifies the slowest quintile among the non-institutionalized participants in the CSHA. Low physical activity was operationalized as scoring 3 or 4 on question 4 from EORTC QLQ-C30 (“Do you need to stay in bed or a chair during the day?”). Frailty was defined as fulfilling three or more of these five criteria, while patients fulfilling one or two were considered pre-

frail. Those with no characteristics were considered robust. As in the original paper by Fried and colleagues, patients considered evaluable for frailty had three or more non-missing frailty components.¹⁴ Table 2 compares the criteria used to operationalize the physical frailty phenotype to the original phenotypic criteria.

Post-operative measurements

Complications were broadly defined as any event occurring within 30 days of surgery requiring treatment measures that are not routinely applied post-operatively for colorectal cancer. In order to present the morbidity data in a standardized and reproducible manner we classified complications as minor (grade I), potentially life-threatening without (grade II) or with (grade III) lasting disability, or fatal (grade IV) based on the morbidity grading system developed by Clavien et al.³⁰ For example, a lower urinary tract infection was classified as a grade I complication, while pneumonia was a grade II complication. This classification of post-operative complications has been used in other studies of gastrointestinal surgery in the elderly,^{31,32} and allows for separate outcome variables according to the severity of morbidity. The following complementary approach was used to ensure a comprehensive collection of morbidity data: data were extracted from all available medical records; including charts, doctor's notes (inpatient and outpatient), nurses' notes, and discharge papers. In uncertain cases the medical team, nursing homes, caregivers, or patients were consulted in order to ensure a complete 30-day recording of complications. The final scoring of complications according to the Clavien classification³⁰ was subsequently done in collaboration with a colorectal surgeon. Post-operative mortality was defined as death within 30 days after surgery.

Information on patients' deaths was retrieved from the National Registry of Norway. All deaths identified as of August 10, 2009 were included in the current analysis.

Statistical analyses

For the frailty categorizations, the degrees of agreement between the two measures were tested with the Kappa Measure of Agreement.

Two dichotomized outcome variables were created for 30-day post-operative morbidity: "severe" complications (grade II or higher according to the classification by Clavien et al.³⁰) versus "no/mild" complication, and "any" complication versus "no" complication. Chi-square tests for trend were used to compare the associations between these outcomes and the potentially predictive factors CGA-classification (fit, intermediate, or frail) and modified physical frailty phenotype (robust, pre-frail, or frail). In addition, bivariate associations between the dichotomized physical frailty indicators weight loss, weakness, exhaustion, slowness, and low activity and the outcome severe complications were assessed using chi-square tests. Physical frailty indicators with a p-value less than 0.10 were entered into a multivariable logistic regression model with elements from the CGA that have previously been identified as bivariately associated with the outcome severe complications.³³ Rectal cancer was a strong independent predictor of severe post-operative complications in this dataset, and tumor location was therefore included in the multivariable model.¹³ Independent predictors of severe complications were then identified through a backward stepwise logistic regression analysis.

Survival curves were estimated by the Kaplan-Meier method and compared by the log rank test. Overall survival was compared between age groups (70-79 years compared to 80-94 years), according to cancer stage (grouped into stages 0-II, III,

and IV), according to CGA-classification (fit, intermediate, or frail), and according to the modified Fried phenotype (robust, pre-frail, or frail). Cancer stage was entered into a Cox proportional hazards model with CGA-classification and the modified Fried phenotype, respectively. As the proportionality assumption was not fulfilled for the CGA-classification, this variable was dichotomized into frail versus non-frail.

All statistical analyses were performed using SPSS 15.0 software (Chicago, IL).

RESULTS

Of the 187 patients included pre-operatively, 176 were evaluable for frailty according to both CGA-classification and the modified physical phenotype of frailty. Age ranged from 70 to 94 years, with a mean and median age of 80 years, and there were 101 (57%) women. A total of 171 (97%) patients lived in their own home, and 84 (48%) lived alone. Of the 92 patients who did not live alone, 87 (95%) lived with their spouse. Thirty-six patients (21%) had public help, while 46 (26%) received help from relatives or friends on a regular basis. The cancer was localized to colon in 125 (71%) patients, while the remainder had rectal cancer. A total of 21 (12%) patients had metastatic disease.

