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A geriatric assessment-based approach for the older patient with cancer and the impact of ageing and cancer on well-being

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Chapter 1. General introduction

The implementation of geriatric assessment in oncology

The time has arrived *now* that large numbers of older people are diagnosed with cancer who are in need of subsequent care and treatment. In a population of about 11 million inhabitants, 67 087 new diagnoses of invasive tumors (excl. non-melanoma skin cancer) were registered in Belgium in 2015 with 30122 (45%) of these patients being older than 70 years (1). The yearly number of patients with a new cancer diagnosis is expected to surpass 79 000 by 2025 with the highest incidence rates in the elderly. These numbers do not even consider older patients with a relapse of their cancer or with progressive disease who also present to the clinic for cancer treatment and care. Given this epidemiologic trend of cancer in older adults, healthcare providers need to be aware of this public health concern. In this dissertation, we focus on some clinical, societal, and psychosocial aspects of ageing and cancer.

Health care providers and policy makers should be aware that older patients with cancer require special attention regarding treatment decisions and care. Many of these patients present with complex clinical presentations for example in terms of comorbidity, functional status, and cognition reflecting differences in biological and chronological age. Oncologists and other specialists who care for patients with cancer face the difficulty in identifying optimal treatment options for older adults. The treating physician has to consider some difficult questions: Is the patient going to die of or with cancer?, Is the patient able to tolerate treatment?, Will any treatment improve quality of life? Is there enough social support during treatment? (2,3). This together with the lack of evidence-based data makes treatment of this population complex. The Comprehensive Geriatric Assessment (CGA), developed by geriatricians, is currently considered the most appropriate way to obtain a better view on the global health and reserve capacity of the older patient. It consists of a set of screening tools and includes the assessment of functional status, co-morbidity, nutritional status, cognition, and psychological status. Several guidelines have recommended a CGA-based approach in oncology to guide treatment decision-making (3-5). The term geriatric assessment (GA) is more and more used in oncology instead of CGA because studies on CGA in this discipline are less ‘comprehensive’ than in geriatrics (4). Both terms are used in this dissertation and a definition of the (C)GA is provided in each relevant chapter. We note that the GA domains that were assessed vary from chapter to chapter. This discrepancy is due to the different studies this work was based on (see below) and the lack of consensus on which geriatric domains to include in a GA. Furthermore, older patients were defined as older than 65 or older than 70 depending which chapter you read, again because of the different studies. It is somewhat contradictory to select a cut-off age for older patients while we are trying to assess their physiological reserve capacity or biological age. However, for the implementation of GA in routine practice, a selection of a cut-off age might be necessary.

Despite recommendations, the GA-based approach is currently not widely implemented in routine oncology practice, in part because of limited resources. There is a need for a short tool that can quickly identify patients who can benefit from a GA (7-8). Two geriatric screening tools will be validated in this dissertation in reference to a GA: the G8 questionnaire and the Groningen Frailty Indicator (GFI). Another topic concerning the implementation of GA in routine practice that will be studied in this dissertation involves geriatric recommendations that follow GA. To what extent are identified geriatric problems addressed in oncology? Which health care professionals or services are the most referred to and for which geriatric problems? Although important for the effectiveness of the GA-based approach, this step following GA has received little research attention.

A major issue confronting oncologists is to find the right balance between providing effective cancer treatment and minimizing treatment toxicity in older patients with cancer, given the increased risk for treatment-related toxicity in this population (9). There are no validated methods to identify older patients fit enough to receive the same treatment as younger patients. Various studies have looked at the predictive value of GA for treatment toxicity showing inconsistent results (10-12). In this dissertation, we will look at the predictive value of the two aforementioned geriatric screening tools, the GFI and G8, for treatment toxicity.

The GA-based approach is recommended to improve the estimation of treatment tolerance but also to improve the estimation of life-expectancy, which is sometimes a difficult task though very important in the treatment decision-making process. Several studies have shown that multiple GA components have some predictive value for overall survival. However, studies that evaluate the prognostic value of GA generally focus on the most prognostic individual GA components or on the best set of GA components and not on the GA as a whole (10-12). In this dissertation, we will quantify the added prognostic value of screening and GA beyond clinical information by comparing a baseline model of clinical information for overall survival with models extended with geriatric information. This analysis approach allows us to quantify and compare the added prognostic value of the GA as a whole (here the 10-item GA), the individual GA components, and screening tools. A recently developed GA summary score, the Leuven Oncogeriatric Screening Tool (LOFS), will be included in this analysis as well. In a separate chapter, we will also include the three commonly measured laboratory parameters hemoglobin, albumin, and C-reactive protein and associated composite scores. Their prognostic value for overall survival has been shown in a range of tumor types (13-15). We will evaluate how much prognostic information these biomarkers add to the baseline model of clinical information and compare this with the added value of geriatric information.

Acknowledging the challenges that come with the growing population of older patients with cancer, several efforts have been made over the past years to improve the care of the older patient with cancer in Belgium. A cancer plan was launched in 2008; one of the initiatives in this plan was to provide support

for pilot projects in the field of clinical geriatric oncology. This led to the implementation of GA in numerous academic and non-academic hospitals between 2009 and 2012 and between 2012 and 2015. In this period, the 'Vlaamse Liga tegen Kanker' (VLK) also provided financial support for projects that aimed to improve care in this population. The knowledge gaps raised above will be addressed based on the aforementioned efforts.

The impact of ageing and cancer on well-being: the Klimop study

The second part of this dissertation will be based on the ongoing Klimop study (16). The primary aims of this longitudinal study are to assess the impact of cancer and ageing on subsequent well-being and to identify factors that predict well-being in older patients with cancer. For this purpose, older patients with cancer (OCP) are compared with two control groups: middle-aged patients with cancer (MCP) and older primary care patients without cancer (ONC). Two analyses are included in this dissertation, as part of this umbrella study.

In the first analysis, we will focus on home care. With the ageing population come societal changes such as declining family size, increased participation of women in the labor market, increased retirement age, and more single-living elderly. This evolution has led to an increased demand for formal care and changes in the balance between formal and informal care. The resulting changes in patterns of care are a challenge for the organization and financing of home care. Over the past decades, several studies have analyzed the use of home care considering different national contexts to prepare for these challenges (17-19). These studies focused on the general population and have informed policy decisions ever since. In this dissertation, we will focus on patients with a recent cancer diagnosis. A diagnosis of cancer and subsequent treatment can have a substantial effect on the well-being of patients and their need for home care. Therefore, we aim to gain a better insight on the utilization of formal and informal care shortly after a cancer diagnosis and one year later in OCP and the two control groups. We will also examine predictors of transitions towards formal care one year after a cancer diagnosis.

In the second analysis, we will focus on coping. The psychosocial care of the older patient with cancer has begun to receive more research attention, acknowledging differences between older patients and their younger counterparts. Although coping is not a stand-alone phenomenon, a better understanding of coping mechanisms used in cancer patients is important because unlike other concepts, like personality, coping is amenable to cognitive-behavioural intervention (20). The large majority of published studies that assess the relationship between coping and well-being are based on cross-sectional data. In this analysis, we will evaluate the predictive value of coping strategies shortly after a cancer diagnosis for subsequent well-being in OCP while disentangling ageing – and diagnosis effects.

Overview of the dissertation

This dissertation is divided in ten chapters. After a general introduction, chapter 2 until chapter 6 will cover several aspects concerning the implementation of geriatric screening and GA in oncology. Chapter 7 and chapter 8 are based on the Klimop study. Chapter 9 entails the general discussion. Chapter 10 provides a summary of the dissertation.

Chapter 2 describes the validation of two geriatric screening tools in reference to a GA. The effects of GA by itself are limited, unless followed by targeted geriatric recommendations and interventions. Chapter 3 describes the geriatric recommendations based on the results of the GA and the implementation of these recommendations in routine practice.

A major research topic in geriatric oncology is the value of geriatric screening and GA for outcome prediction. This could aid physicians in the treatment decision-making process. Chapter 4 describes the predictive value of two geriatric screening tools for severe treatment toxicity in patients who received one cycle of (radio)chemotherapy. Chapter 5 focuses on the added prognostic value of geriatric information beyond a basic prognostic model of clinical information for overall survival. Chapter 6 goes a step further by including three commonly measured laboratory parameters and associated composite scores in the analysis allowing a comparison with geriatric information.

Chapter 7 examines the utilization of formal and informal care shortly after a cancer diagnosis and after one year in OCP and the two control groups. Chapter 8 investigates if baseline coping strategies predict changes in different dimensions of well-being after one year in OCP while disentangling ageing - and cancer effects.

Aims and main research questions

The first part of this dissertation focuses on the GA-based approach in routine oncology practice. Our analysis was based on data from three implementation studies. Two studies implemented GA in oncology from October 2009 until July/December 2011. The third study implemented GA in routine practice between August 2011 and July 2012 and also focused on GA-based recommendations.

The second part of the dissertation focuses on the impact of ageing and cancer on well-being and was based on data from the ongoing Klimop study which started inclusion of patients from 2010. Additional details about each study can be found in each chapter and on page 163 in the 'personal contribution' section.

In this section, we provide an overview of the main research questions that each chapter aims to answer.

Chapter 2

There is a need for a short and accurate screening tool to discriminate fit patients and patients who can benefit from a CGA. Preferably, this screening tool can be used routinely in a busy practice regardless of tumor characteristics.

- What is the diagnostic accuracy of the G8 and the GFI in reference to a CGA and how to they compare?

Chapter 3

The implementation of GA in routine oncology practice should be followed by appropriate geriatric recommendations and interventions. This step following GA is important for the effectiveness of the GA-based approach but has received little research attention.

- What is the proportion of patients that receives geriatric recommendations based on GA results? Which geriatric recommendations and for which geriatric problems?
- How many of the geriatric recommendations are performed after one month? Which geriatric recommendations and for which geriatric problems?

Chapter 4

There are no validated methods to identify older patients fit enough to receive the same cancer treatment as younger patients. Predictive tools for severe treatment toxicity have the potential to minimize undertreatment and overtreatment.

- Do the G8 and the GFI predict severe treatment toxicity in patients who receive one cycle of (radio)chemotherapy?

Chapter 5

One of the aims of the GA-based approach is to improve the estimation of life-expectancy. Studies that evaluate the prognostic value of GA for mortality generally focus on the most prognostic individual GA components or on the best set of GA components. However, these studies do not focus on the GA as a whole or on the additional prognostic value of geriatric information beyond clinical information.

- Does GA improve the estimation of life-expectancy beyond clinical information? How much? What is the relative importance of the individual GA components and the GA as a whole?

Chapter 6

Several studies have shown that multiple routinely measured laboratory parameters and associated composite scores are independent prognostic factors for overall survival in patients with cancer. Very few studies have evaluated the prognostic value of both GA and biomarkers for overall survival.

- Do laboratory parameters improve the estimation of life expectancy beyond clinical information? How does this compare with the added prognostic value of the GA?
- Are laboratory parameters able to optimize the estimation of life expectancy beyond clinical information and information from the GA as a whole?

Chapter 7

The home care literature focuses on the general population and not specifically on patients with cancer. A diagnosis of cancer and subsequent treatment can have a substantial effect on the well-being of patients and their need for home care.

- Is the use of formal care and informal care shortly after a cancer diagnosis different in older patients with cancer compared with the two control groups (MCP and ONC)?
- How does formal care and informal care change after one year in older patients with cancer and the two control groups?
- Which factors predict a transition towards formal care one year after a cancer diagnosis?

Chapter 8

Much of what we know about coping is based on cross-sectional research in younger patients. More psychosocial research is needed that focuses on older patients.

- Do dispositional coping strategies shortly after a cancer diagnosis predict changes in well-being after one year in older patients with cancer?
- What is the impact of ageing and cancer on the relationship between baseline coping and subsequent well-being after one year?

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Chapter 2.

Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer

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Abstract

Objective

In this study, we evaluated the Groningen Frailty Indicator (GFI) and the G8 questionnaire as screening tools for Comprehensive Geriatric Assessment (CGA) in older cancer patients.

Patients and Methods

Eligible patients with various types and stages of cancer were evaluated for frailty before treatment. Patients were categorized as patients with a normal CGA and abnormal CGA (≥ 2 impaired tests). The diagnostic performance of the screening tools was evaluated against the CGA with Receiver Operating Characteristic analysis.

Results

In total, 170 patients (79 women) with median age 77 years old (range 66-97 years) were included. Sixty-four percent of patients had an abnormal CGA while according to the GFI (GFI≥4) and G8 questionnaire (G8≤14) 47% and 76% of patients had an abnormal screening test. Overall, there was no significant difference (p=0.97) in diagnostic performance between the two screening tools. The Area Under the Curve was for both 0.87. For the GFI and G8 questionnaire the sensitivity was respectively 66% (95%CI: 56-75%), 92% (95%CI: 85-96%); the negative predictive value: 59% (95CI%: 49-69%), 78% (95%CI: 63-88%); and the specificity: 87% (95%CI: 76-94%), 52% (95%CI: 39-65%).

Conclusion

In this study, we showed that overall both the GFI and the G8 questionnaire were able to separate older cancer patients with a normal and abnormal CGA. For the G8 questionnaire, an adequate sensitivity and NPV were demonstrated, however at the expense of the specificity. For the GFI, we suggest lowering the threshold with one point to GFI ≥3 to screen patients for a CGA.

Introduction

Cancer is a disease of the elderly and more than 50% of cancer patients are older than 65 years old.[1] The changing demographics will result in an even bigger number of elderly patients facing cancer and who are in need of subsequent care and treatment.

Older cancer patients have been underrepresented in cancer-treatment trials.[2] Because of this, there is a lack of scientific knowledge how to select the elderly cancer patient for different anticancer strategies. The Comprehensive Geriatric Assessment (CGA) is recommended by the International Society of Geriatric Oncology (SIOG) to improve the detection of problems and guide the oncologist in treatment decision-making.[3] The CGA consists of a set of screening tools and includes assessment of functional status, physical performance, co-morbidity and medication use, nutritional status, social support, cognitive and psychological status. This assessment method adds information to Eastern Cooperative Oncology Group (ECOG) performance status[4] and detects more older cancer patients as being unfit for chemotherapy than physicians' judgement[5]. However, its completion is time consuming for the patient and the health care professional and this limits its use in everyday practice.

A two-step approach has been proposed to integrate the CGA in oncology practice. First, patients are screened. Several short screening tools have been developed to quickly identify potentially frail patients.[6] Patients who screen negative (normal test, considered 'fit') are likely to benefit most from standard treatment. Secondly, those patients who screen positive (abnormal test, considered 'unfit' or vulnerable) need a CGA linked to appropriate interventions. In order to follow a two-step approach, a screening tool should have a sufficient predictive ability to distinguish patients that may or may not benefit from a CGA. In this study, we compared the Groningen Frailty Indicator (GFI) and the G8 questionnaire as screening tools for frailty in older cancer patients in reference to the CGA.

Patients and methods

Study design and participants

This was a cross-sectional cohort study. Inclusion criteria were patients with all types and stages of cancer; age ≥ 65 years; an adequate understanding of the Dutch language; and ability to give informed consent. Exclusion criteria included severe known dementia; symptomatic brain metastases; and pre-existing major neurological or psychiatric problems.

Patients were simultaneously screened with the GFI and the G8 questionnaire followed by a CGA in Dutch, before treatment. Patients were seen and evaluated for frailty by a registered nurse or researcher in two non-academic general hospitals in Belgium (ZiekenhuisNetwerkAntwerpen Middelheim, Antwerp (central site) and Jessa hospital, Hasselt). When communication with the patient was difficult, a family member was allowed to help answering the questions. The study protocol was approved by the appropriate Ethical Committee and each patient provided written informed consent prior to study entry.

The Comprehensive Geriatric Assessment

There is no consensus about which tools to include in a CGA. The CGA in this study consisted of eight questionnaires that are widely used in the literature.[7,8] For analysis purposes dichotomous outcomes were used for each questionnaire. For questionnaires that normally don't have a dichotomous outcome in their scoring system, i.e. for nutrition and cognition, we selected a cut-off value so that not only patients who were malnourished or with a severe cognitive impairment were identified but also patients who were at risk of malnourishment and with a mild cognitive impairment. See Table 1 for an overview of the selected cut-off values for the individual questionnaires that comprise the CGA. Consistent with previous studies, we defined patients at risk for frailty if more than one of the individual tests of the CGA scored above the cut-off score for impairment.[9-11] Patients were categorized as patients with a normal CGA (≤1 deficit out of eight tests within the CGA) and patients with an abnormal CGA (≥2 deficits in the CGA).

Function. Function was evaluated by the Katz Activity of Daily Living (ADL)[12] and Lawton-Brody Instrumental Activity of Daily Living (IADL)[13]. Dependence in one or more domains was defined as having an impaired test.[7]

Mobility/Falls. Various cut-off points are found in the literature for the Timed Up and Go test (TUG).[14] A cut-off score of ≥13.5 seconds has been shown to indicate a high risk of falls and was adopted in this study.[15]

Nutrition. Malnourished patients and patients at risk of malnutrition were identified with the full Mini Nutritional Assessment questionnaire (MNA).[16]

Co-morbidity. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was used to assess co-morbidity.[17,18] Guidelines for scoring the CIRS-G are described by Miller and Towers.[19]

Cognition. The Folstein Mini-Mental State Examination (MMSE) is widely used.[20] Patients with a score <24 have an abnormal test.

Depression. For the 30-item Geriatric Depression Scale (GDS-30), we adopted a cut-off value of >10 in line with the original authors.[21]

Social support. Support from family and friends was measured by the Medical Outcomes Study Social Support Scale (MOS-SSS).[22] The 'overall support index' was calculated by averaging the scores of the 19 items.

Table 1. Comprehensive geriatric assessment measures

Geriatric domain	Measure	N° items	Score range	Cut-off value
Function	ADL	6	0-6	≤ 5
	IADL	8	0-8	≤ 7
Mobility	TUG	-	0-90	≥ 13.5 sec
Nutrition	MNA	18	0-30	≤ 23.5
Co-morbidity	CIRS-G	14	-	≥ 1 category at level 3/4 severity
Cognition	MMSE	5	0-30	< 24
Depression	GDS-30	30	0-30	> 10
Social support	MOS-SSS	19	0-5	< 4

ADL: Activity of Daily Living; IADL: Instrumental Activity of Daily Living; TUG: Timed Up and Go test; MNA: Mini Nutritional Assessment; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; MMSE: Mini-Mental State Examination; GDS-30: 30-item Geriatric Depression Scale; MOS-SSS: MOS Social Support Survey

The Groningen Frailty Indicator

The GFI was developed as a screening instrument for the level of frailty in geriatrics that specifically also included psycho-social components (Appendix 1).[23,24] The GFI screens for loss of functions and resources in four domains: physical, cognitive, social, and psychological; and was found to be a one-dimensional concept. The original authors tested the GFI in a sample of 275 older people that included hospital inpatients, nursing home residents, and community-dwelling elderly. Scores range from zero (not frail) to fifteen (very frail). A score of GFI≥4 was regarded as moderately frail according to a panel of geriatric experts. We adopted this cut-off value in our study to define an abnormal screening test. This tool has already been used in various patient groups, oncogeriatric patients included.[11,25-29]

The G8 questionnaire

The G8 questionnaire was recently developed as a screening tool for CGA for elderly patients in oncology. The G8 questionnaire (eight questions) is an easy-to use screening tool with a total score ranging from zero to seventeen (Appendix 2). This tool was developed based on the MNA and includes seven items and age. The G8 screening tool was evaluated in 364 cancer patients older than 70 years prior to chemotherapy.[30] Results suggested 14 as threshold, equivalent to 90% sensitivity, and 60% specificity. Based on these findings, we used in our study a G8 cut-off score of ≤14 to define an abnormal screening test.

Statistical analysis

The ability of the GFI and the G8 questionnaire to differentiate patients with a normal and an abnormal CGA was evaluated. Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of both screening tools against the CGA. The area under the curve (AUC) was calculated to reflect and to compare the predictive value of both screening tools to discriminate patients with a normal and an abnormal CGA. A statistical (nonparametric) comparison of both ROC curves was

carried out with the method of Delong et al.[31] The sensitivity, specificity, Negative Predictive Value (NPV), and Positive Predictive Value (PPV) of the screening tests were determined. This was a pilot study without calculation of a specific sample size. ROC analysis was done with MedCalc for Windows, Version 12.2.1.0 (Medcalc software, Mariakerke, Belgium).

Results

Sample description

A total of 170 eligible cancer patients (79 women) were recruited at two sites in Belgium. From October 2009 to December 2011, the central site included 150 eligible patients. Only four other patients refused participation. The second site included 20 patients for this study.

Patient characteristics are summarized in Table 2. The median age of patients in the study was 77 years with a range of 66-97 years; 89% of patients were ≥70 years old, and 9% of patients were ≥85 years old. From 170 patients, 36% of the patients were hospitalized at the time of frailty assessment. Sixty percent had a newly diagnosed cancer while the other patients had recurrent or progressive disease. Metastatic disease was present in 58% of patients and the treatments received by the patients after frailty assessment are summarized in Table 3.

Table 2. Patient characteristics

Characteristic	Patients (%)
Gender	
Female	79 (46%)
Male	91 (54%)
Median Age (range)	77 (66-97)
Outpatients	109 (64%)
Newly diagnosed	102 (60%)
Cancer type	
Urological	49 (29%)
Digestive system	32 (19%)
Head and neck	28 (16%)
Breast	25 (15%)
Lung	18 (11%)
Other	18 (11%)
Metastatic disease	
Yes	98 (58%)
No	67 (39%)
Unknown	7 (4%)

Table 3. Treatment received

Treatment received	Treatment intent		
	Palliative	Curative	Total
Chemotherapy	60	35	95 (56%)
CRT	1	13	14 (8%)
Radiotherapy	5	5	10 (6%)
Surgery	0	5	5 (3%)
Targeted therapy	6	0	6 (4%)
Hormonal therapy	14	0	14 (8%)
Other*	-	-	25 (15%)

* Wait-and-see policy, patients received best supportive care, refused therapy, or were lost to follow up.

CGA results

All questionnaires were completed for each patient at inclusion. Sixty- one patients (36%) had a normal CGA. Two or three deficits in the CGA were detected in 55 patients (32%) and four or more deficits in 54 patients (32%). In total, 109 patients (64%) had an abnormal CGA. The percentage of patients that had an impairment on the individual CGA components according to the cut-off values described in Table 1 were as follows: ADL: 33%; IADL: 52%; mobility: 35%; nutrition: 53%; co-morbidity: 35%; cognition: 9%; depression: 24%; and social support: 20%. For mobility, 17 patients (10%) were not able to do the TUG because they were hospitalized and/or too weak and were given a predefined maximum score of 90 seconds.

Predictive performance of the GFI

The GFI screened 80 patients (47%) as positive (GFI≥4). The sensitivity was 66% (95% Confidence Interval [CI]: 56-75%) and the specificity 87% (95%CI: 76-94%) for identifying two or more deficits in the CGA. The PPV and the NPV were respectively 90% (95%CI: 82-95%) and 59% (95%CI: 49-69%). The group of patients with an abnormal CGA had a mean GFI score of 4.7 (Standard Deviation [SD] 2.4) and patients with a normal CGA had a mean score of 1.8 (SD 1.3).

The AUC for the GFI was 0.87 (95%CI: 0.81-0.92; Standard Error [SE]: 0.03). The optimal cut-off point to identify patients with an abnormal CGA was estimated at GFI score ≥3. The sensitivity and the specificity for the different cut-off values are given in Table 4.

Predictive performance of the G8 questionnaire

Out of 170 patients, 129 patients (76%) had an abnormal screening test according to the G8 questionnaire. For cut-off value G8 score ≤14, the sensitivity was 92% (95%CI: 85-96%) and the specificity 52% (95%CI: 39-65%). The PPV and NPV were respectively 78% (95%CI: 70-84%) and 78% (95%CI: 63-88%). The mean G8 score was 10.0 (SD 2.9) for patients with an abnormal CGA. Patients with a normal CGA had a mean G8 score of 14.1 (SD 2.0).

The G8 questionnaire had an AUC of 0.87 (95%CI: 0.81-0.92; SE 0.03) and the optimal cut-off value for identifying patients with an abnormal CGA was estimated at G8 score ≤12.5. The results for sensitivity and specificity for different cut-off values are shown in Table 5.

Table 4. The GFI: Sensitivity/specificity for different cut-off values

Cut-off value	%pts	Sensitivity	Specificity
Cut-off ≥2	80%	96%	49%
Cut-off ≥3**	66%	87%	70%
Cut-off ≥4*	47%	66%	87%
Cut-off ≥5	25%	39%	98%

*Cut-off value used in previous studies and in this study. **Cut-off value that corresponded with the highest Youden index in ROC analysis. Abbreviations: % pts: percentage of patients

Table 5. The G8 questionnaire: Sensitivity/specificity for different cut-off values

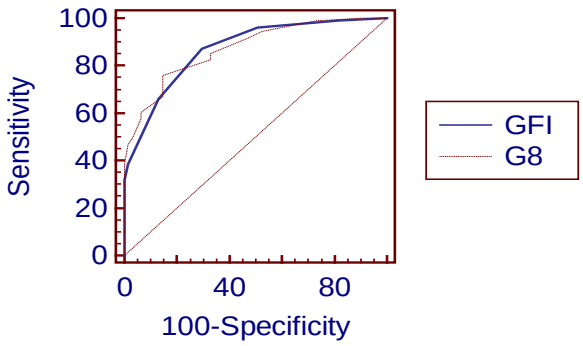
Cut-off value	%pts	Sensitivity	Specificity
Cut-off ≤11	48%	67%	85%
Cut-off ≤12	53%	74%	85%
Cut-off ≤12.5**	54%	76%	85%
Cut-off ≤13	65%	83%	67%
Cut-off ≤14*	76%	92%	52%

*Cut-off value used in previous studies and in this study. **Cut-off value that corresponded with the highest Youden index in ROC analysis. Abbreviations: % pts: percentage of patients

Comparison predictive performance

The ROC curves of the GFI (AUC= 0.87) and the G8 questionnaire (AUC= 0.87) are shown in Figure 1. A pair wise comparison of the ROC curves of both screening tools did not give a significant difference (p=0.97) for the ability to differentiate patients with a normal CGA and patients with an abnormal CGA.

Figure 1. ROC curves of the GFI and the G8 questionnaire



ROC curve comparison for the GFI and the G8 questionnaire. AUC= 0.87 for both screening tools. The significance level of a pairwise comparison of the ROC curves was p= 0.97.

Discussion

Frailty is a useful yet debatable concept.[24,32] The core feature of frailty is increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to decline in homeostatic reserve and resiliency. The main consequence is an increased risk for multiple adverse health-related outcomes. Therefore, frailty is an important factor to be considered in the senior cancer patient when a treatment decision (e.g. chemotherapy or surgery) needs to be made. The integration of CGA in oncology practice could provide valuable guidance for the oncologist in this decision-making process by taking the global health status of the patient into account. To avoid costs and the unnecessary in-depth assessment of 'fit' patients, a two-step approach with screening is recommended. In this study, we showed that overall both the GFI and the G8 questionnaire (no significant difference, p= 0.97) were able to differentiate patients who may or may not benefit from a CGA.

As there is a need for a simple and accurate screening tool that can be used routinely in a busy practice regardless of tumour specific factors, we studied a heterogenic sample of cancer patients. A large proportion of our sample had advanced disease and a smaller proportion was hospitalized at the time of frailty assessment. All patients were assessed at a time when a treatment decision had to be made. Whether the information obtained by the CGA influenced the treatment decision could not be determined in this study.

In our sample, 64% had more than one impaired test in the CGA or had an 'abnormal CGA'. For nutrition, approximately half of the patients had an impaired test. Malnutrition is a common problem among cancer patients especially in patients with cancer of the digestive system and head and neck which together constituted 35% of our sample. For IADL, also approximately half of the patients had an impaired test, i.e. impairment in at least one domain. See Table 1 for an overview of the cut-off values for the individual questionnaires that comprise the CGA. It could be argued whether having one impaired IADL domain (for example doing the laundry) should be weighed equally as being malnourished. This question could be extended to all geriatric domains in a CGA. For the purpose of the study, i.e. to identify at least two impaired tests in the CGA, we believe that this is not necessary. It is also not clear what the best approach would be for such an analysis. Obviously when the results of a CGA are interpreted for decisions concerning treatment or interventions, the different domains are weighed differently. This 'third step' (e.g. interpretation and discussion of results with oncologist/geriatrician, multidisciplinary meeting) after the two-step approach of screening followed by CGA was not investigated in this study.

Two screening tools were evaluated in this study to screen for CGA in older cancer patients. For the evaluation of a screening test, the sensitivity and the NPV are considered the most important characteristics. The sensitivity (92% versus 66%) and the NPV (78% versus 59%) of the G8 questionnaire were superior to the GFI. This was at the expense of the specificity (52% versus 87%) of the G8 questionnaire leading to a high number of false positives. ROC analysis of our sample estimated

G8 score ≤12.5 as the optimal cut-off value for an abnormal screening test. This however resulted in a decrease of the NPV from 78% to 67%. ROC analysis for the GFI estimated GFI ≥3 as the optimal cut-off value with a sensitivity (87%) and NPV (75%) similar to that of the G8 questionnaire. It should be noted that while the G8 questionnaire was designed to screen for CGA in geriatric oncology, the GFI was not. The GFI was developed to screen for frailty in geriatrics where a score of ≥4 was regarded as 'moderately frail'. However, based on our results we suggest selecting cut-off value GFI ≥3 instead of GFI ≥4 when this tool is used in geriatric oncology to screen patients for CGA.

An adequate sensitivity and NPV are important characteristics for a screening tool. A too sensitive tool, however, might make the screening step in this CGA-based approach redundant by excluding only a small proportion of patients for CGA. The percentage of patients with a positive screening test are shown in Table 4, 5 and 6. The G8 questionnaire in our study, for example, would have excluded only 24% patients from a CGA. However, if one considers the time needed for a CGA (30 to 45 minutes) in contrast to the time needed for a screening test (approximately 5 minutes), then this two-step approach might be interesting in a setting where older cancer patients are screened systematically.

Similar studies validating the GFI or the G8 questionnaire are summarized in Table 6. Here, the results of other screening tools (VES-13 and TRST) used for comparison were added. We found two reports validating the GFI. Kellen et al.[11] validated the GFI in reference to a CGA and Kenis et al.[25] in reference to the 'geriatric profile' determined by consensus by a multidisciplinary team. In both studies the patient population consisted of patients with various types of cancer. Both groups reported a lower sensitivity (39% and 57%) and NPV (36% and 40%) than our findings (sensitivity: 66% and NPV 59%). Results for other cut-off values were not explored in these studies. As mentioned above we suggest lowering the threshold with one point for the GFI when this screening tool is used in this setting.

The G8 questionnaire has only recently been developed. More recently an abstract of the Oncodage study, a large prospective multicentre study validating the G8 screening tool, was published.[33] The study population consisted of patients with various types of cancer, approximately half with breast cancer. Corresponding with our findings, an adequate sensitivity and NPV was reported. An adequate reproducibility of the G8 screening tool was also demonstrated in the Oncodage study. This screening tool is also being used in several ongoing studies.

Research in this field is challenging. One major issue is the lack of a gold standard. Usually, frailty screening tools are compared against the CGA. However, there is no unique standardized CGA. The definition for an abnormal CGA, scales, and thresholds vary across studies. For example, the abnormal CGA definition used in the Oncodage study (≥1 impaired CGA test) would result, in this study, to 86% patients with an abnormal CGA.

Table 6. Overview: studies validating the GFI or G8

	N° pts	% abnormal CGA	Screening tool	Screened positive (%)	Sens	Spec	NPV
Soubeyran et al. 2008 [abstract]	363	-	G8	-	90%	60%	-
Kenis et al. 2009 [abstract]	140	NA*	G8	-	80%	40%	35%
			GFI	-	57%	87%	36%
			TRST**	-	92%	50%	63%
Kellen et al. 2010	113	68%***	GFI	31%	39%	86%	40%
			VES13	49%	61%	78%	48%
Soubeyran et al. 2011 Oncodage study [abstract]	1425	80%	G8	68%	77%	64%	-
			VES13	60%	69%	74%	-
			G8+VES13	-	87%	53%	-
This study	170	64%	G8	76%	92%	52%	78%
			GFI	47%	66%	87%	59%
			GFI cut-off ≥3	66%	87%	70%	75%

Results were rounded off; * No CGA was done, but a 'geriatric profile' was present in 79% of the patients as determined by consensus; ** Cut-off value 1; *** Patients had an abnormal CGA or were cognitively impaired. Abbreviations: Pts: Patients; NA: Not Applicable; Sens: sensitivity; Spec: Specificity; NPV: Negative Predictive Value; TRST: Triage Risk Screening Tool; VES13: Vulnerable Elders Survey

As more and more centers are gaining experience in integrating frailty assessment in oncology practice, research should also focus to the subsequent interventions. Prospective studies are also warranted to determine the predictive validity of frailty screening tools for treatment outcome e.g. severe chemotherapy toxicity.

Conclusion

In this study, we showed that overall both the GFI and the G8 questionnaire were able to separate older cancer patients with a normal and abnormal CGA. For the G8 questionnaire, an adequate sensitivity and NPV were demonstrated, however at the expense of the specificity. For the GFI, we suggest lowering the threshold with one point to GFI ≥3 to screen patients for a CGA.

