The role of geriatric assessment prior to chemotherapy in elderly patients with cancer

Aaldrik Albertus Aaldriks

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Introduction

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Introduction

Background

The care of elderly patients is a challenging task. Clinicians have to make difficult decisions influencing and causing disability, which may have major impacts on the quality of life and functioning. It is therefore important for the clinician to use a multidimensional approach, which takes into account aspects of social, mental, and physical health when taking care of elderly patients. The process of aging is associated with loss of functional reserve of multiple organ systems, increased prevalence of chronic diseases and enhanced susceptibility to stress. This process occurs at different ages, resulting in a large variance in phenotype of elderly persons with a certain biological age. The concept of frailty as a state of increased vulnerability to adverse outcomes may be a more valuable entity [1].

One third up to one half of the patients with cancer older than 70 years of age can be qualified as frail [2]. The increasing prevalence of cancer in the elderly, together with the process of aging, results in a large heterogeneity within the group of elderly patients with cancer. Geriatric assessment (GA) may be a useful tool in the management and follow-up of elderly patients with cancer. A GA provides the combined objective and subjective information on comorbidity, nutrition, cognition, functional and psychosocial status [3, 4]. In elderly patients, cancer treatments should be adjusted to life expectancy and the expected increased risk of toxicity aiming for optimal efficacy, acceptable toxicity and the highest attainable quality of life.

There is a paucity of data in the literature concerning treatment strategies of patients with cancer older than 70 years of age. They are often not mentioned in guidelines or state of the art reviews and not in relation to existing comorbidities and limited life expectancy [5-7]. Due to age restrictions elderly patients are often excluded from trial participation and therefore, clinical recommendations are frequently not evidence based [8]. In general, findings from studies in patients with cancer cannot be extrapolated to elderly patients. For example, the prediction of recurrences of breast cancer by the Adjuvant! program proved to be unreliable in patients older than 65 years of age [9]. In other words, it is largely unclear what the predictors are for the outcome of treatment in the older patient group. Moreover, systematic data on toxicity of chemotherapy are limited in elderly patients [10], although some progress has been made in recent

years [11, 12]. It is of great importance to collect and analyze more data on the various forms of treatment of the elderly group of patients with cancer. Although a survival benefit of chemotherapy of the elderly with lymphoma has been demonstrated [13], this is less clear for elderly patients with a variety of solid tumors. It is likely that the use of standard chemotherapy in the elderly –developed and tested in patients with cancer of younger age groups– may contribute to substantial toxicity and consequently excess number of deaths. In this elderly group there is a need for better predictors to select those patients who are likely to benefit from standard chemotherapy [14, 15].

The above mentioned multidimensional approach of the elderly patient with cancer is at present often executed by performing a comprehensive geriatric assessment (CGA). A CGA should be helpful to determine a coördinated and integrated plan for treatment and long-term follow-up of the elderly patient with cancer [4]. Research on the different characteristics of the elderly patient with cancer and the predictive value of a CGA, both for the feasibility of treatment with chemotherapy and the overall survival, forms the basis of this thesis.

Epidemiology

The older population is an important and fast growing segment in the Western world [16, 17]. The incidence and mortality of patients with cancer increases with age. Worldwide, cancer accounted for 8.2 million deaths in 2012. The most commonly diagnosed malignancies were lung (i.e., 1.82 million), breast (i.e., 1.67 million), and colorectal tumors (i.e., 1.36 million) [18]. Projections show that these numbers will increase strongly in the following years rising to more than 13 million worldwide in 2030 [19].

In the Netherlands, the proportion of elderly persons among the total population aged 70 years and over will rise for men from 10% in 2015 to 19% in 2045 and for women from 13% in 2015 to 22% in 2045 (figure 1). This age influence will become stronger by the improved life expectancy of the elderly due to improvement of healthcare and living conditions.

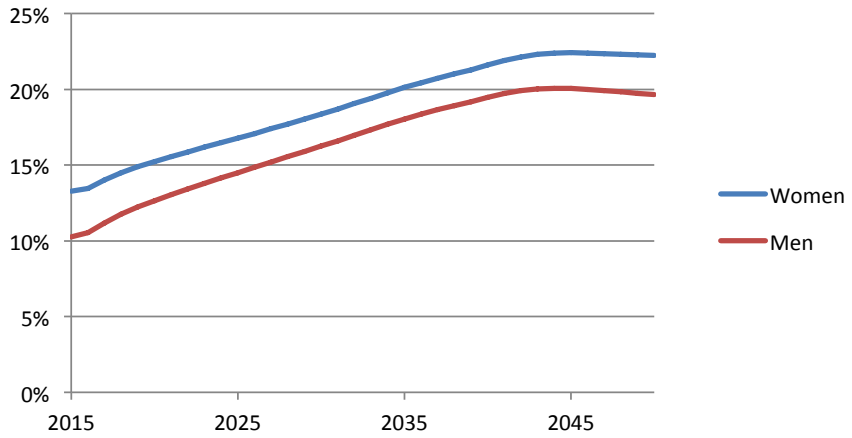
Advancing age is a high risk factor for cancer. Figure 2 shows the incidence of all cancers and specificly non-Hodgkin lymphoma, breast- and colon cancer in the Netherlands in 2013 [20]. In the Western world and also in the Netherlands, more than 2-3 times as many of the invasive cancers occurred in patients aged 70 years and older. More than forty percent of all new patients were between 60 and 75 years old of age, while thirty percent were 75 years or older [20, 21].

Results of the population-based EUROCARE-5 study of cancer survival in Europe show improving rates in cancer survival. Five-year survival rates were higher for patients diagnosed between 2005 and 2007 than for patients diagnosed between 1999 and 2001. The increase in relative survival was over 5% for patients with rectal cancer, prostate cancer, and non-Hodgkin lymphoma [22].

Projections for the year 2015 show increasing survival for lung-, colorectal-, prostate-, stomach cancer and leukemia in men, and for breast-, colorectal-, uterus-, stomach cancer and leukemia in women. However, the lung cancer death rate in women is rising sharply and expected to take over the breast cancer death rate soon. Pancreatic cancer shows a slowly rising death rate in both sexes between 2009 and 2015 [23].

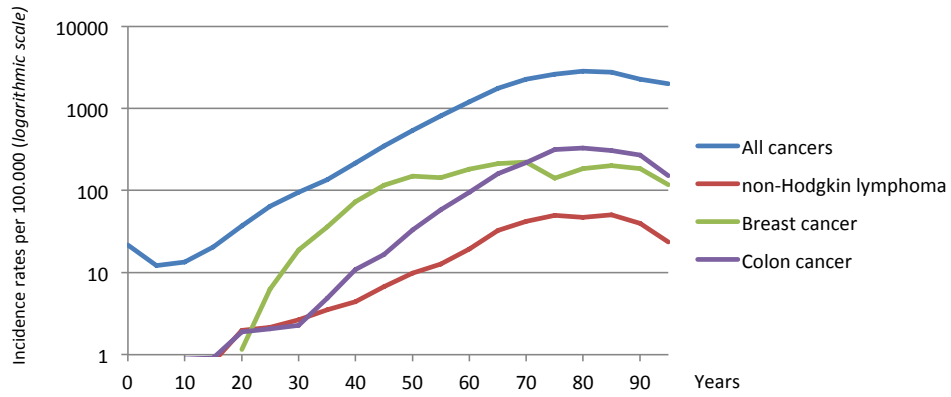
The rising incidence and prevalence of cancer with increasing age, in combination with increasing comorbidities, functional-, mental- en social shortcomings specific for older age, will complicate the care for elderly patients and will require special expertise in both oncology and geriatrics by physicians and other caregivers.

Figure 1. Projection of the expected proportions of men and women aged 70 years and over relative to the whole population until 2050.



CBS 2014

Figure 2. The incidence rate of cancer per 100.000 subjects per year (crude rate, CR) of all cancers, non-Hodgkin lymphoma, breast- and colon cancer in the Netherlands in 2013



The comprehensive geriatric assessment

CGA in the general population.