Based on CGA, the number of patients categorized as fit, intermediate, and frail was 21 (12%), 80 (45%), and 75 (43%), respectively. According to the modified physical phenotype of frailty, 70 (40%) were robust, 84 (48%) were pre-frail, and 22 (13%) were frail. As seen in Table 3, the two measurements selected different patients as frail, and the Kappa Measure of Agreement value was 0.05, representing poor agreement. Of the 75 patients classified as frail according to the CGA, only 17 were frail according to the physical phenotype of frailty. Of the 101 patients classified as non-frail according to the CGA, 96 were classified as non-frail according to the physical phenotype of frailty. When comparing the relationships between the two frailty classifications and the occurrence of post-operative complications, we found that frailty defined from CGA significantly predicted any post-operative complication ($p=0.001$) as well as severe complications ($p=0.002$). The most common severe complications in the frail group were pulmonary complications in 18 patients (24%), cardiac complications in 17 patients (23%), and delirium in 10 patients (13%). The

most common severe complications in the patients who were not frail according to the CGA were wound infection requiring systemic antibiotics in 13 patients (13%), pulmonary complications in 8 patients (8%), and cardiac complications in 8 patients (8%). Anastomotic leakage was observed in 7 patients who were frail according to CGA, compared to 2 patients who were not frail according to CGA (relative risk 5.1, 95% confidence interval 1.03 to 25.28). Increasing frailty identified from the modified physical frailty phenotype was neither a significant predictor of any complication ($p=0.18$) nor of severe complications ($p=0.23$). Of the five physical frailty indicators, only low activity was associated with the outcome severe complications ($p=0.10$). When this indicator was included in a multivariable model with the elements of CGA that were bivariately associated with severe post-operative complications (IADL, co-morbidity, and nutritional status), low activity was the first variable to be removed from the risk prediction model at a p-level of 0.21.

There were no differences in morbidity according to cancer stage in this cohort. Three patients (1%) died within 30 days of surgery.

Overall, the median follow-up time was 20 months (interquartile range, 15 to 25). Both frailty classifications were associated with overall survival, and the results are displayed in Table 4.

When correcting for cancer stage in the Cox regression model, frailty classified by CGA remained an independent predictor of mortality. When correcting for cancer stage in the Cox regression model of the modified physical frailty phenotype, both pre-frailty and frailty were significant predictors of survival. The results are displayed in Table 5.

DISCUSSION

This study of older adults with colorectal cancer demonstrated poor agreement between two different ways of identifying frailty – one based on geriatric assessment criteria and the other based on a modified version of the physical phenotype of frailty criteria. The two classifications were quite consistent in terms of the cases classified as non-frail; however, there was inconsistency between the cases each method considered frail. Interestingly, only one of the frailty classifications was able to predict post-operative complications. The use of a frailty measure as a result of CGA was a much better predictor of 30-day morbidity than the modified physical frailty phenotype. The frailty identified by the physical frailty phenotype was neither a significant predictor of any post-operative complication nor of the severity of complications, whereas the CGA-based frailty measure predicted post-operative complications as well as severe complications. Both frailty classifications were predictive of overall survival.

Frailty is defined by a limited reserve capacity and a heightened vulnerability to adverse events. Thus, aggressive treatment modalities may expose a frail patient to complications and toxicity. Identifying frailty before treatment is initiated may identify patients who would benefit from targeted interventions aimed at improving the patient's tolerance to therapy, or identify patients where the risk versus benefit ratio of therapy is too high. The physical phenotype of frailty does not readily identify remediable conditions that may be optimized pre-operatively, such as comorbidity and polypharmacy, and did not provide pre-operative risk information in our study, as opposed to the CGA-classification. We have previously identified that comorbidity, IADL-dependency, and depression are CGA-elements that independently predict

post-operative complications.³³ The one-dimensional physical frailty phenotype does not include comorbidity or psychological factors, and this appears to limit its usefulness in the pre-operative setting. Our results are difficult to compare to previous studies, as we are not aware of other studies that have examined the predictive ability of these frailty measures for the same outcomes. A recent publication found that the criteria used in the physical phenotype of frailty predicted post-operative complications in a heterogeneous cohort of elderly surgical patients, but the standardized definition of the physical phenotype of frailty was not used in the study: intermediate frailty was defined as fulfilling 2-3 of the five criteria, while frailty was defined as fulfilling 4-5 criteria.³⁴ Thus, the results cannot be directly compared to our results.

