Shared-decision making in older patients with cancer

The added value of frailty screening

Cheryl P. Bruijnen

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Gezamenlijke besluitvorming bij de oudere patiënt met kanker
De toegevoegde waarde van screenen op kwetsbaarheid
(met een samenvatting in het Nederlands)

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Chapter 1

Introduction and outline of thesis

General introduction

Today more than half of patients newly diagnosed with cancer are ≥ 70 years.[1] The number of this older population substantially increases as a result of life expectancy, population aging, and steady increase of cancer incidence with advancing age. Although the older patient with cancer involves the majority of patients we face in our daily clinic, it is still unclear whether the same treatment in older patients have the same outcome as in younger patients. One reason is the fact that the older patient is underrepresented in clinical trials.[2] It is known that only 33% and respectively 10% of the patients included in oncological registration trials were ≥ 65 years or ≥ 75 years of age and that this enrollment remains dismal despite the recommendations of expert societies.[2,3] The few older patients enrolled in cancer trials, typically have fewer functional impairments or comorbid conditions than the average older patient treated in clinical practice.[4–6] Second, older patients often have other chronic health conditions in addition to cancer, which can further complicate life expectancy estimation, affect treatment tolerability, and modify treatment efficacy.[7] Thereby, the heterogeneity of the older population for instance with regard to co-morbidity, physiological reserves, and geriatric conditions further complicates treatment decisions. Treatment goals of the elderly may also differ from younger patients, since multiple studies have shown that older patients are in general less willing to undertake treatment for life extension at the cost of considerable toxicity, especially when this treatment negatively influences their quality of life or functional status.[8–10]

Many questions regarding the optimal treatment of (frail) elderly are still unanswered. Randomized controlled trials (RCTs) generally give the highest level of evidence, but one can question whether this is feasible for older patients. Given the heterogeneity of the population, it might be difficult to generalize results for the whole population and thereby it is not easy to perform. Additionally, older frail patients might be hesitant to participate in a trial, especially in the case of randomization. Therefore, an important step in the improvement of clinical care for frail or older patients is analyzing our current clinical practice.[11,12] The research described in this theses aims to address some of these questions by analyzing real world data obtained from patients treated in our current clinical practice making the treatment decision process a little less challenging. Older patients were defined as patients aged ≥ 70 years.

Defining and detecting frailty

Before a treatment decision is made, we want to predict whether our older patient can tolerate standard cancer treatment with or without modifications or whether he cannot tolerate standard cancer treatment and needs a less intensive treatment option

or that we should decide not to treat him at all. But, where we have to base this prediction on? Because of the highly individualized process of aging, the biological age can slightly differ from the chronological age and therefore it is insufficient to base treatment decision on chronological age alone.[13] Insight into a patient's frailty status can help to discriminate more.[14]

Before we discuss how to differentiate the frail from the fit patient, we first have to define frailty and how to detect this. The definition of frailty has been widely discussed in the geriatric oncology. One of the accepted and increasingly used definition is the biological syndrome of minimal functional reserve to disproportionate changes in health status when exposed to stressor events, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes.[15,16] It is known that frailty can be present even in patients with a good performance score and is easy to miss for the cancer specialist.[17] In other words, the gut feeling of a treating physician is not sufficient to detect frailty. For that reason, the International Society of Geriatric Oncology (SIOG) has recommended to implement some form of geriatric assessment (GA) in the standard care for older patients with cancer.[14,15] A GA is a multidisciplinary, multidimensional, and systematic assessment, and consists of validated scales to identify impairment in somatic, functional, and psychosocial domains with the aim to provide insight into someone's frailty and to construct a multidisciplinary treatment plan.[18]

Over the past decade, the GA has been suggested as a useful geriatric oncology tool for identifying any underlying undetected medical, functional, and psychosocial impairment that may complicate treatment, thereby helping to select the most appropriate treatment.[19–21] Also, several studies have shown associations between items of the GA and the risk of toxicity, morbidity, and mortality during cancer treatment in older patients.[22] It has been ascertained that, after a geriatric evaluation, the treatment plan was altered in almost a quarter of the patients considered for surgical or chemotherapeutic treatment, primarily to a less intensive treatment option. In addition, a positive trend was seen towards more treatment completion and less treatment-related toxicity and complications in the patients who underwent a geriatric evaluation.[23]

Frailty screening

Based on the recommendation of the SIOG, we want to implement the GA in our daily practice for patients with cancer aged ≥ 70 years and with a high risk of frailty at the department of Medical Oncology in the UMC Utrecht. However, there is no consensus regarding which domains should be included in the GA for the patients with cancer. The SIOG suggests exploring several domains (functional status, fatigue, cognition, mental health status, social support, nutrition, and geriatric syndromes), but provides

no clear recommendation.[14] As a result, we did not exactly know which domains we should include in our GA. Therefore, we want to perform a systemic review with the aim to evaluate which domains should minimally be included in a GA.

Conducting a GA is not always necessary for the fit older patient with cancer. Therefore screening tools are used to distinguish the 'frail' older patient from the 'fit' older patient who can tolerate standard cancer treatment without a need to perform a GA.[24] Nowadays, multiple different screening tools have been studied with the aim to select the older patients in need of a GA. The Geriatric 8 (G8) screening tool is such a screenings instrument especially developed for the older patients (≥ 70 years) with cancer (Table 1).[25]

Table 1: Geriatric 8

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake
B	Weight loss during the last 3 months	0 = weight loss > 3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss
C	Mobility	0 = bed or chair bound 1 = able to get out of bed/ chair but does not go 2 = goes out
D	Neuropsychological problems	0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems
E	Body Mass Index (BMI (weight in kg/(height in m^2))	0 = BMI < 19 1 = BMI = 19 to BMI < 21 2 = BMI = 21 to BMI < 23 3 = BMI = 23 and > 23
F	Takes more than 3 medications per day	0 = yes 1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0 = not as good 0.5 = does not known 1 = as good 2 = better
H	Age (years)	0 = > 85 1 = 80-85 2 = < 85
	Total score	0-17

The G8 is an eight-item questionnaire that includes seven items from the 18-item mini-nutritional assessment (MNA) and an age-related item (<80, 80 to 85, or > 85 years).[26] The total score ranges from 0 to 17. A score of ≤ 14 was considered to be abnormal, indicating a need for a GA. It was concluded that the G8 was the most robust since the G8 has consistently demonstrated a good sensitivity for geriatric impairments (> 80% in six of eight studies) with acceptable specificity (> 60% in four studies).[27,28] As a result, in geriatric oncology, the G8 is the most frequently used frailty screening tool in the so-called two-step approach: a geriatric screening tool followed by a GA if the screening tool has an impaired score.

Because the G8 was shown to be the most robust, we choose to use the G8 as screenings tool in this two-step approach. While we were implementing this two-step approach, the department of surgery showed their interest in this approach. In our clinic, every patient aged ≥ 70 years requiring elective surgical treatment under general anesthesia has to visit the pre-operative screening clinic for a geriatric assessment before undergoing the surgical treatment. Our surgeons wondered whether this two-step approach was also useful for distinguishing frailty in their population with (a suspicion for) cancer. Actually, we were not sure that the G8's discriminating power in determining frailty in older patients considered for surgery was just as good as the discriminating power in older patients eligible for systemic anti-cancer treatment, because data specially addressing the use of the G8 in older patients considered for surgery were limited. As a result, we are planned to address this question in this thesis.

Geriatric 8 as predictor for treatment outcomes

The G8 is a useful tool for the identification of frailty. In addition to the diagnostic value, the G8 has also shown to be a predictor for several treatment outcomes. A recent systematic review reported that survival, chemotherapy related toxicity, functional decline, and health related quality of life (HRQoL) are outcomes which can be predicted by the G8, although the results vary.[29]

However, the association between the G8 and occurrence of toxicity of immune check point inhibitors (ICI) has never been evaluated, while having insight in this association has a great importance. The indication for ICI is rapidly increasing and ICI have a more favorable toxicity profile compared to chemotherapy and as a result they are increasingly considered as a tolerable treatment option at older age. With additive evidence of efficacy in distinct subtypes, more than 40% of the patients are now eligible for checkpoint inhibition.[30] As a result, ICI are becoming common practice for every oncologist and also the amount of older patients treated with ICI shall increase.[31,32] Immune-related adverse events (irAEs), the immune-mediated toxicities that occur during ICI, differ from adverse events (AEs) of other systemic antitumor therapies. AEs

can affect multiple organs of the body and mostly they do not resolve after discontinuation but require immunosuppressive treatment. Since irAEs have differed from AEs of, for instance, chemotherapy, we cannot assume that the G8 is also predictive for the occurrence of irAEs. That is why we want to assess the G8's predictive value for irAEs.

Importance of Patient-Reported Outcome Measures

To determine the effects of anti-cancer treatments, the most frequently used outcomes in studies are overall survival, progression-free survival, or response rate.[33] That is striking, since maintaining or improving HRQoL and retaining independence have been preferred as more relevant outcomes by older patients with cancer, limiting the applicability of clinical trial data for use in treatment decision making.[34] This emphases the importance of including patient-related outcomes (PROs) in clinical trials in general and for older patients in particular. PROs cover a range of health outcomes such as symptoms, functional limitations, quality of life, and patient satisfaction. These are generally measured with questionnaires that collect information directly from the patient, without interpretation by others.[35] In our hospital, the Utrecht Symptom Diary (USD) is used to routinely assess and monitor symptoms across the entire continuum of cancer care (Table 2).[36] The USD is an adapted Dutch version of the Edmonton Symptom Assessment System and has been validated in two studies.[36,37]

Table 2: Utrecht Symptom Diary

No pain	1 2 3 4 5 6 7 8 9 10	Worst pain possible
No sleeping problems	1 2 3 4 5 6 7 8 9 10	Worst sleeping problems possible
No dry mouth	1 2 3 4 5 6 7 8 9 10	Worst dry mouth possible
No dysphagia	1 2 3 4 5 6 7 8 9 10	Worst dysphagia possible
No lack of appetite	1 2 3 4 5 6 7 8 9 10	Worst lack of appetite possible
No disturbed stool	1 2 3 4 5 6 7 8 9 10	Worst disturbed stool possible
No nausea	1 2 3 4 5 6 7 8 9 10	Worst nausea possible
No shortness	1 2 3 4 5 6 7 8 9 10	Worst shortness of breath possible
of breath No fatigue	1 2 3 4 5 6 7 8 9 10	Worst fatigue possible
No anxiety	1 2 3 4 5 6 7 8 9 10	Worst anxiety possible
No depressed mood	1 2 3 4 5 6 7 8 9 10	Worst depressed mood possible
Good wellbeing	1 2 3 4 5 6 7 8 9 10	Worst well-being possible

As a result, it would be helpful if the priorities of older patients regarding their treatment outcomes are mirrored in research objectives to help us informing our patients about these aspects of treatment. However, nowadays only 20% of the oncological trails assessed PROs.[38] Compared to all trials, trails exclusively for older patients ad-

dressed more often PROs (respectively 30% versus 20%). A recent study showed that over the last fifteen years, there was an incremental trend in the reporting of PROs, although PROs are still underrepresented in clinical trials including solid malignancies.[38] Therefore, the last aim of our research was to get insight into the impact of anti-tumor treatment on outcomes such as symptom burden and functional decline.

Aims and outline of this thesis

In the first part (**Chapter 2**), we systematically evaluate which domains of the GA could predict mortality, postoperative complications of elective surgery for solid tumors, and systemic treatment-related outcomes and should therefore be included in a GA, when the aim is to predict patients-related outcomes of older patients with cancer.

The second part of this thesis focuses on research on the diagnostic and predictive value of the G8 for adverse events of oncological treatments. We validate in **Chapter 3** whether the G8 is also suitable for identifying frailty in older patients with cancer undergoing surgery. In addition, we investigate the differences in postoperative outcomes between the fit and the frail patients classified by the G8. **Chapter 4** describes the association between frailty according to the G8 and the occurrence of immune related adverse events (irAEs) caused by treatment with immune checkpoint inhibitors (ICI) in older patients with melanoma.

The last part focuses on getting insight into PROs. In **Chapter 5**, we assess the change in functional status and self-reported health status of older patients one year after surgery for head and neck cancer (HNC). Little is known about the long-term effect of surgery of HNC with regard to these outcomes, while these outcomes are particularly relevant in the discussion with older patients, since older patients seem to have a preference for HRQoL over length of life. **Chapter 6** describes the symptom burden of older patients with cancer during systemic anti-tumor therapy. Thereby, we assess predictors for high symptom burden. We are specifically interested in the predictive value of frailty according to the G8 for symptom burden, because that predictive aspect of the G8 has rarely been investigated.

This thesis is completed by a General Discussion in **Chapter 7**, in which the main results and conclusions of the presented studies are discussed, including an interpretation of main findings, conclusions, recommendations for current clinical practice and future research.

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Part I

Geriatric assessment

Chapter 2

Predictive value of each Geriatric Assessment domain for older patients with cancer: A systematic review

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Abstract

Introduction

A geriatric assessment (GA) is increasingly used to help guide treatment decisions in older patients with cancer. However, there is no consensus regarding which domains should be included in the GA. In addition, the field of geriatric oncology moves very fast and as a result many new studies have been published since the last review in 2015. Therefore, the objective of this systematic review is to evaluate which domains of the GA could predict patient-related treatment outcomes of older patients with cancer and thereby should be included in a GA.

Methods

A systematic literature search was performed for publications in English or Dutch between September 2006 and July 2017 addressing the association between individual domains of the GA and mortality, postoperative complications, or systemic treatment-related outcomes in older patients with cancer.

Results

Eight different domains were evaluated in 46 publications, namely functional status, nutritional status, cognition, mood, physical function, fatigue, social support, and falls. All eight domains were predictive for at least one of the investigated outcomes but the results were quite variable across studies. Physical function and nutritional status were the domains most often associated with mortality and systemic treatment-related outcomes, and the domain physical function was most often associated with postoperative complications.

Conclusion

Overall, this review demonstrates that the GA should minimally consist of physical function and nutritional status, when the aim is to predict patients-related outcomes of older patients with cancer, although the results are quite heterogeneous. For the other domains, the findings are too inconsistent to draw conclusions about their overall predictive ability.

Introduction

More than half of patients newly diagnosed with cancer today are 65 years of age or older.[1] The number of older patients with cancer substantially increases as a result of increasing life expectancy, population aging, and steady increase of cancer incidence with advancing age. Unfortunately, because this group is underrepresented in clinical trials, there are less results on which to base treatment decisions.[2] This means that older patients with cancer are more likely to be treated according to recommended treatment guidelines for younger patients, resulting in over-treatment. On the other hand, some older patients are incorrectly denied treatment according to recommended guidelines for fear of higher complications and toxicity rates resulting in under-treatment. Both over-treatment and under-treatment have a strong negative impact on survival. Moreover, older patients often have other chronic health conditions in addition to cancer, which can further complicate life expectancy estimation, affect treatment tolerability, and modify treatment efficacy.[3]

Furthermore, treatment decisions are complicated by the heterogeneity of the older population with regard to co-morbidity, physiological reserves, functional status, social network, and geriatric conditions, making treatment decisions complex. As a result, the biological or functional age can differ significantly from chronological age.[4] Because chronological age alone is a poor descriptor of the highly individualized process of aging, a systematic way of describing the heterogeneity is needed to help guide oncology treatment decisions. A geriatric assessment (GA) can fill this knowledge gap.[5]

A GA is a multidisciplinary, multidimensional, and systematic assessment, and consists of validated scales to identify impairments in geriatric domains.[6] A GA-guided treatment improves survival, quality of life, functional status, and decreases the risk of hospitalization and nursing home placement in non-oncological patients.[6] Over the past decade, the GA has been suggested as a useful geriatric oncology tool for identifying any underlying undetected medical, functional, and psychosocial impairment that may complicate treatment, thereby helping to select the most appropriate treatment.[7–9] Also, several studies have shown associations between items of the GA and the risk of toxicity, morbidity, and mortality during cancer treatment in older patients.[10]

The International Society of Geriatric Oncology (SIOG) has therefore recommended conducting some form of geriatric assessment in the older patient with cancer.[4,11,12] Despite their recommendation, there is no consensus regarding which domains should be included in the GA for patients with cancer. The SIOG suggests exploring several domains (functional status, fatigue, cognition, mental health status, social support, nutrition, and geriatric syndromes), but provides no clear recommendation.[5] In addition, several different measurement tools are available for investigating these domains,

but no one tool has been proven superior to the others. There is also a variation in the cutoff scores for impairment of the tools, resulting in various compositions of the GA, making inter-study comparison difficult. For that reason, there is a need for uniformity in the GA.

To help decide which domains should be included in the GA, the predictive value of each individual domain should be known. To our knowledge, the most recently published overviews of the predictive abilities of individual domains of the GA were published in 2015, reporting literature searches performed in 2013.[13,14] We have therefore concluded that a new systematic review is needed in order to arrive at an overview of the most recent evidence. The aim of this systematic review is to systematically evaluate which domains of the GA could predict patient-related treatment outcomes defined as mortality, postoperative complications of elective surgery for solid tumors, systemic treatment-related outcomes as toxicity, completion of planned treatment, and dose modifications, and should be included in a GA for older patients with cancer.

Methods

Data sources

In July 2017, a systematic search was conducted in four databases: MEDLINE, EMBASE, Cochrane, and Cinahl. The search strategy combined synonyms for 'older patients', 'cancer', 'geriatric assessment', 'mortality', 'treatment outcomes', and 'postoperative complications'. The search was executed in 'title and/or abstract', and was restricted to articles in English or Dutch with a publication date between September 2006 and July 2017 (to avoid outdated evidence). An experienced university librarian assisted in the literature search. The full search syntax is presented in Supplementary 1. The PRISMA statement was used for reporting this systematic review.[15]

Study selection

After duplicates were deleted, the studies were selected in two steps. In the first step, the results were screened based on potentially relevant title and abstract using predefined criteria. A study was eligible for inclusion if all of the following criteria were fulfilled: (1) the study reported on patients 65 years or older diagnosed with cancer (any type of solid tumors or hematological malignancies, except skin cancer), and (2) the study reported on longitudinal, observational, interventional, or retrospective studies that addressed the association between baseline geriatric assessment and the following patient-related outcomes: mortality, postoperative complications of elective surgery for solid tumors, and systemic treatment-related outcomes defined as toxicity of systemic treatment, completion of planned treatment, and dose modifications. Editorials, case studies, reviews, expert opinion papers, and studies that were published as abstracts only were excluded. Because comorbidity is a routine part of the oncological work-up and therefore not considered part of the geriatric assessment, studies assessing the association between comorbidity and patient-related outcomes were excluded. Furthermore, frailty was not considered as an individual domain of the GA since frailty has frequently been defined as the presence of one or more impairments in geriatric domains, e.g. weight loss, fatigue, or low physical activity.

The selection was performed independently by two authors (CB and DH). When one author was uncertain about whether the study met the inclusion criteria or the abstract was unavailable, the study was selected for full text screening. In the second step, the full text was independently reviewed by these authors using the same inclusion and exclusion criteria. Disagreements between authors were resolved by consensus. To obtain the one unavailable full text article, we contacted the authors by email. Finally, the reference list of each selected study was reviewed to identify any additional relevant article.

Quality assessment

The two authors appraised the methodological quality of each of the selected studies independently. The Quality In Prognosis Studies (QUIPS) tool was used to assess the risk of bias for the following five domains (1) the study participation, (2) the study attrition, (3) the assessment of the domains of the GA, (4) the measurement of the outcomes, and (5) statistical analysis and reporting (Supplementary 2).[16,17] These potential bias domains were rated as having high (0 points), moderate (0.5 points), or low risk of bias (1 point), based on the QUIPS study of Hayden et al..[17] Next, we rated the study design. A prospective study was ranked as a low risk of bias (1 point) because the inclusion criteria, the prognostic factors, and outcomes are defined in advance, and the baseline and follow-up data are more often complete, which reduces the risk for data dragging.[18] As a result, a retrospective study was ranked as a high risk of bias (0 points).

Subsequently, the scores of the six items were added. The total score reflected the overall risk of bias of the study: the maximum total score of 6 was regarded as the study with the lowest risk of bias. All discrepancies were resolved by consensus. No study was excluded based on the quality assessment since our aim was to provide a comprehensive overview of all studies assessing the predictive ability of individual domains of the GA for older adults with cancer.

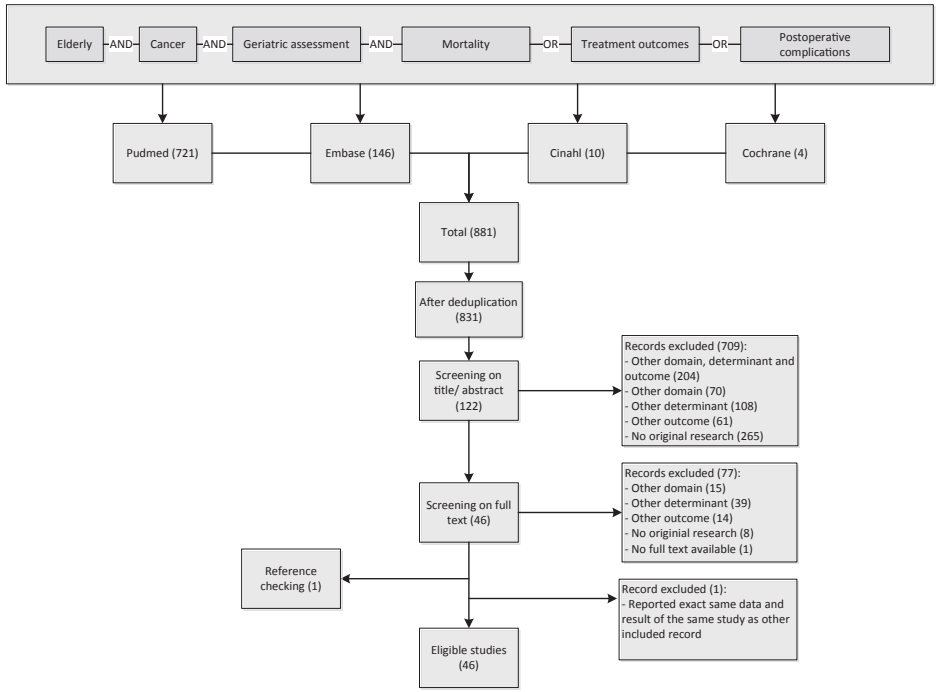
Data abstraction, synthesis and analysis

The two authors extracted the data of each study included independently. A formal meta-analysis was not possible due to the heterogeneity in study designs, diversity in study populations, the use of different geriatric assessment tools with different cutoff points, and the diversity in outcomes. Therefore, we summarized the results of the predictive ability of individual geriatric domains per outcome measure.

Results

The literature search in four databases yielded 881 citations. After removing duplications (n= 50) and screening on titles and abstracts, 122 full texts were reviewed. The full text of one citation remained unavailable, despite contacting the authors.[19] After this review, 46 publications remained eligible for inclusion (Figure 1).

Figure 1: Flowchart of study selection



Next, one publication was excluded because this publication reported the exact same cohort, data, and results as another publication included.[20,21] Reference checking yielded one additional relevant publication. In the end, 46 eligible publications remained for quality assessment and data analysis.

Overall, scores of the quality assessments ranged from 2.0 to 6.0, with a median value of 4.5 (Supplementary 3). Five publications had the lowest risk of bias with a maximum score of 6.[21–25]

Study characteristics

An overview of the characteristics of the 46 eligible publications is shown in Table 1. More than half of the studies were published in 2014 or later (24 out of 46 studies, 52%). Of the 46 publications, 38 were prospective studies, six were retrospective studies, and two had an unclear study design. None of the publications reviewed reported a randomized controlled trial specifically designed to examine the effectiveness of geriatric assessment.

Twelve studies focused on patients with one specific solid tumor type, nine studies included patients with a hematological malignancy, and 25 studies focused on patients with various types of cancer. In total, the 46 publications comprised data of 9,985 unique patients of 44 different cohorts. An average of forty-nine percent of the patients were males. The median number of patients enrolled was 150 (range 44-993). The age of the patients ranged from 65 to 99 years. The following geriatric domains were assessed as being part of a GA: functional status, nutritional status, cognition, mood, physical function, fatigue, social support, and falls. The median number of geriatric domains of the GA reported by study was four (range one-seven).

