Assessment and impact of frailty and comorbidity in older cancer patients

Thesis by

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SUMMARY

Background

Cancer is most commonly diagnosed in older individuals, and approximately half of patients are 70 years or older when diagnosed. Older cancer patients represent a heterogeneous group regarding their overall health, comorbidity, and cognitive and physical functioning. The term 'frailty' is used to describe patients with increased vulnerability to stressors, and in clinical practice geriatricians determine patients' levels of frailty by performing geriatric assessments. Geriatric assessment is a systematic approach assessing areas such as functional and nutritional status, physical and cognitive functioning, as well as a systematic assessment of comorbidity. However, such assessments are rarely applied in clinical oncology practice, and how well oncologists identify frailty and comorbidity in their older cancer patients has scarcely been investigated.

Overall survival is the traditional outcome in oncology research and is also highly relevant for the older cancer patient. However, other outcomes such as quality of life and physical functioning are highly prioritized in this patient group. Still, little knowledge exists on how frailty affects older cancer patients' quality of life and physical functioning during treatment and follow-up.

Aims

In a cohort of advanced NSCLC (non-small-cell lung cancer) patients, we aim to investigate clinicians' ability to identify comorbidity in comparison to a systematic assessment as well as the prognostic impact of comorbidity on survival. Furthermore, in a cohort of cancer patients ≥70 years of age referred for systemic cancer treatment, we aim to investigate clinicians' ability to identify frailty in comparison to systematic assessment, the prognostic impact of frailty on survival, and the predictive ability of systematic frailty assessments on the course of quality of life and physical function at the first year of follow-up.

Methods

Two cohorts of cancer patients were studied in this thesis. In the first study (paper I), data from a randomized chemotherapy trial on advanced NSCLC were analysed. We compared an assessment by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) performed by three trained oncologists using hospital records and the extensive CIRS-G manual (CIRS-G scores), to a simpler assessment based on the original CIRS, performed by the patients' local oncologists/pulmonologists using a brief set of instructions (local investigators = LI-score). By both methods, the severity of comorbidity in 14 organ systems was graded 0 (no problem) to 4 (extremely severe). The agreement between methods was assessed using Bland-Altman analysis and weighted kappa statistics. The impact of comorbidity on survival was analysed by Cox regression.

In the second study (papers II and III), data from a prospective, observational study including patients ≥70 years referred for medical cancer treatment were used. Patients were classified as frail or non-frail at baseline by a modified geriatric assessment; quality of life was measured using the European Organisation for Research and Treatment of Cancer Core Quality-of-Life Questionnaire, administered at inclusion and again at 2, 4, 6 and 12 months. In paper II we compared oncologists' classification of frailty (onc-frail) based on clinical judgement with a

modified geriatric assessment (mGA). The agreement between the two frailty methods was assessed using kappa statistics and the impact of frailty on survival by Cox regression models. In paper III, focusing on physical functioning and global quality of life, we investigated whether frailty identified by a geriatric assessment was associated with higher risk of quality-of-life deterioration during cancer treatment and follow-up using linear mixed models.

Results

In paper I 375 patients were analyzed; the median age was 65 years, and 36% of the included patients were ≥70 years. More comorbidities and higher severity were registered by the CIRS-G compared to the LI-score. Severe comorbidity was registered for 184 (49%) and 94 (25%) patients according to the CIRS-G and LI-scores, respectively, and the agreement was slight (weighted kappa value 0.18 [95% CI 0.10; 0.25]). Mean total score was 7.0 (0–17) (CIRS-G) versus 4.2 (0–16) (LI-score), and the mean severity index (total score/number of categories with score >0) was 1.73 (SD 0.46) versus 1.43 (SD 0.78). Neither the CIRS-G scores nor the LI-scores were prognostic for survival.

In papers II and III 288 patients were included; the median age was 77, and most patients had good performance status (PS) (PS 0–1, n = 244, 85%). Overall, 104/286 (36%) were onc-frail and 140/288 (49%) mGA-frail; the agreement was fair (kappa value 0.30 [95% CI 0.19; 0.41]), and 67 mGA-frail patients who frequently had localised disease, good PS and were receiving curative treatment were missed by the oncologists. Only mGA frailty was independently prognostic for survival (HR 1.61, 95% CI 1.14; 2.27; P:0.007). Furthermore, mGA-frail patients consistently reported poorer scores on all functioning and symptom scales. Independent of age, gender, and major cancer-related factors, frail patients had significantly poorer physical functioning and global quality of life during follow-up, and opposed to non-frail patients they had both a clinically and statistically significant decline in physical functioning from baseline to 12 months.

Conclusion

We found that the CIRS-G scores and LI-scores had poor agreement, indicating that assessment method affects the registration and reported prevalence of comorbidity. Thorough descriptions of how comorbidity is rated in trials are paramount due to lack of a standardized assessment.

Introducing a systematic assessment of geriatric domains can aid oncologists in identifying frail patients with poor survival. Furthermore, geriatric assessment identifies frail patients with increased risk of physical decline, poor functioning, and high symptom burden during and following cancer treatment. These patients may need early symptomatic treatment and introduction of early palliative care in parallel with their oncological treatment.

List of papers

I

Kirkhus L, Jordhøy M, Šaltytė Benth J, Rostoft S, Selbæk G, Hjermstad MJ, Grønberg BH. Comparing comorbidity scales: Attending physician score versus the Cumulative Illness Rating Scale for Geriatrics. *Journal of Geriatric Oncology 7, 90-98, 2016*

II

Kirkhus L, Šaltytė Benth J, Rostoft S, Grønberg BH, Hjermstad MJ, Selbæk G, Wyller TB, Harneshaug M, Jordhøy MS. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. *Br J Cancer 117, 470–477, 2017*

III

Kirkhus L, Šaltytė Benth J, Grønberg BH, Hjermstad MJ, Rostoft S, Harneshaug M, Selbæk G, Wyller TB, Jordhøy MS. Frailty identified by geriatric assessment is associated with poor functioning, high symptom burden and increased risk of physical decline in older cancer patients: Prospective observational study. *Palliat Med. 2019 Mar;33(3):312-322. doi: 10.1177/0269216319825972. Epub 2019 Feb 4.*

Abbreviations

aCGA: Abbreviated Comprehensive Geriatric Assessment

ADL: Activities of Daily Living

ALK: Anaplastic lymphoma Kinase

ATC: Anatomical Therapeutic Chemical Classification System

CCI: Charlson Comorbidity Index

CGA: Comprehensive Geriatric Assessment

CIRS-G: Cumulative Illness Rating Scale for geriatrics

EBRT: External Beam Radiotherapy

ECOG-PS: Eastern Cooperative Oncology Group Performance Status

EGFR: Epidermal growth factor receptor

EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30

FACT-G: Functional Assessment of Cancer Therapy General

GA: Geriatric Assessment

GDS-15: 15 item Geriatric Depression Scale

GFI: Groningen Frailty Indicator

Gy: Gray

HRQoL: Health related Quality of life

IADL: Instrumental Activities of Daily Living

ICD: International Classification of Diseases

KPS: Karnofsky Performance Status

mGA: Modified Geriatric Assessment

MCI: Mild Cognitive Impairment

MMSE: Mini Mental State Examination

MNA: Mini Nutritional Assessment

MoCA: The Montreal Cognitive Assessment

NBCG: Norwegian Breast Cancer Group

NLCG: Norwegian Lung Cancer Group

NSCLC: Non-small cell lung cancer

OS: Overall Survival

PG-SGA: The Patient-Generated Subjective Global Assessment

OARS: Physical Health Section, a subscale of the Older Americans' Resources and Services Questionnaire

ORR: Overall response rate

PRO(M): Patient Reported Outcome (Measure)

PFS: Progression free survival

PS: Performance status

RCT: Randomized Controlled Trial

SCLC: Small cell lung cancer

SIOG: The International Society of Geriatric Oncology

SPPB: Short Physical Performance Battery

TTP: Time to progression

TUG: Timed up-and-go

VES-13: Vulnerable Elders Survey 13

QoL: Health Related Quality of Life

Essential definitions

Older cancer patients: In this study, cancer patients 70 years or older are defined as older.

Comorbidity is defined as a patient's coexisting diseases and conditions in addition to the index disease, which in this thesis is cancer.

Geriatric assessment is a systematic approach assessing areas such as functional- and nutritional status, comorbidity, medication use, as well as physical, cognitive, social and emotional function.

Frailty is widely recognized as a syndrome of increased vulnerability to adverse changes in health status [1]. The consensus definition for the term 'physical frailty' is 'a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death' [2].

Geriatric oncology: A clinical and research field focusing on diagnosis and treatment of older cancer patients. Some countries have developed geriatric oncology clinics and established fellow training programs in geriatric oncology.

Type of cancer: In this thesis, 'type of cancer' is used as a synonym for cancer diagnosis according to organ of origin in accordance with ICD classification.

Preface

The number of older cancer patients is increasing due to a growing and aging population as well as a higher cancer incidence. Approximately half of patients are 70 years or older when diagnosed with cancer. Older cancer patients represent a heterogeneous group with respect to general health, comorbidity, and physical and cognitive functioning that can affect the course and outcomes of cancer treatment. Compared to their younger counterparts, it is more common for older patients to have additional problems, i.e., severe comorbidity, poor physical function, and reduced cognitive function. Due to an underrepresentation of older participants in clinical studies, problems related to age are seldom systematically registered.

Few guidelines exist on how to treat older cancer patients with their additional problems. These patients represent a daily challenge for the treating physician. In most cases it is up to the physician's individual judgement whether a patient should receive standard treatment or if a more tailored approach and/or reduced treatment intensity is more appropriate. Geriatric assessment is a cornerstone of diagnostic workups and treatment in geriatric medicine as well as a recommended appraisal when evaluating older cancer patients. Most countries have yet to implement this assessment into routine clinical practice. Knowledge of whether the physicians who treat cancer patients are able to precisely estimate and identify the patients' vulnerabilities without any systematic approach is lacking.

Furthermore, how age-related problems influence the course and prognosis of cancer has scarcely been investigated. In particular, this applies to outcomes highly prioritized by older patients like physical function and quality of life. Studies including systematic assessment of

age-related problems are needed to increase knowledge about older cancer patients. However, research in this field is challenging for several reasons, amongst them the lack of consensus as to which scales to include in a geriatric assessment. For instance, several comorbidity scales have been used in different studies, and we need knowledge of how the use of different scales may impact reported prevalence of comorbidity and also of what different physicians might emphasize and identify when rating comorbidity.

By studying two patient cohorts in this thesis some of the abovementioned challenges are addressed.

Introduction

Cancer - general aspects

Types of cancer

The term 'cancer' comprises a variety of malignant diseases with varying biological and clinical expressions as well as vastly different prognoses. These diseases can also be categorized in several ways, of which the broadest is to differentiate between solid and non-solid tumors. Generally, a solid tumor forms an abnormal mass, in contrast to leukemia, a systemic disease in which solid tumors are not generally formed [3]. Only patients with solid tumors were included in the studies in this thesis, and non-solid tumors are therefore not further discussed.

Solid tumors are categorized according to organ of origin and histological subtype as confirmed by histological or cytological examination. Carcinomas are most prevalent, developing from epithelial cells lining organs or skin. Common subtypes are squamous cell carcinoma and adenocarcinoma [4]. Some organs can have several histological subtypes depending on organ composition; in the lungs, for instance, squamous cell carcinomas develop from bronchial squamous epithelia and adenocarcinomas from glandular cells typically localized more peripherally in the lung [5].

In the last decade more detailed knowledge of tumor cell gene mutations, as well as their expression of surface receptors, has provided a tool for further sub-classification of tumors [6]. One example of this is BRAF-gene mutation in 10–20% of patients with colorectal cancer, indicating an especially poor prognosis [7]. In time, with detailed knowledge of the tumor cells, the traditional organ-based classification of cancer is likely to be less important. However, in this work, we have applied the traditional cancer classification based on primary organ.

Epidemiology

Cancer is a prevalent disease: in 2018, 18,078,957 new cases of cancer were estimated worldwide [8]. In Norway one in three persons will be diagnosed with cancer before the age of 75, and in 2018, a total of 34,190 new patients received the diagnosis [9]. Approximately half of new cancer patients will be diagnosed with one of the five most common solid tumors in Norway (Table 1) [9].

Table 1 Most common cancer diagnosis in Norway 2018, all ages	
	No of patients
Prostate cancer	4848
Breast cancer	3596
Lung cancer	3351
Colon cancer	3068
Malignant melanoma	2325

Cancer survival is known to be improving [10]. Still, worldwide, 9.6 million cancer deaths are estimated for 2018. In Norway 11,016 cancer deaths were registered in 2017, and cancer is now the most frequent cause of death [9, 11]. The cancer types with the highest mortality rates are listed in Table 2.

Table 2 Cancer types with most frequently cancer deaths in Norway, all ages (2017)	
	No of patients
Lung cancer	2138
Colon cancer	1198
Prostate cancer	934
Pancreas cancer	787
Breast cancer	594

With the exception of a few cancer types (e.g., stomach cancer), the incidence of cancer has increased over the last 60 years [9]. The incidence is predicted to further increase from 12.8 million new cancer cases globally in 2008 to 22.2 million new cases in 2030 [12].

Most commonly, cancer is a diagnosis of older age (Figure 1). In Norway, about 46% of women and 50% of men are at least 70 years old at the time of diagnosis. This is reflected by the median age of diagnosis for most of the common cancers, being 66 for malignant melanoma, 69 for prostate cancer, 71 for lung cancer, and 73 for colon cancer [9]. Patients with breast cancer differ somewhat from the other most common cancer types with a median age at time of diagnosis of only 62 years [9].

Figure 1. Percentage distribution of cancer incidence by age in males and females (2014-2018) Source: The Norwegian Cancer Registry, Cancer in Norway 2018 [9]
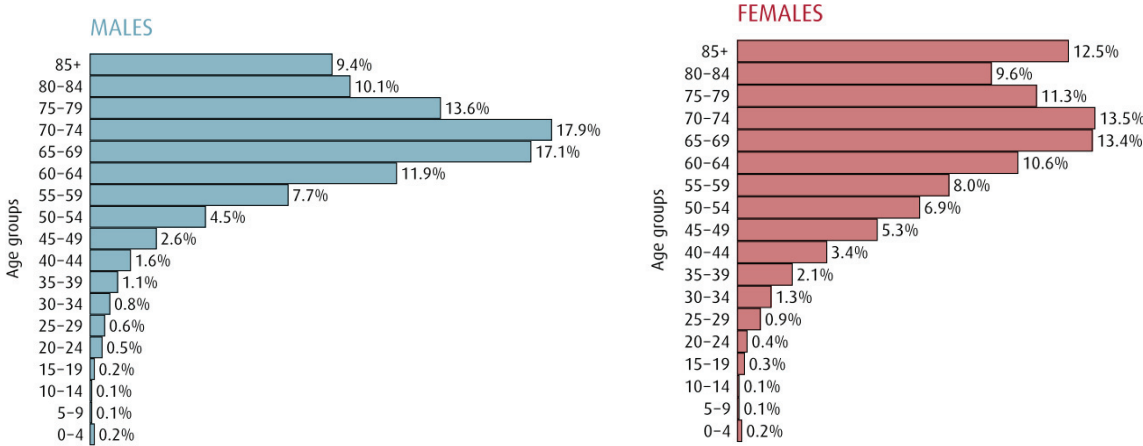
The most common cancer types also vary according to age and gender, and the most common types in patients 70 years or older are listed in Table 3 [9].

Table 3 Most frequent cancer types in patients 70 years + (2014-2018)	
Male	*Female*
Prostate cancer (27%)	Colon cancer (14%)
Lung cancer (11%)	Breast cancer (14%)
Skin, non-melanoma (10%)	Lung cancer (12%)
Colon (9%)	Skin, non-melanoma (11%)
Cancer of the urinary tract (9%)	Malignant melanoma (5%)

Staging of cancer

At time of diagnosis, the extent of disease is staged according to the TNM classification [13]. The TNM classification can be based on exact tumor measurement by the pathologist if the patient is undergoing surgery (pathological TNM) or on imaging techniques, blood samples, and clinical examination (clinical TNM). T indicates the primary tumor, N the lymph node involvement, and M distant metastasis. A separate and detailed TNM classification exists for most solid tumors, and a simplified overview is given in Table 4. The classification has been updated several times and is currently in the eighth edition.

Table 4: The TNM classification system, schematically	
Primary tumor (T)	**Tx** Cannot be evaluated
	T0 No primary tumor
	Tis Carcinoma in situ
	T1-4 Larger number indicates larger size / extension into surrounding tissue
Regional lymph nodes (N)	**Nx** Cannot be evaluated
	N0 No regional lymph nodes
	N1-3 A higher number indicates more severe lymph node involvement
Distant metastasis (M)	**M0** No distant metastasis
	M1 Distant metastases present

It has also been a tradition to classify the extent of disease into four overall stages (I–IV) based on the TNM classification [14], and this staging has been used to guide cancer treatment. Stage I represents a localized tumor with no lymph node involvement, stages II/III larger tumors with lymph-node involvement, and stage IV distant metastasis. Furthermore, when presenting incidence and prevalence according to stage, even simpler classifications are in use, e.g., the threefold classification—local, regional and metastatic—used in the annual report by the Norwegian cancer registry [9].

Cancer treatment

In general, all treatment of cancer is based on evidence from international clinical trials as well as on which treatment is accepted by health authorities. In Norway this evidence is summarized by national tumor groups, mainly organized according to organ of cancer origin, e.g., the Norwegian Breast cancer Group (NBCG) [15] and the Norwegian Lung Cancer Group (NLCG) [16]. Each group consists of national frontline experts appointed by the Norwegian Directorate of Health, and national treatment guidelines have been made for all types of cancers. These are regularly updated and easily available through the Norwegian

Directorate of Health web pages [17]. This helps to ensure equality of cancer treatment independent of hospital or localization.

The basic medical information needed for treatment planning is tumor origin, stage of disease, and histopathological results including morphology, immunohistochemistry, and, more lately, molecular biological investigations [6]. Based on this information, the primary decision on treatment can be made as to whether the disease may be cured (*curative treatment*) or the treatment will be *palliative,* i.e., aiming to prolong life, maintain quality of life, and reduce symptom burden [18]. For solid tumors this is largely dependent on stage of disease. Stage I–II disease generally is regarded as curable. With stage III, which is a locally advanced disease, treatment with curative intent may or may not be possible depending on tumor origin/localization. In stage IV cure is most likely not an option, except for possibly some cases with solitary metastasis or metastasis within one organ only (liver) and possibly patients in advanced stages who are treated with immunotherapy; however, longer follow-up data is needed to reach a conclusion. Curative treatment will often represent intensive treatment with considerable risk of side effects. Thus, for the final treatment decision, the patient's overall health status and relevant patient-related prognostic factors (see pages 19–20) should be considered. If curative treatment is not possible, intolerable, or even life threatening due to co-existing strong, negative prognostic factors, co-existing diseases, or functional impairments, palliative treatment is the option. When planning palliative treatment, it is important to carefully weigh the patient's prognosis, current quality of life, and benefits of treatment against side effects of treatment as well as the patient's goals for care.

Treatment modalities

Regardless of whether the cancer treatment will have a curative or a palliative intent, there are three main treatment modalities, or combinations of these, to be considered: surgery, radiotherapy, and systemic medical treatment.

Surgery is the cornerstone of the curative treatment of solid tumours, the aim being to radically remove the primary tumour tissue with appropriate margins. It has also emerged as having a prominent role in the treatment of metastases for certain cancer types such as liver or lung metastasis in colon cancer. Surgical removal of metastases in such situations has a well-documented life-prolonging impact [7]. Palliative surgery is often indicated to relieve or prevent symptoms, for instance, symptoms caused by urethral, gastrointestinal, or medullary obstructions.

Radiotherapy may be used in both palliative and curative settings and is most commonly administered by an external source of radiation, i.e., external beam radiation therapy (EBRT) [19]. Normally, curative EBRT is given in smaller daily doses (fraction) of 1.8-2 Gray (Gy) five days a week until the planned total dose is reached, which may be up to 78 Gy [20]. In a palliative situation, it is common to deliver hypofractionated treatment with higher daily fractions (3-8Gy) over a shorter time frame and with lower total doses [21]. Indication for palliative radiotherapy is to relieve pain and reduce neurologic symptoms caused by the tumour as well as symptoms of tumour obstruction or bleeding [21]. Side effects of radiotherapy are mostly localized to the target organ or adjacent structures; however, general side effects such as nausea, reduced physical capacity, and fatigue are common.

Stereotactic radiation represents a specific type of EBRT in which the radiation beam is precisely targeted to a smaller tumour volume and given in a few fractions (1–5) with much higher doses (6–24Gy) than in conventional radiotherapy [21].

Systemic treatment

Whereas surgery and radiation therapy represent localised treatment of tumour of origin, metastases, or symptoms, systemic treatment is medication that targets cancer cells irrespective of localisation.

Endocrine therapy is a highly relevant treatment in hormone sensitive cancers, e.g., breast and prostate cancer, due to favourable side effects compared to chemotherapy. Endocrine treatment can be recommended as adjuvant treatment in addition to surgery and/or radiotherapy and/or chemotherapy as well as in a palliative setting. Antioestrogens and aromatase inhibitors are commonly used in breast cancer and androgen-deprivation therapy in prostate cancer. Side effects of treatment include arthralgia, hot flashes, increased risk of thromboembolism, cerebrovascular events, and reduced bone density [22].

Chemotherapy is used in both palliative and curative settings. Most of the drugs favour dividing cells and typically work by direct or indirect damage of DNA or by affecting the cell division process, thus causing cell death. The most common mode of administration is intravenous. Different substances as well as combination regimens are used according to cancer type as recommended in the national treatment guidelines. Common side effects of chemotherapy include hematologic toxicity, nausea/vomiting, cardiotoxicity, and neurotoxicity. However, different chemotherapy regimens have different toxicity profiles [14].

In the last decade**,** introduction of **kinase inhibitors** as well as **monoclonal antibodies** has contributed to improved outcome in several cancer types [23]. These drugs affect specific molecular structures in the tumour cells and thus the tumours' ability to grow and metastasize. Choice of treatment is guided by examining whether the tumour cells produce specific mutated proteins or overexpress certain proteins targeted by the drug. Side effects from treatment are different from chemotherapy and dependent on the drug [6]. For instance, trastuzumab increases the risk of heart failure, and tyrosine kinase inhibitors' potential side effects include diarrhoea, cutaneous side effects, and increased liver enzymes.

Immunotherapy is a treatment that activates the patient's own immune system to kill cancer cells. This fairly new treatment is now being used as standard treatment for several cancer types, e.g., lung cancer and malignant melanoma, and has dramatically improved patient prognosis [24, 25]. Severe side effects of treatment include autoimmune diseases, e.g., colitis, hepatitis and dermatitis. When including patients in our study, immunotherapy was not part of the standard treatment offered.

Combination of modalities is often necessary for treatment with curative intent [14]. Prior to surgery/radiotherapy, *neoadjuvant treatment* may, for instance, be administered to shrink large tumors. After surgery or radiotherapy involving high risk tumors, *adjuvant treatment* is administered to reduce risk of cancer relapse, e.g., postoperative radiotherapy or postoperative adjuvant chemotherapy. Parallel to radiation therapy, *concomitant systemic treatment* can be administered to increase the treatment effect, e.g., chemotherapy in NSCLC patients. For patients with a palliative treatment intent, systemic cancer treatment is the cornerstone. A

combination with surgery or radiotherapy might, however, be indicated to achieve local control or help relieve symptoms.

Predictive and prognostic factors in cancer

A **predictive factor** can be used to select patients who are expected to benefit from a specific treatment [26]. In current guidelines, predictive factors are thus used to guide treatment decisions, e.g., only patients having breast tumours expressing a hormone receptor are treated with endocrine therapy [22], and only patients with mutations in the epidermal growth factor receptor (EGFR), BRAF or anaplastic lymphoma kinase (ALK) are treated with their specific inhibitors [5, 27].

A **prognostic factor** is measured prior to treatment, providing information on patient outcome independent of received treatment [26], and it may be related to either the cancer disease per se or the individual patient's characteristics.

Major prognostic factors related to the cancer itself are type of cancer, stage of disease, and differentiation of tumour cells. Type of cancer significantly affects prognosis, independently of stage. For instance, the five-year relative survival rate for men with localized disease was 91.0% in melanoma of the skin compared with 59.0% for lung cancer (data from 2014–2018) [9]. Advanced stage and poorly differentiated tumours cells with few similarities to the normal organ cells indicate poorer prognosis compared to localized disease and well-differentiated cells, respectively [7, 28, 29]. Prognosis may also be affected by other histopathological and molecular pathological characteristics of the tumor cells such as microsatellite instability (MSI) and the Ki-67 protein [7, 22].

The most important prognostic patient characteristic that is actively used in guidelines and clinical practice is patients' performance status (PS) [7]. PS is a subjective measure of the patient's daily life function and capability of self-care, and it is most commonly assessed by the Karnofsky PS (KPS) [30] or the Eastern Cooperative Oncology Group (ECOG) PS [31] scales. KPS is a scale ranging from 100 (normal, no complaints) to 0 (dead), whereas ECOG PS is a six-point scale worsening from 0 to 5 (Table 5). ECOG PS ≥2 is generally regarded as a poor PS, and poor performance status (PS) is a strong negative prognostic factor [28, 32].

Table 5. ECOG performance status [31]

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Other well-established patient-related negative prognostic factors are weight loss and the presence of active systemic inflammation (measured in terms of inflammatory markers such

as C-reactive protein) [33, 34]. Males generally have poorer prognosis than females [28, 29], and patient-reported perceptions of symptoms, functioning and well-being, e.g., pain, appetite loss, physical functioning, and global quality of life, have also been found to be prognostic [29, 35]. Furthermore, higher age is a negative prognostic factor [29], and problems that are frequent in higher age may also influence prognosis. These issues are further elaborated in the paragraph 'Common specific problems' on page 27.

Outcomes in cancer and cancer research

In all cancer treatment, the main aim is to provide benefits that are relevant for the patients, i.e., improved survival, reduced morbidity, and/or improvement of symptoms or quality of life.

Traditionally, overall survival (OS) has been the gold standard endpoint when testing new cancer treatments [36]. During the last decades, however, and in particular for the evaluation of new drugs, surrogate endpoints such as progression free survival (PFS), time to progression (TTP), and overall response rate (ORR) are increasingly being used [36]. These endpoints are all based on measurements of tumor size and changes.

To evaluate treatment effect on patients' experience of symptoms and quality of life, reports from the patients themselves are needed. Such endpoints are referred to as patient reported outcomes (PRO), and they encompass information retrieved directly from the patient, without being filtered through clinicians or anyone else [37]. PRO measures (PROMs) are developed and used for this purpose. Focusing on person-centred care, the use of PRO and PROMs is increasingly advocated in clinical research as well as in clinical practice [37].

PRO and PROMs cover a range of aspects including quality of life.

Quality of life
The World Health Organization (WHO) defines quality of life as '*an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, physiological state, personal beliefs, social relationships and their relationships to salient features of their environmen*t.' [38]. In clinical practice and research the narrower term 'health-related quality of life' (HRQoL) is used to include aspects of quality of life affected by a disease or its treatment [39]. The shortened QoL is used for HRQoL in this thesis.

Older individuals in the general population report poorer QoL compared to their younger counterparts [40]. Aspects of QoL also vary within the cancer population: a study found that older patients reported poorer functional status and more constipation but better social functioning and less insomnia compared with younger patients [41].

Measurement of QoL
Several instruments have been developed for the assessment of QoL; some are general and may be used independently of patient population characteristics, whereas others are specific to a certain disease or condition. Two commonly used QoL questionnaires have been developed for cancer patients in general, irrespective of cancer diagnosis. These are the Functional Assessment of Cancer Therapy General (FACT-G) and the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ-C30) [42, 43]. None of the questionnaires have been proven to have better psychometric properties than the

others [44]. The FACT-G is mostly used in studies in the US, and the EORTC QLQ-C30 is mostly used in European studies such as the two studies on which this thesis is based.

The content of the EORTC QLQ-C30 reflects the multidimensionality of QoL, hence, the questionnaire includes scales and items covering the global dimension 'global QoL' as well as several specified subdimensions like physical function, and various symptoms [42]. EORTC QLQ-C30 is validated and widely applied in different populations of cancer patients as a method for measuring QoL [44, 45].

Comorbidity and cancer

Definition, prevalence and impact
Comorbidity can be defined as any co-existing ailment other than the disease of interest [46]. Thus, in this thesis, comorbidity refers to any disease or disorder the patient has in addition to cancer.

Comorbidity in cancer patients is common, and the number of comorbidities increases with advancing age [47, 48]. A large cross-sectional study reported that patients between 65 and 84 years had a mean of 2.6 diseases, and those 85 years or older had 3.6 [48]. Data on Medicare beneficiaries in the United States have indicated that about 40% of cancer patients aged > 65 years have at least one comorbidity, and 15% have two or more [49]. However, reported prevalence varies largely across studies, e.g., 14–68% in colorectal cancer patients, 20–35% in breast cancer patients, and 26–81% in lung cancer patients [50]. The prevalence is influenced by the characteristics of the target population as well as the methods used for comorbidity assessment [51]. Besides being related to older age, the prevalence of comorbidity is associated with socioeconomic status and increases with higher levels of deprivation or poverty [51]. Moreover, some types of cancers such as lung cancer are associated with more comorbidities than others [49, 51, 52]. This may be attributed to shared risk factors between type of cancer and the co-existing disorders. Typical examples are smoking being a risk factor for lung cancer as well as for vascular diseases and COPD, as well as the association between hepatitis and hepatocellular carcinomas.

The presence of comorbidities in cancer patients is associated with poorer QoL, increased health care needs [51, 53], and poorer OS, the latter being a consistent finding in a range of studies [49-51]. Although more sparsely documented, comorbidity is also found to adversely affect cancer-specific survival, but results from existing studies are not entirely consistent [50, 51]. The reported impact of comorbidity on cancer patients' survival is, however, variable and seems to depend on several factors including characteristics of the target population, the severity of the comorbid disorders, type and stage of cancer, and which treatments are received [51].

Obviously, comorbidities can represent a competing risk of death. A patient may for instance die from heart failure long before death would be expected if the cancer prognosis is good, whereas the heart condition may be of more minor relevance if the cancer prognosis is poor. In accordance with this, there is evidence that the impact of comorbidity on survival is greater in early stage cancer or cancers with good prognoses than when the prognosis is poor [50, 51, 53]. Comorbidity may also influence choice of treatment and thereby survival. It is well documented that comorbidity is associated with the receipt of less cancer treatment. As summarised by three review papers, patients with comorbidities are less likely to receive curative surgery and adjuvant chemotherapy, and they more often receive chemotherapy with reduced doses or dose delays [50, 51, 54]. There may be good clinical reasons for this. In

some cases, a patient's comorbid condition or disease can be a contraindication for standard cancer therapy. For instance, poor kidney function might exclude patients from having chemotherapy eliminated primarily by the kidneys, and heart disease can exclude patients from potential cardiotoxic treatment that might worsen heart function. Furthermore, patients with comorbidities are in general more vulnerable. In surgery there is an increased risk of morbidity and mortality [50, 51], and a review addressing the tolerance of chemotherapy in patients with comorbidities found a higher incidence of grade III–IV toxicities in these patients [54]. When toxicities occur, the consequences may be more serious. In comparison to patients without severe comorbidities, those who have such conditions may, for instance, be more likely to experience neutropenic fever or death when being neutropenic and to be hospitalised due to chemotherapy-related side effects [53, 55]. Overall, these considerations may result in treatment that is inferior in terms of cancer control, especially in older cancer patients in whom comorbidities are more frequent.

Decisions on withholding or modifying standard treatment regimens for cancer patients with comorbidities are, however, not consistent [56], and they may not always be justified. There is a significant knowledge gap on how comorbidities, cancer, and cancer therapies interact and how outcomes of various cancer therapies for various types and stages of cancer are affected [51]. Patients with comorbid conditions are often excluded from participation in randomised controlled trials (RCTs) [57], and, when included, comorbidity is often not systematically assessed or is assessed by summary measures that provide little information on the impact of individual comorbidities [54]. Consequently, treatment guidelines are often vague, and decisions are left to the individual physician's judgment. Thus, further research is highly needed, and one basic requirement is that assessment of comorbidity among cancer patients is improved.