Author Contributions

Concepts and design: Dirk Schrijvers, Abdelbari Baitar.

Data collection: All authors.

Analysis and interpretation: Abdelbari Baitar, Dirk Schrijvers.

Manuscript preparation: Abdelbari Baitar.

Manuscript review: All authors.

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Appendix A. The Groningen Frailty Indicator (GFI)

Are you able to carry out these tasks single-handed without any help? (The use of aids such as a walking stick, walking frame, wheelchair, is considered as independent)

1 Shopping,
2 Walking around outside (around the house or to the neighbors)
3 Dressing and undressing
4 Going to the toilet

5 What score do you give yourself for physical fitness? (scale 0 to 10)
6 Do you experience problems in daily life due to poor vision?
7 Do you experience problems in daily life due to poor hearing?
8 During the last 6 months (6 kg) have you lost a lot of weight unwillingly? (or 3 kg in 1 month)
9 Do you take 4 or more different types of medicine?
10 Do you have any complaints about your memory?

11 Do you sometimes experience an emptiness around you?
12 Do you sometimes miss people around you?
13 Do you sometimes have the feeling of being left alone?
14 Have you recently felt downhearted or sad?
15 Have you recently felt nervous or anxious?

Scoring:
Questions 1-4: Independent=0; dependent=1
Question 5: 0-6=1; 7-10=0
Question 6-9: No=0; Yes=1
Question 10: No or sometimes=0; Yes=1
Questions 11-15: No=0; sometimes or yes=1

Appendix B. The G8 questionnaire

The G8 questionnaire			
	Items	**Possible answers**	Score
A	Loss of appetite? Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0: severe anorexia 1: moderate anorexia 2: no anorexia	
B	Loss of weight during the last 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 bed/chair but not to go out 2: goes out	
E	Neuropsychological problems	0: severe dementia or depression 1: moderate dementia or depression 2: no psychological problem	
F	Body Mass Index	0: BMI < 18.5 1: BMI between 18.5 and <21 2: BMI 21 to <23 3: BMI ≥23	
H	Takes >3 prescription drugs per day	0: yes 1: no	
P	In comparison with other people of the same age, how do they consider their health status	0: not as good 0.5: does not know 1: as good 2: better	
	Age	0: >85 1: 80-85 2: <80	
	Total score	**0-17**	

Chapter 3.

Implementation of geriatric assessment-based recommendations in older patients with cancer: a multicentre prospective study

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Abstract

Purpose

The main objective of this study was to describe geriatric recommendations based on geriatric assessment (GA) and to evaluate the implementation of these recommendations.

Patients and methods

A two-step approach of screening followed by GA was implemented in nine hospitals in Belgium. Patients ≥70 years were included at diagnosis or at disease progression/relapse. Concrete geriatric recommendations were systematically documented and reported to the treating physicians and consisted of referrals to professional health care workers. Patient charts were reviewed after one month to verify which geriatric recommendations have been performed.

Results

From August 2011 to July 2012, 1550 patients were included for analysis. The median age was 77 (range: 70-97) and 57% were female. A solid tumour was diagnosed in 91.4% and a haematological malignancy in 8.6%. Geriatric screening with the G8 identified 63.6% of the patients for GA (n=986). A median of two geriatric recommendations (range: 1-6) were given for 76.2% (95%CI: 73.4-78.8) of the evaluable patients (n=710). A median of one geriatric recommendation (range: 1-5) was performed in 52.1% (95%CI: 48.4-55.8) of the evaluable patients (n=689). In general, 460 or 35.3% (95%CI: 32.8-38.0) of all the geriatric recommendations were performed. Geriatric recommendations most frequently consisted of referrals to the dietician (60.4%), social worker (40.3%), and psychologist (28.9%).

Conclusion

This implementation study provides insight into GA-based recommendations/interventions in daily oncology practice. Geriatric recommendations were given in about three fourths of patients. About one third of all geriatric recommendations were performed in approximately half of these patients.

Introduction

Cancer and its treatment might precipitate classic geriatric syndromes such as frailty, falls, malnutrition, delirium, or urinary incontinence [1]. It is therefore crucial to have better insights on the impact of 'non-cancer' related health issues when cancer treatment is considered. Comprehensive Geriatric Assessment (CGA), taking patients medical, functional, cognitive and social needs into account, is considered the most appropriate way to obtain a better view on the global health of the older patient. Several guidelines have recommended a CGA-based approach in oncology to guide treatment decision-making and to implement geriatric interventions [2-4].

In Belgium, a Cancer Plan was launched in 2008 in accordance with guidelines of the World Health Organization [5]. One of the initiatives in this plan was to provide support for pilot projects in the field of clinical geriatric oncology which led to the implementation of CGA in numerous academic and non-academic hospitals. Different models for implementation of CGA (e.g. geriatric oncology units) are possible, each with their advantages and disadvantages [2]. The best model of care cannot be determined due to lack of evidence and depends of local preferences and available resources. In the current implementation study, geriatric expertise was brought to both inpatients and outpatients who remained under the supervision of their treating physicians. This model was implemented from 2009 and resulted in various papers showing the feasibility and relevance of systematic geriatric screening followed by geriatric assessment in daily oncology practice [6-8].

From a practical point of view, the implementation of CGA can be divided into five consecutive steps: (i) identifying patients who can benefit from CGA; (ii) assessing these patients; (iii) developing recommendations; (iv) implementing the recommendations; and (v) provision of follow-up and adjustment of the care plan with repeated CGA. Most studies on the implementation of CGA in oncology have mainly focused on the first two steps. For this reason, the recent update of the consensus paper of the International Society of Geriatric Oncology (SIOG) preferred the use of the term Geriatric Assessment (GA) over Comprehensive Geriatric Assessment (CGA) in the approach of the older cancer patient [2]. However, the effects of GA by itself are limited, unless followed by targeted geriatric recommendations and interventions. Few studies have focused on these geriatric interventions in oncology, despite their importance for GA effectiveness. Therefore, this study aims to describe the geriatric recommendations based on the results of the GA and to evaluate the implementation of these recommendations.

Patients and methods

Patient population

Patients with all tumour types (except non-melanoma skin cancer) and haematologic malignancies were assessed in a uniform manner across six academic and three non-academic hospitals spread all over Belgium. Patients 70 years and older were included at diagnosis or at disease progression/relapse, when

a change in therapeutic strategy was considered. Both inpatients and outpatients were recruited from August 2011 until July 2012. This study cohort was preceded in the same hospitals by a GA implementation study between October 2009 and July 2011 that included only six tumour types and only focused on GA and not on GA-based recommendations [7]. The study was approved by the Ethical Committee of each participating hospital.

Geriatric screening and assessment

In each center, a trained health care worker (THCW) (i.e. a (para-)medical graduate attached to the oncology and/or geriatric department) was appointed to identify eligible patients and to perform a geriatric screening with the G8 (range:0-17) [6,9,10]. In patients with an abnormal G8 score (cut-off ≤14), the geriatric screening was followed by a GA, also performed by a THCW. Patients were assessed for the following GA domains: functional status (FS), fall history, fatigue, cognition, depression, nutrition, polypharmacy, and comorbidities. A detailed description of the content of the GA can be found in the supplementary data section of ref 7. In contrast to the preceding study that included patients between October 2009 and July 2011, concrete geriatric recommendations based on GA were now systematically documented and reported to the treating physicians. Patient charts were reviewed after one month to verify which geriatric recommendations were actually performed. Informed consent was obtained from all patients or their caregiver.

Geriatric recommendations based on GA results

Depending on the hospital and its specific process of care, case-specific geriatric recommendations were made by the THCW based on standard protocols approved by the geriatric team, by the THCW in collaboration with geriatrician and/or treating physician and/or internal geriatric liaison, by a geriatrician or by a geriatric oncology team at multidisciplinary team meetings. Geriatric recommendations consisted of referrals to the geriatrician, geriatric liaison team, social worker, occupational therapist, physiotherapist, geronto-psychiatrist, psychologist, dietician, geriatric day clinic, fall clinic, another physician, and other. For each patient, geriatric recommendations were documented in two different ways. Firstly, the frequency of the different types of referrals was documented to get an overview of the different geriatric recommendations for each patient. Secondly, in order to have an overview of which geriatric problems led to which geriatric recommendations, we documented for each patient which geriatric problems, at the level of the GA domains, led to which referrals. For example, a referral to a social worker for a particular patient might be recommended for problems concerning the GA domain ‘social status’ and/or the GA domain ‘functional status’.

Statistical analysis

A descriptive analysis (frequencies, median, and percentages) was performed using SPSS 17.0 software (Chicago, IL). Percentages were associated with a 95% confidence interval calculated in accordance with Wilson's method where appropriate [11].

Results

Patient population

From a total of 1672 patients that were approached, 88 patients refused participation and 34 patients were excluded from the study for not meeting the inclusion criteria. The data of 1550 patients were used for analysis (see Figure 1).

The median age was 77 years (range: 70-97) and 57% were female. A solid tumour was diagnosed in 91.4% of patients and 8.6% of patients were diagnosed with a haematological malignancy. The most frequent diagnoses were cancer of the digestive system (31.4%), breast (26.1%), and genitourinary sites (12.7%). At the moment of evaluation, 69.5% had a newly diagnosed cancer, whereas 30.5% had disease progression or relapse. The most common comorbidities were peripheral vascular disease (21.2%), diabetes without complications (14.7%), congestive heart failure (13.5%), ulcer disease (12.9%), secondary malignancy (12.5%), and chronic pulmonary disease (11.4%). Details on the Charlson comorbidity index and other patient characteristics are summarized in Table 1.

Geriatric screening and assessment

The G8 identified 986 patients (63.6%) with a geriatric risk profile (G8 ≤14) who could benefit from a full GA. A full GA was performed in 979 patients. Geriatric recommendations data based on GA were available for 932 patients (see Figure 1). Patient characteristics and GA results for this patient population are separately summarized in Table 1 and Table 2, respectively. For FS, respectively 57.7% and 63.5% of the patients had impairments for activities of daily living (ADL) and instrumental ADL (IADL). At least one fall incident during the past year was reported by 38.3% of the patients. Fatigue was experienced by 64.4% of the patients; mild/severe cognitive decline was detected in 17.5% of the patients; and 59.6% of the patients were at risk for depression. Screening for nutritional status identified 77.6% of the patients at risk for malnutrition. A complete mini nutritional assessment (MNA) was performed in these patients, of which 17.6% turned out to have a normal nutritional status and 69.0% and 13.4% respectively were at risk for malnutrition and malnourished.

Figure 1. Patient Flowchart

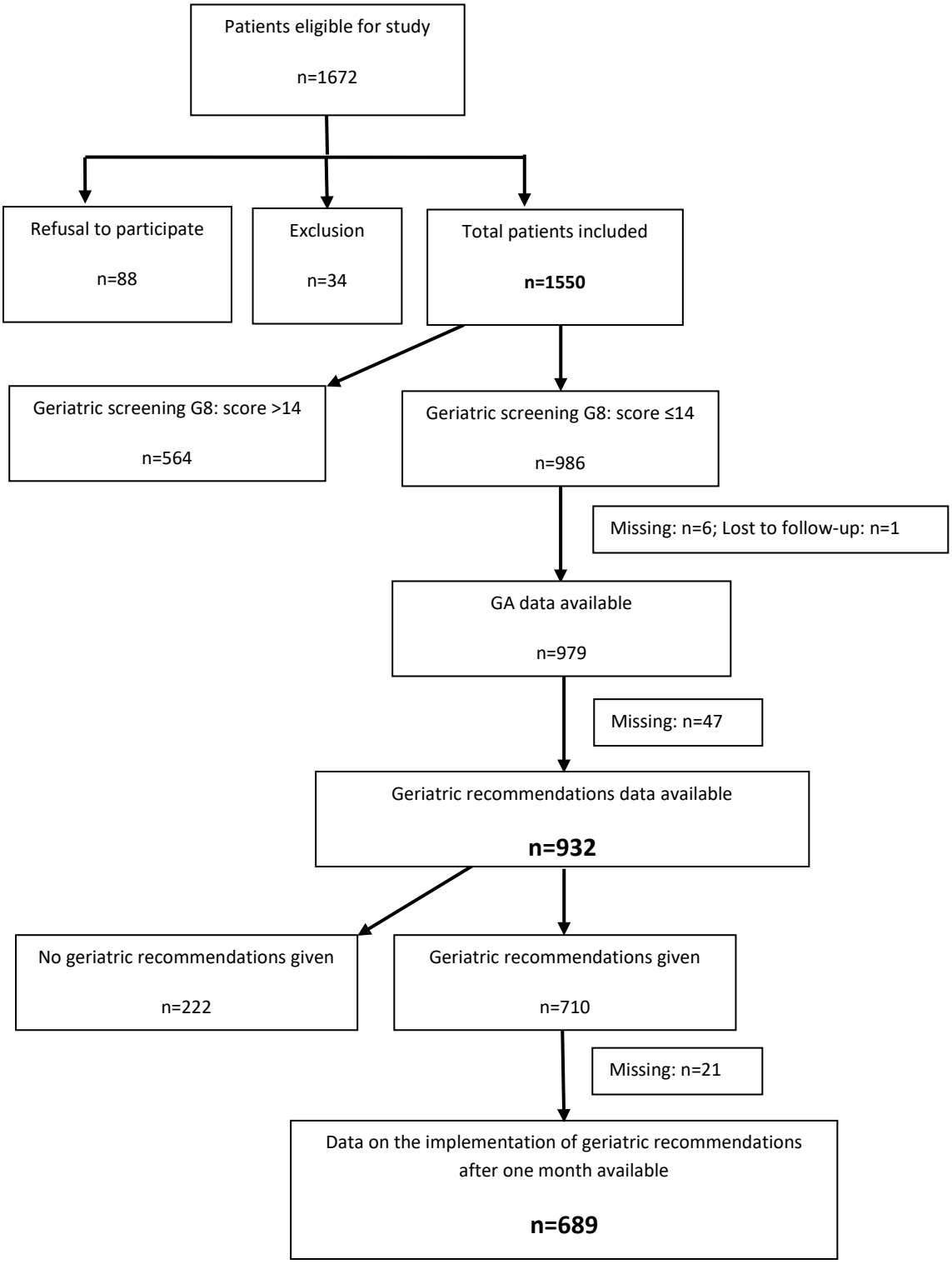

Table 1. Patient and clinical characteristics

	Total of patients included		Patients with geriatric recommendations data at baseline available		Patients with data on the implementation of geriatric recommendations after 1 month available	
	N° pts	%	N° pts	%	N° pts	%
Total N° pts	1550	100	932	100	689	100
Age						
Median (range)	77 (70-97)		79 (70-97)		79 (70-97)	
Gender						
Female	884	57,0	519	55,7	390	56,6
Male	666	43,0	413	44,3	299	43,4
Tumour type						
Carcinoma	1416	91,4	841	90,2	627	91,0
Digestive system	487	31,4	335	35,9	252	36,6
Breast	405	26,1	187	20,1	134	19,4
Genitourinary sites	197	12,7	107	11,5	69	10,0
Gynecologic sites	116	7,5	72	7,7	56	8,1
Thorax	95	6,1	67	7,2	51	7,4
Skin	44	2,8	22	2,4	19	2,8
Head and neck	36	2,3	25	2,7	24	3,5
Musculoskeletal sites	25	1,6	19	2,0	16	2,3
CUP	7	0,5	6	0,6	5	0,7
CNS (brain and spinal cord)	4	0,3	1	0,1	1	0,1
Haematological malignancies	134	8,6	91	9,8	62	9,0
Time point of assessment						
New diagnosis	1078	69,5	633	67,9	463	67,2
At progression	472	30,5	299	32,1	226	32,8
Carcinoma						
Stage	n= 1349		n=811		n=609	
I	183	13,6	83	10,2	53	8,7
II	284	21,1	144	17,8	96	15,8
III	267	19,8	157	19,4	120	19,7
IV	617	45,7	427	52,7	340	55,8
Treatment received	n=1416		n=841		n= 627	
Surgery	693	48,9	363	43,2	252	40,2
Chemotherapy	638	45,1	405	48,2	306	48,8
Radiotherapy	443	31,3	207	24,6	158	25,2
Hormonal therapy	344	24,3	147	17,5	106	16,9
Haematological malignancies						
Setting	n=134		n=91		n=62	
Curative	54	40,3	34	37,4	32	51,6
Palliative	80	59,7	57	62,6	39	62,9
Treatment received	n=134		n=91		n=62	
Surgery	7	5,2	3	3,3	1	1,6
Chemotherapy	104	77,6	68	74,7	48	77,4
Radiotherapy	48	35,8	9	9,9	7	11,3
Comorbidity	n=1547		n=931		n=688	
CCI 0	563	36,4	297	31,9	225	32,7
CCI 1	372	24,0	223	24,0	167	24,3
CCI ≥2	612	39,6	411	44,1	296	43,0
Pain	n=1517		n=931		n=689	
VAS 0	773	51,0	413	44,4	287	41,7
VAS 1-3	262	17,3	168	18,0	107	15,5
VAS 4-10	482	31,8	350	37,6	295	42,8
Polypharmacy	n=1516		n=917		n=679	
n= 0-4	775	51,1	388	42,3	286	42,1
n≥5	741	48,9	529	57,7	393	57,9

Legend: N° pts: Number of patients; CUP: Cancer of Unknown Primary origin; CNS: Central Nervous System; CCI: Charlson Comorbidity Index; ECOG-PS: Eastern Cooperative Oncology Group - Performance Status; VAS: Visual Analogue Scale.

Table 2. GA results

		Patients with geriatric data at baseline available		Patients with data on the implementation of geriatric recommendations after 1 month available	
		N° pts	%	N° pts	%
		932	100	689	100
Demographic data					
Living situation					
Home: alone		314	33,7	264	38,3
Home: with partner		514	55,2	357	51,8
Home: with family member		57	6,1	42	6,1
Service flat		14	1,5	5	0,7
Institution		25	2,7	14	2,0
Other		8	0,9	7	1,0
Marital status					
Single		47	5,0	37	5,4
Married		507	54,4	358	52,0
Divorced		37	4,0	27	3,9
Widow-er		331	35,5	263	38,2
Legally cohabiting		7	0,8	2	0,3
Other		3	0,3	2	0.3
Educational level					
Primary education		88	9,4	63	9,1
Lower secondary education		398	42,7	293	42,5
Higher secondary education		276	29,6	217	31,5
Higher education		88	9,4	63	9,1
University education		62	6,7	42	6,1
Other		20	2,1	10	1,5
Functional status					
ADL (6-24)	Independent	394	42,3	257	37,3
	Dependent (≥7)	538	57,7	432	62,7
IADL	Independent	340	36,5	218	31,6
(0-5/8 for male/female)	Dependent (<5 or <8)	592	63,5	471	68,4
Falls		n=930		n=687	
	No falls	574	61,7	412	60,0
	Fall present	356	38,3	275	40,0
Fatigue		n=925		n=686	
MOB-T (0-6)	No fatigue	329	35,6	230	33,53
	Presence of fatigue (<6)	596	64,4	456	66,47
Cognition		n=906		n=671	
MMSE (0-30)	Normal cognition (≥24)	747	82,5	529	78,8
	Mild decline (18-23)	118	13,0	104	15,5
	Severe decline (≤17)	41	4,5	38	5,7
Depression		n=919		n=682	
GDS-4 (0-4**)**	Normal	371	40,4	255	37,4
	At risk for depression (≥1)	548	59,6	427	62,6
Nutrition		n=929		n=687	
MNA-SF (0-14)	Normal	208	22,4	118	17,2
	At risk for malnutrition (≤11)	721	77,6	569	82,8
		n=717		n=567	
Full MNA (0-30)**	Normal	126	17,6	69	12,2
	At risk for malnutrition (17 - ≤23,5)	495	69,0	415	73,2
	Malnourished (<17)	96	13,4	83	14,6

Legend: ADL: Activities of Daily Living; IADL: Instrumental IADL; MOB-T: Mobility-Tiredness Test; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; MNA(-SF): Mini Nutritional Assessment (-Short Form)

*Defined as the presence of at least 1 item scored as 'tired' on the MOB-T; **A full MNA was conducted in patients with a positive MNA-SF

Geriatric recommendations based on GA results

Frequencies

Concrete geriatric recommendations were given for 710 patients (76.2%, 95% CI: 73.3-78.8%) from the 932 patients with available geriatric recommendations data. A median of two different geriatric recommendations (range: 1-6) were given for each patient. At chart review after one month, 689 patients (see Figure 1) with a total of 1302 given geriatric recommendations were evaluable to determine whether or not geriatric recommendations were performed. Patient characteristics and GA results for this specific patient population are also separately summarized in Table 1 and Table 2, respectively. In Table 3, the numbers of patients are shown according to the number of different (performed) geriatric recommendations per patient. The performed geriatric recommendations can be viewed stratified to the number of geriatric recommendations per patient at baseline. At least one geriatric recommendation was performed in 359 patients (52.1%, 95% CI: 48.4-55.8%) with a median of one performed recommendation (range: 1-5) per patient. A total of 460 different geriatric recommendations (35.3%, 95% CI: 32.8-38.0%) were performed after one month.

Referrals to implement geriatric recommendations

Most patients were referred to the dietician (60.4%), social worker (40.3%), psychologist (28.9%), or geriatric day clinic (16.1%). Referrals to other healthcare professionals or services were recommended in less than 10% of the patients.

The following referrals were the least performed when recommended: geronto-psychiatrist (0%), fall clinic (10.3%), geriatric day clinic (10.8%), physiotherapist (22.5%), another physician (22.6%), and psychologist (25.1%).

More details on referrals are provided in Table 4.

Geriatric recommendations on geriatric domain level

Problems in a specific GA domain led to referrals to various disciplines. An overview of all (performed) geriatric recommendations at the level of the GA domain is presented in Table 5. Problems in one GA domain always corresponded with one referral. Most referrals were recommended to address problems concerning nutrition (66.2%), social status (34.8%), FS (31.8%), or depression (31.6%).

Referrals for the following GA domains were the least performed when recommended: cognition (19.1%), falls (19.8%), and depression (25.7%).

Table 3. Frequency of geriatric recommendations based on GA results

Geriatric recommendations per patient	N° pts	%[a]	N°pts with data on the implementation of geriatric recommendations	N° pts with at least one performed geriatric recommendation	%	Performed geriatric recommendations per patient	N° pts	%[b]
0	222	23,8						
1	325	34,9	313	146	46,6	1	146	46,6
						0	167	53,4
2	212	22,7	208	110	52,9	2	29	13,9
						1	81	38,9
						0	98	47,1
3	118	12,7	114	75	65,8	3	9	7,9
						2	24	21,1
						1	42	36,8
						0	39	34,2
4	41	4,4	40	20	50,0	4	1	2,5
						3	3	7,5
						2	7	17,5
						1	9	22,5
						0	20	50,0
5	13	1,4	13	7	53,8	5	1	7,7
						4	2	15,4
						3	1	7,7
						2	2	15,4
						1	1	7,7
						0	6	46,2
6	1	0,1	1	1	100,0	6-2	0	0,0
						1	1	100,0
						0	0	0,0
Total	**932**		**689**	**359**				

[a] calculated from total N° pts with geriatric recommendations data (n=932 pts)

[b] calculated from the 'N° pts with data on implementation of geriatric recommendations'

Table 4. Recommended and performed referrals to implement geriatric recommendations

Referral	N° pts with recommended referral*	%	95%CI	N° pts with performed referral*	%	95%CI	Ratio (%)
Dietician	416	60,4	56.7-64.0	180	26,1	23.0-29.5	43,3
Social worker	278	40,3	36.7-44.1	127	18,4	15.7-21.5	45,7
Psychologist	199	28,9	25.6-32.4	50	7,3	5.5-9.4	25,1
Geriatric day clinic	111	16,1	13.6-19.0	12	1,7	1.0-3.0	10,8
Other physician	62	9,0	7.1-11.4	14	2,0	1.2-3.4	22,6
Geriatrician	50	7,3	5.5-9.4	22	3,2	2.1-4.8	44,0
Other	44	6,4	4.8-8.5	16	2,3	1.4-3.7	36,4
Geriatric Liaison team	42	6,1	4.5-8.1	19	2,8	1.8-4.3	45,2
Physiotherapist	40	5,8	4.3-7.8	9	1,3	0.7-2.5	22,5
Fall clinic	29	4,2	2.9-6.0	3	0,4	0.1-1.3	10,3
Occupational therapist	25	3,6	2.5-5.3	8	1,2	0.6-2.3	32,0
Geronto-psychiatrist	6	0,9	0.4-1.9	0	0,0	0.0-0.6	0,0

*Data were calculated from the total N° pts with data on implementation of geriatric recommendation at chart review after one month (n=689 pts)

Table 5. Overview of given and performed geriatric recommendations on geriatric domain level

		GA domain							
		Social status	FS	Falls	Fatigue	Cognition	Depression	Nutrition	Other
		% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
Dietician	Recommendation given							60.5 (56.8-64.1)	
	Recommendation performed							26.1 (23.0-29.5)	
Social worker	Recommendation given	31.3 (28.0-34.9)	17.1 (14.5-20.1)	0.3 (0.1-1.1)		1.2 (0.6-2.3)			0.1 (0.0-0.8)
	Recommendation performed	15.1 (12.6-18.0)	6.8 (5.2-9.0)	0.0 (0.0-0.6)		0.6 (0.2-1.5)			0.0 (0.0-0.6)
Psychologist	Recommendation given	0.6 (0.2-1.5)				1.2 (0.6-2.3)	27.1 (24.0-30.6)		
	Recommendation performed	0.1 (0.0-0.8)				0.4 (0.1-1.3)	7.0 (5.3-9.1)		
Geriatric day clinic	Recommendation given	1.3 (0.7-2.5)	5.4 (3.9-7.3)	2.5 (1.5-3.9)	1.7 (1.0-3.0)	12.2 (10.0-14.8)	1.5 (0.8-2.7)	1.3 (0.7-2.5)	
	Recommendation performed	0.4 (0.1-1.3)	0.7 (0.3-1.7)	0.4 (0.1-1.3)	0.6 (0.2-1.5)	1.5 (0.8-2.7)	0.3 (0.1-1.1)	0.4 (0.1-1.3)	
Other physcian	Recommendation given	0.4 (0.1-1.3)	0.7 (0.3-1.7)	1.0 (0.5-2.1)	5.1 (3.7-7.0)	0.9 (0.4-1.9)	0.6 (0.2-1.5)	0.4 (0.1-1.3)	1.6 (0.9-2.8)
	Recommendation performed	0.3 (0.1-1.1)	0.3 (0.1-1.1)	0.3 (0.1-1.1)	1.0 (0.5-2.1)	0.4 (0.1-1.3)	0.1 (0.0-0.8)	0.3 (0.1-1.1)	0.6 (0.2-1.5)
Geriatrician	Recommendation given		1.6 (0.9-2.8)	1.2 (0.6-2.3)	2.0 (1.2-3.4)	2.9 (1.9-4.4)	0.7 (0.3-1.7)	1.6 (0.9-2.8)	1.0 (0.5-2.1)
	Recommendation performed		0.3 (0.1-1.1)	0.1 (0.0-0.8)	0.3 (0.1-1.1)	0.7 (0.3-1.7)	0.1 (0.0-0.8)	1.0 (0.5-2.1)	0.4 (0.1-1.3)
Geriatric liaison team	Recommendation given	0.9 (0.4-1.9)	1.9 (1.1-3.2)	1.2 (0.6-2.3)	1.3 (0.7-2.5)	1.5 (0.8-2.7)	0.6 (0.2-1.5)	1.7 (1.0-3.0)	0.9 (0.4-1.9)
	Recommendation performed	0.4 (0.1-1.3)	0.7 (0.3-1.7)	0.6 (0.2-1.5)	0.7 (0.3-1.7)	0.3 (0.1-1.1)	0.3 (0.1-1.1)	0.9 (0.4-1.9)	0.3 (0.1-1.1)
Physiotherapist	Recommendation given		3.3 (2.2-5.0)	3.2 (2.1-4.8)	0.3 (0.1-1.1)				
	Recommendation performed		1.0 (0.5-2.1)	0.4 (0.1-1.3)	0.0 (0.0-0.6)				
Fall clinic	Recommendation given			4.2 (2.9-6.0)					
	Recommendation performed			0.4 (0.1-1.3)					
Occupational therapist	Recommendation given		0.7 (0.3-1.7)	2.5 (1.5-3.9)					0.3 (0.1-1.1)
	Recommendation performed		0.1 (0.0-0.8)	0.9 (0.4-1.9)					0.1 (0.0-0.8)
Geronto-psychiatrist	Recommendation given					0.4 (0.1-1.3)	0.7 (0.3-1.7)		
	Recommendation performed					0.0 (0.0-0.6)	0.0 (0.0-0.6)		
Other	Recommendation given	0.3 (0.1-1.1)	1.0 (0.5-2.1)	0.3 (0.1-1.1)	0.7 (0.3-1.7)	0.3 (0.1-1.1)	0.4 (0.1-1.3)	0.6 (0.2-1.5)	1.7 (1.0-3.0)
	Recommendation performed	0.1 (0.0-0.8)	0.4 (0.1-1.3)	0.1 (0.0-0.8)	0.4 (0.1-1.3)	0.0 (0.0-0.6)	0.3 (0.1-1.1)	0.1 (0.0-0.8)	1.0 (0.5-2.1)
Total	Recommendation given	34.8 (31.4-38.5)	31.8 (28.4-35.4)	16.8 (14.2-19.8)	11.2 (9.0-13.7)	20.5 (17.6-23.6)	31.6 (28.3-35.2)	66.2 (62.6-69.6)	5.7 (4.2-7.6)
	Recommendation performed	16.5 (14.0-19.5)	10.4 (8.4-13.0)	3.3 (2.2-5.0)	3.0 (2.0-4.6)	3.9 (2.7-5.6)	8.1 (6.3-10.4)	28.9 (25.6-32.4)	2.5 (1.5-3.9)
	ratio %	47,5	32,9	19,8	27,3	19,1	25,7	43,6	43,6

Legend: FS = Functional status

Data were calculated from the total N° pts with data on implementation of geriatric recommendations at chart review after one month (n=689 pts)

Discussion

Geriatric assessment can identify problems that are not always captured by standard anamnesis or physical examination [2]. This information might influence the treatment decision-making process, especially in vulnerable patients for whom intensive cancer treatment is considered [12,13]. However, to what extent are these identified geriatric problems addressed? Which health care professionals or services are the most referred to and for which geriatric problems? To our knowledge, this is the first study to describe the frequency and type of targeted recommendations/interventions based on GA in daily oncology practice on a large scale.

The added value of CGA has been shown over the past two decades in many studies in the geriatric literature, though the benefits seem to arise more from trials with discrete geriatric wards rather than from trials with inpatient geriatric consultation teams [14-18]. Various authors have argued that poor implementation of geriatric recommendations may have accounted in part for the lack of CGA effectiveness in some randomized controlled trials in the general geriatric population [19]. In oncology, many observational studies have been conducted on the value of GA for predicting oncological outcomes [20-22]. None of these studies described in depth recommendations/interventions based on GA and it could be questioned whether in some studies GA was probably used more as a treatment decision-making tool rather than an approach to implement geriatric recommendations [21]. As such, it would be advisable to report information about (non)adherence to GA recommendations in future cancer studies evaluating relevant outcomes including survival, functional decline and quality of life.

Currently, limited data exist regarding interventions following GA in cancer patients. As shown in our results, not all geriatric problems lead to geriatric recommendations and not all geriatric recommendations are carried out. Geriatric recommendations were given in about three fourths of patients (76.2%). This high percentage is not entirely unexpected when we consider the percentage of patients with an impaired test for one of the GA domains shown in Table 2. A third of all the geriatric recommendations (35.3%) were performed in about half (52.1%) of the evaluable patients corresponding to 460 performed recommendations on a total of 1302 given recommendations. The quality and success of implementation of geriatric interventions is dependent on the degree of implementation [23]. In this setting there are no data to compare but our results indicate that there are opportunities for improvement, both in the number of patients that should receive geriatric interventions as in the number of geriatric interventions per patient. However, we have not assessed the reasons for not implementing certain recommendations in this study, and there might be sound and less sound explanations for this. The THCW who performs the GA mostly has an advisory role only with no direct or limited control over patient care [24]. Adherence to a geriatric recommendation is dependent on its importance and anticipated benefit as judged by the treating physician as well as by the patient [25]. It might indeed be that health care workers and physicians do not pay enough attention to the implementation of recommendations. This is a phenomenon that certainly will be present in busy clinics where also

experienced and motivated staff might not be sufficiently available for all patients. Patients can also refuse referrals because they are too busy with oncological appointments and treatments and too exhausted for extra consultations. Or there could be logistical issues, such as too long waiting lists for the geriatric day clinic or other referrals. But on the other hand, treating physicians, teams (and patients) may decide that some of the identified problems are important to know for other reasons (e.g. tolerance of therapy, or life expectancy), but are less priority in terms of approach. In the oncology setting, it makes sense to focus more initially on remediable problems that could interfere with cancer treatment. It should also be acknowledged that 460 performed recommendations in 359 patients is not a small number. Oncological teams may select those recommendations that are most relevant for the patient at that time point. But as we mentioned already, this study does not allow an in-depth evaluation of the reasons for (not) implementing recommendations and further research in this domain is absolutely needed.