Table 1: Study characteristics

Author (year)	Design	Aim of study	Sample size (% males)/ country	Min. age	Age, median years (range)		Tumor type	Follow-up	Inclusion criteria	Geriatric domains of GA	Measurement tool of geriatric domain	Outcomes
Aaldriks(2013)[34]	Pros	To study the prognostic value of GA	55* (4) Netherlands	≥ 70 yr	76[a] (70-88)		Breast cancer	0-57 months	Advanced cancer for whom chemotherapy was prescribed	Nutrition Cognition	MNA MMSE/ IQCODE-N	Early withdrawal chemotherapy Mortality
Aaldriks(2015)[51]	Pros	To investigate the prognostic value of GA	44 (43) Netherlands	≥ 70 yr	78[a] (70-86)		Non-Hodgkin Lymphoma	0-101 months	Fit for chemotherapy	Nutrition Cognition	MNA MMSE/ IQCODE-N	Early withdrawal chemotherapy Mortality
Aaldriks(2011)[8]	Pros	To assess the prognostic value of GA for treatment with chemotherapy	202* (45) Netherlands	≥ 70 yr	77[a] (71-92)		All cancer types	1-33 months	Chemotherapy was prescribed	Nutrition Cognition	MNA MMSE/ IQCODE-N	< 4 cycles chemotherapy vs ≥4 cycles Mortality
Aaldriks(2016)[35]	Pros	To analyze which elements of geriatric screening program were predictive for chemotherapy and mortality	494 (49.9)* Netherlands	≥ 70 yr	75 (70-92)		All cancer types	1-101 months	Considered fit enough for chemotherapy	Nutrition Cognition	MNA MMSE/ IQCODE-N	< 4 cycles chemotherapy vs ≥4 cycles Mortality
Aaldriks(2013)[36]	Pros	To assess the predictive value for tolerance of treatment	143 (59)* Netherlands	≥ 70 yr	75[a] (70-92)		Colorectal	0.5-62 months	Eligible for chemotherapy treatment	Nutrition Cognition	MNA MMSE/ IQCODE-N	< 4 cycles chemotherapy vs ≥4 cycles Mortality
Aparicio(2013)[66]	Pros	To identify predictive factors of treatment feasibility and toxicity	123 (54) France	≥ 75 yr	80.4[a] (NR)		Colorectal	4 months	Fit for chemotherapy	Functional status: IADL Cognition Mood	Lawton-scale MMSE GDS	Grade 3 to 4 toxicity Dose reduction > 33% Hospitalization
Audisio(2008)[43]	Pros	To investigate the value of a GA in assessing the suitability for surgical intervention	460 (34) Europe and Japan	≥ 70 yr	76.9[a] (70-95)		Solid tumors	1 months	Elective cancer surgery No emergency surgical management	Functional status: ADL IADL Cognition Mood Fatigue	Katz-scale Lawton-scale MMSE GDS BFI	Morbidity Post-operative hospital stay
Badgwell(2013)[44]	Pros	To identify factors which may be associated with increased risk in older patients patients undergoing abdominal surgery	111 (55) United States of America	≥ 65 yr	72 (62-89)		Abdominal cancer	3 months	Abdominal cancer surgery	Functional status: IADL Nutrition Cognition Mood Fatigue Falls	Lawton-scale Amount of weight/ 6 months Mini-Cog Test GDS BFI Number of falls/ 6 months	Post-operative complications according to Clavien-Dindo scale Discharge to nursing facility Hospital readmission
Baier(2016)[47]	Pros	Use of GA to predict risks and benefits of interventions	200 (69) Germany	≥ 70 yr	75 (70-88)		Abdominal cancer	6 months	Planned for elective surgery in curative intention, expected survival > 6 months	Functional status: IADL Nutrition Cognition Physical function	Lawton-scale MNA MMSE GUG	Dependence: ADL < 95
Baitar(2014)[67]	Pros	To evaluate the association between the Geriatric 8 and Groninger Frailty Index and severe treatment toxicity	85 (48) Belgium	≥ 65 yr	66 (66-88)		All cancer types	1 months	(Radio)chemotherapy < 3 weeks after screening	Functional status[b]: ADL IADL Nutrition[b] Cognition Mood[b] Social support[b]	Katz-scale Lawton-scale MNA MMSE GDS MOS-SSS	SAE after first cycle of (radio) chemotherapy

Table 1: Study characteristics *Continued*

Author (year)	Design	Aim of study	Sample size (% males)/ country	Min. age	Age, median years (range)	Tumor type	Follow-up	Inclusion criteria	Geriatric domains of GA	Measurement tool of geriatric domain	Outcomes
Biesma(2011)[68]	Pros	To evaluate whether a GA can be used as a tool to predict which patients benefit from chemotherapy	181 (77) Netherlands	≥ 70 yr	74 (70-87)	Non-Small Cell Lung Carcincoma	NR	Inoperable, WHO-performance score ≤ 2	Functional status: ADL IADL Cognition Mood Physical function	Katz-scale Lawton-scale MMSE GDS TUG	Survival
Bila(2015)[69]	NR	To analyze the prognostic and treatment effect of IADL on the outcome of older patients patients	110 (50) Serbia	≥ 65 yr	NR	Multiple myeloma	NR	Treatment with chemotherapy	Functional status: IADL	Lawton-scale	AE Overall survival
Brunello(2016)[42]	Retro	To develop a cancer-specific multidimensional Prognostic Index for mortality prediction	658 (34) Italy	≥ 70 yr	77.16[a] (70-96)	All cancer types	0-8. years	NR	Functional status: ADL IADL Cognition Mood Social support	Katz-scale Lawton-scale MMSE GDS Presence of caregiver	One-year mortality
Choi(2015)[45]	Retro	To evaluate the role of a scoring model in predicting adverse surgical outcomes	281 (0) Korea	≥ 65 yr	76.3[a] (NR)	All cancer types	100 days	Low ASA risk, female, Korean patients undergoing curative cancer surgery	Functional status: ADL IADL Nutrition Cognition Mood	Barthel-index Lawton-scale MNA MMSE GDS	Post-operative complication Length of hospital stay
Clough-Gorr(2010)[41]	NR	To evaluate GA domains in relation to important outcomes	660 (0) United States of America	≥ 65 yr	NR	Breast cancer	7 years	Stage I, II or IIIA	Mood Social support	MHI5 MOS-SSS	Poor treatment tolerance according to opinion patient Mortality
Denewet(2016)[70]	Pros	To assess to which extent GA could be seen as determinant of survival	205 (53) Belgium	≥ 70 yr	79 (70-93)	All cancer types	12 months	New diagnosis or disease progression	Functional status: ADL IADL Nutrition[b] Cognition[b] Mood[b]	Katz-scale Lawton-scale MNA-SF MMSE GDS	Survival
Dubruille(2015)[71]	Pros	To investigate the predictive value of the different GA items	90 (51) Belgium	≥ 65 yr	74 (65-89)	Hematological cancer	1 year	Hospitalized for chemotherapy	Functional status: ADL IADL Nutrtion Cognition Mood Fatigue Falls	Katz-scale Lawton-scale MNA MMSE GDS Mob-t Number of falls/ last year	1-year overall survival
Extermann(2012)[49]	Pros	To create and validate in independent patients a predictive score with potential for clinical application	518(49.8) United States of America	≥ 70 yr	75.5 (70-92)	All cancer types	6 months	Histologically proven cancer and were initiating a new first line to fourth line source of chemotherapy	Functional status: IADL Nutrition Cognition Mood	Lawton-scale MNA MMSE GDS	Grade 4 hematologic toxicity and/or grade 3-4 non-hematologic toxicity
Ferrat(2015)[26]	Pros	To identify GA findings associated with mortality	993 (51) France	≥ 70 yr	80.2[a] (NR)	All cancer types	1 year	NR	Functional status: ADL Nutrition Cognition Mood Physical function	Katz-scale MNA MMSE GDS GUG	Overall 1-year mortality

Table 1: Study characteristics *Continued*

Author (year)	Design	Aim of study	Sample size (% males)/ country	Min. age	Age, median years (range)	Tumor type	Follow-up	Inclusion criteria	Geriatric domains of GA	Measurement tool of geriatric domain	Outcomes
Ghosn(2017)[72]	Pros	To evaluate the predictive value of and abridged GA for mortality in older patients patients with cancer	100 (53) Lebanon	≥ 70 yr	76	All cancer types	Median 1418 days	A performance score ≥ 60 and a MMSE ≥ 23	Functional status ADL IADL Nutrition Cognition Mood Physical function	Katz-scale Lawton-scale MNA MMSE GDS TUG	Overall surivival
Giantin(2013)[22]	Pros	To test the Multidimensional Prognostic Index	160 (45) Italy	≥ 70 yr	79.4[a] (69-93)	Solid tumors	12 months	Inoperable or metastatic solid cancer	Functional status: ADL IADL Nutrition Cognition Mood	Katz-scale Lawton-scale MNA SPMSQ/ MMSE GDS	Mortality
Gírones(2012)[37]	Pros	To investigate the association of GA variables with function and survival	83 (97.6) Spain	≥ 70 yr	77[a] (NR)	Lung cancer	2 years	Lung cancer at any stage	Functional status: ADL IADL Nutrition Cognition Mood	Katz-scale ? Amount of weight loss/ 3 months MMSE GDS	Mortality
Goede(2016)[30]	Pros	To investigate the association between GA and treatment outcome	75 (61) Germany	No cutoff point: 8% below 65 years	75 (48-87)	Chronic Lymphocytic Leukemia	5 years	Treatment with chemotherapy in the Chronic Lymphocytic Leukemia-9 trial	Functional status: IADL Cognition Physical function	Lawton-scale DEMTECT TUG	Dose reduction Treatment delay Treatment discontinuation Overall survival
Hamaker(2013)[73]	Pros	To evaluate the association between baseline GA and toxicity	78 (0) Netherlands	≥ 65 yr	75.9 (65.8-86.8)	Breast cancer	Median 32 months	Metastatic breast cancer patients treated with first line chemotherapy	Functional status: IADL Nutrition Cognition Mood	Lawton-scale BMI MMSE GDS	Grade 3-4 toxicity Mortality
Hamaker(2014)[28]	Pros	To assess the value of Geriatric 8 in predicting 1-year mortality	108 (53) Austria	≥ 67 yr	78.2 (67.1-98.9)	Hematological malignancy	12 months	Newly diagnosed with a hematological malignancy	Functional status: ADL IADL Nutrition Cognition Mood Physical function	Barthel-index Lawton-scale BMI MMSE GDS TUG	1-year mortality
Hamaker(2011)[32]	Pros	To assess which geriatric conditions are associated with mortality	292 (51.2) Netherlands	≥ 65 yr	74.9 (65-96.2)	All cancer types	12 months	Patients admitted to general medicine or oncology	Functional status: ADL IADL Nutrition Cognition Mood Social support	Katz-scale Modified Katz-scale SNAQ IQ-CODE-SF GDS EDIZ	12-month mortality
Hoppe(2013)[48]	Pros	To determine factors associated with functional early functional decline during first-line chemotherapy in older patients	364 (59.2) France	≥ 70 yr	77.35 (70-93)	Colon, pancreatic, stomach, ovarian, bladder, prostate, lung, non-Hodgkin lymphoma, or cancer of unknown primary origin	4 weeks	Patients scheduled to receive first-line chemotherapy	Functional status ADL IADL Nutrition Cognition Mood Physical function	Katz-scale Lawton-scale MNA MMSE GDS TUG	Functional decline after first cycle of chemotherapy: any decrease in ADL score

Table 1: Study characteristics *Continued*

Author (year)	Design	Aim of study	Sample size (% males)/ country	Min. age	Age, median years (range)		Tumor type	Follow-up	Inclusion criteria	Geriatric domains of GA	Measurement tool of geriatric domain	Outcomes
Huisman(2015)[21]	Pros	To investigate the predictive ability of screening tools	328 (38.1)** Europe	≥ 70 yr	76 (70-96)		Solid tumors	1 month	Elective surgery for a solid tumor under general anesthesia	Functional status: ADL IADL Nutrition Cognition Mood Physical function Fatigue	Katz-scale Lawton-scale NRS MMSE GDS TUG BFI	Major complication < 30 days according to Clavien-Dindo scale
Huisman(2014)[23]	Pros	To determine the predictive value of the TUG	263(33.5) Europe	≥ 70 yr	76 (70-96)		Solid tumors	1 month	Elective surgery for a solid tumor	Physical function	TUG	Major complication (gr 3-5) < 30 days according to Clavien-Dindo scale
Hurria(2011)[7]	Pros	To develop a predictive model for grade 3 to 5 toxicity	500(44) United States of America	≥ 65 yr	73[a] (65-91)		Solid tumors	Until the end of chemotherapy	Diagnosis of cancer Stage I-IV and scheduled to receive a new chemotherapy	Functional status[b]: ADL IADL Nutrition[b] Cognition[b] Mood[b] Physical function Falls Social support[b]	Subscale of MOS Physical Health Subscale of OARS BMI BOMC HADS TUG Number of falls/ 6 months MOS-SSS	Grade 3 to 5 toxicity of chemotherapy
Jonna(2016)[74]	Retro	To identify factors associated with shorter survival after following hospitalization	803(51.8) United Stated of America	≥ 65 yr	72.5 (?)		All cancer types	6 years	All patients admitted to the oncology acute care for elders unit who underwent GA	Functional status: ADL IADL Cognition	Katz-scale Lawton-scale Clock	Overall survival
Kanesvaran(2011)[38]	Retro	To determine the impact of each GA domain on overall surivial	249(61.4) Singapore	≥ 70 yr	77 (70-94)		All cancer types	3 years	Diagnosis at any stage	Functional status: ADL IADL Nutrition Cognition Mood	Katz-scale Lawton-scale DETERMINE-NI Clock/ MMSE GDS	Overall survival
Kenig(2015)[24]	Pros	To compare prevalence of frailty depending on the number of incorporated domains of GA and to evaluate its accuracy in predicting postoperative outcomes	75(56) Poland	≥ 65 yr	73 (65-93)		Solid abdominal tumors	1 month	In need of elective surgery under general anesthesia	Functional status: ADL[b] IADL Nutrition Cognition Mood Physical function Fatigue Social support	Katz-scale Lawton-scale MNA BOMC/ Clock/ MMSE GDS TUG BFI MOS-SSS	Any event within 30 days of surgery that required treatment Major complication
Kristjansson(2010)[39]	Retro	To identify independent predictors of post-operative complications and early mortality from a GA	182(43) Norway	≥ 70 yr	80		Colorectal cancer	14-34 months	Planned for surgery of a confirmed or suspected colorectal cancer	Functional status: ADL IADL Nutrition Cognition Mood	Barthel-index NEADL MNA MMSE GDS	Any and severe complications < 30 days of surgery Mortality
Marinello(2009)[75]	Pros	To analyze the role of several factors, including GA, in predicting the occurrence of adverse events during chemotherapy	110(64) Italy	≥ 70 yr	75.1 (70-87)		Any stage of breast, lung and colorectal cancer	The whole treatment period (about 6 months)	Considered sufficiently fit to tolerate chemotherapy	Functional status: ADL IADL Cognition	Katz-scale Lawton-scale SPMSQ	Death Toxicity Treatment interruption

Table 1: Study characteristics *Continued*

Author (year)	Design	Aim of study	Sample size (% males)/ country	Min. age	Age, median years (range)		Tumor type	Follow-up	Inclusion criteria	Geriatric domains of GA	Measurement tool of geriatric domain	Outcomes
Merli(2014)[76]	Pros	To evaluate which among the GA components could help better identify patients	94(34) Italy	≥ 65 yr	78 (65-93)		Diffuse large B-cell lymphoma (DLBCL)	Median 36 months	DLBCL and ECOG 0-3 This study describes the results of the frail patients according to GA	Functional status: ADL	NR	Overall survival
Mokutani(2016)[46]	Pros	To determine whether GA could predict complications of colorectal cancer surgery	156(57) Japan	≥ 75 yr	80.2[a] (75-94)		Colorectal cancer	Complications retrospectively analyzed	With planned radical surgery of confirmed or suspected colorectal cancer	Functional status: ADL Cognition Mood	Barthel-index MMSE GDS	Postoperative complications < 30 days of surgery
Naito(2016)[50]	Retro	To examine whether items in the GA were associated with survival time	93(46) Japan	≥ 65 yr	77 (NR)		Non-Hodgkin Lymphoma	5 years	Who were admitted for the first time for the treatment of Non-Hodgkin Lymphoma	Functional status: ADL IADL Nutrition Cognition Mood	Barthel-index Lawton-scale BMI Hasegawa's scale GDS	Adverse events Overall survival
Ommundsen(2014)[40]	Pros	To explore whether GA also predict 1-year and 5-year survival	178(43) Norway	≥ 70 yr	80 (70-94)		Colorectal cancer	5 years	Scheduled for elective surgery for confirmed or suspected colorectal cancer	Functional status: ADL IADL Nutrition Cognition Mood	Barthel-index NEADL MNA MMSE GDS	1-year survival 5-year survival
Park(2015)[31]	Pros	To evaluate the relation of the GA to tolerability and survival of chemotherapy	70(54.3) Korea	≥ 65 yr	73.5 (65-92)		Aggressive Non-Hodgkin Lymphoma (NHL)	11.8-31.3 months	NHL and treated with chemotherapy for curative intent	Nutrition Cognition Mood	MNA-SF MMSE GDS	Maintenance the planned therapy for 12 weeks or more Overall survival
Puts(2011)[33]	Pros	To explore the association between frailty and treatment toxicity	112(30.4) Canada	≥ 65 yr	74.1 (65-92)		All cancer types	6 months	New diagnosis of solid tumor with or without metastasis, or hematological malignancy	Functional status: ADL IADL Nutrition Cognition Mood Physical function Fatigue	Katz-scale OARS Weight loss MMSE HADS Self-report questions, 4m gait speeds, hand grip strength with dynamometer EORTC QOL C30	Severe toxicity grade 3-5 at 3 and 6 months Death at 6 months
Spina(2012)[77]	Pros	To evaluate the feasibility and efficacy of chemotherapy modulated according to a modified GA	100(41) Italy	≥ 70 yr	75 (70-89)		Diffuse large B-cell lymphoma	Minimal 5 years	No previous chemotherapy	Functional status: ADL IADL	Katz-scale Lawton-scale	Overall survival
Soubeyran(2012)[29]	Pros	To use GA to search for factors associated with higher risk of early death	364(59.5) France	≥ 70 yr	77.45 (70-99.4)		All cancer types (breast excluding)	6 months	Scheduled to receive first-line chemotherapy	Functional status: ADL IADL Nutrition Cognition Mood Physical function	Katz-scale Lawton-scale MNA MMSE GDS TUG	Death < 6 months of chemotherapy
Suh(2014)[25]	Pros	To evaluate the associations of GA with surgical complications	60(0) Korea	≥ 70 yr	73 (70-85)		Gynaecologic cancer	30 days	Who were scheduled to undergo selective surgery	Functional status: ADL IADL Nutrition Cognition Mood Fatigue	Barthel-index Lawton-scale MNA MMSE GDS BFI	Postoperative complications < 30days

Table 1: Study characteristics *Continued*

Author (year)	Design	Aim of study	Sample size (% males)/ country	Min. age	Age, median years (range)		Tumor type	Follow-up	Inclusion criteria	Geriatric domains of GA	Measurement tool of geriatric domain	Outcomes
Ugolini(2015)[27]	Pros	To investigate the variables capable of predicting the long-term risk of mortality	46(52) Italy	≥ 70 yr	80.5		Colorectal cancer	Median follow-up 4.6 years (range 2.9-5.7)	Undergoing elective surgery for colorectal cancer	Functional status: ADL IADL Nutrition Cognition Mood Physical function Fatigue	Katz-scale Lawton-scale MNA MMSE GDS TUG BFI	Long-term mortality Living situation: but number of surviving patients were to small
Wildes(2013)[78]	Pros	To determine whether geriatric assessments are associated with completion of a chemotherapy course	65(41.5) United States of America	≥ 65 yr	73 (65-89)		Colorectal, lung or breast cancer or lymphoma	0.01-47 months	Who were likely to begin a course of chemotherapy	Functional status: ADL IADL Nutrition Cognition Mood Falls	Katz-scale Lawton-scale BMI Unknown Unknown Number of falls/ past month	Completion of chemotherapy Grade III/IV toxicity of chemotherapy Survival

* Same cohort; ** Same cohort; [a] mean age instead of median age; [b] results of this domains not described

Abbreviations: ADL, Activities of Daily Living; AE, Adverse Event; ASA, American Society of Anesthesiologists; BFI, Brief Fatigue Inventory; BMI, Body Mass Index; BOMC, Blessed Orientation-Memory-Concentration Test; GA, Comprehensive Geriatric Assessment; DEMTECT, Dementia Detection Test; DETERMINE-NI, DETERMINE nutritional index; ECOG, Eastern Cooperative Oncology Group; EDIZ, Experienced Burden of Informal Care; EORTC QOL C30, Organization for Research and Treatment of Cancer Quality of life questionnaire fatigue subscale; GDS, Geriatric Depression Scale; GUG, Get-up and Go test; HADS, Hospital Anxiety and Depression Scale; IADL, Instrumental Activities of Daily Living; IQCODE-N, Informant Questionnaire on Cognitive Decline in the Older patients the short Dutch translation; MIH5, Five-item Mental Health Index; Mini-Cog, Mini Cognition Test; MMSE, Mini Mental State Examination; MNA, Mini-Nutritional Assessment; MNA-SF, Mini-Nutritional Assessment Short-Form (MNA-SF); Mob-t, Mobility-tiredness scale; MOS, Medical Outcomes Study; MOS-SSS, Medical Outcomes Study Social Support Scale; NEADL, Nottingham Extended Activities of Daily Living Scale; NR, not reported; NRS, Nutritional Risk Screening; OARS, Older Americans Resources and Services European; Pros, Prospective; Retro, Retrospective; SAE, Severe Adverse Event; SNAQ, Short Nutritional Assessment Questionnaire; SPMSQ, Short Mental Status Questionnaire; TUG, Time Up and Go test; WHO, World Health Organization

Mortality

Thirty-two studies analyzed which domains of the geriatric assessment were predictive for mortality (Table 2). Physical function, assessed with the Time-up and Go-test (TUG), Get-up and Go test (GUG), four-meter gait speed, or hand grip strength, was found to be the domain most often associated with mortality in five out of eight studies (63%).[26–30]

Nutritional status was associated with mortality in thirteen out of 23 studies (57%).[8,26,29,31–40] For Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), cognition, mood, fatigue, and falls, less than 50% of the studies found an association with mortality. In the three studies that assessed the association between social support, no association was found.[32,41,42]

Postoperative complications

As shown in Table 3, nine studies addressed the association between individual geriatric domains and postoperative complications within 30 days[21,23–25,39,43–46], while one study assessed the association with postoperative dependency.[47]

Physical function was also the most associated geriatric domain for postoperative complications in three out of four studies (75%).[21,23,24] In the only study that assessed this domain, social support was a statistically significant predictive factor for postoperative complications.[24]

For ADL, IADL, nutrition, cognition, mood, fatigue, and falls, less than 50% of the studies found an association.

Systemic treatment-related outcomes

Nineteen studies, listed in Table 4, examined the ability of individual geriatric domains to predict systemic treatment-related outcomes. Because all studies examined the outcomes of chemotherapy treatment and no study included patients treated with anti-hormone, immune, or targeted therapy, we will therefore hereinafter call systemic treatment-related outcomes chemotherapy-related outcomes. Chemotherapy-related outcomes consisted of toxicity of chemotherapy, including dose modifications due to toxicity, early withdrawal of chemotherapy, and functional decline after the first cycle of chemotherapy.

All four studies found that physical function was predictive for chemotherapy-related outcomes (100%).[7,30,33,48]

Furthermore, eight out of fourteen studies found that malnutrition was predictive for chemotherapy-related outcomes (57%).[8,31,35,36,48–51] Malnutrition was especially predictive for the risk of early withdrawal of chemotherapy in 86% of the studies (five out of six).[8,31,35,36,51] For falls, one out of two studies (50%) found an association with toxicity of chemotherapy.[7]

Table 2: Association of individual geriatric domain with mortality

Outcome	Study	Cancer type	Nr of patients	Functional status		Nutrition	Cognition	Mood	Physical function	Fatigue	Social Support	Falls
				ADL	IADL							
Overall survival	Aaldriks[34]	Breast	55			++	--					
	Aaldriks[51]	Hematological	44			--	np					
	Aaldriks[8]	Various	202			++	--					
	Aaldriks[35]	Various	494			++	-					
	Aaldriks[36]	Colorectal	143			++	--					
	Biesma[68]	Lung	181	-	-		-	-	-			
	Bila[69]	Hematological	110		+							
	Clough-Gorr[41]	Breast	660					++			--	
	Ghosn[72]	Various	100	-	-	-	-	-	-			
	Gírones[37]	Lung	83	-	+	+	+	+				
	Goede[30]	Hematological	75		-		+		+			-
	Hamaker[57]	Breast	78		-	np	+	+				
	Jonna[74]	Various	803	+	++		++					
	Kanesvaran[38]	Various	249	+	+	++	+	++				
	Kristjansson[39]	Colorectal	182	-	+	++	-	-				
	Merli[76]	Hematological	94	+								
	Naito[50]	Hematological	93	-	+	-	++	-				
	Ommundsen[40]	Colorectal	178	-	++	++	+	-				
	Park[31]	Hematological	70			+	-	-				
	Spina[77]	Hematological	100	+	+							
	Ugolini[27]	Colorectal	46	-	+	-	-	-	+	-		

Table 2: Association of individual geriatric domain with mortality *Continued*

Outcome	Study	Cancer type	Nr of patients	Functional status		Nutrition	Cognition	Mood	Physical function	Fatigue	Social Support	Falls
				ADL	IADL							
	Wildes[78]	Breast, lung, colorectal, and lymphoma	73	-	-	-	-	-				++
1-year mortality	Brunello[42]	Various	658	--	--		--	--			--	
	Denewet[70]	Various	205	--	?	?	-	?				
	Dubruille[71]	Hematological	90	--	--	--	++	--		--		--
	Ferrat[26]	Various	993	++		+	+	+	++			
	Giantin[22]	Solid tumors	160	-	-	-	++	++				
	Hamaker[28]	Hematological	108	-	-	++	-	-	++			
	Hamaker[32]	Various	292	+	-	-	-	-			-	
6-monts mortality	Marinello[75]	Breast, lung, and colorectal	110	np	-		np					
	Puts[33]	Various	112	++	-	+	-	+	-	+		
	Soubeyran[29]	Various	364	-	-	++	+	-	++			
Nr of positive results/ all studies (%)				7/22 (32%)	9/23 (39%)	13/23 (57%)	11/28 (39%)	7/21 (33%)	5/8 (63%)	1/3 (33%)	0/3 (0%)	1/3 (33%)

+, significant in univariate analysis: no multivariate analysis performed or factor in multivariate analysis not significant; ++, significant in multivariate analysis; -, no association in univariate analysis: no multivariate analysis performed or factor not included in multivariate analysis; --, no association in multivariate analysis; ?, results of geriatric domain not described; np, number of compromised patients was too low: statistical analysis was not possible**Abbreviations:** ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living

Table 3: Association of individual geriatric domain with postoperative complications

Outcome	Study	Cancer type	Nr of patients	Functional status		Nutrition	Cognition	Mood	Physical function	Fatigue	Social Support	Falls
				ADL	IADL							
Any complication < 30 days	Audisio[43]	Solid tumors	460	++	+		-	-		+		
	Badgwell[44]	Abdominal	111		-	++	-	-		-		-
	Choi[45]	Various	281	-	-	+	-	-				
	Huisman[21]	Solid tumors	328	++	--	++	++	++	++	++		
	Huisman[23]	Solid tumors	263						++			
	Kenig[24]	Abdominal	75	?	--	--	--	--	++	?	++	
	Kristjansson[39]	Colorectal	182	-	++	-	-	-				
	Mokutani[46]	Colorectal	156	++	--		++	--				
	Suh[25]	Gynaecological	60	-	+	-	-	-		-		
Dependence	Baier[47]	Abdominal	200		--	-	-		-			
Nr of positive results/ all studies (%)				3/7 (43%)	3/9 (33%)	3/7 (43%)	2/9 (22%)	1/8 (13%)	3/4 (75%)	2/5 (40%)	1/1 (100%)	0/1 (0%)

+, significant in univariate analysis: no multivariate analysis performed or factor in multivariate analysis not significant; ++, significant in multivariate analysis; -, no association in univariate analysis: no multivariate analysis performed or factor not included in multivariate analysis; --, no association in multivariate analysis; ?, results of geriatric domain not described; np, number of compromised patients was too low: statistical analysis was not possible
Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living

Table 4: Association of individual geriatric domain with chemotherapy-related outcomes

Outcome	Study	Cancer type	Nr of patients	Functional status		Nutrition	Cognition	Mood	Physical function	Fatigue	Social Support	Falls
				ADL	IADL							
Chemotherapy Toxicity	Aparicio[66]	Colorectal	123		++		++	-				
	Baitar[67]	Various	85	?	?	?	+[a]	?			?	
	Bila[69]	Hematological	110		-							
	Clough-Gorr[41]	Breast	660					++			++	
	Extermann[49]	Various	518	-		+	+	-				
	Goede[30]	Hematological	75		+		-		+			
	Hamaker[73]	Breast	78		-	np	-	-				
	Hurria[7]	Solid tumors	500	?	?	?	?	?	+		?	+
	Marinello[75]	Breast, lung, and colorectal	110	np	-		np					
	Naito[50]	Hematological	93	+	-	+	-	-				
	Puts[33]	Various	112	-	-	-	-	-	++	-		
	Wildes[78]	Colorectal, lung, breast, and lymphoma	65	-	-	-	-	-				-
Chemotherapy Completion	Aaldriks[34]	Breast	55			--	--					
	Aaldriks[51]	Hematological	44			++	--					
	Aaldriks[8]	Various	202			+	+					
	Aaldriks[35]	Various	494			++	-					
	Aaldriks[36]	Colorectal	143			+	+					
	Park[38]	Hematological	70			++	-	-				

Table 4: Association of individual geriatric domain with chemotherapy-related outcomes *Continued*

Outcome	Study	Cancer type	Nr of patients	Functional status		Nutrition	Cognition	Mood	Physical function	Fatigue	Social Support	Falls
				ADL	IADL							
Functional decline after first cycle chemotherapy	Hoppe[48]	Various	364		++	+	+	++	+			
Nr of positive results/ all studies (%)				1/7 (14%)	3/11 (27%)	8/14 (57%)	6/17 (35%)	2/11 (18%)	4/4 (100%)	0/1 (0%)	1/3 (33%)	1/2 (50%)

[a] Better cognitive function had a higher risk for a SAE; +, significant in univariate analysis: no multivariate analysis performed or factor in multivariate analysis not significant; ++, significant in multivariate analysis; -, no association in univariate analysis: no multivariate analysis performed or factor not included in multivariate analysis; --, no association in multivariate analysis; ?, results of geriatric domain not described; np, number of compromised patients was too low: statistical analysis was not possible

Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living

Finally, less than 50% of the studies found an association between toxicity of chemotherapy and social support, ADL, IADL, cognition, and mood. For fatigue and mobility, no association was found.