Assessment of comorbidity.
Several methods for measuring comorbidity have been developed; a review reported 21 different methods had been applied in studies of cancer patients [58]. The most commonly used approaches may be classified as either counts of individual conditions, indices weighting conditions in accordance with their relative impact on key outcomes, and organ- and system-based approaches. The wide range in reported prevalence, as cited in the foregoing chapter, may partly be explained by the variety of methods used for measurement. As the different measures may capture a patient's comorbidity burden in different ways due to differences in construct, content, and complexity [58], the measure being used may also affect study results regarding the impact of comorbidities on survival.

Most comorbidity measures are accomplished by physicians or researchers based on clinical notes or administrative data such as registration of diagnosis according to the International Classification of Diseases (ICD) [58], but patient reports have also been used. An example is the Physical Health Section, a subscale of the Older Americans' Resources and Services Questionnaire (OARS), developed by Fillenbaum et al. and used in studies of older cancer patients by Hurria et al. [59, 60]. The OARS consists of a list of diseases/conditions as well as a grading of how these conditions affect patients' daily activities.

Amongst the most commonly used scales are the Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [61]. The CCI is an example of a weighted index. It consists of 19 categories of conditions and diseases [62]. Each category is registered as being present or not and has a predefined weighting from 1 to 6, based on the adjusted risk of mortality. The sum of all the weights results in a single comorbidity score for the patient. The CCI was developed with hospitalized medical patients and can be scored from

hospital charts or by using the International Classification of Diseases (ICD) codes for diagnoses [63].

CIRS-G is an example of an organ- or system-based approach and was originally developed by Linn et al. [64]. Comorbidities are classified according to 14 organ systems graded on a scale from 0 (no problem) to 4 (extremely severe) (Table 6). Miller et al. modified the CIRS to better reflect the geriatric patient [65], developed a scoring manual [66], and renamed the scale 'CIRS-G'. The CIRS-G manual was later updated according to changes in diagnostic criteria and treatment of common diseases [67].

Table 6:	
Grading CIRS-G in individual organ systems	
"0"	Indicating no problem
"1"	current mild problem or past significant problem
"2"	a moderate disability or morbidity requiring "first-line" therapy
"3"	a severe/constant significant disability or an "uncontrollable" chronic problem
"4"	an extremely severe/immediate treatment required /end organ failure/severe impairment in function
Rating CIRS-G	
Total score = the sum of scores in all organ systems	
Severity index = total score divided on the number of categories with a score >0	
Number of categories with level 3 severity	
Number of categories with level 4 severity	

According to the CIRS-G scoring manual, it is standard procedure to calculate total score, severity index, as well as number of categories with level 3 and level 4 comorbidity (Table 6) [68].

In comparison to the CCI, the CIRS-G is more sensitive since all coexisting diseases are registered [69], and in comparative studies, it appears to provide more prognostic information [70]. Thus, the CIRS-G is considered by many to be the gold standard for measuring comorbidity. It is, however, more time-consuming and less feasible for multicentre studies since assessment by specifically trained personnel is recommended [69]. For the same reasons and despite its advantages, the CIRS-G is also difficult to apply as part of routine clinical practice where, optimally, comorbidity should be systematically rated in all cancer patients. To facilitate an implementation process in busy oncology clinics, brief ratings without the need for a manual or training would be preferred.

Lung cancer: a model disease for comorbidity assessment?

The main risk factor and cause of lung cancer is smoking, which also explains 80–90% of cases [5]. Smoking is also associated with cardiovascular disease and chronic obstructive pulmonary diseases, and comorbidity is particularly prevalent in lung cancer patients [52]. Overall, lung cancer patients also represent an older cancer cohort. Median age at diagnosis is about 71 years. Thus, to study the impact and assessment of comorbidity in this patient population is particularly relevant.

In 2018 3,351 patients were diagnosed with lung cancer in Norway, representing approximately 10% of all new cancer patients in that year [9]. At time of diagnosis, 45%

presented with metastatic disease. Although treatment and survival have improved during the last decade, lung cancer is a highly lethal disease with a five-year relative survival rate of 19% in men and 26% in women [9]. A total of 2,138 patients died of lung cancer in 2017, thus making this the cancer type with the highest mortality rate (Table 2).

The overarching classification of lung cancer is between small cell (SCLC) and non-small-cell lung cancer (NSCLC). The majority of patients have NSCLC, representing 85% of lung cancer patients. As for other solid tumours, NSCLC is staged into I–IV based on the TNM classification. Stages I–II are eligible for curative treatment, which is also the case for some patients in stage III. In cases with the largest tumour size and/or most extensive lymph node involvements (stages III, B–C) [5], however, the patients are offered palliative treatment as are patients with stage IV disease. Most NSCLC patients (≈ 70 %) undergo palliative treatment [5].

First-line palliative treatment in NSCLC has evolved considerably during the last decade. Ten to fifteen years ago, the standard treatment was palliative chemotherapy with a carboplatin-based doublet regimen, regardless of histological subtype. The regimens used included carboplatin plus either vinorelbine, gemcitabine, or pemetrexed [71]. Currently, however, choice of treatment is more complex and guided by morphology (squamous versus non-squamous histology) and further investigation of the tumour cells to detect EGFR mutations, ALK mutations, and cancer cell expression of programmed cell death-L1 (PD-L1). In case of EGFR mutations (≈7.5%), ALK-mutations (2-5%), or ROS1-mutations (1–2% of adenocarcinomas), targeted therapy with specific tyrosine kinase inhibitors is recommended. For patients with non-squamous histology without these mutations as well as for patients with squamous histology with PD-L1 expression >50%, immunotherapy is the first-line treatment of choice. For patients with non-squamous histology without any of these molecular markers present, chemotherapy still is the standard first-line treatment option [5]. As a result of introducing targeted therapy and immunotherapy these last few years, the treatment for NSCLC patients has changed considerably, and this new therapy represents a dramatic improvement in the prognosis for advanced NSCLC patients [24, 72].

The older cancer patient

Age is the most important single risk factor for cancer, as reflected by a steep increase in cancer incidence with increasing age (Figure 1, page 15) [9]. Because of an aging population as well as increasing cancer incidence, the number of older cancer patients is predicted to rapidly increase [73]. In Norway, the number of cancer patients ≥65 years more than doubled from 1975 to 2009, and those ≥80 years had a threefold increase from approximately 2,100 to 6,600 patients [74]. According to future estimations, it is expected that by the year 2040 almost 16,000 patients ≥80 years will be diagnosed with cancer annually [74].

Due to their increasing number, but also for several other reasons, older cancer patients represent a challenge for our health care systems as well as for the individual treating oncologist. First, they are a heterogenous group in terms of health status. This implies a considerable variation in life expectancy within the same age group (Figure 2), which should be considered when cancer treatment is selected [75]. For instance, if a 75-year-old woman belongs to the fittest 25th percentile of the population, she is expected to live another 17 years, whereas if she belongs to the 25th percentile with the poorest health status, her life expectancy may come down to 6.8 years. In any case, most cancer diseases, if poorly controlled, are likely to shorten life spans, making survival an outcome just as important among older cancer patients as among those who are younger.

Figure 2. Upper, Middle and Lower Quartiles of Life Expectancy for Women and Men at Selected Ages.
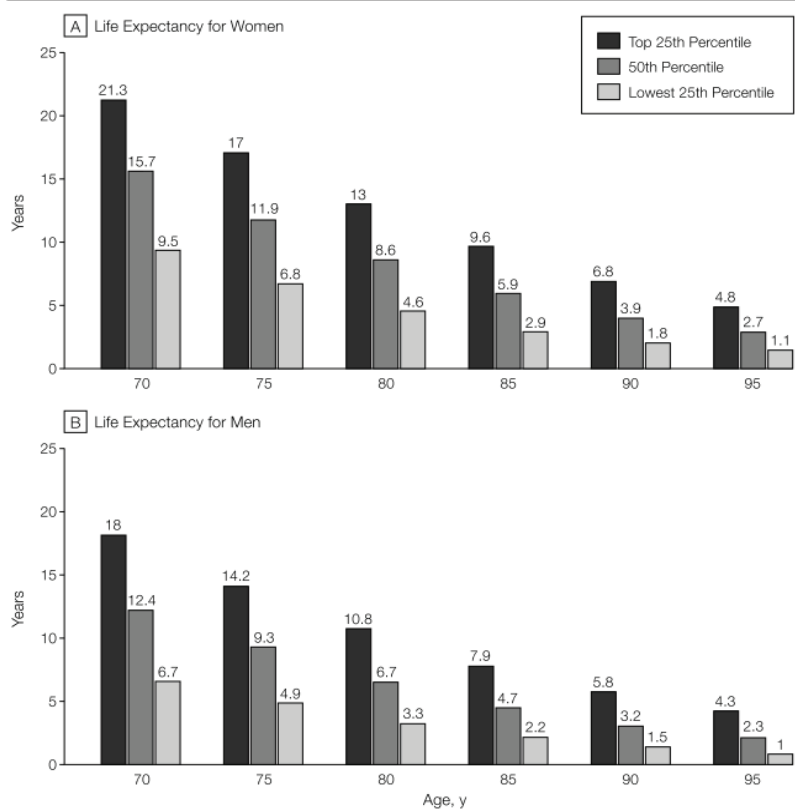
Data from the Life Tables of the United States.[9]

Differences in health status are also highly relevant in relation to treatment tolerance. In general, older patients are regarded as more vulnerable than their younger counterparts, with increased risk of chemotoxicity, side effects of radiation therapy, and increased morbidity and mortality after cancer surgery [76-78]. However, selected subgroups of fit older patients are known to tolerate and benefit from standard treatment equally to younger patients [79], whereas a large group will have increased risk of treatment complications [80]. Chronological age alone does not capture this heterogeneity.

Second, treatment preferences in older patients might differ from those of their younger counterparts. According to a systematic review, a range of factors can influence older patients' decisions about accepting or declining cancer treatment, amongst them risk of side effects from treatment and current quality of life [81]. Older patients may be less willing to exchange current QoL for smaller survival benefits [82]. It is thus crucial to ensure that the side effects of treatment, which might severely affect QoL do not exceed the potential treatment benefits, especially when planning palliative treatment, and to include the patient in the decision-making process. Knowledge about how treatment affects patients' QoL is thus highly relevant. Additionally, ability to maintain independent living is highly prioritized, and older patients have been found to prefer dying over severe impairment and dependence [83, 84]. As independence and physical function are closely interconnected, physical function is an additional outcome of cancer treatment that is highly important.

Thirdly, and probably most importantly, a proper knowledge base on how to treat older cancer patients is lacking [85]. Older patients are consistently underrepresented in clinical trials due to strict inclusion criteria [86], and co-existing health problems have seldom been systematically assessed and reported [61]. Thus, information about treatment effect is mostly based on younger patients and a group of highly selected older cancer patients. Furthermore, outcomes of particular relevance to older people, such as QoL and physical function, have received little attention [87]. Consequently, translation of research results into a benefit for the everyday older cancer patient is challenging, and as guidelines rarely address how to handle patients with health problems that are frequent in older age [88], choice of treatment is subjected to the judgement of individual physicians, and thereby risks of both under and overtreatment exist.

Undertreatment is reported in several studies [89-92] and may also be reflected by an increased difference in survival between older and younger patients [93, 94]. The largest difference in survival is found within the first year after cancer treatment, indicating inferior treatment. The potential risk of overtreatment has received less attention. It is, however, documented for older patients with localized prostate cancer [95], and, obviously, if results from a younger, healthier population are transferred to older patients with poorer health, there is a risk that the adverse effects may be larger than the benefits.

In summary, health status of older cancer patients varies substantially; their preferences may differ from younger patients, and there is a lack of knowledge on how to select the appropriate treatment for each patient. For treatment decisions in older patients, aging as well as common health problems related to aging have to be considered as all these may affect the cancer trajectory as well as tolerance for cancer treatment.

Aging - general aspects

The process of aging is complex, and it is yet to be sufficiently explained. The dominating theory, however, explains aging as a consequence of gradual accumulation of cellular damage during life.

Figure 3. Damage and aging "Reprinted from Cell, Vol 120 /4, Kirkwood, Understanding the odd science of aging, 437-447, Copyright (2020), with permission from Elsevier [96]
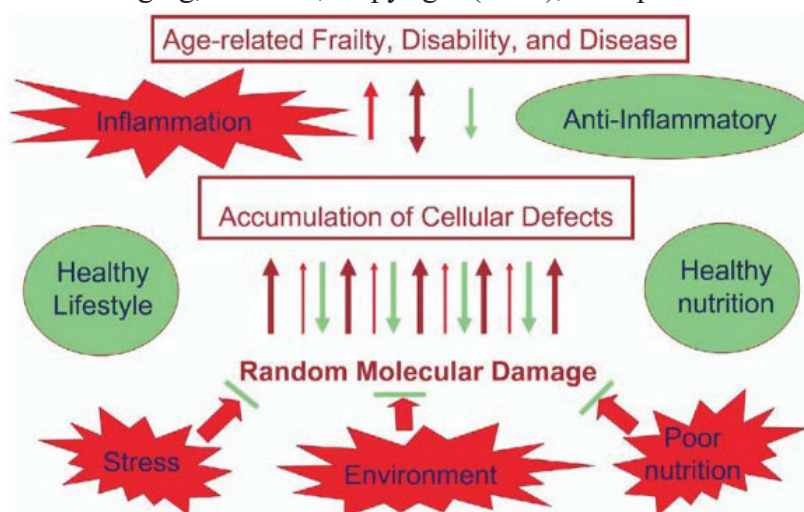
As visualized in Figure 3, we accumulate molecular damage throughout life [96]. A constant threat of different forms of stressors affects the rate at which this molecular damage occurs.

Genetic factors mostly affect our ability for maintenance and repair, and environmental factors can either increase or decrease this rate of molecular damage. In Figure 3 red colors represent environmental stressors that increase the rate of molecular damage, green colors factors that could counter this accumulation of molecular damage. In the long run, age-related frailty and disability occur when active maintenance fails.

The cellular damage accumulating in an organ over time leads to a reduction in physiological and functional reserves, affecting vital systems, i.e., the immune, endocrine, cardiovascular and respiratory systems, as well as skeletal muscle, kidney, and brain [1]. For instance, increased stiffness of the heart muscle as well as fibrosis of the conduction system increase the risk of developing heart failure. In the lungs decline of elastic recoil as well as stiffening of the chest wall lead to reduction in vital capacity, and mucus clearance is less efficient due to poorer mucociliary function, increasing the risk of lung infections [97]. This reduction in physiological and functional reserves leads to increased vulnerability for stressors like cancer and cancer treatment. Furthermore, body composition changes with age: muscle mass and strength diminish (sarcopenia), and the ratio of body fat increases [98]. Because of these changes, older patients have increased risk of adverse effects due to alterations in the pharmacodynamics and pharmacokinetics of drugs, and sarcopenia is associated with increased risk of chemotoxicity and poorer survival [99]. Still, the rate of the aging process is highly individual. Patients of the same chronological age therefore present with marked differences in health status and reserves.

The terms 'biological age' and 'functional age' have been introduced to indicate a patient's health status and reserve capacity. A biologically or functionally old patient has more deficits and less reserve capacity compared to the average person of the same chronological age [100]. To be able to estimate a patient's biological age, there is a general need for assessing vulnerabilities and reserves in a systematic manner.

Common specific problems

Comorbidity
Comorbidity becomes more common with increasing age and may significantly affect cancer treatment and outcomes as already elaborated (see Comorbidity and cancer, pages 21–22)

Polypharmacy
The term 'polypharmacy' covers the use of multiple concurrent medications, but a range of definitions has been used [101]. The most frequent is to count the number of regular medications. Five or more medications is a commonly applied cut-off point [101, 102], which also indicates a need for reviewing patients' medical charts [103].

Since the number of chronic diseases increases with age, older people regularly use a correspondingly high number of medications. In 2017 92% of Norwegian home-dwelling persons ≥65 years had at least one prescription drug; 58% of drug users ≥65 years used >5 drugs [104]. Polypharmacy is also common in cancer patients. Reported frequencies range from 26 to 68% using a cut-off of five or more medications [105-108]. The large difference between studies is probably caused by differences in study populations with respect to treatment, stage, and location of assessment (inpatient/outpatient).

Although several regular medications may be needed to control a patient's symptoms and chronic conditions, polypharmacy may lead to poor compliance and adherence as well as

increased risk of drug-to-drug interactions and adverse events, and this is associated with increased morbidity and mortality [109, 110]. In cancer patients, polypharmacy is reported to increase the risk of postoperative complications, frailty, and chemotoxicity [102].

Impaired physical function
'Physical function' is a broad term that encompasses body structures and function as well as activities and participation [111]. The term is, however, inconsistently used and defined [112], and it may refer to mobility, strength, and endurance in the performance of simple tasks such as walking and sit-to-stand as well as the ability to perform more complex daily life activities, usually referred to as 'functional status'. The latter includes *basic* activities of daily living (ADL) that are required for self-maintenance, i.e., eating, dressing, going to the toilet and maintaining personal hygiene as well as more advanced *instrumental* activities of daily living (IADL), i.e., paying bills, doing laundry, grocery shopping, cooking, and taking medications. A patient's ability to perform ADL and IADL are closely related to strength and mobility [113].

As the aging process is highly individualized, the reduction in strength, endurance and mobility varies considerably among older individuals. In general, however, the reduction increases with advancing age. Chronic conditions or disorders may further contribute to this deterioration. Thus, impairment in functional status is common in older adults. A large American study of community-dwelling adults ≥65 years reported one in four having disability in either ADL or IADL [114]. In another study 17% of those aged 65–69 reported ADL/IADL disability, but this increased to half of those ≥85 years. For older patients with cancer, studies report varying prevalence of impairment in functional status: in surgical colorectal cancer patients, 15% of patients had ADL dependence and 17% IADL dependency, while in patients with various types of cancer scheduled for first-line chemotherapy, 32% had abnormal ADL scores and 73% abnormal IADL scores [106, 115].

Impairments in physical function and the association to adverse health outcomes and poorer survival in older adults is a consistent finding across studies and settings [116-119]. In cancer patients impairment in physical function measured using objective mobility tests is a significant predictor of poorer survival and may also predict physical decline and treatment complications [120]. IADL impairment in older patients has been reported as predictive for survival, chemotherapy toxicity, complications after cancer surgery [35, 106, 121, 122], and PS, which is the traditional measure of functional status and general health in oncology and is established as an important prognostic factor in cancer patients in general (see 'Predictive and prognostic factors in cancer', pages 19-20). Finally, impairment in functional status may also negatively and profoundly affect QoL [123].

Overall, impairment in physical function has a major impact on the older cancer patients' disease trajectories. Thus, assessment of physical function is of substantial importance for several reasons: for evaluation of the older patients' vulnerability, for prognostication, for treatment decisions, and to evaluate outcomes of cancer treatment.

Geriatric syndromes
'Geriatric syndrome' is a term used for common clinical conditions in older patients with a multifactorial aetiology that typically involves more than one organ system. Examples of conditions commonly included under geriatric syndromes are malnutrition, falls, dementia, and depression.

Malnutrition

Malnutrition is a state caused by reduced intake or uptake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass [124] and is considered a geriatric syndrome with several contributing factors [125]. Being at nutritional risk or malnourished are common in old age and in patients with chronic conditions like cancer. The prevalence of malnutrition depends on the population investigated. Hospitalized patients have a much higher prevalence than home-dwelling elderly [126]. In a recent publication addressing Norwegian hospitalized patients, 40% of patients 80 years or older were at nutritional risk, as were 44% of cancer patients of all ages. Among cancer patients 80 years or older, more than half were at nutritional risk [127]. The prevalence of malnutrition in cancer patients varies according to stage of cancer as well as tumor type. A study of 1,952 treatment-naive cancer patients of all ages reported 40% of patients with non-metastatic and 62% of patients with metastatic disease to be malnourished or at risk for malnutrition, and patients with gastroesophageal, pancreas, and lung cancer had an especially high risk [128].

In cancer patients, side effects from treatment, e.g., nausea, stomatitis, and obstipation, can worsen malnutrition. Experiencing weight loss is a poor prognostic factors for survival in a range of studies, and weight loss is inversely correlated with quality of life [99, 129]. Being malnourished increases the length of hospitalizations and is associated with increased mortality and a lower completion rate of chemotherapy [105, 106, 130, 131]. Despite the importance of assessment of nutritional status in older cancer patients, recent reviews have shown that it was only included in 24% and 55% of studies [132, 133].

Falls

Falls are common in the geriatric population: one or more falls during the past year were reported in 19–44% of persons ≥65 years in systematic reviews [134]. In cancer patients, the reported frequency of falls varies, as does the time frame for which falls have been reported [135]. However, according to a systematic review, most studies have reported an incidence of 20–30% in cancer outpatients within the last 3 to 12 months [135].

The multifactorial etiology of falls can make it difficult to determine which factors led to the patient falling. Common risk factors are weakness, balance and gait disorders, poor eyesight and cognitive impairment, which are all common with old age [136]. The severity of falls can be increased by coexisting disorders. For instance, patients with osteoporosis who fall have an increased fracture risk, and patients with conditions requiring anticoagulants have a higher risk of bleeding. Overall, falls are an indication of increased vulnerability, and they are generally associated with increased morbidity and mortality [137].

Hurria et al. developed a predictive model of severe chemotherapy toxicity for cancer patients and found that falls during the past six months was a predictive factor [121]. Furthermore, side effects of cancer treatment can increase the patient's risk of falls. Such side effects may be general such as fatigue and physical decline that may influence balance and strength. More specific side effects of cancer treatment may also increase the risk of falls. For instance, patients with symptoms of chemotherapy-induced peripheral neuropathy were found to be 2.5 times more likely to fall/nearly fall in a prospective study [138], and neurotoxic chemotherapy was associated with fall-related incidents (mainly fractures) in a retrospective study [139]. Knowledge about falls in older cancer patients prior to treatment is therefore important both for treatment planning and to initiate interventions to prevent future falls. Special attention to patients receiving neurotoxic chemotherapy may be indicated.

Cognitive impairments

With normal aging a gradual decline in certain cognitive abilities is usual; however, these age-related changes are subtle and do not impact functioning [140]. Some comorbidities, e.g., previous cerebral infarcts or haemorrhages, can affect a patient's cognitive function. Furthermore, mild cognitive impairment (MCI) and dementia both become more frequent with age [141, 142]. MCI is defined as objectively reduced cognitive function not severe enough to affect a patient's ability to perform daily activities [141]. Dementia is a syndrome caused by a variety of brain disorders, defined by a decline in memory and at least one other cognitive function which interferes with daily life activities and preserved awareness and precipitates changed social behaviour or a decline in emotional control or motivation [143]. Dementia is divided into different subtypes, and patients' levels of functioning depends on the severity of disease, ranging from mild to severe. Patients might have symptoms years before being diagnosed; cognitive decline is suggested to start from 3–7 years before MCI diagnosis and from 1–11 years before dementia diagnosis [144].

MCI is reported in 10–20% of patients at 65 years of age [141]. The prevalence of dementia increases with increasing age; estimated prevalence is 4.3% among 70-year-old persons and 43.1% in 90-year-old persons [142]. In cancer patients, the reported prevalence of cognitive dysfunction varies considerably, from 6% to 42% using the Mini Mental State Examination [145]. The heterogeneity in study populations with respect to diagnosis, stage, as well as age groups, however, makes direct comparisons between trials challenging.

Having MCI or dementia may affect a patient's understanding and ability to adhere to a medicine regimen, and as dementia progresses, the risk of non-adherence or hospitalization due to errors in medication use increase [146]. Patients with a dementia diagnosis have increased risk of several negative health outcomes, amongst them being hospitalized [147]. Furthermore, when patients are hospitalized, having a dementia diagnosis increases the complication rates, e.g., of having delirium and infection [148]. In cancer patients a dementia diagnosis is reported to delay the diagnosis of cancer, and in a surgical cancer cohort those having cognitive impairment had up to a six times higher hazard ratio for dying during the first two years of follow-up [149, 150]. Furthermore, in the course of cancer treatment, subgroups of patients experience cognitive decline [151, 152]. Knowledge of patients' cognitive function is thus highly relevant for oncologists when planning treatment.

Depression

Depression in cancer patients is common: prevalences from 5.6–13.1% have been reported in patients with solid tumors; lung cancer patients had the highest prevalence [153]. In older cancer patients, depressive symptoms were reported ranging from 10 to 65% [145] and from 13 to 61% [154] according to two systematic reviews of geriatric assessment. Older cancer patients are less likely to receive treatment for depression compared with their younger counterparts [153]. Depression is associated with increased mortality risk in non-cancer populations [155]. In cancer patients, being depressed has been associated with poorer quality of life, more self-reported pain [156], increased toxicity of treatment, as well as increased mortality [157]. Having depression might also impact a patient's motivation for undergoing cancer treatment [158]. Identifying previously unknown depression is thus highly relevant for optimizing treatment in older cancer patients.

Summary

Many specific problems affect older patients' tolerance for cancer treatment. However, the largest impact on treatment tolerance may be patients' overall burden of problems as well as

the systematic assessment of a patient's overall level of functioning and whether he or she is fit or frail.

Frailty

Frailty is widely recognized as a syndrome of increased vulnerability to adverse changes in health status [1]. The consensus definition for the term 'physical frailty' is 'A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death' [2]. Frailty is separate from having multiple comorbidities, although having comorbidity can contribute to a patient's frailty level [159]. Although higher age is associated with a higher prevalence of frailty, being old is not equivalent to being frail, and some older individuals remain robust even in advanced age. Furthermore, when patients are frail, it is not necessarily obvious from their physical appearance.

As mentioned earlier (Aging - general aspects, pages 26-27), aging is thought to result from accumulation of cellular damage. It is questioned whether a threshold of cellular damage exists in organ systems beyond which frailty becomes evident [1]. However, frailty is a multidimensional concept, and the condition develops due to age-related impairments in multiple physiological systems [160]. The four best-studied organ systems in the development of frailty are skeletal muscle, the endocrine system, the immune system and the brain, although abnormal function of several other system has been associated with frailty [1]. Loss of skeletal muscle mass, changes in hormone production (reduced insulin-like growth hormone, estradiol and testosterone; increased release of cortisol), abnormal low-grade inflammatory response of the immune system, and structural and physiological changes in brain cells are all components in the process of frailty.

Figure 4. "Vulnerability of frail elderly people to a sudden-change in health status after a minor illness"
"Reprinted from The Lancet, 381, Clegg A et al, Frailty in elderly people, 752-762, Copyright (2020), with permission from Elsevier."
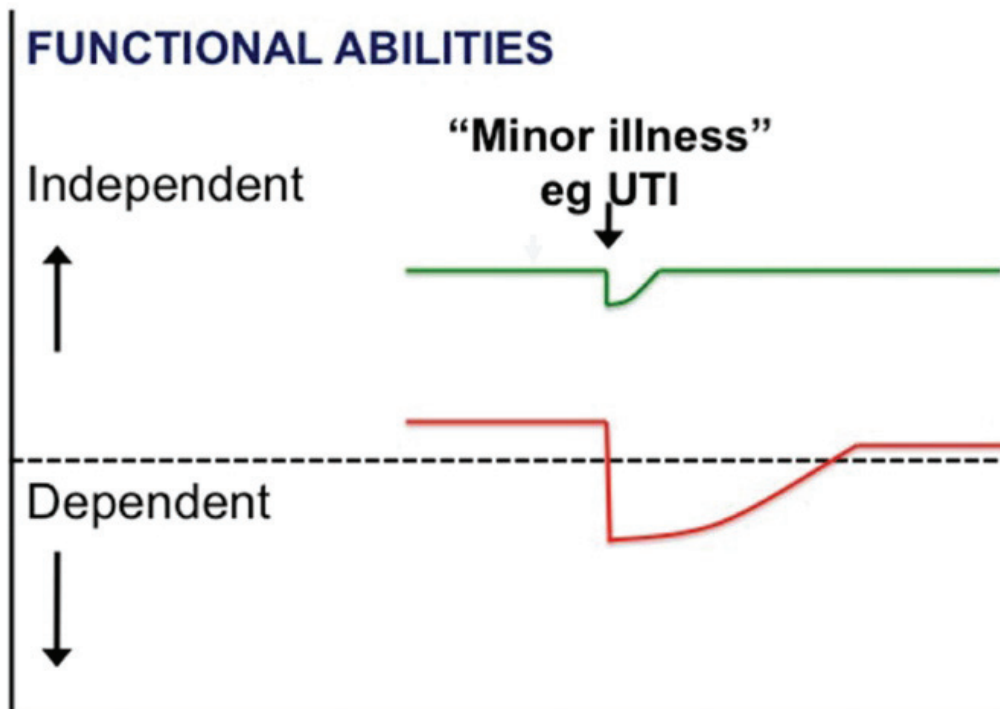
In clinical practice, as illustrated in Figure 4, when a fit older person (green line) is exposed to a minor stressor, a small reduction in function occurs before the individual again returns to homeostasis. A frail individual (red line in Figure 4) exposed to the same stressor experiences a larger reduction and may become dependent. Furthermore, the frail individual is unable to reach baseline homeostasis and after experiencing the stressor is closer to the limit between being dependent and independent (dashed line).

The prevalence of frailty in community-dwelling older (≥65 years) persons has been reported to vary considerably, from 4 to 59% according to a systematic review [161]. Differing criteria for being defined as frail is probably one explanation for this wide range in prevalence. The prevalence of frailty increases with advancing age and is estimated to be present in one in four of persons >85 years [1]. In older cancer patients, a systematic review reported a median prevalence of 42% (range 6–86%) [80]. Being frail increases the risk of negative outcomes. Frail patients have a higher risk of falls and fractures, and frailty increases the likelihood of developing deficiencies in daily activities, hospitalization and death [162, 163].

There is not general agreement on how to assess frailty and a systematic review reported the use of 20 different frailty instruments in the identified studies [164]. Most methods are, however, based on two models for frailty: the physical frailty phenotype model and the cumulative deficit model. *The physical frailty phenotype* was developed by Fried et. al based on community-dwelling participants ≥65 years included in the Cardiovascular Health study [165]. It included five components: unintentional weight loss, exhaustion, low physical activity, slow gait speed, and weak grip strength. Frail participants had three or more of these components; pre-frail had one to two, and robust participants had none [165]. Being frail according to the phenotype model is predictive of worsening mobility, hospitalization and

death. *The cumulative deficit model and the frailty index* were developed by Rockwood and colleagues based on data from the Canadian Study of Health and Aging [166]. This frailty model considers the aging process as an accumulation of deficits (symptoms, signs, abnormal lab results), and the more deficits accumulated, the frailer the patient [167].

In clinical practice, the comprehensive geriatric assessment (CGA) is the preferred approach to assessing frailty. By using the CGA to assess frailty, multiple geriatric domains are taken into consideration and thus the principle is similar to the abovementioned cumulative deficit frailty model.

Comprehensive geriatric assessment

The comprehensive geriatric assessment (CGA) is defined as 'a multidimensional, interdisciplinary, diagnostic process to identify care needs, plan care, and improve outcomes in frail older people' [168]. The CGA is a cornerstone in diagnostic work and treatment in geriatric medicine [169]. It is a systematic assessment of areas where deficits are common in older patients, often divided into four categories: physical health, functional status, psychological health, and socio-environmental parameters (Figure 5) [168].

Figure 5. The four domains of the comprehensive geriatric assessment
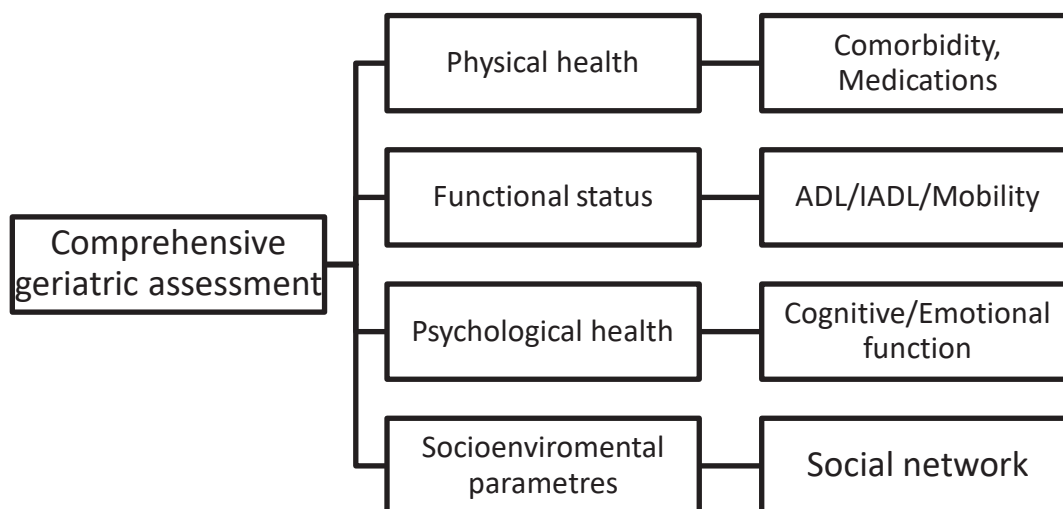
By systematically uncovering patients' vulnerabilities, specific interventions can be planned to improve patient outcomes. Performing CGAs on geriatric patients has been shown to improve several health outcomes: mortality, risk of institutionalization, as well as functional status and cognitive function [170-172]. The setting in which the CGA is performed can, however, modify its effectiveness: CGA performed on inpatients in geriatric units as well as home CGA programs have consistently shown positive effects in several health outcomes, while results are more conflicting in the outpatient settings [170]. How to choose which patients will undergo CGA has also varied in published papers as no universal selection process for administering the CGA exists.