When we look at the type of recommendations, it is clear that many patients are referred to the dietician, social worker, and psychologist at the start of their cancer treatment (Table 4). It might be that oncological teams evaluated these referrals as most important for immediate implementation, but it could also be that these health care workers are most easily accessible. Furthermore, it was noteworthy that not many patients (7.3%) were directly referred to the geriatrician. One important reason for this is the shortage of physicians specialized in this discipline. From a health perspective, it is probably most cost-effective to involve geriatricians for a selected group of more complex patients, while the majority of problems can be initially approached by standard paths of care. It should be emphasized that geriatricians could/should be involved in the establishment of geriatric recommendations or care paths for the entire older population with cancer, without necessarily seeing all the patients personally. Referrals to a psychologist, geriatric day clinic, fall clinic and physiotherapist were not often performed when recommended. This should require further attention.

In order to have a better understanding of which geriatric problems led to which geriatric recommendations and whether or not the geriatric recommendations were performed for these problems, we also looked at referrals at the level of the GA domain (Table 5) as described in the methods section. Patients with problems concerning cognitive function were often referred to the geriatric day clinic (12.2%) and as previously mentioned these referrals were not often performed, irrespective of the type of problem. Next to cognitive problems, follow-up of other problems concerning fall risk, depression, and fatigue should get more attention, if not immediately then certainly on the longer term if relevant.

When interpreting our results, it should be noted that the nine participating hospitals had experience with the GA-based approach in oncology from a previous project (2009-2011). Centres that are at the stage of establishing geriatric oncology programs might have more influence of a learning curve [8]. Furthermore, differences between the nine sites may exist with each having their own processes and

paths of care. We evaluated this aspect, and indeed found differences in the number of performed geriatric recommendations between sites (data not shown). However, the main purpose of our study was to describe the global approach in the whole study cohort allowing to have a view on clinical practice. The lack of information for reasons of (non) implementation of recommendations is a weakness of our study, but is extremely difficult to evaluate, since in the Belgian setting, hundreds of care providers are involved at different levels. Within 'geriatric oncology' units, this might be easier to achieve, but the major disadvantage of this setting is that only limited amounts of older persons can be approached, while our concept of 'mobile' GA brought to the treating oncology teams reached more than 1500 patients in one year.

In conclusion, a better understanding of the GA-based approach will allow improving its implementation in order to optimize its effectiveness; next to this our data are also relevant for policymaking with the eventual goal to deliver high quality care in the growing population of older patients with cancer. This implementation study provides more insight into GA-driven interventions in daily oncology practice. Geriatric recommendations were given in about three fourths of patients. At least one geriatric recommendation was performed in approximately half of these patients and about one third of all geriatric recommendations were performed after one month.

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Chapter 4.

Geriatric screening results and the association with severe treatment toxicity after the first cycle of (radio)chemotherapy.

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Abstract

Background

Screening tools are used in geriatric oncology to determine who should receive a Comprehensive Geriatric Assessment (CGA). However, in this prospective study, we evaluated the association between geriatric screening results, measured with the G8 and Groningen Frailty Indicator (GFI), and severe treatment toxicity.

Methods

Patients over 65 years with various types and stages of cancer were screened with the G8 and the GFI prior to start of treatment. The association between geriatric screening results and Serious Adverse Events (SAE) after the first cycle of (radio)chemotherapy was studied with bivariate analysis (normal versus abnormal screening test) and logistic regression analysis.

Results

From 170 screened patients, 85 patients were eligible for this study. The median age was 76 years (range: 66-88 years). The treatment intent was curative in 46% and palliative in 54%. A SAE occurred in 15 patients (18%) of which three resulted in death. There was no significant association between the G8 as a dichotomous predictor (p=0.376) or as a continuous predictor (p=0.298) and the risk for SAE. We also found no significant association for the GFI analysed as a dichotomous predictor (cut-off ≥4: p=0.384; cut-off ≥3: p= 0.773), nor as a continuous predictor (p= 0.734). All associations remained insignificant when adjusted for treatment type and comorbidity.

Conclusion

The G8 and the GFI can be used to select patients for CGA but they do not seem to be predictive for short-term severe treatment toxicity.

Introduction

Cancer commonly occurs in older patients. Treatment decision-making is complex in this population. A major issue confronting oncologists is how to effectively select older patients for therapies with significant potential toxicity. It is clear that a distinction should be made between chronological age and biological age, as older patients have a very variable health status. The Comprehensive Geriatric Assessment (CGA) is a well-established approach in geriatrics to evaluate the elderly patients' functional and global health status. The CGA has been recommended by several guidelines in the approach of the older patient with cancer for different purposes of which one is to estimate this risk for severe treatment toxicity in order to guide treatment decision-making (1-3). The most important domains that are evaluated in CGA include functional status, nutrition, comorbidity, cognition, mobility, social support, and depression (4-6). It is also well-known that CGA is time-consuming in routine practice and it is currently not reimbursed by health systems. Therefore, a two-step approach of screening followed by CGA when needed has been proposed. Several geriatric instruments that screen for patients who should receive a CGA, have been or are being validated in an oncology setting (7). We previously studied the G8 and the Groningen Frailty Indicator (GFI) as screening tools for CGA in older patients with cancer (8). In this study, we looked at their association with severe treatment toxicity. It is possible that these geriatric screening tools can be used to estimate the risk for treatment toxicity while at the same time can be used to identify patients who should receive a CGA.

Patients and methods

Study design and patients

Patients with various types and stages of cancer, aged ≥65 years, with an adequate understanding of the Dutch language were included. Exclusion criteria included severe known dementia, symptomatic brain metastases, and pre-existing major neurological or psychiatric problems. Patients with newly diagnosed cancer or with recurrent disease were assessed before the start of treatment with two geriatric screening tools and a CGA as part of a validation study described in a previous work published from our group (8). In this prospective study, only patients who received chemotherapy or concomitant radiochemotherapy (CRT) were included and this no later than three weeks after geriatric assessment. In this period, radiotherapy or major surgery was not allowed. Patients who deteriorated in the period between geriatric assessment and start of treatment were excluded (e.g. hospitalisation). Serious adverse events (SAE) were recorded during the first cycle or month of treatment. A SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization; or resulted in persistent or significant disability/incapacity.

Geriatric screening tools

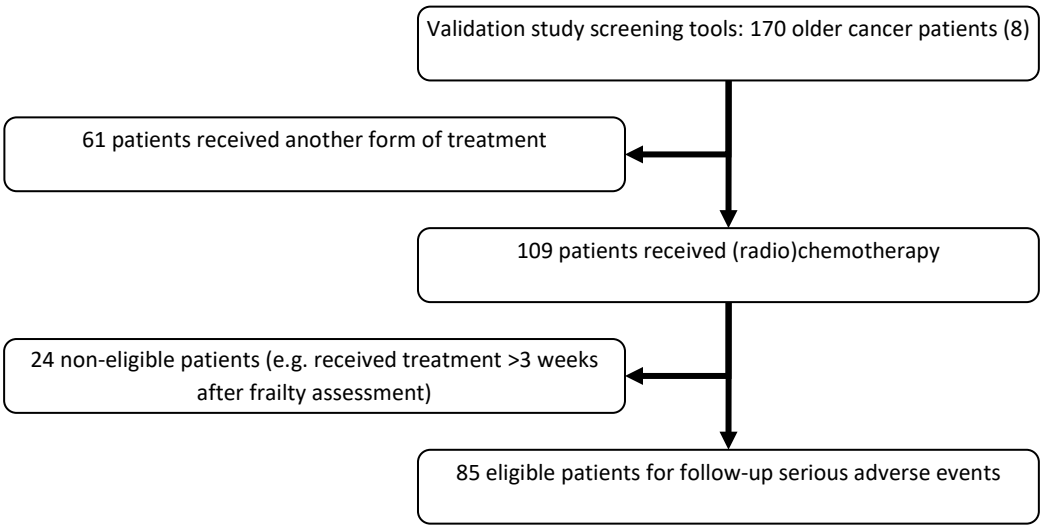
The G8 questionnaire is a screening tool for CGA in geriatric oncology (9). This tool consists of 8 questions and its development was based on the Mini Nutritional Assessment. A score of ≤14 (score range: 0-17) corresponds with an abnormal screening test (8-10).

The Groningen Frailty Indicator (GFI) (15 questions) is a screening instrument for the level of frailty (8,11,12). A GFI score of ≥4 (score range: 0-15) was regarded as moderately frail according to a panel of geriatric experts. This cut-off value is used in various studies. In our previous study, we suggested to use cut-off GFI ≥3 to define an abnormal screening test if the GFI is used in the context of screening for CGA. (8). Both cut-off values were evaluated here.

Data analysis

The G8 and the GFI were both evaluated as a dichotomous predictor (normal screening test versus abnormal screening test) and as a continuous predictor for the risk of SAE. The Fisher's exact test was used in bivariate analysis. Continuous predictors were analysed with univariate logistic regression. A multivariate analysis was conducted to adjust for treatment type and comorbidity. The treatments received by the patients were categorized into five types described below. Comorbidity was evaluated with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and all analyses were conducted with the total CIRS-G score. All p values reported are two-sided, and p values of <0.05 were considered statistically significant. All analyses were performed using the SPSS 17.0 statistical package (Chicago, IL, USA). Ethics approval for the study was obtained from the Ethical Committee and each patient provided written informed consent prior to study entry.

Figure 1. Study recruitment



Results

Patient characteristics and treatment received

From October 2009 to December 2011, 170 patients were screened of which 85 patients were included in this study (Figure 1). Patient characteristics are summarized in Table 1. The median age of patients was 76 years with a range of 66-88 years. Fifty-four patients (63.5%) had newly diagnosed cancer while 31 patients (36.5%) had progressive disease or relapse. Twenty-nine patients (34%) were hospitalized at the time of geriatric assessment. The results from the CGA are depicted in Table 2. All patients were screened and received a CGA prior to treatment which revealed that the tests for the CGA components nutrition (52%) and IADL (44%) were most frequently impaired. There were no missing data. After geriatric assessment, CRT (1) was started in nine patients (10.6%), 37 patients (43.5%) received platinum-containing regimens (2), nine patients (10.6%) were treated with taxanes (3), 20 patients (23.5%) with antimetabolites (4), and 10 patients (11.8%) with topoisomerase inhibitors (5). The treatment intent was curative in 39 patients (46%) and palliative in 46 patients (54%).

Table 1. Patient characteristics

N° patients	85	100%
Gender		
Male	41	48%
Female	44	52%
Age (years)		
Median	76	
Range	66-88	
Type of cancer		
Uro-genital	21	25%
Digestive tract	19	22%
Breast	18	21%
Head and neck	11	13%
Lung	5	6%
Gynaecological	4	5%
Unknown primary site	4	5%
Bone and soft tissue	2	2%
Non-Hodgkin lymphoma	1	1%

Serious Adverse Events

Fifteen SAE (18%) were reported in 15 different patients (seven women). Twelve had newly diagnosed cancer and eight were treated with a palliative intent. Furthermore, 12 patients received chemotherapy and three patients received CRT. Six patients were hospitalized due to haematological toxicity of which one patient (G8=15; GFI=4) died. Two patients with head and neck cancer were hospitalized due to dysphagia and mucositis, three patients due to symptoms that included dizziness and fatigue, one patient due to vomiting, and one patient due to dyspnea. One patient (G8=14; GFI=6) was hospitalized for renal

insufficiency that resulted in death. Another patient (G8=13; GFI=3) developed pleural effusion resulting in respiratory insufficiency and eventually died from respiratory failure.

Table 2. Results for geriatric screening and CGA

	Test result	
	Normal (%)	Abnormal (%)
Geriatric screening		
G8	31	69
GFI (cut-off ≥4)	60	40
GFI (cut-off ≥3)	39	61
CGA		
ADL	81	19
IADL	56	44
Nutrition	48	52
Cognition	94	6
Depression	78	22
Social Support	80	20
Mobility	72	28
Comorbidity	71	29

Abbreviations: ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; GFI: Groningen Frailty Indicator. ADL was evaluated with the Katz scale, IADL with Lawton-Brody Instrumental scale, nutrition with the Mini Nutritional Assessment, cognition with the Mini-Mental State Examination, depression with the 30-item Geriatric Depression Scale, and social support with the MOS social support survey. The scales are described more in detail elsewhere together with the associated cut-off values (8).

Geriatric screening results and the association with SAE

The GFI

The mean GFI score in this sample was 3.2 (SD 2.1). Fifty-one patients (60%) had a normal screening test. The group of patients without a SAE had a mean GFI score of 3.3 (SD 2.3) while the group of patients with a SAE had a mean GFI score of 3.1 (SD 1.3) prior to treatment. For the alternative cut-off value (GFI score ≥3), 33 patients (39%) had a normal screening test. For both cut-off values, there was no significant association for SAE in bivariate analysis, p= 0.384 and p=0.773 respectively. We also found no significant association when the GFI was analysed as a continuous variable in univariate logistic regression(p=0.734). The associations remained insignificant when adjusted for treatment type and comorbidity (Table 3).

The G8

The mean G8 score for the whole sample was 11.9 (SD 3.2). Twenty-six patients (30.6%) had a normal screening test. The mean G8 score for the group of patients with and without a SAE was respectively 12.7 (SD 3.2) and 11.7 (SD 3.2) prior to treatment. There was no significant association between the G8 and the occurrence of SAE in bivariate analysis (p= 0.376), in univariate logistic regression analysis (p=0.298), and when adjusted for treatment type and comorbidity (Table 3).

Table 3. Association between geriatric screening results and severe treatment toxicity

	OR** (95%CI)	p-value	OR*** (95%CI)	p-value
G8 screening tool				
Continuous score	0,91 (0,76-1,09)	0,30	0,86 (0,70-1,06)	0,16
G8 ≤14 vs normal score	0,60 (0,19-1,91)	0,376*	0,52 (0,14-1,89)	0,32
Groningen Frailty Indicator (GFI)				
Continuous score	1,05 (0,80-1,37)	0,73	1,14 (0,84-1,55)	0,41
GFI ≥4 vs normal score	0,49 (0,14-1,67)	0,384*	0,38 (0,10-1,42)	0,15
GFI ≥3 vs normal score	1,33 (0,41-4,32)	0,773*	1,30 (0,36-4,73)	0,69

*Results from bivariate analysis are shown (Fisher's Exact test).
**Unadjusted. ***Adjusted to treatment type and comorbidity.

Discussion

In oncology practice, classical performance status measures (e.g. Karnofsky Performance Status, ECOG) are regarded to be of limited value to estimate whether a patient is likely to tolerate a certain chemotherapy regimen (13,14). Older patients enrolled in clinical trials derive the same treatment benefits as younger patients (2). However, data from clinical trial participants are not representative for all older patients. There are no validated methods to identify older patients fit enough to receive the same treatment as younger patients. A CGA-based approach has been recommended in the approach of the older patient with cancer. In our previous study, we showed that with geriatric screening tools, it is possible to identify most of the patients who should receive a CGA but also that a significant number of false positives should be expected. The completion of the G8 or the GFI only takes a few minutes. However, the benefit of the screening step of the two-step approach has been raised into question by a recent systematic review of available frailty screening methods (7,15). Whereas studies validating these screening tools against the CGA are useful, prospective studies evaluating the association of screening results and treatment tolerance could give us valuable information directly relevant for the clinician.

The G8 was developed to screen patients who should receive a CGA (normal screening test versus abnormal screening test). The GFI, on the other hand, was developed as a (continuous) measure for frailty. This was the rationale to evaluate both screening tools as a dichotomous and continuous variable. It would be interesting to know if there is a significant association with treatment tolerance, even considering that both screening tools were not developed for this purpose. Moreover, results for one of these screening tools might be available anyway in a setting where older patients are screened systematically for CGA. However, our results showed no significant association for both screening tools and SAE after the first cycle of (radio)chemotherapy, also when adjusted for treatment type and comorbidity. Furthermore, it didn't matter if the screening results were interpreted as a dichotomous score or as a continuous score. The results of geriatric screening can be used to determine who should receive a CGA but the GFI and the G8 do not seem to be predictive for severe treatment toxicity. It should be noted that, although we did adjust for treatment type, this adjustment was not at the level of

the individual chemotherapy regimen, as is done with the MAX2 index (16). A confirmation of our results in a more homogeneous and larger sample of patients is warranted. We also mention that recently two promising instruments have been developed specifically to estimate the risk for severe chemotherapy toxicity (14,17). However, further validation is still needed before use in routine practice and such validation is underway.

In this study, we primarily looked at tools that might be used in the first step of the two-step approach of screening followed by CGA. Various studies have evaluated the predictive value of CGA for chemotherapy toxicity, without the screening step (18-21). Over different studies, depression, functional status, general mental health, and social support for example have been identified as independent predictors for toxicity. On the other hand, in other studies weak or no associations were reported (19,21). A recent systematic review also found little consistency for the association of CGA with other relevant clinical outcomes besides chemotherapy toxicity and concluded that the available evidence is currently to inconsistent to guide clinical decision making (22). An explorative analysis on our data showed that when all CGA variables were entered simultaneously, only cognition was borderline significant ($p=0.049$) as being predictive for SAE after the first cycle of therapy (data not shown). Comorbidity tended towards significance ($p=0.062$). Unexpectedly, patients with a better cognitive function had a higher risk for SAE. This association remained significant after adjustment for treatment type. It should be noted that confidence in the robustness of this analysis is limited by the small sample size combined with the high number of predictor variables entered into the model.

Some other considerations need to be made as well when interpreting our study results. Firstly, the lack of a relationship between the studied screening tools and treatment tolerance might be explained by confounding by indication. Vulnerable patients might have been treated with less toxic regimens than fit patients. This might as well explain the observed relationship between cognitive function and the risk for SAE. Also, the treating oncologists had access to the screening and CGA results and this could have influenced the treatment choice which in turn could have influenced treatment tolerance. However, we believe this was unlikely in our study because the oncologists were still getting familiar with the results of a multidimensional CGA and its interpretation. Secondly, for our outcome severe treatment toxicity, we evaluated SAE after the first cycle of chemotherapy. We looked at short-term SAE because patients who develop severe toxicity often do so during the first cycle of chemotherapy (17). SAE were not uncommon (18%) in our sample. But it would be useful to have information for other time-points as well. In this regard, one study showed that the GFI was related to mortality but not to the probability to complete chemotherapy (23). Thirdly, for severe chemotherapy toxicity we evaluated SAE while other studies, but not all, evaluate grade 3 and grade 4 chemotherapy toxicity. The endpoint SAE has the advantage that it relates more to the most severe and possibly life-threatening toxicity. This is the type of toxicity the clinician especially wants to avoid. Then again, other important toxicity that does not fall under the definition of SAE might be missed. It should be noted that SAE in our study could have been

related to the given chemotherapy and/or radiotherapy but also to progressive disease. It would be perhaps interesting to evaluate different definitions of severe treatment toxicity in future studies.

Author Contributions

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Chapter 5.

The added value of geriatric screening and assessment to predict overall survival in older patients with cancer

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This chapter has been accepted for publication in Cancer.

* equal contribution

The online version of the published paper will contain supplementary material which have not been included in this dissertation.

Abstract

Aim

The aim of this study is to determine and compare the added prognostic value of screening tools, geriatric assessment (GA) components and GA summaries to clinical information for overall survival (OS) in older patients with cancer.

Patients and Methods

A screening and a 10-item geriatric assessment (GA) were systematically performed in patients ≥70 years with cancer. Cox regression analyses were conducted to evaluate the added prognostic value for OS of screening tools, GA and GA summaries to clinical information (age, stage, tumor type) in two cohorts (A and B). Cox models were compared based on Akaike Information Criterion and the Concordance Probability Estimate. Analyses were performed on two independent cohorts.

Results

Complete case analysis was available for 763 patients (median age 76) in cohort A and for 402 patients (median age 77) in cohort B. In both cohorts, most individual GA components were independent prognostic factors for OS. Nutritional status (assessed by the Mini Nutritional Assessment-Short Form) and functional status (assessed by Instrumental Activities of Daily Living) consistently displayed a strong capacity to predict OS. Inconsistent results were found for screening tools. GA summaries perform the best in comparison with the screening tools and the individual GA components.

Conclusions

Most individual GA components, especially nutritional status and functional status, are prognostic factors for OS in older patients with cancer. GA summaries provide more prognostic information than individual GA components, but only moderately improve the prognostic baseline model with clinical information.

Introduction

Epidemiologic research announces a significant increase of older patients with cancer in the following decades [1,2]. Because important treatment and outcome variations are reported and due to the heterogeneity and the lack of evidence-based treatment guidelines within this population, international oncologic organizations like the International Society of Geriatric Oncology (SIOG) and the European Organization for Research and Treatment of Cancer (EORTC) recommended that some form of comprehensive geriatric assessment (CGA) should be mandatory to guide oncologic treatment decisions [3,4].

CGA is currently the gold standard to evaluate the global health status and clinical frailty level of individuals and is defined as a multidimensional, interdisciplinary diagnostic process focusing on determining an older person's medical, psychosocial and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up [5]. In the general (non-oncologic) geriatric population, CGA-guided treatment plans have been shown to improve overall survival (OS), quality of life (QoL), functional status (FS) and decrease the risk of hospitalization and nursing home placement [6-10]. When applied to patients with cancer, CGA has been shown to identify previously unknown health problems, to predict treatment-related toxicity and oncologic outcomes including OS, and to influence cancer treatment decisions [11-13]. However, the majority of studies of 'CGA' in the older population with cancer focused on the implementation of systematic geriatric screening and geriatric assessment (GA), the first two steps of the CGA process [5,8]. Several studies have identified items within the GA itself (e.g. FS [14-16], nutritional status [14-18] and mental health [14-16]) that were independent predictors of mortality.

To select patients who would benefit from GA, a number of geriatric screening tools have been developed, like G8, Vulnerable Elders Survey – 13 (VES-13) and the Flemish version of the Triage Risk Screening Tool (fTRST). Some of these screening tools can also provide important information about treatment-related toxicity, risk of functional decline and OS [4,19,20].

However, a GA does not yield a validated 'summary score', so it remains difficult to precisely quantify the patients' global health status. For this reason, some attempts to summarize and categorize GA results have been proposed in geriatric oncology, but the included elements and cut-offs are arbitrary, and do not capture the complexity of GA and the ageing process itself [21]. Despite this, the most consistent finding is the association between mortality and a GA summary score (e.g. frail/vulnerable/fit) [16,22-25].

The aim of this study is to determine and compare the added prognostic value for OS of two geriatric screening tools, individual GA components, and two GA summaries to a baseline model of clinical information in older patients with cancer.

PATIENTS AND METHODS

Design

To determine and to compare the added value of screening, individual GA components, and two GA summaries (henceforth, GA components and GA summaries are called together 'geriatric information') to a baseline model of clinical information to predict OS, this study integrates two different study cohorts, cohort A [4] and cohort B [26] that were extensively reported previously (see figure 1). Both study cohorts come from prospective, multicenter, observational cohort studies. Patients with cancer aged 70 years or older were approached for inclusion during a hospital visit at diagnosis or at disease progression/relapse, when a treatment decision had to be made. In the study of cohort A (n=937; period October 2009 – July 2011), inclusion was limited to the following six tumor types: breast, colorectal, ovarian, lung and prostate cancer and hematologic malignancies. This study focused on the implementation of a systematic geriatric screening and assessment[4]. In the study of cohort B (n=1550; period August 2011 – July 2012), patients with all tumor types (except non-melanoma skin cancer) and hematologic malignancies were included. The focus of this study was on geriatric recommendations based on GA-results[26]. In both studies, patients were assessed in a uniform manner: for study cohort A in two Belgian hospitals ('Universitair Ziekenhuis Brussel' (UZB) and 'Universitaire Ziekenhuizen Leuven' (UZL))[4] and for study cohort B in six academic and three non-academic hospitals spread all over Belgium[26]. The analysis for cohort B was limited to patients of UZB and UZL and to patients with breast, colorectal, lung, prostate, and ovarian cancer so this would correspond with the hospitals and the studied tumor types in cohort A. Patients with a hematologic malignancy were excluded for the analysis presented in this study because classical staging is not applicable for most of these tumors (and so cannot be integrated in prognostic models). Complete case analysis was taken into account, leaving 763 patients in cohort A and 402 patients in cohort B.

Screening and geriatric assessment

At baseline, a trained health care worker (THCW) performed a screening and GA in all patients, as previously reported [4,26].

Patients were assessed by two geriatric screening tools, G8 and fTRST, each evaluating the presence of a geriatric risk profile. G8 includes seven items from the Mini Nutritional Assessment (MNA) and one age-related item. The total score varies from 0–17. A G8 score of ≤ 14 indicates the presence of a geriatric risk profile [27,28]. The fTRST is a five-item screening tool with a range from 0–6[4,29,30]. Within the oncologic population, a score of ≥ 1 indicates the presence of a geriatric risk profile[4]. Also, the Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) was evaluated[31]. This screening tool, not age-specific, is frequently used in oncology to classify the performance status of patients.

The GA included 10 components based on the 2014 SIOG recommendation guideline for GA[13]: social data with living situation, FS assessed by the Katz's Activities of Daily Living (ADL)[32] and by Lawton's

Instrumental Activities of Daily Living (IADL)[33], fall history during the last year[34], fatigue assessed by the MOB-T[35], mental status assessed by the Mini Mental State Examination (MMSE)[36] and Geriatric Depression Scale (GDS-15)[37], nutritional status assessed by the Mini Nutritional Assessment-Short Form (MNA-SF)[38], comorbidities assessed by the Charlson Comorbidity Index (CCI)[39] and a polypharmacy assessment[40].

GA summaries

In this study, the 10-item GA is a GA summary which integrates the results of every GA component mentioned above and thus captures the multidimensional GA evaluating the global health of the older patient with cancer as a whole. All components are integrated dichotomously. However, it doesn't calculate a global GA end score and no cut-off is defined to differentiate between fit and frail.

The 'Leuven Oncogeriatric Frailty Score' (LOFS) is a recently developed tool to summarize clinical frailty. The LOFS is a GA summary score as it calculates a global GA end score that integrates 5 fundamental aspects determining a patient's fitness/frailty status, i.e. capability to autonomously perform activities of daily living (ADL and IADL), mental status (MMSE), nutritional status (MNA-SF) and comorbidities (CCI) into a single, semi-continuous score on a scale from 0 = severely frail to 10 = fit [41] (see appendix A, available in the online publication). In detail, the following categories are included: score 0-2 (severely frail), score 3-4 (frail), score 5-6 (vulnerable), score 7-8 (slightly vulnerable) and score 9-10 (fit).

Statistical analysis

The baseline model of clinical information consisted of age, stage and tumor type. Age was categorized in three levels: 70-74, 75-79, and ≥80 years old. Comparisons of continuous data were done with Student's t test and by the Wilcoxon's test as appropriate, while comparisons of categorical data were performed with Chi Square test and/or with the Fisher's exact test as appropriate. The statistical significance level used was 0.05.

Follow-up time was defined as the difference from the first GA assessment to the last follow-up for all censored patients. Median, minimum and maximum follow-up time are reported.

The Kaplan-Meier method was used to describe survival and log-rank and Wilcoxon tests were used to compare different groups.

Univariable cox proportional hazard regression analyses were conducted to evaluate the prognostic value of patient and clinical characteristics, screening tools and geriatric information. Multivariable analyses were performed as well for the analyses with screening tools and geriatric information to adjust

for clinical information. OS was calculated from date of GA to date of death from any cause or last follow-up for censored patients. Results were considered significant if $p<0.05$.

We performed Cox proportional hazard regression analyses to build multiple prognostic models. To assess the contribution of screening tools and geriatric information, each component was added separately to the baseline model of clinical information. The proportional hazards assumption was tested and not violated. Multicollinearity was also assessed with the variance inflation factor (VIF) and was not present (VIF's<3).

The discriminatory ability of each prognostic model was assessed using the Concordance Probability Estimate (CPE)[42]. The interpretation of the CPE is identical to the widely used but less robust c-index and indicates the proportion of all pairs of patients whose predicted survival times are correctly ordered among all patients that can actually be ordered. In other words, a model with a higher CPE corresponds with a model with a better predictive accuracy. The global fit of the Cox models was compared by means of the difference of Akaike Information Criterion (AIC) of the baseline model and the extended model (ΔAIC). A higher ΔAIC value corresponds with a more explanatory and informative model. The screening tools and all individual GA components were assessed as dichotomous variables. The LOFS was assessed as a categorical variable. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and SPSS 17.0 (Chicago, IL).

The added prognostic value of screening tools and geriatric information was tested on two different consecutive large cohorts of patients, to evaluate the consistency between the results. The aim was not to perform a formal validation, as we did not develop a prognostic tool.

Results

Patient population

In cohort A, a total of 788 patients with carcinoma were considered for data analysis and in cohort B a total of 491 patients. Complete case analysis was available for cohort A and B in 763 and 402 patients respectively (see figure 1).

In cohort A, the median age was 76 years (range: 70-95) with 67.8% women and in cohort B, the median age was 77 years (range: 70-95) with 66.7% women. In both cohort A and B, the most prevalent carcinoma were breast and colorectal cancer in 48.8% and 24.4% of the patients and in 42.0% and 32.8% of the patients respectively. At the moment of inclusion in the study, 63.7% had a newly diagnosed cancer in cohort A and 71.4% in cohort B, whereas 36.3% had disease progression or relapse in cohort A and 28.6% in cohort B. More details of patient demographics and clinical characteristics are listed in table 1. Significant differences between both cohorts were present for tumor type (p=0.019), oncologic setting (p=0.008) and surgical treatment (p=0.006).

After a median follow-up of 61.4 months (range 0.7-75.6 months) in cohort A, and 45.7 months (range 7.3-54.5 months) in cohort B, there was no significant difference (p=0.496) in OS between both cohorts. The median survival time was 33.2 months (range: 0.09-75.6; 471 deaths) and 37.6 months (range: 0.16-54.5; 214 deaths) respectively.

The results of the screening and GA are listed in table 2. Both cohorts were similar based on the results of the G8, ECOG-PS and most individual GA components, though with a significant difference for fTRST (p<0.001), ADL (p<0.001), IADL (p=0.01) and MMSE (p<0.001).

The prognostic value for OS of patient and clinical characteristics, screening tools and geriatric information

The following variables were analyzed: patient and clinical characteristics (gender, age, stage and tumor type), screening tools (G8, fTRST, ECOG-PS), individual GA components (living situation, ADL, IADL, fall history, MOB-T, MMSE, GDS-15, MNA-SF, CCI and polypharmacy), and two GA summaries (10-item GA, LOFS).

The univariable analyses show that all variables were prognostic for OS in both cohorts with the exception of living situation in cohort A and with the exception of living situation and fTRST in cohort B (see table 3 and table 4). Kaplan-Meier curves with associated log-rank tests are shown in appendix B (available in the online publication). The analyses with screening tools and geriatric information were repeated and adjusted for clinical information. This showed that all variables were prognostic for OS with the exception of living situation and comorbidity in cohort A and with the exception of the G8, living situation, and polypharmacy in cohort B (table 4).

The comparison of the performance of models extended with screening tools and geriatric information

Detailed results for cohort A and cohort B are summarized in table 5. A visual overview of the discriminatory ability of the models can be found in figure 2. The baseline model of clinical information had a good discriminatory ability with CPE 0.728 and CPE 0.750 respectively. The addition of the screening tools improved the discriminatory ability (CPE) and the fit of the model (ΔAIC) compared to the baseline model in cohort A. The G8 model improved the baseline model the most among the screening tools with CPE 0.747 and ΔAIC 57.26. In contrast, in cohort B the G8 model decreased the quality of the baseline model (ΔAIC -0.10) while slightly improving in discriminatory ability (CPE 0.753). The ECOG-PS model had the best performance in cohort B with CPE 0.762 and ΔAIC 16.80.

The models extended with the 10 individual GA components did not always improve the discriminatory ability while the fit of the model always improved with the exception of the addition of comorbidity measured by the CCI in cohort A. Nutritional status measured by the MNA-SF (CPE 0.756; ΔAIC 34.11) followed by FS measured by the IADL (CPE 0.754; ΔAIC 31.89) improved the baseline model the most in cohort A in terms of both CPE and ΔAIC. In cohort B, the CPE improved the most by adding

nutritional status measured by the MNA-SF (CPE: 0.772) followed by fatigue measured by the MOB-T (CPE: 0.771) while the fit of the model improved the most by adding IADL (ΔAIC: 10.00) followed by MOB-T (ΔAIC: 9.84) and then by MNA-SF (ΔAIC: 8.78).

The 10-item GA improved the baseline model with CPE 0.755 and ΔAIC 57.72 in cohort A and with CPE 0.775 and ΔAIC 23.58 in cohort B. In comparison, the LOFS improved the baseline model with CPE 0.745 and ΔAIC 37.82 in cohort A and with CPE 0.755 and ΔAIC 34.81 in cohort B.