The discrepancy between the two definitions warrants further discussion. Firstly, the prevalence of CGA-frailty is much higher than the prevalence of frailty identified by the modified physical phenotype. CGA-frailty is conceptually more closely related to frailty measured by deficit accumulation,²⁹ and estimates of frailty based on deficit accumulation were higher than estimates based on the phenotypic definition of frailty in the population-based United States Health and Retirements Study.³⁵ To our knowledge, the prevalence of two such measurements has not been compared in a hospital-based elderly cohort similar to ours. One explanation for the discrepancy may be that severe comorbidity was by far the most frequently appearing CGA-frailty defining criterion in our cohort,¹³ while comorbidity is not part of the physical phenotype of frailty.

The physiologic loss of reserves is a key component of frailty, and it is inherent in the concept that a frail elderly person is less able to integrate an adequate stress response. A bowel resection may be viewed as stress test of a patients' ability to

compensate the surgical trauma, and the occurrence of post-operative complications may to some extent be an indirect measure of loss of functional reserves. However, morbidity is also influenced by several other factors, for example extent of surgery, type of anesthesia, and surgical skills. Even though only the CGA-based frailty measure in our study was associated with morbidity, both frailty measures predicted overall survival, and one can argue that poor survival is also an indication of loss of functional reserves.

A morbidity rate of 60% under elective conditions is higher than reported in most colorectal series; estimates from 20% to 30% being more common.⁹ However, a morbidity rate similar to ours was reported in a recent publication by Audisio et al.¹² Morbidity rates are difficult to compare due to differences in methods of data collection as well as in ways of classifying complications. It has been shown that the estimated rate of wound infections increases by 53-99% when reported by 30-day complete outpatient and inpatient reporting.^{36,37} Furthermore, post-operative delirium is often not reported in the surgical literature, despite being a common and serious complication in elderly surgical patients. In our study, two methodological factors may have contributed to the high rate of complications. Firstly, all events requiring treatment measures not routinely applied post-operatively were considered to be post-operative complications. Secondly, several complementary methods were used in order to ensure a thorough recording of morbidity data, as described in the methods section.

The Cox regression analysis demonstrated that cancer stage and frailty (according to both classifications) were independent predictors of mortality after a median follow-up time of 20 months. Interestingly, increasing age actually resulted in a (non-significant) reduced hazard ratio for mortality. As increasing age was neither a

predictor of post-operative morbidity nor of overall survival in our cohort, it appears that selected octa- and nonagenarians tolerate colorectal cancer surgery well, and should be offered treatment when colorectal cancer impacts on remaining life expectancy or in the likelihood of local tumor complications.

A limitation of our study is that phenotypic frailty was not measured in the exact same way as in the original publication.¹⁴ Furthermore, our hospital-based cohort consists of elderly patients who underwent surgery for cancer, while Fried and colleagues included subjects from the general population and excluded patients with active cancer from the CHS study. Even though the resection rate is high even in advanced age in colorectal cancer,³⁸ our patients have already been selected through primary care and the pre-operative surgical evaluation, and are not representative of the general population. In addition, our cohort is considerably older than the CHS-cohort where 67% of the patients were aged 65-74 years. In contrast, 75% of our cohort was 75 years and older. This may explain the higher prevalence of physical frailty in our study (13% versus 7%). A limitation regarding CGA-frailty is that the cut-off criterion for polypharmacy is not well defined in the literature. Furthermore, MMSE scores were not adjusted for level of education. Another limitation of our analysis is that we have not addressed important endpoints such as physical functioning after surgery. In addition, data regarding post-operative complications were recorded retrospectively, and this is a weakness of the study. However, as described above, we used several complementary approaches to ensure a comprehensive recording of morbidity data. Our results need validation in a separate cohort.

An important strength of our dataset is that the cohort is truly elderly, with a median age of 80 years. Furthermore, all these patients have the same index disease, and

they were thoroughly examined before a relatively standardized major procedure – an elective bowel resection. This allowed us to compare two widely used frailty measurements in a homogeneous cohort. It is still unclear whether identifying frailty may contribute to the decision-making in geriatric medicine, and data regarding the predictive validity of frailty for complications of treatment and survival are lacking.