Geriatric assessment in geriatric oncology and research

During the last decades, a modified approach to the CGA has been adapted to oncology and is recommended by the International Society of Geriatric Oncology (SIOG) [173, 174]. The term geriatric assessment (GA) has commonly been used in geriatric oncology publications, referring to an assessment without intervention [174]. Previous publications regarding GA in cancer patients have included a different number of geriatric domains; some domains that are commonly included are summarized in Table 7. Some have suggested that the term GA should be avoided and suggested the term 'geriatric screening' for less comprehensive assessments than CGA; however, others disagree and argue for keeping the term [169, 175].

Assessment tools

The GA includes well-known and validated scales adopted from general geriatrics to assess each domain. A range of different scales has been used for each domain. Table 7 includes some examples of commonly used scales.

Table 7: GA domains and examples of assessment methods		
Domain	Assessment tool	Short form
Comorbidity	Cumulative Illness Rating Scale for Geriatrics	CIRS-G
	Charlson Comorbidity Index	CCI
Polypharmacy	Number of medications	
Physical function and functional status	Performance Status	PS
	Katz index of independence in Activities of Daily Living	ADL
	The Lawton Instrumental Activities of Daily Living Scale	IADL
	Gait speed	
	Short Physical Performance Battery	SPPB
	Timed up and Go test	TUG
Nutritional status	Mini Nutritional Assessment	MNA
	The Patient-Generated Subjective Global Assessment	PG-SGA
Falls	Number of falls within last 3-12 months	
Cognitive function	Mini Mental State Examination	MMSE
	The Montreal Cognitive Assessment	MoCA
Emotional function	Geriatric Depression Scale	GDS

Comorbidity
Common comorbidity scales are described on pages 22–23.

Physical function and functional status

Two commonly used scales for measuring ADL and IADL are the six-item *Katz index (ADL)* and the eight-item *Lawton (IADL)* [176, 177]. These scales are filled out by health care professionals based on interviews and observation. In oncology the traditional measure of functional status is performance status; however, this is a less sensitive measure compared with IADL in older patients [178]. Objective measures of mobility are gait speed, *the Short Physical Performance Battery (SPPB)*, and the *Timed up and Go test (TUG)* [120, 179, 180]. Gait speed is calculated after timing a specific walking distance. SPPB includes repeated chair stands, timing of a short walking distance, and balance tests. TUG registers the time it takes to rise from an arm chair, walk three metres, turn, walk back and sit down, and it has been reported to be a sensitive and specific measure of frailty [181].

Nutritional status

Two frequently used scales for assessing nutritional status in geriatrics are the *Mini Nutritional Assessment* (MNA) and the *Patient-Generated Subjective Global Assessment* (PG-SGA) [182, 183]. The original MNA was developed for assessing nutritional status in older individuals and included 18 items with a maximum score of 30; scores <24 indicate risk for malnutrition and scores <17 indicate malnutrition. Later, a MNA short-form was developed (MNA-SF) consisting of six graded questions covering weight loss, appetite loss, severe depression, dementia and mobility [184]. The PG-SGA consists of two parts: a patient questionnaire about weight loss and nutritional symptoms, and a questionnaire filled in by health professionals including information about metabolic stress, physical assessment and a categorization of the patient's overall nutritional status into a) well-nourished, b) moderately malnourished, and c) severely malnourished. Severely malnourished patients are defined as having severe weight loss and visible loss of subcutaneous fat tissue and muscle mass, with or without the presence of oedema.

Cognitive impairment

The *Mini Mental State Examination (MMSE)* is the most frequently used screening test for cognitive impairment in geriatric oncology [132, 174, 185]. The MMSE consist of 20 questions testing orientation, attention, recall, language, calculation, and visuospatial function; the maximum score is 30. A revised Norwegian version of the MMSE with a manual has been developed [186]. Some studies have used an MMSE score <24 as a threshold indicating the need for further diagnostic testing; however, the MMSE score depends on a person's age and level of education. A disadvantage of the MMSE scale is poor sensitivity for detecting mild cognitive impairment. The Montreal Cognitive Assessment (MoCA) might be better for differentiating between normal cognition and mild cognitive impairment as it includes more cognitive domains [187].

Emotional function

The Geriatric Depression Scale (GDS) is frequently used to screen for depression in geriatric oncology research [188]. The GDS was developed specifically for the geriatric population and does not include questions about somatic symptoms. The original GDS includes 30 items with a total score of 30; the higher the score, the more depressive symptoms exist. Several short forms of the GDS have been developed, amongst them a 15-item version, GDS-15.

Consensus on assessment tools

In 2015, approximately half-way through our study, experts in the geriatric oncology field reached consensus on a first choice of assessment for older cancer patients [189]. CCI for

comorbidity and a combination of ADL and IADL were preferred to assess functional status, TUG for physical performance, MNA short form for nutrition, MMSE for cognitive function, GDS short form for depressive symptoms, and patient history for assessing social support status and anxiety.

GA to identify frailty

GA has been extensively recommended for identifying frailty. Due to a lack of consensus in defining GA frailty in cancer patients, studies have included both different domains and thresholds to categorize frailty [80]. Comparing the results of existing studies is therefore challenging. A well-known frailty classification is the Balducci criteria, which categorizes patients as fit, intermediate, or frail based on GA results [190]. This categorization was suggested to be used to guide treatment intensity. Table 8 present the criteria for being categorized as frail according to the Balducci criteria. Although age is included as a frailty criteria, this may be considered merely a red flag and not an absolute criteria [191]. Balducci based his categorization on the more inclusive Winograd criteria from 1991, which also incorporates polypharmacy, sensory impairment, and malnutrition [192]. Several geriatric oncology studies have published results using the Balducci criteria or a modification of these to categorize frailty [193-196].

Table 8: Frailty according to the Balducci criteria (one or more)	
Age	≥ 85 years
Comorbidity	≥ 3
Activities of daily living	≥ 1dependency
Geriatric syndrome	≥ 1

Several frailty screening methods have also been developed; however, none of them have sufficient sensitivity or specificity to reliably identify all frail patients compared with GA [197].

Knowledge base 2012 on GA and on frailty in cancer patients

Although some papers about older patients chemotherapy tolerance were published in the eighties [198, 199], most geriatric oncology papers have been published from the mid-nineties, and SIOG was first founded in 2000 [200]. The geriatric oncology field was thus still young when one of the studies this thesis is based upon started inclusion in January 2013, and there have been a large number of publications in this area over the last six years. In the following subsections, the knowledge available by the end of December 2012 is presented.

Benefits of performing GA

Two well-known systematic reviews by Hamaker et al. (including 37 studies) and Puts et al. (including 73 studies) were published in 2012, summarizing the knowledge of GA in geriatric oncology patients up until then [132, 133]. Several studies concluded that performing a GA in cancer patients was feasible, and some but not all publications indicated that performing GA prior to start of treatment could have an effect on treatment decisions [133]. All the geriatric domains were associated with increased mortality in at least one study; IADL and comorbidity were the two domains most consistently associated to this outcome [132].

Deficits in either cognitive function, ADL, or comorbidity were reported to increase the risk of not completing chemotherapy and the need for dose-reduction, and IADL impairments were most consistently associated with perioperative complications after surgery [132]. Findings regarding which geriatric domain affected the risk of chemotoxicity varied [132].

Thus, existing knowledge suggested elements of the GA to be both prognostic and predictive in older cancer patients. However, the abovementioned reviews reported poor to moderate quality of included studies; heterogeneous patient cohorts with respect to cancer type, stage, and treatment; and small sample sizes (a considerable number of studies included fewer than 100 patients). To reach a conclusion on the potential benefits of using GA in older cancer patients, there was a clear need for larger studies of better quality and with longitudinal design.

The impact of frailty

Different definitions of frailty have been used in studies investigating the impact of frailty in cancer patients. Some studies indicated that being frail according to the Fried physical frailty phenotype increased the risk of postoperative complications [201, 202]. Another study could not, however, replicate these findings, but reported CGA frailty to predict postoperative complications [203]. The predictive ability of individual frailty markers was investigated in a few studies: low grip strength predicted toxicity of treatment [204], and cognitive impairment predicted visits to the emergency department [205].

Frailty and survival

The existing research in 2012 suggested that being frail was prognostic for survival. A study including surgical colorectal cancer patients reported being frail according to both the Fried physical frailty phenotype and the CGA to be independent prognostic factors for survival [203]. Another study found poorer five and ten year survival rates in breast cancer patients with ≥3 deficits according to a GA: however, this study did not actually define frailty [206]. There were also indications that some frailty screening tools were prognostic for survival, e.g., the Groningen Frailty Index [207].

Three published studies of patients in a medical oncology setting used the Balducci criteria or a modification of these to categorize frailty and investigated the prognostic effect of being frail [194, 195, 208] (Table 9).

Table 9: Categorizations based on the Balducci frailty categorization

Bamias et al [208].	Basso et al [194].	Tucci et al [195].
Group 1: No comorbidity (CCI), no ADL or IADL deficits	Fit: No relevant comorbidities (CIRS-G), no ADL or IADL, no geriatric syndromes	Fit: <3 grade 3 or no grade 4 comorbidities (CIRS-G), full score of ADL (6), no geriatric syndromes <80
Group 2: ≤2 comorbidities or IADL deficits	Vulnerable: Manageable, non-life-threatening comorbidities, IADL deficiencies, no geriatric syndromes	Unfit: All other patients
Group 3: Either ≥ 3 comorbidities (CCI) or ≥1 ADL deficiencies	Frail: ≥3 grade 3 or 1 grade 4 comorbidity (CIRS-G), ≥1 ADL deficiencies≥ 85 years, geriatric syndromes	

In the prospective single-center study by Bamias et al., the safety and efficacy of gemcitabine and carboplatin for advanced urothelial carcinoma in patients ≥70 years were investigated. Patients were categorized into three groups. Frail patients (19%) had significantly poorer median progression-free survival compared with the other two groups (1.9 months and 6.9 months, respectively), although the analyses were exploratory due to the small sample size (n=34) [208].

Basso and colleagues retrospectively categorized frailty in 117 cancer patients ≥ 70 years with various tumor types and stages being treated with chemotherapy. The included patients were all inpatients at a single hospital. Frail patients (34%) had significantly poorer survival compared to non-frail (fit and vulnerable) patients (6.4 months versus 16.9 months). Analyses were not adjusted for cancer type or treatment [194].

Tucci et al included 84 patients >65 years with diffuse large cell lymphoma at a single institution who were scheduled for either aggressive or palliative chemotherapy. Patients were categorized as fit or unfit. In unadjusted analyses, the 50% of patients classified as unfit had poorer two-year OS compared with fit patients (23.8% and 77.6%, respectively).

In summary, there were indications that frailty according to the Balducci definition was prognostic for survival in older patients treated with medical cancer treatment. However, none of the abovementioned studies performed adjusted analyses, probably due to the small sample sizes, and larger studies verifying these indications are needed.

Frailty, quality of life and physical function

In 2012 longitudinal studies of QoL and the association to frailty in cancer patients receiving systemic treatment in a medical oncology setting were lacking. To the best of our knowledge, only one study assessed baseline QoL according to frailty status; this single-center study included 65 patients 65 years or older with various cancer types and stages, and frail patients were reported to have significantly worse global QoL [209]. However, some publications reported on the association between individual geriatric domains and QoL. Wedding and colleagues found baseline global QoL to be significantly associated with IADL, comorbidity, and PS in older cancer patients [210], and another publication reported that depressive symptoms were associated with worse QoL prior to chemotherapy [156]. A longitudinal study of 112 patients with various cancer types and stages found no associations between global QoL decline and having comorbidity, mood disorders, or low functional status [211]. Thus, little was yet published relating to frailty and QoL, but there were indications that QoL was negatively affected by vulnerabilities detected in geriatric assessments.

Longitudinal studies measuring physical function according to frailty status in older cancer patients were also lacking in 2012. Some studies investigated physical function in cancer patients without considering frailty status. A small (n=49) prospective study of older breast cancer patients given adjuvant chemotherapy reported no significant changes in IADL/ADL or QoL as measured using FACT [212]. Another study including patients with several cancer types and treatments reported that a high symptom burden was significantly associated with loss of physical functioning during follow-up, and patients with higher comorbidity burden and higher age had poorer physical functioning [213, 214].

Thus, little evidence existed in 2012 as to whether frailty affects physical functioning in older cancer patients. Still, since frailty was a predictor of disability and worsening mobility in non-cancer populations [165], studies investigating frailty and its potential impact on cancer patients are needed.

Clinical judgment versus systematic registrations in oncology

In the field of oncology, there has been a long tradition of systematic registrations of diagnosis, histological subtype, as well as stage of cancer. These registrations have been essential for obtaining the knowledge we have of cancer, optimal treatment according to cancer type, as well as prognosis for each patient. Fewer patient-related factors have been systematically obtained. One important exception is performance status, as previously described on page 19. PS has given us prognostic information on the importance of a patient's general condition and is actively used to guide treatment decisions. Systematic registrations in the oncology field have thus proven to be essential. Although it is recommended to perform systematic geriatric assessment and comorbidity assessment in older cancer patients, neither of these are implemented as daily routines in Norway [174]. Thus, assessment of the patient's level of functioning, comorbidity, frailty status, and ability to tolerate cancer treatment are based on the oncologist's clinical judgement. Naturally, the primary focus is likely to be on diseases and disorders that the oncologist considers relevant for planned cancer treatment.

Whether clinicians can detect all problems in the geriatric patient without performing a systematic assessment is questionable. A large study including a systematic GA by Kenis et al. reported that the GA detected unknown geriatric problems in approximately half the patients [215]. The number of reported symptoms in palliative cancer patients is also much higher when systematically assessed compared with when symptoms are volunteered by patients in clinical consultations [216]. Furthermore, clinical judgement differs according to each rating clinician. When two clinicians were asked to rate the same patient's symptoms using the Common Terminology Criteria for Adverse Events, their agreement was at best moderate [217].

A few studies have investigated whether physicians' clinical judgement is an equally effective screening tool for frailty [195, 218, 219]. The results suggest that physicians are more conservative and rate fewer patients as unfit or potentially vulnerable than those identified by GA. Still, an interesting point is whether the clinicians might be able to differentiate between frail patients with poor prognosis and non-frail patients with better prognosis solely by using their clinical experience.

Objectives

The overarching aims of this thesis were to investigate clinicians' ability to identify comorbidity and frailty in their cancer patients and to investigate the prognostic and/or predictive impact of these factors on survival and the course of quality of life.

Paper I
a) To investigate the agreement between retrospective comorbidity ratings by trained professionals using the CIRS-G manual and baseline comorbidity ratings by treating oncologists/pulmonologists using a scale similar to the original CIRS in patients with advanced NSCLC scheduled for first-line chemotherapy.
b) To explore the prognostic impact of oncologists/pulmonologists' comorbidity ratings on OS in advanced NSCLC patients scheduled for first-line chemotherapy.

Paper II
a) To investigate whether clinicians can adequately classify frailty in older cancer patients referred for systemic cancer treatment when compared with a modified geriatric assessment (mGA).
b) To investigate whether baseline frailty categorizations in older cancer patients referred for systemic cancer treatment, either by mGA or by the clinician, is prognostic for OS.

Paper III
a) To investigate whether baseline mGA frailty categorizations in older cancer patients referred for systemic cancer treatment predict the course of QoL during the first year of follow-up.

Materials and methods

This thesis is based on data from two studies involving cancer patients, a randomized clinical trial (RCT) including lung cancer patients (paper I), and an observational study including older cancer patients with solid tumours (papers II and III).

Study design

The randomized clinical trial (PEG-study)

This national RCT was designed by the Norwegian lung cancer study group to compare the effects of two chemotherapy doublets, gemcitabine/carboplatin and pemetrexed/carboplatin, as first-line treatment for advanced NSCLC. Chemotherapy was given with a three-week interval, up to four cycles. At baseline and before each infusion, patients reported QoL on EORTC QLQ-C30 and, thereafter, every eight weeks for the first year.

The primary endpoint was QoL; secondary endpoints were OS and toxicity. Results from the main trial revealed similar QOL and OS, but less toxicity in favour of the chemotherapy doublet pemetrexed/carboplatin [220].

The original protocol also included a sub-study to 1) investigate the significance of severe comorbidity on QoL, OS, and toxicity, and 2) compare comorbidity rated by local investigators (LI-score) with comorbidity rated retrospectively by trained researchers, all oncologists, using patients' medical records (CIRS-G). Previous results revealed that patients with severe comorbidity according to CIRS-G had poorer QoL and more haematological toxicity but similar survival compared to patients without severe comorbidity [53].

Figure 6. The PEG study

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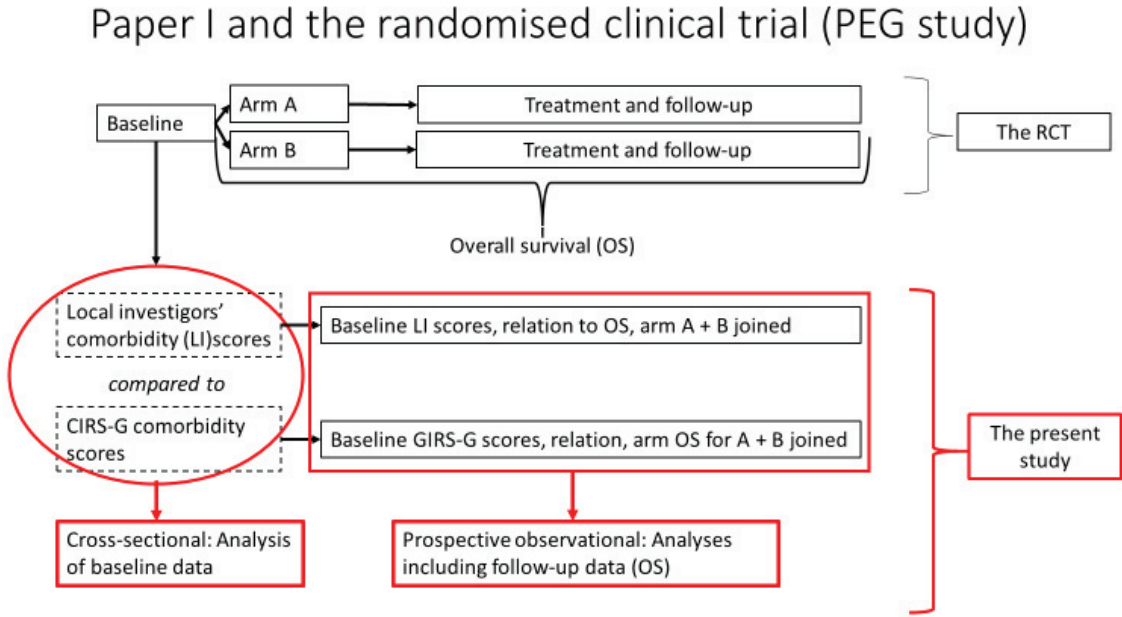
The prospective observational study

This multicentre prospective observational study was designed to investigate predictive abilities of GA-assessed frailty and biological markers (inflammation and muscle depletion) in older (≥70 years) cancer outpatients with solid tumours referred for medical cancer treatment. Innlandet Hospital Trust (six clinics), Akershus University Hospital, and Oslo University Hospital participated in inclusion of patients. Frailty was assessed at baseline, and patients' self-reported QoL was evaluated using EORTC-QLQ-C30. QoL assessment was repeated at 2, 4, 6, and 12 months follow-up.

Primary endpoints were OS and changes in physical function (from the EORTC QLQ-C30) the first two months of follow-up. Secondary endpoints were changes in physical function and global QoL (from the EORTC QLQ-C30) the first year of follow-up.

Figure 7. The prospective observational study

Paper II and III and the prospective observational study
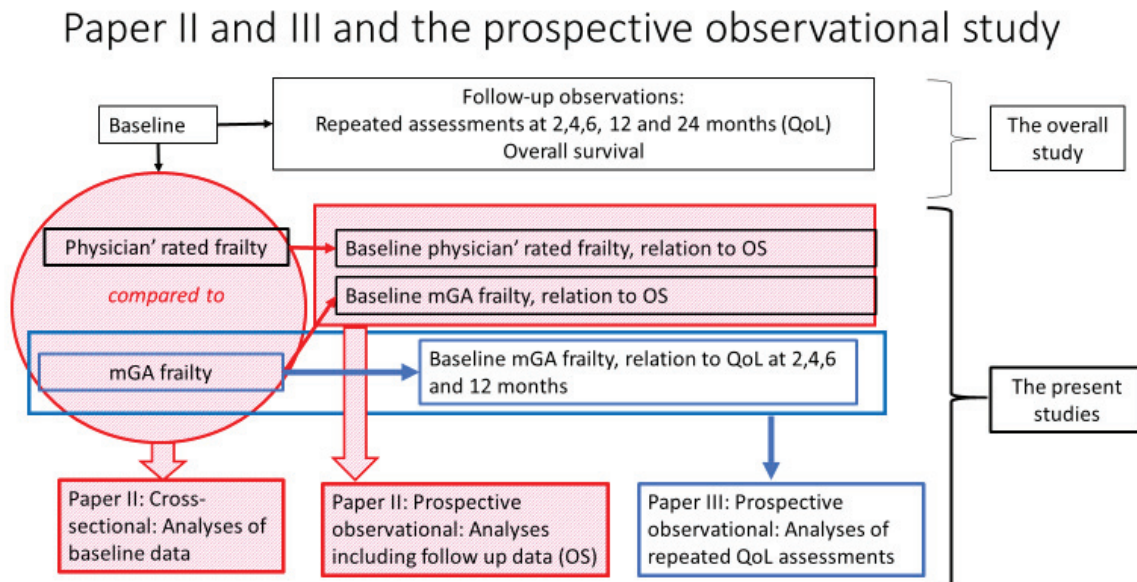
Study population

Paper I

Patients were enrolled at 35 Norwegian hospitals by local oncologists and pulmonologists. The inclusion period was from May 2005 to July 2007.

Inclusion criteria main trial:
- No previous systemic treatment for lung cancer
- >18 years old, no upper age limit
- Histologically/cytologically verified NSCLC
- Stage IIIB (ineligible for curative radiotherapy) or stage IV NSCLC
- Performance status (PS) of 0–2
- Adequate bone marrow and liver function
- Creatinine clearance 45 mL/min (Cockroft-Gault formula)
- Able to understand information provided about the study
- Written informed consent

Exclusion criteria main trial:
- Pregnancy or breast feeding
- Active cancer other than NSCLC
- Use of NSAIDs or high dose ASA and a reduced kidney function

As presented in the flowchart below, 436 patients were analysed in the main trial and thus eligible for comorbidity assessment; however, 13 did not have medical records sent to the study office; 13 received no study treatment, and 8 did not complete the baseline quality of life questionnaire. Thus 402 patients were assessed with CIRS-G. Of these, 27 had no LI-score, and thus 375 patients were eligible for comorbidity comparisons in our study. Of these 375 patients, 36% were ≥70 years, and the median age was 65 years.

Figure 8. Flow-chart paper I
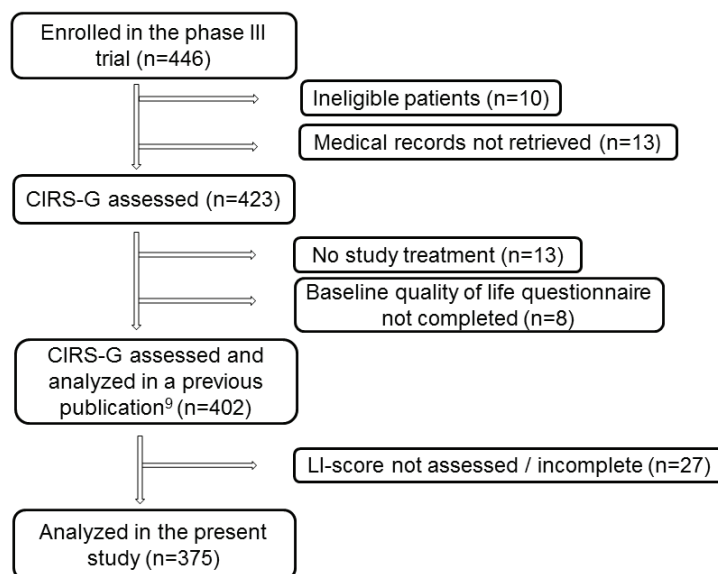
Papers II and III
Older patients with solid tumours referred for medical cancer treatment were consecutively recruited at seven clinics. Patients were included from January 2013 to April 2015. A modified geriatric assessment (mGA) was performed at baseline, based partly on registrations by oncology nurses with specific training in study procedures and partly on patient reports. Patients' frailty status was categorized based on the mGA results.

Inclusion criteria
Age ≥ 70 years
Histologically/cytologically confirmed solid tumour
Referred to cancer clinic for medical cancer treatment
New cancer diagnosis or first relapse after previous curative treatment
Able to provide written, informed consent

As presented in the flow chart below, 307 patients were included; one withdrew consent; 18 had missing baseline questionnaires, and thus 288 patients were eligible for analyses.

Figure 9: Flow-chart paper II and III


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┌─────────────────────────┐
│ Enrolled in the trial   │
│ (n=307)                 │
└─────────────────────────┘
            │
            │──────▶ ┌──────────────────────────────┐
            │        │ Withdrew consent (n=1)       │
            │        └──────────────────────────────┘
            │
            │──────▶ ┌──────────────────────────────┐
            │        │ Missing baseline questionnaires │
            │        │ (n=18)                       │
            │        └──────────────────────────────┘
            ▼
┌─────────────────────────┐
│ Analyzed in the present │
│ study (n= 288)          │
└─────────────────────────┘
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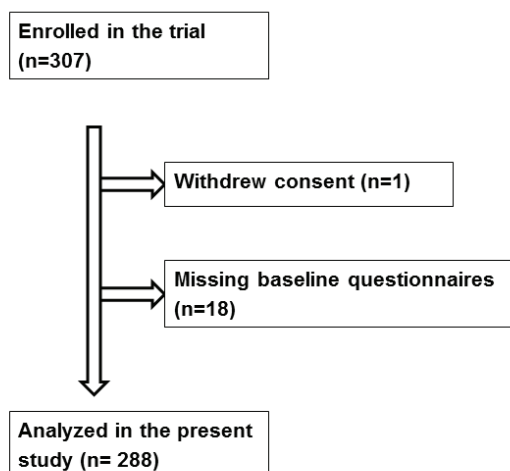
Assessments

Paper I
Only baseline data were used in this paper. Information about stage of disease (TNM classification), histology, smoking history and rating of PS were registered by the including physician at baseline. Quality of life was registered by patient report using the EORTC QLQ-C30. Information about date of death was sent to the study office by the treating physician.

Comorbidity assessments
At baseline the patients' oncologists/pulmonologists (= local investigators) performed prospective comorbidity ratings based on the clinical assessment and knowledge from the patients' medical histories (= LI-score). No formal training in assessing comorbidity was given, just a brief written set of instructions based on the original CIRS.

After all patients had been included in the trial, comorbidity was assessed and scored retrospectively by three trained researchers, all oncologists, using hospital records from the three months prior to randomization and the CIRS-G manual from 1991 [66] (=CIRS-G). For each patient, CIRS-G was assessed independently by two researchers. In case of different scores, the researchers discussed the assessment and reached consensus.

In both prospective and retrospective scores, 14 organ systems/scales were rated and graded from '0' to '4' in accordance with the CIRS-G comorbidity index. Thereafter, total score, severity index, severe comorbidity, and high severity index were calculated.

- Total score = the sum of scores in all organ systems
- Severity index = total score divided into the number of categories with a score >0
- Severe comorbidity = ≥ one score 3 or 4
- High severity index = a severity index >2

Lung cancer patients with a severity index >2 or at least one grade 4 comorbidity are reported to have poorer survival compared with those with less comorbidity [221]. Thus, we defined 'high severity index' as having a severity index >2. To differentiate between a comorbidity

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graded 3 or 4 may be difficult; hence, we defined 'severe comorbidity' as having ≥1 comorbidity grade 3 or 4 in an organ system, as in the previously published study of the prognostic role of comorbidity in advanced NSCLC [53].

Papers II and III

In paper II baseline data are presented as well as data on OS; paper III includes 12 months of follow-up of QoL. An overview of the registrations performed as well as scales used is presented in Table 10 below.

At baseline, oncologists registered medical data about type of cancer (ICD-10), stage of disease (local, locally advanced, distant metastases), planned treatment, and whether treatment was considered to be curative or palliative. They also rated PS and categorized frailty, as further described on page 50. Oncology nurses interviewed patients about sociodemographic data, medication use, and the occurrence of falls, measured height and weight, assessed nutritional status, and tested cognitive and physical function. Information about emotional function, comorbidity, nutritional symptoms, and QoL were self-reported. Data on administered treatment the first two months after inclusion and date of death were retrieved retrospectively from the patients' medical records by checking administered infusions, prescriptions, surgical notes, and notes from the radiotherapy clinic.

Table 10: Overview of the different assessments performed at baseline

	Performed by
Medical data	Oncologist
Performance status	Oncologist
Frailty categorized by oncologist	Oncologist
Sociodemographic data	Nurse
Cognitive function	Nurse
Emotional function	Patient
Comorbidity	Patient
Medications	Nurse or Oncologist
Physical function	Nurse
Number of falls the last 6 months	Nurse
Nutritional status	Nurse and patient
Quality of life	Patient
Information about treatment the first two first months and date of death from hospital records	PhD-student

The baseline modified geriatric assessment (mGA)

The GA was defined as modified (mGA) since it was not performed by an interdisciplinary team but based on assessments by trained oncology nurses and patients' self-reports. The following eight domains were included:

1. Cognitive function tested using the Norwegian Revised Mini Mental State Examination (MMSE) [185, 186].

2. Emotional function reported on the geriatric depression scale (GDS-15) [188].

3. Comorbidity registered using the Physical Health Section, a subscale of the Older Americans' Resources and Services Questionnaire (OARS) [60, 222].

4. Number of medications registered according to the Anatomical Therapeutic Chemical Classification System (ATC).

5. Physical function tested using the Timed Up and Go test (TUG) [179].

6. Falls were defined as unintentional events resulting in a lying position on the floor, the ground, or other lower level. The number of falls during the last six months was registered.

7. Screening for ADL dependencies using question 5 ('Do you need help with eating, dressing, washing yourself or using the toilet?') from EORTC QLQ C30 [42].

8. Nutritional status assessed by the Patient-Generated Subjective Global Assessment (PG-SGA) [182].

Quality of life

QoL was assessed using the patient-reported EORTC QLQ-C30 at baseline and at 2,4, 6, and 12 months of follow-up [42]. The follow-up QoL questionnaires were sent by mail to patients at their home addresses. A reminder was sent if the patient did not reply within two weeks.

QLQ-C30 consists of 30 questions graded from 1 to 4, comprising five functioning scales: physical, role, social, cognitive and emotional functioning, and a global QoL scale; and nine symptom scales: fatigue, pain, nausea/vomiting, sleep disturbances (insomnia), appetite loss, diarrhoea, dyspnoea, constipation, and financial impact. The raw scores on the questions from each scale are transformed into scales from 0 to 100 points [223]. Higher scores on the functioning and global QoL scales represent better functioning, whereas higher scores on symptom scales/items indicate a higher symptom burden.