Discussion

As outlined in the introduction, several GA components have been shown to be independent predictors of mortality in older patients with cancer. This study shows in two separate cohorts that most individual GA components are prognostic factors for OS in patients with cancer independent from clinical information (age, stage, and tumor type) in a heterogeneous oncologic population. Nutritional status and IADL consistently displayed strong individual prognostic capacity compared to the other GA components. Although previous research shows inconsistent results on which GA components are prognostic in populations with various stages and tumor types, the two aforementioned GA components are often found to be prognostic for OS [4,10]. Besides living situation in both cohorts, comorbidity measured by the CCI in cohort A and polypharmacy as a proxy for comorbidity in cohort B were not prognostic factors when adjusted for clinical information. The lack of a prognostic impact of comorbidity might be related to an already poor prognosis in patients with certain tumor characteristics and/or to limitations of the CCI instrument.

In this study, we also examined the added prognostic value of screening tools and geriatric information to predict OS by comparing the performance of multiple extended prognostic models in reference to a baseline model of clinical information (age, tumor type, and stage). This method also allows us to have a better view on the relative importance of the individual GA components and the GA as a whole, i.e. the 10-item GA. In contrast to other studies, we compared the performance of prognostic models with the AIC, which is a more sensitive measure than concordance indices (i.e. CPE, c-index) for model selection. This showed that nutritional status and IADL have a high added value to clinical information compared to the other GA components, which is not surprising since both are strong prognostic factors in cohort A and cohort B.

Furthermore, the AIC results indicate that the models integrating and summarizing different components of GA (10-item GA and LOFS) perform better than the individual GA components. The 10-item GA had the best performance in cohort A and the second best in cohort B after the LOFS. These GA summaries capture more the multidimensional process of ageing, so it is not surprising that they perform better than individual GA components. The prognostic value of the LOFS, a GA summary score, was demonstrated for the first time in this study. The added value of the LOFS in addition to clinical

information was consistent in the two cohorts and was higher than the added value of the best individual GA components in both cohorts. The LOFS seems to be an interesting tool as it has a good prognostic value in addition to clinical information and it summarizes the results of the GA in a single score, which has the advantage of simplicity towards interpretation necessary for daily practice.

While similar results were observed in both cohorts for the most prognostic individual GA components and the screening tool ECOG-PS, inconsistent results are found for some of the other individual GA components and the two geriatric screening tools (G8 and fTRST). The conflicting results of the G8 are especially remarkable when clinical information is taken into account. The G8 showed a poor prognostic contribution in cohort B, in contrast to results in cohort A where the G8 added almost as much prognostic information than the 10-item GA. The majority of the patients in both cohorts had breast cancer or colorectal cancer (CRC), however there were significantly more CRC diagnoses in cohort B, though there was no significant difference in OS between the two cohorts. Given that malnutrition is more prevalent in CRC and the G8 consists of seven questions from the MNA questionnaire, it is likely that the prognostic information provided by both variables overlap which might have contributed to the lack of an added value of the G8 in cohort B. The other variables included in the models (i.e. age, stage, G8 scores) did not differ between the cohorts and so do not explain the different results for the prognostic value of the G8.

Patients in cohort B had more often CRC as discussed previously, more often a new diagnosis, more often surgery, more had a geriatric risk profile according to the fTRST (but not according to the G8), were more dependent for ADL and IADL, and had more often an abnormal score for cognition. This indicates that patients in cohort B might have been more vulnerable than in cohort A, though as mentioned before this did not influence survival but might have influenced the prognostic value of certain aspects of geriatric information in addition to clinical information. Of course, other confounding factors should be taken into account in relation to the heterogeneity of the studied populations, some of which are discussed further at the end of the discussion.

Until now, the discussion has been based on the calculated hazard ratios of the individual parameters and on the performance of the extended models according to the AIC values. With the AIC values, models can be ranked allowing the selection of the best model. However, the AIC does not provide a measure of performance as such as it might select the best model out of a series of poor models. The CPE, on the other hand, does provide an interpretable measure of performance. The baseline models showed good discrimination in both cohorts (cohort A: CPE 0.728; cohort B: CPE 0.750) and were able to correctly order the survival time of two randomly chosen patients about three out of four times. Only small differences in CPE values were observed between the better models and the ranking of models based on the more sensitive AIC and CPE yields different patterns, though the model extended with the 10-item GA was always the best or second best model in accordance with results based on AIC. However, the concordance indices (here CPE) are insensitive to detecting improvements in model

performance when a parameter is added to a model with already important predictors. (43). Based on the CPE, the best models in our study (i.e. the 10-item GA model and the MNA model) improved the overall performance of the model of clinical information by about 2.5 %, so a significant amount of deaths are still not explained by the abovementioned parameters.

Several studies have evaluated the association between GA and mortality in patients with cancer for different purposes. In accordance with our first analyses, most studies focus on the most prognostic individual GA components to improve the identification of patients with an increased mortality risk for appropriate interventions. From these analyses can be concluded that GA has some prognostic value but that due to inconsistent results no specific recommendations can be given to guide treatment-decision making. In contrast to some of these studies, we did not show that certain GA components predict mortality but that most GA components do. This in two separate cohorts. Others focus on the prediction of early death or aim to develop nomograms for example. Prognosis or the estimation of life expectancy is crucial in the treatment decision-making process. However, none of these studies focused on the additional value of the GA as a whole in estimating life expectancy prior to the start of treatment. In this study, we quantified how much the GA as whole improves prognosis, which no prior study has done before.

When interpreting our results some considerations need to be made. Our study population was heterogeneous in terms of oncologic parameters; different tumor types, different staging, different oncologic (molecular) subtypes, different treatments, different susceptibility to treatment, etc. Many of these oncologic factors can have an important impact on OS and are not captured in this study. Ideally, the impact of screening tools and geriatric information should be evaluated in tumor populations with exactly the same tumor and treatment characteristics, while only having differences in geriatric parameters. It is extremely difficult to obtain large samples sizes with such criteria. Moreover, findings in such populations are only relevant for those highly selected populations and would need to be evaluated separately in many other specific tumor settings, which is not realistic. It is possible that in such homogeneous populations, the incremental value of screening tools and geriatric information is larger than about 2.5% because in our current heterogeneous population, these effects might be diluted by major differences in oncologic prognosis. On the other hand, our heterogeneous population in both cohorts can be an advantage as it is representative of a large cancer population. Moreover, OS prediction is far from the only goal of GA. GA is important to estimate the risk of treatment induced toxicity[41,42], to detect previously unknown health problems[9], and to allow directed geriatric interventions that can improve therapy compliance, quality of life, and outcome.

Conclusions

Most individual GA components, especially nutritional status assessed by MNA-SF and functional status assessed by IADL, are independent prognostic factors for OS in older patients with cancer. GA summaries provide more prognostic information than individual GA components, but only moderately improve the prognostic baseline model with clinical information.

Author contributions

conception and design: CK, LD, JPL, JF, KM, HW

data acquisition: CK, LD, HW

data analysis and interpretation: CK, AB, LD, JDG, JPL, JF, KM, HW

writing–initial draft: CK, AB, LD, JPL, HW

writing–critical revision: CK, AB, LD, JDG, JPL, JF, KM, HW

statistical analyses: JPL

supervision: CK, AB, LD, JDG, JPL, JF, KM, HW

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Figure 1: Flow-chart of patient selection

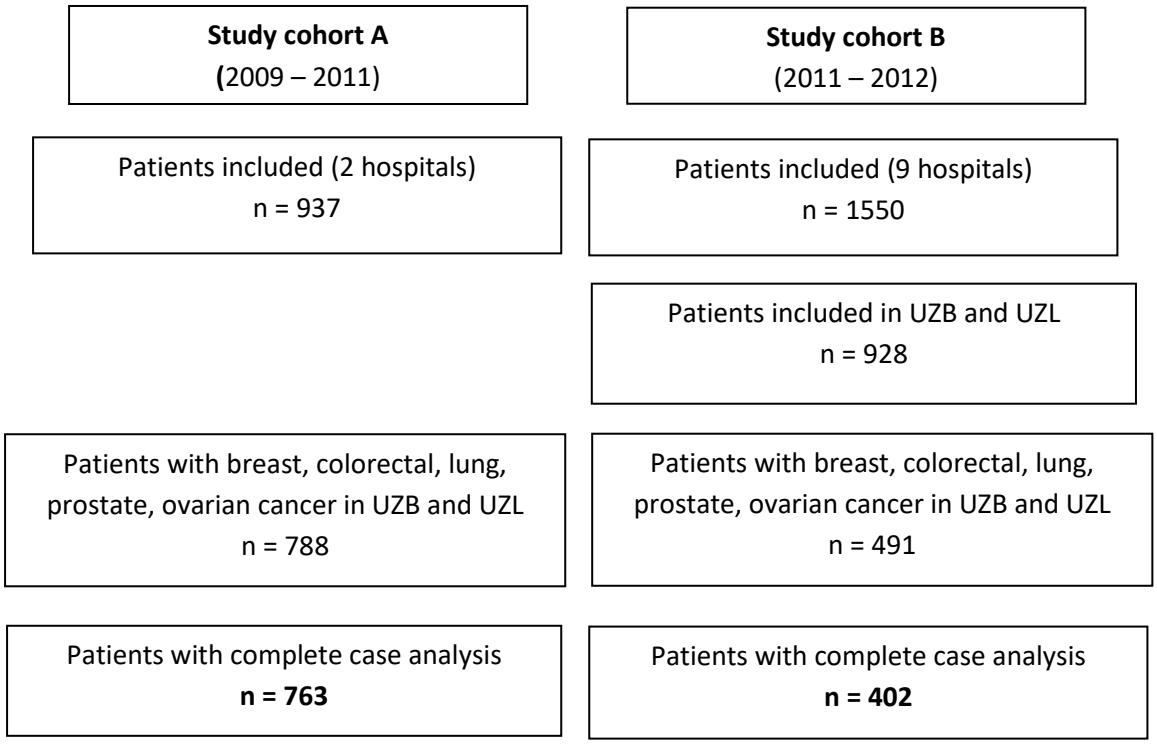

Figure 1: Flow-chart of patient selection. Analyses were conducted on two separate study cohorts: cohort A (n=763) and cohort B (n=402). Abbreviations: UZB = Universitair Ziekenhuis Brussel; UZL = Universitaire Ziekenhuizen Leuven

Table 1: Patient and clinical characteristics

	Cohort A (n=763)		*Cohort B (n=402)*		
Characteristic	N°	%	N°	%	p-value
Age	76 (70-95)		76 (70-95)		
Gender					
Male	517	67,8	268	66,7	0,705
Female	246	32,2	134	33,3	
Tumor type					
Breast	372	48,8	169	42.0	0.019
Colorectal	186	24,4	132	32,8	
Lung	72	9,4	40	10,0	
Ovarian	59	7,7	33	8,2	
Prostate	74	9,7	28	7,0	
Oncologic setting					
New diagnosis	486	63,7	287	71,4	0,008
Progression/relapse	277	36,3	115	28,6	
Stage					
I	88	11,5	46	11,4	0,270
II	171	22,4	102	25,4	
III	112	14,7	70	17,4	
IV	392	51,4	184	45,8	
Treatment received					
Surgery	345	45,2	216	53,7	0,006
Chemotherapy	312	40,9	182	45,3	0,150
Radiotherapy	235	30,8	134	33,3	0,377
Hormonal therapy	297	38,9	140	34,8	0,170
Pain: VAS (0-10)					
Score 0	374	49,1	183	45,5	0.473
Score 1-3	118	15,5	70	17,4	
Score ≥4	270	35,4	149	37,1	

Abbreviations: CI = confidence interval; VAS = Visual Analogue Scale

*Treatment received = patients may have received a combination of treatment modalities.

Table 2: Results of the screening and geriatric assessment

			Cohort A (n = 763)		Cohort B (n = 402)		
Screening tools	**Cut-off**	**Score**	**n**	**%**	**n**	**%**	**p-value**
fTRST (0-6)	≥1	Absence of a geriatric risk profile: score 0	131	17.2	38	9.5	<.001
		Presence of a geriatric risk profile: score ≥1	632	82.8	364	90.6	
G8 (0-17)	≤14	Absence of a geriatric risk profile: score > 14	197	25.8	122	30.4	0.099
		Presence of a geriatric risk profile: score ≤ 14	566	74.2	280	69.7	
ECOG-PS		Score 0-1	559	73.3	299	74.4	0.681
		Score 2-4	204	26.7	103	25.6	
GA components	**Item/ Instrument**	**Score**					
Social data	Living situation	Not living alone	522	68.4	262	65.2	0.262
		Living alone	241	31.6	140	34.8	
Functional Status	ADL (6-24)	Independent: score 6	372	48.8	155	38.6	<.001
		Dependent: score ≥ 7	391	51.3	247	61.4	
	IADL (0-5/8)	Independent: score 8 (female) or 5 (male)	329	43.1	142	35.3	0.010
		Dependent: score < 8 (female) or 5 (male)	434	56.9	206	64.7	
	Fall history	No falls	520	68.2	255	63.4	0.105
		≥ 1 fall	243	31.9	147	36.6	
Fatigue	MOB-T (0-6)	No fatigue	315	41.3	163	40.6	0.808
		Presence of fatigue	448	58.7	239	59.5	
Cognition	MMSE (0-30)	Score ≥ 24 = normal cognition	684	89.7	331	82.3	<.001
		Score ≤ 23 = mild/severe cognitive decline	79	10.4	71	17.7	
Depression	GDS-15 (0-15)	Score 0-4 = not at risk for depression	604	79.2	300	74.6	0.078
		Score 5-15 = at risk for depression	159	20.8	102	25.4	
Nutrition	MNA-SF (0-14)	Score ≥ 12 = normal nutritional status	288	37.8	175	43.5	0.055
		Score 0-11 = risk of malnutrition + malnourished	475	62.3	227	56.5	
Comorbidity	CCI (0-37)	No comorbidities (score 0)	355	46.5	190	47.3	0.811
		Comorbidity score ≥ 1	408	53.5	212	52.7	
Polypharmacy		0-4 different drugs	369	48.4	184	45.8	0.400
		≥ 5 different drugs	394	51.6	218	54.2	
GA summary							
LOFS		Fit: score 9-10	206	27.0	104	25.9	0.730
		Slightly vulnerable: score 7-8	283	37.1	137	34.1	
		Vulnerable: score 5-6	159	20.8	92	22.9	
		Frail: score 3-4	72	9.5	43	10.7	
		Very frail: score 0-2	43	5.6	26	6.4	

Table 2: Results of the screening and geriatric assessment (Continued)

Abbreviations: GA = Geriatric Assessment; fTRST = Flemish version of the Triage Risk Screening Tool; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MOB-T = Mobility – Tiredness Test; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; MNA-SF = Mini Nutritional Assessment – Short Form; CCI = Charlson Comorbidity Index; LOFS: Leuven Oncology Frailty Score

Table 3: Prognostic value for OS of gender and clinical information (univariable analysis)

	Cohort A (n=763)		Cohort B (n=402)	
	HR	**95%CI**	**HR**	**95%CI**
Gender (reference group: men)	0.55*	0.46-0.67	0.59*	0.45-0.78
Age				
70-74 vs 75-79	0.72*	0.57-0.90	0.70*	0.49-1.00
70-74 vs ≥80	0.59*	0.48-0.74	0.54*	0.39-0.76
75-79 vs ≥80	0.83	0.67-1.03	0.78	0.57-1.06
Tumor type				
Breast vs Colorectal	0.42*	0.33-0.52	0.52*	0.37-0.74
Breast vs Lung	0.18*	0.13-0.24	0.12*	0.08-0.19
Breast vs Ovarian	0.37*	0.27-0.51	0.27*	0.17-0.43
Breast vs Prostate	0.70*	0.50-0.98	0.51*	0.29-0.87
Colorectal vs Lung	0.43*	0.32-0.57	0.23*	0.16-0.35
Colorectalvs Ovarian	0.88	0.64-1.22	0.52*	0.33-0.82
Colorectal vs Prostate	1.68*	1.20-2.35	0.97	0.57-1.64
Lung vs Ovarian	2.08*	1.43-3.00	2.25*	1.36-3.73
Lung vs Prostate	3.95*	2.69-5.79	4.17*	2.34-7.45
Ovarian vs Prostate	1.90*	1.27-2.86	1.85*	1.00-3.42
Stage				
I vs II	0.97	0.57-1.65	0.57	0.23-1.40
I vs III	0.32*	0.19-0.53	0.29*	0.12-0.70
I vs IV	0.11*	0.07-0.18	0.07*	0.03-0.16
II vs III	0.33*	0.22-0.49	0.51*	0.29-0.89
II vs IV	0.12*	0.08-0.16	0.13*	0.08-0.19
III vs IV	0.35*	0.27-0.46	0.25*	0.16-0.37

Abbreviations: HR = Hazard Ratio; CI = confidence limits
* indicates 95% CI below 1 (significant)

Table 4: Prognostic value for OS of screening tools and geriatric information

	Cohort A				Cohort B			
	Univariable analysis		adjusted analysis**		Univariable analysis		adjusted analysis**	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Screening tools								
fTRST	0.60*	0.42-0.73	0.62*	0.47-0.82	0.66	0.40-1.10	0.51*	0.31-0.86
G8	0.33*	0.26-0.43	0.39*	0.30-0.50	0.45*	0.32-0.63	0.78	0.55-1.12
ECOG-PS 0-1 vs 2-4	0.46*	0.38-0.56	0.58*	0.47-0.70	0.41*	0.31-0.54	0.50*	0.36-0.68
GA components								
living situation	0.99	0.81-1.20	0.87	0.71-1.06	1.03	0.78-1.37	0.80	0.60-1.07
ADL	0.69*	0.57-0.82	0.63*	0.52-0.76	0.75*	0.57-0.99	0.72*	0.53-0.96
IADL	0.55*	0.46-0.67	0.56*	0.46-0.69	0.55*	0.41-0.75	0.58*	0.42-0.79
falls	0.81*	0.67-0.98	0.78*	0.64-0.95	0.76*	0.58-1.00	0.72*	0.54-0.95
MOBT	0.58*	0.48-0.70	0.75*	0.61-0.91	0.60*	0.45-0.80	0.61*	0.45-0.81
MMSE	0.62*	0.47-0.81	0.67*	0.51-0.89	0.53*	0.39-0.73	0.64*	0.46-0.89
GDS15	0.61*	0.50-0.76	0.66*	0.53-0.82	0.49*	0.37-0.65	0.71*	0.52-0.95
MNA-SF	0.42*	0.34-0.51	0.54*	0.44-0.66	0.53*	0.40-0.70	0.61*	0.46-0.83
CCI	0.78*	0.65-0.94	0.94	0.78-1.13	0.66*	0.50-0.87	0.65*	0.49-0.86
polypharmacy	0.72*	0.60-0.86	0.70*	0.58-0.85	0.68*	0.52-0.90	0.79	0.60-1.05
GA summary								
LOFS								
0-2 vs 3-4	0.61*	0.47-0.79	0.51*	0.33-0.79	0.56*	0.37-0.85	0.77	0.59-1.00
0-2 vs 5-6	0.38*	0.29-0.51	0.40*	0.26-0.61	0.31*	0.20-0.47	0.57*	0.43-0.76
0-2 vs 7-8	0.29*	0.21-0.41	0.26*	0.15-0.42	0.26*	0.16-0.43	0.41*	0.29-0.59
0-2 vs 9-10	0.26*	0.18-0.38	0.16*	0.09-0.29	0.20*	0.11-0.35	0.32*	0.22-0.48
3-4 vs 5-6	0.63*	0.50-0.80	0.77	0.54-1.09	0.55*	0.39-0.78	0.74*	0.58-0.94
3-4 vs 7-8	0.48*	0.35-0.65	0.51*	0.32-0.79	0.47*	0.31-0.71	0.54*	0.40-0.73
3-4 vs 9-10	0.43*	0.30-0.61	0.30*	0.18-0.52	0.36*	0.21-0.59	0.42*	0.29-0.60
5-6 vs 7-8	0.76	0.55-1.04	0.66	0.42-1.03	0.85	0.55-1.29	0.73	0.53-1.00
5-6 vs 9-10	0.68*	0.48-0.97	0.40*	0.23-0.68	0.64	0.39-1.07	0.57*	0.39-0.82
7-8 vs 9-10	0.90	0.60-1.35	0.60	0.33-1.09	0.76	0.43-1.34	0.78	0.52-1.17

Table 4: Prognostic value for OS of screening tools and geriatric information (continued)

Abbreviations: HR = Hazard Ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; fTRST = Flemish version of the Triage Risk Screening Tool; GA = Geriatric Assessment; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MOB-T = Mobility – Tiredness Test; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; MNA-SF = Mini Nutritional Assessment – Short Form; CCI = Charlson Comorbidity Index; LOFS = Leuven Oncogeriatric Frailty Score

* indicates 95% CI below 1 (significant)

** adjusted for age, stage, and tumor type

Table 5: Comparison of the prognostic performance for OS of extended models including screening tools and geriatric information compared to the baseline model of clinical information.

	Cohort A (n=763)			Cohort B (n=402)		
Baseline model (B)	**CPE**	**AIC**	**ΔAIC**	**CPE**	**AIC**	**ΔAIC**
Clinical information (age+stage+tumor type)	0.728	5411.57	0	0.750	2179.53	0
Screening tools						
B + fTRST	0.742	5401.09	10.48	0.746	2173.81	5.72
B + G8	0.747	5354.31	57.26	0.753	2179.63	-0.10
B + ECOG-PS 0-1 vs 2-4	0.737	5384.59	26.98	0.762	2162.73	16.80
GA components						
B + living situation	0.729	5411.54	0.03	0.752	2179.37	0.16
B + ADL	0.726	5390.31	21.26	0.748	2176.37	3.15
B + IADL	0.754	5379.68	31.89	0.745	2169.53	10.00
B + falls	0.730	5407.45	4.12	0.752	2176.21	3.32
B + MOBT	0.724	5405.01	6.56	0.771	2169.69	9.84
B + MMSE	0.727	5406.65	4.92	0.763	2175.08	4.45
B + GDS-15	0.729	5400.16	11.41	0.745	2176.37	3.16
B + MNA-SF	0.756	5377.46	34.11	0.772	2170.75	8.78
B + CCI	0.727	5413.12	-1.54	0.753	2172.46	7.07
B + polypharmacy	0.728	5399.72	11.85	0.749	2178.82	0.71
GA summaries						
B + 10-item GA	0.755	5353.85	57.72	0.775	2155.95	23.58
B + LOFS	0.745	5373.75	37.82	0.755	2144.71	34.81

Abbreviations: fTRST = Flemish version of the Triage Risk Screening Tool; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GA = Geriatric Assessment; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MOB-T = Mobility – Tiredness Test; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; MNA-SF = Mini Nutritional Assessment – Short Form; CCI = Charlson Comorbidity Index; LOFS = Leuven Oncogeriatric Frailty Score; CPE = Concordance Probability Estimate; AIC = Akaike Information Criterion

Figure 2: CPE values demonstrating the discriminatory ability for OS of screening tools and geriatric information in older patients with carcinoma.

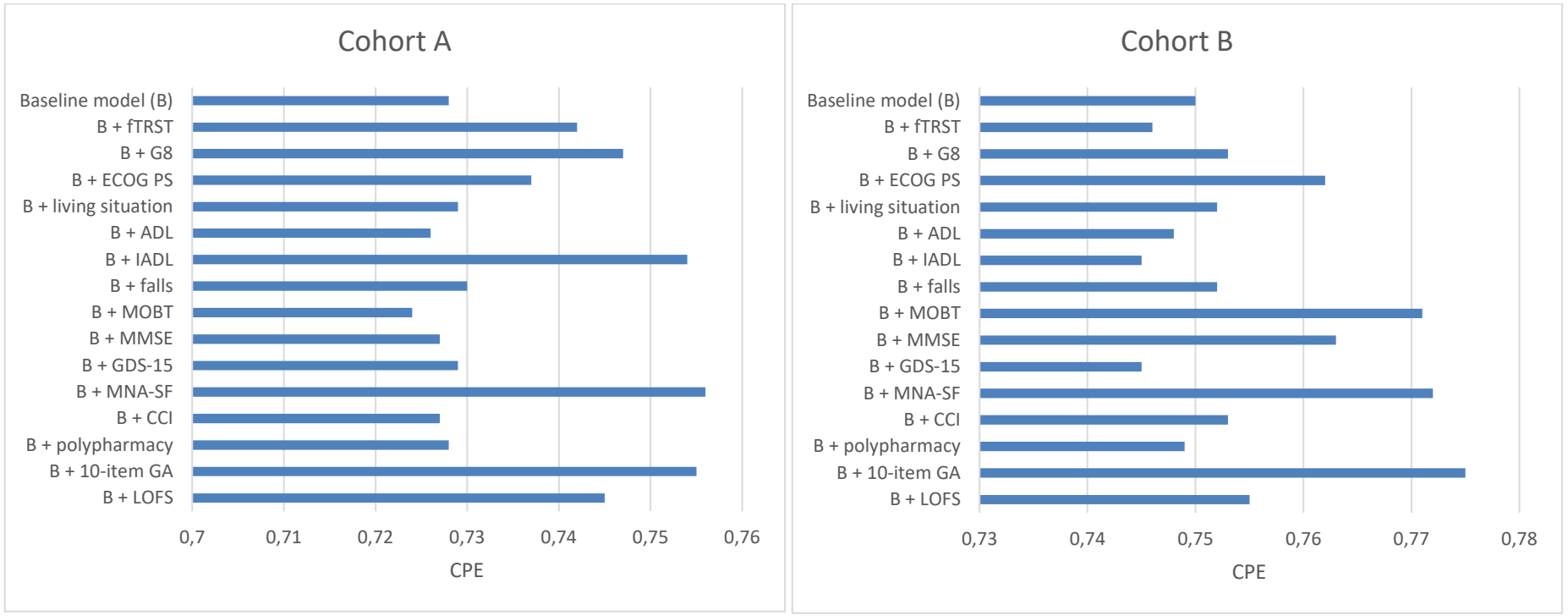

Figure 2: CPE values demonstrating the discriminatory ability for OS of screening tools and geriatric information in older patients with carcinoma. Results are shown for cohort A and cohort B. The baseline model consisted of age, tumor type, and stage as categorical variables. Abbreviations: CPE = Concordance Probability Estimate; fTRST = Flemish version of the Triage Risk Screening Tool; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MOB-T = Mobility – Tiredness Test; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; MNA-SF = Mini Nutritional Assessment – Short Form; CCI = Charlson Comorbidity Index; GA = Geriatric Assessment; LOFS = Leuven Oncogeriatric Frailty Score.

Chapter 6.

The prognostic value of three commonly measured blood parameters and geriatric assessment to predict overall survival in addition to clinical information in older patients with cancer

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* equal contribution

The online version of the published paper will contain supplementary material which have not been included in this dissertation.

Abstract

Aim

To evaluate the prognostic value of laboratory parameters and geriatric assessment (GA) in addition to a baseline model with clinical information for overall survival (OS) in patients with cancer.

Patients and Methods

A GA was systematically performed in patients ≥ 70 years. Our baseline model consisted of age, tumor type, and stage. The incremental prognostic value of the GA as a whole (=10-item GA) and laboratory parameters was assessed separately and combined. The parameters included: hemoglobin (Hb), albumin, C-reactive-protein (CRP), the Glasgow Prognostic Score (GPS). Analyses were conducted with continuous and dichotomized variables. Cox models were compared based on Akaike Information Criterion (ΔAIC) and their discriminatory ability was assessed using the Concordance Probability Estimate (CPE).

Results

A total of 328 patients were considered for this analysis. The baseline model had a CPE of 0.725. The addition of CRP, albumin, and Hb combined resulted in the best performing model (ΔAIC: 40.12; CPE: 0.757) among the laboratory parameters. However, the 10-item GA improved the baseline model even more (ΔAIC: 46.03; CPE: 0.769). Similar results were observed in the analysis with dichotomous variables. The addition of the three laboratory parameters (CRP, albumin, Hb) improved the CPE with 1.4% compared to the baseline model already extended with the 10-item GA. The CPE increase (1.7%) was the highest with the GPS in the analysis with dichotomous variables.

Conclusions

GA adds slightly more prognostic information than laboratory parameters besides clinical information. The laboratory parameters have an additional prognostic value beyond clinical and geriatric information.

Introduction

The implementation of geriatric screening and geriatric assessment (GA) in daily oncology practice is feasible and relevant[1]. To obtain a better view of the global health status of the patient, GA includes the assessment of social needs, functional status (FS), co-morbidity and medication use, cognitive and psychological status, and nutritional status[2]. One of the aims of the GA-based approach is to improve the estimation of life-expectancy which is sometimes a difficult task though very important in the treatment decision-making process. Quick online tools are available that can help estimate the patient's life expectancy in the general population[3]. However, these tools are not entirely suitable in geriatric oncology. In our recent work, we showed that geriatric screening and GA provide additional prognostic information for overall survival (OS) besides clinical information in older patients with a solid tumor[4]. While GA is currently the best tool to estimate a patient's degree of frailty, many efforts are made to identify suitable biomarkers to measure biological age or frailty and to evaluate their predictive value for clinical outcomes like mortality[5-6]. Although many 'aging biomarkers' for biological age, have been proposed in geriatric oncology, none have presently reached a sufficient evidence-base for use in routine clinical practice. Given the complexity of the aging process, it is likely that the best approach would be for the future to work with a combination of geriatric information and biomarkers besides clinical information to aid treatment decision making. Commonly measured laboratory blood values, not necessarily aging biomarkers, might also be interesting for this purpose. A study conducted in 85-year-old persons from the general population showed that a profile of 7 routine blood measurements predicted 5-year mortality as accurately as the known predictors gait speed and instrumental activities of daily living (IADL)[7]. For patients with cancer, various studies have identified several routinely measured blood values at diagnosis as prognostic factors for OS. In a recent study for example, a score was developed to improve the estimation of survival in patients with newly diagnosed brain metastases based solely on standard clinical blood values[8]. In this study, we will focus on hemoglobin (Hb), albumin, and C-reactive protein (CRP). Their prognostic value for OS has been shown in a range of tumor types independent from other prognostic factors[9-11]. Simple inflammatory-based scores have also received much interest in the assessment of prognosis over the past recent years. Three composite scores that combine CRP and albumin values will be included in this study: the Glasgow Prognostic Score (GPS)[12],

the modified GPS (mGPS)[13], and the CRP/albumin ratio. Their prognostic value for mortality has already been shown in multiple studies with various types of cancer in different settings[14-16]. The aim of the present paper is to compare the added prognostic value of the aforementioned laboratory parameters (Hb, albumin, CRP) and the composite scores (GPS, mGPS, CRP/albumin ratio) with the added prognostic value of GA and to evaluate their combined prognostic value for OS besides clinical information in patients with cancer.

Patients and methods

Design

This study was part of a prospective, multicenter, observational study with 763 patients with a solid tumor evaluating the added prognostic value of screening, individual GA components, and two GA summaries for OS to a baseline model of clinical information[4]. This study has been reported extensively previously. In short, the GA-based approach was implemented in routine oncology practice in two academic hospitals ('Universitair Ziekenhuis Brussel' and 'Universitaire Ziekenhuizen Leuven') in Belgium between October 2009 and July 2011. Patients ≥ 70 years were included during a hospital visit at diagnosis or at disease progression/relapse, when a treatment decision had to be made. Inclusion was limited to the following 5 tumor types: breast, colorectal, ovarian, lung and prostate cancer. All data were collected by trained health care workers in both centers[12]. The study was approved by the Ethical Committee of both participating hospitals.

Laboratory parameters

Data on serum Hb, serum albumin, and CRP were used from routinely collected blood samples shortly before or after the date of GA. The three laboratory parameters were categorized for descriptive statistics. Local lab ranges were used from both participating hospitals to dichotomize the laboratory values. Since these did not correspond, different cut-off values were used for each hospital. Hb was dichotomized in below lower limit of normal (<LLN) and ≥LLN. The LLN was 12.0 g/dl or 11.8 g/dl dependent of which hospital. Since the local lab ranges did not distinguish cut-off values for men and women, we used the 1968 WHO criteria (men: Hb < 12.0 g/dl; women: Hb <11.8 g/dl) but also

alternative cut-off values proposed by Beutler E and Waalen J. 2006[18] for older Caucasian adults (men: Hb < 13.2 g/dl; women: Hb < 12.2 g/dl) to evaluate if gender-specific cut-off values would improve the prognostic value of Hb.

Albumin was dichotomized in <LLN and ≥LLN with a LLN of 35.0 g/l or 37.0 g/l. CRP as a continuous variable was analyzed per 10-point increase to allow a more practical interpretation of the results. CRP was also categorized in elevated values with cut-off value >5.0 mg/l or ≥ 5.0 mg/l depending which hospital, and normal values.

The inflammatory-based composite score GPS (score range: 0-2) was defined as follows: score 0: CRP ≤ 10 mg/dl and albumin ≥ 35.0 g/l; score 1: CRP > 10 mg/l or albumin < 35.0 g/l; score 2: CRP > 10 mg/l and albumin < 35.0 g/l[12]. The only difference between the GPS and the mGPS is that the mGPS does not consider hypoalbuminemia (< 35.0 g/l) in the allocation of score 1[13].