Successful surgical care of elderly cancer patients depends on several factors, such as pre-operative patient selection, avoiding emergency surgery, and careful peri-operative handling of patients. Growing evidence indicates that post-operative complications, in addition to decreasing well being of patients and increasing the risk of post-operative mortality, also may have important effects on long-term survival and recovery to pre-operative levels of independence.³⁹⁻⁴¹ According to our findings, a pre-operative CGA may identify elderly patients with a high risk of post-operative complications. Elements from a CGA are superior to measurements of chronological age and ASA-class,¹³ as well as objective functional measurements such as gait speed and grip strength. Particularly relevant CGA-elements in this dataset were severe comorbidity, as measured by CIRS, IADL-dependency, and depression.³³ Comorbidity may be optimized, depression can be treated, and IADL can be supported. A prospective randomized trial of susceptible elderly surgical patients would yield information about whether geriatric assessment and targeted intervention can improve surgical oncology care by decreasing the rate of post-operative complications.

In conclusion, the optimal tool to measure frailty will vary according to the specific outcome in question. For planning health care services on a population level, identifying risk of mortality and worsening mobility through a quick assessment such as the physical frailty phenotype is suitable. This classification has been validated in

several population-based studies as identifying those at high risk for disability, falls, hospitalizations, hip fracture, and mortality.⁴²⁻⁴⁵ For prediction of treatment tolerance, such as post-operative complications, our results indicate that a multi-component classification of frailty based on geriatric assessment criteria is more useful. Furthermore, CGA may unmask remediable problems, and consequently allow for pre-treatment patient optimization. Future studies are needed to test the ability of CGA-guided interventions to decrease surgical morbidity.

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GRAPHICS

Table 1. Comparison of Balducci-criteria for Frailty and Frailty-criteria Used in the Current Study

Characteristic	Balducci-criteria ^{6,17}	CGA-frailty in current study
Age	>85 y	Not used
ADL	Dependency for 1 or more	Dependency for 1 or more
Co-morbidity	3 or more	Severe co-morbidity according to CIRS-scores
Geriatric syndromes	1 or more of the following: <ul style="list-style-type: none"> • Dementia • Depression • Malnutrition • Incontinence • Delirium • Osteoporosis • Falls • Neglect and abuse • Failure to thrive 	1 or more of the following: <ul style="list-style-type: none"> • MMSE score < 24 (range 0-30) • GDS score > 13 (range 0-30) • MNA score < 17 (range 0-30) • Incontinence (ADL)
Polypharmacy	Not used	> 7 daily medications

Abbreviations: CGA, comprehensive geriatric assessment; ADL, activities of daily

Table 2. Frailty-defining Criteria Adapted From the Criteria Based on the Cardiovascular Health Study (Fried criteria)

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Characteristic	Fried criteria	Criteria used in current study
Weight loss	Lost > 10 lbs unintentionally in last y	Weight loss greater than 3 kg during the last 3 months (question B from MNA)
Weakness	Grip strength: lowest 20% (by gender, BMI)	Same as in Fried criteria
Exhaustion	Self-report of either: <ul style="list-style-type: none"> Feeling everything I did was an effort in the last wk Could not get going in the last wk 	Score 3 ("quite a bit") or 4 ("very much") on either question 12 ("Have you felt weak?") or 18 ("Were you tired?") from EORTC QLQ-C30
Slowness	Walking 4.57 m: <ul style="list-style-type: none"> Time \geq 7 s for height < 160 cm Time \geq 6 s for height > 159 cm 	TUG \geq 19 seconds ²⁹
Low activity	MLTA questionnaire (short version) <ul style="list-style-type: none"> Evaluating all 18 items < 270 kcals per wk on activity scale 	Score 3 or 4 on question 4 ("Do you need to stay in bed or a chair during the day?") from EORTC QLQ-C30
Overall frailty status	Robust: 0 criteria Pre-frail: 1 or 2 criteria Frail: 3 or more criteria	Same as in Fried criteria

Abbreviations: MNA, mini nutritional assessment; BMI, body mass index; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer quality of life questionnaire C30; TUG, timed up and go; MLTA, Minnesota Leisure Time Activity; kcals, kilocalories.