Frailty defined according to our mGA (mGA frailty)

To define frailty according to our mGA, we used criteria similar to the modified Balducci criteria formerly applied by Kristjansson et al. [196] and Ommundsen et al. [224]. Patients were defined as frail if they met one of the following criteria: dependencies in ADL, had significant comorbidity or one or more geriatric syndromes defined as impaired function according to MMSE (cognitive function), GDS (depression), SGA (malnutrition), or frequency of falls. Furthermore, in accordance with Winograd's criteria for frailty [192] and similar to Kristjansson et al. [196], we included polypharmacy as a criterion but also added impairment according to TUG.

Table 11: An overview of the domains and cut-offs in the modified Geriatric assessment

The modified Geriatric Assessment mGA frail defined as deficits in ≥1 domain		
Domain	**Scale**	**Cut-off value for frailty**
Cognitive function	MMSE	<24 points
Emotional function	GDS-15	≥7 points
Comorbidity	OARS	>3 points
Medications, polypharmacy	ATC	>7 regular medications (ointments & common vitamins excluded)
Physical function	TUG	>14 seconds
Falls		Patient reports ≥2 falls the last 6 months
ADL	EORTC QLQ-C30	If reported yes, a little/quite a bit/very much on question 5
Nutritional status	PG-SGA	Considered severely malnourished by nurse or self-reported weight loss ≥10% the last 6 months.

Chosen cut-offs in each domain
All cut-offs were decided a priori based on literature if available or after consensus in the study group.

- ✓ The MMSE cut-off <24 was set as this indicates cognitive impairment and has previously been used in cancer trials performing GA [225, 226] as well as GA frailty classifications [196].
- ✓ For GDS-15 a cut-off of ≥5 has been suggested to identify patients at risk for depression in GA [227]. However, since our frailty assessment required only one deficit to be considered frail, we were interested in selecting patients with a high burden of depressive symptoms, and a cut-off of ≥7 was thus set to ensure high specificity [228, 229].
- ✓ There are no well-known cut-off points for frailty using the OARS in the literature; however, four or more comorbidities was set as the cut-off since it was indicated as a threshold for shorter survival in a previous study on cancer patients [230].
- ✓ Eight or more regular medications were set as a cut-off for polypharmacy in accordance with Kristjansson et al. [196].
- ✓ Cut-offs >14 s/>14.5 seconds for TUG have been used to identify GA deficits in cancer trials [178, 231, 232] and were also used in our study.
- ✓ We chose two or more falls as cut-off as this number previously has been used to identify GA deficits in cancer trials [178, 231].
- ✓ All patients who responded any grade of yes to the need for help with ADL on EORTC QLQ-C30 question 5 were considered frail.
- ✓ A weight loss ≥10% during the last six months is generally considered as an indicator of severe malnutrition [233]. Patients were categorized as frail if considered severely malnourished by study nurses or had a weight loss of at least 10% over the last six months.

Frailty categorized by oncologists based on clinical judgement (paper II)

The patients' oncologists were asked to classify the patient as fit, intermediate, or frail after their first consultation. They received no instructions or training to perform this task, and prior to performing the categorization, they were blinded to the results from the mGA.

Handling of missing data

In paper 1, as presented in the flow chart on page 45, patients without comorbidity ratings were excluded, and thus missing data were not an issue in this paper.

In papers II and III missing values in MMSE (n=3) and GDS-15 (n=27) were imputed by drawing one random number per value from the empirical distribution based on non-missing values. In total, 31 patients had one or several missing items in the OARS subscale. Missing items on the OARS subscale were imputed by retrieving information from hospital charts.

A few patients had missing domains in the mGA (reported in Table 3, paper II): OARS (n=1), ADL (n=5), GDS-15 (n=4), and falls (n=1). The most frequent domain that was incomplete was patient-reported weight loss over the last six months (n=24), but all these patients had a nutritional assessment by a study nurse. Overall, 13 patients had no TUG registration by a study nurse. Patients were categorized as frail or non-frail based on available assessments.

Missing values in QLQ-C30 multi-item scales were imputed according to the official manual if at least half the scale had been answered [223].

Analyses and statistical considerations

Paper I

We compared the LI-scores to the CIRS-G scores and assessed the agreement between them. First, the proportion of patients with LI- and CIRS-G scores ≥1 and ≥3 in each organ system were compared using χ2 scores or Fisher's exact test. The total score, severity index, high severity index, and severe comorbidity were calculated for each patient for both LI- and CIRS-G scores. Bland-Altman analyses were used to assess the level of agreement between the CIRS-G scores and the LI-scores in the continuous variables 'Total score' and 'Severity index'. Weighted kappa statistics were used to estimate the level of agreement on the categorical variable 'Severe comorbidity'.

Survival time was defined as time from randomization until death. Two Cox regression models were estimated to investigate the prognostic impact of 'severe comorbidity LI-score' and 'high severity index LI-score' on survival. Multiple Cox regression models were estimated to adjust for established prognostic factors in advanced NSCLC (PS, stage of disease, gender, smoking history, baseline global QoL, and appetite loss) and study treatment. As previously mentioned under study design, survival analyses of the CIRS-G assessments have been published [53]. However, since we investigated a smaller subgroup of patients, we chose to repeat these analyses. The prognostic impact of 'severe comorbidity CIRS-G' and 'high severity index CIRS-G' were thus analyzed in the same manner as the LI-scores. Explorative Cox regression models of the prognostic impact of 'severe comorbidity LI-score', 'high severity index LI-score', 'severe comorbidity CIRS-G', and 'high severity index CIRS-G' were repeated in the subgroup of patients ≥70 years. The predictive ability of the different comorbidity models was evaluated by calculating a C-index.

Paper II

The oncologists' original threefold classification was dichotomised into onc-non-frail (patients considered fit) and onc-frail (patients considered frail or intermediate) and compared with mGA-frail/mGA-non-frail. Medical and sociodemographic factors were compared between groups by independent sample t-tests or X^2-test. The agreement between mGA-non-frail/mGA-frail and onc-non-frail/onc-frail was assessed by kappa statistics.

We estimated bi- and multi-variate Cox regression models to investigate whether being mGA-frail was a prognostic factor for OS. The association between clinicians' judgement of being onc-frail and OS was thereafter analysed accordingly.

Adjusting factors in the multivariate models were known prognostic factors: PS (0–1 or 2–4), stage (local, locally advanced, or metastatic), age, cancer type, gender, as well as type of treatment. Types of treatment were classified as 1) curative treatment, i.e., patients referred for neoadjuvant treatment, adjuvant treatment after curative surgery, or curative radiotherapy, 2) palliative chemotherapy, 3) other palliative systemic cancer treatment, and 4) non-systemic palliative treatment the first two months after inclusion (i.e., radiotherapy, surgery, or palliative care). Proportional hazards assumption was assessed by examining Schoenfeld's residuals. Multicollinearity issue was considered by calculating variance inflation factor. Kaplan–Meier OS curves were presented.

Paper III

Changes in QoL according to frailty status were investigated by predefined endpoints. The primary endpoint was changes in PF during the two first months of follow-up; secondary endpoints were changes in PF and global QoL during 12 months of follow-up. Changes during 12 months for the remaining QLQ-C30 scales and items were assessed by exploratory analyses using the same approach as for the main endpoints.

Differences between mGA frail and mGA non-frail patients in changes over time were assessed by linear mixed models. Linear mixed models were chosen to handle dependencies in our data set (due to repeated measurements in the same patients and clusters of patients within cancer clinics). All models therefore included random intercepts for cancer clinics and for patients nested within cancer clinics to account for intra-patient correlations due to repeated measurements and possible within-clinic cluster effects. The models also included fixed effects for frailty group, time, and the interaction term between frailty group and time (frail*time). In the models assessing data on 12-months follow-up, time was a second-order polynomial to account for non-linear trends. A significant interaction term would imply that there were differences in change between frail and non-frail patients.

Models adjusting for age, sex, cancer type, PS, stage, and treatment were also estimated. The results were tabulated as regression coefficients with standard errors (SE) and p-values for the primary and secondary analyses of PF and global QoL. The results from unadjusted models were also presented graphically as estimated mean values with 95% confidence intervals (CI) for all QLQ-C30 scales/items. Within- and between-group differences with the corresponding 95% CI and p-values were calculated from the models. For the EORTC QLQ-C30 scores, a difference of ≥10 points on the functional and symptom scales/items was considered a clinically significant change [234].

Statistical analyses and significance

Statistical analyses were performed using IBM SPSS Statistics for Windows v 22 (IBM Corp, Armonk, NY) and STATA v 12 (Stata Corp, College Station, Texas). For all analyses in all papers, the level of significance was set at 0.05.

Ethical considerations

Paper I

The RCT was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Medicines Agency, the Norwegian Social Science Data Services, and the Norwegian Directorate for Health and Social Affairs. The comorbidity registrations were performed by physicians and did not inflict any extra burden on the patients. Of ethical concern is the storing of sensitive data. However, patients provided written informed consent after receiving information about the study and were able to withdraw their consent at any time during the study period without any effect on treatment or follow-up. Further, performing these analyses on already gathered patient data helped ensure that the data were used as planned in the study protocol.

Papers II and III

The observational study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway 09.02.2012 (reference number 2012/104). Data collection and storage procedures were also approved by the data protection supervisor at all participating hospitals. The study is performed according to the Helsinki declaration. Information gathered in the study did not have any effect on treatment or follow-up of the patients. However, exceptions were made if the assessment revealed severe medical problems requiring attention; then, the nurses were instructed to inform the patients' oncologists. The baseline registrations and follow-up questionnaires, however, required the time and energy of patients with severe cancer diagnoses, and sensitive information about the patients was also stored. Patients were given oral and written study information, including the option to withdraw consent at any time during the study period, before providing informed consent.

Results

Paper I. Comparing comorbidity ratings by the patients' oncologist/pulmonologist and trained researches in patients with advanced lung cancer

Of the 375 patients analyzed 29% had stage IIIB and 71% stage IV NSCLC. Median age was 65 years; 36% of the included patients were ≥70 years. The majority had good PS: a total of 79% had PS 0 or 1.

Fewer patients had comorbidities registered by local investigators (n = 325, 87%) than by trained researchers (n= 371, 99%). For most individual organ systems/scales, the LI-scores included a lower number of comorbidities than the GIRS-G scores.

Overall, 94 (25%) versus 184 (49%) patients had severe comorbidity according to the LI- and CIRS-G-scores, respectively. When comparing the two scores of 'severe comorbidity', weighted kappa was 0.18 (95% CI 0.10; 0.25), suggesting only a slight agreement between the scores.

The mean total LI-score was 4.2 (range 0–16), and the mean total CIRS-G score was 7.0 (range 0–17). The scatter plot indicated poor agreement between the two total comorbidity scores. We found a significant bias of -2.87 ($p < 0.001$), confirming that the total CIRS-G scores were consistently higher than the total LI-scores. A wide 95% limit of agreement (±6.40) in the Bland-Altman plot further confirmed the poor agreement between the two comorbidity scores.

The mean severity index was 1.43 (SD 0.78) versus 1.73 (SD 0.46) according to the LI-scores and CIRS-G, respectively. A scatter plot comparing the two severity indices also revealed poor agreement.

According to unadjusted and adjusted Cox regression analyses neither the 'high severity index' nor 'severe comorbidity' scores from LI-scores or CIRS-G scores were significant prognostic factors of survival.

Paper II. Comparing frailty ratings by the patients' oncologists and a systematic modified geriatric assessment

Median age was 77; most patients had PS 0–1 (n = 244, 85%), and nearly all lived at home (n = 275, 96%). The most common diagnoses were colorectal, lung, and prostate cancer, and chemotherapy was the primary systemic treatment for 200 (69%) patients.

According to mGA, 140 (49%) patients were frail. The three most common frailty domains were comorbidity (n = 82, 28%), polypharmacy (n = 37, 13%), and malnutrition (n = 43, 15%). Overall, 73 (25%) patients had a deficit in one mGA domain, 42 (15%) in two domains, and 25 (9%) in three or more. The oncologists considered 15 patients (5%) as frail and 89 (31%) as intermediate, giving a total of 104 (36%) onc-frail according to the dichotomized classification.

The mGA-frail/mGA-non-frail classification coincided with the onc-frail/onc-non-frail classification for 187 (65%) patients; 72 (25%) patients were found mGA-frail and onc-frail, while 115 (40%) patients were mGA-non-frail and onc-non-frail. Of the 67 (23%) patients classified as mGA-frail but judged by the clinicians to be fit, favorable cancer-related prognostic factors were frequent, and most of these patients had one mGA deficit (n = 46, 69%). In contrast, only 36% (n = 26) had one mGA deficit among those who were both mGA-frail and onc-frail. The most frequent mGA deficit missed by the oncologists was comorbidity. Of the 32 (11%) patients who were mGA-non-frail and onc-frail, the frequency of established negative cancer-related prognostic factors was high and similar to the group that was both mGA-frail and onc-frail. The kappa statistic was 0.30 (95% CI 0.19; 0.41), indicating only fair agreement between the oncologists' clinical judgement and the mGA.

Both mGA-frail and onc-frail patients had poorer median OS compared with mGA-non-frail and onc-non-frail patients, respectively (mGA-frail: 15.0 months, mGA-non-frail: 29.1 months; P<0.001) (onc-frail: 12.9 months, onc-non-frail: 27.4 months; P<0.001). The few patients (5%) originally categorized as frail by the oncologists had a median OS of only 7.4 months.

In bivariate Cox regression analyses mGA-frail and onc-frail were both significantly negatively associated with OS. The HR for mGA-frail was 1.86 (95% CI 1.36; 2.56) (P<0.001), and the HR for onc-frail was 1.94 (95% CI 1.41; 2.66) (P<0.001). In adjusted analyses, mGA frailty was an independent negative prognostic factor for OS with a HR of 1.61 (95% CI 1.14; 2.27) (P=0.007); being frail according to the oncologist did not however, reach statistical significance (p=0.07).

Paper III. Long-term quality of life according to frailty status in older medical cancer patients

The description of the patient population has already been included in the results from paper II.

A higher proportion of frail than non-frail patients died during follow-up, and at 12 months 83 (59%) of frail and 112 (76%) of non-frail patients were alive. The proportion of completed questionnaires ranged between 89% and 95% for those alive at the various assessment points.

Frail patients reported poorer functioning and more symptoms than non-frail patients on all scales/items at baseline.

Both frail and non-frail patients reported a statistically but not clinically significant decline in PF from baseline to two months. The decline was not significantly different between frail and non-frail patients (adjusted model: p = 0.218). There were, however, statistically significant differences in PF scores between the two groups in disfavour of frail patients. In the adjusted linear mixed model, the mean difference was 12.2 (CI 7.5; 16.9) points at baseline and 9.2 (CI 4.4; 14.1) at two months (p<0.001). For PF during 12 months of follow-up, both unadjusted and adjusted models showed that frail patients had a statistically significant non-linear decline (p<0.001). The decline was clinically significant (≥10 points) from baseline to six and 12 months, respectively, in both the unadjusted and adjusted models, and it was found to be significantly steeper for frail patients (p=0.022) in adjusted analyses.

For global QoL during 12 months of follow-up, there was no significant difference between frail and non-frail patients in the course of changes (p = 0.273 in adjusted models). Both

models demonstrated that frail patients had statistically and clinically significantly worse scores compared to non-frail patients at all assessment points (p<0.001).

In exploratory analyses of the other QoL scales, frail patients had a clinically and statistically significant decline in role functioning from baseline to six months (p<0.001) in adjusted analyses. None of the other scales showed any clinically significant changes from baseline in the adjusted models, either in frail or non-frail groups. Diarrhoea showed a statistically but not clinically significant increase from baseline to six months for frail patients (adjusted model, p = 0.023). In all the other scales, the course of the trajectories was not significantly different between the groups. Adjusted models showed that frail patients had statistically and clinically significantly more constipation (p < 0.01) and worse role (p<0.001), social (p<0.01), and emotional functioning (p<0.01) at all assessments than non-frail patients.

Discussion

Methodological considerations

To interpret results from clinical research, a thorough evaluation of study quality is needed. This includes appropriateness of the chosen design, the representativeness of the study population (external validity), and the internal validity of the study results. The latter refers to the study's ability to measure what it was planned to measure, and to evaluate this, risks of bias and confounding need to be assessed [235]. These risks, i.e., all issues and factors that may interfere with the results and their validity, vary according to study design.

Study design

In paper I (Figure 6, page 43), we used data from a national RCT comparing two first-line chemotherapy regimens in NSCLC patients. Two methods for comorbidity registrations were compared: local investigators' (LI) scores and CIRS-G scores. The local investigators performed their assessments at baseline, before randomisations. Although being retrieved retrospectively from hospital charts, the CIRS-G scores were also based only on information available at baseline. Thus, this comparison constitutes in principle a cross-sectional study. To investigate the prognostic impact of each comorbidity score on survival, the two treatment groups in the RCT were joined and treated as one cohort, i.e., consistent with a prospective observational design. As there was no difference in survival between the two treatment groups, we find this approach appropriate.

Similar to paper I, paper II (Figure 7, page 44) includes a cross-sectional study, i.e., comparison of the prevalence of frailty according to two measures; physician-rated frailty and mGA frailty. Otherwise, all analyses in paper II and paper III are based on a prospective observational design. Paper II only address the relationship between baseline assessments and survival, while paper III includes analyses of the relationship between mGA frailty and repeated measures of QoL.

All results in this thesis thus emerge from observational methodology: cross-sectional and prospective observational. The latter follows patients over time and can be referred to as a cohort study. Observational designs are often seen as inferior to RCT; whether this is the case depends on the purpose of the research. RCTs are undoubtedly the gold standard to document cause/effect relationships [236]. However, observational studies represent methods that are suitable to establish prevalence (cross-sectional studies), describe the natural development of a condition, and investigate associations between exposures and outcome (cohort studies) [237, 238]. Thus, considering our study objectives, we believe that our designs are appropriate. Furthermore, our objectives were all in accordance with the pre-planned protocols of the RCT and the prospective study. At the time the studies were initiated, the issues addressed by these objectives were scarcely investigated; current knowledge was insufficient for initiating interventional studies, and observational methodology was the most suitable to increase existing knowledge.

The study populations

For clinicians, knowledge of the generalisability, i.e., the external validity, of the study results is required to be able to translate the results to other patients and situations. The main questions for our studies are therefore: Are the enrolled patients representative of the population they are supposed to represent? Did any selection occur that might have threatened

the external and/or internal validity? Are the physicians who performed the ratings of comorbidity and frailty representative of the average physician routinely treating the respective group of patients? These questions are answered in the following sections.

Patients - paper I

The NSCLC patients in paper I were all included in an RTC, and a challenge with such trials is that the patient samples often represent a selected population, fitter than the average patient with the same diagnosis [236]. In this trial, however, patients were included nationwide from local as well as university hospitals, and the study population included 22% with PS 2, and 18% were 75 years or older [220]. Although eligibility criteria in the phase III trial were wide, there were some restrictions regarding liver, kidney, and bone marrow function, as well as performance status. Furthermore, taking the Norwegian incidence of NSCLC by age group into consideration, the proportion enrolled in the trial was lower for older than for younger patients (≥70 years: 12%, <70 years: 23%; p = 0.001), possibly indicating that physicians were more hesitant to include those of higher age [53].

As formerly demonstrated (method section, page 43), our paper I study was not based on the overall RCT study sample, but on a cohort addressing CIRS-G-rated comorbidity in relation to survival and QoL [220]. For these analyses, a total of 44 patients were excluded due to ineligibility (in the RCT), missing CIRS-G ratings or baseline QoL questionnaires, or because the patients did not receive the study treatment. For our study, another 27 patients were excluded due to missing local investigators' scores which were needed for the comparison. Thus, 375 of 446 patients (84%) from the RCT were eligible. The distribution of characteristics of these patients was, however, comparable to the overall sample [220]. We have no reason to believe that the CIRS-G scores, LI scores, and baseline QoL assessments were missing in a non-random manner. The exclusion of patients who did not receive the study treatment may, however, represent a systematic error (patients being too ill), but we find that their number was too low to be of significance for our results.

Overall, and although our patients were slightly younger than the average NSCLC patient, we believe that they are representative of advanced NSCLC patients eligible for first-line chemotherapy and that the exclusion of some patients from the original sample does not imply any selection bias compromising the internal validity of our results. Whether our findings may be transferred to patients whom the physicians do not find fit enough to tolerate such regimens may be questioned.

Patients - papers II and III

The prospective observational study that was the basis of papers II and III also included patients at both local and university clinics and had broad inclusion criteria. There were no exclusion criteria or requirements regarding PS, comorbidity, or age in this study. Thus, all patients with a confirmed solid tumour referred for treatment of a new cancer diagnosis or first relapse of a former cancer could be included if they were able to fill in questionnaires in Norwegian and consent to participation. Although planned, we were not able to accurately register the number of potentially eligible patients who were not included at the various participating clinics. We do know, however, that not all eligible patients were enrolled, but according to the project nurses, non-inclusion mainly occurred by random due to lack of time to identify and include patients among their routine clinical tasks.

In the included cohort 18 patients had incomplete baseline assessments, mainly because their patient self-report questionnaires were missing. These patients were excluded from further

analyses since the information needed to rate frailty was missing. We believe that the questionnaires were missing due to random practicalities such as patients having no time to fill in the questionnaire at the clinic so they brought it home and forgot to return it or the project nurse being too busy to ask about the questionnaire at the following consultations. In retrospect, a reminder should have been sent to the patients for baseline questionnaires as was done for the follow-up assessments.

In summary, we believe that there was no selection bias that may have threatened the validity of the results and that the included patients are representative of the average, older cancer patient referred for medical cancer treatment. However, we cannot rule out that they represent a fitter subgroup of older cancer patients. There is some risk that the frailest patients with the poorest overall health more often declined or were less frequently invited to participate due to concerns about the additional burden the study tests represented.

The assessing physicians - papers I and II
No personal characteristics such as age, gender, or experience were registered for either the physicians who performed the comorbidity assessments, i.e., the local investigator scores in paper I, or for those who performed the clinical frailty assessment in paper II.

Despite this lack of information, it is reasonable to believe that the assessing clinicians in paper I are representative of the everyday Norwegian clinician treating lung cancer, since the study was based on a national RCT including patients at 35 different hospitals.

In the prospective observational study representing the basis for papers II and III, the patients were included from six small, local centres in addition to two university hospitals. Retrospective contact with the participating clinics indicated that about 40 consultants were involved during the trial period, and to the best of our knowledge, the minimum number of patients per physician was one and the maximum was 27 or 28. The skewedness of this data might indicate a risk that the difference between mGA frailty and clinicians' evaluations of frailty could be related to misjudgment of only a few physicians. Therefore, as thoroughly as possible, we attempted to determine who evaluated the patients classified as frail according to mGA but missed by the oncologist. We found that these patients were represented by 28 consultants, each evaluating from 1 to 7 patients. The overall sample of consultants included an equal share of juniors and seniors (with up to 30 years of experience); thus, their experience varied widely. Length of oncological expertise, however, might not be relevant for identitfying frailty. Wedding et al. reported similar results regarding clinician-rated frailty, and their results were based on clinicians with at least 10 years of experience [218]. Norwegian oncologists and trainees receive no formal training in geriatric oncology, and the inadequacy of training to assess and identify geriatric problems is widely recognized [239]. Thus, in our opinion, the relatively large number of physicians with varying oncological expertise involved in our study reflects the everyday situation, thereby strengthening the results.

Baseline assessments
In the present studies we compare two methods for baseline assessment of comorbidity and frailty, respectively (papers I and II), and thereafter investigate their association to patient outcomes. Thus, the accuracy and validity of these baseline assessments should be carefully considered. For the cross-sectional analyses (papers I and II) there is also the need to consider whether a comparison of the two methods used was appropriate.

Comorbidity assessments, paper I

Although some consider CIRS-G as the gold standard for assessing comorbidity, this approach is time-consuming and requires trained personnel. It is thus highly relevant to consider whether a less comprehensive and quicker assessment e.g., our LI-score, can provide the same information. Also, since the LI-score was based on the original CIRS, including the same organ systems and rating scales, comparison of the two scores was both feasible and appropriate.

CIRS-G registrations were performed retrospectively based on information from hospital charts. Three trained oncologists participated in the assessment. For all patients, CIRS-G was rated independently by two of these researchers to ensure that the correct rating was obtained. In case of different scores, the researches discussed the assessment and reached consensus. Most disagreements occurred because one of the researchers missed a minor comorbidity in the patient's medical records. Overall, we consider the CIRS-G ratings as valid and with low risk of systematic error. Ideally, however, the CIRS-G registrations should have been performed prospectively, that is, when the patients were included in the study. The retrospective approach means that hospital charts were the only information available. One concern is therefore the completeness of these charts with regard to less severe comorbidity, which might have been considered irrelevant in light of the patient's lethal cancer diagnosis. There is thus some risk that less severe comorbidities were underreported in the CIRS-G scores and that the actual difference between CIRS-G and LI-scores on this point might have been even more pronounced than reported in our results. It is, however, highly unlikely that missing information on non-severe comorbidity should have any impact on our results that show no association between comorbidity and survival.

Frailty assessments, papers II and III

For the systematic assessment of frailty, we performed a geriatric assessment, referred to as a modified geriatric assessment (mGA) as it was not performed by a geriatrician or a multidisciplinary team but by patient reports and trained nurses using validated tests or questionnaires. Patients were identified as frail or non-frail based on pre-specified cut-offs for deficits within each domain and a modification of the criteria recommended by Balducci and Extermann [189, 190]. The modification of the Balducci criteria included using polypharmacy as a criterion, as formerly applied by Kristjansons et al. [196], as well as deficits according to TUG that have been reported as being a sensitive and specific measure of frailty [181]. Only one of the pre-defined criteria had to be fulfilled to be classified as frail. In paper II this frailty classification was compared to the treating oncologists' subjective assessments of patients being fit, vulnerable, or frail, which for the analyses were dichotomized into fit versus vulnerable or frail.

Our approach raises several questions which are all discussed in the following paragraphs: Was our mGA an appropriate basis for identification of frailty, and were the appropriate domains included? Were the mGA tests/instruments and the cut-off points that were used valid and appropriate? Did we identify patients who were truly frail, and if not, how may this have influenced our results? The latter question also applies to the dichotomization of physicians' original classifications.

Choice of GA and included domains

When choosing GA to assess the older cancer patients, we leaned upon recommendations from experts in the field of geriatric oncology as well as previous publications reporting this approach to be feasible in this patient population [133, 173, 240]. Our choice of domains was

based on knowledge of areas in which older patients frequently have trouble (as described in page 27–30) and reports of domains used in previous geriatric oncology studies [132, 133]. At the beginning of this study, no consensus as to which domains to include in a GA existed; still, our mGA included most of the domains (except for anxiety and social support) that in 2015 were recommended in a consensus paper [189]. We thus consider the domains of our mGA to be appropriate.

GA is commonly regarded as the best clinical approach for detecting frailty [1] and has been widely used in the oncology literature [80]. In a systematic review by Handforth et al., 16 out of 22 studies used GA for the diagnosis of frailty [80]. Thus, we believe that applying a modified GA as the assessment method should not be controversial.

Choice of instruments included in the mGA
Our choice of instruments was mainly based on well-known scales validated in Norwegian, i.e., TUG for physical performance, GDS-15 for depression, MMSE for cognition, and PG-SGA for assessing nutrition. The first three instruments are in accordance with later consensus. However, MNA is recommended instead of PG-SGA for assessing nutritional status [189]. We chose PG-SGA since it is validated for assessment of nutritional status in cancer patients [182]. Polypharmacy was considered in the consensus paper, but no agreement on assessment method was reached. We assessed medication by counting the number of regular medications used as this is the most common basis for defining polypharmacy [101]. We also chose to include fall assessment in our mGA as this geriatric syndrome is an indication of increased vulnerability and is generally associated with increased morbidity and mortality [137].

In contrast to the consensus paper recommending CCI, we used OARS for measuring comorbidity. We considered using a more comprehensive scale like CIRS-G, but as this requires training of study personnel and the use of comprehensive scoring manual, it was found impractical for a multicenter study like ours. OARS was chosen since it had previously been applied in studies of cancer patients [59]. Furthermore, it has the advantage that it is patient-reported, and we thereby avoided burdening physicians with comorbidity assessment, which was considered essential for the study feasibility. OARS includes a list of conditions as well as grading of how they affect patients' daily activities. We were unfortunately unable to use the grading part of OARS due to poor compliance on this part of the questionnaire. Our comorbidity assessment is therefore merely a count from a list of comorbidities. This is not an ideal approach and represents a limitation in our mGA. By using the self-reported OARS, all degrees of comorbidity were included, regardless of severity; this scale might have been more inclusive than if we had used another comorbidity scale. Still, recent publications suggest that cancer patients' self-reporting of comorbidity gives a fairly concise and complete picture of patients' comorbidity burden [241].

We included question 5 from the QLQ-C30 to screen for activities of daily living as our study did not include an ADL scale. This is also a limitation in our mGA. An ADL scale might have been more sensitive and might have identified more patients as frail compared to merely screening for ADL difficulties. Still, seeing as this was a study on outpatients of which almost all (96%) lived at home, the risk that we missed many frail patients due to a missing ADL scale seems unlikely. Another concern is that question 5 on QLQ-C30 is one of the items of the questionnaire's physical function scale, which was also used as the primary outcome. A total of 12 patients were categorized as frail due to deficits in ADL, and 11 of these were frail

according to more than one category. This means that only one patient was defined as frail based on the self-reported physical function item only. Therefore, we find it highly unlikely that this single patient would significantly influence our results.

Our chosen cut-offs
When setting the cut-offs for the different domains, we wanted to keep each individual frailty criteria conservative since only one criterion was needed for a definition of frailty.
A cut-off on MMSE <24 for defining cognitive impairment, two or more falls in the last six months, or having difficulties of any degree in ADL are in accordance with previous publications as described in the methods section on page 49. Some of the other chosen cut-offs, however, need further discussion.

We set a cut-off of >14 for defining physical impairment according to TUG. Whether this is optimal is disputable as what is considered an abnormal TUG score varies in different studies [120]. Also, TUG has been performed at different paces in different studies. Whereas the original publication by Podsiadlo and Richardson instructed patients to walk at a comfortable pace, in our study TUG was performed at a fast pace. A systematic review by Beauchet found that the pace at which TUG was performed did not change its association with falls [242]. Having a TUG >10 is associated with chemotoxicity [121], a score >14 with increased fall risk [232], and a score >20 predicts early death in patients undergoing chemotherapy and postoperative complications in onco-geriatric surgical patients [225, 243]. When comparing our cut-off value with those used in other studies, we consider it neither too strict nor too inclusive and thus appropriate in our patient population as well as in line with other geriatric oncology studies using this assessment [178, 231].

For GDS-15 the cut-off for frailty was set at ≥7. This scale has been used in several geriatric oncology studies [107, 115], and the common cut-off for being at risk for depression is ≥5. We intentionally chose a higher cut-off to ensure a high specificity. Many of the patients included in our study had received information about having a severe and potentially life-threatening disease within weeks of being referred to the oncology clinic. Some depressive symptoms might be worsened by such news, and by choosing a high cut-off we wanted to ensure that only patients with a high number of depressive symptoms affecting functioning were classified as frail.

Based on data from the PG-SGA, we defined patients as frail if they had at least ≥10% weight loss or were considered severely malnourished by the study nurse. As 5% weight loss is diagnostic of cancer cachexia [244]; some may consider this very conservative, but this was in line with our goal of having strict criteria in each domain.

Four or more comorbidities in the physical health section of OARS was our cut-off for being frail according to number of comorbidities. We chose this cut-off partly based on a previous study indicating four or more comorbidities in OARS being a threshold for poorer OS [230] and partly on clinical judgement in the research group, where four or more comorbidities was considered a high level indicating frailty.

We defined polypharmacy as having eight or more medications. Five or more medications is a more common cut-off [245], but this cut-off is debated in clinical practice since having two properly treated comorbidities might require at least five medications [246]. Eight or more medications has previously been used as a frailty measure in a geriatric oncology study by

members of our study group [203], and this is also in accordance with our need of keeping each individual frailty criteria strict.

Our definition of frailty

As described in the paragraphs above, we find that there are good arguments for using GA to define frailty as well as for the included geriatric domains, instruments and chosen cut-off points. Still, our frailty definition may be subject to discussion. The main reason is that our definition cannot be definitely approved or rejected due to the lack of a consensus method for identifying frailty, no appropriately validated frailty classification based on GA in cancer patients, and no consensus on cut-off points to define deficits for the various measures of the GA domains.