Geriatric assessment

The GA included 10 components based on the 2014 SIOG recommendation guideline for GA [2]: social data with living situation, FS assessed by the Katz's Activities of Daily Living (ADL)[19] and by Lawton's Instrumental Activities of Daily Living (IADL)[20], fall history during the last year[21], fatigue assessed by the MOB-T[22], mental status assessed by the Mini Mental State Examination (MMSE)[23] and Geriatric Depression Scale (GDS-15)[24] , nutritional status assessed by the Mini Nutritional Assessment-Short Form (MNA-SF)[25], comorbidities assessed by the Charlson Comorbidity Index (CCI)[26] and a polypharmacy assessment[27]. When taken together, this 10-item GA is a GA summary, which integrates the results of every GA component mentioned above and thus captures the multidimensional GA as a whole evaluating the global health of the older patient with cancer. However, it doesn't calculate a global GA end score. In our other paper, we showed that the 10-item GA provides more prognostic information than the individual GA components and screening tools because 'GA summaries' are likely better at capturing the multidimensional process of aging[4]. Therefore, in this paper, we primarily compared the added prognostic value of the 10-item GA with that of laboratory parameters. However, for comparative reasons we also included the individual GA components, the 'Leuven Oncogeriatric Frailty Score' (LOFS) (also a GA summary), the G8, the Flemish version of the Triage Risk Screening Tool (fTRST),

and the Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) in the current analysis. The G8 (score range: 0-17, cut-off ≤ 14) and the fTRST (score range: 0-6, cut-off ≥ 1) are geriatric screening tools to identify patients who would benefit from a GA[28-31]. The ECOG-PS is frequently used in oncology to classify the performance status of patients[32]. The LOFS is a recently developed tool to summarize clinical frailty[4,6]. It integrates information from 5 GA components into a single global end score (range: 0-10). The following categories are included: score 0-2 (severely frail), score 3-4 (frail), score 5-6 (vulnerable), score 7-8 (slightly vulnerable) and score 9-10 (fit).

Statistical analysis

Patient and clinical characteristics, screening and GA results were compared between the groups of patients included and excluded from the main analysis by means of the chi-square test and the Mann-Whitney test as appropriate. The median survival time of the two groups was compared with the log-rank test.

Univariable cox proportional hazard regression analyses were conducted to evaluate the prognostic value of laboratory parameters, screening tools, individual GA components, and the LOFS. Multivariable analyses were performed as well to adjust for clinical information (age, stage, tumor type). OS was calculated from date of GA to date of death from any cause or last follow-up for censored patients. Results were considered significant if $p<0.05$.

We performed Cox proportional hazard regression analyses to build multiple prognostic models. The baseline clinical model consisted of age as a continuous variable and tumor type and stage as categorical variables. To assess the contribution of the laboratory parameters, the 10-item GA and the two combined, each was added separately to the baseline model of clinical information. The goodness-of-fit of the nested models were compared with the likelihood-ratio test. We added the individual GA components, the screening tools, and the LOFS as well in the analysis. Multicollinearity was assessed with the variance inflation factor (VIF) and was not present (VIF's<3). The cox.zph function revealed that the proportional hazards assumption was not satisfied for age, albumin as a continuous variable, CRP and Hb as a dichotomous variable, and the (m)GPS in some of the multivariable models. We

decided not to modify these models, since our objective was to compare the performance of the examined models and not to adjust the construction of the models to get a better fit.

The discriminatory ability of each prognostic model was assessed using the Concordance Probability Estimate (CPE)[33]. The global fit of the Cox models was compared by means of the difference of Akaike Information Criterion (AIC) of the baseline model and the extended model (ΔAIC). A higher ΔAIC value corresponds with a more explanatory and informative model.

Separate analyses were conducted with the GA components and laboratory parameters as continuous variables and as dichotomized variables where possible. Because the baseline model was identical in both analyses, we were able to quantify the expected loss of information and thus loss in prediction due to the dichotomization of the data. The LOFS was analyzed as a categorical variable and a continuous variable (per 1-point increase). The (m)GPS (score range: 0-2) was analyzed as a categorical variable but also as a continuous variable when calculating the hazard ratios in order to have the risk per unit increase as well. All analyses were performed using SPSS 23 (Chicago, IL) and R version 3.3.3.

Results

Patient population

For more information on the total sample we refer to our previous publication (cohort A, n=763)[4]. For the current paper, a subgroup of 328 patients with information available on the three laboratory parameters was considered. The median age was 77 years (range: 70-95 years). The most prevalent tumors were from the breast (38.4%), colorectal (35.4%), lung (15.5%), and prostate (6.4%). At the moment of inclusion in the study, 63.7% had a newly diagnosed cancer, whereas 36.3% had disease progression or relapse. Considering comorbidity, 54.9% had a score of ≥1 on the CCI. More details of patient demographics and clinical characteristics, including patients that were excluded from the analysis, are listed in Table 1. The results of the GA are listed in Table 2. The studied subgroup was more often male, had a different pattern of tumor types, had more advanced disease, received less surgery but more often chemotherapy and radiotherapy than the group of patients excluded from the analysis (n=435). The GA revealed that the studied subgroup had more often a geriatric risk profile according to the G8 and was more often depressed. Furthermore, the survival was significantly lower

with a median survival time of 21.3 months (95%CI: 18.1-29.3; 239 deaths (72.9%)) compared to a median survival time of 50.7 months (95%CI: 40.2-65.4; 232 deaths (53.3%); log-rank test: p<0.001). The median follow-up, calculated with the reversed Kaplan-Meier method[34], was 60.3 months (95%CI: 58.6-62.6) and 62.6 months (95%CI: 61.4-64.3), respectively.

The prognostic value of laboratory parameters

Blood samples were on average 7.7 days (SD 10.0) collected from the date on which a GA was performed. In total, 58.8% (n=193) of the patients had an elevated CRP level; 28.4% (n=93) of the patients had an albumin level <LLN; and 41.8% (n=137) of the patients had a Hb level <LLN. For the GPS, 169 patients (51.5%) were allocated score 0, 93 patients (28.4%) score 1, and 66 patients (20.1%) score 2. The results according to the mGPS were as follows: score 0: 178 patients (54.3%); score 1: 84 patients (25.6%); and score 2: 66 patients (20.1%).

Kaplan-Meier plots from the three individual laboratory parameters and the GPS are shown in Figure 1. The prognostic values of the laboratory parameters (CRP, albumin, Hb) and the composite scores (GPS, mGPS, CRP/albumin) are shown in Table 3. Every laboratory-based parameter (continuous, dichotomized, categorical) was prognostic for OS in univariable and adjusted analyses. Results for the individual GA components, screening tools and LOFS are also included in Table 3.

We conducted additional analyses for Hb taken into account gender-specific cut-off values. This resulted in an additional number of 30 patients and 41 patients who were categorized as having abnormal Hb values according to the WHO criteria and the alternative cut-off values proposed by Beutler E and Waalen J. 2006, respectively. Their estimated hazard ratios are included in Table 3.

Comparison of prognostic models

The baseline model had a good discriminatory ability with CPE 0.725. The added value of the laboratory parameters and GA are shown in Table 4. Based on CPE and AIC results, albumin performed better than CRP in the analyses with continuous and dichotomous variables. Both parameters clearly performed far better than Hb. The GPS (ΔAIC: 32.54; CPE: 0.750) had the best performance compared to the 2 other composite scores (mGPS, CRP/albumin ratio), though not better than albumin as a continuous variable

(ΔAIC: 34.22; CPE: 0.755) or when all three continuous laboratory parameters (CRP, albumin, Hb) were combined which resulted in the best performing model among the models extended with laboratory parameters (ΔAIC: 40.12; CPE: 0.757). However, this model (with CRP, albumin, Hb) did not improve the baseline model as much as the model extended with the 10-item GA (ΔAIC: 46.03; CPE: 0.769). The model with the three laboratory parameters (ΔAIC: 25.49; CPE: 0.747) or any other model laboratory parameters did also not outperform the model with the 10-item GA (ΔAIC: 37.52; CPE: 0.763) when analyzed with dichotomous variables.

Results for the individual GA components, the LOFS, and the screening tools (G8, fTRST, ECOG-PS) were included in Table 4 for comparison. None of these models performed better than the best performing models with laboratory parameters. When comparing the individual GA components with the laboratory parameters, it is important to note that a model might have a better discriminatory ability (CPE) than another while the prognostic information (ΔAIC) contained in that model might be lower. Nutritional status measured by the MNA-SF as a continuous variable for example added more prognostic information than albumin (ΔAIC: 37.91 vs ΔAIC: 34.22) while the MNA-SF model had a lower CPE (CPE: 0.749 vs CPE: 0.755).

The analyses that evaluated the laboratory parameters in addition to the baseline model already extended with the 10-item GA show that the laboratory parameters have an added prognostic value beyond clinical and geriatric information. Results are summarized in Table 4. We added the GPS and the mGPS, which are categorical variables, in the two analyses with the 10-item GA analyzed with continuous and dichotomous variables. In order of the ΔAIC results, the following models had the best performance when analyzed with continuous variables: the models with CRP (ΔAIC: 68.03; CPE: 0.780, the three laboratory parameters combined (ΔAIC:67.18; CPE: 0.783), CRP/albumin ratio (ΔAIC: 66.99; CPE: 0.780), and the GPS (ΔAIC: 66.22; CPE: 0.782). The following ranking was observed in the analyses with dichotomous variables: the models with the GPS (ΔAIC: 63.58; CPE: 0.780), the mGPS (ΔAIC: 58.48; CPE: 0.778), the three laboratory parameters combined (ΔAIC: 49.12; CPE: 0.773), and CRP (ΔAIC: 48.28; CPE: 0.771).

A visual overview of the improved performance of the models extended with the three laboratory parameters (CRP, albumin, Hb) and the 10-item GA can be found in Figure 2. The addition of every laboratory parameter improved the goodness-of-fit of each model, with the exception of Hb as a dichotomous variable beyond the model already extended with the 10-item GA. The small improvement with Hb was only significant when it was dichotomized according to the gender-specific cut-off values proposed by Beutler E and Waalen J. 2006 (likelihood-ratio test: p=0.04).

Discussion

CRP, albumin, and Hb in cancer patients

CRP levels increase in response to inflammation and are elevated in a variety of illnesses, including cancer. Inflammation markers like CRP are also potential aging biomarkers since low-level increases in general/non-specific inflammation accompany aging (inflammaging)[5]. A prognostic value of CRP for mortality in older patients with cancer might thus be explained by processes related to the cancer and/or aging. The two other commonly measured laboratory parameters studied here, albumin and Hb, should be viewed less in the context of aging and more in the context of underlying diseases like cancer. Serum albumin is generally used to assess the nutritional status. However, both inflammation and malnutrition reduce albumin levels by decreasing its rate of synthesis[10]. Lower Hb levels or anemia is common in patients with cancer and can develop from multiple causes. Also, when related to cancer itself, multiple mechanisms can interfere with normal erythrocyte production but is usually secondary to an imbalance of cytokines[29]. In this study, anemia is unlikely related to cancer treatment since blood samples were used around the time of a treatment decision.

Irrespective of the cause of changes in levels of these three commonly measured laboratory measures, this study confirms that CRP, albumin, Hb, and the composite scores based on CRP and albumin (GPS, mGPS, CRP/albumin ratio) are prognostic factors for OS independent from clinical information (age, stage, tumor type) in older patients with cancer.

The comparison of the added prognostic value of laboratory parameters and GA

We previously showed that most individual GA components are prognostic factors independent from clinical information for OS[4]. Studies that evaluate the prognostic value of GA generally focus on the most prognostic individual GA components or on the best set of GA components[36-40]. In our previous analysis, we took a more extensive approach and also studied the added prognostic value of the GA as a whole (the 10-item GA) by comparing the performance of a baseline model of clinical information with models extended with geriatric information[4]. This allowed us for example to quantify the superior prognostic value of the GA as a whole compared to the individual GA components in addition to clinical information.

A comparison of the added prognostic value of the laboratory parameters and the individual GA components in the current study is sometimes difficult since the comparison varies whether you look at ΔAIC or CPE results and whether you look at the analysis with continuous or dichotomous variables. On the other hand, sometimes results were easy to interpret. From the individual GA components, only nutritional status (MNA-SF) rivaled the performance of that of the best performing laboratory parameters in the analysis with continuous variables. Furthermore, as expected, the dichotomization of the laboratory parameters and the GA components significantly reduced the performance of the models. This is important to note since many studies dichotomize data and because many clinicians are used to work with categorized information. PS (ADL, IADL, ECOG-PS) is an important domain in the assessment of the patients' global health status. IADL was one of the most prognostic GA components in our analysis of the full sample (n=763, ref 4). However, PS did not perform as well in this subgroup, regardless of the data type. A possible explanation might be that PS is more driven by tumor type and stage compared to other GA components and that the more advanced disease (and different pattern of tumor types) observed in this subgroup might have reduced the independent prognostic impact of PS while other GA components that reflect other aspects of the patients' global health status were less influenced. In this regard, we note that the inflammation-based composite scores, which may also be regarded as driven by tumor characteristics, performed better than PS. The comparison of the composite scores GPS and mGPS with the other variables should be interpreted carefully. The (m)GPS is a score

with three levels and was added unchanged in the analyses with continuous and dichotomous variables. This explains why the GPS performed in the same range as albumin and CRP in the analysis with continuous variables while it clearly performed better than albumin and CRP in the analysis with dichotomous variables. In the analysis with dichotomous variables, we also conducted additional analyses with Hb since the threshold defining anemia has received considerable scientific debate. Various cut-off values are used in the literature. In this study, we considered two alternative gender-specific cut-off values to examine if this would improve the prognostic value of Hb. A small improvement was indeed observed in the stratification of patients, however the added prognostic value of Hb was throughout the study inferior to the other laboratory parameters.

The comparison of the laboratory parameters with the 10-item GA shows that the latter is superior based on ΔAIC and CPE results. The AIC is a more sensitive method than the CPE to rank different models, however the CPE provides an interpretable measure of performance. According to the CPE results, the addition of the 10-item GA increased the performance of the baseline model with 4.4% whereas the best performing model with laboratory parameters (i.e., with CRP, albumin, Hb) resulted in a lower increase of 3.2% in the analysis with continuous variables. In the analysis with dichotomous variables, the GPS added more than the three laboratory parameters combined, i.e. 2.5% vs 2.2%. However, the 10-item GA added more with a CPE increase of 3.9%. In other words, the model with the 10-item GA performs better than the best model incorporating laboratory parameters with a CPE difference of 1.2% or 1.4%, considering the data type. Obviously, the laboratory parameters have the advantage of being objective, reproducible, inexpensive, and fast whereas the implementation of GA in routine practice requires the necessary time and resources. However, we emphasize that the GA-based approach is also important for other reasons in this context like to estimate the risk of treatment-induced toxicity, to detect previously unknown health problems, and to allow directed geriatric interventions that can improve therapy compliance and outcome.

The incremental prognostic value of laboratory parameters beyond GA

Our findings show that laboratory parameters and GA improve the estimation of life expectancy separately. However, given the complexity of the processes related to aging, cancer, and their

interaction, the combination of different types of information is likely to improve the accuracy of prognosis assessment. Very few studies have evaluated the prognostic value of both GA and biomarkers for OS. Aaldriks et al. 2015 studied patients with non-Hodgkin lymphoma by looking at the hazard ratios after entering individual GA components and biomarkers in a multivariable model[41]. A recent study from Honecker et al. 2017 evaluated the simultaneous impact of GA and biomarkers in patients with breast cancer by selecting the best set of factors through elimination starting from a multivariable model incorporating all candidate parameters (backward stepwise analysis)[42]. In this study, we used another analysis approach since we were interested in the incremental value of biomarkers for OS. To the best of our knowledge, this is the first study to compare the incremental value of different biomarkers beyond the GA as a whole. Our analysis showed that the laboratory parameters continue to add prognostic information beyond the model with both clinical information and the 10-item GA. As previously noted, differences were sometimes small, and the ranking of the models depends of AIC and CPE results. According to the more sensitive AIC results, CRP added the most prognostic information. However, the CPE increased the most when the combination of the three laboratory parameters was added resulting in CPE increase of 5.8% relative to the baseline model and 1.4% relative to the baseline model already extended with the 10-item GA. In the analysis with dichotomous variables, it was the GPS that added the most in terms of both AIC and CPE results. The CPE increased with 5.6% relative to the baseline model and with 1.7% relative to baseline model extended with the 10-item GA.

In theory there exists some overlap in prognostic information provided by geriatric information and biomarkers (e.g. nutritional status and albumin). Honecker et al. 2017 suggested there was almost no overlap based on the variables retained in their final model for OS. In this study, we were able to investigate this more accurately when we put the analyses where the baseline model is extended with the laboratory parameters and the 10-item GA separately together with the analyses where both are added simultaneously. To illustrate this with numbers from the analysis with continuous variables. The model extended with the three laboratory parameters combined (CRP, albumin, Hb) improved the CPE with 3.2% (ΔAIC: 40.12) and when extended with the 10-item GA with 4.4% (ΔAIC: 46.03). One might expect an CPE increase of 7.6% (ΔAIC: 86.15) when the baseline model is extended with both.

However, when both the three laboratory parameters and the 10-item GA are actually added to the baseline model, the CPE only increased with 5.8% (ΔAIC: 67.18). Still, as quantified in this study, the combination of geriatric information and biomarkers improves the estimation of life expectancy more than separately.

Strengths and limitations

The strengths of this study include the relatively large sample size, the prospective study design, the many domains covered by the GA, the analysis approach and the long follow-up. However, some considerations need to be taken into account when interpreting the results. Ideally, 'aging' biomarkers should not be influenced by underlying health conditions and the timing of the blood collections is another possible confounding factor limiting their use in routine clinical practice[5]. In this study, this pertains to CRP because CRP levels might be increased due to inflammatory reactions caused by the cancer or another underlying health condition but also due to recent surgery for example. However, we did work with blood samples that were taken at a fixed time, i.e. shortly before or after GA, and hence at the time of diagnosis or progression/relapse. Future studies with a more homogenous population and more detailed information on treatment should make a distinction between these two settings, given the hypothesized pro-aging effects of many cancer treatments.

Our findings are applicable to a population for which all three studied laboratory parameters are evaluated in routine practice. As our results show, this subgroup is as expected more vulnerable and has a worse survival compared to the group of patients for who all three laboratory parameters were not tested. Patients were often excluded from our analysis because the combination CRP and albumin was not tested (reducing the sample size to n=329). However, additional analyses considering one laboratory parameter and thus larger sample sizes due to less missing data (CRP: n=501; albumin: n=423; Hb: n=692), did not change our conclusions which suggests that our results are also relevant for patients for who generally all three laboratory parameters are not tested (Additional file 1).

Furthermore, our heterogeneous population is a disadvantage since many relevant prognostic parameters are not captured but at the same time it is an advantage as it is representative of a larger cancer population.

Conclusions

GA adds slightly more prognostic information than laboratory parameters besides clinical information.

The laboratory parameters have an additional prognostic value beyond clinical and geriatric information.

Author contributions

conception and design: CK, LD, JPL, JF, KM, HW

data acquisition: CK, LD, HW

data analysis and interpretation: AB, CK, LD, JDG, JPL, JF, KM, HW

writing–initial draft: AB, CK, LD, JPL, HW

writing–critical revision: AB, CK, LD, JDG, JPL, JF, KM, HW

statistical analyses: AB

supervision: AB, CK, LD, JDG, JPL, JF, KM, HW

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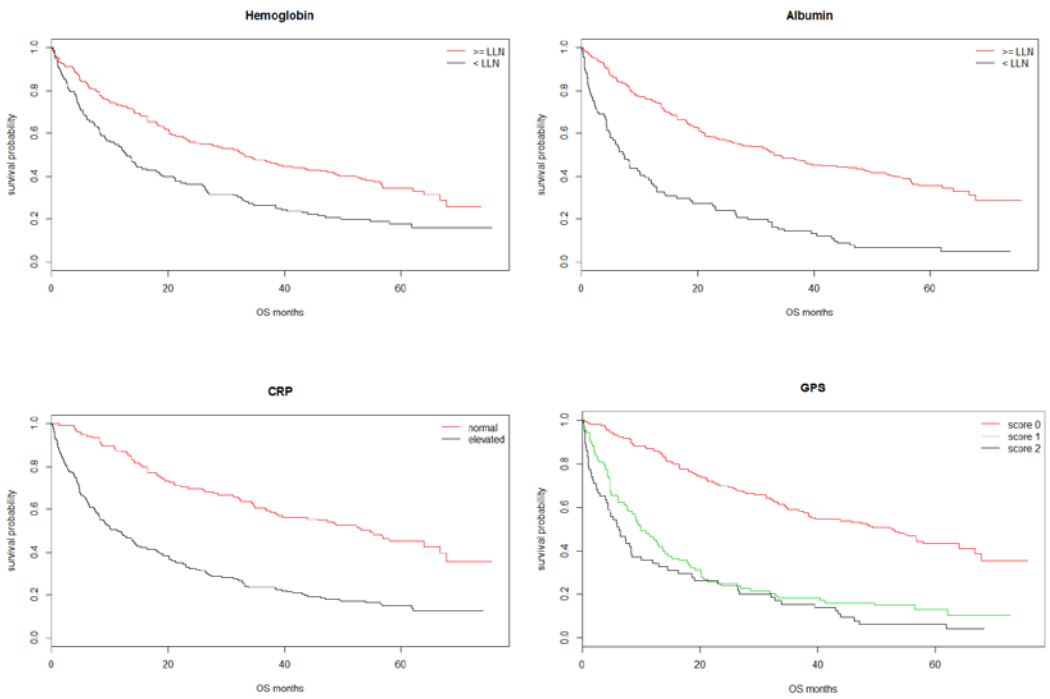

Figure 1. Prognostic value of laboratory parameters (n=328). Kaplan-Meier overall survival curves are shown stratified for normal and abnormal values of hemoglobin, albumin, and CRP. The Glasgow Prognostic Score (GPS) is shown as well.

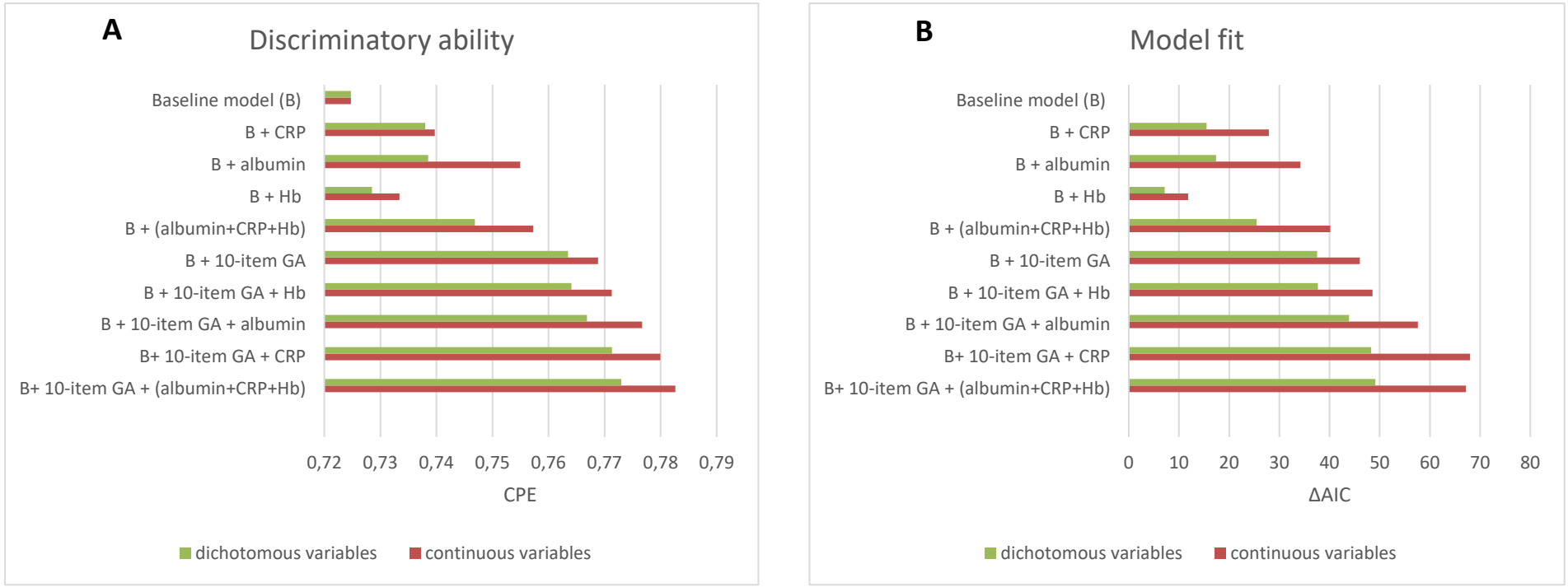

Figure 2. Overview of the added performance of the extended models with laboratory parameters and GA. Overview of (A) the discriminatory ability (CPE) and (B) the model fit (ΔAIC) of the baseline model of clinical information and the models extended with laboratory parameters and GA. Models are shown analysed with continuous variables and dichotomized variables. The baseline model was analysed with age as a continuous variable; and stage and tumor type as categorical variables. Abbreviations. GA = Geriatric Assessment; CPE = Concordance Probability Estimate; AIC = Akaike Information Criterion; Hb = Hemoglobin

Table 1. Patient and clinical characteristics

	Included		*Excluded*		
Characteristic	N°	%	N°	%	p-value
Total	328	100	435	100	
Age (years)					0.384
Median (range)	77 (70-95)		76 (70-93)		
Gender					<0.001
Female	194	59.1	323	74.3	
Male	134	40.9	112	25.7	
Tumor type					<0.001
Breast	126	38.4	246	56.6	
Colorectal	116	35.4	70	16.1	
Lung	51	15.5	21	4.8	
Prostate	21	6.4	53	12.2	
Ovarian	14	4.3	45	10.3	
Time point of assessment					0.991
New diagnosis	209	63.7	277	63.7	
Progression/relapse	119	36.3	158	36.3	
Stage					<0.001
I	22	6.7	66	15.2	
II	59	18.0	112	25.7	
III	50	15.2	62	14.3	
IV	197	60.1	195	44.8	
Treatment received					
Surgery	125	38.1	220	50.6	0.001
Chemotherapy	172	52.4	140	32.2	<0.001
Radiotherapy	80	24.4	155	35.6	0.001
Hormonal therapy	89	27.1	208	47.8	<0.001
Pain: VAS (0-10)					0.218
Score 0	153	46.8	221	50.8	
Score 1-3	59	18.0	59	13.6	
Score ≥4	115	35.2	155	35.6	

Abbreviations: VAS: Visual Analogue Scale.

* more than one modality is possible

Patients that were excluded from the analysis were compared with the included patients by means of the chi-square test and the Mann-Whitney test.

Table 2: Results of screening and geriatric assessment

			Included		Excluded		
Screening tools	**Cut-off**	**Score**	**n**	**%**	**n**	**%**	**p-value**
G8 (0-17)	≤14	Absence of a geriatric risk profile: score > 14	72	22.0	125	28.7	0.034
		Presence of a geriatric risk profile: score ≤ 14	256	78.0	310	71.3	
fTRST	≥1	Absence of a geriatric risk profile: score 0	51	15.5	80	18.4	0.303
		Presence of a geriatric risk profile: score ≥1	277	84.5	355	81.6	
ECOG-PS		Score 0-1	234	71.3	325	74.7	0.298
		Score 2-4	94	28.7	110	25.3	
GA components	**Item/ Instrument**	**Score**					
Social data	Living situation	Not living alone	232	70.7	290	66.7	0.232
		Living alone	96	29.3	145	33.3	
Functional Status	ADL (6-24)	Independent: score 6	158	48.2	214	49.2	0.779
		Dependent: score ≥ 7	170	51.8	221	50.8	
	IADL (0-5/8)	Independent: score 8 (female) or 5 (male)	137	41.8	192	44.1	0.513
		Dependent: score < 8 (female) or 5 (male)	191	58.2	243	55.9	
	Fall history	No falls	216	65.9	304	69.9	0.237
		≥ 1 fall	112	34.1	131	30.1	
Fatigue	MOB-T (0-6)	No fatigue	135	41.2	180	41.4	0.951
		Presence of fatigue	193	58.8	255	58.6	
Cognition	MMSE (0-30)	Score ≥ 24 = normal cognition	286	87.2	398	91.5	0.054
		Score ≤ 23 = mild/severe cognitive decline	42	12.8	37	8.5	
Depression	GDS-15 (0-15)	Score 0-4 = not at risk for depression	247	75.3	357	82.1	0.023
		Score 5-15 = at risk for depression	81	24.7	78	17.9	
Nutrition	MNA-SF (0-14)	Score ≥ 12 = normal nutritional status	112	34.1	176	40.5	0.075
		Score 0-11 = risk of malnutrition + malnourished	216	65.9	259	59.5	
Comorbidity	CCI (0-37)	No comorbidities (score 0)	148	45.1	207	47.6	0.499
		Comorbidity score ≥ 1	180	54.9	228	52.4	
Polypharmacy		0-4 different drugs	152	46.3	217	49.9	0.332
		≥ 5 different drugs	176	53.7	218	50.1	
GA summary							
LOFS							0.085
		9-10 (fit)	79	24.1	127	29.2	
		7-8 (slightly vulnerable)	122	37.2	161	37.0	
		5-6 (vulnerable)	65	19.8	94	21.6	
		3-4 (frail)	37	11.3	35	8.0	
		2-1 (very frail)	25	7.6	18	4.1	

Abbreviations: CI = confidence interval; GA = Geriatric Assessment; fTRST = Flemish version of the Triage Risk Screening Tool; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MOB-T = Mobility – Tiredness Test; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; MNA-SF = Mini Nutritional Assessment – Short Form; CCI = Charlson Comorbidity Index; LOFS = Leuven Oncogeriatric Frailty Scale.
Patients that were excluded from the analysis were compared with the included patients by means of the chi-square test**.**

Table 3: Prognostic value of laboratory parameters and GA for OS

	Continuous variables[d]				Dichotomous variables			
	Univariable		Adjusted[e]		Univariable		Adjusted[e]	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Laboratory parameters								
CRP (mg/L)[a]	1.12*	1.09-1.14	1.08*	1.06-1.11	2.79*	2.11-3.68	1.82*	1.37-2.43
Albumin (g/L)	0.91*	0.89-0.93	0.92*	0.90-0.95	2.91*	2.22-3.81	2.91*	1.44-2.52
Hb (g/dl)	0.84*	0.78-0.90	0.86*	0.79-0.93	1.73*	1.34-2.23	1.51*	1.16-1.96
Hb gender-specific (WHO)[b]	NA	NA	NA	NA	1.88*	1.45-2.44	1.52*	1.15-2.00
Hb gender-specific[c]	NA	NA	NA	NA	1.92*	1.48-2.49	1.62*	1.22-2.13
GPS (categorical)					NA	NA	NA	NA
- Score 0	Ref		Ref					
- Score 1	3.03*	2.24-4.09	2.05*	1.47-2.86				
- Score 2	4.05*	2.93-5.61	2.64*	1.88-3.71				
mGPS (categorical)					NA	NA	NA	NA
- Score 0	Ref		Ref					
- Score 1	2.64*	1.95-3.58	1.76*	1.26-2.46				
- Score 2	3.74*	2.71-5.14	2.46*	1.76-3.43				
GPS (continuous)	2.06*	1.77-2.40	1.65*	1.40-1.94	NA	NA	NA	NA
mGPS (continuous)	1.97*	1.69-2.30	1.58*	1.34-1.86	NA	NA	NA	NA
CRP/albumin ratio	1.30*	1.24-1.37	1.25*	1.18-1.34	NA	NA	NA	NA
GA components								
MNA-SF	0.82*	0.78-0.86	0.86*	0.82-0.90	2.88*	2.13-3.90	2.15*	1.58-2.93
GDS-15	1.11*	1.06-1.16	1.14*	1.09-1.21	1.95*	1.47-2.58	2.13*	1.59-2.85
ADL	1.09*	1.04-1.14	1.10*	1.05-1.15	1.35*	1.05-1.75	1.54*	1.17-2.04
IADL	NA	NA	NA	NA	1.67*	1.28-2.18	1.67*	1.27-2.21
MMSE	0.95*	0.92-0.98	0.94*	0.90-0.97	1.41	0.98-2.03	1.55*	1.04-2.32
Fall history	NA	NA	NA	NA	1.19	0.91-1.55	1.64*	1.24-2.16
MOB-T	0.89*	0.85-0.94	0.92*	0.87-0.97	1.44*	1.10-1.87	1.11	0.84-1.46
CCI	1.08*	1.00-1.16	1.10*	1.01-1.19	1.11	0.86-1.43	1.00	0.77-1.30
Living situation	NA	NA	NA	NA	1.13	0.86-1.50	1.18	0.89-1.57
Polypharmacy	1.03	0.99-1.08	1.03	0.98-1.07	1.21	0.94-1.56	1.12	0.86-1.45

Table 3: continued

	Continuous variables[d]				Dichotomous variables			
	Univariable		Adjusted[e]		Univariable		Adjusted[e]	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Screening and LOFS								
G8	0.84*	0.80-0.87	0.87*	0.83-0.90	3.09*	2.11-4.51	2.80*	1.89-4.15
fTRST	1.28*	1.15-1.42	1.30*	1.16-1.47	1.81*	1.23-2.67	1.46	0.98-2.16
ECOG-PS	1.33*	1.19-1.48	1.31*	1.16-1.48	2.00*	1.53-2.61	1.77*	1.34-2.35
LOFS: continuous	0.86*	0.82-0.90	0.84*	0.79-0.89				
LOFS: categorical								
9-10 (fit)	Ref		Ref					
7-8 (slightly vulnerable)	1.53*	1.06-2.21	1.21	0.82-1.78				
5-6 (vulnerable)	2.47*	1.65-3.69	1.76*	1.16-2.67				
3-4 (frail)	3.50*	2.23-5.52	2.50*	1.52-4.09				
2-1 (very frail)	3.00*	1.82-4.95	3.91*	2.22-6.90				