Table 3. Comparison of Frailty-defining Criteria and Relations to Severe Post-operative Complications

Modified physical phenotype of frailty					
CGA-classification	Robust	Pre-frail	Frail	Total	No. severe morbidity (%)
Fit	12	9	0	21	7 (33)
Intermediate	42	33	5	80	29 (39)
Frail	16	42	17	75	46 (61)
Total / no. severe morbidity (%)	70 / 28 (40)	84 / 43 (51)	22 / 11 (50)	176	82 (47)

Table 4. Bivariate Analyses of Age, Cancer Stage, and Modified Frailty-classifications and Overall Survival

Variables	No. of Patients		P (Log-Rank Test)
	Died	Total	
Age, years			.260
70-79	26	87	
80-94	20	89	
Cancer stage ^a			< .001
TNM 0-II	14	108	
TNM III	15	43	
TNM IV	17	21	
CGA-classification			.001
Fit	3	21	
Intermediate	13	80	
Frail	30	75	
Modified Fried phenotype			.056
Robust	12	70	
Pre-frail	25	84	
Frail	9	22	

Abbreviations: CGA, comprehensive geriatric assessment.

^a4 patients were unclassified according to TNM

Table 5. Frailty-classifications as Predictors of Mortality by Cox Regression Analyses. The Final Models Are Corrected for Cancer Stage and Age.

Variables	Hazard Ratio	95% CI	P
Model with CGA-frailty			
Cancer stage			
TNM 0, I, and II	1.00		
TNM III	3.14	1.51 - 6.53	.002
TNM IV	10.62	5.04 - 22.37	< .001
Age			
70-79	1.00		
80-94	0.74	0.41 - 1.34	.32
CGA-classification			
Non-frail	1.00		
Frail	3.39	1.82 - 6.29	< .001

Model with modified Fried phenotype

Cancer stage			
TNM 0, I, and II	1.00		
TNM III	2.77	1.30 - 5.90	.008
TNM IV	11.87	5.52 - 23.74	< .001
Age			
70-79	1.00		
80-94	0.78	0.43 - 1.41	.40
Modified Fried phenotype			
Robust	1.00		
Pre-frail	2.33	1.16 - 4.67	.018
Frail	2.67	1.11 - 6.83	.029

Abbreviations: CI, confidence interval; CGA, comprehensive geriatric assessment.

SUPPLEMENTARY DATA

Appendix 1

CGA assessment tools and frailty classifications.

Functional dependence was assessed by the Barthel Index and the Nottingham Extended Activities of Daily Living Scale, (NEADL) [1,2]. To evaluate comorbidity and nutritional status, the Cumulative Illness Rating Scale (CIRS) and the Mini Nutritional Assessment (MNA) were used [3,4]. Depression and cognitive function were measured by the Geriatric Depression Scale (GDS) and the Mini Mental State Examination (MMSE), respectively [5,6].

Objective measures of physical function were the timed up-and-go test (TUG) and grip strength. TUG measures time needed to get up from a chair, walk three meters, turn, walk back and sit down again [7]. Dominant side grip strength was measured using a Jamar® handheld dynamometer.

Finally, patients completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). This validated questionnaire includes questions regarding physical, cognitive, emotional, social and role functioning, as well as symptoms. Questions are answered on a four-point scale ranging from “not at all”, “a little”, “quite a bit” to “very much”. In addition, patients are asked to grade their overall health status and quality of life on a numeric scale from one to seven [8].

Patients were classified as frail according to the CGA if they had either severe comorbidity or used more than seven medications daily, were functionally dependent in personal activities of daily living, were malnourished, had reduced cognitive function or depression. To be fit, patients had to fulfil all of the following criteria: mild or no comorbidity, less than four daily medications, functional independence, normal nutritional status, normal cognitive function and no depression. Patients were classified as intermediate if they had no frailty-criteria, but did not fulfil all fit-criteria. For cut-off criteria, see table A, Appendix 2.