Another point concerning our definition is whether it might be too inclusive, especially since comorbidity was registered using OARS as previously elaborated and only one deficit was necessary for patients to be regarded as frail. In previously published trials using GA, a range from one to four geriatric deficits has been used as a cut-off for frailty [80]. As formerly described, our cut-off was set in accordance with the criteria suggested by Balducci and Extermann [190] and also those used by Kristjanson et al. [196]. Furthermore, Kristjanson et al. reported that their similar approach was superior to Fried's physical frailty phenotype in its ability to identify post-operative complications [203]. However, we cannot with certainty say that we have captured the truly frail patients using our approach. Still, with our definition we detected a group of vulnerable patients with poorer survival, poorer quality of life, as well as poorer functioning who were in need of increased attention in clinical practice.

When deciding on how to define frailty, the intended use needs to be considered. A wide frailty definition with high sensitivity can detect frail patients in clinical practice in need of geriatric interventions, whereas a narrower definition might be more appropriate when investigating frailty as a predictive or prognostic factor in a clinical trial. Our approach is comparable to other studies using GA to classify frailty; however, there is a great need for standardized definitions of frailty based on GA.

Clinician's rating of frailty and comparison to mGA frailty

When comparing frailty classifications, we dichotomized the original threefold ratings performed by clinicians. Thereby we compared a group that was identified as either intermediate or frail (onc-frail groups) with mGA frail patients. This may have introduced a risk of misinterpreting the oncologists' assessments. However, in the original threefold classification, the oncologist classified only 15 patients (5%) as being frail. These patients had even poorer OS than the combined onc-frail group, but as for the overall group, the oncologists' frailty classifications seemed mostly based on well-known negative prognostic cancer-related factors. Any meaningful statistical comparison between the mGA-frail patients and those identified as frail by the oncologists was not possible due to the small number in the latter group. We therefore chose to dichotomize the oncologists' classifications. In our opinion, this does not affect our conclusion. On the contrary, even when we included those who were judged as intermediate or vulnerable, the oncologists failed to identify a considerable number of patients with poor prognosis.

Another concern is whether our mGA frailty definition may be considered too broad and unable to detect the truly frail patients. Following this, the question arises, Was the

comparison to the oncologists' frailty assessments adequate to perform? Applying a narrower frailty definition instead of our mGA might have resulted in better agreement. However, according to our results it is clear that the clinicians primarily based their frailty ratings on cancer-related factors and failed to identify patients' age-related vulnerabilities. Therefore, we concluded that it was relevant to compare these two frailty assessments.

Analyses and results, including follow-up data
As formerly pointed out, all three papers in this thesis include analyses attempting to establish an association between baseline factors and patient outcomes. Whether the outcomes were appropriate and the results valid, i.e., not subject to any bias or distorted by any confounding factors, needs consideration.

The outcomes
In papers I and II we investigated the association between OS and comorbidity and frailty, respectively. OS is regarded as a gold standard end-point in clinical trials [247], but since we in both papers investigated the impact of factors that may represent competing risks to the cancer, i.e., comorbidities and frailty, the use of cancer-specific survival as an additional or alternative outcome may have been relevant to consider. Unfortunately, neither of the studies on which our papers are based included data regarding cause of death, except that treatment-related deaths (serious adverse events) were registered for the RCT. For the NSCLC patients (paper I), however, cancer specific survival is probably of little relevance since survival was generally poor, and comorbidity burden did not influence survival. In the cohort in paper II, we found that mGA frailty was prognostic for OS independent of cancer diagnosis and stage, and one may argue that OS gives sufficient information for the clinicians who are planning to start cancer treatment in older patients.

In paper III patient-reported physical function and global QoL were the defined primary and secondary endpoints. Both measures were assessed by the EORTC QLQ-C30, which is widely used, well validated, and responsive to change [45]. Guidelines for interpretation of minimum important difference are available as well as a validated Norwegian version and Norwegian normative data for all age groups [234, 248]. Thus, based on its intended use in cancer patients irrespective of cancer diagnosis and age, we find that our choice of questionnaire was appropriate.

However, as physical function was our defined primary endpoint, using a patient-reported measure instead of more objective measures such as observer-rated ADL or IADL or performance tests may be discussed. Self-reported functional disabilities have previously been shown as strongly associated to gait speed as well as to survival in older cancer patients [249]. Also, similar psychometric properties (validity, sensitivity to change, responsiveness) as well as equally acceptable results have been reported in self-reported measures when compared to objective performance measures [250]. Furthermore, our study's aim was to investigate whether being frail had an impact on physical functioning, not a precise estimation of the patients' physical capacity per se. For this purpose, a self-report measure may actually be better than observation or performance. When self-reporting, the respondent will refer to his or her day-to-day function, whereas in a short observation or performance, factors that actually contribute to impaired physical function in daily life may be sustained or not present and therefore go undetected [250]. Overall, we believe that using the QLQ-C30 for measuring physical function is appropriate and has correctly identified patients with impaired physical function. However, as repeated registrations of self-reported physical function were performed in this longitudinal study, we cannot rule out that a potential response shift may

have occurred, meaning that the patients adapted psychologically to changing health status and potentially scored their physical function better than it actually was. Therefore, the decline reported in PF and QoL may have been even more profound than what was shown by the patients' scores.

Attrition
Attrition is the loss of patients during a longitudinal study; patients might die, be too sick to reply, or stop replying for unknown reasons. If patients leaving the study systematically differ from those who remain, this might introduce a bias.

For papers I and II OS was the outcome, and attrition bias was not an issue since we had complete data on survival for all patients. For paper III attrition bias needed to be considered. Although we achieved high response rates on the follow-up QoL questionnaires, the response rate was not 100%. Earlier research suggests that patients not responding, especially those dropping out early in a study, have poorer QoL and PS than responders [251]. There is thus a risk that our QoL scores are overly optimistic. Since our response rate was similar for both frail and non-frail patients, this could be an issue for both patient groups and therefore not likely to affect comparisons between the two groups. There was, however, a higher death rate among frail compared with non-frail patients; attrition bias may have resulted in an underestimation of differences between frail and non-frail patients [252]. A consequence of this potential attrition bias might be that differences in QoL between frail and non-frail patients were even greater than suggested by our results.

Confounding
'Confounding is a mixing or blurring of effects: a researcher attempts to relate an exposure to an outcome but actually measures the effect of a third variable (confounding variable)'[235]. In RCTs confounders are handled by randomizing the patients, in observational studies by statistical adjustments.

Paper I investigated the association between comorbidity and OS. We adjusted for established prognostic factors in NSCLC (PS, stage of disease, gender, smoking history, baseline global QoL, and appetite loss) in cancer patients as well as for treatment. We cannot with absolute certainty exclude that other unknown factors may also contribute, but we believe that we have adjusted for the most relevant in our analyses.

In paper II, investigating the association between frailty and OS in a heterogenic patient cohort, we appropriately adjusted for well-known prognostic factors like PS, age, gender, stage of disease, and cancer type. Since quality of life also is reported to differ according to age, cancer type, gender, performance status, and stage [40, 41, 252, 253], the same factors were adjusted for in paper III.

A limitation with the study design was that it did not prospectively register patients' treatment during follow-up. To be able to adjust for this important confounder, patients' medical journals were retrospectively investigated, and patients were classified into four groups based on treatment received in the first two months of inclusion. We adjusted for this treatment variable in both papers II and III. Unfortunately, in this heterogenic patient cohort, we did not adjust for when patients received an optimal treatment regimen, if they needed a reduced dose of treatment, or if treatment was discontinued. Furthermore, we have no information on course of disease. Therefore, we cannot exclude that part of the differences in QoL or OS between frail and non-frail patients was caused by differences in treatment intensity or tumor

progression. There is a need to confirm our results in more homogenic cohorts where one can account for treatment regimens as well as treatment response.

Discussion of main results

Comorbidity as a prognostic factor in patients with non-small-cell lung cancer
In our patient cohort of advanced NSCLC patients, neither physician-rated comorbidity nor CIRS-G-rated comorbidity was an independent prognostic factor for survival.

Few studies have investigated the prognostic impact of comorbidity rated by CIRS-G in NSCLC patients, and we are not aware of any other reports from cohorts with advanced stage NSCLC cancer receiving chemotherapy. However, Firat et al. reported comorbidity rated by CIRS-G to be an independent prognostic factor in stage I NSCLC patients treated with surgery or radiotherapy as well as in stage III patients treated with radiotherapy with or without concomitant chemotherapy [70, 221, 254, 255].

More commonly used comorbidity scales in studies of lung cancer patients are the CCI and the Simplified Comorbidity Score. By using these scales, comorbidity as a negative prognostic factor in lung cancer has been demonstrated in several patient cohorts with early stage NSCLC treated with surgery or radiotherapy [256-259] as well as in cohorts of all stages of lung cancer [260-263]. The results from studies of advanced NSCLC patients receiving chemotherapy are somewhat mixed. Some find comorbidity to be a prognostic factor [264], while others do not, i.e., consistent with our findings [35, 265]. The results of all the studies mentioned above are, however, not directly comparable to ours since they either differed in the comorbidity scale used, stages of disease included, or types of treatment given.

Overall, it seems evident that comorbidity is prognostic for survival in the early stages of NSCLC, but this is less clear for more advanced stages. One explanation may be that comorbidity has a higher impact in early stage cancer or cancers with good prognoses than when the prognosis is poor [50, 266]. For the same reason, variation in distribution of negative prognostic factors between cohorts, and thereby differences in OS, may also contribute to inconsistent findings in advanced lung cancer. In our study, we included a fair number of patients with PS 2 (21%) who in general have poor prognosis, and the OS was relatively short; therefore, comorbidity might have been of lesser importance than in a cohort of advanced NSCLC comprising patients with better PS and longer survival. Another contributing factor to the reported discrepancies in results between studies of advanced stages may be that different scales have been used to measure comorbidity. The impact of using different scales is clearly demonstrated in studies that have applied two comorbidity indices in the same patient cohort and have reported comorbidity to be a prognostic factor according to one scale but not according to the other [221, 267, 268].

Although comorbidity was not found to be of prognostic importance in our study, and its impact on survival in advanced NSCLC is not clear according to existing evidence, this does not mean that comorbidity should not receive attention in this group of patients in the future. During the last few years, treatment for advanced NSCLC patients has changed considerably. These patients are now mostly treated with immunotherapy and targeted therapy instead of chemotherapy, and life expectancy in advanced cancer is largely improved [24, 72]. Consequently, it is highly possible that comorbidity may now have a more pronounced impact due to prolonged OS. Performing systematic comorbidity assessments is therefore still

relevant in advanced NSCLC patients. There is a need to determine which comorbidities may have the largest impact on OS and other outcomes such as QoL in NSCLC patients treated according to current guidelines. Furthermore, regardless of the uncertainties about the prognostic ability of comorbidity in advanced stages of NSCLC, performing comorbidity assessments gives an appropriate summary of patients' other conditions upon starting cancer treatment and is an important part of the much-recommended geriatric assessment needed to assess patients' vulnerabilities and general health status.

Frailty in older cancer patients
Approximately half the study participants in our patient cohort were frail according to our mGA. As elaborated earlier in the discussion, we cannot with certainty say that we have detected the truly frail patients using our assessment. Still, our frailty prevalence is well within range of what has been observed in other studies [80]. However, the frequency of health problems assessed by our mGA may have been affected by the cancer or cancer treatment received prior to inclusion, which thereby affected our frailty prevalence. Some of our study participants underwent surgery prior to inclusion. It is likely that, for instance, abdominal surgery for colorectal cancer could have had a negative impact on a patient's nutritional status or physical function. Furthermore, cancer symptoms might also negatively affect the domains assessed by our mGA and may have contributed to the patient being classified as frail. We have no knowledge of how and when the patients began having the health problems that rendered them frail according to our definition. Regardless of the cause for being frail, by performing a modified geriatric assessment we identified a larger subgroup of our patients who, independent of well-known cancer-related prognostic factors, had poor survival. Furthermore, these patients consistently reported poorer scores on all functioning and symptom scales from baseline throughout our follow-up period. They also had a more profound deterioration in self-reported physical functioning compared to non-frail patients. This indicates that performing GA in older oncology patients for the presence of frailty is highly relevant.

Several other studies have reported frailty classified according to the Balducci criteria to be prognostic for survival in different patient cohorts, i.e., in surgical colorectal cancer patients [224], in lymphoma patients treated with chemotherapy [195], as well as in studies of mixed cancer diagnoses and stages [194, 269]. The prognostic ability of frailty for survival has also been documented for other frailty definitions. Being frail according to the Fried physical phenotype was associated to poorer survival in studies of both various cancer types and a cohort of pancreas cancer patients [270, 271]. Frailty according to the deficit accumulation method was prognostic for survival in a study of breast cancer patients [272]. Furthermore, frailty screening tools like the Groningen frailty indicator as well as components of the GA also have been reported to be prognostic for survival [130]. Overall, being defined as frail, regardless of the approaches used to detect frailty or vulnerability, seems to have a consistent and significant impact on survival.

A few other studies have investigated how frail older cancer patients perceive their QoL, and the findings are in line with our results. Frail patients seem to be at a considerable disadvantage throughout the disease trajectory, reporting a substantial symptom burden and poor functioning compared to non-frail patients [273-277]. We used QLQ-C30 for our assessments, and although this is generally regarded as an excellent QoL questionnaire, it is debatable whether it captures how the patients' health problems actually affect their quality of life in a broader sense. The questions in the QLQ-C30 are mainly focused on different aspects of health, and some would argue that it assesses perceived health status, not quality of life [278]. However, by using this questionnaire, important information about the patients'

experiences could be retrieved, revealing that frail patients had significantly worse functioning as well as more symptoms compared to those who were non-frail. Increased attention to this vulnerable group is clearly needed. Besides being the cause of severe distress and suffering, poor functioning and a high symptom burden may also hamper patients' ability to live independently, which is one of the most highly prioritized treatment preferences for older patients [279, 280]. To be able to intervene, provide relief, and prevent functional deterioration, knowledge of patients' symptoms and functioning during the course of disease is necessary. A PROM like QLQ-C30 can be an excellent tool for systematic and continuous monitoring. There is also evidence suggesting that systematic symptom monitoring using PROM followed by targeted intervention may improve cancer patients' outcomes [281]. Furthermore, information provided by PROMs is also highly relevant to include in shared decision-making consultations.

Setting aside physical function, which is discussed in more detail below, the findings for most QoL aspects in our cohort are in agreement with what has been found by others, i.e., that although QoL is poorer, changes mainly follow a similar course in frail and non-frail cancer patients. Increased risk of long-term deterioration has, however, been suggested [152, 273]. How an observed similarity of changes in QoL trajectories of frail and non-frail patients should be interpreted is not obvious. One might argue that this indicates that frail patients tolerate cancer therapy equally as well as non-frail patients. Such a conclusion would, however, be dubious based on our data. No information concerning treatment response was registered, and we have no data on whether treatment may have been stopped earlier among frail patients due to side effects and poor treatment tolerance. Detailed information concerning the administered treatment regimens was also unavailable in our heterogeneous patient group. Thus, we do not know if frail patients may have received less intensive treatment (i.e., monotherapy or dose-reduced regimens) than those who were non-frail. Although this seems unlikely due to the fact that the physicians were blinded to the mGA results and the agreement between frailty registered by the oncologist and the mGA was only fair, it cannot be ruled out as a reason for similar QoL trajectories. To clearly untangle how treatment affects outcomes in frail patients in comparison to non-frail, there is a need for further studies in patient cohorts given similar treatment. However, although frail and non-frail patients' QoL scores mainly followed a similar course in our study cohort, a major point is that frail patients were significantly worse off from the start. Despite some of the assessed symptoms being obvious targets for potentially efficient palliative or supportive measures, e.g., pain and constipation, no improvements were registered. Furthermore, it should be kept in mind that changes in the same magnitude may affect frail patients more profoundly than those who are non-frail. Even smaller changes in, for instance, physical functioning may result in loss of independence.

There are few studies investigating longitudinal changes in physical function in relation to frailty status in cancer patients. We are only aware of two other studies that have addressed this association using a PROM for physical functioning and a GA-based frailty categorization. Similar to the findings in our study, both studies reported frail patients to have poorer physical function compared to their non-frail counterparts. Frailty was, however, not found to be predictive of physical decline in either of these studies [274, 275].

Other studies have investigated frailty and scores obtained by frailty screening tools in association with observer-rated physical decline. Several frailty screening tools have been used, amongst them G8, Groningen Frailty Indicator (GFI), Vulnerable Elders Survey-13 (VES-13), and abbreviated Comprehensive Geriatric Assessment (aCGA). The results from

these studies are inconsistent as to whether frailty or frailty screening tool scores are predictive of functional decline. One study found that G8 scores were predictive of early functional decline in 292 patients treated with first-line chemotherapy [282]. A second study found the Fried physical frailty phenotype and the VES-13 scores, but not frailty according to the Balducci criteria, to be predictive of functional decline in 185 older cancer patients with solid tumors mainly receiving systemic treatment [283]. A third study, however, reported neither the GFI, G8, VES-13, nor the aCGA to be predictive of functional decline in 134 cancer patients, amongst whom 29% received chemotherapy [284]. These inconsistencies in results are also present when investigating the impact of deficits in individual geriatric domains. Four studies reported deficits in individual geriatric domains to be predictive of observer-rated physical decline in older cancer patients; in two of these studies patients received chemotherapy or neoadjuvant/adjuvant treatment [115, 245]; in the others a subgroup was given chemotherapy [285, 286]. Two other studies did not, however, find any such association. One of these was a study of a heterogenic cohort of older cancer patients among whom 40% received extensive treatment (for instance, double agent chemotherapy or surgery plus chemotherapy) and had six months of follow-up [287]. The other was a study of lung cancer patients among whom half were treated with chemotherapy and had three months of follow-up [288].

The results from the abovementioned studies as to whether frailty, frailty screening tools, or deficits in individual geriatric domains are predictive of decline in physical function are not consistent. Some of the studies support our findings, while others do not. It is, however, a complex task to compare our results to those of others and to compare findings between different studies for several reasons. First, most of the studies have used observer-rated physical decline and not patients' self-reports, and these are not necessarily comparable. Patients' self-reports, as elaborated earlier in the discussion, refer to patients' day-to-day function, whereas short, objective observation might not detect all factors contributing to impaired physical function in daily life [250]. Self-report might thus be more sensitive to subtle changes in physical function compared to observer-rated tests. Second, the study cohorts varied considerably with respect to cancer types included, which type of treatment the patients received, as well as in follow-up time varying from months to several years. For instance, in the two studies using PROM to report physical function, the patient cohorts were quite dissimilar from ours. One of these cohort included patients with colorectal cancer receiving surgery [275] and patients with head and neck cancer treated mainly with radiotherapy [274]. It is possible that a protracted course of chemotherapy, which was the treatment received by most of our patients, may have a greater impact on frail patients' physical functioning than surgery or radiotherapy. Furthermore, in the study including patients treated with radiotherapy [274], specific assessments of physical functioning were reported at only four weeks after start of therapy, and as indicated by our results, a significant decline may take longer to develop. Third, different methods for identifying frailty were used, and frailty screening tools as well as individual geriatric domains were investigated. These large discrepancies in what was measured, combined with different cut-offs set to define functional decline, may also explain some of the differences in results between the abovementioned study cohorts.

Based on these results it is clear that it is impossible to draw a general conclusion regarding the significance of frailty or deficits in individual geriatric domains for the development of physical function during and after cancer treatment. We do, however, believe QLQ-C30 to be a sensitive and valid PROM for measuring patients' daily physical functioning and might be even more sensitive than mere observation. Our results are also in accordance with what has

been shown in other areas of medicine where frailty is associated with increased risk of falls, fractures, and disability [289]. From a clinical point of view, it is reasonable to assume that physical function might be affected by systemic cancer treatment like chemotherapy. Overall, we believe our results give a strong indication that by performing a systematic mGA in older cancer patients at medical oncology clinics, we can identify a vulnerable patient group with poor physical function at risk for experiencing physical decline during cancer treatment and in need of attention as well as intervention to prevent further physical decline. However, to be able to further document this, there is a need for further studies involving more homogenic patient cohorts.

Overall, our study makes a significant contribution to the growing evidence that frailty has a large impact on important outcomes in older cancer patients [290] as well as in other areas of medicine [162]. Performing GA and detecting patients' vulnerabilities may be the first step towards optimizing treatment for frail older cancer patients.

Clinicians' assessments versus systematic registrations of comorbidity and frailty
Despite frailty and comorbidity being prognostic and predictive factors, no systematic assessment of these factors has been implemented as routine in clinical practice. Thus, how thoroughly an older patient is assessed in these areas depends on the patient's oncologist. Our findings in both papers I and II indicate that clinicians without additional training are unable to detect comorbidity and frailty as effectively as a systematic assessment. In paper I we found poor agreement between comorbidity rated by the local investigators and that rated by trained oncologists using the CIRS-G manual. More comorbidity was identified for most of the organ systems, and the scores were generally higher for the CIRS-G scores compared with the LI-assessments. In paper II the oncologists classified very few patients as frail, and even when pooling frail and intermediate patients (according to the oncologists), they missed almost half the patients who were frail according to the systematic mGA. The most commonly missed frailty domain was comorbidity. Furthermore, the prognostic value of the oncologists' frailty assessments was not independent of other well-established prognostic factors.

To our knowledge, there are no previously published studies that compare in detail the results of CIRS-G comorbidity assessments in patients with NSCLC and a similar but less comprehensive assessment performed by local investigators. However, the amount of comorbidity registered seems to be highly dependent on what is used for assessment [291]. There are several plausible explanations for the differences in ratings between the local investigators and the trained researchers. The local investigators rated comorbidity only as part of the inclusion process, as opposed to the trained oncologists rating comorbidity as their primary aim. This difference in primary focus might have resulted in local investigators to a larger degree overlooking less severe comorbidity, for instance, well-regulated comorbidities only noticeable by examining patients' lists of regular medications. It is also likely that the local investigators focused on comorbidities that were relevant for treating the patient and that less severe comorbidity may have been perceived as irrelevant in light of the patient's lethal cancer disease. Furthermore, severe comorbidity as classified by the CIRS-G manual from 1991 might have been perceived as less severe comorbidity by the local investigators due to progress in medical treatment. In our patient cohort, the local investigators missed a large number of comorbidities compared with trained oncologists using the CIRS-G manual; however, neither of the comorbidity ratings were significant prognostic factors for survival in our patient cohort.

Our physicians were more conservative when rating frailty than was a systematic GA, this in accordance with the findings of others [195, 218]. In our study the oncologists' frailty assessments were not independent prognostic factors for survival when adjusted for other well-known prognostic factors, and their classifications of frailty seemed to be based mostly on cancer-related prognostic factors. Oncologists are experienced in evaluating cancer-related health, but training in identifying patients' overall vulnerability, including geriatric problems that may affect prognosis, seems insufficient. The domain (or reason for frailty) most frequently missed by the oncologists in paper II was comorbidity, thus underlining the need for systematic comorbidity assessment in clinical care.

Systematic approaches to assess frailty and comorbidity thus represent more sensitive methods than merely using oncologists' clinical judgement. This is in accordance with studies of symptom reporting in palliative patients: more symptoms are detected using systematic symptom assessments compared to patient interviews [216]. Furthermore, systematic symptom registrations and interventions have been shown to reduce the need for hospitalization, have a positive impact on HRQoL, and increase the treatment duration of palliative chemotherapy [281].

Future directions

Since the start of our study, the challenges posed for our health care systems by an aging population and a growing number of older patients with cancer, have been increasingly recognized. Considering not only the growing number of new cancer diagnosis in older people, but also the improvement of modern treatment and a growing number of older cancer survivors, the situation has been referred to as a "silver tsunami". Following this, treatment and care for older patients with cancer have gained increasing focus, and among the areas having received particular attention are the assessment of age-related problems including comorbidity, identification of frailty, and the impact of these factors on cancer outcomes.

Within the expanding field of geriatric oncology, the GA or modifications of this, is a recommended approach for the assessment of older patients with cancer, and during the last few years its' usefulness has become increasingly evident. A range of more recent studies have shown that performing GA can help identify patients' vulnerabilities that would otherwise have gone unrecognized [215], help predict complications of cancer treatment [106, 122] as well as predict survival [145]. These findings are supported by studies from other patient groups, e.g., older patients undergoing cardiac surgery [292] or patients undergoing surgery after a hip fracture [293], and our results add significant evidence to the benefit of performing GA in older cancer patients.

As in our studies, GA has also repeatedly been used to identify frailty. Whether this results in the most optimal classification of frail versus non-frail patients in all circumstances is a subject for discussion. From a clinical point of view, however, this may not be the most important. In clinical practice, we meet a continuum of frailty among our patients, and the main objective would be to identify their individual vulnerabilities. We found that the oncologists failed to recognize frailty in a large number of patients, and also missed a range of comorbidities. On the other hand, by performing our mGA, we identified patients with poor QoL, high symptom burden and poor survival, who needs particular attention. These findings underline the need for a broad systematic assessment of older cancer patients, and based on current evidence as well as present results, GA may be the preferred method.

Although still young, the geriatric oncology field is growing, and around the world there have been established research units, fellow training programs as well as clinical units especially focused on geriatric oncology [294]. Despite GA being highly recommended in older cancer patients [174, 189], this assessment is yet to be implemented as a routine in clinical care in Norway. Introducing GA into an already busy oncology clinic requires time as well as skills in geriatrics and the implementation process needs to be adapted to local structures and available recourses. In larger hospitals having both geriatric and oncology expertise this might be achieved by establishing a close collaboration and special geriatric oncology teams to perform GA in older cancer patients. In smaller hospitals, however, there is often few geriatricians available. To be able to introduce geriatric oncology into all hospitals it is also reasonable to educate oncologist in basic geriatrics as part of their fellow training. Furthermore, whether all older cancer patients need a full GA is questionable. Introducing a simple frailty screening tool, e.g., G8 or VES-13, as part of the standard assessments of older cancer patients is simple, requires minimal time and recourses, and might be the most efficient and useful way to introduce geriatric assessment into oncology. All patients scoring above a certain cut-off value in the frailty screening tools could then be recommended be assessed by a full GA. The need for introducing some sort of GA or frailty screening becomes

increasingly important as our cancer population ages and patients are being treated with several lines of different systemic treatment.

Although GA gives us important knowledge of the older cancer patient, most studies so far have focused on the prognostic and predictive ability of a geriatric assessment, while little documentation exists of whether intervening on geriatric deficits identified by a GA will improve older cancer patients' outcomes. We need future studies specifically planned for older cancer patients that investigate whether intervening on geriatric deficits can improve patients' treatment tolerance, OS or QoL. There is also a need for interventional studies to investigate whether by adjusting treatment according to frailty level, one can improve outcomes for frail older cancer patients. A well-known study of advanced NSCLC patients, for instance, used GA and randomized patients to receive either standard treatment or treatment based on frailty level [295]. Despite significantly more patients being treated with best supportive care in the GA-arm, survival in the two groups was similar, and patients in the GA-arm reported significantly less toxicity. Results from other RCTs including GA are pending [296, 297].

In general, older patients are still underrepresented in clinical trials investigating new forms of cancer treatment. Thus, continuous work to increase the number of older patients into all ongoing cancer trials is essential to gain knowledge of treatment tolerance and prognosis. There is a need for more studies including GA in older patients receiving systemic cancer therapy. Optimally, to avoid potential confounders, these studies should include more homogeneous population cohorts with respect to cancer type and treatment as well as information about treatment response and the need for dose reduction or treatment delays. Furthermore, by including information from systematic comorbidity and frailty registrations we can achieve information about patients' treatment tolerance according to frailty and comorbidity level. By measuring outcomes highly valued by older cancer patients, e.g., introducing a PROM like QLQ-C30 as a longitudinal outcome, we can gain knowledge of older patients functioning and symptoms during cancer treatment. This information is of major importance for them being able to engage in shared decision making when planning cancer treatment. Furthermore, although consensus of which areas to include in a GA has been reached, it would be an advantage to reach a consensus on a frailty definition based on a GA as well as cut-offs of different assessment tools to ease comparison between trials.

Conclusions

Systematic assessment of comorbidity and frailty in cancer patients detects more comorbidity and frailty when compared with physician's clinical judgement.

The assessment method used to measure comorbidity and frailty affects the amount of registered comorbidities and frailty. Thorough description of comorbidity and frailty registrations in trials are paramount due to lack of a standardized assessment.

Being frail according to a systematic geriatric assessment is an independent prognostic factor for overall survival.

Geriatric assessment identifies frail patients with increased risk of physical decline, poor functioning and high symptom burden during and following cancer treatment.

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Clinical Trials

Comparing comorbidity scales: Attending physician score versus the Cumulative Illness Rating Scale for Geriatrics

CrossMark

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ABSTRACT

Objectives: Assessing comorbidity using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and its comprehensive manual is time consuming. We investigated if similar information could be obtained by a simpler assessment based on the original CIRS.

Materials and Methods: Data from a randomized chemotherapy trial (RCT) on advanced NSCLC (non-small cell lung cancer) were analyzed. Baseline comorbidity was assessed by 1) trained oncologists using hospital records and the CIRS-G manual (CIRS-G), 2) by patients' oncologists/pulmonologists (local investigators = LI-score) using a brief set of instructions. By both methods, the severity of comorbidity in 14 organ systems was graded 0 (no problem) to 4 (extremely severe). The agreement between methods was assessed using Bland–Altman analysis and weighted kappa statistics. The impact of comorbidity on survival was analyzed by Cox regression.

Results: Complete data were available for 375/446 (84%) patients enrolled in the RCT. Median age was 65 years (25–85). Overall, more comorbidities and higher severity were registered by the CIRS-G compared to the LI-score. Severe comorbidity was registered for 184 (49%) and 94 (25%) patients according to the CIRS-G and LI-scores, respectively. Mean total score was 7.0

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(0–17) (CIRS-G) versus 4.2 (0–16) (LI-score), and mean severity index (total score/number of categories with score >0) was 1.73 (SD 0.46) versus 1.43 (SD 0.78). Neither the CIRS-G scores nor the LI-scores were prognostic for survival.

Conclusion: The CIRS-G scores and LI-scores had poor agreement, indicating that assessment method affects the registration of comorbidity. Thorough descriptions of comorbidity registrations in trials are paramount due to lack of a standardized assessment.

1. Introduction

The proportion of older patients with cancer is increasing, and comorbidity is more frequent in older age.[1–3] Comorbidity is reported as an independent prognostic factor for survival in patients with cancer.[4–6] Whether this is a result of the comorbid disease itself or caused by inferior treatment is not clear. However, it is known that patients with cancer with higher comorbidity burden are less likely to receive similar tumor treatment as their healthier counterparts.[7, 8] This may be caused by an assumption of less benefit from treatment due to shorter survival expectancy. It may also be due to concerns about more toxicity, as indicated in some studies.[9, 10] The association between treatment tolerability and various coexisting diseases has, however, been poorly investigated. To better understand how patients with coexisting diseases should be treated, a valid method for systematic assessment of comorbidity in clinical trials is required.

Several methods for assessing comorbidity have been developed. Among the most commonly used are the Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[11–13] CCI is the most widely used. It is easy to complete and can be scored from hospital charts or by using the International Classification of Diseases (ICD) codes for diagnoses.[14,15] The original CIRS scale was developed by Linn et al.[16] Comorbidity was classified according to organ system and graded on a scale from 0-4. Miller et al modified CIRS to better reflect the geriatric patient,[13] developed a scoring manual[17] and renamed the scale as CIRS-G. The CIRS-G manual has later been updated according to changes in diagnostic criteria and treatment of common diseases.[18] In comparison to CCI, CIRS-G is more sensitive since all coexisting diseases are registered,[11] and in comparative studies, it appears to provide more prognostic information.[19] It is, however, more time-consuming and less feasible in multicenter studies since assessment by specifically trained personnel is recommended.[11]

The present study is based on data from a Norwegian multicenter phase III trial comparing two first-line chemotherapy regimens in advanced non-small cell lung cancer (NSCLC).[20] When patients were enrolled, the patients' oncologists/pulmonologists were asked to assess comorbidity in 14 organ systems using a brief set of instructions based on the original CIRS[16] (local investigator-score = LI-score). Later, trained researchers (oncologists) at the trial office assessed the patients' comorbidity from the medical records using the CIRS-G manual (CIRS-G).[17] The aim was to compare the LI-scores to the CIRS-G scores, and to assess the agreement between these scores. We also aimed to explore the prognostic impact of the LI-score. In a previous publication, no association between the CIRS-G scores and survival in this cohort of patients was reported.[9] Our hypothesis was that the local investigators, with detailed knowledge about their patients, were better at identifying the comorbidities that were likely to affect the patients' prognosis, and hence that these scores might be associated with survival.