Discussion

Since the SIOG's recommendation to conduct a GA, many studies were published about the predictive ability of individual GA domains for relevant oncological outcomes. However, the composition of the GA differs between studies, which makes inter-study comparison difficult. The aim of the current systematic review was to systematically evaluate which domains of the GA could predict patient-related treatment outcomes and should be included in a GA for patients with cancer. Patient-related outcomes were defined as mortality, postoperative complications of elective surgery for solid tumors, and chemotherapy-related outcomes as toxicity, completion of planned treatment, and dose modifications.

In this systematic review, eight geriatric domains were evaluated in 46 publications, namely functional status, nutritional status, cognition, mood, physical function, fatigue, social support, and falls. All of these domains were predictive for at least one of the reviewed outcomes, but the results varied between the studies. Physical function and nutritional status were the most predictive domains for mortality; physical function was the most predictive domain for postoperative complications; and for chemotherapy-related outcomes, physical function and nutritional status were the most predictive domains. In conclusion, the only truly consistent finding was that physical function was the most predictive domain of the GA for mortality, as well as for postoperative complications and for chemotherapy-related outcomes.

The reason for variation in results is the heterogeneity of the studies and study populations. First, the studies differed in study design, sample size, tumor type, and tumor stage. Second, the studies varied in the minimum age of participants: some studies also included the younger old patients (65 years or older), while other studies only included the oldest old (75 years and older). Third, the studies used different measurement tools to assess the same geriatric domain with various definitions of impairment. Finally, the studies varied in the way they reported their outcomes. Some studies reported adjusted Odds and Hazard Ratios, while others used a Chi-square test to compare the incidence of an impaired domain between the group with the outcome and the group without the outcome.

The eligible studies not only showed inconsistent results, but often also did not show a positive predictive ability of the individual domain for an oncological outcome. A reason for this null effect could be that the GA was originally not designed to predict

adverse oncological outcomes but to predict functional decline and falls in an older population with cognitive and functional impairments.[6] Therefore, the used measurement tools have been validated in the traditional geriatric population instead of the oncological geriatric population. The properties of these measurement tools in oncological population may differ from the traditional geriatric ones, because the oncological population may be faced with referral bias. The most vulnerable older patients with cancer are less likely to be referred to the oncologist. As a result, the population in the oncological setting has less functional and cognitive impairment than the population in which these tools were developed and tested.

Another reason for the null effects of the GA in predicting outcomes is the occurrence of other potential sources of bias. First, all patients were considered fit enough to undergo oncological treatment, and the decision whether a patient was eligible for chemotherapy or surgery had already been taken, leading to selection bias. For instance, a frequently used exclusion criterion for study participation was the presence of dementia or cognitive impairment – even in studies that aimed to assess the predictive value of cognitive impairment for oncological outcomes. Another potential bias is that often the treating physician was not blinded from the outcome of the GA. Hence, the treating physician might assume that patients with an impaired GA would not be able to tolerate standard treatment, and, consequently, he might decide to offer the patient adapted oncologic treatment based on the outcome of the GA affecting the outcome. Lastly, the ceiling effects of some measurements could explain the fact that only a few studies found components of the GA to be useful in predicting outcomes. The ceiling effect, as noted by Hurria et al., is the effect that arises when most of the participants score the maximum score possible on a test because the test is unable to distinguish between individuals at the higher score range of the test.[52]

This review has several strengths. We used systematic methods to select all relevant studies, and two reviewers independently assessed the selected studies on relevance and quality according to the QUIPS tool, a tool especially designed to assess the quality of prognostic studies.[16,17] In addition, no studies were excluded on the basis of quality assessment, because we have attempted to deliver a complete overview of all the current published evidence in an unbiased and reproducible way. We then provided an overview of the positive as well as the negative results. Last, we limited the selection of studies to the age cutoff of 65 years to avoid reviewing the GA domains in the "youngest old" (60-65 years) or young patients because these results may be difficult to extrapolate to our target group: the older patients with cancer (≥70 years or older).

This review also has several limitations. The scientific quality of the studies varied widely, and some quality criteria were not reported and consequently rated as having a high risk of bias. Another limitation might be the risk of publication bias. The literature

is probably populated with positive studies that would not have been submitted or published had the results been different. Finally, in this systematic review we focused on studies assessing multiple geriatric domains as part of a GA. Studies focusing on single geriatric conditions or including multiple conditions but not labelled as geriatric assessment, may have been overlooked by our search strategy.

This is not the first systematic review assessing the predictive value of geriatric assessment. In 2012, Puts et al. were the first authors to conduct a systematic review of the use of geriatric assessment in oncology.[53] Since Puts' review was published, several systematic reviews have followed. To our knowledge, the most recent systematic reviews were published in 2015 and the authors performed their literature search in respectively September 2013 and June 2013.[13,14] Thus a new systematic review was needed to obtain an overview of the most recent evidence, since more than half of the studies selected in our review were published in 2014 or later.

Moreover, some systematic reviews did not provide a complete overview of the current evidence for the predictive ability of the individual GA domains because they applied strict eligibility criteria. Caillet et al.[54] only selected the studies with a prospective study design, a sample size of at least 100 patients with a solid tumor, and in which the GA consisted of at least five GA domains. Similarly, Handforth et al.[13] and Ramjaun et al.[55] only included studies if they used a GA in which respectively three and six domains were assessed.

Three systematic reviews were published with the same aim, a similar literature search, and comparable inclusion criteria as our review. The first review, Puts et al., concluded that ADL, comorbidity, and cognition were the domains consistently associated with mortality, postoperative complications, and chemotherapy-related outcomes.[53] The second systematic review, Puts et al., an update of Puts' first review, concluded that ADL, IADL, performance status, depression, and frailty were associated with poor health outcomes.[56] The third review, Hamaker et al., concluded that different conditions appeared to be predictive for the primary outcome measures and that the only consistent finding was the association between a summary score of the geriatric assessment and mortality.[57] These findings differed from our findings for the following reasons: first, we made a clear distinction between domains that should be part of the geriatric assessment and domains that should be part of the routine oncological work-up (such as comorbidity and polypharmacy). In our opinion, comorbidity and polypharmacy should be explored in every patient, regardless of age, and therefore should not be considered part of the GA. Secondly, our only consistent finding was the predictive ability of physical function for mortality, postoperative complications, and chemotherapy-related outcomes, whereas Puts et al. found ADL as the consistently associated domain and Hamaker et al. did not find a consistent domain at all. These

different findings could be explained by the fact that our literature search was more recent. For instance, the majority of the studies including physical function in their GA were published in 2014 or later. Another explanation could be that we only selected studies reporting predictive values of the individual domains, whereas Puts et al. and Hamaker et al. also selected studies that assessed the predictive ability of geriatric domains as part of a summary score or as part of the definition of frailty.

Interestingly, no study assessed the ability of individual geriatric domains in predicting systemic treatment-related outcomes other than chemotherapy. Other systemic antitumor treatments, such as targeted therapy or immune therapy, may lead to side effects other than chemotherapy impacting the predictive ability of the individual geriatric domains.

Based on the current systematic review, we may conclude that physical function and nutritional status are the best domains to predict mortality, postoperative complications, and chemotherapy-related outcomes in older patients with cancer and therefore should certainly be included in the GA. However, whether this means that assessing the other domains is redundant is debatable. First, the content of the GA should depend on which primary outcome one wants to predict with the GA. Every geriatric domain appears to be predictive for a different oncological outcome. For example, in almost half of the studies, an impaired ADL was significantly predictive for postoperative complications. On the contrary, no study found an association between an impaired ADL and toxicity of chemotherapy. Second, because of the heterogeneity of studies, it remains questionable whether the same geriatric impairments are relevant for patient with breast cancer undergoing surgery as for a patient with lung cancer receiving palliative chemotherapy. Still, there is no consensus regarding which assessment tools and cutoff scores should be used to identify an impaired domain.

Nevertheless, in our opinion, the aim of the GA is not only to predict various outcomes, but it should be used as a tool to develop individually tailored geriatric interventions. Interventions could be based on the identified impaired GA domains to improve tolerability of the antitumor treatment, and even more important, to maintain the quality of life and the independency as much as possible. According to a review by Hamaker et al., more than 70% of the GAs have resulted in geriatric recommendations and interventions in older patients with cancer.[58] In the non-cancer population, the implementation of these GA-based interventions have been shown to improve a variety of outcomes, such as decreased risk of death and a decreased risk of nursing home placement.[59] Unfortunately, there has been little investigation into the benefit of GA-based interventions for the older patient with cancer. Consequently, the few RCTs that have been performed are not generalizable to daily practice, because few have been applied in a chemotherapy setting, the studies focused on one particular domain,

and the studies were conducted in older patients with just one tumor type.[60–65] To our knowledge, only one recent prospective cohort study published the impact of GA-based intervention on chemotherapy tolerance in older patients with cancer. In this study, the intervention group was more likely to complete antitumor treatment and required fewer treatment modifications compared to the control group without the interference of a geriatrician.[65] Fortunately, RCTs are currently ongoing to establish whether GA-based interventions may improve the impaired geriatric domains and may result in an improved tolerability of antitumor treatment, thereby contributing to better quality of life and maintenance of independency.

In conclusion, physical function and nutritional status should be included in the GA for older patients with cancer, especially when the GA's most important aim is predicting outcomes. Nevertheless, physical function and nutritional status have not only appeared to be the domains most predictive for our defined outcomes, but interventions to improve these domains may also be simple to implement, such as physiotherapy for muscle reinforcement in case of an impaired physical function, or referral to the dietician for advices on increasing dietary uptake or nutritional supplements in case of malnutrition. For the other domains, the findings are too inconsistent to draw conclusions about their inclusion in or exclusion from the GA with the aim to predict relevant outcomes. However, when the GA is used as a tool for optimizing care for older patients with cancer, a broad geriatric assessment is needed to identify all present impairments, serving as a base for a geriatric treatment plan as well as for geriatric follow-up.

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Supplementary A: Search syntax MEDLINE

((((((((((geriatric assessment[MeSH Terms]) OR geriatric assessment[Title/Abstract]) OR frailty assessment[Title/Abstract]) OR needs assessment[Title/Abstract]) OR Needs assessment[MeSH Terms]) OR need assessment*[Title/Abstract])))) AND ((((((((((((aged[MeSH Terms]) OR elder[Title/Abstract]) OR older adult[Title/Abstract]) AND Neoplasms[MeSH Terms]) OR neoplasm[Title/Abstract]) OR tumor[Title/Abstract]) OR tumour[Title/Abstract]) OR cancer[Title/Abstract]) OR carcinom[Title/Abstract]) OR malignan*[Title/Abstract]) OR Carcinoma[MeSH Terms])))))) AND ((((((((((((comorbidit*[Title/Abstract]) OR "Comorbidity"[Mesh]) OR adverse effect*[Title/Abstract]) OR adverse event*[Title/Abstract]) OR ((drug related side effect*[Title/Abstract]) OR post operative complication*[Title/Abstract])) OR postoperative complication*[Title/Abstract]) OR postoperative adverse outcome*[Title/Abstract]) OR postoperative adverse reaction*[Title/Abstract]) OR mortality[MeSH Terms]) OR mortality[Title/Abstract]) OR ((mortality[Title/Abstract]) OR mortalities[Title/Abstract])) OR "chemotherapy intolerance"[Title/Abstract]) OR treatment outcome*[Title/Abstract])

Supplementary B: Results of quality assessment

Author (year of publication)	Design	Study participation	Study attrition	Prognostic factor	Outcome	Statistical analysis	Points (max. 6.0)
Aaldriks(2013)[1]	PS	◐	◐	●	◐	●	4.5
Aaldriks(2015)[2]	PS	●	◐	●	◐	●	5.0
Aaldriks(2011)[3]	PS	◐	○	◐	●	◐	3.5
Aaldriks(2016)[4]	PS	◐	◐	●	●	●	5.0
Aaldriks(2013)[5]	PS	●	○	◐	●	●	4.5
Aparicio(2013)[6]	PS	◐	◐	◐	●	●	4.5
Audisio(2008)[7]	PS	◐	○	◐	●	●	4.0
Bagdwell(2013)[8]	PS	●	◐	●	●	◐	5.0
Baier(2016)[9]	PS	●	◐	◐	●	◐	4.5
Baitar(2014)[10]	PS	◐	●	●	●	●	5.5
Biesma(2011)[11]	PS	●	◐	◐	●	◐	4.5
Bila(2015)[12]	?	○	○	●	◐	◐	2.0
Brunello(2016)[13]	RS	◐	●	◐	◐	●	3.5
Choi(2015)[14]	RS	●	●	●	●	◐	4.5
Clough-Gorr(2010)[15]	?	●	◐	●	●	●	4.5
Denewet(2016)[16]	PS	◐	○	◐	●	○	3.0
Dubruille(2015)[17]	PS	●	●	●	●	◐	5.5
Extermann(2012)[18]	PS	●	◐	◐	●	●	5.0
Ferrat(2015)[19]	RS	◐	◐	●	●	●	4.0
Ghosn(2017)[20]	PS	◐	○	◐	●	◐	3.5
Giantin(2013)[21]	PS	●	●	●	●	●	6.0
Gírones(2012)[22]	PS	●	●	◐	◐	◐	4.5
Goede(2016)[23]	PS	◐	◐	◐	●	◐	4.0
Hamaker(2011)[24]	PS	●	○	●	●	◐	4.5
Hamaker(2013)[25]	PS	●	◐	●	●	●	5.5
Hamaker(2014)[26]	PS	●	◐	●	●	●	5.5
Hoppe(2013)[27]	PS	●	○	●	●	●	5.0
Huisman(2015)[28]	PS	●	●	●	●	●	6.0
Huisman(2014)[29]	PS	●	●	●	●	●	6.0
Hurria(2011)[30]	PS	●	○	◐	●	◐	4.0
Jonna(2016)[31]	RS	●	●	◐	◐	◐	3.5
Kanesvaran(2011)[32]	RS	●	●	◐	●	●	4.5
Kenig(2015)[33]	PS	●	●	●	●	●	6.0
Kristjansson(2010)[34]	PS	●	●	◐	●	●	5.5
Marinello(2009)[35]	PS	◐	●	●	●	●	5.5
Merli(2014)[36]	PS	◐	○	◐	●	◐	3.5
Mokutani(2016)[37]	PS	◐	◐	●	◐	◐	4.0
Naito(2016)[38]	RS	●	◐	◐	◐	◐	3.0

Author (year of publication)	Design	Study participation	Study attrition	Prognostic factor	Outcome	Statistical analysis	Points (max. 6.0)
Ommundsen(2014)[39]	PS	●	◐	◐	●	◐	4.5
Park(2015)[40]	PS	●	○	◐	●	◐	4.0
Puts(2011)[41]	PS	●	●	●	◐	●	5.5
Soubeyran(2012)[42]	PS	●	◐	●	●	◐	5.0
Spina(2012)[43]	PS	●	◐	●	●	◐	5.0
Suh(2014)[44]	PS	●	●	●	●	●	6.0
Ugolini(2015)[45]	PS	◐	○	◐	◐	○	2.5
Wildes(2013)[46]	PS	●	○	○	◐	◐	3.0

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Part II

Added value of the Geriatric 8

Chapter 3

Validation of the G8 screening tool in older patients with cancer considered for surgical treatment

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Abstract

Introduction

The Geriatric 8 (G8) has proven to be one of the most sensitive frailty-screening tools for older patients with cancer undergoing systemic treatment. In this study we validated whether the G8 is also suitable for identifying impairments in their comprehensive geriatric assessment (CGA) in older patients with cancer undergoing surgery. Thereby, we investigated the differences in postoperative outcomes between the fit and frail patients classified by the G8.

Methods

Patients ≥ 70 years with a surgery indication because of a (suspected) malignant disease were prospectively enrolled. In all patients, a CGA was performed. The G8 results were assessed in parallel. The diagnostic value of the G8 was determined by comparing the result with the CGA as a reference test. Deficits in CGA was defined as ≥ two impairments of the CGA. Postoperative complications were retrospectively obtained from the medical record and compared between the fit and frail patients.

Results

In total, 143 patients were enrolled. The sensitivity, specificity, and negative predictive value of the G8 were 82% (95% CI 70-91), 63% (95% CI 52-73), and 85% (95% CI 75-91). In the patients with an impaired G8, a significantly prolonged hospital stay, higher rate of delirium, and higher 1-year mortality rate were seen.

Conclusion

The G8 is a simple and useful screening tool for identifying deficits in CGA in older patients with cancer requiring surgery. Second, we concluded that patients with an impaired G8 are more at risk for a complicated recovery from surgery.

Introduction

The incidence of cancer increases disproportionately with age and today more than half of the patients newly diagnosed with cancer are 65 years of age or older.[1,2] In the coming decades, the number of older patients with cancer will increase significantly as a result of the aging of the population and an increasing life expectancy in Western societies. Treatment of these patients demands a specific approach due to the heterogeneity of the older population. As a result, tailoring of care is especially needed in this population, based on a thorough evaluation of the patient's health status in addition to tumor characteristics and patient preferences. Consequently, some form of geriatric assessment is increasingly being incorporated into oncologic care since unidimensional measurements, such as performance status or the American Society of Anesthesiologists classification (ASA), are insufficient.[3,4]

Originally, a comprehensive geriatric assessment (CGA) multidisciplinary team determines an older patient's medical, psychosocial, functional, and environmental capabilities and limitations in order to develop an overall plan for treatment and follow-up.[5] In the field of geriatric oncology, the term CGA has commonly been used to describe the comprehensive approach using geriatric instruments to diagnose frailty based on the amount of impaired instruments. In this setting, prior studies have demonstrated that this CGA can predict the morbidity and mortality rates in older patients and that it is therefore a useful geriatric oncology tool for helping to select the most appropriate treatment.[6–10] It was ascertained that after a geriatric evaluation, the treatment plan was altered primarily to a less intensive treatment option in almost a quarter of the patients considered for surgical or chemotherapeutic treatment. In addition, effects on treatment outcome varied, although a positive trend was seen towards more treatment completion, and less treatment-related toxicity and complications in the patients who underwent a geriatric evaluation.[11]

However, it was suggested that it was not useful or efficient to complete a CGA on every older patient in the non-oncological geriatric setting. [12] As a result, SIOG currently recommends to select screening tools with a high sensitivity and a high negative predictive value to identify those older patients with cancer in need of geriatric assessment (GA) and multidisciplinary approach. Consequently, several screening tools have been developed to separate fit older patients with cancer who are able to tolerate standard cancer treatment from vulnerable patients who require a CGA prior to treatment.[13] It was concluded that the Geriatric 8 (G8), specifically developed for older patients with cancer, was the most robust since the G8 had been extensively studied and had consistently demonstrated a good sensitivity for geriatric impairments (> 80% in six

of eight studies) with acceptable specificity (> 60% in four studies).[13,14] As a result, the G8 is the most frequently used frailty screening tool in geriatric oncology.

The G8's discriminative power in determining geriatric impairments has mostly been investigated in older patients with cancer eligible for chemotherapeutic treatment. Data specifically addressing the use of G8 in older patients considered for surgery are limited and particularly performed in a homogenous population with one tumor type or one kind of surgery.[15]. Therefore, the aim of this prospective study was to validate the value of the G8 as a screening tool for deficits in CGA, in older patients with cancer requiring surgery.

In previous years, the predictive value of frailty – defined as deficits in (C)GA or frailty indicators – on postoperative outcomes was studied extensively in various tumor types and surgical procedures. Almost all studies described an association between frailty, defined as above, and postoperative outcomes.[16–18] However, there is heterogeneity in the definition of frailty and the definition of postoperative outcomes making inter study comparison difficult. Also, the association between the G8 scores and post-operative outcomes has been studied before, but the results seem to differ indicating the need for further investigations. For that reason, we also investigated whether there was a difference in postoperative outcomes between the patients with a normal score and those with an impaired G8 score. Postoperative outcomes of interest were major 30-days post-operative complications, rates of unplanned readmissions, duration of hospital stay, discharge to a rehabilitation unit, and 1-year overall survival (OS).

Methods

Study population

Between September 2016 and December 2017, patients aged 70 years or older requiring elective surgical treatment under general anesthesia for a (suspected) solid malignancy were enrolled in this prospective study at the department of Geriatrics at the University Medical Center Utrecht in Utrecht, Netherlands. All patients considered eligible for surgery by a surgeon visited the pre-operative screening clinic before undergoing surgical treatment.

This study was reviewed and approved by the local ethics committee.

Geriatric Assessment

Prior to the surgery, a CGA was carried out by specialized geriatric nurse practitioners. The instruments used in the CGA consisted of the same instruments that the CGA used as the gold standard in the G8 development study of Bellera et al.[19] The instruments used in the CGA were: activities of daily living (ADL) assessed with Katz-6[20],

instrumental activities of daily living (IADL) assessed with Katz-9[21], nutritional status assessed with the malnutrition universal screening tool (MUST)[22], cognition assessed with the mini-mental state examination (MMSE)[23] or the Montreal Cognitive Assessment (MOCA)[24] if patients were suspected of having above average intelligence based on their highest level of education, mood assessed with the Patient Health Questionnaire-2 (PHQ-2)[25] followed by a Geriatric Depression Scale 15 (GDS-15)[26] in case of a positive PHQ-2, physical function assessed with the 4-meter walk test (4-MWT)[27], and comorbidity assessed with the Charlson comorbidity index (CCI).[28] Points for age and malignancy were not included in calculating the CCI since this involved every patient.

Each instrument was defined as abnormal according to validated cutoff scores: Katz-6 ≥ 1, Katz-9 ≥ 1, MUST ≥ 1, MMSE ≤ 23, PHQ-2 ≥ 1, 4-MWT > 1 second/meter, and a CCI ≥ 2. Overall, a patient was considered to have deficits in CGA if at least two of the seven instruments used had an abnormal outcome.

If values were missing on one or more CGA instruments, we included patients nevertheless if at least two impaired instruments were available for these patients, as these patients would be considered frail according to our definition anyway.

G8 screening tool

In parallel, the G8 screening tool was completed by the same specialized geriatric nurse practitioner who was not blinded to the outcomes of the CGA. The G8 is an eight-item questionnaire that includes seven items from the 18-item mini-nutritional assessment (MNA) and an age-related item (<80, 80 to 85, or > 85 years).[29] The total score ranges from 0 to 17. A score of ≤ 14 was considered to be abnormal, indicating a need for a CGA.

Postoperative outcomes

Thirty-days postoperative complications were retrospectively obtained from the medical record and classified by the primary investigator according to the Clavien-Dindo classification.[30] Our primary endpoint was a major complication classified as Clavien-Dindo grade ≥ III including complications requiring surgical, endoscopic or radiological intervention (grade three), life-threatening complications requiring Intensive Care management (grade four), and death of a patient (grade five). Complications grade I or II were considered as minor complication. In minor complications, we focused on the occurrence of delirium. Delirium was said to occur when its presence was described in the medical record and/or antipsychotics were prescribed.

Besides data on 30-days postoperative complications, we collected data about the postoperative hospital stay (defined as the number of postoperative days spent in hospital until discharge or until transfer to a rehabilitation unit), the rate of unplanned readmissions, the rate of discharges to a rehabilitation unit, and the 1-year mortality.

Statistical analyses

Descriptive analyses were performed to report patient, tumor, and treatment characteristics, deficits in CGA instruments, and postoperative outcomes. The categorical variables were described using numbers (N) and percentages (%). Means and standard deviations (SD) were used to describe continuous variables.

For comparisons of baseline characteristics and postoperative outcomes between patients with a normal G8 score and those with an impaired G8 score, the chi-squared test or the Fisher's exact test was used for nominal and ordinal variables depending on the sample size. For continuous variables with a normal distribution, the Student's *t* test was used. The Mann-Whitney test was used in case of an abnormal distribution. A p value of ≤ 0.05 was considered to be statistically significant. The occurrence of postoperative outcomes was compared between patients with a G8 ≥ 14 and a G8 < 14.

The sensitivity, specificity, negative predictive value (NPV), and the positive predictive value (PPV) of the G8 screening tool for detecting deficits in CGA were calculated from a 2x2 cross-table. Subsequently, a receiver operating characteristic (ROC) curve was performed showing graphically the connection between clinical sensitivity and specificity for every possible cut-off. Second, an area under this curve (AUC) was calculated to measure the usefulness of the G8. Confidence intervals (95% CI) were reported.

The SPSS (Statistical Package for the Social Sciences) version 21.0 was used for the analyses.

Results

Baseline characteristics

In total, 143 patients were prospectively included in this study. The baseline characteristics are summarized in table 1. The mean age was 77 years (63-100 years). About half of the population was screened pre-operatively because of a tumor in the gastrointestinal tract (49.7%). The majority had an impaired G8 score (54.5%). In the group with an impaired G8, the mean age was significantly higher in comparison with the group with an unimpaired G8 (78.1 years versus 75.5 years, p-value 0.01), and there were significantly more patients with an American Society Anesthesiology score ≥ 3 (32.2% versus 11.9%, p-value < 0.001).