Data from the CGA were used to create an approximation to the Fried frailty phenotype. To fulfil the weight loss criterion, patients had to have lost > 3 kg over the past three months. Reduced walking speed was defined as using >19 seconds to complete the TUG-test [9]. For the muscle weakness criterion, grip strength cut-off values from the original paper by Fried et al. were used [10]. Self-reported exhaustion was defined as answering "quite a bit" or "very much" to either one of the questions: "*Have you felt weak*" or "*Were you tired*", from the EORTC QLQ-C30. Low physical activity was defined as giving one of the same answers to the question "*Do you need to stay in bed or a chair during the day?*" from this questionnaire. Patients fulfilling three or more criteria were considered frail; those with one or two criteria were pre-frail and patients not fulfilling any criteria were robust. The presence of assessment data in at least three domains was required to be eligible for classification

References

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Appendix 2

Table A

CGA-classification criteria.

	Fit – all of the following criteria	Frail – one or more of the following criteria	Intermediate
CIRS	No > grade 2 comorbidity + < 3 grade 3 comorbidities	>1 grade 4 comorbidity / > 2 grade 3 comorbidities	Patients who neither fulfilled the criteria for being fit, nor frail, were classified as intermediate.
Polypharmacy	< 5 daily medications	>7 daily medications	
Barthel Index	>18	<19	
NEADL	>43		
MMSE	>26	<24	
MNA	>23.5	<17	
GDS		>13	

CGA = Comprehensive Geriatric Assessment

CIRS = Cumulative Illness Rating Scale

NEADL = Nottingham Extended Activities of Daily Living

MMSE = Mini Mental State Examination

MNA = Mini Nutritional Assessment

GDS = Geriatric Depression Scale

Appendix 3

Preoperative blood samples

Blood samples were collected for routine preoperative testing and additional blood was drawn for serum preparation, by centrifugation according to guidelines at the individual hospital laboratories (3400-3700 rpm for 10-12 minutes). Serum was kept on ice during transport to be stored at -70° C.

The D-dimer analyses were performed at the respective hospital laboratories, with the STA Liatest® D-Di (Diagnostica Stago, Asnières, France).

CRP levels were determined in our laboratory using an enzyme linked immunosorbent assay (DRG Instruments GmbH, Germany), detection limit 0.1 mg/L, coefficient of variation (CV) <5%. The remaining biomarkers were measured using enzyme-linked immuno assays with commercially available kits (R&D Systems Europe, Abingdon, Oxon, UK): IL-6 (CV (in our lab) 10.5%) and TNF-a (CV 8,5%).

Appendix 4

Postoperative complications

Postoperative complications were classified according to severity [1]. A grade I complication was a minor event that did not require treatment other than simple symptomatic drugs (for fever, pain or nausea). Simple urinary tract infection and urine retention were also included

in this group. Another important criterion for a grade I complication was that it did not lead to a hospital stay “longer than twice the median stay for the procedure”.

A grade II complication was a potentially life-threatening event, or an event that led to prolonged hospitalization beyond that of a grade I complication. A further subclassification was based on intervention characteristics; grade IIa required only medical therapy, parenteral nutrition or blood transfusion, whereas grade IIb could be resolved by invasive procedures.

A grade III complication was also a potentially life-threatening event, further recognized by the development of lasting disability.

Finally, a grade IV complication denoted the death of a patient due to a complication.

The Clavien classification system was first developed for use in cholecystectomies, a goal being that it should be applicable to other types of surgical procedures. Because it is a highly comprehensive system, it is suitable for use in older patients, where even small events may lead to considerable discomfort.

References

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Appendix 5

Table B

Patient characteristics (n=137)

Median age, years (min-max)	80 (70-94)
Sex	
- Male	62 (45%)
- Female	75 (55%)
Mean BMI, kg (SD)	24.6 (4.3)
Tumour type:	
- Localized	83 (61%)
- Regional lymph node metastases	35 (25%)
- Distant metastases*	15 (11%)
- Not determined	4 (3%)
Tumour location	
- Colon	94 (69%)
- Rectum	43 (31%)
Physical frailty:	
- Robust	62 (45%)
- Pre-frail	59 (43%)
- Frail	16 (12%)
CGA-category:	
- Fit	16 (12%)
- Intermediate	66 (48%)
- Frail	55 (40%)

*Patients with distant metastases did not have significantly higher levels of biomarkers than those with localized disease, and were therefore included in the analyses.

BMI= Body mass index

SD= Standard deviation

IQR= Interquartile range