2. Materials and Methods

2.1. Patients

Patients enrolled in a phase III trial comparing gemcitabine/carboplatin with pemetrexed/carboplatin as first-line treatment of advanced NSCLC were considered for the present study.[20] Eligible patients had given written informed consent, completed the baseline European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), received at least one cycle of chemotherapy and both LI-score and CIRS-G scores were available (Fig. 1). No differences in overall survival or quality of life (QoL) between the two trial arms were reported in the main trial, and there were only minor differences in toxicity.[20] Thus, all patients were analyzed jointly.

2.2. Assessment of Comorbidity

Both local investigators (oncologists and pulmonologists) and the oncologists who performed the CIRS-G scores assessed the severity of coexisting diseases in 14 organ systems/scales in accordance with the CIRS-G comorbidity index. Severity ranged from 0 to 4: "0" indicating no problem, "1" a current mild problem or past significant problem, "2" a moderate disability or morbidity requiring "first-line" therapy, "3" a
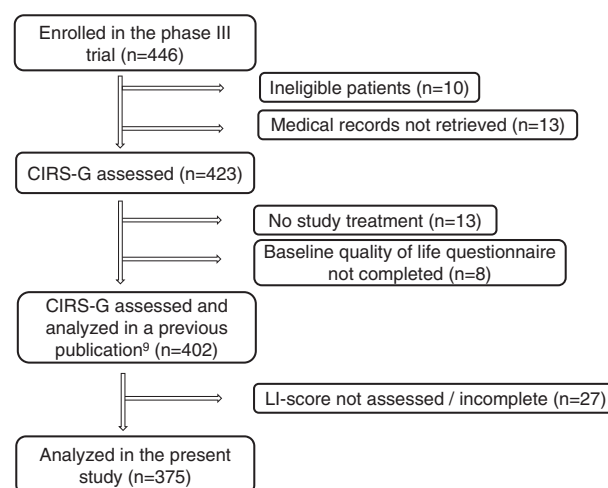

Fig. 1 – Patient selection.

severe/constant significant disability or an "uncontrollable" chronic problem, and "4" an extremely severe/immediate treatment required/end organ failure/severe impairment in function.

The local investigators received no formal training in assessing comorbidity, just a brief written set of instructions based on the original CIRS (Table 1). They performed the comorbidity rating when enrolling patients in the trial, based on clinical assessment and knowledge of patients' medical history.

Retrospectively, three trained researchers, all oncologists, assessed and scored comorbidity from hospital records of the three months prior to randomization using the CIRS-G manual from 1991.[17] For each patient, CIRS-G was assessed independently by two researchers. In case of different scores, the researchers discussed the assessment and reached consensus. The most common reason for different scores was that one of the investigators had overlooked a minor comorbidity in the medical records.

2.3. Analyses and Statistical Considerations

Demographic and clinical characteristics at baseline are presented as median/mean with range, or frequencies and percentages. The proportions of patients with LI- and CIRS-G scores ≥1 and ≥3 in each organ system were compared using χ^2 or Fisher's exact test depending on the percentage of observations in each cell (cut-off value was 5%).

For both LI- and CIRS-G scores, the total score (=the sum of scores in all organ systems), severity index (=total score/number of categories with a score >0), and severe comorbidity (≥one score 3 or 4) were calculated for each patient. Previous studies on patients with lung cancer have reported inferior survival in patients having a severity index >2 or at least one grade 4 comorbidity compared with patients having less comorbidity.[5,19] Thus we defined "high severity index" as having a severity index >2. However, to differentiate between a comorbidity graded 3 or 4 may be difficult; hence, we defined "severe comorbidity" as having ≥1 comorbidity grade 3 or 4 in an organ system, as in our previously published study of the prognostic role of comorbidity in advanced NSCLC.[9]

We used the Bland–Altman analysis to assess the level of agreement between the CIRS-G scores and the LI-scores on "Total score" and "Severity index." Weighted kappa statistics was used to estimate the level of agreement on the "Severe comorbidity" scores.

Survival time was defined as time from randomization until death. Cox regression analyses adjusting for established prognostic factors in advanced NSCLC (performance status (PS)[21], stage of disease,[22] gender,[9, 23] smoking history,[24] baseline global

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Table 1 – Written instructions for local investigators on how to rate comorbidity.

SCORING OF COMORBIDITY

0 No morbidity
1 Mild morbidity or previously significant morbidity.
All conditions that have given discomfort, except from e.g. childhood illnesses, small surgery, or uncomplicated fractures.
Cancer diagnosis without any signs of activity in the last 10 years.
2 Moderate disability or morbidity in need of simple treatment.
Conditions that require daily (regular) medication. "First-line treatment." Cancer diagnosis without any signs of activity in the last 5 years.
3 Severe/constant impairment.
Chronic conditions that require more than first-line treatment—"second-line treatment." Cancer treatment the last 5 years
(apart from NSCLC).
4 Extremely severe condition/acute treatment necessary/organ failure/severe disability.
End stage of a disease/disability. Despite treatment, the condition is symptomatic and/or reduces the patient's functional status
(except when caused by the lung cancer).
If several conditions in an organ system: register the condition with the highest score.

SIMPLE GUIDELINES FOR THE DIFFERENT ORGAN SYSTEMS

Cardiac: E.g. ischemic heart disease, heart failure, arrhythmia, valve disease, pericarditis.
Vascular: E.g. hypertension, atherosclerosis, aortic aneurysm. Note: Intracranial vascular events are scored under neurologic status.
Hematopoietic (blood, bone marrow, spleen, lymph nodes): Note: Not changes in hematology presumed secondary to the patient's
lung cancer.
Respiratory (lungs, bronchia, trachea): E.g. asthma, chronic obstructive lung disease, infections. Smoking history: 10–20
pack years = score 1, 20–40 = score 2, >40 = score 3.
Eye/Ear/Nose/Throat (incl. larynx): Sight, hearing, vertigo, dizziness.
Upper GI (esophagus, stomach, duodenum): E.g. hiatus hernia, gastritis, dyspepsia.
Lower GI (bowel, hernia): E.g. constipation, diverticulitis, hemorrhoids.
Liver (included bile/pancreas): E.g. gallbladder problems, hepatitis, pancreatitis.
Kidney: E.g. kidney disease, kidney stone.
Genitourinary system (ureters, bladder, urethra, prostate, genitalia): E.g. incontinence, local prostatic cancer, cervical cancer,
urinary retention, recurrent urinary tract infections.
Musculo-skeletal system (muscles, bones, skin): E.g. skin cancer, rheumatoid disease, osteoporosis.
Neurology (brain, spinal cord, nerves): E.g. headache, TIA, stroke, Parkinson's disease, MS, ALS. Note:
Register vertigo/dizziness under ear/nose/throat, dementia under psychiatry.
Endocrine/metabolic and breasts (included diffuse infections and poisonings): E.g. diabetes, hypothyroidism, obesity,
pathology in breast.
Psychiatric: incl. dementia.

QoL[25] and appetite loss[26]) and study treatment were conducted in order to investigate whether any comorbidity scores were independent prognostic factors for survival. The models were then repeated in an explorative analysis in a subgroup of patients ≥70 years. Appetite loss and global QoL were retrieved from the baseline EORTC QLQ-C30. Appetite loss was defined as having a score >0 on the item "have you lacked appetite" and the global QoL scale ranging from 0 to 100 was dichotomized at a cut-off 66.[9] The predictive ability of the different comorbidity models was evaluated by calculating a C-index. Statistically significant levels were defined as p < 0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows v 22 (IBM Corp, Armonk, NY) and STATA v 12 (Stata Corp, College Station, Texas).

2.4. Approvals

The study was approved by the Regional Committee for Medical Research Ethics in Central Norway, the Norwegian Medicines Agency, the Norwegian Social Science Data Services, and the Norwegian Directorate for Health and Social Affairs.

3. Results

3.1. Patients

Complete data were available for 375/446 (84%) patients enrolled in the phase III trial (Fig. 1). Of the 402 patients who previously had their CIRS-G scores analyzed, 375 (93%) had complete LI-scores. Baseline patient characteristics are shown

Table 2 – Baseline patient characteristics and study treatment for all patients.

Characteristic	All patients (n = 375)	
Age, median (range)	65 years (25–85)	
	No. of patients	%
≥75 years	70	19
Gender		
Male	213	57
Female	162	43
Performance status		
0-1	295	79
2	80	21
Extent of disease		
Stage IIIB	108	29
Stage IV	267	71
Histology		
Squamous cell carcinoma	95	25
Adenocarcinoma	188	50
Other	92	25
Smoking history		
Never-smoker	27	7
Ever-smoker	348	93
Study treatment		
Pemetrexed/carboplatin	186	50
Gemcitabine/carboplatin	189	50

in Table 2. Median age was 65 years, 135 (36%) of the patients were ≥70 years, 213 (57%) were men, 295 patients (79%) had PS 0-1, 108 (29%) patients had stage IIIB.

3.2. Comorbidity

Fewer patients had one or more comorbidities registered by the local investigators (n = 325, 87%) than by the trained researchers (n = 371, 99%) (Table 3). For most individual organ systems/scales, the LI-scores included a lower number of comorbidities than the GIRS-G scores (Table 3). The largest difference in scores in favor of the CIRS-G was found for the hematopoietic system where 12 and 191 patients had one or more comorbidities according to the LI- and CIRS-G scores, respectively. The exceptions were eye/ear/nose/throat diseases (similar frequencies of comorbidity for both comorbidity scales) and upper-GI and renal diseases (the LI-scores were higher than the CIRS-G scores).

Overall, 94 (25%) versus 184 (49%) patients had severe comorbidity according to the LI- and CIRS-G-scores, respectively (Table 3). A total of 74 (20%) and 140 (37%) patients had one severe comorbidity according to the LI- and CIRS-G-scores, respectively, whereas two severe comorbidities were registered in 16 (4%) and 38 (10%) patients. Only 4 (1%) and 6 (2%) patients had three or four severe comorbidities, respectively. Investigating the agreement between LI- and CIRS-G scores for severe comorbidity, weighted kappa was 0.18 (95% CI 0.10; 0.25), suggesting a slight agreement between the two scores. Values from 0.41 to 0.60 are considered to represent a moderate agreement, 0.61–0.80 substantial agreement.[27]

Fig. 2A and B show the distribution of the patients' total comorbidity scores. The total LI-scores were skewed toward lower total scores (Fig. 2A), whereas the CIRS-G total scores had a more normal distribution (Fig. 2B). The mean total LI-score was 4.2 (range 0–16), and the mean total CIRS-G score was 7.0 (range 0–17). A scatter plot comparing the two total comorbidity scores showed a broad scatter with little tendency to concentrate in the vicinity of the identity line, indicating poor agreement between the two comorbidity scores (Fig. 2C). We found a significant bias of −2.87 (p < 0.001) confirming that the total CIRS-G scores were consistently higher than the total LI-scores. A wide 95% limits of agreement (±6.40) in the Bland–Altman plot (Fig. 2D) further confirmed the poor agreement between the two comorbidity scores.

The mean severity index was 1.43 (SD 0.78) versus 1.73 (SD 0.46) according to the LI-scores and CIRS-G, respectively. Overall, 46 (12%) patients had a high severity index (>2) according to the LI-scores versus 58 patients (16%) according to the CIRS-G scores. A scatter plot comparing the two severity indices (not presented) revealed a poor agreement. Moreover, the disagreement seemed to increase with higher values.

3.3. Survival

According to both univariate and the four multivariate analyses (Table 4), neither the "high severity index" nor "severe comorbidity" scores from LI-scores or CIRS-G scores were significant prognostic factors of survival. In the univariate survival analyses, gender (p = .02), smoking history (p = .04), baseline global QoL (p = .01), performance status (p = .01), and

Table 3 – Number of patients with ≥1 comorbidity and severe comorbidity (>score 2) according to organ system.										
	≥1 comorbidity					Severe comorbidity				
	CIRS-G	%[a]	LI-score	%[a]	P-value	CIRS-G	%of all[b]	LI-score	% of all[b]	P-value
Respiratory	314	84	203	54	<0.01[*]	94	30	49	24	<0.01[*]
Hematopoietic	191	51	12	3	0.14[**]	9	5	0	–	–
Vascular	165	44	108	29	<0.01[*]	37	22	12	11	<0.01[**]
Musculo-skeletal system	154	41	128	34	<0.01[*]	13	8	17	13	0.02[**]
Genitourinary system	133	35	72	19	<0.01[*]	16	12	3	4	0.01[**]
Cardiac	107	29	99	26	<0.01[**]	36	34	13	13	<0.01[**]
Lower GI	101	27	46	12	0.01[*]	1	1	0	–	–
Eye/Ear/Nose/Throat	68	18	67	18	<0.01[*]	3	4	6	9	<0.01[**]
Neurology	65	17	53	14	<0.01[**]	9	14	9	17	<0.01[**]
Liver	61	16	17	5	<0.01[**]	4	7	0	–	–
Endocrine/metabolic/breast	51	14	39	10	<0.01[**]	1	2	4	10	0.01[**]
Upper GI	49	13	68	18	<0.01[**]	3	6	3	4	1.00[**]
Psychiatric	47	13	33	9	<0.01[*]	9	19	1	3	0.02[**]
Kidney	8	2	19	5	<0.01[**]	0	–	1	5	–
≥1 comorbidity (total)	371	99	325	87						
Severe comorbidity, (total (%))						184 (49)		94 (25)		

[a] Percent of all study patients.
[b] Percent of all comorbidities registered within the organ system in question.
[*] Differences between scales (χ^2-test).
[**] Differences between scales (Fisher's exact test).

appetite loss (p = .02) were all found to be significant prognostic factors, whereas only gender and smoking history remained significant in the multivariate analyses.

All four multivariate models had a moderate predictive ability. For the models with severe comorbidity as predictor, the C-index was 0.62 (CI 0.58; 0.65) and 0.61 (CI 0.58; 0.65) for the LI- and CIRS-G scores, respectively. For the models with severity index as predictor, the corresponding indices were 0.61 (CI 0.58; 0.65) (LI) and 0.62 (CI 0.58; 0.65) (CIRS-G). When comparing the four C-indices, they were not significantly different from each other; hence, there were no indications that any comorbidity variable outperforms the other.

Finally, we explored if comorbidity was more frequent in older (≥70 years) than in younger (<70 years) patients and influenced survival in the older group in particular. According to the LI-scores, 27% and 9% of the older patients had severe comorbidity and high severity index respectively, compared to 24% and 14% of the younger. According to the CIRS-G scores, severe comorbidity and high severity index were registered in 62% and 16% in the older subgroup, and in 42% and 15% in the younger. Neither LI-scores nor CIRS-G scores were significant prognostic factors for survival when analyzing patients ≥70 years separately (Appendix 1).
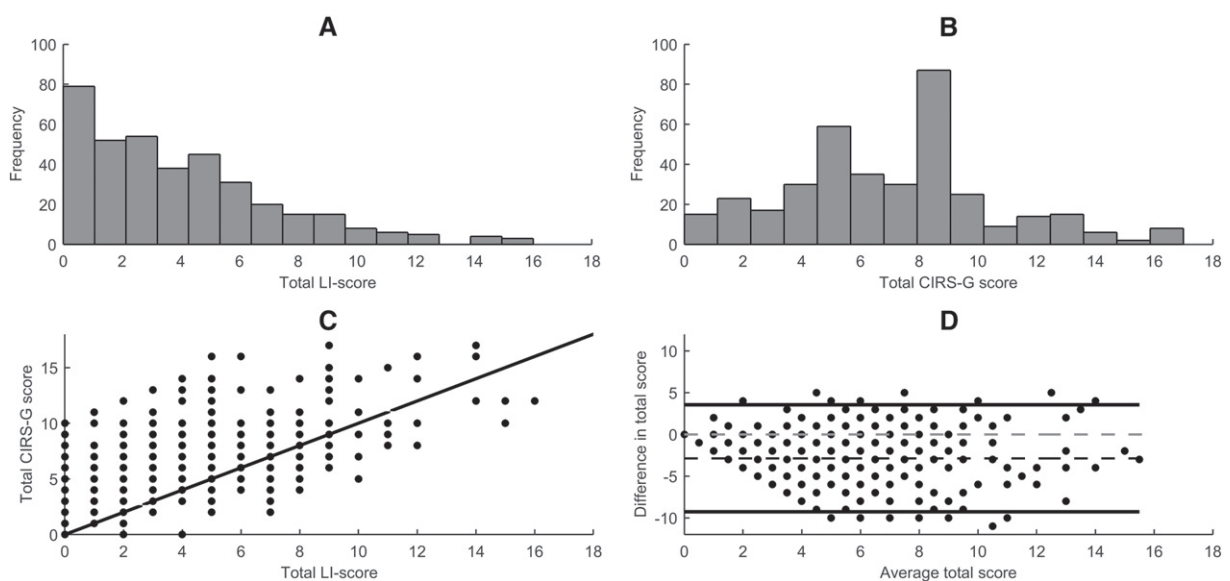

Fig. 2 – The distribution of (A) total LI-score and (B) total CIRS-G score. (C) Scatterplot of total LI-score versus total CIRS-G score and (D) Bland–Altman plot of differences in total score between the two comorbidity assessments with a negative bias (higher total CIRS-G scores than total LI-scores) and wide limits of agreement.

Table 4 – Univariate and multivariate Cox regression analyses of the prognostic impact of both CIRS-G and LI-score on survival.

Variable	N (%)	Univariate analyses		Multivariate analyses[a]							
		HR (95%CI)[b]	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Severe comorbidity CIRS-G[c] (ref. no severe)	184 (49.1)	1.11 (0.89;1.40)	.35	1.07 (0.84;1.37)	.59						
High severity index CIRS G[d] (ref. low)	58 (15.5)	0.96 (0.71; 1.31)	.80			0.94 (0.69; 1.29)	.71				
Severe comorbidity LI-score (ref. no severe)	94 (25.1)	1.03 (0.79; 1.33)	.85					0.89 (0.68;1.17)	.40		
High severity index LI-score (ref. low)	46 (12.3)	1.10 (0.79; 1.55)	.57							0.98 (0.68; 1.42)	.93
Performance status 1 (ref. 0)	217 (57.9)	1.04 (0.78;1.40)	.78	0.95 (0.70;1.30)	.76	0.97 (0.71;1.32)	.85	0.98 (0.71;1.33)	.87	0.97 (0.71; 1.32)	.83
2 (ref. 0)	80 (21.3)	1.63 (1.15;2.30)	.01	1.37 (0.94;1.99)	.10	1.39 (0.96; 2.02)	.08	1.43 (0.98;2.09)	.06	1.39 (0.95; 2.04)	.09
Stage IV (ref. IIIB)	267 (71.2)	1.19 (0.92;1.54)	.18	1.25 (0.96;1.63)	.10	1.22 (0.94;1.59)	.13	1.22 (0.94;1.58)	.14	1.23 (0.95;1.59)	.12
Gender Women (ref. men)	162 (43.2)	0.76 (0.60; 0.95)	.02	0.77 (0.60;0.98)	.03	0.75 (0.59;0.96)	.02	0.75 (0.59;0.95)	.02	0.76 (0.60; 0.96)	.02
Smoker Former (ref. never)	199 (53.1)	1.65 (1.02;2.67)	.04	1.70 (1.05;2.76)	.03	1.73 (1.07;2.81)	.03	1.74 (1.08;2.82)	.02	1.72 (1.07; 2.79)	.03
Current (ref. never)	149 (39.7)	1.61 (0.99;2.61)	.06	1.63 (0.99;2.68)	.05	1.67 (1.02;2.73)	.04	1.67 (1.02;2.74)	.04	1.66 (1.01;2.71)	.05
Age, years ≥75 (ref. <75)	70 (18.7)	1.01 (0.75;1.34)	.97	1.00 (0.74;1.34)	.97	1.00 (0.74;1.35)	.99	1.01 (0.75;1.36)	.97	1.00 (0.74;1.35)	.99
Treatment Gem/Carbo[e] (ref Pem/Carbo[f])	189 (50.4)	1.12 (0.90;1.41)	.31	1.01 (0.80;1.27)	.97	1.01 (0.80;1.28)	.92	1.01 (0.80;1.28)	.91	1.01 (0.80;1.28)	.92
Global quality of life[g] High (ref. low)	133 (35.5)	0.74 (0.58;0.93)	.01	0.80 (0.61;1.04)	.10	0.80 (0.61;1.04)	.09	0.80 (0.61;1.04)	.09	0.80 (0.61;1.04)	.10
Appetite loss[g] Yes (ref. no)	203 (54.1)	1.30 (1.04;1.63)	.02	1.26 (0.99;1.60)	.06	1.24 (0.98;1.58)	.08	1.23 (0.97;1.57)	.09	1.25 (0.98;1.59)	.08

[a] Multivariate analyses with both comorbidity scales (CIRS-G/LI-score) and both comorbidity measurements (high severity index/severe comorbidity) adjusting for established prognostic factors in NSCLC.
[b] CI = Confidence interval.
[c] Severe comorbidity = Scores >2.
[d] High severity index = Score >2.0.
[e] Gemcitabin/Carboplatin.
[f] Pemetrexed/Carboplatin.
[g] Retrieved from baseline EORTC QLQ-C30.

4. Discussion

This multicenter trial demonstrated that the local investigators had excellent compliance in completing a short comorbidity scale. There was, however, poor agreement between the comorbidity scores registered by the local investigators and those made by trained oncologists using the CIRS-G manual. In the CIRS-G assessments, more comorbidity was identified for most of the organ systems and the scores were generally higher compared with the LI-assessments. Neither the LI-scores nor the CIRS-G scores were significant prognostic factors of survival in the overall cohort or among patients ≥70 years.

To our knowledge, there are no previously published studies that compare in detail the results of CIRS-G comorbidity assessment in patients with NSCLC and a similar but less comprehensive assessment performed by local investigators. There are, however, three studies that describe the occurrence and severity of comorbidity in patient cohorts according to both CIRS-G and CCI.[5,19,28] In two of these studies, CCI was found to be a less sensitive comorbidity index compared with CIRS-G.[5,19] These findings are supported by Extermann et al. that reported the prevalence of comorbidity in a patient cohort of older patients with cancer with different tumor types to be 36% according to CCI and 94% according to CIRS-G.[12] Our study confirms that the method used for comorbidity scoring largely influences the number and severity of coexisting diseases detected.

Few studies have investigated the occurrence and severity of comorbidity using CIRS-G in NSCLC.[10,19,29] The reported frequency varied, but with the exception of some selected subgroups,[10,29] the proportion of patients with comorbidity was similar or higher than that found in our study. However, the cohorts of these studies are not directly comparable with ours since they included patients who underwent radiotherapy[19,29] and selected cohorts of older patients (≥70 years) or patients with poor PS.[10]

The CIRS-G assessments in this study were performed retrospectively based on hospital medical records including lists of every patient's medication. These records may be incomplete, potentially reducing the sensitivity of our CIRS-G assessments. The accuracy of the CIRS-G assessments may also be affected by the use of the old manual by Miller from 1991[17] instead of the new manual with updated diagnostic criteria, classification, and treatment of common diseases.[18] However, despite the limitations with our CIRS-G scores, the number and severity of comorbidities registered with these scores were higher than the LI-scores, indicating that the medical records contained more information than identified by the local investigators.

There are several possible explanations why less comorbidity was registered by the local investigators than by the trained oncologists. The local investigators had no training, were provided with a brief instruction and rated comorbidity only as part of the patient inclusion procedure. In contrast, the trained oncologists rated comorbidity as their primary objective and strictly according to the CIRS-G manual. The trained oncologists often found medications indicating comorbidities that were not mentioned in the text in the medical records (e.g. hypothyroidism). This might have been overlooked by the local investigators rating LI-score if the condition was well controlled with medication. Another explanation may be that treatment outcomes of common comorbidities have changed significantly since the CIRS-G manual was developed in 1991.[13,17] This medical progress might have affected the local investigators perception of how severe comorbidities are, e.g., when rating a previous myocardial infarction. Possible reasons for the large discrepancies in the hematopoietic system may be that the local investigators did not look at the blood counts when rating comorbidity, or they considered the abnormalities to be caused by the lung cancer. Some of the local investigators were possibly above all concerned about conditions relevant for the treatment and follow-up of lung cancer. An asymptomatic or medically well-regulated comorbidity might be considered as less severe or irrelevant in light of the patient's aggressive cancer. However, the local investigators did not only rate comorbidity relevant for treatment of the patient's lung cancer, since some of them scored minor comorbidities rated in all organ systems, including, e.g. the musculo-skeletal system.

As for the CIRS-G scores in our previously published study,[9] no significant association between LI-scores and survival was found. Hence, our hypothesis that local investigators were able to detect comorbidities with significant impact on survival was not confirmed. A negative prognostic influence of comorbidity in NSCLC has been demonstrated in studies analyzing mixed cohorts with different disease stages.[4,19,30–32] However, results from studies in advanced lung cancer are consistent with our findings.[25,33] A possible explanation might be that in this stage, the cancer itself is a highly lethal disease with poor prognosis. As shown by Read and colleagues, the impact of comorbidity on survival is smaller in aggressive cancer with short life expectancy.[34] It is still possible that comorbidity might particularly affect survival in older age groups. However, this was not confirmed in our patients ≥70 years who may represent a selected group. Although eligibility criteria in the phase III trial were wide, there were restrictions regarding liver, kidney, and bone marrow function, as well as performance status. Furthermore, taking the Norwegian incidence of NSCLC by age group into considerations, the proportion enrolled in the trial was lower for older than for younger patients (≥70 years: 12%, <70 years: 23%; p = .001), possibly indicating that physicians were more hesitant to include those with higher age.[9] Thus, our study population may not be representative for all patients with advanced NSCLC. It should, however, be noted that independent of whether comorbidity in advanced NSCLC adds prognostic value or not, a comorbidity assessment is crucial for several reasons. It is helpful to identify patients with higher risk of treatment complications[9] and to detect needs for treatment modifications, or discontinuation of treatment no longer indicated. Comorbidity ratings are also an important part of the more extensive geriatric assessment (GA) which can detect problems potentially interfering with cancer treatment.[35]

This study adds evidence to other studies showing that the method for comorbidity assessment largely influences the number and severity of coexisting diseases detected. There is a need for a standardized comorbidity assessment in cancer research. Until such a tool is developed, a thorough description

of how comorbidity is rated is paramount for trials reporting comorbidity data.

In summary, the high response rate in this study shows that rather comprehensive comorbidity assessments can be performed by local investigators in multicenter phase III trials. There was, however, poor agreement with the CIRS-G assessment. None of the comorbidity scores were independent prognostic factors for survival.

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Disclosures and Conflict of Interest Statements

The authors have no conflicts of interest to disclose.

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Study concept: BH Grønberg, M Jordhøy, L Kirkhus
Study design: BH Grønberg, M Jordhøy, L Kirkhus
Data acquisition: BH Grønberg, M Jordhøy
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Data analysis and interpretation: BH Grønberg, M Jordhøy, J Šaltytė Benth, S Rostoft, G Selbæk, MJ Hjermstad, L Kirkhus
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II

Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty

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Background: Frailty is a syndrome associated with increased vulnerability and an important predictor of outcomes in older cancer patients. Systematic assessments to identify frailty are seldom applied, and oncologists' ability to identify frailty is scarcely investigated.

Methods: We compared oncologists' classification of frailty (onc-frail) based on clinical judgement with a modified geriatric assessment (mGA), and investigated associations between frailty and overall survival. Patients ⩾70 years referred for medical cancer treatment were eligible. mGA-frailty was defined as impairment in at least one of the following: daily activities, comorbidity, polypharmacy, physical function or at least one geriatric syndrome (cognitive impairment, depression, malnutrition, falls).

Results: Three hundred and seven patients were enroled, 288 (94%) completed the mGA, 286 (93%) were rated by oncologists. Median age was 77 years, 56% had metastases, 85% performance status (PS) 0–1. Overall, 104/286 (36%) were onc-frail and 140/288 (49%) mGA-frail, the agreement was fair (kappa value 0.30 (95% CI 0.19; 0.41)), and 67 mGA-frail patients who frequently had localised disease, good PS and received curative treatment, were missed by the oncologists. Only mGA-frailty was independently prognostic for survival (HR 1.61, 95% CI 1.14; 2.27; $P = 0.007$).

Conclusions: Systematic assessment of geriatric domains is needed to aid oncologists in identifying frail patients with poor survival.

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Approximately half of patients diagnosed with cancer are ⩾70 years, and owing to an aging population the number of older cancer patients is rapidly increasing (Syse, 2012; Cancer Research UK, 2016). The heterogenic health status of this large cohort of patients complicates treatment decisions. Age-related decrease in physiological reserves and co-existing problems, such as physical and cognitive impairments and comorbidities that may affect both treatment and outcomes (Clough-Gorr et al, 2010; Kristjansson et al, 2010), vary considerably between individuals. For appropriate treatment planning it is paramount to identify those who are fit and may tolerate standard treatment, and those who are frail and may profit from less-intensive treatment (Balducci and Extermann, 2000).

Frailty is widely recognised as a syndrome of increased vulnerability to adverse changes in health status (Clegg et al, 2013). There is, however, no consensus on how to best identify frail patients. In clinical trials, the Fried Phenotype model or indices based on accumulation of deficits (Huisingh-Scheetz and Walston, 2017) are commonly used. Geriatric assessment (GA) includes a systematic assessment of areas where problems are frequent in older age, such as comorbidity, medication, physical and cognitive function, and is the most frequently applied approach to assess vulnerability and frailty in cancer patients (Handforth et al, 2015). Consensus statements on what GA in this setting should include are, however, not entirely consistent (Wildiers et al, 2014; Mohile et al, 2015) and there are no agreed criteria to define frailty based on GA. Thus, varying domains and thresholds have been used (Handforth et al, 2015), and several studies have applied frailty criteria as proposed by Balducci and Extermann, 2000, or a modification of these (Basso et al, 2008; Tucci et al, 2009; Kristjansson et al, 2010). Frailty defined according to this approach is demonstrated to be prognostic for survival (Basso et al, 2008; Tucci et al, 2009; Ommundsen et al, 2014). Performing a full GA is time and resource consuming, and although highly recommended, is yet to be established in routine clinical practice (Magnuson et al, 2016). Easily applicable screening tools have therefore been sought, and some have documented ability to predict survival (Soubeyran et al, 2014). However, compared with a complete GA, none has demonstrated sufficient sensitivity and specificity to reliably identify frail patients (Hamaker et al, 2012). Based on the excellent prognostic performance of simple physician-rated scales such as the Eastern Cooperative Oncology Group Performance Status (PS) (Schiller et al, 2002), few studies have investigated whether physicians' clinical judgement is an equally effective screening tool for frailty (Wedding et al, 2007; Tucci et al, 2009; Clough-Gorr et al, 2010). The results suggest that physicians are more conservative and rate fewer patients as unfit or potentially vulnerable than those identified by GA (Wedding et al, 2007; Tucci et al, 2009; Clough-Gorr et al, 2010). However, two of these studies either used a retrospective evaluation of the patients' overall health at the time of diagnosis (Clough-Gorr et al, 2010) or the physicians' decision for palliative or more intensive treatment for comparison with GA (Tucci et al, 2009). Only one study actually asked the physician to identify frailty, and no treatment outcomes were reported (Wedding et al, 2007). To establish the ability of physicians' frailty ratings to predict outcomes, i.e., in comparison with GA, prospective comparative studies are needed.

In the present study we aimed to (1) compare oncologists' classification of frailty with a systematic modified geriatric assessment (mGA) of frailty, (2) describe what information oncologists emphasise when rating frailty and (3) investigate the associations of these frailty classifications with overall survival (OS).

MATERIALS AND METHODS

Patients. From January 2013 until April 2015, patients referred for medical cancer treatment were consecutively recruited at eight different outpatient oncology clinics in South East Norway (two university hospitals and six local hospitals). Eligible patients were ⩾70 years with a histologically confirmed solid tumour (newly diagnosed or first relapse after previous curative treatment). All patients provided written, informed consent. The patients were identified by referral, and oncology nurses with specific training in study procedures performed baseline interviews and mGA-testing, aiming at retrieving all information before treatment started.