Abbreviations: HR = Hazard Ratio; CI = confidence interval; GA = Geriatric Assessment; Hb = hemoglobin; (m)GPS = (modified) Glasgow Prognostic Score; MNA-SF = Mini Nutritional Assessment – Short Form; GDS = Geriatric Depression Scale; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini Mental State Examination; MOB-T = Mobility – Tiredness Test; CCI = Charlson Comorbidity Index; fTRST = Flemish version of the Triage Risk Screening Tool; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; LOFS = Leuven Oncogeriatric Frailty Scale

[a] CRP as a continuous variable was analysed per 10-unit increase

[b] Hb was dichotomized according to gender-specific cut-off values proposed by the WHO (Hb < 13.0 g/dl for men; Hb <12.0 g/dl for women)

[c] Hb was dichotomized according to gender-specific cut-off values proposed by Beutler E, Waalen J. Blood. 2006 (Hb < 13.2 g/dl for men; Hb <12.2 g/dl for women)

[d] Unless specified otherwise (categorical)

[e] Adjusted for age, stage, tumor type

* $p < 0.05$

Table 4: Comparison of the performance of the baseline clinical model and extended models for overall survival

	CPE	AIC	ΔAIC	CPE	AIC	ΔAIC
Baseline model (B)						
Clinical information (age+stage+tumor type)	0.725	2336.86	0	0.725	2336.86	0
	Continuous variables[e]			**Dichotomous variables**		
Laboratory parameters						
B + CRP (mg/L)[a]	0.740	2308.96	27.90	0.738	2321.34	15.52
B + Albumin (g/L)	0.755	2302.65	34.22	0.739	2319.48	17.39
B + Hb (g/dl)	0.733	2325.03	11.83	0.729	2329.70	7.17
B + (CRP + albumin + Hb)	0.757	2296.74	40.12	0.747	2311.37	25.49
B + Hb gender-specific (WHO)[b]	NA	NA	NA	0.730	2329.89	6.97
B + Hb gender-specific[c]	NA	NA	NA	0.732	2327.21	9.66
B + GPS (categorical)[d]	0.750	2304.33	32.54	0.750	2304.33	32.54
B + mGPS (categorical)[d]	0.745	2311.29	25.57	0.745	2311.29	25.57
B + CRP/albumin ratio	0.742	2306.82	30.04	NA	NA	NA
10-item GA and laboratory parameters						
B + 10-item GA	0.769	2290.83	46.03	0.763	2299.34	37.52
B + 10-item GA + CRP [a]	0.780	2268.84	68.03	0.771	2288.59	48.28
B + 10-item GA + albumin	0.777	2279.27	57.60	0.767	2293.00	43.86
B + 10-item GA + Hb	0.771	2288.31	48.56	0.764	2299.20	37.66
B + 10-item GA + (CRP +albumin + Hb)	0.783	2269.69	67.18	0.773	2287.74	49.12
B + 10-item GA +Hb gender-specific (WHO)[b]	NA	NA	NA	0.765	2298.25	38.62
B + 10-item GA + Hb gender-specific[c]	NA	NA	NA	0.766	2297.12	39.74
B + 10-item GA + GPS[d]	0.782	2270.64	66.22	0.780	2273.28	63.58
B + 10-item GA + mGPS[d]	0.779	2275.47	61.40	0.778	2278.39	58.48
B + 10-item GA + CRP/albumin	0.780	2269.88	66.99	NA	NA	NA
GA components						
B + living situation	NA	NA	NA	0.726	2337.55	-0.69
B + ADL	0.737	2323.00	13.87	0.731	2329.37	7.50
B + IADL	NA	NA	NA	0.735	2325.09	11.77
B + falls	NA	NA	NA	0.734	2327.21	9.66
B + MOBT	0.730	2329.91	6.95	0.725	2338.35	-1.48
B + MMSE	0.732	2329.17	7.70	0.727	2334.63	2.24
B + GDS-15	0.741	2315.99	20.87	0.740	2315.43	21.43
B + MNA-SF	0.749	2298.95	37.91	0.746	2312.65	24.22
B + CCI	0.729	2334.50	2.36	0.725	2338.86	-2.00
B + polypharmacy	0.725	2337.45	-0.58	0.725	2338.20	-1.33

Table 4: continued

	CPE	AIC	ΔAIC	CPE	AIC	ΔAIC
Baseline model (B)						
Clinical information (age+stage+tumor type)	0.725	2336.86	0	0.725	2336.86	0
	Continuous variables[d]			**Dichotomous variables**		
Screening and LOFS						
B + G8	0.748	2300.30	36.57	0.749	2306.66	30.20
B + fTRST	0.741	2320.02	16.84	0.727	2335.07	1.79
B + ECOG-PS	0.736	2321.82	15.05	0.734	2323.77	13.10
B + LOFS continuous	0.746	2307.61	29.26	NA	NA	NA
B + LOFS categorical	0.745	2313.73	23.13	NA	NA	NA

Abbreviations: CI = confidence interval; Hb = hemoglobin; (m)GPS = (modified) Glasgow Prognostic Score; GA = Geriatric Assessment; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MOB-T = Mobility – Tiredness Test; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; MNA-SF = Mini Nutritional Assessment – Short Form; CCI = Charlson Comorbidity Index; fTRST = Flemish version of the Triage Risk Screening Tool; ECOG-PS = Eastern Cooperative Oncology Group - Performance Status; LOFS = Leuven Oncogeriatric Frailty Score; CPE = Concordance Probability Estimate; AIC = Akaike Information Criterion

[a] CRP as a continuous variable was analysed per 10-unit increase

[b] Hb was dichotomized according to gender-specific cut-off values proposed by the WHO

[c] Hb was dichotomized according to gender-specific cut-off values proposed by Beutler E, Waalen J. Blood. 2006

[d] The (m)GPS was analysed as a categorical variable in the left and right column while the 10-item GA was analysed with continuous where possible and dichotomous variables, respectively.

[e] Unless specified otherwise (categorical)

Chapter 7.

The utilization of formal and informal home care by older patients with cancer: a Belgian cohort study with two control groups

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The online version of the published paper contains supplementary material which have not been included in this dissertation.

Abstract

Background

The purpose of this paper is to analyse the utilization of formal and informal home care among older patients with cancer (OCP) and to compare this with middle-aged patients with cancer (MCP) and older patients without cancer (ONC). Additionally, we examined predictors of transitions towards formal care one year after a cancer diagnosis.

Methods

OCP and MCP had to be recruited within three months after a cancer diagnosis and have an estimated life expectancy over six months. ONC consisted of patients without known cancer, seen by the general practitioner. Formal and informal care were compared between the patient groups at baseline, i.e. shortly after a cancer diagnosis and changes in care were studied after one year.

Results

A total of 844 patients were evaluable for formal care at baseline and 469 patients (56%) at follow-up. At baseline, about half of older adults and 18% of MCP used formal care, while about 85% of cancer patients and 57% ONC used informal care. Formal care increased for all groups after one year though not significantly in OCP. The amount of informal care only changed in MCP which decreased after one year. Cancer-related factors and changes in need factors predict a transition towards formal care after a cancer diagnosis.

Conclusions

A cancer diagnosis has a different impact on the use of formal and informal care than ageing as such. The first year after a cancer diagnosis is an important time to follow-up on the patients' needs for home care.

Introduction

The increasing population of older people and changes in health policy have resulted in a shift from institutional care to home care. It is obvious that functional status plays an important role in the use of professional home care. Therefore, in Belgium and other countries planning and financing of both home nursing and nursing homes are largely based on levels of functioning (1). Other factors known to be associated with professional home care use include age, gender, educational level, marital status, and informal care (2-5). Most of this evidence was based on cross-sectional analyses comparing older people already using professional home care with non-users. Kempen et al. specifically compared older people who started to use professional home care to matched non-users which is more appropriate to understand factors that explain the use of professional home care (2). Geerlings et al. focused on the process of becoming a user of informal and professional home care by studying transitions in the use of care based on longitudinal data in the Netherlands (6). More recent studies, based on the Survey of Health, Ageing and Retirement in Europe (SHARE) data, showed cross-national differences in the dynamics of care between various European countries (7-9). In the present study, we focused on a specific population, Flemish older patients with cancer (OCP). The rising population of older people is accompanied by an increase of cancer prevalence rates. A diagnosis of cancer and subsequent treatment can have a substantial effect on the well-being of patients and their need for home care. As shown in our recent work, patients with cancer have increased levels of depression, loneliness, and increasing difficulties in cognitive functioning over the course of one year (10,11). In light of this, we expect to see significant transitions in care after a diagnosis of cancer. The purpose of this paper is to analyse the utilization of formal and informal home care among OCP shortly after diagnosis and to examine changes after one year. The OCP will be compared to two control groups, a group of middle-aged patients with cancer (MCP) and a group of older primary care patients without cancer (ONC). A second goal is to examine predictors of transitions from no formal care to formal care following a cancer diagnosis.

Patients and methods

Study design and population

This analysis was performed on baseline and one-year follow-up data from the Klimop study, which is an ongoing study in Belgium and the Netherlands on the impact of cancer, aging, and their interaction on the well-being of OCP. For this purpose, OCP are compared with MCP (aging effect) and with ONC (diagnosis effect). The same design was used for the current analysis on home care, however based on our results it sometimes made more sense to compare all patients with cancer to ONC in the discussion section. Full details of the Klimop study have been described elsewhere (12). In short, OCP (≥ 70 years), MCP (50-69 years), and ONC (≥ 70 years) are longitudinally compared for different measures of well-being. The group of cancer patients consisted of patients with breast, gastro-intestinal, and lung cancer. Patients had to be recruited within three months after a cancer diagnosis and had to have an estimated life expectancy of more than six months. Data have been collected through personal interviews at

baseline (T0), after one year (T1), and subsequently every two years. The analysis for this paper was restricted to patients living at home and who were recruited in Belgium only, given the different homecare system in the Netherlands.

Measurements

Formal care

Professional home care or formal care was dichotomized in 'users' and 'non-users'. Users were defined in this study as having received help from at least one of the following paid professionals in the last three months: home nurse, home help services, physiotherapist, meals on wheels, adult day care, and cleaning help. Formal care was only recorded if the participants had at least five contacts in the last three months prior to the interview in order to avoid the measurement of sporadic use and to be able to evaluate recent use.

Informal care

Participants were asked to indicate who cared for them, apart from professional help. This could be a partner, children, other relatives, friends, neighbours, or volunteers. Informal care was defined as help provided by any of them (partners, children, other relatives, friends, neighbours, or volunteers).

Independent variables

Consistent with previous research on home care, we used Andersen and Newman's behavioural model as a theoretical framework to order variables at the individual level in predisposing, enabling and need factors to predict the utilization of formal care (13). Predisposing variables were age, gender, marital status, and educational level. We considered the availability of informal care as an enabling variable. As need factors we considered functional status, depression, loneliness, fatigue, cognitive status, nutrition, polypharmacy and comorbidity. Since the focus of this study is on cancer, we also evaluated the cancer-related factors tumour type, stage, and treatment.

Functional status was measured with the Katz index of Activities of Daily Living (ADL) (range: 0-6) and the Lawton Instrumental ADL (IADL) scale (range: 0-8 for woman, range: 0-5 for men) (13-14). Dependence in one or more domains for each test was defined as having an impaired test result. Depression was measured using the Geriatric Depression Scale (range: 0-15, cut-off $\geq$5), loneliness with the loneliness scale of De Jong-Gierveld (range: 0-11, cut-off $\geq$3), fatigue with a Visual Analogue Scale (range: 0-10, cut-off $\geq$4), cognitive status with the Mini Mental State Examination (range: 0-30, cut-off <24), and comorbidity with the Charlson Comorbidity Index (CCI) (range: 0-37, cut-off $\geq$1) (16-19). Nutrition was measured with a new and adapted version of the Mini Nutritional Assessment-short form (range: 0-14, cut-off $\leq$11), which is currently being validated by our group (20).

Data analysis

Firstly, formal and informal care were studied separately. Individual home care services, as specified in our definition of formal care, were studied as well. Finally, we considered formal care and informal care simultaneously. This entails four possible situations at baseline: no care, informal care only, formal care only, and the availability of both formal and informal care. Hence, 16 alternative transitions are possible after one year. Next to transitions to formal care or informal care, we also evaluated whether both types of care substitute ('substitution') or complement ('complementarity') each other to better understand the relationship between formal and informal care. Substitution was defined as the sum of transitions from formal to informal care and vice versa. Complementarity was defined as the sum of transitions from no care or (in)formal care only towards combined formal and informal care.

We performed comparative analyses between OCP and two control groups ONC and MCP at baseline by means of the chi-square test. Changes in care over time were studied by comparing formal and informal care between baseline and one-year follow-up within each patient group with the McNemar test and by calculating the percentages of every transition in and between formal and informal care. We set alpha at 0.05 for all analyses to denote statistical significance.

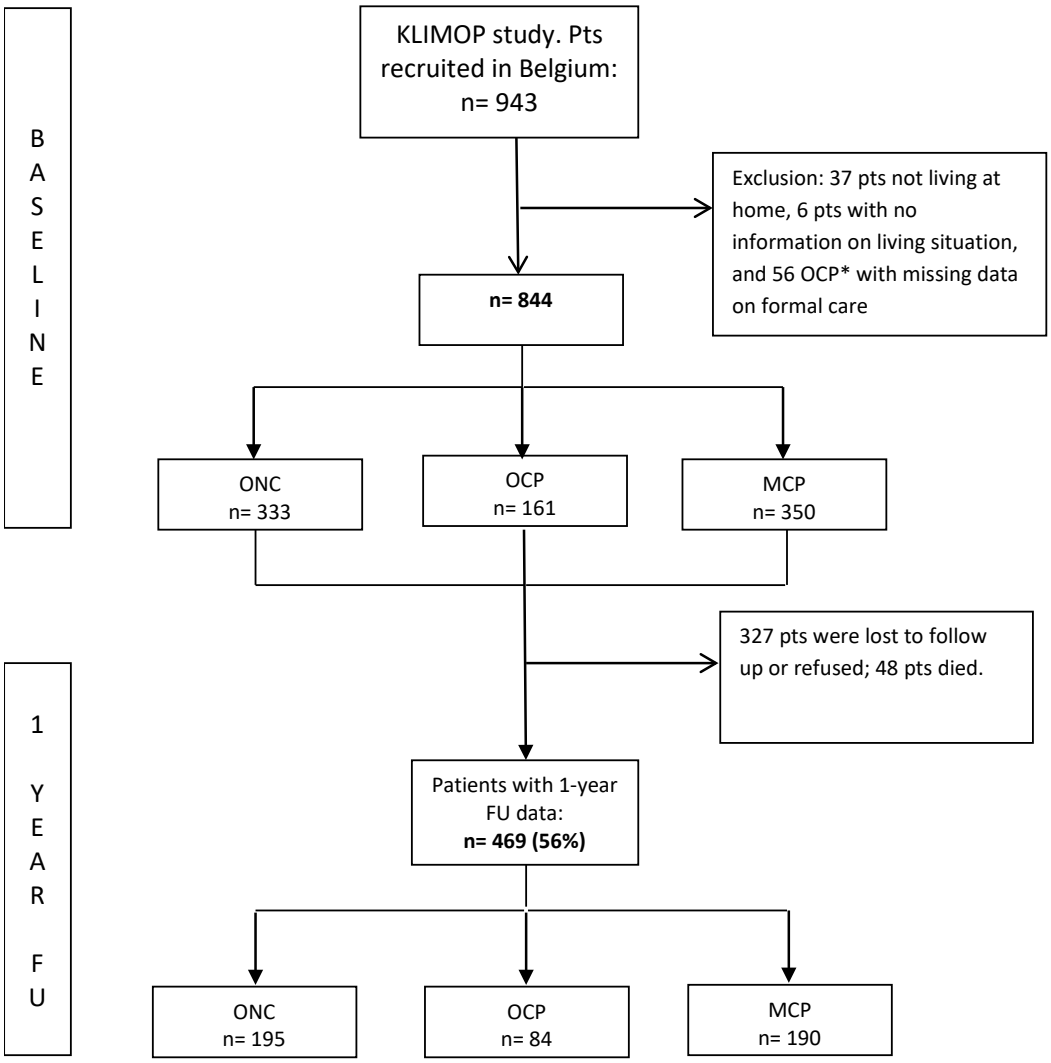
For the second goal of our analysis, logistic regression analyses were conducted to explain the transition of no formal care to formal care in patients with cancer, both OCP and MCP. Separate analyses for OCP and MCP were not conducted due to a small sample size for OCP. Univariate analyses were performed with all predisposing, enabling, and need factors as continuous predictors with the exception of IADL which was analyzed as a dichotomous variable due to the different score range for women and men. In addition, we considered changes of need factors over time by dichotomizing them and identifying changes in categories between baseline and one-year follow-up. All analyses were performed using SPSS 23 software (Chicago, IL).

Results

Study population

A total of 844 patients, recruited between April 2010 and November 2013, were available for analysis at baseline. At follow-up, data for formal care were also available for a total of 469 patients (56%) (see Figure 1). Missing follow-up data were due to death (2.7% ONC, 10.6% OCP, and 6.3% MCP) or to loss of follow-up/refusal (38.7%, 37.3%, and 39.4%). Patient characteristics of OCP and the two control groups are shown in Table 1. Differences in need factors for formal care are found in Table 2. The majority of the patients were female (ONC: 61.3%, OCP: 69.6%, MCP: 75.1%). Compared to ONC, OCP had a worse nutritional status, were less lonely, and had less comorbidity and polypharmacy.

Figure 1. The utilization of formal care: Patient flow chart



* In one hospital, data collection at T0 was integrated in a routine geriatric assessment; therefore data on home care were not available for 56 OCP.

Table 1. Patient characteristics of the three patient groups at baseline

	ONC			OCP			MCP	
	n	%	p-value	n	%	p-value	n	%
Total N° pts	333	100,0		161	100,0		350	100,0
Age								
Mean (SD)	78.7 (5.7)			76.9 (5.0)			59.8 (5.4)	
Gender			0,07			0,19		
Female	204	61,3		112	69,6		263	75,1
Male	129	38,7		49	30,4		87	24,9
Living situation			0,75			**< 0.001**		
Alone	109	32,7		55	34,2		48	13,7
Not alone	224	67,3		106	65,8		302	86,3
Marital status			0,68			**< 0.001**		
Married/living together	209	62,8		98	60,9		285	81,4
Unmarried/widow/divorced	124	37,2		63	39,1		65	18,6
Educational level	n=328		0,66	n=157		**< 0.001**	n=344	
≤ 14 years	94	28,7		50	31,8		37	10,8
15-19 years	150	45,7		72	45,9		161	46,8
≥ 19 years	84	25,6		35	22,3		146	42,4
Tumour type						0,07		
Breast				86	53,4		217	62,0
Gastrointestinal				69	42,9		114	32,6
Lung				6	3,7		19	5,4
Stage				n=137		**0,004**	n=327	
I				18	13,1		87	26,6
II				69	50,4		121	37,0
III				35	25,5		93	28,4
IV				15	10,9		26	8,0
Treatment *								
Surgery**				132	89,8	0,77	304	88,9
Chemotherapy**				63	43,4	**<0,001**	210	61,6
Radiotherapy**				71	49,3	**<0,001**	232	68,0
Hormonal**				59	40,7	**0,03**	175	51,6

OCP were compared to the two control groups with the chi-square test. P < 0,05 denotes statistical significance.

* More than one possibility.

** Percentages were calculated on valid cases

Table 2. Need factors for formal care of the three patient groups at baseline

	ONC			OCP			MCP	
	n	%	p-value	n	%	p-value	n	%
Total N° pts	333	100,0		161	100,0		350	100,0
ADL			0,80			**<0,001**		
Independent	184	55,3		87	54,0		273	78,0
Dependent	149	44,7		74	46,0		77	22,0
IADL	n=329		0,55	n=160		**<0,001**	n=344	
Independent	184	55,9		94	58,8		269	78,2
Dependent	145	44,1		66	41,3		75	21,8
Depression	n=322		0,53	n=148		0,34	n=322	
Normal	276	85,7		130	87,8		292	90,7
Impaired	46	14,3		18	12,2		30	9,3
Cognition			0,72			**0,01**		
Normal	292	87,7		143	88,8		333	95,1
Impaired	41	12,3		18	11,2		17	4,9
Nutrition	n=280		**<0,001**	n=135		0,45	n=320	
Normal	229	81,8		48	35,6		102	31,9
At risk/malnourished	51	18,2		87	64,4		218	68,1
Loneliness	n=318		**0,004**	n=138		**0,03**	n=322	
Not lonely	178	56,0		97	70,3		257	79,8
Lonely	140	44,0		41	29,7		65	20,2
Fatigue	n=331		0,19	n=149		0,18	n=336	
No fatigue	150	45,3		58	38,9		153	45,5
Fatigue	181	54,7		91	61,1		183	54,5
Polypharmacy			**<0,001**			**<0,001**		
< 5 drugs	150	45,0		109	67,7		305	87,1
≥ 5 drugs	183	55,0		52	32,3		45	12,9
Comorbidity	n=326		**<0,001**	n=148		**<0.001**	n=339	
CCI 0	145	44,5		92	62,2		269	79,4
CCI ≥ 1	181	55,5		56	37,8		70	20,6

OCP were compared to the two control groups with the chi-square test. P < 0,05 denotes statistical significance.

The comparison of formal and informal care at baseline

Results of the baseline comparisons between OCP and the two control groups are summarized in Table 3. About half of the OCP were users of formal care (51.6%). There was no difference with the group ONC (50.2%), but significantly less MCP (18.0%) were users.

Table 3. The comparison of formal and informal care at baseline between OCP and two control groups

	ONC			OCP			MCP	
	n	%	p-value	n	%	p-value	n	%
Formal care	n=333		0,77	n=161		**< 0.001**	n=350	
Users	167	50,2		83	51,6		63	18,0
Non-users	166	49,8		78	48,4		287	82,0
Individual home care service								
Home nursing	66	19,8	0,86	33	20,5	**< 0.001**	14	4,0
Home help services	24	7,2	0,50	9	5,6	**0,01**	5	1,4
Cleaning help	140	42,0	0,41	74	46,0	**< 0.001**	49	14,0
Physiotherapist	37	11,1	**0,003**	5	3,1	0,62	14	4,0
Meals on wheels	26	7,8	0,24	8	5,0	**< 0.001**	0	0,0
Informal care	n=331		**< 0.001**	n=157		0,86	n=335	
Present	188	56,8		135	86,0		286	85,4
Not present	143	43,2		22	14,0		49	14,6
Formal care + informal care	n=331			n=157			n=335	
No care	84	25,4	**< 0,001**	11	7,0	0,13	38	11,3
Informal care only	80	24,2	**< 0,001**	66	42,0	**< 0,001**	237	70,7
Formal care only	59	17,8	**0,001**	11	7,0	0,06	11	3,3
Informal care + formal care	108	32,6	**0,02**	69	43,9	**<0,001**	49	14,6

OCP were compared to the two control groups with the chi-square test. P < 0,05 denotes statistical significance.

The analysis of the individual home care services only show a significant difference (p=0.003) for seeking help from a physiotherapist between OCP (3.1%) and ONC (11.1%). Compared to MCP, we observed no difference for help from the physiotherapist but OCP made significantly more use for all other home care services. None of the patients made use of adult day care. An overview of the number of home care services per patient at T0 is shown in Additional file 1 (available in the online publication). While most MCP received 1 or 2 individual home care services, more than 10% of the OCP and ONC relied on 3 or more services.

Furthermore, our results showed that OCP (86.0%) could rely as much on informal care as MCP (85.4%) and more so than ONC (56.8%).

When considering both formal and informal care, the distribution of types of care differed in every aspect between OCP and ONC. ONC had a higher proportion (25.4%) of patients with no care compared to the two cancer cohorts (OCP: 7.0%, MCP: 11.3%). MCP had more informal care only (70.7%) than OCP (42.0%) while OCP relied more on both types of care (43.9%) than MCP (14.6%).

Tabel 4. The comparison of formal and informal care between T0 and T1 in each patient group

	ONC					OCP					MCP				
	T0		T1			T0		T1			T0		T1		
	n	%	n	%	p-value	n	%	n	%	p-value	n	%	n	%	p-value
Formal care	n=333		n=195		**0,03**	n=161		n=84		0,06	n=350		n=190		**< 0,001**
Users	167	50,2	110	56,4		83	51,6	55	65,5		63	18,0	77	40,5	
Non-users	166	49,8	85	43,6		78	48,4	29	34,5		287	82,0	113	59,5	
Individual home care service															
Home nursing	66	19,8	42	21,5	0,08	33	20,5	20	23,8	1,00	14	4,0	21	11,1	**0,01**
Home help services	24	7,2	9	4,6	0,21	9	5,6	6	7,1	0,73	5	1,4	3	1,6	1,00
Cleaning help	140	42,0	92	47,2	0,29	74	46,0	43	51,2	1,00	49	14,0	44	23,2	**0,02**
Physiotherapy	37	11,1	23	11,8	0,66	5	3,1	16	19,0	**0,01**	14	4,0	34	17,9	**< 0,001**
Meals on wheels	26	7,8	11	5,6	0,11	8	5,0	3	3,6	1,00	0	0,0	1	0,5	1,00
Informal care	n=331		n=191		1,00	n=157		n=80		0,65	n=335		n=185		**0,03**
Present	188	56,8	103	53,9		135	86,0	63	78,8		286	85,4	140	75,7	
Not present	143	43,2	88	46,1		22	14,0	17	21,3		49	14,6	45	24,3	
Formal care + informal care	n=331		n=191			n=157		n=80			n=335		n=185		
No care	84	25,4	40	20,9	0,10	11	7,0	7	8,8	1,00	38	11,3	30	16,2	0,24
Informal care only	80	24,2	43	22,5	1,00	66	42,0	19	23,8	**0,01**	237	70,7	79	42,7	**< 0,001**
Formal care only	59	17,8	48	25,1	0,07	11	7,0	10	12,5	0,79	11	3,3	15	8,1	0,08
Informal care + formal care	108	32,6	60	31,4	1,00	69	43,9	44	55,0	0,06	49	14,6	61	33,0	**< 0,001**

Proportions between T0 and T1 were compared with the McNemar test. P < 0,05 denotes statistical significance.

The comparison of formal and informal care between T0 and T1

Table 4 presents the differences in care between T0 and T1 in the three patient groups. In the group ONC, there was overall an increase of formal care at T1. No other differences were observed.

In the group OCP, there was overall an increase of formal care at T1. However, this difference was not statistically significant (p=0.06). At the level of individual home care services, significantly more patients saw a physiotherapist after one year (from 3.1% to 19.0%, p=0.01). There was no significant difference in informal care between T0 and T1 (p=0.65). However, when considering both formal and informal care, fewer patients received only informal care (p=0.01) at T1.

In the group MCP, there was overall an increase of formal care at T1. Increased help from a home nurse (from 4.0% to 11.1%), cleaning help (from 14.0% to 23.2%), and a physiotherapist (from 4.0% to 17.9%) was reported. From the patients who received physiotherapy, 71.4% and 94.1% had breast cancer at respectively T0 and T1. Informal care decreased at T1 (from 85.4% to 75.7%). When considering both formal and informal care, fewer patients received only informal care and more patients received both formal and informal care.

Table 5. Transitions in formal and informal home care analyzed separately

	ONC			**OCP**			**MCP**	
	n	%	p-value	n	%	p-value	n	%
	Formal care							
Transition	n=195			n=84			n=190	
No formal care at T0 and T1	80	41,0	**0,05**	24	28,6	**< 0,001**	101	53,2
Formal care at T0 and T1	94	48,2	0,93	41	48,8	**< 0,001**	26	13,7
No formal care --> Formal care	16	8,2	**0,04**	14	16,7	0,07	51	26,8
Formal care --> No formal care	5	2,6	0,16	5	6,0	0,91	12	6,3
	Informal care							
Transition	n=190			n=79			n=178	
No informal care at T0 and T1	62	32,6	**< 0,001**	6	7,6	0,55	10	5,6
Informal care at T0 and T1	79	41,6	**< 0,001**	54	68,4	0,88	120	67,4
No informal care --> Informal care	24	12,6	0,56	8	10,1	0,77	16	9,0
Informal care --> No informal care	25	13,2	0,87	11	13,9	0,42	32	18,0

OCP were compared to the two control groups with the chi-square test. P < 0,05 denotes statistical significance.

Transitions in formal and informal care after one year

Transitions in formal and informal care were analyzed separately in Table 5. There was a significant difference in the transition from no formal care to formal care between OCP and the two control groups. For the group OCP, 16.7% made this transition compared to 8.2% ONC (p=0.04) and 26.8% MCP (p=0.07). For the transition from formal care to no formal care, a similar proportion OCP (6.0%) stopped

formal care compared to MCP (6.3%) after one year. Only a small proportion of ONC (2.6%, p=0.16) stopped relying upon formal care.

Transitions in informal care were similar between OCP and the two control groups. In the groups ONC, OCP, and MCP respectively 12.6%, 10.1%, and 9.0% made a transition to informal care at T1 while respectively 13.2%, 13.9%, and 18.0 stopped relying on informal care.

Transitions considering the availability of formal care and informal care simultaneously are summarized in Additional file 2 (available in the online publication). Transitions in care, from any type, were observed in ONC, OCP, and MCP in respectively 33.2%, 39.2%, and 49.4% of the patients. The analysis of substitution and complementarity of care shows that in 5.1% of OCP formal and informal care substitute each other, while in 17.7% both types of care complement each other at T1. Results for the control groups are shown in Table 6.

Table 6. Substitution and complementarity of formal and informal care

	ONC			OCP			MCP	
	n	%	p-value	n	%	p-value	n	%
Transition	n=190			n=79			n=178	
Substitution	0	,0	0,07	4	5,1	1,0	11	6,2
Complementarity	19	10,0	0,08	14	17,7	0,44	39	21,9

OCP were compared to the two control groups with the chi-square test or fisher's exact test where appropriate.
p < 0,05 denotes statistical significance.

Predictors of the transition no formal care to formal care after a cancer diagnosis

The studied sample for this analysis consisted of a total of 190 patients with cancer (20.0% OCP), of which 65 made the transition from no formal care to formal care. Significant predictors in univariate analysis are shown in Table 7. Next to a higher value for the need factors fatigue and polypharmacy, certain changes (or the lack of) in ADL, IADL, depression, fatigue, and polypharmacy were predictive for a transition towards formal home care. Furthermore, a worse cancer stage and having received chemotherapy or radiotherapy were predictive as well. Factors that were not predictive included predisposing variables, ADL, IADL, informal care, and belonging to the group OCP or MCP.

Table 7. Predictors of the transition no formal to formal care 1 year after a cancer diagnosis (OCP and MCP combined, n=190)

	Univariate*		
	OR	95%CI	p-value
Need factors			
Fatigue	1,24	1,09-1,41	0,001
Polypharmacy	1,18	1,01-1,38	0,04
Cancer-related factors			
Stage			0,09
I	ref		
II	2,01	0,85-4,78	0,11
III	2,67	1,02-6,96	0,05
IV	5,93	1,18-29,68	0,03
Chemotherapy	2,21	1,17-4,19	0,02
Radiotherapy	2,38	1,19-4,77	0,02
Changes in need factors			
ADL			0,01
persistently independent	ref		
became indepedent	0,93	0,27-3,13	0,90
became dependent	3,19	1,55-6,54	0,002
persistently dependent	0,85	0,28-2,54	0,77
IADL			0,04
persistently independent	ref		
became indepedent	1,81	0,60-5,50	0,29
became dependent	2,86	1,36-6,04	0,01
persistently dependent	2,04	0,66-6,33	0,22
Depression			0,06
persistently normal	ref		
became normal	2,53	0,77-8,32	0,13
became depressed	3,03	1,21-7,60	0,02
persistently depressed	2,53	0,34-18,59	0,36
Fatigue			0,003
persistently normal	ref		
became normal	6,00	1,55-23,19	0,01
became impaired	4,00	1,19-13,42	0,03
persistently impaired	8,27	2,61-26,22	<0,001
Polypharmacy			0,04
persistently normal	ref		
became normal	2,51	0,60-10,52	0,21
became impaired	2,72	1,15-6,46	0,02
persistently impaired	2,93	0,93-9,25	0,07

* Predictors of univariate logistic regression analyses are shown with $p < 0,05$

Discussion

Transitions in home care depend on the situation. A diagnosis of cancer might be considered a situation of greater need for care and as such we observed transitions in formal and informal care in ONC, OCP, and MCP in respectively 33.2%, 39.2%, and 49.4% after one year. Our results also showed an expected increase in new users of formal care in cancer patients: 16.7% for OCP, 26.8% for MCP compared to 8.2% for ONC. However, at baseline, i.e. shortly after diagnosis, some important differences were already observed between the patient groups in terms of care but also in patient characteristics. While many differences between OCP and MCP can be explained due to age-related factors, some differences between OCP and ONC were less obvious. OCP had a lower comorbidity burden and polypharmacy. This can partially be explained by a referral bias for OCP; the frailest patients are not always referred to the oncologist. OCP reported to be less lonely despite no difference in marital status or living situation. Previously, we already showed that at baseline fewer patients with cancer had feelings of loneliness than ONC and that after one year the proportion of cancer patients with loneliness increased significantly reaching the levels of ONC (11). Our current analysis might explain these differences in loneliness by looking at the received informal care. More patients with cancer relied on informal care compared to ONC at baseline. This care was likely provided only recently around the time the patient was informed about a cancer diagnosis which could explain the difference in baseline loneliness between patients with cancer and ONC. Furthermore, informal care decreased after one year in both cancer cohorts, although not significantly in OCP, which could contribute to the increase in loneliness in both cancer cohorts. It is to be expected that newly diagnosed patients receive much help and support from their environment at first but less so after completing their treatment and this might have an impact on feelings of loneliness, an important measure of well-being.