The health status of the elderly is compromised by unknown disabilities and unreported needs, as such reported in the literature for the first time in 1964 [24]. The need for geriatric assessments in a geriatric unit was recognized and described in 1987. In this way, a (C)GA has been developed as a tool to find deficits and define frailty in elderly patients in order to create a tailor-made treatment- and intervention plan [25]. A meta-analysis of trials with CGA showed a larger likelihood to live at home and improved survival through the application of CGA [26]. A controlled trial on the effects of intervention programs with geriatric expertise and management did not show advantage in survival, but demonstrated mental and physical improvement of functions [27]. Other studies demonstrated the usefulness of the application of frailty criteria to guide interventions in health care of the elderly patient [28-30].

Comprehensive geriatric assessment in patients with cancer and the application of screening tools.

Elderly with cancer form a heterogeneous group of patients. Chronological age as an indicator for health risks can differ significantly from biological or functional age. CGA can be used to systematically assess medical, functional, cognitive, social, nutritional and psychological parameters in older people with cancer [31-

38]. There is, however, much controversy about which elements should be part of the CGA and there is a great overlap of the different domains between the assessments and screening tools. To conduct a full CGA is time consuming and probably not necessary for every older patient. Therefore, a two-step approach by using a brief assessment or screening tool has been developed to identify patients who need a full CGA [39-41]. However, it must be realized that currently used screening tools lack adequate sensitivity, specificity and sufficient discriminative power to replace the full CGA [40, 41]. Recently, the International Society of Geriatric Oncology (SIOG) updated recommendations on geriatric assessment (GA) in elderly patients with cancer [4]. The panel recommended that the following domains should be evaluated in a GA: functional status, comorbidity, cognition, mental health status, fatigue, social status and support, nutrition, polypharmacy and presence of geriatric syndromes.

Functional status includes person's ability to perform tasks of everyday living, such as eating, bathing, dressing, toileting, transferring, using a telephone, doing laundry, and handling finances. This may be measured by the Activities of Daily Living (ADL) [42], the Instrumental Activities of Daily Living scale (IADL) [43] and the Eastern Cooperative Oncology Group Performance Status (ECOG PS) [44]. Mobility can be measured by the Get Up and Go test (GUG) [45] and muscle function by the Handgrip strength test (HGS) [46].

Mental status assessment includes cognition and mood and can be measured by the Mini-Mental State Examination (MMSE) [47], the Geriatric Depression Scale (GDS) [48], the Hospital Anxiety and Depression scale (HADS) [49] and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [50].

Physical status assessment includes the number of prescribed drugs and comorbidity; the latter may be measured by the Charlson comorbidity index (CCMI) [51] and The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [52]. The nutritional status can be measured by the Mini Nutritional Assessment (MNA) [53].

The different domains form a part of and are measured by screening tools. The most frequently used tools are the Vulnerable Elders Survey (VES-13) [2, 54], the abbreviated CGA [55], the Flemish version of the Triage Risk Screening Tool (fTRST) [56, 57], the Groningen Frailty Indicator (GFI) [58] and the Geriatric 8 (G8) [57, 59-61].

Different assessments and screening tools

Assessment tools	Geriatric domain	A/S	Scale	Interpretation
ADL [42]	Functional status	A	-	Measures limitations in self care activities
IADL [43]	Functional status	A	-	Measures ability to complete activities required to maintain independence in the community
ECOG PS [44]	Functional status	A	0-5	Higher scores indicate poorer performance (i.e., functional impairment)
GUG [45]	Functional status	A	1-5	Higher scores indicate a higher level of abnormalities of gait, balance or difficulty by stand up from a chair, walk a short distance, turn around, return, and sit down again.
HGS [46]	Functional status	A	Grip strength in kg	Measurement of muscle function
MMSE [47]	Cognitive function	A	0-30	≤ 23 indicates cognitive dysfunction
IQCODE [50]	Cognitive function	A	1-5	≥ 3.31 indicates cognitive decline over past ten years
GDS [48]	Mental status	A	0-30	Measurement of severity of depressive symptoms
HADS [49]	Mental status	A	0-21 for anxiety or depression	≥8 indicates anxiety or depression
CCMI [51]	Comorbidity	A	-	Classification of comorbidity
CIRS-G [52]	Comorbidity	A	0-4 per item	Evaluates cumulative comorbidity in 14 items
MNA [53]	Nutritional status	A	0-14 (Screening) 0-16 (Assessment)	<17 pts indicates malnourishment 17-23.5 pts indicates a risk of malnutrition
VES-13 [54]	Frailty	S	0-13	A score ≥ 3 indicates vulnerability
aCGA [55]	Frailty	S	-	≥ 1 among a total of 15 items of GA (3 of ADL, 4 of IADL, 4 of MMSE and 4 items of GDS) indicates increased geriatric risk
fTRST [56]	Frailty	S	1-6	Higher score indicates an increased geriatric risk profile
GFI [58]	Frailty	S	0-15	≥ 4 indicates frailty
Geriatric 8 (G8) [61]	Frailty	S	0-17	≤ 14 indicates an increased geriatric risk

Abbreviations: A/S, Assessment/Screening

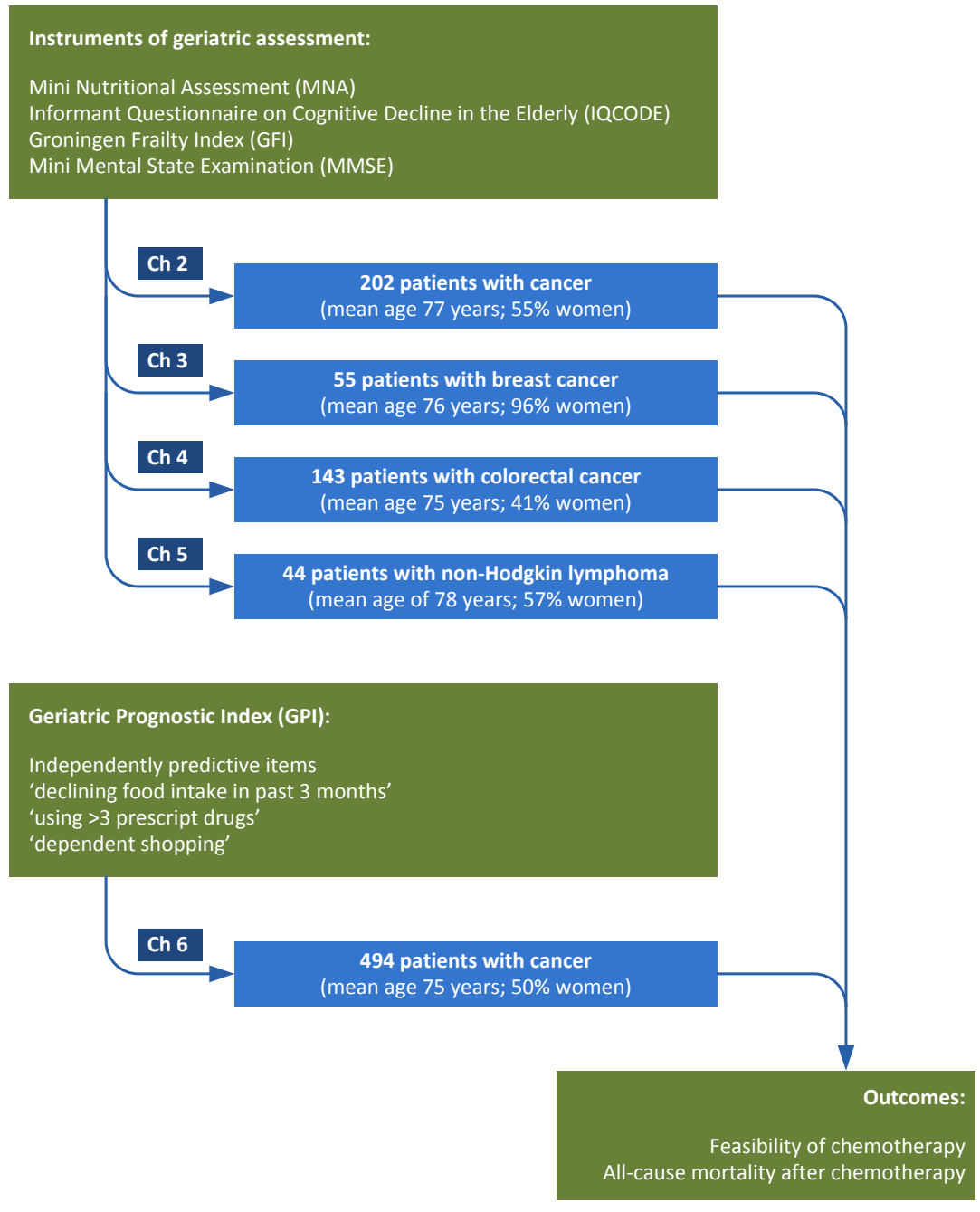
Aim and outline of the thesis

Comprehensive Geriatric Assessment in a broad sense is time consuming and expensive. Therefore, it was decided to concentrate on a limited dataset that comprised items of nutrition, comorbidity, functional status, psychosocial status, cognition, and laboratory values. The following questionnaires and tests were considered appropriate to obtain a practical GA: MNA, GFI, IQCODE, MMSE, and laboratory values of albumin, creatinine, lactate dehydrogenase and hemoglobin. If shortcomings occurred with the questionnaires a geriatrician and/or dietician could be consulted.