Baseline assessments. Medical data were reported by the oncologists and included cancer type (ICD-10), stage of disease (local, locally advanced or metastatic), location of metastatic sites, planned treatment and rating of PS.

We defined our GA as a modified GA (mGA) as it was not performed by a geriatrician or a geriatric team. The mGA included assessment of eight domains. Nutritional status and related symptoms were registered partly by nurses and partly by patients' self-report. Medication, falls, physical and cognitive function were tested and/or registered by the oncology nurses. Comorbidity, activities of daily living (ADL) and depressive symptoms were assessed by patients' self-report.

Nutritional status was assessed using the Patient-Generated Subjective Global Assessment (PG-SGA) (Ottery, 1996; Persson et al, 1999). The PG-SGA includes two parts. One is a patient questionnaire about weight loss and nutritional symptoms, whereas the other is filled in by health professionals and includes a categorisation of a patient's overall nutritional status into (A) well-nourished, (B) moderately malnourished/suspected malnutrition and (C) severely malnourished. Severely malnourished patients are defined as having severe weight loss, visible loss of subcutaneous fat tissue and muscle mass, with or without the presence of oedema. Comorbidity was registered using the Physical Health Section, a subscale of the Older Americans' Resources and Services Questionnaire (OARS) (Fillenbaum and Smyer, 1981; Hurria et al, 2005). The Physical Health Section consists of a list of 15 diseases/conditions as well as a grading of how these conditions affect daily activities. Medication was registered according to the Anatomical Therapeutic Chemical Classification System. Falls were defined as unintentional events resulting in a laying position on the floor, the ground or other lower level, and the number of falls the last 6 months was registered. To screen for deficits in basic ADL we used question 5 ('Do you need help with eating, dressing, washing yourself or using the toilet?') from the 'European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ C30)(Aaronson et al, 1993). Questions 1–28 in EORTC QLQ C30 are graded into four categories, 'Not at all', 'A little', 'Quite a bit' and 'Very much'. Depressive symptoms were self-reported on the geriatric depression scale (GDS-15) (Yesavage et al, 1982). This scale consists of 15 items and the total score ranges from 0 to 15. A higher score indicates more depressive symptoms. Physical performance was tested using the Timed Up and Go test (TUG) (Podsiadlo and Richardson, 1991) which registers the time it takes to rise from an arm chair, walk three metres, turn, walk back and sit down, and patients were instructed to walk at a fast pace (Beauchet et al, 2011). Cognitive function was assessed using the Norwegian Revised Mini Mental State Examination (MMSE-NR) (Folstein et al, 1975). MMSE-NR consists of 20 items and the total score ranges from 0 to 30. The higher score, the better the cognitive function.

The oncologists were asked to classify the patient as fit, intermediate or frail after their first consultation at baseline. Prior to this, they were blinded for the results from the mGA and not given any specific instructions or training. In case the mGA assessments revealed severe medical problems requiring attention, the nurses gave this information to the patients' oncologist afterwards.

Table 1. The modified geriatric assessment[a]

Domain	Scale	Range	Rated by	Cutoff value for frailty	Rationale for cutoff values
Activities of daily living	EORTC QLQ-C30 Q5[b]		Patient	If reported yes a little/quite a bit/very much on the question 'Do you need help with eating, dressing, washing yourself or using the toilet'	ADL-deficiencies previously used in frailty classifications of cancer patients (Balducci and Extermann, 2000)
Comorbidity	OARS[c]	0–15 (Higher score indicates more comorbidities)	Patient	>3 points	Threshold for shorter survival in previous study of cancer patients (Klepin et al, 2014)
Medications, polypharmacy	ATC[d]	0–13	Nurse/ MD	>7 regular medications (ointments & common vitamins excluded)	Previously used in frailty classifications of cancer patients (Ommundsen et al, 2014)
Physical function	TUG[e]		Nurse	>14 seconds	Similar cut-offs ($\geqslant 14/>14.5$) used to identify GA deficits in cancer trials (Owusu et al, 2011; Jolly et al, 2015; Williams et al, 2015)
Cognitive function	MMSE[f]	0–30 (Higher score indicates better function)	Nurse	<24 points	Previously used in frailty classifications of cancer patients (Ommundsen et al, 2014)
Depressive symptoms	GDS-15[g]	0–15 (Higher score indicates more symptoms)	Patient	$\geqslant 7$ points	Chosen to ensure high specificity (Friedman et al, 2005; Cullum et al; 2006)
Nutritional status	PG-SGA[h]		Nurse/Patient	Considered severely malnourished by nurse or self-reported weight loss $\geqslant 10\%$ the last 6 months.	Weight loss $\geqslant 10\%$ the last six months is generally considered as an indicator of severe malnutrition (Nitenberg and Raynard, 2000)
Falls			Nurse	Patient reports $\geqslant 2$ falls the last 6 months	Previously used to identify GA deficits in cancer trials (Owusu et al, 2011; Jolly et al, 2015)

[a] Patients were classified as mGA-frail if having $\geqslant$ 1 of the criteria listed in the table.
[b] The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire.
[c] The Physical Health Section of the Older Americans' Resources and Services Questionnaire.
[d] Anatomical Therapeutic Chemical Classification System.
[e] Timed up and Go test.
[f] Norwegian Revised Mini Mental State Examination.
[g] Geriatric depression scale.
[h] Patient-generated Subjective Global Assessment.

Information regarding administered cancer treatment and date of death was registered from the patients' medical records. OS was defined as the main outcome. The study was not designed to assess cancer-specific survival.

Statistical analyses. To define frailty according to mGA, we used criteria similar to the modified Balducci criteria formerly applied by Kristjansson et al (2010) and Ommundsen et al (2014), and defined patients as frail if they met one of the following criteria: dependencies in ADL, had significant comorbidity, or one or more geriatric syndromes defined as impaired function according to MMSE (cognitive function), GDS (depression), SGA (malnutrition) or frequency of falls. Furthermore, in accordance with Winograd's criteria for frailty (Winograd et al, 1991) and similar to Kristjansson et al (2010), we included polypharmacy as a criterion, but also added impairment according to TUG, which has been reported as a sensitive and specific measure of frailty (Savva et al, 2013). Pre-defined cutoffs for impaired function within each domain are summarised in Table 1. To enable comparisons between the two procedures for assessment of frailty, and because very few patients were considered frail by the oncologists, their original threefold classification was dichotomised to either onc-non-frail (patients considered fit) or onc-frail (patients considered frail or intermediate).

Demographic and clinical characteristics as well as mGA domains at baseline were presented as median (min, max), mean (standard deviation (SD)), or frequencies and percentages.

Medical and sociodemographic factors were compared between groups by independent sample t-tests or χ^2-test. The agreement between mGA-non-frail/mGA-frail and the onc-non-frail/onc-frail was assessed by kappa statistics.

Survival time was defined as time from inclusion until death or the last observation date. PS was dichotomised as 0–1 and 2–4. Treatment was classified into four categories based on the first treatment the patients received; (1) Curative treatment, i.e., patients referred for neoadjuvant treatment, adjuvant treatment after curative surgery or curative radiotherapy (2) Palliative chemotherapy, (3) Other palliative systemic cancer treatment (4) Non-systemic palliative treatment the first two months after inclusion (i.e., radiotherapy, palliative surgery or palliative care). The association between mGA-frailty and OS was first assessed by bivariate Cox regression model. The multiple Cox regression model was estimated to adjust for age, sex, cancer type, PS, stage and treatment. The association between clinicians' judgement of being onc-frail and OS was analysed accordingly. Proportional hazards assumption was assessed by examining Schoenfeld's residuals. Multicollinearity issue was considered by calculating variance inflation factor. Kaplan–Meier OS curves were presented. Significance level was set at 0.05.

Missing values in MMSE ($n = 3$) and GDS-15 ($n = 27$) were imputed by drawing one random number per value from the empirical distribution based on non-missing values. In total, 31 patients had one or several missing items in the OARS subscale. Missing items on the OARS subscale were imputed by retrieving information from hospital charts.

Table 2. Baseline patient characteristics according to the mGA and the oncologists' classification

| | | | Modified geriatric assessment | | | | | The oncologists classification | | | | |
| | | | mGA-frail | | mGA-non-frail | | | Onc-frail | | Onc-non-frail | | |
	N (288)	%	*N* (140)	%	*N* (148)	%	*P*-value	*N* (104)	%	*N* (182)	%	*P*-value
Age, mean (s.d.)	76.9 (5.1)		77.5 (5.2)		76.2 (5.0)		**0.032**[a]	77.2 (5.4)		76.6 (5.0)		0.346[a]
Gender												
Female	126	44	64	46	62	42	0.513[b]	43	41	81	45	0.604[b]
Cancer type												
Colorectal	83	29	39	28	44	30		18	17	64	35	
Lung	59	21	35	25	24	16		34	33	25	14	
Prostate	56	19	22	16	34	23	**0.045**[b]	25	24	31	17	**<0.001**[b]
Other gastrointestinal	34	12	19	14	15	10		8	8	25	14	
Breast	30	10	9	6	21	14		6	6	24	13	
Other	26	9	16	11	10	7		13	13	13	7	
Stage												
Localised	73	25	30	21	43	29		12	12	61	34	
Locally advanced	55	19	23	16	32	22	0.091[b]	22	21	32	18	**<0.001**[b]
Distant metastasis	160	56	87	62	73	49		70	67	89	49	
ECOG PS												
0–1	244	85	106	76	138	93		62	60	181	100	
2–4	43	15	33	24	10	7	**<0.001**[b]	42	40	0		**<0.001**[b]
Missing	1		1					0		1		
Treatment												
Curative[c]	91	32	31	22	60	41		14	14	77	42	
Palliative chemotherapy	126	44	75	54	51	35		60	58	66	36	
Other palliative systemic cancer treatment	51	18	22	16	29	20	**0.002**[b]	21	20	30	17	**<0.001**[b]
Non-systemic palliative treatment[d]	20	7	12	9	8	5		9	9	9	5	

[a]Independent samples t-test.
[b]Pearson χ^2-test.
[c]Referred for neoadjuvant treatment, adjuvant treatment after curative surgery or curative radiotherapy.
[d]Radiotherapy, palliative surgery or palliative care.
Bold numbers are statistically significant.

The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway and was registered at clinicaltrials.gov (NCT01742442).

RESULTS

Study recruitment and patient characteristics. The approximate time needed to perform the interview and testing by study nurses was 45 min. A total of 307 patients were enroled, 18 had missing baseline questionnaires and one withdrew consent. Thus, 288 (94%) patients underwent the mGA and 286 (93%) were assessed by oncologists. All patients were followed until death or last observation date. The median follow-up time was 16.9 months (min 0.6, max 40). Last observation date was 31 May 2016. By then, 158 (55%) patients had died.

Baseline characteristics are shown in Table 2. Median age was 77 years (min 70, max 95), 126 (44%) were females. The most common cancer types were colorectal (*n* = 83, 29%), lung (*n* = 59, 21%) and prostate cancer (*n* = 56, 19%), the majority of patients had PS 0–1 (*n* = 244, 85%) and received palliative treatment (*n* = 197, 68%). Chemotherapy was the primary systemic treatment for 200 (69%) patients, (palliative *n* = 126, adjuvant *n* = 74). Almost all patients lived at home (*n* = 275, 96%), and 93 (34%) of the patients living at home lived alone.

Frailty according to classification procedure. According to mGA, 140 (49%) patients were frail. The three most common frailty domains were comorbidity (*n* = 82, 28%), polypharmacy (*n* = 37, 13%) and malnutrition (*n* = 43, 15%) (Table 3). Overall, 73 (25%) patients had a deficit in one mGA domain, 42 (15%) in two domains and 25 (9%) in three or more. The oncologists considered 15 patients (5%) as frail and 89 (31%) as intermediate,

Table 3. Frailty according to mGA category and median scores of the different scales

	No. frail	%	Median (min, max)	No. missing
Nutritional status, malnutrition[a]	43	15		24
Comorbidity (OARS > 3)	82	28	3 (0–9)	1
Medications, polypharmacy (> 7)	37	13	4 (0–13)	0
Falls (⩾ 2)	10	3		1
Activities of daily living[b]	12	4		5
Depressive symptoms (GDS ⩾ 7)	35	12	2 (0–13)	4
Physical function (TUG > 14s)	18	6	8 (4–25)	13
Cognitive function (MMSE < 24)	9	3	29 (19–30)	0
Frail according to any category	140	49		

[a]Self-reported ⩾ 10% weight loss the last 6 months or classified as severely malnourished by nurse. No. with missing information about weight loss last 6 months from patient.
[b]Patient-reported on Question 5 EORTC QLQ C30.

giving a total of 104 (36%) onc-frail according to the dichotomised classification.

According to both classifications, there were significantly more patients with good PS and curative treatment among the non-frail than among the frail (Table 2). For the oncologists' classification, there were significant differences in cancer type and stage of disease between frail and non-frail patients, i.e., the most frequent cancer types were lung cancer in the onc-frail group and colorectal

cancer in the onc-non-frail group. The onc-non-frail group also comprised significantly more patients with localised disease (Table 2). When comparing the mGA-frail and mGA-non-frail patients, similar findings with significantly more frequent lung cancer in the mGA-frail group was found for cancer type.

In the small subgroup classified as frail by the oncologists in the original threefold classification, all patients had a poor PS. All but one had PS 2–4, and of the six patients in the overall cohort with PS 3–4, five belonged to this group. Otherwise their characteristics were similar to the overall onc-frail cohort: The most common diagnosis was lung cancer (33%), the majority had metastatic disease (67%), and none received treatment with curative intention.

The mGA-frail/mGA-non-frail classification coincided with the onc-frail/onc-non-frail classification for 187 (65%) patients; 72 (25%) patients were found mGA-frail and onc-frail, while 115 (40%) patients were mGA-non-frail and onc-non-frail. A total of 67 (23%) patients were classified as mGA-frail, but judged by the clinicians to be fit. In comparison to those who were both mGA-frail and onc-frail, this group included fewer patients with lung cancer (15% vs 35%), and PS 2–4 (0% vs 44%), but larger proportions of patients with colorectal cancer (39% vs 17%), localised disease (30% vs 14%), PS 0 (61% vs 3%) and curative treatment (33% vs 13%) (Supplementary material). Hence, favourable cancer-related prognostic factors were more frequent among these 67 patients. In terms of mGA deficits, the majority of these patients had one deficit ($n = 46$, 69%), whereas only 36% ($n = 26$) had one deficit among those who were both mGA-frail and onc-frail. The most frequent mGA deficit missed by the oncologists was comorbidity. A total of 32 (11%) patients were mGA-non-frail and onc-frail. The frequency of established, negative cancer-related prognostic factors (lung cancer, poor PS, advanced stages of disease, palliative treatment) was high in this group, similar to the group that was both mGA-frail and onc-frail.

The kappa statistic was 0.30 (95% CI 0.19; 0.41), indicating only fair agreement between the oncologists' clinical judgement and the mGA.

OS according to frailty status. Median OS was 21.5 months, 93 (32%) patients died within their first year of follow-up. Both mGA-frail and onc-frail patients had poorer median OS compared with mGA-non-frail and onc-non-frail patients, respectively (mGA-frail: 15.0 months, mGA-non-frail: 29.1 months; $P < 0.001$) (onc-frail: 12.9 months, onc-non-frail: 27.4 months; $P < 0.001$). The few patients (5%) originally categorised as frail by the oncologists, had a median OS of only 7.4 months.

In bivariate Cox regression analyses, mGA-frail and onc-frail were both significantly negatively associated with OS (Table 4 and Figure 1A and B). The HR for mGA-frail was 1.86 (95% CI 1.36; 2.56) ($P < 0.001$) and the HR for onc-frail was 1.94 (95% CI 1.41; 2.66) ($P < 0.001$). In analyses adjusting for age, sex, cancer type, PS, stage and treatment, only mGA frailty was an independent negative prognostic factor for OS with a HR of 1.61 (95% CI 1.14; 2.27) ($P = 0.007$).

Finally, we explored possible differences in survival between four groups of patients; frail according to both assessments, non-frail according to both assessments, frail according to only the mGA, and frail only according to our onc-frail definition. Kaplan–Meier OS curves of these four patient groups are presented in Figure 1C. The group classified as non-frail according to both assessments had the best OS and the group classified as frail according to both assessments had the poorest OS.

DISCUSSION

We found only fair agreement between frailty classified by a systematic, modified GA, and the oncologists' clinical judgement of frailty. The oncologists classified very few patients as frail, and even when pooling frail and intermediate patients (according to the oncologists), they missed almost half of the patients who were frail according to the mGA. The oncologists most commonly missed frailty due to comorbidity. Although both classification procedures succeeded in identifying patients with poorer survival, only mGA-frailty remained significantly associated to OS when other, established cancer related prognostic factors such as cancer type, stage, PS and treatment were taken into account.

The finding that physicians are more conservative in rating frailty than a systematic GA is in accordance with the results of others (Wedding et al, 2007; Tucci et al, 2009). To the best of our knowledge, no former study of cancer patients has reported the prognostic value of frailty rated merely by the oncologists' clinical judgement. Consistent with our findings, a study found physician-rated health to be prognostic for survival (Clough-Gorr et al, 2010). In that study, however, being considered moderately ill/severely ill by the physician was an independent prognostic factor. As only breast cancer patients with stage I-III were included, and neither PS nor treatment was taken into account, differences in patient populations and analyses may explain why the results were somewhat different from ours. The prognostic importance of being mGA frail is consistent with previous studies (Basso et al, 2008; Tucci et al, 2009; Ommundsen et al, 2014).

Our results suggest that the oncologists emphasise cancer-related factors when asked to rate frailty. Unfavourable prognostic factors such as lung cancer and advanced stage of disease were significantly more frequent in the onc-frail group compared with the onc-non-frail. The prognostic value of the oncologists' frailty assessment was not independent of other well-established prognostic factors. Furthermore, established negative cancer related prognostic factors were frequent among patients who were classified as onc-frail and not mGA frail, whereas the opposite was the case for those who were mGA-frail and onc-non-frail. Thus, the focus of the two classification procedures seemed to be different. Consequently, as demonstrated by our exploratory survival curves, the oncologists identified some patients with no mGA deficits and poor prognosis, whereas a larger group of patients who were frail according to mGA, and also had poorer prognosis compared to non-frail patients, was missed. This indicates that whereas the oncologists are experienced in evaluating cancer related health, training in identifying patients' overall vulnerability, including geriatric problems that may affect prognosis, is insufficient. Thus, increased education and awareness, and preferably inclusion of GA into routine clinical practice, may improve the physicians' ability to identify patients with otherwise unrecognised vulnerability (Wildiers et al, 2014), prevent undertreatment and harmful overtreatment, and reduce the frequency and severity of treatment-related adverse events. However, prospective studies are needed to investigate if GA followed by targeted interventions can improve cancer patients' prognosis and outcomes of therapy.

Strengths of this study are inclusion at multiple centres, a heterogeneous patient group with respect to type of cancer, stage of disease and planned treatment thus representative of a large group of patients commonly seen in clinical practice. The cohort is also fairly large compared with other studies investigating frailty in older cancer patients (Handforth et al, 2015). Our mGA included the main domains recommended for GA (Wildiers et al, 2014; Mohile et al, 2015), and we used well-known and validated scales (Folstein et al, 1975; Fillenbaum and Smyer, 1981; Yesavage et al, 1982; Podsiadlo and Richardson, 1991; Ottery, 1996; Persson et al, 1999). As patients needed to have deficits according to only one pre-defined criterion to be considered mGA-frail, we defined rather strict cutoff values in each of the domains included (Table 1) (Balducci and Extermann, 2000; Nitenberg and Raynard, 2000; Friedman et al, 2005; Cullum et al, 2006; Owusu et al, 2011; Klepin et al, 2014; Ommundsen et al, 2014; Jolly et al, 2015; Williams et al, 2015). Still, the validity of our mGA and chosen cutoff is open for discussion as

Table 4. Cox regression analyses of the association between both frailty classifications and overall survival

	N 288	Unadjusted HR (95% CI)	P-value	Adjusted model with mGA[a] HR (95% CI)	P-value	Adjusted model with oncologists classification[a] HR (95% CI)	P-value
Systematic mGA							
mGA-non-frail	148						
mGA-frail	140	1.86 (1.36; 2.56)	<0.001	1.61 (1.14; 2.27)	0.007		
Oncologists' assessment							
Onc-non-frail	182						
Onc-frail	104	1.94 (1.41; 2.66)	<0.001			1.43 (0.97; 2.10)	0.071
Age (continuous)		1.02 (0.99; 1.05)	0.185	1.05 (1.01; 1.09)	0.010	1.06 (1.02; 1.10)	0.002
Gender							
Male	162	1[b]		1[b]		1[b]	
Female	126	0,64 (0.46; 0.89)	0.007	0.62 (0.41; 0.93)	0.019	0.66 (0.45; 0.98)	0.040
Cancer type							
Breast	30	1[b]		1[b]		1[b]	
Prostate	56	7.18 (2.20; 23.42)	0.001		n.s.		n.s.
Other gastrointestinal	34	19.31 (5.84; 63.79)	<0.001	6.25 (1.75; 22.32)	0.005	7.59 (2.12; 27.20)	0.002
Lung	59	16.28 (5.05; 52.43)	<0.001	5.17 (1.48; 18.13)	0.010	5.85 (1.67; 20.51)	0.006
Colorectal	83	4.37 (1.34; 14.26)	0.014		n.s.		n.s.
Other	26	8.40 (2.43; 29.05)	0.001		n.s.		n.s.
Stage							
Local	73	1[b]		1[b]		1[b]	
Locally advanced	55	3.04 (1.69; 5.47)	<0.001		n.s.		n.s.
Metastasised	160	4.63 (2.77; 7.74)	<0.001	1.84 (0.95; 3.58)	0.071	1.77 (0.91; 3.43)	0.094
Treatment							
Curative	91	1[b]		1[b]		1[b]	
Palliative chemotherapy	126	7.76 (4.67; 12.89)	<0.001	2.54 (1.27; 5.11)	0.009	2.57 (1.28; 5.18)	0.008
Other palliative systemic cancer treatment	51	2.74 (1.49; 5.05)	0.001		n.s		n.s.
Non-systemic palliative treatment	20	9.47 (4.81; 18.67)	<0.001	4.95 (2.31; 10.63)	<0.001	6.01 (2.79; 12.97)	<0.001
ECOG							
0–1	244	1[b]		1[b]		1[b]	
2–4	43	1.79 (1.20; 2.66)	0.004		n.s.		n.s.

[a]Cox regression analysis adjusted for age, sex, diagnosis, stage, treatment and ECOG-PS.
[b]Reference category.
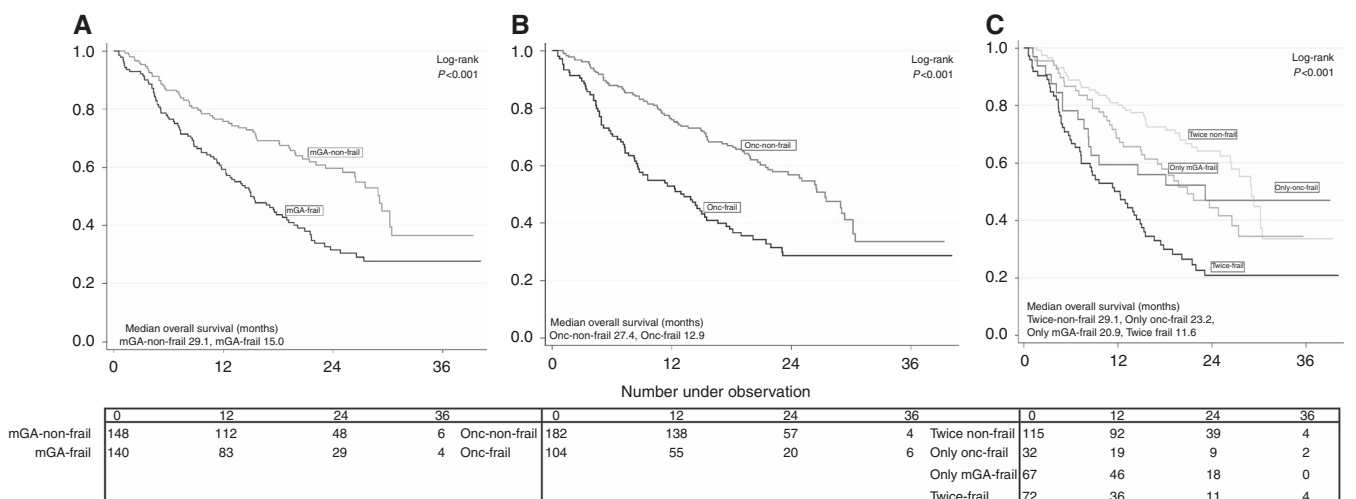Bold numbers are statistically significant.

Figure 1. Kaplan Meier curves of overall survival (months) according to (**A**) mGA-non-frail/mGA frail, (**B**) onc-non-frail/onc-frail (**C**) both frailty classifications combined.

no gold standard currently exists (Handforth *et al*, 2015). More importantly, our definition of frailty may be questioned. It was, however, adapted from Balducci's criteria, and a similar approach has formerly been used and found superior to the physical phenotype of frailty in predicting post-operative complications in cancer patients, as well as being prognostic for survival (Kristjansson *et al*, 2012). We consider the inclusion of TUG as a frailty criterion is a potential strength rather than a weakness. Thus, the main objection may be the use of OARS for comorbidity registration, and that the severity of these conditions was not taken into account.

Despite this, and although our comorbidity criterion was the most frequent reason for mGA frailty, we clearly demonstrate the independent prognostic value of our frailty measure. A frailty prevalence of 49% seems to be well within range of what has been observed in other studies (Handforth *et al*, 2015). Whether our definition actually capture the concept of frailty can, however, not be confirmed and the results should be interpreted with this in mind.

Another study limitation is the lack of data on eligible patients who were referred to the participating clinics and not included in our study. Furthermore, no information about the oncologists was systematically registered. Retrospectively, the participating clinics indicate that approximately 40 consultants evaluated from one to about 27–28 patients each, whereas 28 consultants are confirmed having assessed from one to seven of the mGA frail patients who were missed. An equal share of juniors and seniors with up to 30 years of oncology practice were represented. Thus, their oncological experience varied largely. This might, however, not be relevant when rating frailty. Insufficient training in assessing and managing geriatric syndromes is a widely recognised problem within several settings, including oncology (Hsu, 2016; Morris *et al*, 2017), and our prevalence of physician-rated frailty was similar to a study in which participating physicians had at least 10 years of clinical experience (Wedding *et al*, 2007). It should also be noted that dichotomising the oncologists' original threefold classification and thereby comparing a group identified as either intermediate or frail with mGA frail patients, may introduce a risk of misinterpreting the oncologists' assessments. Based on the difference in median survival between the frail patients and the overall cohort defined as onc-frail, there is no doubt that the oncologists were able to identify groups of patients with poor and very poor prognosis, respectively. However, for both groups, this prognostication seemed to be based on well-known negative cancer-related factors. Hence, the fact remains that the oncologists missed to identify a considerable number of patients with poor prognosis and frailty due to geriatric deficits.

In conclusion, our results demonstrate that a mGA can aid the oncologists in identifying otherwise unrecognised frail older patients' with poor prognosis, as well as those non-frail patients without geriatric deficits and thus a better prognosis. The oncologists using their clinical judgement are good at evaluating cancer related prognostic factors, but may need training in geriatric assessment to better assess patient's overall vulnerability and prognosis. A geriatric assessment may thus provide information contributing to oncologists making more appropriate treatment decisions for their old cancer patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Original Article

Frailty identified by geriatric assessment is associated with poor functioning, high symptom burden and increased risk of physical decline in older cancer patients: Prospective observational study

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Abstract

Background: Maintaining quality of life including physical functioning is highly prioritized among older cancer patients. Geriatric assessment is a recommended approach to identify patients with increased vulnerability to stressors (frailty). How frailty affects quality of life and physical functioning in older cancer patients has scarcely been investigated.

Aim: Focusing on physical functioning and global quality of life, we investigated whether frailty identified by a geriatric assessment was associated with higher risk of quality-of-life deterioration during cancer treatment and follow-up.

Design: Prospective, observational study. Patients were classified as frail or non-frail by a modified geriatric assessment. Quality of life was measured using the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire at inclusion, 2, 4, 6 and 12 months.

Setting: Eight Norwegian outpatient cancer clinics.

Participants: Patients ⩾70 years with solid tumours referred for palliative or curative systemic medical cancer treatment.

Results: Among 288 patients included, 140 (49%) were frail and 148 (51%) non-frail. Frail patients consistently reported poorer scores on all functioning and symptom scales. Independent of age, gender and major cancer-related factors, frail patients had significantly poorer physical functioning and global quality of life during follow-up, and opposed to non-frail patients they had both a clinically and statistically significant decline in physical functioning from baseline until 12 months.

Conclusions: Geriatric assessment identifies frail patients with increased risk of physical decline, poor functioning and high symptom burden during and following cancer treatment. Frail patients should therefore receive early supportive or palliative care.

Keywords

Geriatric assessment, frailty, quality of life, cancer, observational study, EORTC QLQ-C30

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What is already known about the topic?

- Frailty identified by geriatric assessment is associated with increased risk of death and treatment complications in older cancer patients.
- Although geriatric assessment is recommended for older cancer patients, it is rarely implemented into clinical practice.
- Studies investigating the impact of frailty on highly relevant outcomes like physical functioning and quality of life are scarce.

What this paper adds (outcome)?

- Frailty identified by geriatric assessment independently predicts a clinically significant decline in physical functioning.
- Frailty is associated with worse global quality of life, poorer functioning and a higher symptom burden throughout the cancer trajectory

Implications for practice, theory or policy

- Including routine geriatric assessment for older cancer patients undergoing systemic medical cancer treatment will aid oncologists in identifying frail patients who need early supportive and palliative care.

Introduction

Prolonging survival is usually considered the main goal of cancer care. However, maintaining or improving quality of life can be equally important. This applies especially to older patients, who have poorer survival in comparison with their younger counterparts and may be less willing to exchange current quality of life for smaller survival benefits.[1,2] The quality-of-life concept embraces multiple dimensions: emotional, social, existential as well as physical, the latter including aspects such as patient-reported somatic symptoms and physical functioning. Physical functioning is strongly associated with independent living, which is highly prioritized among older patients,[3,4] and is also a key driver for how they perceive their overall quality of life.[5,6] Thus, making appropriate treatment decisions for older cancer patients requires knowledge on how quality of life may be affected and ability to identify patients at risk of deterioration. Particular attention to physical functioning seems essential.

Frailty is defined as increased vulnerability to adverse changes in health status[7] and is associated with increased mortality, postoperative complications and intolerance to cancer treatment.[8,9] Frail patients have been found to have poorer quality of life than non-frail patients,[10–12] but longitudinal studies investigating the impact of frailty on quality of life during and after cancer treatment are scarce. Results from those available are not consistent,

having shown both similar changes in quality-of-life trajectories of frail and non-frail patients[10,11] as well as accelerated decline of some dimensions among frail patients.[13]

A challenge to all frailty research is the lack of universally accepted operational criteria. Over 70 different methods for measuring frailty have been developed, most of which are linked to the two dominating pathophysiological theories of frailty: the physical frailty phenotype and the cumulative deficit model.[14,15] In the oncology literature, geriatric assessment is the recommended approach to identifying frailty[14] and to guide treatment decisions for older patients.[16] This approach includes a systematic assessment of areas such as functional status, mobility, cognitive function, comorbidity and geriatric syndromes.[8,16] Still, geriatric assessment remains to be widely implemented into oncology practice, perhaps hampered by its comprehensiveness. Simpler frailty screening tools are more time-efficient and might be easier to implement into clinical practice, but their lower sensitivity and specificity is a challenge.[17] Thus, geriatric assessment is considered the gold standard,[14] although screening tools may be used to select patients for a complete geriatric assessment.[18] There is, however, no general agreement on how frailty should be defined based on a geriatric assessment. Varying domains and thresholds have been applied in different studies,[8] but the criteria as proposed by Balducci and Extermann[19] have commonly been used.[20,21]

We have formerly demonstrated that frailty identified by a modified geriatric assessment and a modification of the Balducci criteria[22,23] was independently predictive of survival in cancer patients ≥70 years of age.[24] In this study, targeting the same population, we aimed at investigating whether frailty was associated with higher risk of quality-of-life deterioration during treatment and follow-up. Our main hypothesis was that patients classified as frail upon start of treatment would experience a steeper decline in both physical functioning and global quality of life than non-frail patients.