Table 1: Baseline characteristics

Variable	Mean (standard deviation)					*p*-value
	Total population N=143	G8 >14 N=65 (45%)		G8 ≤14 N=78 (55%)		
		Unimpaired CGA N = 55	Impaired CGA N = 10	Unimpaired CGA N = 32	Impaired CGA N = 46	
Age	76.9 (6.1)	75.6 (4.2)		78.1 (7.2)		*0.01*
		75.0 (3.8)	78.2 (5.7)	76.6 (5.0)	79.1 (8.3)	
BMI	25.9 (4.8)	26.7 (4.1)		25.3 (5.2)		0.10
		26.14 (3.8)	29.3 (4.8)	25.3 (5.9)	25.4 (4.7)	
Number of medications	5.13 (3.70)	4.4 (3.2)		5.74 (4.00)		*0.04*
		4.0 (3.2)	6.6 (2.7)	3.8 (3.9)	7.2 (3.4)	
	Number of patients (proportion)					
Gender: male	80 (56)	40 (62)		40 (51)		0.22
		37 (57)	3 (5)	16 (20)	24 (31)	
Tumor types						
Higher digestive tract*	38 (27)	14 (22)		24 (31)		0.21
		11 (17)	3 (5)	15 (19)	9 (12)	
Colorectal	33 (23)	19 (29)		14 (18)		0.11
		19 (29)	0 (0)	7 (9)	7 (9)	
Urological	12 (8)	4 (6)		8 (10)		0.38
		4 (6)	0 (0)	2 (2)	6 (8)	
Gynaecological	16 (11)	9 (14)		7 (9)		0.36
		6 (9)	3 (5)	4 (5)	3 (4)	
Mamma	2 (1)	1 (2)		1 (1)		0.90
		0 (0)	1 (2)	0 (0)	1 (1)	

Table 1: Baseline characteristics *Continued*

Variable	Mean (standard deviation)					*p*-value
	Total population N=143	G8 >14 N=65 (45%)		G8 ≤14 N=78 (55%)		
		Unimpaired CGA N = 55	Impaired CGA N = 10	Unimpaired CGA N = 32	Impaired CGA N = 46	
Head & neck	23 (16)	6 (9)		17 (22)		*0.04*
		4 (6)	2 (3)	3 (4)	14 (18)	
Other	15 (11)	9 (14)		6 (8)		0.23
		9 (14)	0 (0)	0 (0)	6 (8)	
No malignancy	4 (3)	3 (5)		1 (1)		0.23
		2 (3)	1 (2)	1 (1)	0 (0)	
Curative treatment intention	140 (98)	64 (99)		76 (97)		0.67
		54 (83)	10 (16)	30 (39)	46 (59)	
Neoadjuvant chemotherapy	30 (21)	13 (20)		17 (22		0.79
		8 (12)	5 (8)	13 (17)	4 (5)	
ASA score ≥3	63 (44)	17 (26)		46 (59)		*<0.001*
		12 (19)	5 (8)	10 (13)	36 (46)	
Living independently*	139 (97)	65 (100)		74 (95)		0.06
		55 (85)	10 (15)	32 (41)	42 (54)	
Polyfarmacy (>5 medication)	75 (53)	29 (44)		46 (61)		0.06
		21 (32)	8 (12)	11 (15)	35 (46)	

Geriatric 8 (G8); Comprehensive Geriatric Assessment (CGA); Body mass index (BMI); American Society of Anesthesiologists classification (ASA);

*L iving at home with possibly professional help

**CCI after having excluded age and malignancy

Reference test: geriatric assessment

Out of the total population, 56 patients (39.2%) had deficits in CGA. The IADL and nutrition were the most often impaired CGA instruments (37.8% and 32.2%, respectively), and cognition was the least frequently impaired CGA instrument (2.1%) as shown in table 2. Physical functioning – assessed on the basis of the walking speed – had the most missing values (4.2%), with four missing tests. The rest of the instruments were either not missed or only missed once.

Table 2: Deficits in CGA instruments

Variable	Number of patients (proportion %)					*p*-value
	Total population N=143	G8 >14 N=65 (45%)		G8 ≤14 N=78 (55%)		
		Unimpaired CGA N = 53	Impaired CGA N = 8	Unimpaired CGA N = 32	Impaired CGA N = 46	
KATZ6 >1	27 (19%)	4 (6)		23 (30)		*<0.001*
		2 (3)	2 (3)	0 (0)	23 (30)	
KATZ9>1	54 (38%)	14 (22)		40 (52)		*<0.001*
		6 (9)	8 (13)	4 (5)	36 (47)	
MUST impaired	46 (32%)	7 (11)		39 (51)		*<0.001*
		6 (9)	1 (2)	18 (24)	21 (27)	
Cognition impaired	3 (2%)	0		3 (4)		0.10
		0 (0)	0 (0)	0 (0)	3 (4)	
GDS impaired	26 (18%)	5 (8)		21 (27)		*0.00*
		3 (5)	2 (3)	1 (3)	20 (26)	
Walking speed > 1second/meter 32 (22%)		8 (13)		24 (32)		*0.00*
		3 (5)	5 (8)	0 (0)	24 (32)	
CCI ex ≥2**	24 (17%)	6 (10)		18 (23)		*0.03*
		3 (5)	3 (5)	1 (1)	17 (22)	

Geriatric 8 (G8); Comprehensive Geriatric Assessment (CGA); Malnutrition universal screening tool (MUST); Geriatric Depression Scale (GDS); Charlson comorbidity index (CCI)

In patients with an impaired G8 the ADL, IADL nutrition, mood, and physical function measured with the walking speed were statistically significantly more impaired compared to the patients with an unimpaired G8, although CGA impairments were not limited to the group with an impaired G8. In addition, in patients with an impaired G8 a statistically significantly higher CCI was seen.

Performance of the screening tool

With our reference standard defined as ≥ two impaired instruments of the CGA, the sensitivity and specificity of the G8 were 82.1 (95% CI 69.9-91.1) and 63.2 (95% CI 52.2-73.3), respectively, with a PPV and NPV of 59.0 (95% CI 51.5-66.0) and 84.6 (95% CI 75.4-90.8). The AUC was 0.79 (95% CI 0.72-0.87).

Postoperative outcomes

Ten patients did not receive their planned surgery mostly because of having too poor of a clinical condition or metastatic disease. Out of the operated patients (n= 133), in 25 patients (19%) a major 30-days postoperative complication occurred as shown in table 3. There was no difference in the occurrence of major 30-days postoperative complications between the patients with a G8 ≥ 14 and G8 <14. One patient died within 30-days because of an abdominal sepsis due to a leakage of the anastomosis.

Table 3: Postoperative outcomes

Variable	Total N =133 (%)	G8 > 14 N = 62 (%)	G8 ≤ 14 N = 71 (%)	*p*-value
Complications grade ≥ III	25 (19)	11 (18)	14 (20)	0.77
Grade III	16 (12)	10 (16)	6 (9)	
Grade IV	8 (6)	1 (2)	7 (10)	
Grade V	1 (1)	0 (0)	1 (1)	
Complications grade ≥ II	102 (78)	49 (75)	53 (81)	0.44
Median number of complications (+/- SD) **Min-max**	1 (1.9) 0-8	1 (1.2)	2 (2.2)	0.29[b]
Delirium	11 (8)	2 (3)	9 (13)	*0.05*
Discharge to a rehabilitation unit	18 (14)	5 (8)	13 (18)	0.08
Readmission < 30 days	14 (11)	6 (10)	8 (11)	0.76
Median duration of hospitalization (days) (+/- SD) **Min-max**	7 (12.) 0-11)3	5.5 (4.9)	9.0 (16.0)	*0.00*[b]
Death	36 (27)	12 (19)	24 (34)	0.06
1-year mortality	22 (17)	5 (8)	17 (24)	*0.01*

[b] Mann-Whitney
Geriatric 8 (G8); Comprehensive Geriatric Assessment (CGA); Standard Deviation (SD); Minimum (Min); Maximum (max)

In patients with an impaired G8, a statistically significant higher rate of delirium (nine patients versus two patients, *p* value 0.05) and a longer median postoperative hospital stay (nine days versus five days, *p* value 0.00) occurred. Also, the amount of discharges to a rehabilitation unit was higher in the group of patients with an impaired G8 score (thirteen patients versus five patients), though it was not statistically significant (*p*

value 0.08). Lastly, the 1-year mortality had higher statistically significance in the patients with a G8 < 14 (seventeen patients versus five patients, *p* value 0.01).

Discussion

The primary aim of our study was to validate the value of the G8 as a screening tool for identifying deficits in CGA in older patients with cancer requiring surgery. In our population, 54.5% had an impaired G8 score and were identified as being at risk for frailty. Using our reference test, a threshold of ≥ two abnormal instruments in the CGA, 39% of our patients had deficits in CGA, resulting in, for the G8, a sensitivity, specificity, and NPV of 82%, 63%, and 85%, respectively.

These findings showed that the G8 is an acceptable screening tool due to the high sensitivity and NPV while maintaining sufficient specificity. We considered the sensitivity and NPV to be the most important characteristics of this screening tool because we wish to ensure that almost every frail patient is identified with our screening. Because of the duality between sensitivity and specificity, both parameters cannot be simultaneously maximized.

Kenig et al. is the only study that evaluated the diagnostic value of the G8 specifically in older patients with cancer in need of surgery.[15] However, their population consisted entirely of 184 patients undergoing abdominal surgery. They determined their reference test as ≥ two out of eight impaired instruments in the CGA. In comparison with our study, the prevalence of deficits in CGA (73%) was much higher. In addition, far more patients had an impaired G8 score (85% versus 54.5%). The diagnostic values were similar to our results with respect to high sensitivity (97%) and NPV (84%), and a specificity of 44%.

Our calculated diagnostic values of the G8 are also comparable to the test characteristics of the G8 studied in mostly non-surgical patients. In a recent systematic review, nineteen studies were summarized that compare the G8 with the CGA in cumulatively 5,204 patients.[31] Sensitivity ranged from 38% to 92% and was more than 80% in eleven studies. Specificity ranged from 28% to 100% and was more than 60% in eleven studies. Overall, the G8 was considered to be an acceptable screening tool for identifying frailty in patients with cancer, independent of the treating modality. The included studies used different ways to define and assess frailty. Within the literature, there is no consensus on how to define the widely used term of frailty. Most studies, like our study, used an assessment, including CGA instruments, and used self-defined criteria to classify patients as frail or not.

Interpreting these data, we must take into account the fact that all studies used different instruments and cutoff values, making direct inter-study comparison difficult.

This heterogeneity can be explained by the fact that there is no consensus about which specific instruments should be included in a CGA.[12] These variations in the CGA may influence the prevalence of frailty and thereby influence the diagnostic value of the G8: a higher disease prevalence increases the sensitivity and positive predictive value of a test, and lowers the specificity and NPV.[32] In contrast, van Walree concluded that the median sensitivity and specificity were similar for studies using a cut-off ≥ one impaired instrument and for studies using a cut-off ≥ two impaired instruments (85% and 65% versus 84% and 61%).[31] However, in this review different reference instruments were compared.

The secondary aim of our study was to investigate whether there is a difference in postoperative outcomes between the patients with a G8 ≥ 14 and the patients with a G8 < 14. The occurrence of major 30-days complications (defined as Clavien-Dindo grade ≥ III) did not differ between both groups. However, in the patients with an impaired G8 the occurrence of delirium, the median postoperative hospital stay, and the 1-year mortality had higher statistically significance than in patients with a G8 > 14. These results may suggest that frail patients according to the G8 are not at risk for more surgical complications – possibly caused by innovative and less invasive surgical techniques. On the other hand, these patients seem to be more at risk for a complicated postoperative recovery leading to a higher rate of delirium and discharge to a rehabilitation unit, a prolonged hospital stay, and a higher 1-year mortality. As a result, it seems important to invest in preventive interventions to avoid these complicated recoveries during pre-, and postoperative care.

The association between the G8 and postoperative complications was studied before with inconsistent results. One study in 78 patients operated on for colorectal cancer described an association between the G8 and the occurrence of Clavien-Dindo grade ≥ II complications in univariate analysis, but not in multivariate analysis.[33] Two other studies respectively, 71 patients treated for hepatocellular carcinoma and 184 patients in need of emergency abdominal surgery (also non-oncological patients), found an association between the G8 and the occurrence of Clavien-Dindo grade ≥ II and III, mortality, and a longer hospital stay in both univariate and multivariate analyses.[34,35] In another study, the G8 also seemed to be associated with postoperative complications after surgery for cutaneous head and neck cancer.[36] On the other hand, a study with 139 patients surgical treated for colorectal cancer did not find a predictive value of the G8 of any postoperative outcome.[37] In conclusion, the predictive value of the G8 on postoperative complications is still unclear and further studies with bigger sample sizes are needed.

In addition, the abovementioned studies investigated the association between the G8 and mortality, mostly defined as a 1-year mortality. In these studies, there was no

association between an impaired G8 and a higher (1-year) mortality rate. This was in contrast to studies on non-surgical oncological populations, in that an association between an impaired G8 and mortality was seen in the majority of these studies addressing patients receiving chemotherapy and/or radiotherapy.[31] It is difficult to compare these results with our results, because the abovementioned studies studied a homogeneous population with the same tumor type and operation, while our population consisted of various tumor types and consequently a wide variation of surgeries. Lastly, it is important to mention that screening tools like G8 were originally not designed for predicting postoperative complications.

This study has some limitations. First, our study population is from a tertiary hospital, which could make it more difficult to apply our results to hospital populations in general. Second, there is a risk of incorporation bias. All the questions of the G8 – except for age – have come from the mini-nutritional assessment (MNA), a simple tool for measuring nutritional status in older patients. Since nutritional status is one of the seven geriatric instruments of our CGA, an abnormal G8 will more than likely result in an abnormal CGA. This, in turn, leads to an incorporation bias, which means that the tested score will be included in the reference test. The fact that the assessor completed both the G8 and the CGA is also a limitation, as this could introduce an assessment bias with the risk of a possible overestimation of the agreement between the two assessments. Another limitation is the retrospective collection of the postoperative outcomes. As a result, the occurrence of delirium was probably underreported in the medical records and as a result we may have underestimated the rate of delirium. This may also be the case for the rate of readmissions or mortality, as readmissions in other hospitals or deaths may be lost to follow-up.

The risk of selection bias was not considered as a problem. This is because the pre-operative geriatric screening is a hallmark in our hospital and none of our patients will be operated on without visiting the geriatrician for a CGA.

Despite these limitations, our study is unique as our study population consists of only older patients with all different kinds of solid tumors requiring surgery. To our knowledge, little research has been done to validate the diagnostic value of the G8 in patients who need primary surgery.

In conclusion, the G8 is a simple and useful screening tool for identifying deficits in CGA in older patients with cancer requiring surgery. In addition, patients with an impaired G8 are more at risk for a complicated recovery after surgery resulting in a prolonged hospital stay, admission to rehabilitation units, or a shorter 1-year OS.

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Chapter 4

Frailty and checkpoint inhibitor toxicity in older melanoma patients
The impact of immune-related adverse events

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Abstract

Introduction

Immune checkpoint inhibitors (ICI) can cause immune-related adverse events (irAEs) ranging from mild to life-threatening. Age itself does not seem to be a predictor for the occurrence of irAEs. It is unknown whether frailty plays a role in the occurrence of irAEs. Therefore, we assessed whether irAEs and their sequelae occur more often in frail patients than in fit patients, according to the Geriatric 8 (G8).

Methods

Melanoma patients ≥70 years, about to start with ICI and screened with a G8, were enrolled in this prospective observational study. Patients were classified by the G8 as fit or frail. The primary outcome was the occurrence of grade ≥3 irAEs.

Results

In total, 92 patients were included for statistical analyses, 26 (29%) of whom were classified as frail. Grade ≥ 3 irAE occurred in 20% of patients. There was no significant difference in grade ≥3 irAE occurrences between fit and frail patients (17% versus 27%, p = 0.26). Frail patients were admitted to the hospital due to irAEs significantly more often (29% versus 54%, p = 0.02) and showed a trend towards increased length of hospitalization (5 versus 8 days, p = 0.06) and more frequent use of immunosuppressants or ICI discontinuation for irAEs (36% versus 58%, p= 0.06)

Conclusion

Although frailty appears to be unrelated to the occurrence of severe irAEs, it is an indicator of irAE-related adverse sequelae such as hospital admission. Screening of frailty can be of added value in the shared decision-making process for older patients who qualify for ICI treatment.

Introduction

Immune checkpoint inhibitors (ICI) have become first-line therapy in advanced stages of different tumor types such as melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC).[1–3] With additive evidence of efficacy in distinct subtypes of colon and breast cancer, more than 40% of cancer patients are now eligible for checkpoint inhibitors.[4] As a result, several ICIs, such as anti-programmed cell death 1 (PD-1) and anti-programmed cell death ligand 1 (PDL-1), are becoming a common practice for every oncologist.[5,6] Besides having demonstrated superior efficacy, often with durable clinical benefits in many tumor types, the safety profile of ICI generally compares favorably to chemotherapy and targeted therapy.[3,7] Immune-related adverse events (irAEs), the immune-mediated toxicities that occur during ICI, differ from adverse events (AEs) of other systemic antitumor therapies. AEs can affect multiple organs of the body and mostly do not resolve after discontinuation but require immunosuppressive treatment. IrAEs can be mild, allowing ICI to be continued. Nevertheless, moderate to severe irAEs may be associated with severe declines in organ function and quality of life and can even be fatal. Consequently, these toxicities require early detection and proper management.[8] Besides discontinuation of ICI, irAE management consists of corticosteroids and other immunosuppressants in case of steroid refractory irAE, which can induce significant side effects (especially in older patients), including psychosis, diabetes mellitus, myopathy, and infection.[8]

Because of the favorable safety profile of ICI, they are considered a tolerable treatment option at an older age.[9,10] Published data do not suggest an increased rate of irAEs with age.[11–13] However, in these trials, patients older than 70 years were consistently underrepresented and those who were included were in good health with a good World Health Organization (WHO) performance status (PS) and without substantial comorbidity. As a result, it seems questionable whether these results are generalizable to the context of care in daily clinical practice. Therefore, there is a need for studying the occurrence of irAEs in real-world older populations.

With respect to chemotherapy, it is known that age is a predictor for the occurrence of AEs.[14] In addition to age, frailty is also associated with a decreased tolerance of chemotherapy.[15] To gain insight into someone's frailty, a geriatric assessment (GA) has been implemented in geriatric oncology. A GA is a multidisciplinary, multidimensional, and systematic assessment, and consists of validated scales to identify impairments in the four geriatric domains: somatic, functional, nutritional, and psychosocial.[16] Several studies have shown associations between items of the GA and the risk of toxicity during cytotoxic antitumor therapy in older patients.[17,18] Since not all patients are in need of a GA, screening methods have been developed to identify those at risk for adverse

health outcomes who may benefit from a GA. At present, several screening methods are proposed in the international society of geriatric oncology (SIOG) guideline to select patients for a subsequent GA.[19] The Geriatric 8 (G8) is one such screening tool which has specifically been developed for older cancer patients.[20] The G8 has consistently demonstrated a good sensitivity for geriatric impairments.[19] Besides identifying those patients who will benefit from a GA, there is evidence that the G8 can be used to predict toxicity of treatment with chemotherapy, radiation therapy, and aromatase inhibitors.[21–24] However, to our knowledge, the predictive value of the G8 for irAEs has never been evaluated in older patients with melanoma.

Therefore, the primary aim of this study is to assess whether irAEs and their sequelae occur more often in patients who are classified as frail using the G8 than in fit patients.

Methods

From January 2016 to January 2021, all patients aged 70 years or older, diagnosed with melanoma, about to start with a PD1-inhibitor (nivolumab or pembrolizumab), and screened with a G8, were enrolled in this prospective observational study at the University Medical Center Utrecht in the Netherlands. This study included both stage III and IV melanoma patients as defined by the American Joint Committee on Cancer 2009 classification, 7th edition (AJCC 7).[25]

The G8 was completed by the treating physician or nurse practitioner prior to treatment. The G8 is an eight-item questionnaire that includes seven items from the 18-item mini-nutritional assessment (MNA) and an age-related item (<80, 80 to 85, or > 85 years).[26] The total score ranges from 0 to 17. Patients were classified according to the G8 score as "fit" (G8 score > 14) or "frail" (G8 score ≤ 14).[20] In case of an impaired G8, the patient could be referred to the geriatrician for a GA.

Baseline patient and tumor characteristics such as age, WHO PS, tumor stage, and type of PD1-inhibitor were extracted from the medical records. Comorbidity was assessed with the Charlson Comorbidity Index (CCI), but points for age and malignancy were not included since this involved every patient included.[27]

The severity of the irAEs was graded as per the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE).[28] The grade of toxicity was determined by the treating physician/nurse practitioner each treatment cycle and when the patient contacted their treating physician/nurse practitioner temporarily because of irAEs. Our primary endpoint was a grade ≥ 3 irAE. Second, we reported the incidence of irAEs that required systemic immunosuppressive treatment such as steroids and/or led to treatment discontinuation. Those irAEs were labeled "clinically relevant irAEs." Furthermore, we collected information about emergency department visits and hospital admissions. Efficacy of ICI in unresectable stage III and stage IV melanoma was assessed using the best overall response (BOR) on imaging in accordance to RECIST criteria version 1.1 determined by the radiologist.[29] BOR is the best response recorded from the start of the treatment until the end of treatment.[29] The objective response rate (ORR) was defined as the percentage of patients with a complete response (CR) or partial response (PR) as BOR.

This research was not considered subject to the Medical Research Involving Human Subjects Act by the Institutional review board of the UMC Utrecht.

Statistical analysis

Descriptive analyses were performed to report patient, tumor, and treatment characteristics. For comparisons between fit and frail patients, the chi-square or the Fisher's exact test was used for nominal and ordinal variables depending on the sample size of the categories. For continuous variables with a normal distribution, the Student's *t* test was used. In case of non-normally distributed continuous variables, the Mann-Whitney test was used. Two-sided *p*-values of ≤ 0.05 were considered statistically significant.

SPSS (Statistical Package for the Social Sciences) version 21.0 was used for the analyses.

Results

In total, 92 patients aged ≥ 70 years were enrolled in this study. Baseline characteristics are presented in Table 1. Median age was 76.0 years (range 70-89). Fifty-three patients were diagnosed with a stage IV melanoma. Sixty-six patients (71%) had a G8 > 14 and were classified as fit, 26 patients (29%) had a G8 ≤ 14 and were classified as frail. In the majority of the frail patients (62%), a GA was performed. Fit patients were significantly younger and had a better WHO PS at baseline compared to frail patients. Other baseline characteristics did not differ statistically significantly between fit and frail patients. At the date of analysis, median follow-up was 11.0 months (range 1.0-53.0 months).

Table 1: Baseline characteristics

Variable	Total (n= 92)	Fit patients (n= 66)	Frail patients (n=26)	*p*-value
Gender (%)	56 (61)	43 (65)	13 (50)	0.18
Male	36 (39)	23 (35)	13 (50)	
Female				
Age at diagnosis in years, median (SD)	76.0 (±4.6)	75.0 (±3.6)	79.0 (±58)	*0.02*
WHO PS (%)				
0	25 (27)	24 (36)	1 (4)21 (81)	*0.00*
1	55 (60)	34 (52)	4 (15)	
2	8 (9)	4 (6)	0	
Unknown	4 (4)	4 (6)		
BMI, median (±SD)	25.4 (±3.8)	25.6 (±4.0)	25.1 (±2.8)	0.27
CCI (%)				0.80
0	40 (44)	28 (42)	12 (46)	
1	31 (34)	21 (32)	10 (39)	
2	16 (17)	12 (18)	4 (15)	
≥ 3	5 (5)	5 (8)	0	
Stage melanoma (%)				0.31
III				
IIIA	2 (2)	2 (3)	0	0.06
IIIB	13 (14)	10 (15)	3 (12)	
IIIC	24 (26)	18 (27)	6 (23)	
IV				
IV M1a	11 (12)	8 (13)	3 (12)	
IV M1b	11 (12)	10 (15)	1 (4)	
IV M1c	31 (34)	18 (27)	13 (50)	
Brain metastases	5 (5)	3 (5)	2 (7)	0.59
LDH > ULN (250U/L)	19 (21)	11 (17)	8 (30)	0.17
Type of immune checkpoint inhibitor (%)				0.64
Pembrolizumab	60 (65)	44 (67)	16 (61)	
Nivolumab	32 (35)	22 (33)	10 (39)	

Geriatric 8 (G8); standard deviation (SD); WHO Performance score (WHO PS); Body Mass Index (BMI); Charlson Comorbidity Index (CCI); American Joint Committee on Cancer (AJCC 7th edition)'Lactate Dehydrogenase (LDH); Upper limit of normal (ULN)

Immune-related adverse events

Eighteen patients (20%) experienced grade ≥ 3 irAEs. The occurrence of grade ≥ 3 irAEs did not statistically significantly differ between fit and frail patients (17% versus 27%, $p = 0.26$, Table 2). Clinically relevant irAEs requiring immunosuppressants and/or leading to treatment discontinuation occurred in 39 patients (42%); in 24 (36%) fit patients and 15 (58%) frail patients ($p= 0.06$). The clinically relevant irAEs mostly consisted of arthralgia or myalgia (n=8), pneumonitis (n=7), colitis (n=5), and hepatitis (n=5).

Frequency of discontinuation of ICI did not differ between fit and frail patients and there were no significant differences in reason for discontinuation (toxicity, progression, or response, Table 2). The duration of steroids use did not significantly differ between both groups.

Table 2: Summary of immune-related adverse events

Variable	Total (n= 92)	Fit patients (n= 66)	Frail patients (n=26)	*p*-value
Grade ≥ 3 irAEs, n (%)	18 (20)	11 (17)	7 (27)	0.26
Clinically relevant irAE, n (%)	39 (42)	24 (36)	15 (58)	0.06
Requiring immunosuppressants	8 (9)	5 (8)	3 (12)	
Discontinuation ICI	8 (9)	5 (8)	3 (12)	
Both	23 (25)	14 (21)	9 (35)	
Type of clinically relevant irAE, n (%)				
Hepatitis	5 (7)	3 (6)	2 (8)	
Nephritis	3 (4)	0	3 (13)	
Colitis	5 (7)	3 (6)	2 (8)	
Pneumonitis	7 (9)	4 (8)	3 (13)	
Cholangitis	2 (3)	1 (2)	1 (4)	
Dermatitis	1 (1)	0	1 (4)	
Arthralgia/myalgia	8 (10)	7 (13)	1 (4)	
Hypophysitis	2 (3)	2 (4)	0	
Diabetes Mellitus	1 (1)	0	1 (4)	
Neurologic toxicity	3 (4)	3 (6)	0	
Discontinuation of ICI, n(%)	68 (74)	48 (73)	20 (77)	0.68
Due to toxicity	32 (35)	21 (32)	11 (42)	0.34
Due to progression	24 (26)	19 (29)	5 (19)	0.35
Due to ongoing response	36 (39)	26 (39)	10 (39)	0.93
Duration of steroids use in weeks, median (95% CI)	41 (33-49)	40 (31-50)	37 (29-45)	0.56
Emergency department visits, n (%)	34 (37)	21 (32)	13 (50)	0.10
Number of emergency department visits, median (min-max)	0 (0-5)	0 (0-5)	0.5 (0-5)	0.13
Hospital admission, n (%)	35 (36)	19 (29)	14 (54)	*0.02*
Due to toxicity	21 (23)	10 (15)	11 (42)	*<0.01*
Number of hospitalizations, median (min-max)	0 (0-3)	0 (0-3)	1.0 (0-2)	*0.02*
Duration of hospitalization in days, median (min-max)	6 (2-38)	5 (2-30)	8 (4-38)	0.06
Time to Grade ≥ 3 irAEs in months, median (95% CI)	4.0 (1.1-6.9)	2.0 (0.0-5.1)	5.0 (1.6-8.4)	0.97
Time to clinically relevant irAE in months, median (95% CI)	4.0 (3.2-4.8)	4.0 (2.5-5.5)	4.0 (2.6-5.4)	0.73[c]

Geriatric 8 (G8); immune-related adverse event (irAE); Immune checkpoint inhibitors (ICI); Confidence Interval (CI)

No patient died due to an irAE. Median time to occurrence of grade ≥ 3 irAEs and to occurrence of clinically relevant irAEs was 4.0 months for both groups (range respectively 1.1-6.9 and 3.2-4.8).