The main questions we tried to answer were firstly to assess the predictive value prior to the start of chemotherapy of the chosen GA with respect to the probability to complete the planned chemotherapy and overall survival and secondly to analyze and determine wich elements of the chosen GA were independently predictive to complete chemotherapy and which elements predicted early mortality.

A first analysis of the role of GA in 202 patients with a variety of cancers, all of them treated in the Reinier de Graaf Hospital in Delft, is described in **Chapter 2**. Tumor-specific analyses are presented in **Chapters 3 through 5**. **Chapter 3** provides details on 55 patients with breast cancer. Analyses have been performed of the results of GA and laboratory tests for albumin, hemoglobin, creatinine and lactate dehydrogenase in relation to the outcome of palliative therapy with chemotherapy. The analysis of GA on 143 patients with colorectal cancer is described in **Chapter 4**, separately for patients treated with palliative or adjuvant intent. The additional value of GA and laboratory tests, apart from and in comparison with the age-adjusted International Prognostic Index, on the outcome of 44 patients with aggressive non-Hodgkin lymphoma treated with combination chemo-immunotherapy (R-CHOP), is described in **Chapter 5**. Finally, a more detailed analysis was performed to elucidate which elements of GA have the most impact on the outcome of the whole cohort of 494 patients collected in the region of the Comprehensive Cancer Center West (Reinier de Graaf hospital-Delft, HAGA hospital-The Hague, Groene Hart hospital-Gouda and Leiden University Medical Center-Leiden) and selected by the treating clinician who estimated that chemotherapy was feasible on clinical grounds. The results of this analysis are described in **Chapter 6**. Based on these results we constructed a Geriatric Prognostic Index as risk profile for mortality prior to chemotherapy in the elderly. In **Chapter 7** our findings are summarized, discussed in a broader context and put in perspective.

Overview of the studies presented in this thesis



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Chapter

Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy

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Crit Rev Oncol Hematol, 2011. 79(2): p. 205-12

Abstract

Introduction. Comprehensive geriatric assessment (CGA) gives useful information on the functional status of older cancer patients. However, its meaning for a proper selection of elderly patients before chemotherapy and, even more important, the influence of chemotherapy on the outcome of geriatric assessment is unknown.

Methods. 202 cancer patients, for whom an indication for chemotherapy was made by the medical oncologist, underwent a GA before start of chemotherapy by Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Index (GFI) and Mini Mental State Examination (MMSE). After completion of a minimum of four cycles of chemotherapy or at six months after the start of chemotherapy the GFI and MMSE assessment was repeated.

Results. Frailty was shown in 10% of patients by means of MMSE, 32% by MNA, 37% by GFI and in 15% by IQ-CODE. Compared to patients who received 4 or more cycles of chemotherapy, the MNA and MMSE scores were significantly lower for patients treated with less than 4 cycles (p=0.001 and p=0.04 respectively). The mortality rate after start of chemotherapy was increased for patients with low MNA and high GFI scores with hazard ratios of 2.19 (95% confidence interval [CI]: 1.42-3.39; p<0.001) and 1.80 (95% CI: 1.17-2.78; p=0.007), respectively. After adjusting for sex, age, purpose of chemotherapy and type of malignancy these hazard ratios remained significant (p<0.001 and p= 0.004), respectively. Finally, for the 51 patients who underwent repeated post-chemotherapy evaluation by GFI and MMSE, a statistically significant deterioration for the MMSE (p=0.041) was found but not for the GFI.

Conclusions. Both inferior MNA and MMSE scores increased the probability not to complete chemotherapy. Also, an inferior score for MNA and GFI showed an increased mortality risk after the start of chemotherapy. The mean MMSE score worsened significantly during chemotherapy.

Introduction

The incidence and mortality of patients with cancer increases with age. Sixty per-

cent of all cancers and 70% of cancer mortality is found above 65 years of age [1]. As a result of the ageing population in western countries the demand for care of older people with cancer will strongly increase in the coming decades, also due to comorbidity, diminished organ functions, impairment of daily vital functions and development of cognitive dysfunctions. It seems to be logical to use biologic age as an indicator for health risks in the elderly but it is not a very sensitive and specific risk marker. The concept of frailty may be more valuable. Comprehensive geriatric assessment (CGA) provides information on the functional status of older cancer patients [2, 3, 4], consisting of objective information on comorbidity, functional status, nutritional status and psychosocial status. CGA can therefore disclose the existence of geriatric syndromes, which may complicate cancer treatment and vice versa may deteriorate during the course of treatment.

Several cross sectional studies have demonstrated associations between CGA and toxicity, morbidity and mortality during cancer treatment in older patients [5, 6, 7, 8, 9, 10, 11]. The effects of chemotherapy on cognitive function have been extensively studied prospectively in women with breast cancer [12, 13]. In other types of cancer, geriatric assessment has been studied more scarcely [14, 15]. Deterioration of cognition during chemotherapy has been hypothesized to be due to either direct chemical toxicity affecting neuroneogenesis, or by indirect effect through an increased (auto)inflammatory reaction [16, 17].

In the present study, we describe a basic GA of 202 cancer patients aged 70 years and above, with the aim to assess its prognostic value for treatment with chemotherapy, both with respect to the probability to complete chemotherapy and with respect to survival probabilities. Furthermore, among 51 patients the assessment was repeated after at least four courses of chemotherapy or at six months after start of treatment with the aim to assess the impact of chemotherapy on GA.

Patients and Methods

Patients

Between May 2004 and September 2007 all patients with cancer older than 70 years of age (n=202) for whom chemotherapy was prescribed by their medical oncologist in the hospital of the Reinier de Graaf Groep (Delft, the Netherlands), were prospectively assessed before chemotherapy using the following tests: Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State

Examination (MMSE). The tests were performed by trained nurses. All patients who underwent Geriatric Assessment (GA) started with chemotherapy. The test evaluation did not induce any delay in chemotherapy that the patients received. Patients completing at least four cycles of chemotherapy were again assessed by GFI and MMSE at the end of chemotherapy or six months after the start of chemotherapy. If indicated by the test results, a dietician and/or a geriatrician were consulted.

The MNA is a stepwise test and is comprised of two sections. First, there is the screening section (6 items). When the score is less than 12 points, indicating the possibility of malnutrition, the assessment section (12 items) is filled in. With the assessment section, a score of 24-30 points is indicative of being well-nourished, 17-23.5 points for being at risk of malnutrition, and a score less than 17 points for being malnourished. The test makes it possible to identify patients at risk for malnutrition, before severe changes in weight or albumin levels occur [18, 19]. This scoring system for malnutrition has a sensitivity of 96%, specificity of 98% and positive predictive value of 97% [20].

The IQCODE is a well validated instrument that screens for cognitive decline by interviewing family members or care givers [21]. The 16 items are rated on 5-point Likert scales, ranging from much improved to much worsened, and the average score is used in the analyses that ranges from 1 to 5. We used the short Dutch translation IQCODE-N [22]. In clinical settings, a cut-off score of 3.31 is a reasonably balance between sensitivity and specificity on the outcome of cognitive decline [23, 24]. Patients with a score of 3.30 or higher were examined by a geriatrician.

The risk for individual mortality, which can be seen as the ultimate outcome of age and frailty, can be predicted better by frailty than by chronologic age [25, 26]. The GFI has been developed as a simple screening instrument for frailty and a case finder for elderly patients who would benefit from integrated (geriatric) care [27, 28]. The GFI screens on physical, cognitive, social and emotional items. The maximum score is 15 points (see appendix). Patients scoring 4 or more points were considered moderately frail and were examined by a geriatrician.