The analysis of the individual home care services showed that cleaning help was clearly the most used service in the three patient groups. In this regard, we note that we did not document whether the use of this service was related to any health-related issues. Furthermore, at baseline fewer cancer patients visited the physiotherapist compared to ONC. However, after one year a strong increase in physiotherapy was observed in both cancer cohorts, mainly in patients with breast cancer. This might be related to lymphoedema following breast cancer surgery or radiotherapy. While, besides physiotherapy, no other changes were observed after one year in OCP, MCP made more use of home nursing and cleaning help next to an increase in physiotherapy. A possible explanation for this is that due to lymphoedema, MCP are less able to do household tasks like cleaning or are advised to limit the strenuous use of their arm. Also, an important proportion of patients with cancer will have had an intestinal stoma. These patients, OCP likely more than MCP, might rely upon home nursing for stoma care. These increases of home nursing and cleaning help after one year in MCP are however not observed in OCP. However, the baseline percentages for both home care services are already high in OCP and new tasks might have been covered by the already available care in this group.

About half of the OCP and ONC received formal care at baseline. This formal care was more often in combination with informal care in OCP than in ONC. When considering both formal care and informal care after one year, the main trend observed in both cancer cohorts, in contrast to ONC, is the decrease in the number of patients who rely on informal care only and the increase in patients with formal care whether or not with informal care. This distinction between ONC and cancer patients can be explained by the dynamics in informal care in cancer patients as discussed previously and by the expected increased need for formal care in cancer patients which was quantified in this study. Another important observation is the lack of any change in the proportion of patients with no care whatsoever in the three patient groups.

Several studies in the general population suggest that formal and informal care complement rather than substitute each other (6-8). This is also shown in our three patient groups. Our rates for substitution and complementarity for ONC are similar with other reports for the general population in Belgium (8). These rates are however higher in our studied cancer cohorts, particularly for complementarity. In the context of cancer, more technical skills (e.g. injections, stoma care, and physiotherapy) for care might be required and this care will complement rather than substitute informal care. Several care models have been proposed for the general population (21). For patients diagnosed with cancer, formal and informal care might be better explained with a complementarity and task-specific model.

Our results show different dynamics in care between older patients with and without cancer but also between OCP and MCP. International guidelines recommend the implementation of a geriatric assessment in OCP to guide treatment decisions in routine oncology practice (22). This assessment will lead to the necessary referrals for many patients with cancer (23). In contrast to the general population, many OCP will be seen by a social worker in the hospital which will also drive changes in formal care. In this regard, we mention the Belgian implementation of the InterRAI instruments (BelRAI) which is an ambitious web-based comprehensive assessment system to improve the quality and continuity of care across different health care settings, including home care (24-26). It is advisable to harmonize recommendations in geriatric oncology to implement geriatric assessment in daily practice with efforts like the BelRAI for the general population at a national level for future policies.

For the second goal of our study, we analyzed predictors for the transition from no formal care to formal care one year after a cancer diagnosis. Functional status, the availability of informal care, and dispositional factors did not predict the transition towards formal care in patients with cancer. Cancer-related factors, i.e. more advanced disease or a more extensive treatment, and the related worsening of need factors (more than their baseline values) were significant predictors. In contrast, an analogous analysis on ONC showed that only developing a nutritional impairment predicted a transition towards formal care (data not reported). Our results show that the first year after a cancer diagnosis is an important time to follow-up on the patients' needs for home care at different time points during the

disease trajectory. More longitudinal research is needed to determine to what degree a cancer diagnosis is a turning point towards more formal care or whether the increased use of formal care is more of a temporary nature. Another evolution to follow in the future relevant to homecare, is the parenteral administration of cancer treatments at home. The first pilot projects in this regard have been started in Belgium.

When interpreting our results, some considerations should be made. The study of both formal and informal care is a strength of this study, however the collection of more detailed information on informal care would have been beneficial for our analysis. Many patients were lost to follow-up (LTFU), i.e. a total of 38.7% when not considering the patients that died (5.7%). Additional analyses (Additional file 3 available in the online publication) show no major baseline differences between LTFU patients who were alive and patients with one-year follow-up data. LTFU patients had less cleaning help and more informal care only, no other differences were observed for home care. Furthermore, there was a similar proportion of LTFU patients (excluding deaths) in the three patient groups. Another point to consider is that our results apply for Belgium, a well-developed welfare state with well-developed formal services. A lot has been written in the home care literature, which focuses on the general population, about the different dynamics of formal and informal care between European countries, about the influence of the strength of family ties, and a north-south gradient (8). To our knowledge, there are no similar studies to which we can compare our results with that evaluate changes in both formal and informal care after a cancer diagnosis.

Conclusions

A cancer diagnosis has a different impact on the use of formal and informal care than ageing as such. The first year after a cancer diagnosis is an important time to follow-up on the patients' needs for home care.

Author contributions

This study was designed by AB, FB, MvdA, whereas the umbrella study KLIMOP was designed and set up by FB, MvdA, LD, PB and HW. Data collection was performed by all authors. AB, FB, TdB, MvdA drafted the manuscript, which was commented by all authors. Statistical analysis was performed by AB and discussed with FB, MvdA, and TdB. All authors read and approved the final manuscript.

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Chapter 8.

The influence of coping strategies on subsequent well-being in older patients with cancer: a comparison with two control groups.

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Abstract

Objective

To evaluate dispositional coping strategies as predictors for changes in well-being after one year in older patients with cancer (OCP) and two control groups.

Methods

OCP were compared with two control groups: middle-aged patients with cancer (MCP) (aging effect) and older patients without cancer (ONC) (cancer effect). Patients were interviewed shortly after a cancer diagnosis and one year later. Dispositional coping was measured with the Short Utrecht Coping List. For well-being, we considered psychological well-being (depression, loneliness, distress) and physical health (fatigue, ADL, IADL). Logistic regression analyses were performed to study baseline coping as predictor for subsequent well-being while controlling for important baseline covariates.

Results

A total of 1245 patients were included in the analysis at baseline: 263 OCP, 590 ONC, and 392 MCP. Overall, active tackling was employed most often. With the exception of palliative reacting, OCP utilized each coping strategy less frequently than MCP. At one-year follow-up, 833 patients (66.9%) were interviewed. Active coping strategies (active tackling and seeking social support) predicted subsequent well-being only in MCP. Avoidance coping strategies did not predict well-being in any of the patient groups. Palliative reacting predicted distress in OCP; depression and dependency for ADL in MCP.

Conclusions

Coping strategies influence subsequent well-being in patients with cancer, but the impact is different in the age groups. Palliative reacting was the only coping strategy that predicted well-being (i.e. distress) in OCP and is therefore, especially in this population, a target for coping skills interventions.

Background

Knowledge of effective and maladaptive coping strategies in relation to a cancer diagnosis is important in the development of interventions. Many studies have focused on the association between coping and well-being in patients dealing with cancer. The large majority of these studies have a cross-sectional design using different measures of coping. Although findings are not entirely consistent, active coping (e.g. active tackling, seeking social support) in contrast to passive coping (e.g. avoidance, palliative reacting) is thought to have a beneficial effect on both psychological and physical outcomes (1-2). However, reciprocal relationships between coping and well-being should be considered (3-4). A small number of longitudinal studies have evaluated coping following a cancer diagnosis as a predictor for subsequent well-being (2,5-10). The findings of these studies are difficult to summarize as they vary for example in study aim and design, in the classification of coping, in health-related outcomes, and in follow-up time. Nonetheless, they demonstrated an influence of coping on subsequent well-being. One study in patients with breast cancer even showed that avoidance coping used within six months after diagnosis predicted psychological well-being three years later (6).

The current paper on coping and subsequent well-being is part of the larger 'Klimop' study. The primary aims of this study are to assess the impact of cancer and ageing on subsequent well-being and to identify factors that predict well-being in older patients with cancer. (11). For this purpose, older patients with cancer (OCP) are compared with two control groups: middle-aged patients with cancer (MCP) and older primary care patients without cancer (ONC). From two previous analyses based on the Klimop study, we know that OCP cope differently than MCP shortly after a cancer diagnosis (baseline) and that increasing levels of psychosocial problems are observed one year later in both patient groups (12-13). These findings might suggest that if coping predicts subsequent well-being that this relationship will be different in OCP and MCP. Furthermore, the relationship between dispositional coping and subsequent well-being might be different between OCP and ONC considering changes in well-being related to the cancer.

A better understanding of coping strategies and a potential influence on subsequent health is important because interventions targeting coping skills might improve outcomes. The aim of the present paper is to investigate if baseline coping strategies predict changes in different dimensions of psychological well-being and physical health after one year in OCP while disentangling ageing effects (OCP versus MCP) and cancer effects (OCP versus ONC). In addition, we compared the frequencies of baseline coping strategies in each patient group and compared coping and well-being between OCP and the two control groups at baseline.

Patients and methods

Study design and population

This analysis was performed on baseline and 1-year follow-up data from the Klimop study, which is an ongoing study in Belgium and the Netherlands on the impact of cancer, ageing, and their interaction on well-being. Full methodological details have been described elsewhere (11). In short, OCP (≥ 70 years) are longitudinally compared with MCP (50-69 years) and ONC (≥ 70 years) for different measures of well-being. ONC consisted of patients without known cancer, seen by their general practitioner. The group of patients with cancer consisted of patients with breast, gastro-intestinal, prostate and lung cancer. Patients had to be recruited within three months after cancer diagnosis. All participants had to have an estimated life expectancy of more than six months and no formal diagnosis of dementia. Data have been collected through personal interviews at baseline, after one year, and subsequently every two years.

Coping

Coping was assessed with the short version of the Utrecht Coping List (UCL) (14-15). The UCL evaluates dispositional coping by asking participants about the frequency of coping strategies they use in response to problems or unpleasant situations in general. In this approach, coping strategies are viewed as relatively stable over the course of time and across different situations which allows greater comparison of coping strategies across different samples.

The short UCL consists of 15 items and covers four subscales (Appendix 1). Each question was answered on a four-point Likert scale. For each subscale, sum scores were divided by the number of questions. Total scores for each subscale range from 1 to 4. A higher score indicates that a certain coping strategy is used more often.

Active coping

Active tackling (five questions): this refers to behaviour directed at confronting or solving the problem or situation.

Seeking social support (five questions): this refers to efforts to actively pursue informational, physical, and/or emotional support.

Passive coping

Avoidance and awaiting (three questions): this refers to behaviour to avoid dealing with a situation like seeking distraction.

Palliative reacting (two questions): this refers to behaviour that involves giving up any effort to deal with the situation.

Well-being

For well-being we studied psychological well-being and physical health with tools that are widely used in the literature. A more in-depth description of the tools can also be found in previous publications from the Klimop study (12-13,16).

For psychological well-being, we considered depression, loneliness, and distress measured with the Geriatric Depression Scale (range:0-15, cut-off ≥5) (17), the loneliness scale of De Jong-Gierveld (range: 0-11, cut-off ≥3) (18), and the distress barometer (range:0-10, cut-off ≥4) (19) respectively.

For physical health, we considered fatigue measured with the Visual Analogue Scale (range: 0-10, cut-off ≥4) (20-22); Activities of Daily Living (ADL) measured with the Katz index (range: 0-6) (23); and Instrumental ADL (IADL) measured with the Lawton IADL scale (range: 0-8 for woman, range:0-5 for men) (24). Dependence in one or more domains of ADL and IADL was defined as having an impairment.

Statistical analysis

We compared OCP with the two control groups for patient characteristics, comorbidity, cancer-related factors, and well-being with the chi-square test; and coping strategies with the Mann-Whitney U test. We used the Wilcoxon signed rank test to evaluate within-group differences in coping strategies. To study the predictive value of baseline coping strategies for changes in well-being, we used logistic regression and not linear regression considering advantages towards interpretability of results and relevance for clinicians. We first performed univariate logistic regression analyses with patient characteristics (age, gender, living situation, marital status, educational level), comorbidity (Charlson comorbidity index), and cancer-related factors (tumour type, stage, treatment) as predictors for every dimension of psychological well-being and physical health at 1-year follow-up. With the exception of age, all predictors were analysed as categorized variables. Secondly, multiple logistic regression analyses were performed with baseline coping as predictor for well-being at 1-year follow-up adjusted for the studied baseline values of well-being as well as for covariates that were found significant in univariate analysis. Sample sizes varied somewhat for each measure of well-being due to missing data. To test the robustness of the analysis for presence of missing data, worst-case best-case sensitivity analyses

were performed. The significance threshold was set at 0.05 for every analysis. All analyses were performed using SPSS 23 software (Chicago, IL).

Ethics

The study protocol was approved by the Ethical Review Board of KU Leuven and UZ Leuven (S52097-ML6279) (Belgium) and the Maastricht University Medical Centre (Nl31414.068.10) (the Netherlands). All patients signed informed consent.

Results

Participants

A total of 1490 patients were included at baseline. For 245 patients (16.4%), there was no or incomplete information on coping, resulting in 1245 patients (83.6%) eligible for analyses: 263 OCP, 590 MCP, and 392 ONC. From these patients 833 (66.9%) could be interviewed at 1-year follow-up. Missing follow-up data were due to death (n= 59, 14.3%) or to loss of follow-up/refusal (n= 353, 85.7%). Patient characteristics of OCP and the two control groups at baseline are shown in Table 1. The most frequent types of cancer were breast and gastrointestinal cancer. Advanced cancer (stage III-IV) was present in 41.2% of OCP and in 34.6% of MCP. Comparative analyses showed that OCP had a lower comorbidity index than ONC and several differences were observed between OCP and MCP. For example, less OCP were female and they received less intensive cancer treatment than MCP (Table 1).

Well-being and coping at baseline

Considering baseline psychological well-being, OCP were more often depressed and distressed but less often lonely than ONC. Compared to MCP, they had more often feelings of loneliness. OCP were more often dependent for ADL and IADL than MCP. There was no difference in physical health compared to ONC (Table 2).

Within-group analyses showed that in each patient group, patients utilized active tackling more frequently than the other three coping strategies ($p < 0.05$). The comparison between OCP and the two control groups for coping strategies are shown in Table 2. The frequency of every coping strategy was different between OCP and MCP. OCP used less active tackling, seeking social support, and avoidance coping than MCP, while palliative reacting was more frequent in OCP. No differences were observed between OCP and ONC

Table 1. Patient characteristics of the three patient groups at baseline

	ONC			OCP			MCP	
	n	%	p-value[a]	n	%	p-value[b]	n	%
Total N° pts	392	100,0		263	100,0		590	100,0
Age								
Mean (SD)	78,2 (5,31)			76,2 (4,54)			60,48 (5,46)	
Gender			0,30			0,001		
Female	235	59,9		147	55,9		402	68,1
Male	157	40,1		116	44,1		188	31,9
Living situation	n=388		0,92			< 0,001	n=587	
Alone	112	28,9		75	28,5		92	15,7
Not alone	276	71,1		188	71,5		495	84,3
Marital status	n=388		0,88			< 0,001	n=587	
Married/living together	253	65,2		170	64,6		466	79,4
Unmarried/widow/divorced	135	34,8		93	35,4		121	20,6
Educational level	n=383		0,17	n=254		< 0,001	n=575	
≤ 14 years	113	29,5		60	23,6		63	11,0
15-19 years	175	45,7		134	52,8		279	48,5
≥ 19 years	95	24,8		60	23,6		233	40,5
Comorbidity	n=334		0,01	n=241		< 0,001	n=566	
CCI 0-1	229	68,6		189	78,4		504	89,0
CCI ≥2	105	31,4		52	21,6		62	11,0
Tumour type				n=229		0,15	n=541	
Breast				112	48,9		312	57,7
Gastrointestinal				70	30,6		137	25,3
Lung				28	12,2		50	9,2
Prostate				19	8,3		42	7,8
Stage				n=233		0,08	n=552	
I-II				137	58,8		361	65,4
III-IV				96	41,2		191	34,6
Treatment *								
Surgery**				184	75,1	0,001	485	84,5
chemotherapy**				94	38,7	< 0,001	314	54,7
radiotherapy**				115	47,5	< 0,001	370	64,5
hormonal**				91	37,4	0,12	248	43,4

OCP were compared to the two control groups with the chi-square test; [a] OCP versus ONC; [b] OCP versus MCP

CCI: Charlson comorbidity index

* More than one possibility.

** Percentages were calculated on valid cases

Table 2. Well-being and coping at baseline: comparison between OCP and control group

	ONC			OCP			MCP	
	n	%	p-value[a]	n	%	p-value[b]	n	%
	392	100,0		263	100,0		590	100,0
	Psychological well-being							
Depression			**0,03**			0,52		
normal	353	90,1		222	84,4		508	86,1
impaired	39	9,9		41	15,6		82	13,9
Loneliness	n=391		**0,02**			**0,01**	n=587	
normal	240	61,4		184	70,0		457	77,9
impaired	151	38,6		79	30,0		130	22,1
Distress	n=381		**0,002**	n=251		0,27	n=558	
normal	302	79,3		171	68,1		358	64,2
impaired	79	20,7		80	31,9		200	35,8
	Physical health							
Fatigue			0,09	n=255		0,47	n=576	
no fatigue	174	44,4		96	37,6		232	40,3
Fatigue	218	55,6		159	62,4		344	59,7
ADL			0,40			**0,001**		
independent	244	62,2		155	58,9		414	70,2
dependent	148	37,8		108	41,1		176	29,8
IADL	n=391		0,27	n=261		**0,001**	n=574	
independent	249	63,7		155	59,4		407	70,9
dependent	142	36,3		106	40,6		167	29,1
	Coping							
Coping strategy	Mean (SD)			Mean (SD)			Mean (SD)	
active tackling	2,69 (0,58)		0,38	2,66 (0,55)		**<0,001**	2,87 (0,51)	
social support	2,08 (0,57)		0,63	2,06 (0,61)		**<0,001**	2,23 (0,62)	
avoidance	2,05 (0,55)		0,31	2,10 (0,55)		**0,004**	2,19 (0,52)	
palliative reacting	2,17 (0,69)		0,07	2,06 (0,66)		**0,003**	1,92 (0,65)	

Well-being in OCP were compared to the two control groups with the chi-square test.

Coping strategies in OCP were compared with the control groups by using the Mann-Whitney test.

[a] OCP versus ONC; [b] OCP versus MCP

The relation between baseline coping and changes after 1 year in well-being

The predictive value of baseline coping for well-being after one year is shown in Table 3. Active tackling predicted only less often distress in MCP. Social support seeking predicted only less often loneliness in MCP. Avoidance coping did not predict any of the measures of well-being in the three patient groups. Palliative reacting predicted distress in OCP, and depression and dependency for ADL in MCP.

Table 3. Adjusted analyses of baseline coping as predictor for subsequent well-being

	Psychological well-being after 1 year			Physical health after 1 year		
Coping at baseline	**Depression**	**Loneliness**	**Distress**	**Fatigue**	**ADL**	**IADL**
	OCP					
	n= 153/263 (58,2%)	n= 150/263 (57,0%)	n= 142/263 (54,0%)	n= 131/263 (49,8%)	n= 172/263 (65,4%)	n= 139/263 (52,9%)
Active tackling	1,15 (0,45-2,96)	1,19 (0,56-2,51)	0,50 (0,19-1,33)	0,63 (0,28-1,44)	0,93 (0,48-1,78)	1,00 (0,48-2,08)
Social support	0,77 (0,32-1,87)	0,55 (0,25-1,19)	1,74 (0,74-4,07)	0,69 (0,33-1,45)	1,30 (0,70-2,44)	1,28 (0,64-2,57)
Avoidance	0,97 (0,36-2,63)	1,00 (0,43-2,32)	0,93 (0,37-2,34)	2,34 (0,91-5,97)	1,53 (0,75-3,12)	0,83 (0,37-1,86)
Palliative reacting	1,86 (0,87-3,99)	1,31 (0,70-2,48)	**2,61 (1,24-5,51)**	0,99 (0,52-1,85)	0,89 (0,52-1,51)	1,76 (0,94-3,29)
	MCP					
	n= 367/590 (62,2%)	n= 367/590 (62,2%)	n= 292/590 (49,5%)	n= 323/590 (54,7%)	n= 354/590 (60,0%)	n= 305/590 (51,7%)
Active tackling	0,71 (0,37-1,36)	0,93 (0,57-1,54)	**0,50 (0,27-0,96)**	1,10 (0,67-1,79)	1,12 (0,67-1,89)	1,02 (0,55-1,90)
Social support	0,81 (0,49-1,34)	**0,64 (0,41-0,98)**	1,15 (0,71-1,87)	0,71 (0,48-1,07)	0,77 (0,51-1,17)	0,60 (0,35-1,01)
Avoidance	1,28 (0,64-2,54)	1,52 (0,87-2,65)	0,99 (0,52-1,89)	0,95 (0,56-1,60)	0,97 (0,57-1,63)	1,19 (0,63-2,28)
Palliative reacting	**2,29 (1,31-3,99)**	1,35 (0,87-2,11)	1,07 (0,62-1,84)	1,54 (0,99-2,39)	**1,81 (1,16-2,83)**	1,22 (0,71-2,11)
	ONC					
	n= 204/392 (52,0%)	n= 246/392 (62,8%)	n= 187/392 (47,7%)	n= 202/392 (51,5%)	n= 252/392 (64,3%)	n= 198/392 (50,5%)
Active tackling	0,64 (0,27-1,47)	1,26 (0,72-2,21)	1,62 (0,76-3,46)	0,69 (0,38-1,25)	0,83 (0,46-1,49)	0,98 (0,48-2,02)
Social support	1,12 (0,50-2,48)	0,76 (0,44-1,31)	1,40 (0,71-2,74)	0,82 (0,46-1,46)	1,53 (0,86-2,73)	1,02 (0,48-2,19)
Avoidance	0,74 (0,29-1,89)	0,90 (0,51-1,60)	1,14 (0,54-2,39)	0,91 (0,48-1,69)	1,01 (0,54-1,86)	1,18 (0,52-2,64)
Palliative reacting	1,41 (0,72-2,76)	1,51 (0,96-2,37)	1,38 (0,74-2,55)	1,24 (0,75-2,06)	1,50 (0,93-2,42)	1,12 (0,60-2,09)

OR (95%CI) are shown. Values with p<0,05 are in bold.

Abrreviations. OCP: older patients with cancer; MCP: middle-aged patients with cancer; ONC: older patients without cancer

Logistic regression analyses were adjusted for covariates significant in univariate analyses and for baseline well-being status

Depression was adjusted in MCP for age; in ONC for age and comorbidity

Loneliness was adjusted in OCP for living situation and marital status; in MCP for living situation; in ONC for gender and educationl level

Distress was adjusted in MCP for marital status, tumour type, and radiotherapy; in ONC for educational level and comorbidity

Fatigue was adjusted in OCP for age, gender, and tumour type; in MCP for comorbidity, tumour type, chemotherapy, and radiotherapy; in ONC for educational level and comorbidity

ADL was adjusted in OCP for gender; in MCP for educational level, tumour type, and comorbidity; in ONC for age, gender, marital status, and educational level

IADL was adjusted in OCP for age and educational level; in MCP for tumour type, stage, surgery, chemotherapy, and radiotherapy; in ONC for age, educational level, and comorbidity

Discussion

Main findings

The results of our main analysis showed that some baseline coping strategies influenced psychological well-being and physical health one year later in patients with cancer, even after controlling for important covariates including cancer-related factors. This relation between coping and well-being differs between OCP and the two control groups. However, there were few significant associations overall, no associations were observed in ONC, and most associations were observed in MCP.

The analysis of the individual coping strategies showed that active tackling and seeking social support did not predict well-being in OCP and ONC. Avoidance coping did not predict any of the outcomes in the three patient groups. Three out of a total of five significant associations were observed for palliative reacting. It was the only coping strategy that predicted physical health, though only in MCP. Furthermore, palliative reacting was the only coping strategy that predicted any of the outcomes (i.e. distress) in OCP.

Our additional analyses at baseline described differences in well-being and showed that active tackling was used most often in the three patient groups. Furthermore, coping strategies did not differ between older patients with and without cancer. On the other hand, coping patterns differed between the age groups in patients with cancer.

Comparison with literature and discussion

Older patients with cancer often experience less psychological morbidity compared to younger patients (5,25). One possible explanation for this difference in well-being suggests that older people are more skilled at matching coping strategies to situational demands (coping flexibility) compared to their younger counterparts (26). However, in this study we did not study younger patients (often < 50 years in studies) but MCP (50-70 years) which might explain why we did not find a difference in distress or depression between OCP and MCP at baseline.

While we did not see an ageing-related effect for psychological well-being (except for loneliness) in cancer patients, we did observe such an effect for dispositional coping at baseline. Available evidence suggests that in later life there is a decline in the use of most coping strategies in the general population (27). We also observed this decline in the current study when comparing OCP with MCP, with the exception of palliative reacting. Different explanations can be given for the age difference in coping patterns (27-29). One general interpretation suggests that older patients are more likely to devote less energy to coping when

faced with stressful situations due to psychological and social changes that often accompany ageing.

The main goal of the current paper was to assess the predictive value of baseline coping for subsequent well-being after one year in OCP while disentangling ageing and diagnosis effects. We found no diagnosis effect (OCP versus ONC) on dispositional coping at baseline and, not considering palliative reacting, there was also no diagnosis effect in the relationship between coping and well-being. Perhaps also not entirely unexpected since we did not specifically measure coping in response to cancer. Still, a cancer diagnosis in patients who generally utilize palliative reacting more often predicted distress in OCP after one year while such an association was not observed in ONC. This might reflect the difficulty of these patients to return to normal life a year after a cancer diagnosis.

The differential relationship that we observed for coping and subsequent well-being between OCP and MCP is not unexpected given the ageing effect on dispositional coping described above. Our findings indicate that the association between palliative reacting and negative outcomes seems to persist with ageing (both present in MCP and OCP) while the association between active coping (active tackling, seeking social support) and positive outcomes does not (only present in MCP). The lack of any association with avoidance coping in this study is unexpected since it is linked to decreased psychological well-being in previous cross-sectional and prospective research (6,30). With four observed associations in MCP and only one in OCP, it seems that the ageing effect attenuates the association between coping shortly after a cancer diagnosis and well-being after one year. One possible interpretation of these results suggests that older patients are more likely to trivialize a cancer diagnosis, hence the lower utilization of active coping and avoidance coping in OCP compared to MCP, which could mute the impact of the diagnosis on well-being (29). Our results are an illustration of the inappropriateness of the extrapolation of evidence obtained from younger patients to the older population. Similarly, to decisions related to the medical treatment of OCP, different aspects of ageing should be taken into account in the psychosocial care of OCP. Our observation that age does not seem to affect the association between palliative reacting and decreased psychological well-being one year after a cancer diagnosis is important for clinical purposes and is discussed below.

Strengths and limitations

Major strengths of this study include the relatively large study population, the possibility for longitudinal analyses, and the availability of two control groups for OCP which allowed us to distinguish between age-linked effects and cancer (-diagnosis) effects. Furthermore, we were

able to study simultaneously multiple dimensions of well-being. A short-coming of this study is the high percentage of patients that were lost to follow-up after one year. However, many associations were confirmed in sensitivity analyses (Appendix S1 available in the online publication). Additional analyses showed that lost to follow-up patients were not fundamentally different in terms of baseline coping compared to patients that were included in the analysis. The former utilized active tackling less frequently while no differences were observed for the other coping strategies (data not shown). Another point to consider is that although we focused on four key coping strategies in this study, other strategies that are not covered by the short UCL might provide additional information on the association with well-being.

Clinical implications and future research

A comprehensive geriatric assessment is recommended in OCP to guide treatment decision-making considering the variability of health status in the older population (31). This entails the assessment of multiple geriatric domains like functional status but also psychological status prior to cancer treatment. This is also a good moment to identify early on OCP with inadequate coping tendencies and offers the opportunity for prevention programs. It is already well established that distress should be assessed routinely in patients with cancer. Particularly in OCP, future intervention studies should focus on cognitive behavioural therapy aimed at palliative reacting and its impact on distress on the short- and long-term given that psychosocial interventions might only have short-term effects (32). Future research should also focus on the validity and reliability of the short version of the UCL.

Conclusions

Coping strategies influence subsequent well-being in patients with cancer, but the impact is different in the age groups. Palliative reacting was the only coping strategy that predicted well-being (i.e. distress) in OCP and is therefore, especially in this population, a target for coping skills interventions.

Author Contributions

This study was designed by AB, FB, MvdA, whereas the umbrella study KLIMOP was designed and set up by FB, MvdA, LD, and HW. Data collection was performed by AB and LD. AB, FB, TdB, MvdA drafted the manuscript, which was commented by all authors. Statistical analysis was performed by AB and discussed with FB, MvdA, and TdB. All authors read and approved the final manuscript.

Appendix 1. The short UCL (15 questions)

	Zelden of nooit	Soms	Vaak	Zeer vaak
1. Toegeven om moeilijke situaties te vermijden (A)	☐	☐	☐	☐
2. U neerleggen bij de gang van zaken (PR)	☐	☐	☐	☐
3. Uw zorgen met iemand delen (SS)	☐	☐	☐	☐
4. Direct ingrijpen als er moeilijkheden zijn (AT)	☐	☐	☐	☐
5. Afleiding zoeken (A)	☐	☐	☐	☐
6. Een probleem van alle kanten bekijken (AT)	☐	☐	☐	☐
7. Moeilijke situaties zoveel mogelijk uit de weg gaan (PR)	☐	☐	☐	☐
8. Verschillende mogelijkheden bedenken om een probleem op te lossen (AT)	☐	☐	☐	☐
9. Doelgericht te werk gaan om een probleem op te lossen (AT)	☐	☐	☐	☐
10. Iemand om hulp vragen (SS)	☐	☐	☐	☐
11. De zaken eerst op een rij zetten (AT)	☐	☐	☐	☐
12. Aan andere dingen denken die niet met het probleem te maken hebben (A)	☐	☐	☐	☐
13. Uw gevoelens tonen (SS)	☐	☐	☐	☐
14. Troost en begrip zoeken (SS)	☐	☐	☐	☐
15. Laten merken dat u ergens mee zit (SS)	☐	☐	☐	☐

A formal translation of this version of the short UCL is not available. We added the following in the questionnaire for clarity: Active tackling (AT), seeking social support (SS), Avoidance (A), and Palliative reaction (PR).

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Chapter 9. General discussion

Discussion

The implementation of geriatric assessment in oncology

Geriatric screening and geriatric recommendations

A geriatric care program was put in place in Belgium since 2007 in response to the ageing population (1). Mobile internal geriatric consultation teams were implemented to increase the availability of geriatric expertise throughout the hospital. However, their focus is primarily on hospitalized patients older than 75 years. Between 2009 and 2015, multiple Belgian hospitals implemented geriatric assessment (GA) in routine oncology practice with the financial support of the federal government. Although the implementation varied somewhat across hospitals, a GA-based model was followed that allowed screening and assessment of both inpatients and outpatients on a large scale, which is important given that the majority of patients receive cancer treatment ambulatory. The most cited barriers for implementation, according to a Belgian survey, were a high workload, lack of time or financial/staffing problems (2). However, research has shown repeatedly that GA detects unknown, possibly modifiable, health problems that could interfere with cancer treatment. Furthermore, GA influences treatment decision-making by facilitating better informed decisions which in a minority of patients leads to an adjustment of the cancer treatment plan (e.g. dose modifications, less aggressive treatment), primarily in patients who are considered for chemotherapy (3,4). In this regard, it is important to know that less than half of older patients with cancer are estimated to be fit (5). On the other hand, surely there are oncologists and others involved in the care of the older patient who believe they do not generally need the GA to treat this population. We believe that a better understanding of the GA-based approach will allow improving its implementation in order to optimize its effectiveness. Therefore, the evidence base for the GA-based approach should be improved. In the time between the start and the finalization of this dissertation, a lot of progress has been made in the geriatric oncology field. During this time for example, the first systematic reviews were published on two topics covered in this dissertation: the performance of geriatric screening tools (6-7) and the prognostic and predictive value of GA for clinical outcomes (8-12).