After starting the ICI, 34 patients (37%) visited the emergency department. Numerically, more frail patients (50%) visited the emergency department due to irAEs compared to fit patients (32%), although it was not statistically significant (p = 0.10). Significantly more frail patients were admitted to the hospital because of irAEs compared to fit patients: 11 patients (42%) versus 19 patients (29%), p = < 0.01. In addition, the median duration of hospitalization was non-significantly longer for the frail patients (8 versus 5 days, p = 0.06).

Treatment efficacy in patients with stage IV melanoma

Efficacy of ICIs was assessed in 53 patients with stage IV melanoma only (table 3). The majority of these patients were classified as fit according to the G8 (n= 41, 77%) and twelve patients (23%) as frail.

The ORR was 56% (28 patients: 21 PR and 7 CR). Furthermore, ten patients had stable disease as best response. There were no statistically significant differences in ORR between fit and frail patients (ORR 53% vs 62% respectively).

At the time of analysis, 28 patients had PD as shown in Table 3.

Table 3: Efficacy of ICIs in patients with Stage IV melanoma

Variable	Total (n= 53)	Fit patients (n= 41)	Frail patients (n=12)	*p*-value
Best objective response, n (%)				0.16
Complete response	7 (14)	6 (18)	1 (6)	
Partial response	21 (42)	12 (35)	9 (56)	
Stable disease	11 (22)	10 (29)	1 (6)	
Progressive disease	11 (22)	6 (18)	5 (31)	
Clinically relevant irAE, n (%)	26 (49)	16 (42)	11 (65)	0.12
irAE of ≥ grade 3, n (%)	12 (23)	7 (19)	5 (29)	0.42

Immune checkpoint inhibitors (ICI); Geriatric 8 (G8); Immune-related adverse event (irAE); 95% Confidence Interval (95% CI)

Discussion

In this prospective cohort study in stage III and IV melanoma patients ≥ 70 years treated with anti-PD1 monotherapy, we found no difference between grade ≥ 3 irAEs in fit and frail older patients. Nevertheless, frail patients more often experienced irAE-related sequelae such as hospitalization and tended to have an increased length of hospitalization. These results could be of value when counseling frail patients for ICI.

With 20% grade ≥ 3 irAEs found in this study, our data confirm findings from randomized controlled trails (which enrolled younger patients), showing that the occurrence of irAEs of grade ≥ 3 ranged from 9% to 22% and that older age itself was not associated with a higher risk of irAEs.[7,30–33] Also, our observed efficacy was comparable to another real-world data study.[34–36] Thus, chronological age alone should not cause physicians to withhold treatment from older patients with ICIs.

However, grade ≥ 3 irAEs are not the only irAEs of which one should be aware when treating older patients with ICIs. IrAEs of grade < 3 can result in treatment discontinuation, hospitalization, possibly impacting functional status and quality of life, or treatment with immunosuppressants, or both, especially in frail patients. In our study, almost half of the patients (42%) experienced such a "clinically relevant irAE" and, in 35% of the patients, toxicity led to treatment discontinuation. In the literature, the percentage of discontinuation of ICIs in older patients because of toxicity is inconsistent and varies between 14% and 63%.[37–41] Studies directly comparing ICI tolerance between younger and older patients generally described more frequent discontinuation of ICI treatment due to toxicity in older patients, although this difference was not always statistically significant.[37,40,42]

We found just one other study assessing the relation between an impaired G8 and the occurrence of irAEs. Kubo et al. retrospectively studied the safety of ICI in 95 NSCLC patients ≥ 75 years and retrospectively calculated a modified G8 using data from the medical records and excluding patients with a WHO PS 3. They concluded that an impaired modified G8 was not associated with more irAEs of grade ≥ 2.[43] This result is in line with our findings, although their study population differs from our population with respect to tumor type and age group.

Although the G8 was developed as a frailty-screening tool to select patients who could benefit from a GA, it was not intended to be a predictive tool. The association between an impaired G8 and the occurrence of AEs has already been shown for antitumor treatments other than ICI, such as chemotherapy, radiation, and aromatase inhibitors.[21–24]

The association between frailty assessed by instruments other than the G8 and the occurrence of irAEs has been explored in small studies. A retrospective small study in 28 patients did not find an association between impairments in GA domains and the occurrence of irAEs.[44] Another study assessed whether frailty defined by a GA or, lacking a GA, defined by having a WHO PS ≥3, CCI score ≥11, and/or falls in the prior 6 months, was associated with the occurrence of irAEs of any grade. The authors did not find a statistically significant difference, however, and this study was also limited by a small study population (n= 51).[39]

We found that frailty according to the G8 was associated with more hospital admissions due to irAEs and with an increased length of hospitalization. Gomes et al. also described an impaired G8 to be a predictor for hospital admissions in patients treated

with ICI, although only 32% of these hospital admissions were irAE-related.[37] Apparently, frailty does not influence the occurrence of an irAE, but when an irAE occurs, it more often leads to hospital admission in frail patients compared to fit patients. This supports the fact that the management and impact of all irAEs, irrespective of grade, can be more challenging in frail patients. Further illustrating this point, Gomes et al. also showed that older patients had a longer duration of exposure to systemic steroids used to treat irAEs.[37] Our study showed that frailty was not associated with a longer duration of steroid treatment.

This study has several limitations. First, the small number of patients restricted the use of statistical analyses for identifying predictive factors of the occurrence of irAEs in older patients. With a larger sample size, a study with the goal of developing a prediction model for irAEs in older patients could be developed to explore the predictive value of individual factors incorporated in the G8 for irAE and their sequelae. IrAE-risk stratification would help clinicians council their patients in the selection of the most appropriate treatment strategy and would provide opportunities to discuss advanced care planning when treatment is withheld. Secondly, only 29% of our patients were classified as frail according to the G8, which was lower than anticipated, as most published evidence suggests percentages between 50-80%.[45] This is most likely due to the selection of patients treated with ICI. Another explanation of our low rate of frail patients is the fact that the G8 involves multiple items about nutritional status. Almost half of our population consisted of patients with stage III melanoma receiving anti-PD1 in the adjuvant (curative) setting. The nutritional status in this patient group is possibly better than in patients with advanced disease, resulting in an unimpaired G8 and a classification as fit. Last, the majority of the frail patients underwent a GA. A GA could lead to GA-based interventions which may have influenced their treatment outcomes.

The strength of our study is the fact that this is the first study prospectively assessing the occurrence of irAEs in the elderly with a high risk of frailty according to the G8 in patients with melanoma. In addition to assessing the occurrence of grade ≥ 3 irAEs, we also focused on the incidence of irAEs requiring immunosuppressants and/or leading to treatment discontinuation, on hospital admissions, and on visits to the emergency department

In conclusion, this study provides insufficient evidence that frailty, according to the G8, is associated with a higher occurrence of irAEs of grade ≥ 3. Nonetheless, the increased incidence of hospital admission due to irAEs in the frail group suggests that the impact of irAEs is greater in frail patients. While frailty in itself was not statistically associated with the occurrence of irAEs, providing insight into a patient's risk of frailty can aid in identifying those frail older patients with a higher risk of hospital admissions and with a higher risk of the occurrence of irAEs, requiring treatment with

immunosuppressants and/or leading to discontinuation. Therefore, implementation of the G8 for older patients undergoing ICI treatment is feasible and should be considered. Ultimately, insight into a patient's frailty serves as a guide in making individualized treatment decisions.

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Part III

Importance of Patient-Related Outcomes Measures

Chapter 5

Functional decline after surgery in older patients with head and neck cancer

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Abstract

Introduction

In addition to classical endpoints such as survival and complication rates, other outcomes such as quality of life and functional status are increasingly recognized as important endpoints, especially for elderly patients. However, little is known about the long-term effect of surgery with regard to these other outcomes. Our aim is to investigate the functional status and self-reported health status of patients ≥ 70 years one year after surgery for head and neck cancer.

Methods

We present one-year follow-up data of patients ≥ 70 year who and underwent surgery for HNC. During an interview by telephone, functional status was evaluated by using the Katz-15 Index of Independence questionnaire including six items covering basic Activities of Daily Living (ADL) and nine items covering Instrumental Activities of Daily Living (IADL). Measurements were compared with those obtained preoperatively.

Results

In total, 126 patients were included and eventually we collected follow-up data of 68 patients. There was a statistically significant decrease in functional status on the total Katz-15 and on the IADL questionnaire scores one year after surgery (mean 1.34 versus 2.42, *p* -value 0.00 and mean 1.21 versus 1.94, *p*- value 0.00). There was no significant change concerning ADL dependence (*p* -value 0.18) and cognitive status (*p* -value 0.11). The self-reported health status improved postoperatively, although not statistically significantly so (mean 67.36 versus 71.25, *p* -value 0.12).

Conclusion

Approximately one year after surgery for HNC, there is a significant decline in functional status indicating a higher level of dependency.

Introduction

Head and neck cancer (HNC) is a heterogeneous group of cancer which includes those cancers originating in the oral cavity and lip, the pharynx, the larynx, the salivary glands, the nasal cavity, and paranasal sinuses. HNC is primarily a cancer that occurs among the older population. In the Netherlands, 40% of the patients newly diagnosed with HNC in 2019 was older than 70 years.[1] With the increase in the aging population and the increasing cancer burden, the incidence of HNC is expected to rise even more in the following years.[2]

In the past decades, there have been multiple improvements in the treatment of HNC resulting in prolonged survival and better disease control.[3] However, older patients are often considered poor candidates for multimodality treatment and are subsequently less likely to receive the standard of care treatment that younger patients receive.[4,5] As a result, previous randomized trials in HNC included relatively few older patients and, predominantly, those that were included had a good performance status and less comorbidity. This strongly limits the evidence base for the older population, where geriatric deficits and comorbidity are much more prevalent.[4,5] Thus, the outcomes of these trials may not be applicable to the older patients we encounter in our clinic.

In addition, existing oncological trials focus primarily on the classical endpoints such as overall survival and complication rates whereas other outcomes, such as health-related quality of life and retaining independence are increasingly being recognized as important. All this information would ideally be discussed with the patient, when personalized decisions are made concerning cancer treatment. These outcomes are particularly relevant in the discussion with older patients, since older patients generally seem to have a preference for quality of life (QoL) over length of life.[6,7] However, in elderly patients information concerning the long-term effects of HNC surgery on functionality, independence, and quality of life is lacking at this time.[8] Based on the very rare evidence, we hypothesize that HNC surgery at least impacts functionality.

Taking this into consideration, the primary aim of this study is to provide insight into the long-term effects of surgery on functionality in HNC patients older than 70 years to explore whether HNC surgery indeed impacts this. In addition to functionality, assessed by measuring the Instrumental Activities of Daily Living (IADL) and the Activities of Daily Living (ADL), the long-term effect on cognition, mood, and the quality of life by using the self-reported health status will also be assessed.

Methods

Patient selection

Between September 2015 and July 2019, patients aged 70 years or older who were scheduled for surgery and visited the pre-operative screening clinic before undergoing surgical treatment were enrolled in this prospective study at the department of Geriatrics at the University Medical Center Utrecht in Utrecht, the Netherlands.

Approximately one year after surgical treatment, patients were approached for follow-up by telephone. If the medical record showed the patients had not been in contact with their physician for over three months, the patient's general practitioner was called first to check if the patient was still alive. Patients were excluded if they had not given informed consent for the follow-up by telephone or if they were not able to complete the follow-up by telephone due to deafness, dementia, or a terminal condition caused by progressive disease. The study was reviewed and approved by the local ethics committee.

Demographic and treatment data

Patient characteristics such as age, gender, marital status, and living situation were obtained from the medical record. Tumor and treatment characteristics involved localization, stage, type of surgery, and postoperative radiation. Treatments were grouped based on extent and duration of surgery. Comorbidity was assessed with the Charlson Comorbidity Index (CCI), excluding points for age and current malignancy.[9]

Outcome measurement

Data about functional status, cognition, and mood was collected by questionnaires both preoperatively as well as at follow-up by telephone. Functional status was assessed by the Katz-15 Index of Independence that measures ADL and IADL.[10,11] This questionnaire consists of six ADL items that are also found in the Katz-6 index[12] (i.e. bathing, dressing, eating, toileting, continence, transferring), and nine IADL items adapted from the Lawton IADL index[13] (i.e. traveling, grooming, preparing a meal, use of telephone, shopping, household tasks, managing medications, managing finances and mobility). Each item was given a score of zero (no disability) or one (yes, disabled), and then all items were totaled, leading to a range of 0-15 for the Katz-15 score, with a higher score indicating a higher level of dependency. Patients were considered dependent in ADL if there was ≥ 1 disabled item in the Katz-6 index and dependent in IADL if there was ≥ 1 disabled item in the remaining nine items of the Katz-15. The Katz-15 has been demonstrated to be a reliable and valid measurement of ADL and IADL.[11]

Cognition was preoperatively assessed with the mini-mental state examination (MMSE).[14] The telephone interview for cognitive status (TICS) was used to assess cognition at the follow-up by telephone.[15] This score was converted to a score corresponding with the MMSE as validated in the study of Fong et al.[16] Mood was assessed with the Patient Health Questionnaire-2 (PHQ-2).[17] This instrument consists of two questions: (1) "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and (2) "During the past month, have you often been bothered by little interest or pleasure in doing things?". If one or both questions were answered with "yes", the mood was considered as impaired.

To acquire insight into the quality of life by using the self-reported health status, the EuroQol Visual Analog Scale (EQ-VAS) was used developed by the EuroQoL Group.[18] With the EQ-VAS, patients were asked to indicate their health status between 0 and 100, where 0 represents their worst imaginable health status and 100 represents their best imaginable health status. The EQ-VAS was demonstrated as a valid instrument for monitoring the patients' health status in time.[18–20] Lastly, the interview by telephone included a question about weight.

Statistical analysis

Descriptive statistics were used to summarize patient and tumor characteristics. The categorical variables were described using numbers and percentages. Medians and standard deviations were used to describe continuous variables. For a comparison of patients and tumor characteristics between the patients included in the follow-up by telephone with the total population including patients excluded from follow-up by telephone, the chi-squared test was used. For continuous variables with a normal distribution the Student's *t* test was used. The Mann-Whitney *U* test was used if there was an abnormal distribution.

The primary endpoint of this study was the functional decline one year after surgery expressed as a change in the Katz-15. Second, we assessed changes in ADL impairment and IADL impairment separately. As secondary endpoints we analyzed the change in cognitive function, mood, self-reported health status, and weight. To determine changes between data collected at baseline and during follow-up by telephone, the Wilcoxon signed rank test was used for paired continuous variables without a normal distribution. To analyze paired dichotomous variables the McNemar's test was used. A p-value of ≤ 0.05 was considered as statistically significant.

The Statistical Package for the Social Sciences (SPSS) version 21.0 was used for the analyses.

Results

Baseline characteristics

In total, 126 patients were included in this study. These patients visited the pre-operative screening clinic as part of the schedule for surgery. The baseline characteristics were summarized in table 1. The median age was 80.5 years old and 57.9% were men. Almost half of the tumors were localized in the oral cavity (49.2%). Twenty-five patients (20%) died in the first year, so 101 patients were approached for follow-up by telephone as shown in figure 1. Finally, follow-up data from 68 patients was collected. The follow-up population was significantly younger compared with the total population, lived independently more often, and had statistically significant less comorbidity according to the CCI (table 1). Moreover, this population had less IADL impairment, and less cognition impairment as shown in table 2. Median time to follow-up was 13 months (range 5 -24 months).

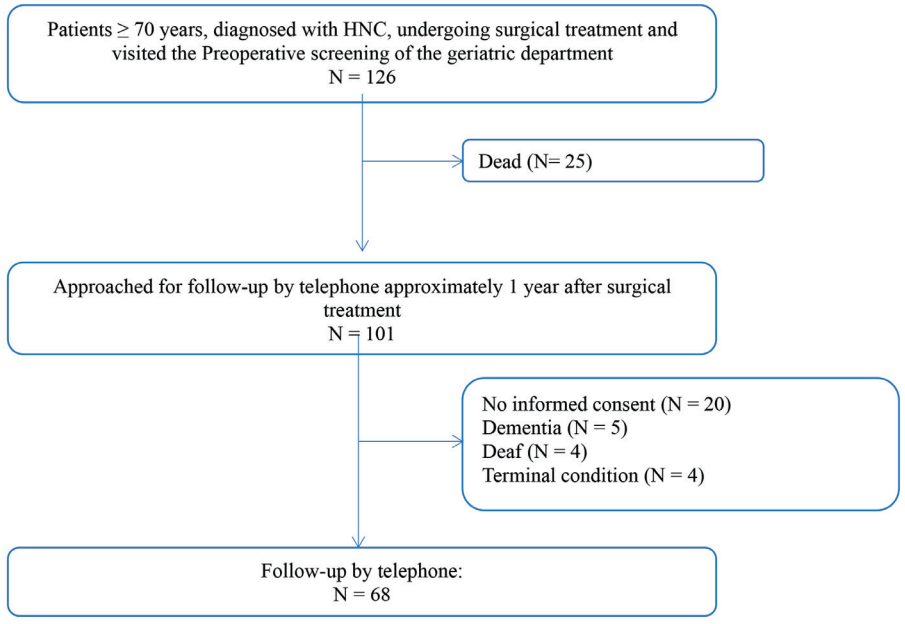

Figure 1: Flowchart of patient inclusion

Table 1: Baseline characteristics

Variable	Total (n=126)	Follow-up data available (n= 68)	*p*-value
	No. (%)	No. (%)	
Male	73 (57.9)	42 (61.8)	0.35
Median age in years ± SD	80.5 ± 6.35	79.0 ± 5.6	*0.03*
70-79	56 (44.4)	37 (54.4)	*0.03*
80-89	54 (42.9)	26 (38.2)	
≥ 90	16 (12.7)	5 (7.4)	
Living situation			*0.02*
Independently	109 (86.4)	64 (94.1)	
Assisted	17 (13.6)	4 (5.9)	
BMI in kg/m2	25.2 ± 4.06	25.9 ± 3.75	0.25
Medication use ≥ 5	75 (59.5)	43 (63.2)	0.36
CCI ≥ 3	27 (21.6)	10 (14.7)	*0.04*
ASA ≥ 3	88 (71.5)	45 (67.2)	0.24
Tumor localization			0.22
Lip	3 (2.4)	1 (1.5)	
Oral cavity	62 (49.2)	32 (47.1)	
Pharynx	6 (4.8)	2 (2.9)	
Larynx	16 (12.7)	7 (10.3)	
Salivary glands	11 (8.7)	8 (11.8)	
Nasal cavity	2 (1.6)	0 (0.0)	
Skin	24 (19.0)	16 (23.5)	
Unknown	2 (1.6)	2 (2.9)	
Stage			0.17
0	5 (4.0)	4 (5.9)	
I	26 (20.6)	18 (26.5)	
II	34 (27.0)	18 (26.5)	
III	17 (13.5)	9 (13.2)	
IV	40 (31.8)	16 (23.6)	
Unknown	4 (3.2)	3 (4.4)	
Surgery category			0.71
Endoscopy/ examination under general anesthesia	17 (13)	8 (12)	
Excision primary tumor skin or oral cavity	41 (33)	20 (29)	
Neck dissection/ parotidectomy	27 (21)	20 (29)	
Laryngectomy with/without neck dissection / excision primary tumor, neck dissection and reconstruction with pedicle or free flap	41 (33)	20 (29)	
Postoperative radiotherapy	45 (38.1)	23 (35.9)	0.59

Number (No.); Body Mass Index (BMI); Charlson Comorbidity Index (CCI); American Society of Anesthesiologists (ASA); Comprehensive Geriatric Assessment (CGA); 4-meter Walk Test (4MWT);

Outcome of functional status

Of the 68 patients included for follow-up, 26 patients (38.2%) had a Katz-15 score ≥ 1 preoperatively as shown in table 2. One year later, 51 patients (75.0%) had a Katz-15 score ≥ 1. The mean score of the KATZ-15 increased statistically significantly from a mean of 1.34 to a mean of 2.42 (*p*-value 0.00). With regard to ADL, 13 patients (19.2%) had an impaired ADL preoperatively. At follow-up, 18 patients (26.5%) had an impaired ADL (*p*-value 0.18). The mean ADL score changed from 0.24 preoperatively to 0.47 at follow-up (*p*-value 0.18). In 25 patients (22.1%) the IADL was preoperatively impaired and in 48 patients (70.6%) the IADL was impaired at the one-year follow-up (*p*- value

< 0.001). The mean score of the IADL increased statistically significantly from a mean of 1.21 to a mean of 1.94 (*p*-value 0.00).

Table 2: Differences in baseline functional status, cognition, mood, and self-reported health status between the total population and the follow-up population

	Total (n=126)	Follow-up data available (n= 68)	*p*-value
Variable	**No. (%)**	**No. (%)**	
Functional status:			
Impaired Katz-15	60 (47.6)	26 (38.2)	*0.02*
ADL impairment	31 (24.6)	13 (19.1)	0.16
IADL impairment	58 (46.0)	25 (36.8)	*0.02*
Cognition:			
MMSE < 24	6 (5.0)	1 (1.5)	*0.05*
Mood:			
PHQ-2 impaired	16 (12.7)	10 (14.7)	0.46
Self-reported health status:			
Mean EQ-5D VAS ± SD	66.90 ± 15.58	67.70 ± 15.92	0.64

Activity of Daily Living (ADL); Instrumental Activities of Daily Living (IADL); Minimal Mental State Examination (MMSE); Patient Health Questionnaire-2 (PHQ-2); EQ-5D Visual Analog Scale (EQ-5D VAS)

Disability in activity with housekeeping, walking, travelling, and shopping most often occurred both preoperatively and at follow-up (figure 2).

Table 3: Preoperative outcomes compared with one-year follow-up

	Preoperatively (n= 68)	Follow-up (n=68)	*p*-value
Variable (mean +- SD)	**No. (%)**	**No. (%)**	
Dependency by Katz-15	42 (61.8)	17 (25.0)	*0.00*
0	26 (38.2)	51 (75.0)	
≥ 1	1.34 ± 2.16	2.42 ± 2.75	
ADL by Katz-6	55 (80.8)	50 (73.5)	0.18
0	13 (19.2)	18 (26.5)	
≥ 1	0.24 ± 0.55	0.47 ± 1.00	
IADL bij Katz-9	53 (77.9)	20 (29.4)	*< 0.001*
0	25 (22.1)	48 (70.6)	
≥ 1	1.21 ± 1.84	1.94 ± 2.06	
MMSE	28.64 ± 1.36	28.83 ± 2.1	0.11
PHQ-2			0.15
0	58 (85.3)	64 (94.1)	
≥ 1	10 (14.7)	4 (5.9)	
EQ-VAS, mean ± SD	67.36 ± 16.01	71.25 ± 13.49	0.12
Mean weight ± SD	75.91 ± 13.12	74.94 ± 13.39	*0.04*
Gain weight		20 (29.4)	
Lost weight		37 (54.4)	
No weight change		10 (14.7)	

Number (No.); Activity of Daily Living (ADL); Instrumental Activities of Daily Living (IADL); Minimal Mental State Examination (MMSE) ; Patient Health Questionnaire-2 (PHQ-2); EuroQoL Visual Analog Scale (EQ-VAS)

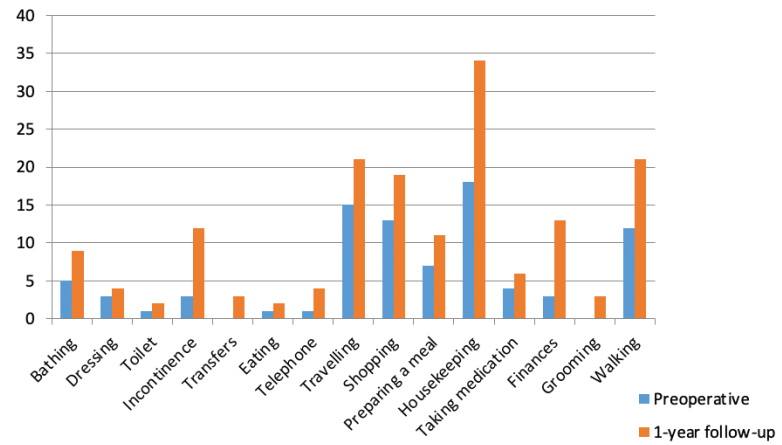

Figure 2: Dependence Katz-15 per question at baseline and follow-up

Before surgery, the mean MMSE was 28.64 ± 1.36. At follow-up by telephone, three TICS were not completed because of hearing problems. The mean MMSE of the 65 patients with completed data after one year was 28.83 ± 2.1 (*p*-value 0.11). Three patients had an impaired MMSE < 24 at follow-up compared with one patient preoperatively.

Concerning mood, there were less patients with an impaired PHQ-2 at follow-up by telephone compared to preoperatively (ten patients at baseline versus four patients after follow up, *p*-value 0.15).

The self-reported health status at the follow-up by telephone, assessed with the EQ-VAS, improved by a mean of four points (from 67.36 to 71.25), although it was not statistically significant (*p*-value 0.12).

The mean weight at follow-up by telephone decreased statistically significantly from 75.91 kilogram (kg) to 74.94 kg (*p*- value 0.04). The majority of patients (54.4%) had lost weight one year after surgery.

Discussion

One year after surgical treatment for HNC, patients ≥ 70 year old were statistically significantly more disabled according to the Katz-15 questionnaire compared to preoperatively indicating a higher level of dependency. Approximately, 10% (19% versus 27%) of the patients had lost ADL function and 37% (38% versus 75%) of the patients had lost IADL function.

In contrast to ADL, IADL declined statistically significantly. It is well known that impairments in IADL normally precede impairments in ADL.[21,22] ADL consists of those activities essential for an independent life, while carrying out the IADL is more complex. Complex activities were affected to a higher degree than basic daily functions. The decline in IADL we noticed may represent a substantially clinically relevant impact on an individual's functional dependency, because it indicates that this patients will need assistance from a family member, care giver, or long-term care services.[23,24] Our results showed that these patients mainly need assistance in housekeeping, travelling, shopping, and mobility.

Our findings are overall in line with other studies investigating functional decline after oncologic surgery in older patients.[25–28] Rønning et al. found a decline in ADL in one third of the 84 patients and a decline in IADL in two third of the patients 16-28 months after surgery for colorectal cancer.[29] Another study, comprising of 1,007 older patients with stage I-IIIa non-small cell lung cancer, reported a decline in ADL in 5% of the patients one year after surgery.[30] Giannotti et al. enrolled 99 patients undergoing elective surgery for gastro-intestinal cancer and found a decline in ADL in 13% of the patients after one year.[28] .