The MMSE has been tested extensively and is considered to be a standard test for cognitive function. Sensitivity of the MMSE for cognitive dysfunction is 88%, the specificity is 93% [29, 30, 31, 32]. Patients scoring 24 points or less were seen by a geriatrician.

Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables as means ± standard deviations (SD), with their range. Chi-square tests were used for the analysis of categorical variables. Survival probabilities were estimated using Kaplan Meier curves and the log-rank test was used to test for difference in survival between categories of baseline CGA data. Cox proportional hazard regression was used to calculate hazard ratios (for MNA 2 categories were used: well nourished and risk of malnutrition / malnourished). Hazard ratios were adjusted for sex, age, purpose of chemotherapy (using 3 categories: adjuvant/curative; palliative and unknown) and type of malignancy (using 5 categories: digestive tract; breast cancer; ovarian cancer; hematological malignancies; other or missing). Changes in GA data over time were analyzed using the paired sample t-test. A p value less than 0.05 was considered significant. SPSS 17.0 for Windows® (SPSS inc. Chicago, IL.) was used for statistical analyses.

Results

Table 1 shows the baseline characteristics of the 202 included patients: 90 men (45%) and 112 women (55%). The mean age was 77.2 years (range 71—92). Fifty percent of patients received at least four cycles of chemotherapy. The duration of the follow-up, defined as the difference between the date of the first GA and the date of the last follow-up, showed a median of nine months (range 1-33).

Table 2 shows the results of geriatric assessment at baseline. With MNA, 65% of the patients were well nourished, while 30% of the patients were at risk for malnutrition and 3% were malnourished. A MMSE score of 24 points or lower, meaning a serious cognitive reduction, was seen in 10% of the patients. IQCODE showed an average score of 3.10 points. A GFI score of 4 or more points, meaning increased frailty, was found in 37% of the patients.

Table 3 depicts the results comparing less than 4 versus 4 or more chemotherapy cycles. With MNA and MMSE , there was a significant difference between the number of patients who underwent less than 4 cycles compared to patients who underwent 4 cycles or more. The mean reasons for not finishing the 4 cycles of chemotherapy were cancer progression, toxicity and insufficient benefit.

Figure 1 shows the Kaplan-Meier curves of overall survival according to predefined cut-off scores for the MNA, IQCODE, GFI and MMSE. Patients scoring lower than 24 points for MNA and 4 or more points for GFI showed significantly

worse survival ($p < 0.001$ and $p = 0.007$, respectively).

Table 4 gives the hazard ratios for mortality, indicating that a worse MNA score was associated with an increased mortality risk with a hazard ratio (HR) of 2.19 (95% confidence interval [CI]: 1.42-3.39; p<0.001) and a worse GFI score was associated with an increased risk with a HR of 1.80 (95% CI: 1.17-2.78; p=0.007). The sex- and age-adjusted hazard ratios for mortality were largely unaffected (model 1). When we additionally adjusted for the purpose of chemotherapy and type of malignancy, the hazard ratios for mortality with worse MNA and GFI scores were 2.54 (95% CI: 1.55-4.15; p<0.001) and 2.00 (95% CI: 1.26-3.17; p=0.004), respectively (model 2).

For the 51 patients with complete data for MMSE and GFI scores at baseline and after four or more cycles of chemotherapy, the MMSE showed a statistically significant deterioration after the chemotherapy (p=0.04; see Table 5).

Discussion

In this study, a basic GA was obtained of patients with cancer above the age of 70 years who were treated with chemotherapy. After at least four cycles of chemotherapy or at six months after the start of treatment, the GA was partly repeated with GFI and MMSE. The aim of this study was to develop tools for medical oncologists in their advice concerning treatment of elderly patients with chemotherapy. Malnutrition and cognition appeared independently related to the probability not to complete chemotherapy, while malnutrition and frailty (defined by GFI of 4 or more points) were associated with increased mortality. In addition, MMSE deteriorated slightly during the course of chemotherapy.

Traditionally, the Karnofsky Performance Scale or the World Health Organisation scores are used to determine the performance status of cancer patients. However, geriatricians have developed other scales to assess the functional status of older patients, for instance with ADL, IADL and the Charlson Comorbidity Index. We pragmatically selected the GFI, IQCODE, MMSE and MNA tests for performing a GA, striving for a maximum of 45 minutes to complete the interview. For the second assessment we repeated the GFI and MMSE. The IQCODE could not be used in the second assessment, because this instrument gives information on cognitive function over the past ten years. With the MMSE it is possible to measure deterioration after a short period. The used batch of tests should give a broad spectrum of data for coverage of GA with little overlap between the tests.

Approaches that are often used to assess functional status of older cancer patients are the Vulnerable Elders Survey (VES-13) [33], the abbreviated CGA (aCGA) [34], the clinical criteria by Fried et al. [35], the Edmonton Frailty scale [36] and the Groningen Frailty Indicator [37]. Puts et al. [38] demonstrated the importance of psychological markers in the concept of frailty. They showed that frailty was an independent risk factor for a decline in physical functioning, institutionalization and mortality. To measure frailty, the GFI is a short and easy practical instrument, and it seems a reasonable and manageable alternative compared to chronological age as a selection criterion for interventions [27]. Slaets et al. investigated the predictive values of chronologic age and frailty and the predictive power of the GFI in clinical studies comparing the GFI with the Quality of life Questionnaire (QLQ) C-30, the Charlson comorbidity index (CCMI) and the 10- to 30-day morbidity index. The GFI could predict most of the QLQ C-30 scales significantly. They found clinical relevant and significant differences between the frail and the nonfrail groups in mean scores on physical-, role-, and emotional function and fatigue [37]. The present analysis also showed a relation between GFI and survival, which remained significant after multivariable adjustment for sex, age, purpose of chemotherapy and type of malignancy.

The results of the MNA were almost identical with the findings of Toliusiene et al, who found that 50% of older men with prostate cancer were at risk for malnutrition [18]. Patients at risk were referred to a dietician because weight loss, low body mass index (BMI) and poor nutritional status are associated with increased risk of mortality, and more depressive symptoms [39, 40, 41, 42]. In the present study patients with normal MNA scores had a higher probability to complete pre-planned chemotherapy and a better survival, also after adjusting for the confounders mentioned earlier for GFI.

With MMSE, 11% of the patients showed serious cognitive impairment. Other studies found cognitive impairment in 25% to 38% of patients [3, 43, 44, 45, 46]. The present study showed, that a worse score for MMSE was associated with a larger probability of not completing 4 or more cycles of chemotherapy. Furthermore, the MMSE score at the second assessment in a limited number of patients was somewhat worsened compared to the assessment at baseline. Although this difference was significant, it did not appear to be a clinically meaningful difference. Comparison with other studies is difficult because there is no consistency in the definitions of cognitive dysfunction used in the literature [47, 48]. Hurria et al. found that fifty percent of the patients of 65 years or older, having received chemotherapy, reported cognitive decline 6 months after chemotherapy, especially concerning declined memory and the ability to learn new in-

formation [14]. The duration of cognitive impairment after chemotherapy is not clear. Some studies reported cognitive dysfunction in patients 2 to 10 years post chemotherapy [49, 50] but most patients in these studies were younger than 65 years. For patients over 70 years of age severity of cognitive impairment is probably more important than its duration. Fried et al. reported that if the outcome for a certain treatment was cure at the cost of severe functional- or cognitive impairment, 74.4 % and 88.8 % of serious ill patients, respectively, would not choose this treatment [44].

The multivariate analysis of the present study stipulates the importance of screening with MNA and GFI, as poor test results predicted for an increased mortality rate. The MMSE might contribute to the prediction whether chemotherapy can be completed, which was more powerful shown for the MNA. The IQCODE, which gives information of cognitive function over the past decade, did not show any predictive power in the present GA. Both MNA and GFI seem to be promising predictive screening tests for outcome when chemotherapy is considered in elderly patients with cancer.

A limitation of this study is the heterogeneity of patients with a wide diversity of types of cancer, different stages of cancer and different treatments. Furthermore, it could be that there are unaccounted confounders for example alcohol consumption, smoking and socio-economic status. Comparison with other studies is difficult because of the paucity of data in the literature. Further research is needed for clarification of the tools available for geriatric assessment. In this way, the care for older patients with cancer, treated with chemotherapy can result in a more tailor-made approach, aiming for optimal balance between efficacy and toxicity of treatment.