A GA is not necessary for all older patients. The need for a short and accurate screening tool to quickly identify vulnerable patients who could benefit from a GA is illustrated by the number

of publications on this subject in recent years. Several tools have been studied for this purpose. In **chapter 2**, we validated and directly compared the G8 screening tool and the Groningen Frailty Indicator (GFI) in reference to a GA (13). Overall, there was no difference in the diagnostic accuracy of both screening tools (AUC= 0.87 for both screening tools). However, an adequate sensitivity and negative predictive value (NPV) are the most important characteristics for a screening tool while a lower specificity can be tolerated. The G8 demonstrated an adequate sensitivity (92%) and NPV (78%), however at the expense of the specificity (52%). In contrast, the GFI had a better specificity (87%) compared to the G8, but the more important sensitivity (66%) and NPV (59%) were inadequate. In contrast to other research, we also focused on other cut-off values for the two screening tools. We suggested an alternative cut-off value (GFI score ≥3) for the GFI corresponding with similar diagnostic characteristics than the G8. An external analysis on data of the Klimop study supported the alternative cut-off value for the GFI (unpublished data). Whilst no best screening tool can convincingly be selected based on our work and that of others, the G8 was specifically developed for older patients with cancer and is one of the most studied tools in geriatric oncology. With this tool about 30% of the screened patients are exempted from a full GA. More recently, two studies developed a modified G8, a different version in each study, that improved the diagnostic performance properties of the original tool (14,15). One study reported a more stable diagnostic accuracy across tumor sites with the modified G8 (see below). As discussed in chapter 2, an important limitation of studies evaluating screening tools is the lack of a gold standard with differences between studies in the selection of scales, cut-off values for impairment, and in the definition of an 'abnormal' GA. Furthermore, others have reported significant differences in the performance of the G8 across different tumor sites and metastatic disease status (15, 16). Although not studied, this is probably an issue for other screening tools as well. More data on the performance of screening tools are expected to follow in the coming years.

In **chapter 3**, we gained more insight on the frequency and type of geriatric recommendations following a GA in routine practice and the implementation of these recommendations (17). Our aim was to have a view on clinical practice over nine hospitals spread all over Belgium and not to study differences between hospitals. Geriatric screening was performed in 1550 patients over a time period of one year. Our study revealed that geriatric recommendations were given in about three fourths of patients. Most referrals were made to the dietician, social worker and psychologist. After one month, at least one geriatric recommendation was performed in

approximately half of these patients and about one third of all geriatric recommendations were performed. Referrals that were not often performed included the geriatric day clinic and the fall clinic. Our results indicated that there are opportunities for improvement and we discussed several possible reasons for (non) adherence to geriatric recommendations. To our knowledge, this is the first study on geriatric recommendations in the oncology setting on a large scale.

As discussed in chapter 3, the benefit of CGA and associated geriatric interventions has been shown for different clinical outcomes (e.g. functional status, institutionalization, mortality) in patients with non-malignant disease. We also mentioned that the poor implementation of geriatric recommendations has been suggested as a possible reason for the lack of CGA effectiveness in some randomized controlled trials (RCT's). This would not be different in geriatric oncology. The few RCT's in patients with cancer that focus on the impact of geriatric interventions show conflicting results (18). However, RCT's evaluating a GA-based approach in oncology similarly to that as implemented in Belgium have only recently been started (11,18,19). Our study illustrates that a learning curve should be considered in the implementation of the GA in routine oncology practice where continued efforts towards efficient collaboration, coordination, and communication are imperative. Future research, preferably RCT's, on the effectiveness of the GA-based approach in oncology should take the adherence of geriatric recommendations into account next to the experience of the participating hospitals with this approach.

The predictive value of geriatric screening tools for treatment toxicity

In chapter 2, we evaluated the diagnostic performance of two screening tools to select patients who should receive a GA. A distinction should be made between the ability of a screening tool to discriminate patients with a normal and abnormal GA and its ability to predict oncological outcomes. Several studies have demonstrated the prognostic value of geriatric screening tools for clinical outcomes in patients with cancer (6-7,20). We also demonstrated the prognostic value of the G8 and the Flemish version of the Triage Risk Screening Tool (fTRST) in univariate and multivariate analyses for overall survival in chapter 5. While there is evidence for the predictive value of screening tools for mortality, less data is available for treatment toxicity. In **chapter 4**, we evaluated the predictive value of the G8 and the GFI for treatment toxicity.

In an interim analysis, previously published as an abstract, we reported that the G8 and the GFI predict severe treatment toxicity in patients who received one cycle of (radio)chemotherapy

(21). However, our analysis with the full data revealed that both screening tools did not predict short-term treatment toxicity (22). These results need to be confirmed in a larger sample. However, other recent studies with the G8 and the GFI could also not demonstrate a predictive value for treatment toxicity (including postoperative complications). To our knowledge, no other studies have evaluated the association between the GFI and chemotherapy toxicity. However, other research could not demonstrate an association between the GFI and postoperative complications in patients with cancer (23-25). For the G8, we found one study (abstract) that reported an association with severe chemotherapy toxicity (26). However, this was not the case in a smaller study (abstract) for patients with hematological malignancies (27). An association with postoperative complications could not be shown in a recent multivariate analysis with colorectal cancer patients (28). Of note, two recent risk prediction models, containing GA components, have been developed specifically to predict chemotherapy toxicity and have received great interest but still need further external validation (29-30).

The prognostic value of geriatric information and laboratory parameters for overall survival

In **chapter 5**, we studied the prognostic value of GA for mortality. The predictive value of GA for treatment toxicity was beyond the scope of this dissertation (see ref 3, 10-12). One of the important questions clinicians have to consider in the treatment decision-making process is whether a particular older patient is going to die of or with cancer. For example, a patient with a limited life expectancy due to comorbidity might have no benefit from adjuvant treatment. In our study, we showed that geriatric screening and GA improved the estimation of life expectancy beyond clinical information (age, stage, tumor type) in two separate cohorts (31). Most individual GA components predicted mortality in univariate and adjusted analyses, especially nutritional status and functional status (i.e. instrumental activities of daily living). The prognostic value of the 'Leuven Oncogeriatric Frailty Score' (LOFS) was demonstrated for the first time in this study. The LOFS summarizes the results of the GA in a single score which has the advantage of simplicity towards interpretation. Furthermore, our results showed that GA summaries, i.e. the GA as a whole and the LOFS, provide more prognostic information than individual GA components. It would be reasonable to assume that GA summaries are more able to capture the multidimensional process of aging than individual GA components. However, mortality was largely explained by clinical information and the incremental value of GA was only moderate.

The prognostic value of GA for mortality is studied using different analysis techniques (8-12). Some of these analyses have not been adjusted appropriately for age, stage, or tumor type to

account for the heterogeneity of the populations. This might in part explain why little consistency is found between studies as to which GA components predict mortality. Studies often select GA components and other variables that are found statistically significant in univariate analyses for inclusion in multivariate analysis. Variable selection regression methods (e.g. backward stepwise) are also sometimes used to select the best set of variables or GA components. These studies show that certain individual GA components or a subset of GA components predict mortality, but they do not evaluate the prognostic value of the GA as a whole nor do they evaluate the incremental value of the GA in addition to clinical information. Although it is important to have a view on the most prognostic GA components, information from every GA component is needed to evaluate the global health status of the patient, to identify unknown health problems that could interfere with treatment and to implement geriatric interventions as previously discussed. Therefore, we quantified the prognostic value of the GA as a whole by comparing the performance of a basic model with clinical information with a model extended with all individual GA components, which no prior study has done before. We did not perform an analysis with variable selection methods. These types of analyses are for example more appropriate for the improvement of existing prognostic calculators with additional variables to estimate life expectancy. Such online tools have been shown not to function well in older patients with cancer (32). Other studies have shown that a classification of patients, based on the results of the GA, is able to differentiate risk groups for overall survival (e.g. fit, vulnerable, frail). However, the definition of each risk group is based on consensus and different approaches are used to classify patients. A continuous GA summary score might be more precise in quantifying the patient's global health status than a classification in three risk groups. For this reason, we included the recently developed LOFS in our analysis which proved to be an interesting tool.

Since our study showed that geriatric information only moderately improved the estimation of life expectancy, further research is needed in this area. The use of biomarkers might hold promise in the assessment of prognosis beyond clinical information (33-34). **In chapter 6,** we focused on three commonly measured laboratory parameters CRP, albumin, hemoglobin and three inflammation-based composite scores that combine CRP and albumin values: the Glasgow Prognostic Score (GPS), the modified GPS (mGPS), and the CRP/albumin ratio. We performed a subgroup analysis of the study described in chapter 5 and compared the performance of biomarkers with that of the GA and evaluated if biomarkers have an added prognostic value beyond clinical and geriatric information. Our analysis showed that the GA

adds slightly more prognostic information than the laboratory parameters which are known to be strong prognostic factors (35). It also showed that the extended model with GA could be further optimized with biomarkers. To the best of our knowledge, this is the first study to compare the incremental value of different biomarkers beyond the GA as a whole.

The impact of aging and cancer on well-being: the Klimop study

The utilization of formal and informal care

The Belgian healthcare system covers almost the entire population and has developed a wide range of home care services (36). The Belgian government also provides a number of financial incentives to families to promote informal care (37). In **chapter 7**, we evaluated the use of formal and informal care shortly after a cancer diagnosis (baseline) in older patients with cancer (OCP) and two control groups: older primary care patients without cancer (ONC) and middle-aged patients with cancer (MCP) (38). At baseline, about half of older adults (OCP and ONC) and 18% of MCP used formal care, while about 85% of cancer patients (OCP and MCP) and 57% of ONC relied on informal care. Formal care increased for all groups after one year though not significantly in OCP. The amount of informal care only changed in MCP which decreased after one year.

Differences in care at baseline and changes in patterns of care after one year were further discussed in more detail. For formal care, this was done at the level of individual services. A link was made between the disease trajectory, dynamics in informal care, and feelings of loneliness. The influence of a cancer diagnosis on the relationship between formal care and informal care was discussed as well. We provided possible explanations for differences in care between the patient groups. Furthermore, we determined that cancer-related factors and associated changes in need factors explain a transition towards formal care in newly-diagnosed patients with cancer. Finally, we discussed policy implications in the approach of OCP while considering the recommended implementation of GA in routine oncology practice. This study provides a better insight into the current utilization of home care in Flanders after a cancer diagnosis and concludes that the first year after a cancer diagnosis is an important time to follow-up on the patient's needs for home care.

In this study, we focused more on formal care than on informal care given the available data. There is considerable variation in the definition of formal care in the literature. Physiotherapy is sometimes not included in this definition for example. One of the advantages of our study is that we studied the utilization of formal care in general but also individual home care services

were examined. This showed for example interesting trends for physiotherapy. Although the intention of our study was not to study specific tasks performed by caregivers, we referred to certain tasks to provide possible explanations for differences in formal care between cancer and non-cancer patients (e.g. the need for physiotherapy due to lymphedema of the arm after breast cancer surgery). Increases in formal care could be explained in this way for MCP. Except for physiotherapy, these increases in care (i.e. home nursing and cleaning help) were not observed in OCP. As explained in chapter 8, the use of formal care was already high at baseline in this cohort compared to MCP and new tasks were likely covered by the already available formal care. A better understanding of these suggested 'new' tasks for OCP would require further study, however the trends that we described in MCP provide some hints.

In the Belgian context, a series of recent policy reforms aims at more patient-centered, continuous, and integrated care or 'transmural care' which entails a close collaboration between primary and specialized care providers. This will shift hospital care further towards primary care and home care organizations. In our study, we focused on the first year after a cancer diagnosis, an important time frame in the cancer trajectory. Newly diagnosed patients generally start and complete their treatment (e.g. chemotherapy, surgery, radiotherapy) during this year. The majority of these patients are treated on an outpatient basis and need to visit the clinic frequently. New forms of care are explored in recent pilot projects for patients with cancer. Several projects are evaluating the feasibility of the administration of certain cancer treatments at home (sometimes referred to as 'hospital at home') (39,40). Others are exploring approaches that would improve the chemotherapy process and service by collaborating with home care organizations. In a pilot project, prechemotherapy blood collections were performed at home instead of in the hospital avoiding extra visits to the clinic and/or long waiting times (41). Another recent pilot project developed and evaluated a transmural care trajectory for patients with glioma and their informal caregivers (42). This involved the collaboration of a coordinator of the hospital and a coordinator of the home care organization, a care model that could be extended to patients with other types of cancer.

If deemed feasible and safe, these types of initiatives have the potential to improve patient satisfaction and well-being (and that of the informal caregiver). It might also reduce the burden on busy oncology day care units and perhaps reduce costs. However, a good collaboration and coordination of all stake holders involved will be required. The advantages for patients would apply for young and old but would be perhaps even more important for OCP with a geriatric profile. If these new forms of care arrangements are implemented on a larger scale, it will

always be important to evaluate the global health and physiological reserves of the OCP for which we refer to the first part of this dissertation.

Coping and subsequent well-being

A cancer diagnosis and treatment affect the lives of patients and their environment in many ways. During the first year of a cancer diagnosis, patients have to deal with the news of the diagnosis and face many uncertainties. They might get surgery and other cancer treatments with significant toxicities besides dealing with symptoms related to cancer; they usually have to visit the clinic frequently, they might need to visit the emergency department and they might need to be admitted to the hospital; they have to undergo repeated surveillance CT-scans and deal with the fear that the treatment might not be working. Psychological distress is common in patients with cancer and it is sometimes referred to as the sixth vital sign to assess next to body temperature, blood pressure, pulse, respiratory rate, and pain (43). During this time, patients use multiple coping strategies simultaneously influencing their effects and what works effectively will depend on the context and the patients' individual characteristics (e.g. personality). The goodness of fit hypothesis is worth mentioning here. According to this hypothesis, emotion-focused coping is more adaptive for uncontrollable situations and unsolvable situations while problem-focused coping is more adaptive in controllable situations (44). In this regard, we mentioned in chapter 9 that older people might be more skilled at matching coping strategies to situational demands (coping flexibility) when discussing differences in well-being between older patients and their younger counterparts shortly after a cancer diagnosis. Situational coping should not be confused with the focus of our study: dispositional coping (45). Dispositional coping refers to coping tendencies in response to problems or unpleasant situations in general and not to specific situations (e.g. a cancer diagnosis). These are viewed as relatively stable over time and situations which allows a better comparison between different patient groups.

There is a large body of literature on coping with stressful life events, however coping strategies have not been studied often as predictor variables in longitudinal studies. In **chapter 9**, we described that there were few significant associations overall between dispositional coping and subsequent well-being (46). From the 4 coping strategies that were studied, only palliative reacting predicted subsequent well-being in OCP. No diagnosis effect (OCP vs ONC) was observed in the relation between baseline coping and subsequent well-being. However, an aging effect (OCP vs MCP) was observed. Out of 5 significant associations, 1 was observed in OCP and 4 in MCP. We discussed that our results support the notion that the use of most coping strategies declines in later life. Moreover, we suggested that older patients are more likely to

trivialize a cancer diagnosis which could mute the impact of a cancer diagnosis on well-being. Furthermore, most associations were observed with palliative reacting and this coping strategy was the only strategy that predicted well-being (i.e. distress) in OCP. Palliative reacting refers to behaviour that involves giving up any effort to deal with the situation and we concluded that this type of passive coping should be studied further in future intervention studies in OCP. In discussing the clinical implications of our results, we emphasized the need for the evaluation of psychological status as part of the geriatric assessment prior to cancer treatment as psychosocial care is an essential part of cancer treatment (47).

Future perspectives

The implementation of the GA-based approach in Belgium has made much progress over recent years. This was made possible by the national cancer plan and the financing of the federal government of several projects in geriatric oncology. Unfortunately, financing has been stopped from 2015 and this has had a negative impact on the systematic screening and assessment of older patients with cancer in clinical practice. New initiatives and efforts are needed to continue and expand the developed expertise in Belgium. Other countries have also made a lot of progress with the development of geriatric oncology programs and for example the development of teaching programs. In this section, we discuss some future perspectives on the topics covered in this dissertation.

Our research and other work could not clearly identify the most accurate geriatric screening tool to select patients for a full GA. Given results from more recent research, future research should explore the accuracy of screening tools in different tumor types. While further research is ongoing, many experts agree it is better to screen patients with an imperfect tool than not to screen patients at all.

The role of geriatric interventions following a GA in patients with cancer was emphasized in this dissertation. We gained more insight into geriatric recommendation and their implementation in routine oncology practice. This information could inform future policymaking regarding the care of the older patient with cancer. Further (qualitative) research is needed to better understand why certain referrals are performed and others are not and for example which specific actions were undertaken. The specific process of care in each hospital should be taken into account when trying to understand the GA-based approach beyond the first two steps of screening and GA. Efforts to improve the collaboration between different disciplines and efforts to improve communication will undoubtedly be important for the future. Although this was not the focus of our research, we also note that more research is needed to evaluate the impact of geriatric interventions on cancer. Future research on geriatric interventions or hospitals planning to integrate the GA-based approach in oncology for the first time should always be aware of a learning curve.

Several studies on the predictive and prognostic value of geriatric information for oncological outcomes have been published over the past recent years. More research has focused on mortality than on treatment toxicity. More research is especially needed for the latter. In accordance with our work, future research should not only focus on the question whether GA

is predictive and prognostic for clinical outcomes but also how much it adds to clinical information. In accordance with our work on routinely measured laboratory parameters, future research should also focus on the combination of GA and biomarkers, given the complexity of the processes related to aging, cancer, and their interaction. More research is warranted to assess the incremental prognostic value of other potential biomarkers (including imaging biomarkers for sarcopenia) to improve the estimation of life expectancy and other relevant clinical outcomes. In this regard, the European Organisation for Research and Treatment of Cancer (EORTC) has initiated an aging biomarker program to examine the value of potential aging biomarkers with the aim to optimize treatment decision-making and care in general in older patients with cancer.

The future of geriatric oncology in Belgium will likely be influenced by current and planned changes in the organisation and payment system of hospitals. Furthermore, primary care and home care organisations are expected to play a greater role in our future healthcare system. Our analysis based on the Klimop study provided a better insight into the current utilization of formal and informal home care by older patients shortly after a cancer diagnosis and after one year in Flanders. Future analyses from this ongoing study will be able to evaluate the use of home care at later time points. Other future research should collect more detailed information on informal care as our society is under constant change. It also remains to see how a web-based comprehensive assessment system (BelRAI) in Belgium will influence the use of home care in older patients recently diagnosed with cancer.

Finally, our analysis on coping could be a basis for future intervention studies that focus on cognitive behavioural therapy aimed at palliative reacting and its impact on distress in older patients with cancer. And although knowledge about the development of coping over the life span has increased, research on coping theory should give more attention to OCP. After examining the literature, we also suggest that future research should focus on the validity and reliability of the short version of the Utrecht Coping List.

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Chapter 10. Summary (English & Nederlands)

Summary

The number of older patients with cancer will further increase due to the increasing life expectancy and ageing population. Health care providers and policy makers should be aware that older patients with cancer require special attention regarding treatment decisions and care. Treatment in older patients with cancer is complex due to the heterogeneity in global health status, physiological reserve capacity and the lack of evidence-based data for this population. In this dissertation, we focus on some clinical, societal, and psychosocial aspects of ageing and cancer.

International guidelines recommend the implementation of geriatric assessment (GA) in routine oncology practice to detect previously unknown health problems, implement geriatric interventions, improve the estimation of life expectancy and the risk of treatment toxicity. In other words, the aim of GA is to guide treatment decision-making. Multiple Belgian hospitals implemented GA in routine oncology practice between 2009 and 2015 with the financial support of the federal government. Given that the majority of patients with cancer are treated ambulatory, a GA-based model was followed that allowed the approach of both inpatients and outpatients. Based on the data from these implementation studies, we validated two geriatric screening tools to select patients for GA in a two-step approach and studied geriatric recommendations following a GA. A better understanding of the GA-based approach will allow improving its implementation in order to optimize its effectiveness. Our study on the implementation of geriatric recommendations indicated that there are opportunities for improvement and we discussed several possible reasons for (non) adherence to these recommendations.

In order to help physicians guide treatment decision-making, geriatric screening and GA should ideally have a predictive and prognostic value for oncological outcomes. We could not demonstrate a predictive value of two geriatric screening tools for short-term treatment toxicity in patients who received (radio)chemotherapy. On the other hand, we showed that geriatric screening and GA improved the estimation of life expectancy beyond clinical information, though the improvement was moderate. Especially nutritional status and functional status (i.e. instrumental activities of daily living) add more prognostic information compared to the other GA components. However, our results showed that GA summaries, i.e. the GA as a whole and a recently developed tool summarizing the results of a GA in a single score (the LOFS), provide

more prognostic information than individual GA components. GA summaries are more able to capture the multidimensional process of ageing. In a separate analysis, we showed that GA as a whole adds slightly more prognostic information to clinical information than known prognostic biomarkers (e.g. albumin, CRP, Glasgow Prognostic Score). Furthermore, we showed that with routinely measured laboratory parameters life expectancy is estimated more precisely than with only clinical and geriatric information.

The second part of this dissertation comprises of two analyses based on the Klimop study, an ongoing longitudinal cohort study on the impact of ageing and cancer on well-being. In a first analysis, we provided a better insight into the current utilization of formal and informal care in Flanders shortly after a cancer diagnosis and showed that the first year after a cancer diagnosis is an important time to follow-up on the patient's needs for home care. We expect to see some significant changes in the utilization of home care by older patients with cancer in the coming years in light of recent policy reforms with a focus on more transmural care.

In the second analysis, we showed that ageing influences the association between coping strategies shortly after a cancer diagnosis and subsequent well-being in patients with cancer. Different aspects of ageing should be taken into account in the psychosocial care of older patients with cancer. Based on our results, we suggested that this population is more likely to trivialize a cancer diagnosis which could mute the impact of the diagnosis on well-being. Palliative reacting, which involves giving up any effort to deal with the situation, was the only coping strategy that predicted well-being (i.e. distress) in older patients with cancer after one year. This type of passive coping should be a target for future intervention studies, especially in this population.

Samenvatting

Het aantal oudere patiënten met kanker zal verder toenemen als gevolg van de stijgende levensverwachting en de vergrijzing van de bevolking. Zorgverleners en beleidsmakers moeten zich ervan bewust zijn dat oudere patiënten met kanker speciale aandacht nodig hebben bij het nemen van beslissingen rond hun behandeling en hun zorg in het algemeen. De behandeling van oudere patiënten met kanker is complex vanwege de heterogeniteit in hun globale gezondheidsstatus, fysiologische reserve capaciteit en het gebrek aan evidence-based data voor deze populatie. In dit proefschrift richten we ons op enkele klinische, maatschappelijke en psychosociale aspecten van veroudering en kanker.

Internationale richtlijnen bevelen aan om een geriatrische 'assessment' (GA) te implementeren in de dagelijkse oncologie praktijk om eerder onbekende gezondheidsproblemen te detecteren, geriatrische interventies te implementeren, de levensverwachting van de patiënt beter te kunnen inschatten en om beter het risico op toxiciteit ten gevolge van een kankerbehandeling te kunnen inschatten. Kortom, de GA dient als leidraad bij het nemen van beslissingen over de behandeling van de oudere patiënt. Met de financiële steun van de federale overheid, hebben meerdere Belgische ziekenhuizen een GA geïmplementeerd in de dagelijkse oncologie praktijk tussen 2009 en 2015. Aangezien de meerderheid van de patiënten met kanker ambulant wordt behandeld, werd een model gevolgd waarbij zowel ambulante als gehospitaliseerde patiënten konden bereikt worden. Op basis van de gegevens van deze implementatiestudies, valideerden we twee geriatrische screening tools om patiënten te selecteren voor GA in een tweestap benadering en bestudeerden we geriatrische aanbevelingen die volgden na een GA. Meer kennis rond deze aanpak in de oncologie zal het mogelijk maken om de implementatie van GA te verbeteren en om de effectiviteit ervan te optimaliseren. Ons onderzoek naar de uitvoering van geriatrische aanbevelingen wees uit dat er mogelijkheden voor verbetering zijn en we bespraken verschillende mogelijke redenen voor het al dan niet naleven van deze aanbevelingen.

Geriatrische screening en GA zouden idealiter een voorspellende en prognostische waarde moeten hebben voor oncologische uitkomsten opdat de GA als leidraad kan dienen bij de behandeling van de oudere patiënt. We konden geen voorspellende waarde aantonen van twee geriatrische screeningsinstrumenten voor toxiciteit op korte termijn bij patiënten die (radio) chemotherapie kregen. Anderzijds toonden we aan dat geriatrische screening en GA de inschatting van de levensverwachting verbeterden ten opzichte van een inschatting met alleen klinische informatie. Deze verbetering was echter matig. Vooral voedingsstatus en functionele status (instrumentele activiteiten van het dagelijks leven) voegen meer prognostische informatie

toe in vergelijking met de andere GA componenten. Onze resultaten toonden echter aan dat 'GA-samenvattingen', hier de GA als geheel en een recent ontwikkeld instrument dat de resultaten van een GA in een enkele score (de LOFS) samenvat, meer prognostische informatie verschaffen dan individuele GA componenten. GA-samenvattingen zijn beter in staat om het multidimensionale proces van veroudering vast te leggen. In een afzonderlijke analyse hebben we aangetoond dat de GA als geheel iets meer prognostische informatie toevoegt aan klinische informatie dan gekende prognostische biomerkers (e.g. albumine, CRP, Glasgow Prognostic Score). Bovendien toonden we aan dat met routine laboratoriumparameters de levensverwachting nauwkeuriger wordt ingeschat dan met alleen klinische en geriatrische informatie.

Het tweede deel van dit proefschrift bestaat uit twee analyses op basis van de Klimop-studie, een lopend longitudinaal cohortonderzoek naar de invloed van veroudering en kanker op welzijn. In een eerste analyse hebben we het huidige gebruik van formele en informele zorg in Vlaanderen kort na een diagnose van kanker beschreven en hebben we aangetoond dat het eerste jaar na een diagnose van kanker een belangrijke periode is om de nood voor thuiszorg op te volgen. We verwachten de komende jaren een aantal belangrijke veranderingen rond thuiszorg bij oudere patiënten met kanker gezien de recente beleidshervormingen die zich meer richten op transmurale zorg.

In de tweede analyse hebben we aangetoond dat veroudering een invloed heeft op de associatie tussen coping strategieën kort na een diagnose van kanker en welzijn na 1 jaar. Bij de psychosociale zorg van oudere patiënten met kanker moet rekening worden gehouden met verschillende aspecten van veroudering. Op basis van onze resultaten suggereerden we dat de kans groter is dat oudere patiënten een diagnose van kanker zullen trivialiseren. Dit zou de impact van de diagnose op het welzijn kunnen beperken. 'Palliatief reageren', wat inhoudt dat elke poging om de situatie aan te pakken werd opgegeven, was de enige coping strategie die welzijn (meer bepaald distress) na één jaar bij oudere patiënten met kanker voorspelde. Vooral in deze populatie, is deze vorm van passieve coping een doelwit voor toekomstige interventie studies.

Scientific acknowledgement

For the authors contributions we refer to the end of each chapter.

Personal contribution

Study 1

Geriatric assessment (GA) was implemented in ZNA Middelheim and Jessa ziekenhuis between October 2009 and December 2011. ZNA Middelheim coordinated this study. Chapter 2 and Chapter 4 were based on this study.

The doctoral candidate tasks included the coordination of the study, literature study, geriatric screening and GA of patients in ZNA Middelheim, data management and analysis, and manuscript writing.

Study 2

GA was implemented in nine hospitals across Belgium between August 2011 and July 2012. 'De universitaire ziekenhuizen Leuven' coordinated this project. Chapter 3 and Chapter 5 (cohort B) were based on this study.

The doctoral candidate tasks included the discussion of the analysis plan, literature study, data management and analysis, and manuscript writing.

Study 3

GA was implemented in 'de universitaire ziekenhuizen Leuven' and in 'het universitair ziekenhuis Brussel' in Belgium between August 2009 and July 2011. 'De universitaire ziekenhuizen Leuven' coordinated this project. Chapter 5 (cohort A) and chapter 6 were based on this study.

The doctoral candidate tasks included the discussion of the analysis plan, literature study, data management and analysis, and manuscript writing.

Study 4

The Klimop study is an ongoing longitudinal cohort study in Belgium and the Netherlands. The department of public health and primary care of the KU Leuven coordinated this study in Belgium. Chapter 7 and chapter 8 were based on this study.

The doctoral candidate tasks included the discussion of the analysis plan, literature study, interviewing patients at home during follow-up visits, data analysis, and manuscript writing.

Conflict of interest statement

The authors indicated no potential conflicts of interest.

Professional career

Abdelbari Baitar received his Masters in Biomedical sciences at the K.U. Leuven in 2006. After working about 2 years in a chemistry laboratory, he started as a part-time researcher in ZNA Middelheim in Antwerp. There he mainly worked on a geriatric oncology project between 2009-2012 (National Cancer plan action 24). His responsibilities included the coordination of the project, which was in collaboration with Virga Jesse, Hasselt. A similar project was at that time ongoing in UZ Leuven which lead to the start of his PhD in 2012 at the K.U. Leuven. The project in ZNA Middelheim was extended between 2012-2015. The extended project, including 22 participating hospitals, was coordinated by UZ Leuven. Meanwhile, he also joined the Klimop study linked to the department of public health and primary care, K.U. Leuven. He continued to work part-time in the department of oncology in ZNA Middelheim after the finalization of these projects.

While doing his work focused on cancer, he also worked from 2009 until 2018 part-time for vzw Farmaka, an evidence-based medicine organization. For their academic detailing project financed by the government, he visited and informed primary care physicians by presenting three different topics a year with the aim to promote the rational use of drugs. From 2018, he started to work as a part-time scientific collaborator for ‘the BCFI’ (the Belgian Centre for Pharmacotherapeutic Information), a non-profit, non-governmental organization. The BCFI provides independent information on all drugs prescribed in Belgium and promotes rational prescribing of drugs.

Publications: Full Articles

Quinten C, Kenis C, Decoster L, Debruyne PR, De Groof I, Focan C,…,Baitar A et al. Determining clinically important changes in health-related quality of life in unfit elderly patients undergoing chemotherapy or surgery as cancer treatment. Under review.

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Schrijvers D, Baitar A, De Vos M, Mebis J, Vroman P. Evaluation of the Groningen Frailty Index (GFI) as a screening tool in elderly patients (pts) : an interim analysis. Ann Oncol (2010) 21 (suppl 8): viii185-viii188. [abstr 566PD]

Baitar A, De Vos M, Vandebroek A, Schrijvers S. Carboplatin and gemcitabine in elderly and/or frail patients with advanced transitional cell carcinoma (TCC): a phase II study. Ann Oncol (2010) 21 (suppl 8): viii271-viii303

Studies I worked on as a data manager/study coordinator in ZNA Middelheim:

SPECTA: Screening cancer patients for efficient clinical trial access (EORTC-1553)

A Phase 1b/2, Open-Label, Multicentre Study Assessing the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumor Activity of MEDI4736 in Combination With AZD9150 or AZD5069 in Patients With Advanced Solid Malignancies and Subsequently Comparing AZD9150 and AZD5069 Both as Monotherapy and in Combination With MEDI4736 as Second Line Treatment in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck.

BT-414 alone or ABT-414 plus temozolomide versus lomustine or temozolomide for recurrent glioblastoma: a randomized phase II study of the EORTC brain tumor group.

A phase 3 randomized, placebo-controlled trial of carboplatin and paclitaxel with or without veliparib (ABT-888) in HER2-negative metastatic or locally advanced unresectable BRCA-associated breast cancer.

A Phase 3 Randomized, Multicenter, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC).

A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with chemotherapy in pts with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy.

Reassure study: Radium-223 alpha emitter agent safety study in mCRPC population for long-term evaluation.

A phase II study of IV vinvlunine in combination with methotrexate versus methotrexate alone in pts with recurrent or metastatic squamous cell carcinoma of the head and neck previously treated with platinum-based chemotherapy.

Real life observations on Innohep thrombosis management in oncology patients: an observational study of treatment of DVT and/or PE in cancer patients with Innohep.

Observational study to obtain information on the efficacy and safety of Erbitux (cetuximab) in combination with standard chemotherapy in daily clinical practice in Belgium in 1st line treatment of mCRC patients with KRAS wild-type tumor.

Prospective non-interventional multicenter observational phase IV trial to describe first line anti-cancer treatment in patients with metastatic renal cell cancer in Belgium.

Prospective non-interventional study to collect data on the use of Avastin and conventional chemotherapy for the treatment of previously untreated metastatic colorectal cancer in pts ≥70 years.

European survey of oncology patient's experience of breakthrough pain.

Observational study to obtain information on the safety and efficacy of Erbitux (cetuximab) in daily clinical practice in Belgium in 2e line treatment of mCRC patients with KRAS wild-type tumor.

Academic detailing for vzw Farmaka (www.farmaka.be)

Topics presented to family physicians individually and in group from the year 2009 until 2018:

2009: Hulp bij rookstop
2010: Aanpak acute COPD exacerbatie; Aanpak van neuropathische pijn; Vitaminen en mineralen
2011: Insomnia; Hormonale anticonceptie I; Urine incontinentie
2012: Hormonale anticonceptie II; Majeure depressie; Osteoporose
2013: Aanpak van Artrose; Polyfarmacie I; Hypercholesterolemie in primaire preventie
2014: Preventie van thrombo-embolie bij VKF; Polyfarmacie II; Acute hoest bij kinderen
2015: Angststoornissen; Diabetes type II; Nierinsufficiëntie
2016: Inhalatiemedicatie bij COPD; CV preventie bij diabetes; Bariatrische heelkunde-opvolging
2017: Langdurig PPI gebruik; Probleemgedrag bij dementie; Antibiotica bij hoest?