Studies specifically focusing on the effect on dependency after HNC surgery are rare. As far as we know, Silver et al. published the only study covering this subject in HNC patients so far.[31] Their findings differed from our results: six months after surgery, the need for assistance with ADL quadrupled and the need for assistance with IADL doubled in 60 Brazilian HNC patients. The applicability of these results to our patients is doubtful, since the presentation, clinical course, and outcomes of HNC in developing countries may differ from those in developed countries.

Although all abovementioned studies found a negative change in the functional status of older patients after oncological surgery, inter-study comparison of these studies is difficult, because these studies vary in study design, analyses, time to follow-up, and in measurement and definition of functional decline. A systematic review covering studies with non-oncological patients, showed that there is conceptual uniformity in the measurement of ADL with a little variability of items within Katz ADL and IADL questionnaires, but that there is far less uniformity in the definition of functional decline and the cutoff scores reflecting functional decline ranged from about 2% to 20% of the instruments' total score range.[10] As a result, it is unclear when we should speak of a clinical relevant decline in functioning. Therefore, further research should also focus on the patients' self-report of functioning and quality of life.[32]

We also aimed to acquire insight in the quality of life of HNC patients one year after surgery. The EQ-VAS improved postoperatively, although not statistically significant, indicating that patients may rank their health status higher than preoperatively. Although an extended examination of the quality of life, for instance by using the EQ-5D questionnaire, was lacking, the results of the EQ-VAS might suggest that patients do at least not experienced a decline in their quality of life at one year follow-up. In contrast, the quality of life might be improved by the fact that postoperatively the fear and the insecurity about their diagnosis and treatment had been resolved. This finding may also be taken into account in counselling our older patient.

In addition to functional status, we also investigated the effect on cognitive status. We did not find a significant difference in the MMSE before and one year after surgery. However, we have to take selection bias into account. Preoperatively, hardly any patient was not cognitively impaired. Additionally, at follow-up by telephone we excluded five patients because their cognitive status hindered an interview by telephone. As a result, all patients analyzed were functioning well cognitively.

Also, we did not find a significant decrease in mood. On the contrary, we may note a carefully improving trend of the PHQ-2. Patients themselves explained their improved mood due to the fact that fear for the cancer diagnosis and the upcoming surgery could have impacted their mood preoperatively. In a study on stepped care targeting psychological distress, recovery was observed after 2 weeks of watchful waiting in 30%

of distressed HNC and lung cancer patients.[33] Although the PHQ-2 could be seen as a rough scale for depression, the validation study showed that a "no" response to both questions made depression very unlikely.[17] Thus, in 94% of our patients, depression was very unlikely one year after surgery. This may be different from other studies which report on depression symptoms at follow-up in 20-37% of HNC patients of all ages.[34–36]

In a systematic review the pooled prevalence of depression in cancer patients ranged from 8% to 24% and differed according to the type of instrument, type of cancer and treatment phase.[35] In a study on (mainly surgically treated) oral cancer patients, the situation most frequently involved in our study, age did not contribute to the presence of depression.[34]

Lastly, we noticed a statistically significant weight decrease post-operatively, although the difference was small (1kg). In a study on post-treatment weight change in oral cavity and oropharyngeal squamous cell carcinoma patients (mean age 60.0 ± 12.0 years old), the mean weight loss from pre-treatment to 0–6 months post-treatment was 5 kg (6% of baseline mean body weight), and the mean weight gain from the 0–6 month-follow-up period to the 18–24-month follow-up period was 2 kg (2% of baseline mean body weight).[37] In addition, the patients with primary surgery with or without adjuvant therapy had significantly more weight gain from baseline to 12–18-month follow-up as compared to the patients with primary radiation and/or chemotherapy. Therefore, the point of timeweighing post treatment seems important in determining if weight decrease or increase is present. In the present study the median follow-up weight measurement was 13 months.

Maintaining independence and quality of life has been shown to be an important treatment outcome in older patients. In one study of patient preferences, including 226 patients over 60 years old with a diagnosis of cancer, heart failure, or chronic obstructive pulmonary disease, 74% stated that they would refuse to, or be reluctant to receive treatment resulting in severe functional impairment.[7] Of course, HNC is a lethal disease when left untreated, so there is little doubt that surgery is a proper course of action not only to achieve oncological cure, but also to minimize the functional, cosmetic, and psychosocial impact of the disease.[38] Besides discussing the prognosis and complication rates of a surgical procedure for HNC, it is important to discuss the long-term effect on functionality. Based on our findings, we could now inform our patients about the fact that a surgical procedure may lead to a decline in functional status, specifically more dependency in IADL activities. However, we can also reassure our patients, it does not influence their self-reported health status negatively. Indeed, we noticed an improvement in self-reported health status in contrast to other studies in which a functional decline was correlated to a decreased quality of life.[39] .

The strength of our study lies in the fact that this is, as far as we know, the first study prospectively assessing the functional status, quality of life by using the self-reported health status, mood, and cognition status in older HNC patients one year after surgery in a Western population.

Our study also had some limitations. First of all, the size of our study population was limited. Our sample size limited the use of a statistical analyses for identifying predictive factors of functional decline. For instance, it is possible that postoperative radiation therapy further impacts functional outcome. In the future, more research like this study should be conducted, possibly with the goal of developing a prediction model for functional decline after surgery in elderly HNC patients which could then be used to counsel these patients better in their choice of therapy. Thereby, adequate detection of risk factors of functional decline and the implementation of recommendation to address them could lead to interventions which may prevent or delay functional decline.[40] The sample size also limited the performance of a subgroup analyses by surgical procedures. Our population was treated with different surgical treatments. It is possible that the functionality may decline more in patients treated with major surgery. Using a larger study population should therefore be considered. When determining the size of the study population, the high mortality rates of HNC in elderly patients should be taken into account. In this study, 25 of the 126 patients (20%) died: seven patients were deceased within the first three months and 18 were deceased within 12 months after surgery. Another five patients were deceased more than a year after surgery but before they were approached for follow-up. On the other hand, despite the limited size of our sample we found a statistically significant decrease in the Katz-15 and in IADL scores.

Another limitation is the risk of selection bias. It is possible that the fittest patients participated in the follow-up by telephone, because the follow-up population was significantly younger than the non-follow-up population and had statistically significant less comorbidity according to the CCI, less IADL impairment, and less cognition impairment. This means that patients with cognitive disorders or with a terminal condition due to progressive disease were excluded from follow-up by telephone. As a result, the functional decline could be underestimated with this study. Third, objective physical performance measurements such as hand grip strength and gait speed could have given some additional information about functional status. In addition, to acquire more insight into the quality of life, a questionnaire that is more extensive than the EQ-VAS should be utilized.

In conclusion, a statistically significant decline in functional status was found in older patients with HNC one year after surgery indicating a higher level of dependency. The impact of surgical treatment on patient-centered outcomes such as functional

status and quality of life should be part of the discussion in counselling older patients in treatment-decision making.

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Chapter 6

Symptom burden of older patients with cancer during systemic therapy and its relationship with frailty: A prospective observational study

Under review

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Abstract

Introduction

Maintaining or improving HRQoL has an especially high priority with respect to older patients with cancer. Therefore, it is important to understand which patients are at risk for a high symptom burden. The primary aim of this study was to assess whether frailty, measured by the Geriatric 8 screening tool (G8), was associated with a high symptom burden (measured by the Utrecht Symptom Diary (USD)) in older patients before and during systemic cancer therapy. Second, we investigated other predictors for a high symptom burden in these patients.

Methods

This observational study used prospectively collected data of patients with cancer ≥ 70 years. We enrolled all patients treated with systemic anti-cancer treatment who completed the G8 and a USD before treatment and at least one USD prior to the second or last cycle of treatment.

Results

A total of 232 patients was included; 45% of them were classified as frail. Multivariate analysis showed that frailty was statistically significantly associated with a higher symptom burden (Incidence Rate Ratio (IRR) 1.546 (p = 0.032)). Female gender and a higher WHO performance status were also statistically significant predictors with an IRR 1.429 (p = 0.024) and IRR 1.372 (p = 0.047).

Conclusion

Frailty, measured by the G8, is associated with a higher symptom burden before and during systemic cancer treatment. Therefore, we recommend the systemic usage of both the G8 and a symptom diary in older cancer patients receiving systemic therapy because this may achieve a more appropriate individualization of treatment.

Introduction

Many patients with cancer have multiple symptoms caused by the disease and/or its treatment.[1] In more than half of the patients with incurable cancer, this symptom burden consists of fatigue, pain, lack of energy, weakness, and/or appetite loss.[1] It has been shown that a high symptom burden negatively affects health-related quality of life (HRQoL), functional status, and overall survival.[2–4] In order to adequately assess these symptoms, symptom diaries, also known as a Patient-Reported Outcome Measurements (PROMs), were introduced. Adequate symptom management by using PROMs is associated with a better survival, a better toleration of chemotherapy, and a better HRQoL.[5,6] The Utrecht Symptom Diary (USD) is such a PROM and has been implemented and validated in two studies.[7,8]

In general, the most frequent main goals of cancer care are improving overall survival and progression free survival and decreasing complication rates. However, maintaining or improving HRQoL and retaining independence are preferred as more relevant outcomes by older patients with cancer. Lack of inclusion of (frail) older patients and lack of information about symptom burden and its effects on HRQoL in clinical trials limits the applicability of clinical trial data for treatment decision-making in these patients.[9–11] Most studies on symptom burden focus on younger adults with cancer and the few older patients who were enrolled were predominantly those with a good performance status and little comorbidity. Although the effect of treatment on the symptom burden is an important consideration for all patients, it is particularly relevant for the older frail patient, where the impact of the treatment easily outweighs the benefits of the treatment.

To help guide treatment decision-making in older cancer patients, the International Society of Geriatric Oncology (SIOG) has recommended conducting some form of geriatric evaluation in the older patient with cancer to acquire insight into their frailty.[12,13] Insight into frailty is important because frail patients have shown to be at higher risk of increased mortality, postoperative complications, intolerance to cancer treatment, and a poorer HRQoL.[14–16] Since a geriatric evaluation is not feasible and necessary for every older patient with cancer, screening tools are used to distinguish 'frail' older patients who might benefit from a geriatric evaluation from 'fit' older patients who can tolerate standard cancer treatment without a need to perform a geriatric evaluation.[17] The Geriatric 8 (G8) screening tool is such a screening instrument developed especially for older patients with cancer.[18] An impaired G8 has been demonstrated to be predictive for a lower overall survival, more treatment-related toxicity, functional decline, and a lower HRQoL.[19,20]

Taking all of the above into account, it appears essential to pay attention to both the symptom burden and frailty and its effect on the HRQoL when making appropriate treatment decisions for older patients with cancer. However, studies assessing the impact of frailty on symptom burden during cancer treatment are rare.

Therefore, the main goal of this study was to assess whether frailty is associated with symptom burden, assessed by the USD, before and during systemic anti-cancer treatment of older patients. Our main hypothesis was that patients classified as frail, according to the G8, would experience a higher symptom burden than non-frail patients. Second, we assessed whether there were other predictors of a high symptom burden.

Methods

Study design and data collection

This observational study used prospectively collected data of patients with cancer ≥ 70 years treated with systemic anti-cancer treatment at the department of Medical Oncology, University Medical Center in Utrecht, between December 2014 and February 2020. We enrolled all patients who completed the G8 and a USD before treatment and at least one USD prior to the second or last cycle of treatment. In our clinic, both the G8 and the USD are used systematically in daily practice. This study was approved by the local medical ethical board.

Data on age, gender, WHO Performance Score (WHO PS), the primary tumor, and treatment characteristics were obtained from the medical records. Treatment characteristics included the type of systemic anti-cancer treatment and whether patients finished their treatment according to the treatment protocol. When their treatment deviated from the original plan, the reason for the dose modification or discontinuation was noted. Comorbidity was calculated using the Charlson Comorbidity Index (CCI) score.[21] Polypharmacy was defined as the use of ≥ 3 medications except for inhaled medication and medication prescribed as-needed.

G8 screening tool

Before starting systemic cancer therapy, the G8 screening tool was completed by the treating physician. The G8 consists of eight questions, including seven questions extracted from the 18-item mini-nutritional assessment (MNA) and an age-related item (<80, 80 to 85, or > 85 years) (Supplementary 1).[22] The total score ranges from 0 to 17 points. Patients with a score of >14 points are classified as 'fit', whereas patients with a score of ≤14 points are classified as 'frail'.[18] Since the studies assessing the G8 used ≥ 70 years as a cutoff point, we choose to select patients ≥ 70 years.

Utrecht Symptom Dairy

Patients completed a USD at baseline and prior to most cycles of systemic anti-cancer therapy in order to assess symptoms and start interventions to reduce symptom burden. The USD is a slightly altered and validated Dutch version of the extensively used and validated Edmonton Symptom Assessment System (ESAS).[8,23] It is a 12-item PROM which measures the patients' physical and psychological symptoms and includes pain, sleeping problems, dry mouth, dysphagia, lack of appetite, abnormal stool, nausea, shortness of breath, fatigue, anxiety, depressed mood, and unwell-being (Supplementary 2). Each item is scored from zero (no symptom burden at all) to ten (worst symptom burden). A symptom is considered to be clinically relevant when a symptom is rated as ≥ 3.[7,8] On the basis of clinical trials and expert consensus, disease and treatment-specific USD modules have been developed. As a result the module USD for patients receiving chemotherapy or targeted therapy differs slightly from the USD for patients treated with immunotherapy. Because the USD items 'dry mouth' and 'dysphagia' are not part of the USD Immunotherapy, these two items are excluded in the current analysis. The USD filled in prior to starting treatment was used as baseline. The USDs completed prior to the second and last cycle of treatment were used for this analysis. Symptom burden was determined as our primary outcome, which was defined as the number of USD items scored as ≥ 3 at each time point.

Statistical analysis

To compare baseline characteristics of the frail and non-frail group for categorical variables, the chi-square test was used. The Mann-Whitney *U* test or the independent samples median test was used for continuous baseline variables.

All items of the USD were dichotomized, using the cut-off point of ≥ 3 in conformity with the validation study and compared between the two groups (frail/non-frail) at the three time points (baseline, second and last cycle) using the chi-square test.

To determine which variables are associated with symptom burden, a univariate generalized linear model analysis with a negative binomial distribution was performed with correction for the number of USDs the patient filled in. All variables with a p-value < 0.10 were combined in a multivariate generalized linear model analysis with a negative binomial distribution. The outcome measure is an Incidence Rate Ratio (IRR), which can be interpreted as a relative difference measure used to compare the incidence rate in an exposed group divided by the incidence rate in a comparison group. All variables with a *p*-value < 0.05 in the multivariate analysis were considered a significant predictor.

Lastly, the course of the symptom burden was analyzed. The means of the outcome (number of USD items with a score of ≥3) at the three measuring points were plotted

in a line graph for both groups. A Wilcoxon signed rank test was performed to assess differences in the course of symptom burden (between baseline and second cycle; between baseline and last cycle; and between second cycle and last cycle) for both groups.

All analyses were performed using Statistical Package for the Social Sciences (SPSS), version 25.

Results

Baseline characteristics

A total of 232 patients were included. Baseline characteristics are presented in Table 1. The median age of the population was 74.0 (range 70-89 years). Half of the patients were female. The most common tumor types were gastroenterological or gynecological in origin (respectively 31% and 16%) or were melanomas (25%). Most of the patients were treated with a palliative intent (66%). In 73%, the systemic anti-cancer treatment consisted of chemotherapy. Only one patient was treated with targeted therapy. Forty percent of the patients finished the treatment according to the treatment plan.

Table 1: Baseline characteristics

	Total (%) (n=232)	**Non-frail (%) (n=127)**	**Frail (%) (n=105)**	***p*-value**
Age [mean ± SD]	74.6 ± 3.9	74.4 ± 3.4	74.9 ± 4.5	0.93
Age category				
70-74	122 (53)	64 (50)	58 (55)	0.46
75-79	84 (36)	53 (42)	31 (30)	0.05
80-84	18 (8)	9 (7)	9 (9)	0.67
>84	8 (3)	1 (1)	7 (7)	*0.02*
Female	116 (50)	62 (49)	54 (51)	0.69
Polypharmacy (≥3 medicines)	119 (52)	48 (38)	71 (68)	*< 0.001*
CCI score [Median ± SD]	9.00± 2.0	9.00± 1.9	9.00± 2.0	*0.005*
WHO PS				
0	48 (23)	37 (33)	11 (11)	*< 0.001*
1	136 (65)	66 (58)	70 (71)	*0.05*
2	25 (12)	10 (9)	15 (15)	0.15
3	2 (1)	0 (0)	2 (2)	0.13
Stage				
Curative stage	78 (34)	35 (28)	43 (41)	*0.03*
Palliative stage	154 (66)	92 (72)	62 (59)	*0.03*
Tumor category				
Gastroenterological	72 (31)	20 (16)	52 (50)	*< 0.001*
Gynaecological	36 (16)	20 (16)	16 (15)	0.91

Table 1: Baseline characteristics *Continued*

	Total (%) (n=232)	**Non-frail (%) (n=127)**	**Frail (%) (n=105)**	***p*-value**
Urogenital	18 (8)	14 (11)	4 (4)	*0.04*
Head & Neck	6 (3)	2 (2)	4 (4)	0.29
Melanoma	57 (25)	36 (28)	21 (20)	0.14
Brain	24 (10)	19 (15)	5 (5)	*0.01*
Breast	14 (6)	12 (9)	2 (2)	*0.02*
Other	5 (2)	4 (3)	1 (1)	0.25
Treatment				
Chemotherapy or chemoradiation	169 (73)	87 (69)	82 (78)	0.10
Immunotherapy	62 (27)	39 (31)	23 (22)	0.13
Targeted therapy	1 (0.4)	1 (1)	0 (0)	0.36

Standard deviation (SD); Charlson Comorbidity Index (CCI); World Health Organization Performance status (WHO PS)

In total, 127 (55%) patients were classified by the G8 as non-frail and 105 (45%) patients were classified as frail. Frail patients were significantly more likely to use ≥ 3 medicines ($p < 0.01$), to have more comorbidities ($p = 0.005$), a higher WHO performance score ($p = 0.05$,) and a gastroenterological malignancy ($p < 0.01$). Additionally, the frail group consisted of significantly more patients in a curative stage ($p = 0.03$).

192 patients (83%) completed a USD at baseline, whereas 153 (66%) and 118 (51%) patients filled in a USD before the second and before the last cycle of systemic therapy, respectively, as shown in Table 2. In total, 36 patients of the 93 patients on treatment (39%) completed all three USDs. There were no significant differences between non-frail and frail patients with respect to completion of USDs at any time point.

Table 2: Number of completed USDs at the different measuring moments

	Total (%) n=232	**Non-frail (%) n=127**	**Frail (%) n=105**	***p*-value**
USD at baseline	192 (83)	106 (83)	86 (82)	0.75
USD before second cycle	153 (66)	89 (70)	64 (61)	0.14
USD before last cycle	118 (51)	68 (54)	50 (48)	0.37
All three USDs	71 (31)	44 (35)	27 (26)	0.14
USD at baseline AND before second cycle	120 (52)	73 (57)	47 (45)	*0.05*
USD at baseline AND before last cycle	95 (41)	55 (43)	40 (38)	0.42
USD before second AND last cycle	87 (38)	52 (41)	35 (33)	0.23

Utrecht Symptom Diary (USD)

Table 3: Outcome of USDs and treatment outcomes

Variable	Total (%) n=232	Non-frail (%) n=127	Frail (%) n=105	*p*-value
USD outcomes				
USD items scored ≥ 3 at baseline [Mean ± SD]	2.64 ± 2.58	2.00 ± 2.31	3.41 ± 2.67	*< 0.001*
USD items scored ≥ 3 before second cycle [Mean ± SD]	2.68 ± 2.46	2.19 ± 2.38	3.33 ± 2.43	*< 0.001*
USD items scored ≥ 3 before last cycle [Mean ± SD]	2.75 ± 2.51	2.31 ± 2.51	3.29 ± 2.41	*< 0.001*
Treatment outcomes				
Modification of treatment in second cycle	44 (19)	21 (17)	23 (22)	0.30
Finished therapy according to treatment plan				
Yes	93 (40)	56 (44)	37 (35)	0.17
No, side effects	75 (32)	36 (28)	39 (37)	0.15
No, progression	43 (19)	25 (20)	18 (17)	0.62
No, side effects and progression	10 (4)	4 (3)	6 (6)	0.34
Therapy ongoing	11 (5)	6 (5)	5 (5)	0.99

Utrecht Symptom Diary (USD); Standard Deviation (SD)

Table 4: Items of the USD scored ≥ 3

	Baseline					Before second cycle					Before last cycle				
Symptom	**Total n = 192 (%)**	**Non-frail n = 106 (%)**	**Frail n= 86 (%)**	***p*-value**	**Missing (%)**	**Total n = 153 (%)**	**Non-frail n = 89 (%)**	**Frail n = 64 (%)**	***p*-value**	**Missing (%)**	**Total n = 118 (%)**	**Non-frail n = 68 (%)**	**Frail n = 50 (%)**	***p*-value**	**Missing (%)**
Pain	55 (29)	27 (26)	28 (33)	0.28	0 (0)	41 (27)	19 (21)	22 (35)	0.06	1 (1)	29 (25)	16 (24)	13 (27)	0.71	4 (3)
Sleeping problems	65 (34)	36 (34)	29 (34)	0.97	0 (0)	37 (25)	20 (23)	17 (28)	0.48	4 (3)	30 (26)	15 (23)	15 (31)	0.37	4 (3)
Lack of appetite	64 (34)	20 (19)	44 (52)	*< 0.001*	2 (1)	51 (34)	21 (24)	30 (48)	*0.002*	3 (2)	46 (40)	22 (33)	24 (50)	0.07	4 (3)
Abnormal stool	50 (26)	19 (18)	31 (37)	*0.003*	2 (1)	49 (33)	25 (28)	24 (39)	0.16	4 (3)	40 (35)	20 (30)	20 (41)	0.22	2 (2)
Nausea	15 (8)	4 (4)	11 (13)	*0.02*	1 (1)	26 (17)	8 (9)	18 (29)	*0.001*	3 (2)	20 (18)	8 (12)	12 (25)	0.09	4 (3)
Shortness of breath	19 (10)	8 (8)	11 (13)	0.24	1 (1)	16 (11)	9 (10)	7 (11)	0.86	2 (1)	13 (12)	6 (10)	7 (14)	0.46	5 (4)
Fatigue	81 (42)	34 (32)	47 (55)	*0.002*	1 (1)	85 (56)	43 (49)	42 (67)	*0.03*	2 (1)	62 (54)	26 (40)	36 (72)	*0.001*	3 (3)
Anxiety	46 (24)	21 (20)	25 (29)	0.15	1 (1)	19 (13)	12 (14)	7 (11)	0.66	1 (1)	11 (10)	8 (12)	3 (6)	0.30	6 (5)
Depressed mood	36 (19)	12 (12)	24 (28)	*0.005*	3 (2)	21 (14)	10 (12)	11 (18)	0.30	3 (2)	17 (15)	8 (13)	9 (19)	0.36	6 (5)
Unwell- being	78 (46)	31 (35)	47 (57)	*0.003*	21 (11)	62 (46)	28 (35)	34 (61)	*0.003*	17 (11)	56 (54)	28 (47)	28 (64)	0.09	14 (12)

USD items

As shown in Table 3, frail patients have statistically significantly more items with USD-score ≥ 3 at all measuring points: mean 3.41 versus 2.00 (p <0.001) at baseline, 3.33 versus 2.19 (p= 0.001) before the second cycle, and 3.29 versus 2.31 (p= 0.01) before the last cycle. If we look at the items of the USD, we notice that, at baseline in the frail group, statistically significantly more patients scored ≥ 3 on the items 'lack of appetite' (p <0.01), 'abnormal stool' (p < 0.01), 'nausea' (p 0.02), 'fatigue' (p = 0.02), 'depressed mood' (p < 0.01) and 'unwell-being' (p < 0.01) (Table 4). Before the second cycle of systemic anti-cancer therapy, frail patients were significantly more likely to score ≥3 on the items 'lack of appetite' (p < 0.01), 'nausea' (p < 0.01), 'fatigue' (p = 0.03) and 'unwell-being' (p < 0.01). Before the last cycle of treatment, frail patients were only significantly more likely to have a USD-score ≥3 for fatigue (p < 0.01). The item 'un-well-being' was the most frequently missing item at the three measuring points (11%, 11% and 12%, respectively).

Treatment outcomes

Forty percent of the patients finished the treatment according to the treatment plan (Table 3). There were no differences between the frail and the non-frail patients in the number of patients who finished their treatment according to the treatment plan or the number of patients who had to discontinue treatment because of toxicity.

Predictors of symptom burden

Multivariate analysis (Table 5) showed that frailty according to the G8 (IRR 1.338 (95% CI 1.025-1.748), p = 0.03), female gender (IRR 1.382 (1.044-1.830), p = 0.02), and WHO performance status (IRR 1.259 (1.003-1.580), p = 0.05) were statistically significant predictors for a higher symptom burden.

Symptom burden over time

When compared to the frail group, the non-frail group showed a relatively low symptom burden at baseline, increasing statistically significantly over time (Figure 1). The baseline symptom burden of the frail group was much higher but had a statistically non-significant decrease over time. The number of USD items scored ≥ 3 remained higher compared to the non-frail group.

Table 5: Predictors of a higher symptom burden: results of the univariate and multivariate generalized linear model analysis

	Univariate		Multivariate	
Variable	***p*-value**	**IRR (95% CI)**	***p*-value**	**IRR (95% CI)**
G8<14 (frail)	*0.001*	1.546 (1.203-1.985)	*0.032*	1.338 (1.025-1.748)
Age at diagnosis	0.740	1.006 (0.973-1.039)		
Female	*0.006*	1.429 (1.110-1.839)	*0.024*	1.382 (1.044-1.830)
CCI score	0.039	1.075 (1.004-1.152)	0.205	1.054 (0.972-1.144)
WHO performance status	*0.008*	1.372 (1.086-1.734)	*0.047*	1.259 (1.003-1.580)
Palliative	0.776	1.040 (0.793-1.365)		
Tumor category:				
Gastroenterologic	0.140	1.235 (0.933-1.634)		
Gynaecologic	*0.007*	1.584 (1.131-2.217)	0.304	1.238 (0.824-1.859)
Urologic	0.286	0.768 (0.473-1.247)		
Head & neck	0.366	1.441 (0.653-3.177)		
Melanoma	*0.013*	0.685 (0.507-0.924)	0.096	0.492 (0.213-1.134)
Brain	*0.092*	0.668 (0.418-1.068)	0.453	0.811 (0.469-1.402)
Mamma	0.264	0.731 (0.422-1.266)		
Other	0.936	0.965 (0.407-2.289)		
Immunotherapy	*0.027*	0.719 (0.536-0.964)	0.407	0.448 (0.067-2.998)
Chemotherapy/chemoradiation	*0.049*	1.339 (1.001-1.791)	0.223	0.338 (0.059-1.932)
Targeted therapy	0.339	2.514 (0.380-16.647)		

Charlson Comorbidity Index (CCI); Confidence Interval (CI); Geriatric 8 (G8), Incidence Rate Ratio (IRR), World Health Organization Performance status (WHO PS)

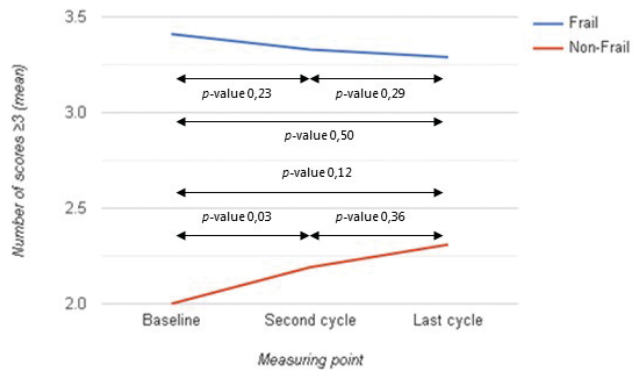

Figure 1: Trajectory of items of USD scored ≥ 3 for the non-frail and the frail group

Discussion

The primary aim of our study was to assess whether frailty was associated with symptom burden before and during systemic anti-cancer treatment in patients ≥ 70 years. We demonstrated that frailty, according to the G8, was associated with a higher symptom burden measured by the USD both before and during treatment. Because of the clear association between a high symptom burden and a low HRQoL,[3,4,24,25] we may assume that frailty is predictive for a poorer HRQoL, although we did not use specific HRQoL questionnaires to measure this.