Table 1
Characteristics of patients (n = 202)

		years	SD	
Age	Mean	77	4.22	
	Minimum	71		
	Maximum	92		
			n	**%**
Gender	Male		90	45
	Female		112	55
Number of chemotherapy cycles	< 4		74	37
	≥ 4		118	58
	unknown		10	5
Type of malignancy	Upper digestive tract		19	9
	Colorectal cancer		60	30
	Breast cancer		34	17
	Ovarian cancer		20	10
	Hematological malignancies		36	18
	Other types*		28	14
	Unknown		5	2
Purpose of chemotherapy	Adjuvant/curative		80	40
	Palliative		111	55
	Unknown		7	3
	Missing		4	2

*The category other types of malignancy consisted mainly of prostate cancer (n=12), lung cancer (n=7) and urothelial cell cancer (n=5)

Table 2
Results of the geriatric assessments at baseline (n=202)

Test	Score	n	%
MNA	well nourished (>12 pts* and 24-30 pts[§])	131	65
	risk of malnutrition (17-23.5 pts[§])	60	30
	malnourished assessment (less than 17 pts[§])	5	3
	unknown	6	2
MMSE	> 24 pts	178	88
	≤ 24 pts	21	10
	unknown	3	2
IQCODE	> 3.30 pts	30	15
	≤ 3.30 pts	163	81
	Unknown	9	4
GFI	<4 pts	127	63
	≥4 pts	75	37

*MNA screening section
[§] MNA assessment section

Table 3.
Baseline test results in 192 subjects, comparing patients who received less than four cycles to patients who received four or more cycles of chemotherapy

		Number of cycles				
		<4 (n=74)		**≥4** (n=118)		
Test	**Score**	**n**	**%**	**n**	**%**	***p*- value**
MNA:	well nourished	37	51	86	75	0.001
	risk of malnutrition/ malnourished	35	49	29	25	
	missings	2		3		
IQCODE:	≥ 3.3	14	20	15	13	0.20
	< 3.3	55	80	99	87	
	missings	5		4		
GFI:	< 4	42	57	79	67	0.15
	≥ 4	32	43	39	33	
MMSE:	> 24	64	89	113	97	0.04
	≤ 24	8	11	4	3	
	missings	2		1		

For 10 patients it was unknown whether they finished 4 cycles because they just started and were ongoing with chemotherapy.
Well nourished meaning >12 pts in MNA screening section or 24-30 pts in the MNA assessment section; risk of malnutrition /malnourished meaning less than 24 pts in the MNA assessment section.
P-values are obtained from Pearson chi-square tests (missings were not included in chi-square tests).

Table 4.
Hazard ratios (95% confidence intervals) for mortality in 202 cancer patients

Test	Score	Crude	Model 1	Model 2
MNA:	well nourished	1.00	1.00	1.00
	risk of malnutrition / malnourished	2.19 (1.42-3.39)	2.34 (1.49-3.66)	2.54 (1.55-4.15)
		p<0.001	*p*<0.001	*p*<0.001
IQCODE:	≥ 3.3	1.00	1.00	1.00
	< 3.3	0.84 (0.46-1.53)	0.86 (0.47-1.57)	0.93 (0.49-1.73)
		p=0.57	*p*=0.63	*p*=0.81
GFI:	< 4	1.00	1.00	1.00
	≥ 4	1.80 (1.17-2.78)	1.89 (1.22-2.94)	2.00 (1.26-3.17)
		p=0.007	*p*=0.005	*p*=0.004
MMSE:	> 24	1.00	1.00	1.00
	≤ 24	1.05 (0.51-2.18)	0.99 (0.48-2.07)	0.92 (0.44-1.93)
		p=0.89	*p*=0.87	*p*=0.82

Baseline MNA, IQCODE, GFI and MMSE data are dichotomized.
Well nourished meaning >12 pts in MNA screening section or 24-30 pts in the MNA assessment section; risk of malnutrition / malnourished meaning less than 24 pts in the MNA assessment section.
Model 1: adjusted for sex and age;
Model 2: additionally adjusted for purpose of chemotherapy and type of malignancy.

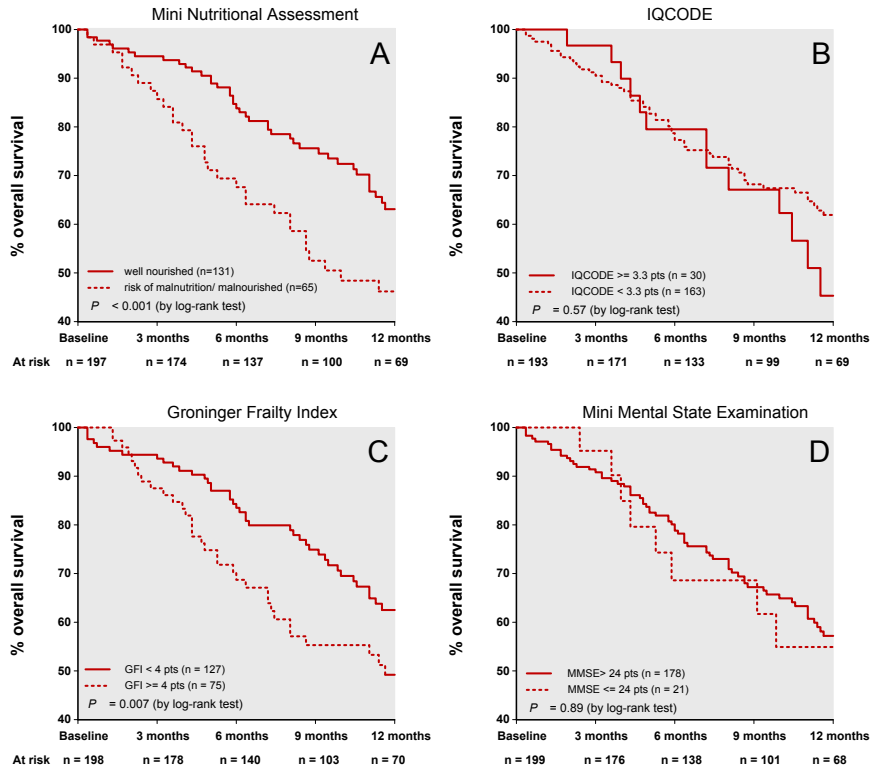
Table 5
Differences between baseline- and second assessment (after at least 4 cycli) of MMSE and GFI (n=51)

	At baseline			2e assessment					
	Median	P25	P75	Median	P25	P75	Mean change	SE	*p*-value*
MMSE	30	28	30	29	27	30	-0.86	0.41	0.041
GFI	2	1	3	2	1	5	0.24	0.33	0.476

*t-test for paired samples

Figure 1

Kaplan-Meier curves of overall survival for different categories of MNA **[A]**, IQCODE **[B]**, GFI **[C]** and MMSE **[D]**.



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Chapter

Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy

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Abstract

Introduction: The prognostic value of geriatric assessment in older patients with breast cancer treated with chemotherapy is largely unknown.

Methods: Fifty-five patients with advanced breast cancer aged 70 years or older were assessed by Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State Examination (MMSE). Levels of albumin, hemoglobin, creatinine and lactate dehydrogenase were measured. Patients completing at least four cycles of chemotherapy were reassessed by GFI and MMSE and mortality was evaluated using Cox regression analysis.

Results: The mean age was 76 year (SD 4.8). Inferior MNA and GFI scores were associated with increased hazard ratios for mortality: 3.05 (95% confidence interval [CI]: 1.44-6.45; p=0.004) and 3.40 (95% CI: 1.62-7.10; p=0.001), respectively. Physical aspects of frailty worsened during the course of chemotherapy. Laboratory values were not associated with assessment scores nor were they predictive for mortality.

Conclusions: Malnutrition and frailty, rather than cognitive impairment and laboratory values, were associated with an increased mortality risk in these elderly breast cancer patients with advanced breast cancer.

Introduction

In developed countries, breast cancer accounts for nearly one third of all new cases of cancer in women [1]. Older age is an important risk factor for breast cancer. More than 40% of breast cancer diagnoses and nearly 60% of breast cancer deaths occur in women aged 65 years or older [1]. Because older cancer patients are hardly represented in randomized clinical trials of chemotherapy, the results of these studies cannot predict for outcomes and toxicities of treatment in this population. Therefore, population based studies should address outcome- and treatment modifying factors in older patients to provide future methods to distinguish older patients who are likely to benefit from treatment from those who are not.