Materials and methods

Patients

Patients were consecutively recruited from January 2013 until April 2015 at eight Norwegian outpatient oncology clinics (two university hospitals and six local hospitals). Eligible patients were ≥70 years and referred for systemic medical cancer treatment (chemotherapy, hormonal or targeted therapy) with a histologically confirmed solid tumour (newly diagnosed or first relapse after previous curative treatment). Patients provided written, informed consent.

Assessments

Oncologists reported cancer type (10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10)), stage of disease,

Table 1. The modified geriatric assessment[a].

Area	Assessment method	Scores	Performer	Cut-off value above which patients were defined as frail
Activities of daily living	EORTC QLQ-C30 Q5		Patient	If reported yes, a little/quite a bit/very much on the question 'Do you need help with eating, dressing, washing yourself or using the toilet'
Comorbidity	OARS	0–15 (higher score indicates more comorbidities)	Patient	>3 points
Medications and polypharmacy	ATC	0–13	Nurse/physician	>7 regular medications (ointments and common vitamins excluded)
Cognitive function	MMSE	0–30 (higher score indicates better function)	Nurse	<24 points
Depressive symptoms	GDS-15	0–15 (higher score indicates more symptoms)	Patient	≥7 points
Nutritional status	PG-SGA		Nurse/patient	Considered severely malnourished by nurse or self-reported weight loss ≥10% the last 6 months
Falls			Nurse	Patient reports ≥2 falls the last 6 months
Physical function	TUG		Nurse	>14 s

EORTC QLQ-C30 Q5: European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire; OARS: The Physical Health Section of the Older Americans' Resources and Services Questionnaire; ATC: Anatomical Therapeutic Chemical Classification System; MMSE: Norwegian Revised Mini Mental State Examination; GDS-15: geriatric depression scale–15 items; PG-SGA: Patient-Generated Subjective Global Assessment; TUG: Timed Up and Go test.
[a]Patients were classified as frail if having ≥1 of the criteria listed in the table.

planned treatment and the Eastern Cooperative Oncology Group (ECOG) performance status. Data on administered treatment were retrieved from the patients' medical records. Physical functioning and global quality of life was assessed by the European Organisation for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (QLQ-C30)[25] at inclusion and after 2, 4, 6 and 12 months. QLQ-C30 consists of 30 questions comprising five functioning scales, nine symptom scales/items and a global quality of life scale. The functioning scales include physical, role, social, cognitive and emotional functioning. Symptoms include fatigue, pain, nausea/vomiting, sleep disturbances (insomnia), appetite loss, diarrhoea, dyspnoea and constipation and financial impact. The raw scores are transformed into scales from 0 to 100 points.[26] Higher scores on the functioning and global quality-of-life scales represent better functioning, whereas higher scores on symptom scales/items indicate a higher symptom burden.

Frailty was identified by a geriatric assessment which we have referred to as modified since it was not performed by an interdisciplinary team, but by trained oncology nurses and patients' self-report,[24] using well-known and validated instruments for each included domain[27–31] (Table 1). Our frailty definition was predefined, and following the Balducci criteria, patients were categorized as frail if they fulfilled at least one of the following: dependencies on activities of daily living, significant comorbidity or one or more geriatric syndromes (cognitive function, depression, malnutrition and falls). Similar to Kristjansson et al.,[22] we included polypharmacy as a criterion and added impairment according to Timed Up and Go,[27] a sensitive and specific measure of frailty.[32] Cut-off values for each domain were chosen in line with former reports and practice (Table 1).[23,33–40] A detailed explanation is found in a previous paper.[24] To screen for deficits in activities of daily living, a question from the QLQ-C30 physical functioning scale ('Do you need help with eating, dressing, washing yourself or using the toilet?') was used.

Statistical analyses

Medical and sociodemographic factors were compared between frail and non-frail patients by independent samples t-tests or χ^2-test. Our predefined main endpoints were changes in physical functioning during the first 2 months of follow-up (primary) and changes in physical functioning and global quality of life during 12 months (secondary). Changes during 12 months for the remaining QLQ-C30 scales and items were assessed by exploratory analyses using the same approach as for the main endpoints.

Differences between frail and non-frail patients in changes over time were assessed by linear mixed models. All models included random intercepts for cancer clinics and for patients nested within cancer clinics to account for intra-patient correlations due to repeated measurements and possible within-clinic cluster effect. The models also included fixed effects for frailty group, time (as second-order polynomial to account for non-linear trends in models assessing data on 12-month follow-up), and the interaction term between frailty group and time (frail × time). A significant interaction term would imply that there were differences in change between frail and non-frail patients. Models adjusting for age, sex, cancer type, performance status, stage and treatment were also estimated. Treatment was classified as (1) curative treatment, that is, patients referred for neoadjuvant chemotherapy treatment, adjuvant chemotherapy and/or endocrine treatment after curative surgery or curative radiotherapy; (2) palliative chemotherapy; (3) other palliative systemic cancer treatment and (4) non-systemic palliative treatment the first 2 months after inclusion (i.e. radiotherapy, surgery or palliative care). Performance status was classified as 0–1 or 2–4 and stage as local, locally advanced or metastatic. The results were tabulated as regression coefficients with standard errors (SE) and p values for the primary and secondary analyses of physical functioning and global quality of life. The results from unadjusted models were also presented graphically as estimated mean values with 95% confidence intervals (CI) for all QLQ-C30 scales/items. Within- and between-group differences with the corresponding 95% CI and p values were calculated from the models. Significance level was set at 5%. A difference of $\geqslant$10 points on the functional and symptom scales/items was considered a clinically significant change.[41]

Missing values in QLQ-C30 multi-item scales were imputed according to the official manual if at least half of the scale had been answered.[26] The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway 09.02.2012 (Reference number 2012/104) and registered at clinicaltrials.gov (NCT01742442).

Results

Patients

From January 2013 to April 2015, a total of 307 patients were included. One patient withdrew consent and 18 had missing baseline questionnaires and therefore incomplete geriatric assessments. Thus, 288 (94%) patients were eligible for the present frailty study. A total of 140 patients (49%) fulfilled one or more of the predefined criteria and were categorized as frail. The most frequent deficits were comorbidity (n = 82, 28%), malnutrition (n = 43, 15%), polypharmacy (n = 37, 13%) and depressive symptoms (n = 35, 12%). In all, 40 patients (14%) had deficits in physical functional aspects: activities of daily living (12 patients), Timed Up and Go (18 patients) and number of falls (10 patients). Nine patients (3%) had cognitive impairment. Of the 140 patients categorized as frail, 67 (48%) patients had two or more registered deficits. Only one patient was classified frail based on the activities of daily living criterion alone, which was screened for by using question 5 from the physical functioning scale of QLQ-C30.

The patients' baseline characteristics are shown in Table 2. Mean age was 76.9 (5.1) years, 56% were male and the most common cancer types were colorectal (29%), lung (21%) and prostate cancer (19%). The majority of patients had distant metastases (56%), and overall, 68% received palliative treatment. A higher percentage of frail compared to non-frail patients had lung cancer, distant metastases, performance status 2–4 and received palliative chemotherapy.

At 2, 4, 6 and 12 months of follow-up, 13 (5%), 27 (9%), 52 (18%) and 93 (32%) patients of the overall cohort had died. Median overall survival was shorter among frail than non-frail patients (15 vs 29 months).[24] The first 12 months, 83 (59%) of frail and 112 (76%) of non-frail patients were alive, resulting in relative risk of death of 1.7 (95% CI: 1.2–2.4) for frail compared to non-frail patients. The proportion of completed questionnaires ranged between 89% and 95% for those alive at the various assessment points (Figure 1). The mean proportion of missing items ranged from 0.51% to 0.96%.

Quality-of-life analyses

At baseline, frail patients reported poorer functioning and more symptoms than non-frail patients on all scales/items (Table 2). Both frail and non-frail patients reported a statistically, but not clinically significant decline in physical functioning from baseline to 2 months. The decline was not significantly different between frail and non-frail patients (unadjusted model: p = 0.181, adjusted model: p = 0.218). According to the unadjusted linear mixed model, there were, however, statistically significant differences in physical functioning scores between the two groups in disfavour of frail patients, mean 18.2 (95% CI: 13.3–23.1) points at baseline and 15.0 (CI 9.9; 20.0) points at 2 months ($p <$ 0.001; Figure 2, Table 3). The differences remained statistically significant when adjusting for age, gender, cancer type, stage, performance status and treatment (12.2 (95% CI: 7.5–16.9) points at baseline and 9.2 (95% CI: 4.4–14.1) at 2 months; $p <$ 0.001; Figure 2, Table 3).

For our secondary endpoint, physical functioning during 12 months of follow-up, a statistically significant decline was found for non-frail patients from baseline to 6 months and for frail patients from baseline to both 6 and

Table 2. Baseline patient characteristics according to frailty status.

	All		Frail		Non-frail		p value
	N (288)	%	N (140)	%	N (148)	%	
Age, mean (SD)	76.9 (5.1)		77.5 (5.2)		76.2 (5.0)		0.032*
Gender							
Female	126	44	64	46	62	42	0.513**
Cancer type							
Colorectal	83	29	39	28	44	30	
Lung	59	21	35	25	24	16	0.045**
Prostate	56	19	22	16	34	23	
Other gastrointestinal	34	12	19	14	15	10	
Breast	30	10	9	6	21	14	
Other	26	9	16	11	10	7	
Stage							
Localized	73	25	30	21	43	29	0.091**
Locally advanced	55	19	23	16	32	22	
Distant metastasis	160	56	87	62	73	49	
ECOG performance status							
0–1	244	85	106	76	138	93	
2–4	43	15	33	24	10	7	<0.001**
Missing	1		1				
Treatment							
Curative[a]	91	32	31	22	60	41	
Palliative chemotherapy	126	44	75	54	51	35	0.002**
Other palliative systemic cancer treatment	51	18	22	16	29	20	
Non-systemic palliative treatment[b]	20	7	12	9	8	5	
	Mean	SD	Mean	SD	Mean	SD	
Functioning scales and global health status							
Physical functioning	72.9	21.4	63.5	21.3	81.7	17.4	
Global quality of life	64.1	23.1	54.5	22.1	73.4	20.1	
Role functioning	65.5	32.1	52.0	31.7	78.4	26.8	
Emotional functioning	83.9	18.1	77.7	21.1	89.8	12.2	
Cognitive functioning	87.6	16.0	83.6	18.1	91.4	12.7	
Social functioning	76.0	25.9	68.3	28.5	83.2	20.9	
Symptom scales/items							
Fatigue	38.8	24.2	48.7	25.6	29.4	18.5	
Nausea and vomiting	6.8	14.8	10.6	18.7	3.3	8.6	
Pain	24.8	29.4	32.9	31.7	17.1	24.9	
Dyspnoea	25.7	31.4	33.3	34.1	18.5	26.8	
Insomnia	26.2	28.5	32.1	30.9	20.5	24.8	
Appetite loss	21.4	31.4	30.7	36.0	12.6	23.2	
Constipation	24.0	29.3	30.5	32.4	17.9	24.8	
Diarrhoea	15.2	22.4	17.1	24.2	13.2	20.5	

ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.
[a]Referred for neoadjuvant treatment, adjuvant treatment after curative surgery or curative radiotherapy.
[b]Radiotherapy, palliative surgery or palliative care.
*Independent samples *t*-test.
**Pearson chi-square.

12 months. Only frail patients had a clinically significant (≥10 points) decline. In unadjusted models, the decline in physical functioning for frail and non-frail patients was not significantly different ($p = 0.089$; Table 3, Figure 2). However, when adjusting for age, gender, cancer type, stage, performance status and treatment, the decline was found to be significantly steeper for frail patients ($p = 0.022$; Table 3). Thus, the observed difference in scores in disfavour of frail patients during the first 2 months increased throughout the follow-up period and remained statistically and clinically significant, both according to unadjusted (Figure 2, Table 3) and adjusted models (Table 3; $p < 0.001$).
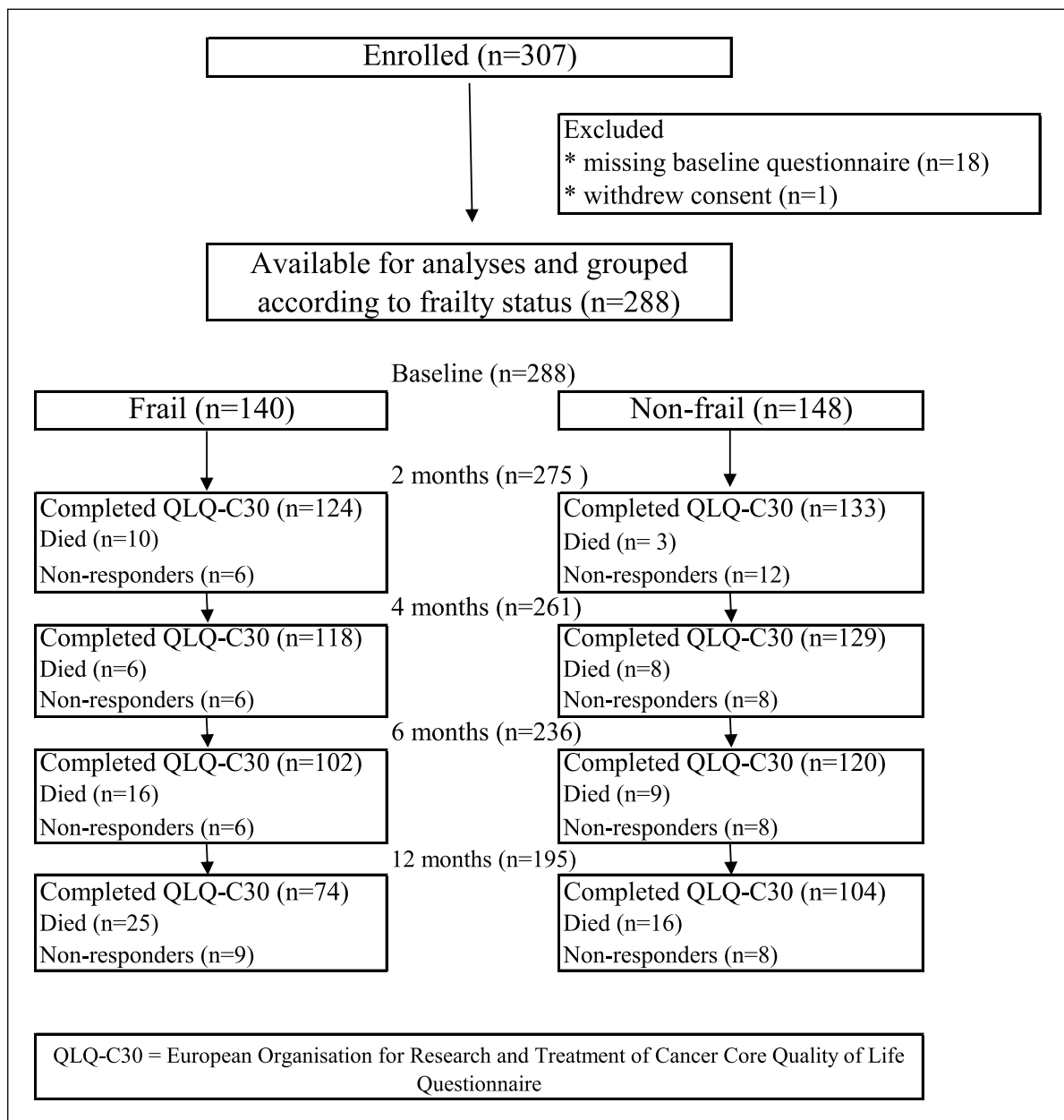
Figure 1. Flow diagram of patient enrolment and follow-up.

For global quality of life during 12 months of follow-up, there was no significant difference between frail and non-frail patients in the course of changes ($p = 0.369$ in unadjusted models; $p = 0.273$ in adjusted models; Table 3). Both models demonstrated that frail patients had statistically and clinically significantly worse scores compared to non-frail patients at all assessment points ($p < 0.001$; Figure 2, Table 3).

Unadjusted trajectories for frail and non-frail patients for the remaining functioning and symptom scales are shown in Figures 2 and 3. Differences that were both statistically and clinically significant according to unadjusted and adjusted analyses are indicated. In the adjusted

model, frail patients had a clinically and statistically significant decline in role functioning from baseline to 6 months ($p < 0.001$). None of the other scales showed any clinically significant changes from baseline in the adjusted models, neither in frail nor non-frail groups. Except for diarrhoea (adjusted model, $p = 0.023$), with a statistically but not clinically significant increase in symptoms from baseline to 6 months for frail patients, the course of the trajectories was not significantly different between the groups. However, adjusted models showed that frail patients had statistically and clinically significant more constipation ($p < 0.01$) and worse role- ($p < 0.001$), social- ($p < 0.01$) and emotional functioning ($p < 0.01$) at
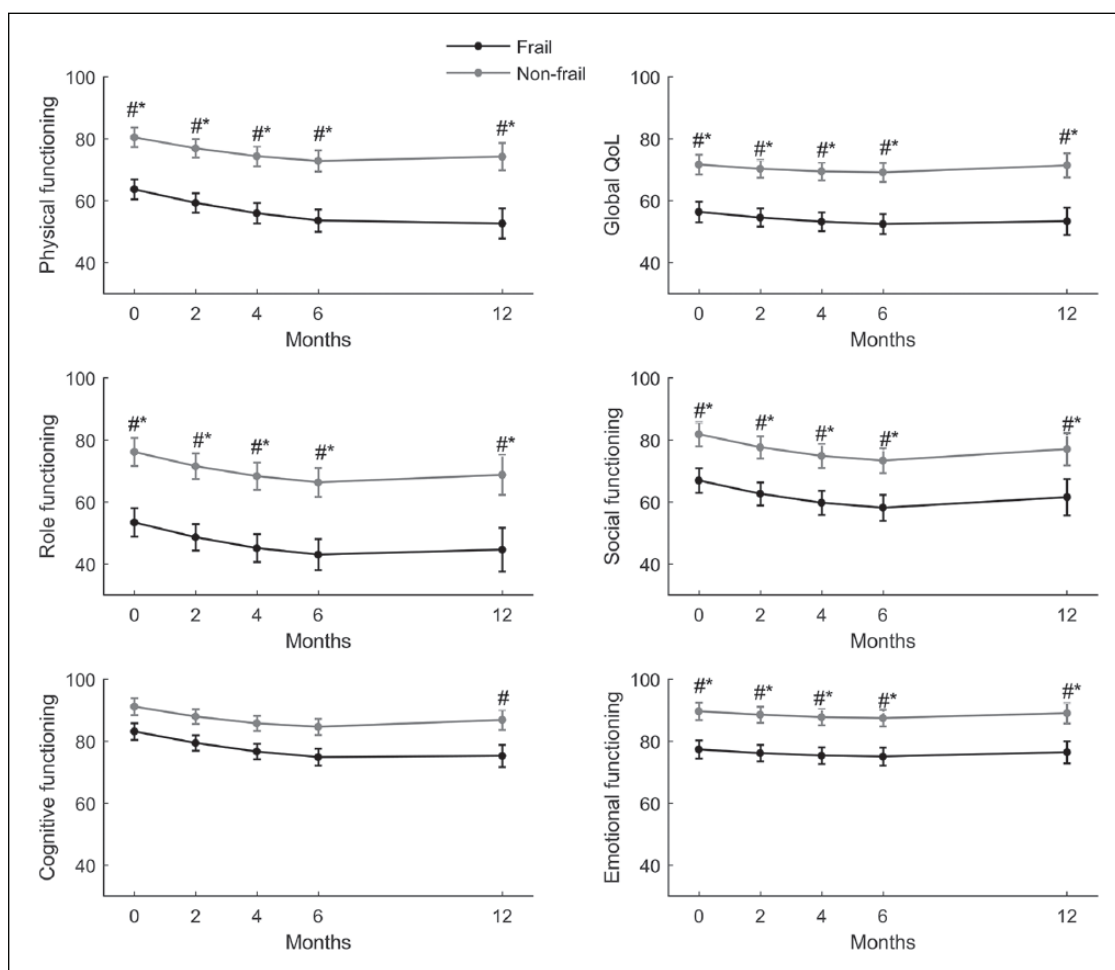
Figure 2. Global quality-of-life and function scores for frail and non-frail patients at baseline and at 2, 4, 6 and 12 months of follow-up, according to unadjusted mixed linear models.

#Clinically and statistically significant differences in unadjusted models.

*Clinically and statistically significant differences in adjusted models.

For these QLQ-C30 functioning scales, higher scores indicate better functioning.

all assessments. Accordingly, significant differences between the frailty groups were found at some but not all assessment points for dyspnoea, insomnia, appetite loss and fatigue (Figure 3).

Discussion

In this longitudinal study, older cancer patients were assessed by a modified geriatric assessment, and we identified a group of frail patients who in comparison to non-frail patients had substantially poorer functioning and more symptoms. Independent of age, gender and major cancer-related prognostic factors, they reported significantly worse global quality of life; physical-, role-, social,– and emotional functioning and more constipation during treatment and follow-up. They also reported a long-term decline in physical functioning that was clinically significant and significantly steeper than for non-frail patients.

To the best of our knowledge, this study is the first to report a longitudinal comparison of self-reported physical functioning between frail and non-frail older patients mainly receiving systemic cancer therapy and the first to suggest a more profound deterioration in this quality-of-life dimension among frail patients after adjusting for other relevant confounders. Our finding is supported by two former studies reporting frailty indicators to be predictive of observer-rated physical decline in older cancer patients receiving chemotherapy or neoadjuvant/adjuvant treatment.[42,43] No such impact of frailty was found in studies of patients receiving surgery and radiochemotherapy, respectively.[10,11] In the latter, however, specific assessments of physical functioning were reported only at 4 weeks after start of therapy, and as indicated by our results, a significant decline may take longer to develop. It is also likely that a protracted course of chemotherapy, which was the treatment received by most of our patients,

Table 3. Linear mixed models of the trajectories of physical functioning in frail versus non-frail patients during 2 months of follow-up and of physical functioning and global quality of life during the first 12 months of follow-up.

Variable	Unadjusted model			Adjusted model[a]		
	Coefficient	*SE*	*p value*	*Coefficient*	*SE*	*p value*
Physical functioning the first 2 months[b]						
Intercept	81.86	1.73	**<0.001**	117.90	18.11	**<0.001**
Frailty (ref. non-frail)[c]	−18.20	2.48	**<0.001**	−12.21	2.40	**<0.001**
Time of 2 months (ref. baseline)	−7.02	1.69	**<0.001**	−7.36	1.67	**<0.001**
Frail × time[d]	3.25	2.43	0.181	2.98	2.41	0.218
Physical functioning the first 12 months[b]						
Intercept	80.41	1.61	**<0.001**	124.74	18.52	**<0.001**
Frailty (ref. non-frail)[c]	−16.80	2.23	**<0.001**	−10.44	2.31	**<0.001**
Time	−2.03	0.35	**<0.001**	−2.13	0.35	**<0.001**
Time^2	0.13	0.03	**<0.001**	0.14	0.03	**<0.001**
Frail × time[d]	−0.40	0.23	0.089	−0.49	0.21	**0.022**
Global quality of life the first 12 months[b]						
Intercept	71.62	1.65	**<0.001**	87.78	18.62	**<0.001**
Frailty (ref. non-frail)[c]	−15.27	2.24	**<0.001**	−12.59	2.37	**<0.001**
Time	−0.83	0.41	**0.046**	−0.91	0.41	**0.029**
Time^2	0.07	0.03	**0.034**	0.07	0.03	**0.025**
Frail × time[d]	−0.23	0.25	0.369	−0.28	0.25	0.273

SE: standard error.
[a]Adjusted for age, gender, cancer type, stage, performance status and treatment.
[b]Physical functioning and global quality of life from the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire.
[c]Frailty (ref. non-frail) refers to estimates of the difference in score between frail and non-frail patients.
[d]Frail × time refers to the interaction term between the frail group and time. A significant interaction term implies significant differences in changes over time between frail and non-frail patients.
Bold numbers are statistically significant.

may have a larger impact on frail patients' physical functioning than surgery.

The results of the few previous studies that have investigated how frail older cancer patients perceive their quality of life are largely consistent with our remaining findings. Frail patients seem to be at a considerable disadvantage throughout the disease trajectory, reporting a substantial symptom burden and poor functioning compared to non-frail patients.[10,11,44] In line with the findings for most quality-of-life aspects in our cohort, others have also found that although quality of life is poorer, changes mainly follow a similar course in frail and non-frail cancer patients. Increased risks of long-term deterioration has, however, been suggested.[13,44] How an observed similarity of changes in quality-of-life trajectories of frail and non-frail patients should be interpreted is not obvious. One might argue that this indicates that frail patients tolerate cancer therapy equally to non-frail patients. However, as frail patients are worse off from the start, changes in the same magnitude may affect these patients more profoundly than those who are non-frail.

Our study has several strengths, that is, a fairly large patient cohort, 12 months follow-up, use of a well-validated quality-of-life questionnaire, high completion rate and statistics controlling for major factors that may affect quality of life. Still, the results should be interpreted with

some caution. First, the population was heterogeneous, details of the chemotherapy regimens were not accounted for and we cannot rule out that frail patients received modified or less aggressive regimens than those who were non-frail. This is, however, unlikely as the physicians were blinded for the results of the modified geriatric assessment. Also, as formerly reported, there was only a fair agreement between the frailty classification based on this assessment and physician-rated frailty.[24] Second, we were not able to accurately register the number of potentially eligible patients who were not included at the various participating clinics. According to the project nurses, however, non-inclusion mainly occurred by random due to lack of time to identify and include patients among their routine clinical tasks. Still, there is some risk that the frailest patients with the poorest overall health more often declined participation or were less frequently invited to participate due to concerns of the additional burden the study tests represented. Third, due to a higher death rate among frail patients, attrition bias may have resulted in underestimation of differences between frail and non-frail patients.[45] Fourth, physical function, as assessed by Timed Up and Go, number of falls and one item from the physical functioning scale of the EORTC QLQ-C30, is a key component of a geriatric assessment and frailty definition and can probably explain some of
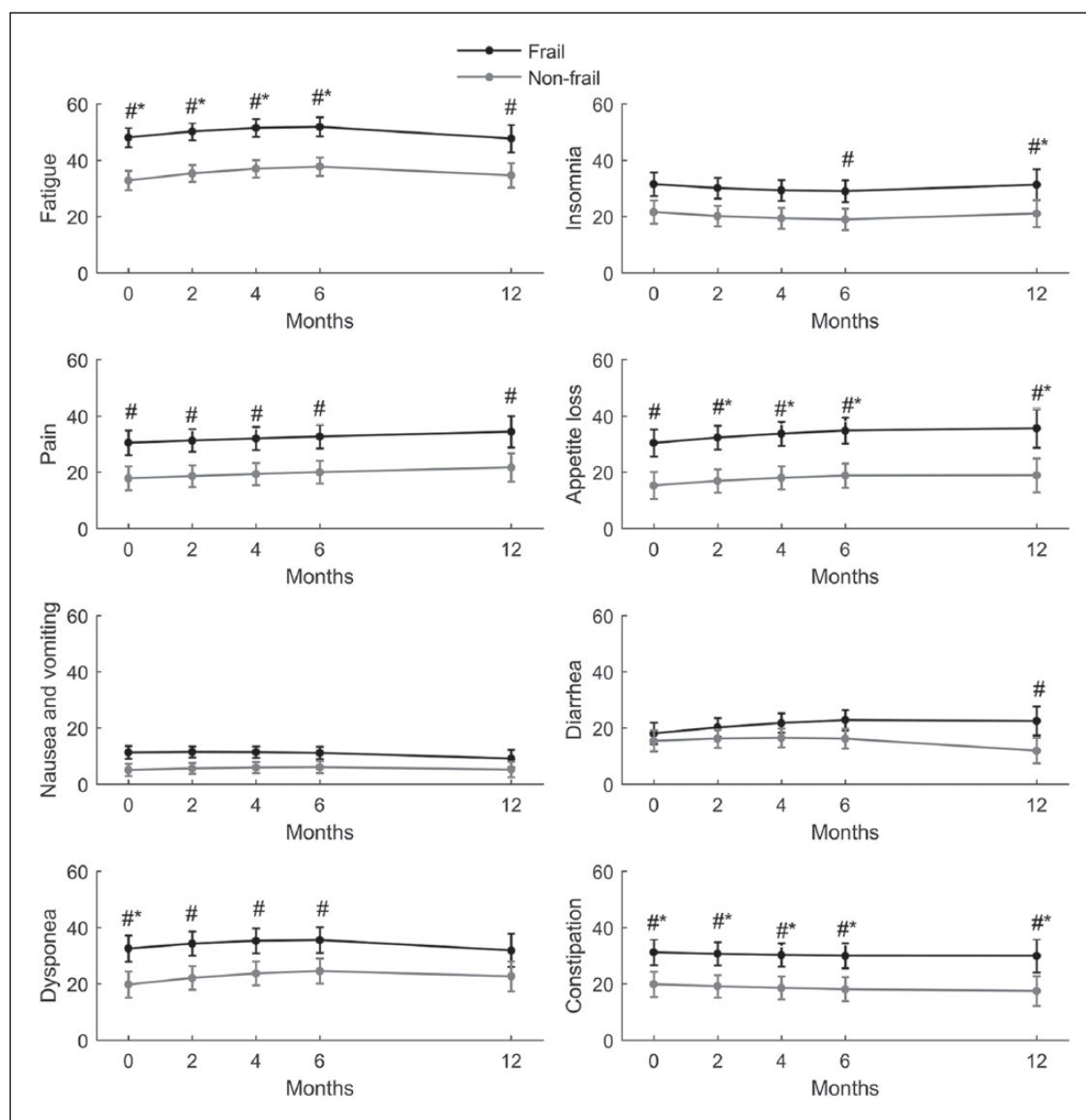
Figure 3. Symptom scores for frail and non-frail patients at baseline and at 2, 4, 6 and 12 months of follow-up, according to unadjusted mixed linear models.
#Clinically and statistically significant differences in unadjusted models.
*Clinically and statistically significant differences in adjusted models.
For these QLQ-C30 symptom scales/items, higher scores indicate more symptoms.

the baseline difference we found in functioning between frail and non-frail patients. However, it is not inherent in our frailty definition that frail patients experience a steeper decline in physical functioning compared to non-frail. Moreover, only a minority of the patients fulfilled these criteria, and the main point to be noted is the overall burden of problems among these frail patients. An additional point of consideration is that we used one question from the QLQ-C30 physical functioning scale, which was also our main endpoint, to identify frailty. Only one patient was classified as frail based on this criterion alone; hence, we believe that this did not affect our results. Finally, as there is no consensus on how frailty

should be identified, it may be discussed if our frailty definition captures the true concept. One may argue that it was too broad as only one criterion was needed to be classified as frail. A stricter definition might have resulted in larger discrepancies between frail and non-frail patients. However, our approach was adapted from the Balducci criteria, and a similar definition was found superior to the physical frailty phenotype in identifying postoperative complications in cancer patients.[46] There is a need for standardisations of cut-off-values for frailty;[8] nevertheless, the consistency of findings across studies indicates that geriatric assessment can identify patients who need particular attention.

Our study shows that frailty as identified by a modified geriatric assessment has a severe impact on the patients' quality of life throughout the disease trajectory, independent of cancer-related factors. Thus, by introducing geriatric assessment into clinical work, a more correct individualization of treatment can be achieved.[47] Furthermore, targeted interventions to improve quality of life and maintain functioning may be initiated. Early introduction of palliative care has been shown to improve quality of life, reduce aggressiveness of treatment and improve survival.[48] Similar studies in frail old cancer patients are needed to examine whether improvement of quality of life can be obtained. Ideally, these studies should include interventions on geriatric deficits and measure their effect on quality of life. Particular attention should be paid on avoiding physical decline, which may considerably increase the risk of dependency, a predominant fear among older patients.[3,4] As indicated by the findings in our study, frail patients report significantly poorer physical functioning than those who are non-frail, meaning that any decline is likely to have more serious consequences.

In conclusion, introducing geriatric assessment into routine clinical practice may help oncologists identify patients with significantly worse quality of life and enable better individualization of treatment. This may also facilitate early and correctly targeted interventions. Future research is, however, needed to explore whether intervening on frailty domains can improve functional status, global quality of life, symptom burden or tolerance to cancer therapy.

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