This result is of great importance, because this finding may guide clinicians to inform older patients about their symptom burden during systemic anti-cancer therapy, based on assessment of frailty using the G8. Symptom burden should be an important topic to discuss with patients when making appropriate treatment decisions because older patients attach more value to HRQoL than to overall survival.[26,27] In addition, having insight into the degree of symptom burden may lead to better symptom management and thus improvement of HRQoL and maintaining functioning as shown in previous research.[5,6]

We found only one other study that assessed the association between frailty and symptom burden in patients with cancer.[28] This study supports our finding that frail patients had a significantly higher symptom burden at baseline and during and after systemic anti-cancer treatment. However, this study differed in the measurement of frailty and in the choice of symptom diary. They defined frailty according to the Baldacci classification. Symptom burden was investigated by the European Organization for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (QLQ-C30). Our study shows that frailty assessed by a geriatric screening tool is also related to a higher

symptom burden. This offers unique information, because the G8 is easy to use in daily practice – not only for selecting older patients who require a comprehensive geriatric assessment, but also for decision-making. In the non-oncological setting, a significant association between frailty and a higher symptom burden was also demonstrated.[29–31]

Although the association between frailty and symptom burden has rarely been studied, the association between frailty and HRQoL has been well researched. All studies showed that frail patients reported their HRQoL as low compared to the non-frail patients both at baseline and during anti-cancer treatment.[15,16,32] Frailty was defined using both the G8 and a geriatric assessment.

Our study showed that, in addition to frailty, female gender and a higher WHO Performance were important independent predictors for a higher symptom burden before and during treatment. These results are in line with other studies assessing the relation between symptom burden and these demographic characteristics, with the exception that most studies also showed that co-morbidity was an important predictor.[28,33–37] In our study, the median CCI score was significantly higher in the frail group and a significant predictor in the univariate analysis. However, when adjusted for confounders in the multivariate analysis, this was not significantly related to symptom burden. Regarding gender, more symptom burden in women has been observed in some studies, but results are inconsistent.[33,36] It is suggested that women differ from men in pain sensitivity and in pain relief, but it is unclear whether women are more likely to report symptoms and/or less likely to receive adequate symptom treatment or whether there is a biologic explanation.[38]

As well, women had consistently worse symptom scores than men. Worse outcomes in women have been observed in some studies,[3,42] but results are inconsistent.[43] A recent review suggests that females have greater pain sensitivity and may have different treatment responses, although the mechanisms are unclear.[44] This research area requires further investigation to determine
whether women are more likely to report symptoms, less likely to receive adequate symptom treatment, or whether there is a biologic basis for worse outcomes

With respect to the course of the symptom burden, we found that the symptom burden of the non-frail group increased over time. The baseline symptom burden of the frail group was higher but, in contrast to the non-frail group, decreased slightly over time (non-significantly). This difference in the course of symptom burden between the non-frail and frail group is striking and could possibly be partially explained by the fact that the frail group suffers more from tumor-related complaints at baseline that may disappear because of the anti-cancer treatment and also from non-tumor related complaints. Previous studies regarding the course of symptoms during treatment in patients with cancer have shown heterogeneous results. In a study evaluating the

trajectory of symptom burden in older (> 65 years old) patients with head and neck cancer undergoing curative radio(chemo)therapy, symptoms increased in both the frail and non-frail group.[15] The severity of symptoms in frail patients was higher prior to therapy, compared to the non-frail patients, which is consistent with our results. Other studies on patients with cancer in general found an overall decrease of symptoms over time.[35,39] However, inter-study comparison is difficult, because these studies varied in type of cancer, disease stage, and treatment. All these factors may influence symptom burden because symptom burden can be seen as a net effect of both an increase in symptoms due to toxicity of the (systemic) anti-cancer treatment and a decrease in tumor-related symptoms because of response of the (systemic) anti-cancer treatment. The latter effect was specifically described in older patients treated with surgery for colorectal cancer.[16]

Our study shows that frail patients experienced lack of appetite, abnormal stool, nausea, fatigue, depressed mood, and unwell-being significantly more frequently at baseline compared to non-frail patients. Of these symptoms, severe fatigue was the most prevalent and severe nausea the least prevalent symptom, which is in line with previous studies.[28,33,37,39] The fact that frail patients experience lack of appetite, abnormal stool, and nausea more often at baseline could be partly explained by the fact that frail patients suffered from a tumor in the gastroenterological tract significantly more often than non-frail patients.

Our study has several strengths. As noted before, the topic of this study is of great importance since, for older patients, symptom burden and quality of life are more important than overall or progression free survival.[26,27] Second, a large number of patients was included in the current analysis. Finally, in our main analysis we adjusted for potentially influencing factors.

Some limitations must be considered. First, selection bias could play a role since we only enrolled those patients who completed the G8 and a USD. This may have introduced selection bias. Second, a fairly high number of USDs was missing. These missing diaries were partly attributable to the fact that patients were not offered a symptom diary before every cycle of treatment or that patients themselves chose not to complete the USD every time. Frailty seems not to play a role whether a patient fills in the USD or not. This missing data may also have induced selection bias. However, the analyses regarding our main goal (assessing whether frailty and symptom burden were related) were not affected by the number of missing USDs since we corrected for the number of completed USDs. As most of our data was non-normally distributed, we were limited in our choice for statistical tests, although this did not affect our main analysis. In addition, our population consisted of different types of tumors and consequently different types of treatments, which limits inter-study comparison. On the other hand, this heterogeneous population reflects the heterogeneous population we treat in our daily clinic. Next, this study is a single-center study, consisting of data collected in a tertiary center, which could make it more difficult to apply our results to hospital populations in general. Lastly, it is important to mention that the screening tools like the G8 were not originally designed to replace the GA in diagnosing frailty.

In conclusion, frailty measured by the G8 is a predictor for higher symptom burden in elderly patients with cancer before and during systemic cancer therapy, but frailty does not lead to an increase in symptom burden during treatment Therefore, we recommend the systemic usage of both the G8 and a symptom diary in clinical practice because this can result in achieving a more appropriate individualization of treatment.

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Part IV

General discussion and summary

Chapter 7

General discussion

Discussion

The primary aim of this thesis was to address the research questions which arisen while we were implementing frailty screening by the Geriatric 8 (G8) followed by a Geriatric Assessment (GA) if required in patients aged ≥ 70 years in our daily clinical practice conform the recommendation of the International Society of the Geriatric Oncology (SIOG).[1–4]. Our most important conclusion is that screening of frailty by the G8 is of added value in the shared-decision making process in older patients with cancer, because completing a G8 addressed two important aspects in the treatment decision making in older patients with cancer. First, identifying those patients who are at risk for complications of an anti-tumor treatment so treatment can be tailored to the ability of patients to tolerate this treatment. Second, providing information about the impact of anti-tumor treatment on patient-related outcomes (PROs) which is of added value to progression free survival (PFS) and survival data, so that the patient can take the PROs into account when shared-decisions about his treatment are made.

Our research was focused on prospectively obtained real world data and therefore our results can directly be applied in daily consultation when facing an older patient with cancer.

Identifying factors that affect treatment outcomes

Geriatric assessment

Since chronological age has been a poor descriptor of biological age, there is a need for a systematic way of describing the heterogeneity of the older patient to help guide treatment decisions, because decrease in physiological reserves and co-existing problems, such as physical and cognitive impairments and comorbidities, varies considerably between individuals.[5,6] The clinical judgment of the treating physician is not accurate enough to fill this knowledge gap.[7–9] Therefore, a GA in the work-up for all older patients with cancer is increasingly implemented in daily practice. However, there is no consensus regarding which domains should be included in the GA for patients with cancer resulting in various compositions of the GA making inter-study comparison difficult.

Our systemic review described in Chapter 2 shows that the domain physical function was consistently predictive for mortality, postoperative complications, and chemotherapy-related outcomes. This finding is confirmed by other recently published reviews and meta-analyses.[10,11] Notable, physical function outcomes prior to an anti-cancer treatment reflect the physical fitness with cancer unaffected by the cancer treatment. As a result, it could be essential for a treating physician to be informed about the patient's physical function independent of the performance of a complete GA. However,

at this moment it is not clear which test is recommended for practical use, because the assessment tools and the cut-off points vary widely in studies assessing the predictive value of physical function in older patients with cancer.[10,11] The Time-Up and Go Test (TUG) is a promising tool, because it seems to be to most predictive test for treatment outcomes. Thereby, it is a simple tool and can be easily performed to assess a person's mobility and evaluates both status and dynamic balance.[12]

Since an impaired physical function may have negatively affected anti-tumor treatment outcomes, increasing the physiological reserve by prehabilitation and its effect on treatment outcomes is an interesting focus for further research. Patient engagement and the fact that time for prehabilitation is short, because an anti-tumor treatment has to start rapidly, have been shown as major obstacles to implement prehabilitation programs.[13]

Also the GA-domain nutritional status was consistently predictive for treatment outcomes in Chapter 2. Approximately 70% of patients with cancer develop malnutrition and the prevalence is higher and more severe among older patients.[14] Since malnutrition has negative consequences on treatment outcomes, nutritional care should play a central role in the whole management of the cancer patient independent of age. Despite the knowledge that an early intervention could influence treatment outcomes, a significant number of malnourished patients still remains undetected and only half of them receives an appropriate intervention.[15–18] Thus, patients' nutritional risk should be assessed early and monitored during the whole treatment course in order to improve tolerance, ameliorate health-related quality of life (HRQoL), and achieve better clinical outcomes.[19]

The fact that the GA-domains physical function and nutritional status were most predictive for mortality, postoperative complications, and chemotherapy related outcomes, does not mean that we advise to include only these two domains in a GA and that assessing other domains is redundant. In this systemic review, we focused on the predictive value of every domain. However, predicting treatment outcomes is not the main reason to refer a patient for a GA. In our opinion, a broad GA is needed to identify all present impairments, serving as a base for a geriatric treatment plan including GA-based interventions as well as for geriatric follow-up with the aim to improve treatment outcomes.

In the non-oncological setting, it is shown that GA-based interventions can reduce mortality, hospitalizations, and functional decline. But what are the benefits of GA-based interventions on cancer-specific outcomes? Recently, three large randomized controlled trials (RCTs) reported that GA-based interventions reduce chemotherapy toxicity without compromising treatment efficacy.[20–22] Based on this results, we have to conclude that we should not only focus on the implementation of a GA in our daily

clinical practice, but also on the implementation of the recommendations as part of a GA. In abovementioned studies, a broad GA was performed in all older patients treated with chemotherapy regardless of a screening tool such as the G8. This could be a defense to refer every patient for a broad GA and to abandon frailty screening. However, another study only enrolled patients with an impaired G8 for a GA and also concluded that GA-based interventions lead to more treatment completions in patients with colorectal cancer.[23] This may suggest that it is feasible to continue frailty screening.

Whereas our research questions did not focus on the results of the GA and the GA-based recommendations, most of our patients with an impaired G8 are referred for a GA. Because of the relevance of the implementation of interventions based on the GA, further research should focus on following the advices of a geriatrician and its impact on all clinical outcomes, not only on treatment tolerance, but also on patient-related outcomes (PROs) such as HRQoL and maintenance of independency.

Geriatric 8

Although a GA provides insights into someone's frailty and some geriatric domains of the GA can be useful for predicting negative treatment outcomes, performing a GA in every older patient with cancer is unnecessary. The G8 is a good screening tool to distinguish the frail patient in need of a GA from the fit patients who does not.[3,24] The G8's discriminative power in determining geriatric impairments has mostly been investigated in older patients with cancer considered for chemotherapeutic treatment. Also for the older patient with cancer requiring surgical treatment, the G8 has shown to be a useful screening tool (Chapter 3). Based on our findings, not every older patients with cancer requiring surgical treatment should be referred to the geriatrician for a pre-operative GA. For selecting the patients who benefit of a GA pre-operatively, the G8 can be used.

The G8 is originally designed to identify those potentially frail older patients who may benefit from a GA, although the association of the G8 with clinical outcomes such as treatment complications, physical functioning after treatment, and survival has increasingly been studied.[25] A systematic review reported that almost two-thirds of the studies that assessed the association of the G8 with survival and 43% of the studies on treatment-related complications found that impaired G8 scores (≤ 14) were associated with poorer outcomes.[25] In this thesis, we focused on the association between an impaired G8 and postoperative recovery, the occurrence of immune-related adverse events (irAEs) due to immune check point inhibitors (ICI), and the association with symptom burden before and during systemic anti-tumor treatment.

First, we found no difference in the occurrence of postoperative complications within 30 days of surgery between patients with a normal and with an impaired G8

(Chapter 3). Although, in the patients with an impaired G8 the occurrence of delirium, the median postoperative hospital stay, and the 1-year mortality had higher statistically significance than in patients with a normal G8. These results may suggest that frail patients according to the G8 are not at risk for more surgical complications by itself, but that these patients seem to be more at risk for a complicated postoperative recovery leading to a higher rate of delirium and discharge to a rehabilitation unit, a prolonged hospital stay, and a higher 1-year mortality. In line with this, our study assessing the association between the G8 and the occurrence of immune-related adverse events (irAEs) (Chapter 4) has a comparable conclusion: melanoma patients with an impaired G8 are not at risk for an higher occurrence of grade ≥ 3 irAEs, but they do have a higher risk to experience irAE-related sequelae such as hospitalizations. Chapter 6 shows that an impaired G8 is associated with a higher symptom burden both before and during treatment. Frail patients according to the G8 experienced statistically significantly more lack of appetite, abnormal stool, nausea, fatigue, depressed mood, and unwell being before start of a systemic anti-tumor treatment. On the other hand, there were no differences between the fit and the frail patients in treatment completions or in treatment discontinuations because of toxicity.

The abovementioned findings are of added value to the existing knowledge. The results of our studies fulfill several gaps of knowledge and confirm that the G8 is easy to use in daily practice – not only for selecting older patients who require a GA, but also to guide shared-decision-making. Until now, it was unknown whether the G8 was associated with the occurrence of irAEs in melanoma patients. Also the association between symptom burden and the G8 in patients treated with systemic anti-tumor treatment has never been evaluated before. In addition, our conclusions could directly be applied in our daily consultation when facing an older patient with cancer. In all three studies, we prospectively enrolled patients of our daily clinical practice without exclusion criteria. So, our study results were based on real life data and therefore our study populations reflect the older patients we face in our daily clinical practice. The G8 can be seen as an additional tool in counseling our patients for a specific anti-tumor treatment.

In conclusion, a G8 should be routinely performed before treatments options are discussed with an older patient with cancer. An impaired G8 (≤ 14) indicates that this patient is at risk for frailty and consequently at risk for negative treatment outcomes and both aspects should be discussed with our patient. Additionally, the patient could be referred for a GA. The GA makes clear whether this patient is frail indeed and which factors – in other words which GA-domains- contribute to his frailty. Based on the impaired GA-domains, interventions are recommended if required according to the geriatrician judgement which benefits treatment outcomes.

However, the implementation of frailty screening followed by a GA, and GA-based interventions is still a challenge. Conducting a G8 can be seen as a part of the routine that has to tick off without paying attention to the value of the actual G8-score. The treating physician may be mainly focused at the oncological treatment, so he can lose sight of the impact of an impaired G8-score and the benefits of GA-based interventions. Not only the treating physicians have to be aware of the importance of frailty screening, also the patients have to be informed about the profits of a GA if required according to the G8. Some patients refuse a referral for a GA with the reason they are too busy with oncological appointments and treatments, too exhausted for extra consultations, or they classified themselves as fit and think a GA has no additional value for them.[26]

For that reason, in addition to improving research, current education can also be developed further. By increasing awareness of the differences in care between fit and frail patients and the importance of a GA if required according to the frailty screening, we can improve quality of care delivered to the frail older patient.

Providing information about the impact of anti-tumor treatment on patient-related outcomes (PROs)

It is known that older patients are willing to accept a poorer oncological outcome or shorter remaining life-expectancy if this would increase the likelihood of maintaining independence or HRQoL.[27–29] In the same way, patients who experienced more side-effects from an anti-tumor treatment are those patients regretting their treatment decision more often.[30] In addition, most patients with cancer found the presence or absence of specific symptoms less relevant than the impact of those symptoms on their physical or social functioning.[31] When consulted about research priorities, patients with cancer rated the impact of cancer on life and how to cope with the after-effects as by far the most important subject for future research.[32] Against this background, information on the impact that an anti-tumor treatment will have on functioning and quality of life (also known as patient-related outcomes (PROs)) should play an important role in treatment decision making. However, information about PROs is still underrepresented in clinical trials. Clinical trials mainly focus on disease- and treatment related outcomes such as progressive free survival, overall survival, and toxicity rates. This highlights the importance of studies assessing PROs.

In this thesis, we have acquired insight into the impact of several anti-tumor treatments on PROs. First, we showed that surgery in older patients with head and neck cancer (HNC) results in a significant decline in functional status one year after surgical treatment (Chapter 5). This decline in functional status may represent a substantially clinically relevant impact on an individual's functional dependency, because it indicates

that this patient will need assistance from a family member, care giver, or long-term care services. These patients mainly need assistance in housekeeping, travelling, shopping, and mobility. In contrast to the functional status, the self-reported health status of HNC patients did not decline one year postoperatively. In fact, the self-reported health status might even be improved possibly by the fact that postoperatively the fear and the insecurity about their diagnosis and treatment had been resolved. This unique prospective study makes that we could now inform our patients better about the fact that a surgical procedure for HNC may lead to a decline in functional status. In addition, we can also reassure our patients, it does not influence their self-reported health status negatively. We do not think that this information will lead to more refusals of the surgical treatment for HNC, because HNC is obviously a lethal disease when left untreated and surgery is a proper course of action not only to achieve oncological cure, but also to minimize the functional, cosmetic, and psychosocial impact of the disease.[33] Nevertheless, we think it will lead to more well-considered decisions and possibly to less intensive surgery. Additionally, we think there is a role for rehabilitation.[34,35] Interdisciplinary cancer rehabilitation is not a new concept, however, the literature is mainly limited to descriptions of programs, with little documentation of their effects on patient outcomes.[36,37] In patients with HNC, it is shown that individual aspects of cancer rehabilitation, such as nutrition, exercise, and psychosocial support can improve quality of life.[38–40] Because these studies were generally small in sample sizes and hampered by study design, the positive findings of rehabilitation warrant confirmation through properly designed controlled trials.

In Chapter 6, we gave insight in the symptom burden of patients treated with systemic anti-cancer treatment and assessed the association between a high symptom burden and an impaired G8. We demonstrated that an impaired G8 was associated with a higher symptom burden both before and during treatment. With respect to the course of the symptom burden, we found that the symptom burden of the group with a normal G8 increased over time. The baseline symptom burden of the group with an impaired G8 was higher but, in contrast to the other group, decreased slightly over time (non-significantly). This finding may guide treating physicians to inform older patients about their symptom burden during systemic anti-cancer therapy, based on assessment of frailty using the G8. Because of the clear association between a high symptom burden and a low HRQoL[42–45], symptom burden should be an important topic to discuss with patients when making appropriate treatment decisions since older patients attach a great value to HRQoL.[28,41] In addition, having insight into the degree of symptom burden may lead to better symptom management and thus improvement of HRQoL and maintaining functioning as shown in previous research.[46,47]

Both Chapter 5 as Chapter 6 offer unique information. We were the first who prospectively assessed the functional status and HRQoL by using the self-reported health status in older HNC patients one year after surgery in a Western population. In addition, we were also the first assessing the association between frailty according to a screening tool and symptom burden in patients with cancer. Of course, the effect of an anti-tumor treatment on the functional status, self-reported health status, and symptom burden is an important consideration for all patients irrespective their age. However, it is particularly relevant for the older (frail) patient, where the impact of the treatment easily outweighs the benefits of the treatment.

To summarize, discussing the impact on PROs such as functioning, quality of life, and after effects of an anti-tumor treatment should be an essential part in the conservation with the older patients with cancer when treatment decisions were made. This does not mean that discussing the treatment options and the prognosis is not important. On the contrary, patients ranked information about the prognosis and the chance of cure as the most important topics, although there were significant differences in how certain information topics were ranked across studies.[48] Apparently, there is no one-size-fits-all when it comes to information provision. Thus, information has to be tailored to the patient's individual needs, which will require an ongoing dialogue between treating physicians and the patient to identify which information categories have the highest priority at any given time.[49]

Conclusion

Achieving an appropriate individualization of treatment in older patients with cancer remains complex and challenging. In ~~these~~ thesis, we have addressed important aspects of this problem. We have contributed to our knowledge on the added value of frailty screening in our clinical practice. The G8 provides a risk assessment for treatment outcomes. In addition, we have provided information about the impact of anti-cancer treatment on two kind of PROs, namely functional decline and symptom burden. Both the outcome of frailty screening as the impact of a treatment on PROs should be a topic in the conservation with your patient and could guide the shared-decision making process.

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Chapter 8

Summary in English

Summary in English

Today more than half of patients newly diagnosed with cancer are ≥ 70 years. The coming years, the number of older patients with cancer will substantially increase as a result of life expectancy, population aging, and steady increase of cancer incidence with advancing age. Although the older patient with cancer involves the majority of patients we face in our daily clinic, it is still unclear whether the same treatment in older patients have the same outcome as in younger patients. One reason is the fact that the older patient is underrepresented in clinical trials and the few older patients enrolled in cancer trials, typically have fewer functional impairments or comorbid conditions than the average older patient treated in clinical practice. Second, older patients often have other chronic health conditions in addition to cancer, which can further complicate life expectancy estimation, affect treatment tolerability, and modify treatment efficacy. Thereby, the heterogeneity of the older population for instance with regard to co-morbidity, physiological reserves, and geriatric conditions further complicates treatment decisions. Last, treatment goals of the elderly may also differ from younger patients, since multiple studies have shown that older patients are in general less willing to undertake treatment for life extension at the cost of considerable toxicity, especially when this treatment negatively influences their quality of life or functional status.

So, the older population with cancer is a very heterogeneous population. This means that one older patient is fit and can tolerate standard cancer treatment with or without modifications, while the other patient is frail, which means that he cannot tolerate standard cancer treatment and needs a less intensive treatment option or that we should decide not to treat him at all. But how can we differentiate the fit from the frail patient? It is known that a cancer specialist can easily miss someone's frailty. For that reason, the International Society of Geriatric Oncology (SIOG) has recommended to implement some form of geriatric assessment (GA) in the standard care for older patients with cancer. A GA is a multidisciplinary, multidimensional, and systematic assessment, and consists of validated scales to identify impairment in somatic, functional, and psychosocial domains with the aim to provide insight into someone's frailty and to construct a multidisciplinary treatment plan.

However, conducting a GA is not always necessary for the fit older patient with cancer. Therefore screening tools are used to distinguish the 'frail' older patient from the 'fit' older patient who can tolerate standard cancer treatment without a need to perform a GA. Nowadays, multiple different screening tools have been studied with the aim to select the older patients in need of a GA. The Geriatric 8 (G8) screening tool is such a screenings instrument especially developed for the older patients (≥ 70 years)

with cancer. The G8 is an eight-item questionnaire. The total score ranges from 0 to 17. A score of ≤ 14 was considered to be abnormal, indicating a need for a GA. As a result, in geriatric oncology, the G8 is the most frequently used frailty screening tool in the so-called two-step approach: a geriatric screening tool followed by a GA if the screening tool has an impaired score.

In the treatment of older patients with cancer, it is not only important to identify frailty. Also having insight in the impact of an anti-cancer treatment on patient-related outcomes (PROs) is very important, since maintaining or improving quality of life (QoL) and retaining independence have been preferred as more relevant outcomes than prolonged survival by older patients with cancer. PROs cover a range of health outcomes such as symptoms, functional limitations, and QoL. These are generally measured with questionnaires that collect information directly from the patient. In our hospital, the Utrecht Symptom Diary (USD) is used to routinely assess and monitor symptoms.
The research described in this thesis focused on two important research questions, which arisen while we were implementing frailty screening by the G8 in our daily clinical practice. First, we focused on whether the G8 is also useful for identifying those patients who are at risk for complications of an anti-tumor treatment so treatment can be tailored to the ability of patients to tolerate this treatment (Part II). Second, we provided information about the impact of an anti-tumor treatment on PROs, so that the patient can take the PROs into account when shard-decisions about his treatment are made (Part III).

Geriatric assessment

A GA is increasingly implemented in the work-up for all older patients with cancer in daily practice. However, there is no consensus regarding which domains should be included in the GA. Therefore, we evaluated by a systematic literature search which domains of the GA could predict mortality, postoperative complications of elective surgery for solid tumors, and systemic treatment related outcomes and therefore should be concluded in the GA.

Chapter 2 describes the results of this systematic review. Eight different domains were evaluated in 46 publications, namely functional status, nutritional status, cognition, mood, physical function, fatigue, social support, and falls. All eight domains were predictive for at least one of the investigated outcomes but the results were quite variable across studies. Physical function and nutritional status were the domains most often associated with mortality and systemic treatment-related outcomes, and the domain physical function was most often associated with postoperative complications.

Based on this findings, you may conclude that a GA should minimally consist of physical function and nutritional status. However, this does not mean that assessing

other domains is redundant. In this systemic review, we focused on the predictive value of every domain. However, predicting treatment outcomes is not the mean reason to refer a patient for a GA. In our opinion, a broad GA is needed to identify all present impairments, serving as a base for a geriatric treatment plan with the aim to improve treatment outcomes.

Using the G8 for identifying patients who are at risk for complications

In **Chapter 3** we assessed both the diagnostic as predictive value of the G8 in older patients with cancer requiring surgical treatment. The G8's discriminative power in determining geriatric impairments has mostly investigated in older patients with cancer considered for chemotherapeutic treatment. In this chapter, we showed that also for the older patients with cancer requiring surgical treatment, the G8 is a useful screening tool. The sensitivity, specificity, and negative predictive value of the G8 were 82% (95% Confidence Interval (CI) 70-91), 63% (95% CI 52-73), and 85% (95% CI 75-91). These calculated diagnostic values of the G8 are comparable to the test characteristics of the G8 studied in mostly non-surgical patients. As a result, not every older patients with cancer requiring surgical treatment should be referred to the geriatrician for a preoperative GA. For selecting the patients who benefit of a GA pre-operatively, the G8 can be used.