A comprehensive geriatric assessment (CGA) can be used to systematically

assess health and functional status in older people [2-4]. A CGA may disclose the existence of geriatric syndromes, such as frailty and cognitive dysfunction not previously recognized by the treating physician. Several studies use the concept of frailty as a hallmark of geriatric syndromes, in accordance with Balducci's algorithm for the management of elderly cancer patients [5-7]. It has previously been shown that psycho-social deficits and comorbidity are associated with poor treatment tolerance and mortality, independent of age and stage of disease [8]. Also, cognition deficits and frailty predict for toxicity and early treatment withdrawal in patients treated with chemotherapy [9, 10]. Furthermore, malnutrition has been identified as a predictor of increased mortality [11, 12].

The impact of cognitive dysfunction on tolerance of chemotherapy and mortality is largely unknown. The main focus of research on cancer treatment and its cognitive side effects have concentrated on adjuvant treatment in breast cancer patients [13]. A recently published meta-analysis showed that cognitive deficits after chemotherapy in breast cancer patients are small in magnitude and limited to the domains of verbal and visiospatial ability [14] and in an accompanying editorial the suggestion was made that the effect of chemotherapy on cognition is underestimated and that more research is needed [15].

Anemia, hypoalbuminemia and renal dysfunction were identified by others as risk factors for frailty and chemotherapy toxicity [16, 17]. For example, anemia is a powerful prognostic factor for the development of frailty related problems such as muscle weakness, reduced performance, falls, and mortality [18-20]. It is interesting to know if laboratory measurements are more predictive for the number of chemotherapy cycles and mortality than GA.

We performed a GA that provided combined information on several domains of health and function in older patients: cognition, nutritional status, comorbidity, functional-, and psychosocial status. For practical reasons we decided to use a limited set of questionnaires and tests instead of a complete CGA. We considered this as an effective method to capture a broad spectrum of data and at the same time minimizing resources and time spent by health care providers. Such a cost-effective choice might broaden the reach of such assessments [10, 21]. Furthermore, laboratory values of serum albumin, creatinine, lactate dehydrogenase (LDH) and hemoglobin were measured

With this variant of an abbreviated GA and selected laboratory tests we studied outcome modifying factors in older breast cancer patients treated with chemotherapy. In patients who completed at least four cycles of chemotherapy GFI and MMSE were repeated in order to examine the effect of chemotherapy on these parameters of frailty and cognition.

Patients and methods

Study design

This clinical cohort study involved patients aged 70 years or older (n=55) with advanced breast cancer for whom chemotherapy was prescribed by their medical oncologist. Patients were recruited between May 2004 and February 2010 from the outpatient oncology practices of three general and one university hospital. Participating hospitals were situated in the western part of the Netherlands: Reinier de Graaf Groep in Delft, Groene Hart Hospital in Gouda, HAGA hospital in The Hague and the Leiden University Medical Center. Participation of these hospitals started at different time points because of time needed for training of dedicated nurses in the technique of GA.

During the study period all patients aged 70 years or older for whom a treatment plan was made that involved chemotherapy were prospectively assessed by trained nurse practitioners using the following tests: Mini Nutritional Assessment (MNA) [22], Groningen Frailty Indicator (GFI) [23], Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [24], and Mini Mental State Examination (MMSE) [25]. If possible, the IQCODE was filled in by family or caregivers. These validated tests were selected to assess in the elderly patients the important domains of mobility, physical fitness, polypharmacy, psychosocial resources, cognition, weight loss and nutrition, striving for a minimum of overlap between the domains. Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) were not separately assessed as GFI is considered to screen for dependency. Given the fact that many older patients have a time limited span of attention, we considered 45 minutes the timelimit per interview. For patients completing at least four cycles of chemotherapy, assessment by GFI and MMSE was repeated at the end of chemotherapy or at six months after start of chemotherapy

Patients received treatment according to standard of care, therefore, ethical approval and consent were not considered necessary to be obtained. Patients with brain metastases were excluded.

For this paper, we selected all women with advanced breast cancer from a larger cohort of patients treated with chemotherapy for a variety of cancers. A part of this cohort has been previously described [26]. A flow diagram of the study is given in figure 1.

Assessment

The used tests have been described in detail [26]. In brief, the MNA makes it possible to identify patients at risk for malnutrition, before severe changes in weight or albumin levels occur [27, 28]. A score of 24-30 points is indicative of being well-nourished, 17-23.5 points for being at risk of malnutrition, and a score of less than 17 points indicates malnutrition. The GFI consists of items on physical, cognitive, social and emotional functioning with a maximum score of 15 points (see appendix). Patients with 4 or more points are considered frail. For screening on cognition we used both the IQCODE and MMSE. The IQCODE screens for cognitive decline over the last 10 years by interviewing family members or care givers, while with MMSE it is possible to measure deterioration after a short period. For IQCODE we used the short Dutch translation IQCODE-N [29]. In clinical settings, a cut-off score of 3.31 reasonably balances between sensitivity and specificity on the outcome of cognitive decline, higher scores indicating poorer cognition. The MMSE has been tested extensively and is considered to be a standard test for current cognitive function. The cut-off point for poorer cognition is 24 points or less [25].

Data collection

Laboratory values, comorbidity, medication history, WHO-performance and reasons for not finishing the planned cycles of chemotherapy were recorded from the medical files by a trained registrar. Laboratory values of serum albumin, creatinine, LDH and haemoglobin were registered. Comorbidity was registered by using Charlson's comorbidity scoring system [30]. Performance status was registered by the scoring system WHO or Karnofsky (KI) [31, 32].

Treatment period and follow-up

The treatment period was left to the discretion of the medical oncologist. Receiving less than four cycles of chemotherapy was considered early treatment withdrawal. The follow-up was defined as the time between the date of the first GA and the date of the last follow-up. The follow-up period varied because of different time points of entry in the study and ended after last control in the oncology ward. Vital status and last follow-up date were recorded from the patient's medical record. Vital status was crosschecked with the municipal registry on June 2010.

Patients completing at least four cycles of chemotherapy were assessed once more by GFI and MMSE at the end of chemotherapy or at six months after the start of chemotherapy, and this succeeded in 21 of 39 patients.

Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables as means ± standard deviations (SD), with their range, or as medians with their interquartile range in case of skewed distributions. Chi-square tests were used to compare categorical variables between subgroups. The correlation between GA measures was calculated using the non-parametric Spearman's correlation coefficient and this was also used for correlation between GA and WHO performance status. Univariate and multivariate linear regression analysis was used to study the associations between GA test results and laboratory measures, both crude and after adjustment for age and comorbidity. Standardized regression coefficients, which are in the case of univariate regression equal to the Pearson's correlation coefficients are reported. Survival probabilities were estimated using Kaplan Meier curves and the log-rank test was used to test for difference in survival rates among subgroups.

We also dichotomized MNA (cutoff <24 points in the MNA assessment section indicated risk of malnutrition/malnourished); GFI (cutoff ≥4 points indicated frailty); IQCODE (cutoff ≥3.3 points indicated cognitive decline); MMSE (cutoff ≤24 points indicated cognitive dysfunction); albumin (cutoff < 35g/L); haemoglobin (cutoff < 7.5mmol/L); creatinine (cutoff ≥ 100 μmol/L) and LDH (cutoff ≥ 250 U/L). Logistic regression analysis was used to analyze the associations between dichotomized variables and receiving more or less than 4 chemotherapy cycles with adjustment for confounding variables (age, comorbidity and WHO performance status).

Cox proportional hazard regression was used to calculate mortality risks according to categories of the MNA, GFI, IQCODE and MMSE scores. Hazard ratios (HRs) were adjusted for age and comorbidities (0, 1, 2 or more). In sensitivity analyses, continuous values for the geriatric assessment and laboratory test values were used. Changes in GA data over time (before chemotherapy and after at least 4 cycles) were analyzed using the paired sample t-test. A p value less than 0.05 was considered significant. SPSS 17.0 for Windows® (SPSS inc. Chicago, IL.) was used for statistical analyses.

Results

Table1 shows the baseline characteristics of the 55 included patients with advanced breast cancer, two of whom were men (4%). Two patients, who had been planned for chemotherapy and hence were assessed with basic GA, after all did not start chemotherapy. One declined and one unexpectedly died. The mean age was 76 years (range70–88). Twenty percent of patients was 80 years or older. Median follow-up was 11 months (range 0–57). No comorbidities were documented in 33% of the patients and 70% of the patients had a WHO-performance in categories 0 or 1. Thirteen percent of the patients did not use any (co-)medication, while 38% used one to three co-medications and 45% four or more co-medications.

GA test results and laboratory outcomes were not significantly correlated, neither after adjustment for age and comorbidity. The MNA and GFI were inversely correlated (r = –0.43; P<0.001), and the IQCODE and MMSE were also inversely correlated (r = –0.36; P=0.01). No other significant correlations between the GA test results were found. Using Spearman 's correlation coefficients, more disability according to WHO performance status or KI was associated with malnourishment on the MNA and frailty as defined by a score of 4 or more with the GFI (r = –0.28; P=0.044 and r = 0.38; P=0.004, respectively).

Table 3 shows the results of the geriatric assessment and laboratory results and the relation between these parameters and either early treatment withdrawal or treatment with four or more cycles of chemotherapy. Thirty-nine patients completed at least 4 cycles of chemotherapy. The main reasons for early withdrawal were cancer progression, insufficient therapeutic benefit and toxicity. Patients who experienced early withdrawal could not be distinguished from patients who received at least 4 cycles of chemotherapy by either GA or laboratory parameters, neither after adjustment for age, comorbidity and performance status. When geriatric assessment and laboratory test values were analysed as continuous variables, the results did not alter (data not shown).

The MNA indicated that 23 (42%) patients were at risk for malnutrition or were malnourished. Frailty as measured by the GFI, was present in 28 (51%) patients. The IQCODE was indicative of cognitive decline in 10 (18%) patients. Five (9%) patients had a MMSE score of 24 points or lower, indicating serious cognitive dysfunction. The majority of patients had normal values for albumin (67%) and creatinine (87%), but abnormal values for haemoglobin (decreased in 78% of patients) and LDH (elevated in 84% of patients).

Table 4 shows mortality according to geriatric assessment and laboratory test results. After a mean follow-up of 16.0 months (SD 13.7 months) 41 of 55 (75%) patients had died. Poor MNA and GFI scores were associated with increased mortality, with hazard ratios of 3.05 (95% CI: 1.44–6.45; p =0.004) and 3.40 (95% CI: 1.62–7.10; p = 0.001), respectively. When MNA and GFI were combined in one multivariate Cox regression model, both tests independently

contributed to prognostic value (p =0.04 for MNA and p =0.02 for GFI).

The Kaplan–Meier curves for survival, according to predefined cut-off scores for MNA and GFI, are shown in figure 2. Patients scoring lower than 24 points for MNA and 4 or more points for GFI showed a significantly higher mortality risk (p = 0.004 and p < 0.001, respectively). The median survival difference for the MNA (well nourished vs. malnourished) and GFI (not frail vs. frail) was more than 12 months for both tests.

Due to logistical problems or patient refusal, only 21 of 39 patients, completing at least 4 cycles of chemotherapy, could be assessed a second time for GFI and MMSE. The median time between the first and the second assessment was 6 months (range 2-26). No significant changes did occur over time, as shown in table 5. When we separately considered physical- and psychosocial items of the GFI, items representing physical health deteriorated significantly between the two assessments (p = 0.05).

Discussion

This study demonstrates that indicators of frailty and malnutrition, detected with the GFI and MNA respectively, were associated with dismal survival in older patients with advanced breast cancer selected for treatment with chemotherapy by a medical oncologist. In contrast, cognitive deficits or abnormal laboratory values at base line did not predict for mortality. Twenty-five patients (46%) were part of a previously published study of 202 patients with a diversity of cancers, also showing increased mortality risk with an inferior score for MNA and GFI [26]. This tumour specific analysis with a larger number of patients with breast cancer confirms the previous findings and adds on the meaning of laboratory measurements in this cohort.

In this study, 45% of patients was at risk for malnutrition or malnourished. This percentage is higher than the 29% (range 15%–44%), described in an overview of 7 studies including 2798 community dwelling elderly persons [33]. Apparently, the presence of malnutrition is either not noticed by oncologists or not considered to be a reason to withhold chemotherapy. However, our results demonstrate that underweight or malnourished patients with breast cancer, who are treated with chemotherapy, have a limited survival and carry a high risk to die during or shortly after chemotherapy. Others have also shown that weight loss is associated with a decreased response to chemotherapy and reduced survival [11]. A cohort of elderly patients in Southwest France with a variety of cancers

had shortcomings in MNA in 65% of them, predicting early death [12]. However, breast cancer patients were not included in this cohort. In a cohort of elderly Asian patients, few of whom had breast cancer, malnutrition was a predictor of mortality with a hazard ratio of 1.84 [34].

Half of the breast cancer patients that started with chemotherapy had indicators of frailty and again, these patients had a limited survival and carried a large risk to die during, or shortly after, chemotherapy. Our results are in agreement with a study of elderly breast cancer survivors, showing that deficits in clinical-, functional- and psychosocial domains are associated with poor treatment tolerance and mortality [8]. Although it has been recognized that frailty screening tools have insufficient discriminative power in comparison with full CGA to detect all aspects of frailty [35], the GFI has a fair negative predictive value (specificity 86%) [36].

MNA as well as GFI were strongly and independently associated with an increased mortality risk, but were also strongly intercorrelated. It is therefore likely that both tests showed some overlap and therefore both identified frailty in elderly breast cancer patients. However, the WHO-performance status also showed a correlation with inferior scores for MNA and GFI. Nevertheless, with MNA and GFI more in depth information is gathered than is obtained with a WHO performance score, thereby elaborating the possibilities to interfere with care for the elder patient with these relatively simple tests [4].

Cognitive deficits, screened with MMSE and IQCODE, were rather rare among these elderly patients selected for chemotherapy and did not predict for early mortality. Moreover, no significant decline in the MMSE was seen after at least four cycles of chemotherapy or at 6 months after the start of chemotherapy in the 21 patients with complete data. This is in contrast with a prospective pilot study, demonstrating a decline in cognitive function in older breast cancer patients during adjuvant chemotherapy given for 6 months [37].

In the present study abnormal values for hemoglobin and LDH, which were present in respectively 78% and 84% of the patients, were unrelated to mortality. A study among Asian patients (2% breast cancer) showed that serum albumin among other factors was a significant predictor for survival [34]. In our study, GA test results and laboratory outcome were not significantly correlated. Our findings therefore suggest that the GA has a stronger predictive power than laboratory measurements for mortality in patients aged 70 years or older treated with chemotherapy.

In our study, frailty and malnutrition could not predict for early withdrawal of treatment, nor could any other item of the assessment or abnormal laboratory

values. Apparently, in the selection of older breast cancer patients that may tolerate at least four cycles of chemotherapy, this limited geriatric assessment did not contribute any extra benefit to the clinical judgment of the participating oncologists. Others have shown that malnutrition as well as elevated LDH was correlated with grade 3-4 non-haematological toxicity in a cohort of elderly patients, treated with chemotherapy, 20% of whom had breast cancer [38]. In a cohort of 500 patients (11% breast cancer patients), eleven risk factors were identified to predict chemotherapy toxicity, among which anemia and renal dysfunction [39].

In the present study, frailty scores with GFI were measured before and after four cycles of chemotherapy and no major changes in these scores were observed. However, when physical and psychosocial aspects of the GFI were studied separately, the physical aspects (ADL and IADL elements) showed a significant decline (p=0.05) in the course of treatment. The loss of (instrumental) activities of everyday living may severely affect well being of elderly patients and an assistance with these activities may improve their quality of life.

The strong association of frailty indicators and malnutrition with a very limited lifespan may have important consequences in daily breast cancer practice. In the present study, it was shown that a limited geriatric assessment can reveal deficits that, although they do not predict for early therapy withdrawal, are highly predictive for early mortality. Hence, for patients with frailty indicators at the start of chemotherapy, a limited life span must be anticipated and therefore, patient preferences with regard to chemotherapy near the end of life should specifically be addressed [40].