In addition, we assessed the association between the G8 and the occurrence of postoperative complications within 30 days of surgery. We found no difference in the occurrence of postoperative complications. Although, in the patients with an impaired G8 (the frail patients) the occurrence of delirium and the 1-year mortality was higher, and the length of the hospital stay prolonged. These results may suggest that frail patients according to the G8 are not at risk for more surgical complications by itself, but that these patients seem to be more at risk for a complicated postoperative recovery leading to a higher rate of delirium and discharge to a rehabilitation unit, a prolonged hospital stay, and a higher 1-year mortality.

Originally, the G8 is designed to identify those potentially frail older patients who may benefit from a GA, although the association of the G8 with clinical outcomes such as treatment complications, physical functioning after treatment, and survival has increasingly been studied. However, the association between the G8 and the occurrence of toxicity of immune checkpoint inhibitors (ICI) has never been evaluated, while having insight in this association has a great importance. The indication for ICIs rapidly increasingly and ICI have a more favorable toxicity profile compared to chemotherapy. For that reason, ICI are increasingly considered as a tolerable treatment option at older age. In **Chapter 4**, we assessed the association between the G8 and the occurrence of toxicity of ICI, also known as immune-related adverse events (irAEs) in older patients with melanoma.

In 92 patients, we did not found an association between frailty according to the G8 and the occurrence of irAEs. However, in frail patients we did noticed more hospital admissions because of irAEs and a prolonged hospital stay. In other words, melanoma patients with an impaired G8 are not at risk for a higher occurrence of irAEs, but when an irAE occurred in this patient this could have more impact.

Based on our findings in **Chapter 3 and 4**, we concluded that the G8 can be seen as an additional tool in guide shared-decision making. The G8 not only informs the treating oncologist about whether his patient benefits of a referral to the geriatrician for a GA, but the G8 also gives information about whether his patient is at risk for a complicated treatment outcome. This risk estimation should be discussed with the patient and should play a role in counseling our patients.

Providing information about the impact on anti-tumor treatment on patient-related outcomes

The importance of getting insight in patient-related outcomes (PROs) has been stated above. In this thesis, we have acquired insight into the impact of several anti-tumor treatments on PROs.

Chapter 5 describes the impact of surgery in older patients with head and neck cancer (HNC) on functional decline one year after surgery. Preoperatively, patients were asked for their (Instrumental) Activities of Daily Living (IADL and ADL). For instance, they were asked for their ability to bath, to dress, to go the toilet, and to prepare a meal. One year after surgical treatment, we found a significant decline in functional status. This decline in functional status may represent a substantially clinically relevant impact on an individual's functional dependency, because it indicates that these patients will need assistance from a family member, care giver, or long-term care services. These patients mainly need assistance in house-keeping, travelling, shopping, and mobility.

In contrast to the functional status, the self-reported health status of HNC patients did not decline one year postoperatively. In fact, the self-reported health status might even be improved possibly by the fact that postoperatively the fear and the insecurity about their diagnosis and treatment had been resolved. This unique prospective study makes that we could now inform our patients better about the fact that a surgical procedure for HNC may lead to a decline in functional status. In addition, we can also reassure our patients, it does not influence their self-reported health status negatively.

In **Chapter 6**, we gave insight in the symptom burden of patients treated with systemic anti-cancer treatment and assessed the association between a high symptom burden and an impaired G8. Symptom burden was defined as the number of symptoms of the USD scored as ≥ 3. The USD consists of questions about pain, sleeping problems, dysphagia, lack of appetite, disturbed stool, nausea, shortness of breath, fatigue, anxiety, depressed mood, and well-being. A symptom was scored from zero (no symptom burden at all) to ten (worst symptom burden). Multivariate analysis showed that frailty according to the G8, female gender, and clinical condition expressed with the World Health Organisation Performance Score (WHO PS) were statistically significant predictors for a higher symptom burden both before and during treatment. Frail patients according to the G8 experienced statistically significantly more lack of appetite, abnormal stool, nausea, fatigue, depressed mood, and unwell being before start of a systemic anti-tumor treatment. With respect to the course of the symptom burden, we found that the symptom burden of the group with a normal G8 increased over time. The baseline symptom burden of the group with an impaired G8 was higher but, in contrast to the other group, decreased slightly over time. This difference in the course of symptom burden between the non-frail and frail group is striking and could be partially explained by the fact that the frail group suffers more from tumor-related complains at baseline that may disappear because of the anti-cancer treatment and also from non-tumor related complaints.

These findings may guide treating physicians to inform older patients about their risk of higher symptom burden during systemic anti-cancer therapy, based on frailty screening by the G8. Symptom burden should be an important topic to discuss with patients when making appropriate treatment decisions because older patients attach a great value QoL. Because of the clear association between a high symptom burden and a low QoL, high symptom burden reflects the HRQoL. In addition, having insight into the degree of symptom burden may lead to better symptom management and thus improvement of QoL and maintaining functioning as shown in previous research.

Conclusion

Achieving an appropriate individualization of treatment in older patients with cancer remains complex and challenging. In this thesis, we have addressed important aspects of this problem. We concluded that the G8 can be seen as an additional tool in guide shared-decision making. The G8 not only informs the treating oncologist about whether his patient benefits of a referral to the geriatrician for a GA, but the G8 also gives information about whether his patient is at risk for a complicated treatment outcome. This risk estimation should be discussed with the patient and should play a role in counseling our patients.

In addition, we have provided information about the impact of anti-cancer treatment on two kind of PROs, namely functional decline and symptom burden. Both the outcome of frailty screening as the impact of a treatment of PROs should be a topic in the conservation with your patient and could guide the shared-decision making process.

Appendices

Summary in Dutch

Meer dan de helft van de patiënten die worden gediagnosticeerd met kanker is 70 jaar of ouder. De komende jaren neemt het aantal oudere patiënten met kanker naar verwachting alleen maar verder toe. Dit komt onder andere doordat we überhaupt meer kanker zien, door de vergrijzing en de toegenomen levensverwachting. Het is echter nog steeds onduidelijk hoe de oudere patiënt met kanker precies behandeld moet worden, terwijl het merendeel van de patiënten met kanker die we zien in de spreekkamer 70 jaar of ouder is. Deze onduidelijkheid komt onder andere voort uit het feit dat de oudere patiënt met kanker ondervertegenwoordigd is in de studies waar we onze oncologische behandeling op baseren. De weinig oudere patiënten die werden opgenomen in deze studies zijn vaak fitter dan de oudere patiënt die we dagelijks zien in de spreekkamer en dus niet representatief voor de patiënten die we daadwerkelijk behandelen. Daarbij hebben oudere patiënten doorgaans andere chronische ziektes onder de leden die de levensverwachting, maar ook de tolerantie van een anti-tumor-behandeling kunnen beïnvloeden. Uit onderzoek blijkt eveneens dat de oudere patiënt vaak andere behandeldoelen nastreeft: de jonge patiënt met kanker vindt levensverlenging het belangrijkste behandeldoel. De oudere patiënt daarentegen hecht meer waarde aan behoud van kwaliteit van leven en zelfstandigheid.

Kortom, de oudere patiënt met kanker maakt deel uit van een erg heterogene groep. Dit betekent dat de ene oudere patiënt fit is en de standaard behandeling goed tolereert zonder aanpassingen, terwijl de andere oudere patiënt kwetsbaar is en waarschijnlijk de standaard behandeling niet goed tolereert, zodat de behandeling moet worden aangepast of geheel achterwege moet worden gelaten. Maar hoe onderscheiden we de fitte van de kwetsbare patiënt? Uit onderzoek blijkt dat de behandelaar op basis van zijn klinische blik niet goed kan inschatten welke patiënt fit is en welke patiënt kwetsbaar. Wij zien als behandelaren iemands kwetsbaarheid gemakkelijk over het hoofd en overschatten vaak de fitheid van onze patiënt. Daarom beveelt the International Society of Geriatric Oncology (SIOG) aan om bij elke oudere patiënt met kanker een geriatrisch assessment (GA) te verrichten. Een GA is een multidimensionaal, multidisciplinair en systematisch onderzoek uitgevoerd door een geriater en bestaat uit gevalideerde meetinstrumenten om kwetsbaarheden op het somatische, functionele, en psychosociale vlak in kaart te brengen. Uiteindelijk geeft het GA een totaal beeld van de kwetsbaarheid van patiënt.

Het is echter niet nodig om bij elke fitte oudere patiënt met kanker een GA te verrichten. Je zou dus iedere oudere patiënt met kanker willen screenen om te zien of hij kwetsbaar is en baat heeft bij een GA, of dat hij juist fit is en de standaard behandeling tolereert zonder dat daarvoor een GA afgenomen hoeft te worden. Verschillende scree-

ningsinstrumenten zijn inmiddels onderzocht. Eén van deze screeningsinstrumenten is de Geriatric 8 (G8). De G8 is speciaal ontwikkeld om de fitte oudere patiënt met kanker te onderscheiden van de kwetsbare patiënt. De G8 bestaat uit acht vragen. De totale score kan variëren van 0 tot 17 punten. Een score van ≤ 14 wordt als afwijkend beschouwd en dat betekent dat deze patiënten moeten worden doorverwezen naar de geriater voor een GA. De G8 is binnen de geriatrische oncologie het meest gebruikte screeningsinstrument.

Het vaststellen van iemands kwetsbaarheid is niet het enige wat van belang is om met de patiënt gezamenlijk tot een individueel oncologisch behandelplan te komen. In deze gezamenlijke besluitvorming moet de impact van een anti-kanker behandeling op patiënt-gerelateerde uitkomsten ook worden meegewogen, aangezien oudere patiënten met kanker meer belang hechten aan het behouden van kwaliteit van leven en behoud van zelfstandigheid dan aan levensverlenging. Patiënt-gerelateerde uitkomsten (patient-related outcomes (PROs)) geven de waardering van een patiënt over zijn eigen gezondheid weer**.** De vragenlijsten die worden gebruikt om deze uitkomsten te genereren worden PROMs genoemd: Patient Reported Outcome Measures. In het UMC Utrecht wordt het Utrechts Symptom Dagboek (USD) gebruikt om de PROs te evalueren.

In dit proefschrift zijn twee belangrijke onderzoeksvragen onderzocht. Ten eerste hebben we onderzocht of de G8, naast patiënten die kwetsbaar zijn, ook patiënten identificeert die een verhoogd risico hebben op complicaties van een anti-kankerbehandeling, zodat een anti-kankerbehandeling op voorhand kan worden aangepast (Deel II). Ten tweede, hebben we gekeken naar de impact van een anti-kankerbehandeling op patiënt-gerelateerde uitkomsten, zodat een patiënt deze informatie kan meenemen in de gezamenlijke besluitvorming (Deel III).

Het Geriatrisch Assessment

Sinds de aanbeveling van de SIOG om bij iedere oudere patiënt met kanker een GA te verrichten, wordt het GA steeds meer geïmplementeerd in de zorg voor de oudere patiënt met kanker. Er is echter geen consensus over waar het GA daadwerkelijk uit moet bestaan en welke geriatrisch domein, bijvoorbeeld voeding en cognitie, minimaal onderzocht moet worden. Wij hebben daarom een systematisch literatuuronderzoek verricht met als doel te bekijken welke domeinen voorspellend zijn voor mortaliteit, postoperatieve complicaties en complicaties ten gevolge van de systemische anti-kankerbehandeling, zoals chemotherapie. Deze domeinen zouden tenminste onderdeel moeten zijn van het GA.

Hoofdstuk 2 beschrijft de resultaten van dit literatuuronderzoek. Acht verschillende domeinen zijn onderzocht in 46 publicaties, te weten mobiliteit, voeding, cognitie, gemoedstoestand, (Instrumentele) Activiteiten van het Dagelijks Leven (IADL en ADL), vermoeidheid, sociale ondersteuning en het valrisico. Alle acht domeinen blijken voorspellend voor tenminste één van onderzochte uitkomsten (mortaliteit, postoperatieve complicaties en complicaties ten gevolge van de systemische anti-kankerbehandeling zoals bijvoorbeeld chemotherapie), maar de resultaten zijn niet consistent en variëren tussen studies onderling. Mobiliteit en voeding zijn de domeinen welke het meest geassocieerd zijn met mortaliteit en complicaties ten gevolge van de systemische anti-kankerbehandeling. Mobiliteit is daarnaast ook geassocieerd met postoperatieve complicaties.

Op basis van bovenstaande bevindingen, kan geconcludeerd worden dat met een GA minimaal de domeinen mobiliteit en voeding geëvalueerd moeten worden als het doel van het GA is om uitkomsten te voorspellen. Voor de andere domeinen waren de resultaten te inconsistent om daar daadwerkelijk conclusies aan te verbinden. Dit betekent echter niet dat onderzoek naar de andere domeinen niet van belang is. In tegendeel, een uitgebreid GA, en dus onderzoek naar alle domeinen, is nodig om alle kwetsbaarheden van een patiënt in beeld te brengen, zodat een behandeling daarop kan worden aangepast.

Een verhoogd risico op complicaties van een behandeling identificeren met de Geriatric 8

In **Hoofdstuk 3** hebben we zowel de diagnostische als voorspellende waarde van de G8 onderzocht in oudere patiënten met kanker die een chirurgische behandeling moeten ondergaan. De diagnostische waarde van de G8 om kwetsbaarheid te identificeren is voornamelijk onderzocht bij oudere patiënten met kanker die een behandeling met chemotherapie voorgeschreven krijgen. De vraag is of deze diagnostische waarde ook geldt voor oudere patiënt met kanker die een chirurgische behandeling moet ondergaan. In dit hoofdstuk hebben we aangetoond dat de G8 ook een bruikbaar screeningsinstrument is voor de oudere patiënten met kanker die chirurgie moeten ondergaan. De sensitiviteit, specificiteit en negatief voorspellende waarde van de G8 waren 82% (95% betrouwbaarheidsinterval (BI) 97-91), 63% (95% BI 52-73) en 85% (95% BI 75-91). Deze berekende diagnostische waarden komen overeen met de resultaten van studies waarin de testkarakteristieken van de G8 bij niet-chirurgische patiënten is onderzocht.

Op basis van deze bevindingen kan worden geconcludeerd dat niet elke oudere patiënt met kanker die een chirurgische behandeling moet ondergaan naar de geriater hoeft te worden verwezen voor een peroperatief GA, zoals in vele ziekenhuizen nu gebeurt, maar dat de verwijzing kan worden gebaseerd op de score van de G8.

In Hoofdstuk 3 hebben we tevens gekeken naar de associatie tussen de G8 en het optreden van postoperatieve complicaties binnen 30 dagen. We hebben geen verschil in het optreden van postoperatieve complicaties gezien tussen de patiënten met een afwijkende G8 (de kwetsbare patiënten) en de patiënten met een normale G8 (de fitte patiënten). Daarentegen zagen we bij de kwetsbare patiënten wel significant vaker een delirium optreden, een hogere 1-jaars mortaliteit en een langere ziekenhuisopname. Hieruit valt te concluderen dat kwetsbare patiënten volgens de G8 geen verhoogd risico hebben op chirurgische complicaties ansich, maar dat deze patiënten wel een verhoogd risico hebben op een gecompliceerd herstel van een operatie resulterend in een delier, langere ziekenhuisopname en een verhoogd risico op overlijden binnen één jaar.

De G8 is oorspronkelijk ontworpen om die kwetsbare oudere patiënt met kanker te identificeren die baat heeft bij een GA. De laatste jaren is ook de associatie tussen de G8 en klinische uitkomsten, zoals bijvoorbeeld overleving of bijwerkingen van een systemische anti-kankerbehandeling, veelvuldig onderzocht. De associatie tussen de G8 en het optreden van bijwerkingen van immune checkpoint inhibitors (ICI) was echter nog niet onderzocht. Steeds meer oudere patiënten met kanker worden behandeld met ICI, omdat ICI bij steeds meer tumorsoorten deel uitmaken van de behandeling. Daarnaast hebben ICI mildere bijwerkingen dan chemotherapie, waardoor deze behandeling ook steeds meer bij ouderen wordt toegepast. In **Hoofdstuk 4** hebben we de associatie tussen de G8 en het optreden van ernstige bijwerkingen van ICI, ook wel bekend als immuun-gerelateerde bijwerkingen graad ≥ 3, onderzocht bij oudere patiënten met een melanoom. Er werd geen associatie gevonden tussen een afwijkend G8 en het optreden van immuun-gerelateerde bijwerkingen. Kwetsbare patiënten werden echter wel significant vaker opgenomen in het ziekenhuis in verband met een immuun-gerelateerde bijwerking en eenmaal opgenomen in het ziekenhuis duurde deze opname ook langer. Kortom, patiënten met een melanoom en een afwijkende G8 hebben geen verhoogd risico op een immuun-gerelateerde bijwerking van de ICI, maar wanneer een immuun-gerelateerde bijwerking optreedt heeft dit wel meer impact op de kwetsbare patiënt.

Zowel hoofdstuk 3 als hoofdstuk 4 laten zien dat met de G8 een verhoogd risico op complicaties van een anti-kankerbehandeling, in dit geval chirurgie en ICI, kan worden geïdentificeerd. Naar onze mening is de G8 daarom van toegevoegde waarde in de gezamenlijke besluitvorming bij de oudere patiënt met kanker. De G8 informeert namelijk niet alleen de behandelaar of zijn patiënt baat heeft bij een GA en naar de geriater verwezen moet worden, maar de G8 geeft ook aan of een patiënt een verhoogd risico heeft op een complicatie als gevolge van de behandeling. Deze risicoinschatting kan met de patiënt worden besproken en worden meegenomen in de gezamenlijke besluitvorming.

De impact van een anti-kankerbehandeling op patiënt-gerelateerde uitkomsten

Zoals al eerder beschreven, is het niet alleen van belang om de impact van een behandeling op de overleving en/of progressievrije overleving te weten. Ook de impact van een behandeling op patiënt-gerelateerde uitkomsten is belangrijk, zeker voor de oudere patiënt met kanker. In dit proefschrift hebben we gekeken naar de impact van verschillende anti-kankerbehandelingen op patiënt-gerelateerde uitkomsten.

Hoofdstuk 5 beschrijft ons onderzoek naar de impact van chirurgie op de functionaliteit van de oudere patiënt met hoofd-halskanker één jaar na chirurgie. Zowel preoperatief als één jaar na de chirurgie werden de patiënten gevraagd naar hun Activiteiten van het Dagelijks Leven (ADL) en hun Instrumentele Activiteiten van het Dagelijks Leven (IADL). De ADL en IADL werden uitgevraagd middels gevalideerde vragenlijsten en bevatten onder andere vragen over of een patiënt in staat is zichzelf te wassen, aan te kleden, naar het toilet te gaan of om een maaltijd te bereiden. We vonden één jaar na de chirurgie een significante afname van het functioneren, hetgeen als afname van de zelfstandigheid kan worden gezien. Uit onze studie is verder gebleken dat patiënten voornamelijk hulp nodig hebben bij de huishouding, bij reizen, bij het doen van hun boodschappen en bij de mobiliteit. Hoewel er sprake was van een afname van het functioneren één jaar na de operatie, gaven patiënten aan dat er geen sprake was van een afname van hun kwaliteit van leven. Integendeel, de kwaliteit van leven lijkt wellicht wat te zijn verbeterd. Dit kan worden verklaard doordat één jaar na de diagnose én behandeling van de hoofd-halskanker de angst en onzekerheid over hun diagnose en behandeling is verdwenen. De resultaten uit hoofdstuk 5 maken dat we onze patiënten met hoofd-halskanker die chirurgie moeten ondergaan nu beter kunnen informeren over de impact van de behandeling op de lange termijn, namelijk dat de chirurgie uiteindelijk kan leiden tot een afname van hun functioneren en wellicht ook tot een afname van hun zelfstandigheid, maar dat deze afname hun kwaliteit van leven niet lijkt te beïnvloeden.

In **hoofdstuk 6** geven we de symptoomlast van oudere patiënten weer die worden behandeld met een systemische anti-kankerbehandeling, zoals chemotherapie of behandeling met ICI. Met symptoomlast wordt het aantal symptomen bedoeld, die een patiënt een score heeft gegeven van drie of meer op het USD. Het USD vraagt naar pijn, slaapproblemen, slikproblemen, eetlust, stoelgang, misselijkheid, kortademigheid, vermoeidheid, angst, somberheid en algeheel welzijn op een schaal van 0 tot 10. Een score van 0 betekent geen last, terwijl een score van 10 de hoogst denkbare last betekent. We onderzochten eveneens of er een associatie is tussen een afwijkende G8 en een hoge symptoomlast zowel voor start van de behandeling als tijdens de behandeling. Uit multivariate analyse is gebleken dat een afwijkende G8 significant geassocieerd is met een hogere symptoomlast. Ook een verminderde conditie, uitgedrukt middels de

World Performance Score, en het vrouwelijke geslacht zijn geassocieerd met een hogere symptoomlast zowel voor als tijdens de behandeling. Patiënten met een afwijkende G8 hadden significant meer last van verlies van eetlust, een veranderde stoelgang, misselijkheid, vermoeidheid, somberheid en een verminderd algeheel welbevinden voor start van de behandeling. Als we kijken naar het verloop van deze symptoomlast, dan zagen we de symptoomlast van de patiënten met een normale G8 gedurende de behandeling toenemen. De symptoomlast van patiënten met een afwijkende G8 lag hoger, maar nam gedurende de behandeling echter af. Een verklaring voor deze afname kan zijn dat een deel van de symptoomlast van de kwetsbare patiënten waarschijnlijk tumorgerelateerd is en respondeert op de systemische anti-kankerbehandeling. Deze studie laat zien dat je op basis van een kwetsbaarheidsscreening met de G8 een patiënt kan informeren over hun symptoomlast voor en tijdens de behandeling. Aangezien eerder onderzoek heeft uitgewezen dat een hoge symptoomlast een verminderde kwaliteit van leven betekent, zou je kunnen stellen dat de G8 een risicoschatting maakt over de kwaliteit van leven voor en tijdens de behandeling met systemische anti-kankerbehandeling. Daarnaast is het van belang om inzage te hebben in de symptoomlast van patiënten, zodat deze symptomen kunnen worden verlicht in de hoop de kwaliteit van leven te verbeteren.

Conclusie

De behandeling van de oudere patiënt met kanker is complex en uitdagend. Het is van belang om met iedere patiënt tot een individueel behandelplan te komen. Dit proefschrift laat zien dat de G8 toegevoegde waarde heeft in deze gezamenlijke besluitvorming. De G8 laat namelijk niet alleen zien of een patiënt baat heeft bij een GA, maar de G8 geeft ook aan of een patiënt een verhoogd risico heeft op een gecompliceerd beloop van zijn behandeling.

Dit proefschrift heeft zich bovendien ook gericht op patiënt-gerelateerde uitkomsten, namelijk functionaliteit en symptoomlast, en de impact van een anti-kankerbehandeling op deze uitkomsten. Zowel de risicoinschatting met de G8 als de impact van de anti-kankerhandeling op patiënt-gerelateerde uitkomsten dienen onderdeel te zijn van het gesprek met de patiënt, zodat deze kunnen worden meegenomen in de gezamenlijke besluitvorming.

List of Publications

Symptom burden of older patients with cancer during systemic therapy and its relationship with frailty: A prospective observational study
C.P. Bruijnen, C.E.A. Laeven, J.J. Koldenhof, A. de Graeff, P.O. Witteveen, M.H. Emmelot- Vonk, F. van den Bos
Submitted to Cancer

Frailty and checkpoint inhibitor toxicity in older melanoma patients
C.P. Bruijnen, J.J. Koldenhof, R.J. Verheijden, F. van den Bos, M.H. Emmelot-Vonk, P.O. Witteveen, K.P.M. Suijkerbuijk
Accepted in Cancer

Functional decline after surgery in older patients with head and neck cancer
C.P. Bruijnen, L.G.R. de Groot, A.M. Vondeling, R. de Bree, F. van den Bos, P.O. Witteveen, M.H. Emmelot-Vonk
Oral Oncology 2021 Dec: 123:105584

Validation of the G8 screening tool in older patients with cancer considered for surgical treatment
C.P. Bruijnen, A. Heijmer, D.G. van Harten-Krouwel, F. van den Bos, R. de Bree, P.O. Witteveen, M.H. Emmelot-Vonk
Journal of Geriatric Oncology 2021 Jun:12(5):793-798

Predictive value of each geriatric assesment domain for older older patients with cancer: A systematic review
C.P. Bruijnen, D.G. van Harten-Krouwel, J.J. Koldenhof, M.H. Emmelot-Vonk, P.O. Witteveen
Journal of Geriatric Oncology, 2019 Nov;10(6):859-873

Not included in this thesis:

Retrospectief cohortonderzoek UMC Utrecht onder oudere en jongeren patiënten: Geen verschil in behandeling en behandeluitkomsten bij ovariumcarcinoom
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Curriculum Vitae

Cheryl Phyllis Bruijnen werd geboren op 16 mei 1986 te Rotterdam en groeide op in een warm gezin met haar jongere broer Colin en haar jongere zus Constance.

Na het behalen van het VWO-diploma in 2004 aan het Erasmiaans Gymnasium te Rotterdam, ging zij geneeskunde studeren aan de Universiteit van Utrecht. In 2010 behaalde zij haar artsexamen, waarna zij startte als ANIOS interne geneeskunde in het St. Antonius Ziekenhuis (onder leiding van dr. A.B.M. Geers). Zij vervolgde haar carrière in eerste instantie met de opleiding tot longarts (opleider dr. F.M.N.H. Schramel), maar besloot tijdens de vooropleiding interne geneeskunde toch om internist te worden en stapte over naar deze opleiding (opleider dr. A.B.M. Geers). In 2014 zette zij haar opleiding tot internist voort in het UMC Utrecht. (opleider. Prof. dr. H.A.H. Kaasjager).

In 2015 onderbrak zij haar opleiding voor twee jaar om zich toe te leggen op haar PhD project gericht op de implementatie van de Geriatric 8 in de klinische praktijk. Resultaten uit dit onderzoek zijn gepresenteerd op diverse congressen; SIOG (International Society of Geriatric Oncology), EMSO (European Society of Medical Oncology) Annual Meeting en op het Symposium voor Geriatrische Oncologie.

In 2017 hervatte zij de opleiding en startte met haar differentiatie tot internist-oncoloog in het UMC Utrecht (opleider. Prof. P.O. Witteveen). Haar titel tot internist-oncoloog werd in juli 2020 behaald en vervolgens ging zij werken als staflid binnen de medische staf van de afdeling Medische Oncologie van het UMC Utrecht. Hier is zij nog steeds werkzaam als internist-oncoloog met een specifieke expertise voor de urogenitale en geriatrische oncologie.

Cheryl is getrouwd met Daan van de Watering en woont in Utrecht. Samen hebben zij drie kinderen: Fiene (2016), Faas (2018) en Tom (2021).