Some limitations need to be discussed. First, the study size is relative small. However, in view of the paucity of data in the medical literature on outcome of elderly patients related to GA, we consider our data important. Second, all patients had been considered suitable for chemotherapy by an oncologist, hence introducing selection bias. These patients were considered fit for treatment, hence decreasing the likelihood of functional or health deficits as compared to an unselected elderly population. Nevertheless, despite the selection, GA showed discriminative power especially with respect to GFI and MNA. Third, we did not adjust for severity of metastatic burden and therefore frailty may have reflected tumour load. As a consequence, the association between frailty and mortality may have been confounded by tumour load. However, the association of high GFI score and mortality remains a valid one. Fourth, we only studied the effect of treatment on GFI and MMSE in patients that completed 4 or more cycles of chemotherapy. After four cycles of chemotherapy, in every day practice tumor evaluations are usually planned [41]. We therefore selected patients without

early progression, who could tolerate treatment and had no serious toxicity. It can be argued that patients with a decline in MMSE or GFI during chemotherapy will not continue onto the fourth course.

We conclude that deficits with MNA and GFI seem strongly associated with increased mortality risk in patients with advanced breast cancer treated with chemotherapy. Furthermore, in this descriptive study a simplified GA was more prognostic for mortality than laboratory parameters. Our findings are of clinical importance to make treatment decisions and to counsel elderly patients with breast cancer. Whether interventions directed at the observed deficits may improve outcomes should be investigated in future prospective studies. Already initiatives have emerged [12].

Table 1. Baseline characteristics in 55 breast cancer patients.

Age (yr)		*Mean*	*SD*
		76	4.80
		n	%
	70-74 yrs	26	47
	75-79 yrs	18	33
	80+ yrs	11	20
Gender			
	Women	53	96
	Men	2	4
WHO-performance / Karnofski Index			
	0 - (KI 90-100%)	27	48
	1 - (KI 70-80%)	12	22
	2 - (KI 50-60%)	2	4
	3 - (KI 30-40%)	2	4
	Unknown	12	22
Comorbidity (Charlson index)			
	None	18	33
	One	21	38
	Two or more	14	25
	Unknown	2	4
Chemotherapy			
	Mono-chemotherapy	32	58
	Combination of chemotherapy	10	18
	Chemotherapy + trastuzumab	7	13
	Chemotherapy + bevacizumab	3	5
	Trastuzumab	1	2
	None	2	4

Table 2. Correlation between geriatric assessment test results and laboratory test results in breast cancer patients.

	Albumin	Hemoglobin	Creatinine	LDH
MNA				
Crude	–0.13 (P=0.38)	0.05 (P=0.72)	–0.14 (P=0.32)	–0.15 (P=0.30)
Adjusted	–0.12 (P=0.49)	0.03 (P=0.85)	–0.08 (P=0.62)	–0.25 (P=0.09)
GFI				
Crude	0.24 (P=0.11)	0.09 (P=0.53)	–0.09 (P=0.53)	0.04 (P=0.77)
Adjusted	0.22 (P=0.17)	0.10 (P=0.48)	–0.17 (P=0.26)	0.11 (P=0.44)
IQCODE				
Crude	0.07 (P=0.66)	0.14 (P=0.33)	–0.03 (P=0.84)	0.20 (P=0.16)
Adjusted	0.08 (P=0.62)	0.15 (P=0.26)	–0.02 (P=0.87)	0.19 (P=0.16)
MMSE				
Crude	–0.02 (P=0.89)	–0.16 (P=0.25)	–0.04 (P=0.80)	–0.01 (P=0.96)
Adjusted	–0.02 (P=0.86)	–0.14 (P=0.33)	–0.05 (P=0.71)	–0.02 (P=0.90)

Standardized regression coefficients derived from a linear regression analysis are reported with P values. Adjusted model: adjusted for age and comorbidity.

Table 3. Baseline geriatric assessment and laboratory test results according to the number of cycles of chemotherapy

	All patients (n=55)					
	≥4 cycles (n=39)	<4 cycles (n=16)	Crude odds ratio	*p*	Adjusted odds ratio	*p*
Geriatric assessment:	n (%)	n (%)				
MNA:						
well nourished	23 (59)	7 (50)				
malnourished	16 (41)	7 (50)	0.70 (0.20-2.37)	0.56	1.03 (0.26-4.16)	0.96
GFI:						
not frail < 4	21 (54)	6 (38)				
frail ≥ 4	18 (46)	10 (62)	0.51 (0.16-1.70)	0.27	0.73 (0.16-2.72)	0.64
IQCODE:						
normal risk < 3.3	32 (84)	12 (75)				
cognitive decline ≥ 3.3	6 (16)	4 (25)	0.56 (0.14-2.35)	0.43	0.67 (0.14-3.29)	0.62
MMSE:						
no cognitive decline > 24	33 (87)	16 (100)				
cognitive dysfunction ≤ 24	5 (13)	0 (0)	–		–	
Laboratory tests:						
Albumin:						
normal (≥35 g/L)	8 (53)	24 (73)				
decreased (<35 g/L)	9 (27)	7 (47)	2.33 (0.66-8.32)	0.19	2.43 (0.62-9.51)	0.20
Hemoglobin:						
normal (≥7.5 mmol/L)	9 (24)	3 (19)				
decreased (<7.5 mmol/L)	29 (76)	13 (81)	1.35 (0.31-5.80)	0.69	1.17 (0.25-5.56)	0.84
Creatinine:						
normal (<100 µmol/L)	33 (87)	14 (87)				
elevated (≥100 µmol/L)	5 (13)	2 (13)	1.06 (0.18-6.13)	0.95	1.04 (0.16-6.88)	0.97
LDH:						
normal (<250 U/L)	5 (13)	4 (25)				
elevated (≥250 U/L)	34 (87)	12 (75)	2.27 (0.52-9.86)	0.28	2.27 (0.48-10.66)	0.30

Data are number (percentage) and odds ratio for receiving <4 *vs*. ≥4 cycles (with the accompanying 95% confidence intervals) with *p*-values by logistic regression analysis. Because of the empty cell for patients with a low MMSE and receiving less than 4 cycles of chemotherapy, odds ratios could not be estimated (*p*-value by Fisher's exact test).
Adjusted model: age, comorbidity and WHO performance status.
Patients with missing data are excluded.
Cut-off score Hb for woman <7.5 mmol/l, for men <8.5 mmol/l.

Table 4. Risk for overall mortality according to geriatric assessment and laboratory test results.

	All patients (n=55)				
	n (%)	Crude hazard ratio	*p*-value	Adjusted hazard ratio	*p*-value
Geriatric assessment:					
MNA:					
well nourished*	30 (55)	1.0		1.0	
malnourished	23 (42)	2.85 (1.48-5.50)	0.002	3.05 (1.44-6.45)	0.004
GFI:					
not frail < 4	27 (49)	1.0		1.0	
frail ≥ 4	28 (51)	3.46 (1.69-7.10)	0.001	3.40 (1.62-7.10)	0.001
IQCODE:					
normal risk < 3.3	44 (80)	1.0		1.0	
cognitive decline ≥ 3.3	10 (18)	1.11 (0.51-2.44)	0.78	1.07 (0.49-2.37)	0.86
MMSE:					
no cognitive decline > 24	49 (89)	1.0		1.0	
cognitive dysfunction ≤ 24	5 (9)	1.12 (0.34-3.68)	0.85	1.68 (0.49-5.78)	0.41
Laboratory tests:					
Albumin:					
normal (≥35 g/L)	32 (58)	1.0		1.0	
decreased (<35 g/L)	16 (29)	1.35 (0.68-2.70)	0.39	1.39 (0.65-2.98)	0.40
Hemoglobin:					
normal (≥7.5 mmol/L)**	12 (22)	1.0		1.0	
decreased (<7.5 mmol/L)	42 (76)	1.11 (0.52-2.35)	0.80	0.95 (0.43-2.12)	0.90
Creatinine:					
normal (<100 µmol/L)	47 (86)	1.0		1.0	
elevated (≥100 µmol/L)	7 (13)	0.63 (0.22-1.78)	0.38	0.63 (0.20-1.98)	0.43
LDH:					
normal (<250 U/L)	9 (16)	1.0		1.0	
elevated (≥250 U/L)	46 (84)	1.18 (0.46-3.02)	0.73	1.24 (0.48-3.23)	0.66

*: Being well nourished was defined as a score of >12 on the MNA screening section or 24-30 pts on the assessment section.
**: A cut off of Hb <7.5 mmol/L (12 g/dL) for women was used, while for the 4 men a cut off of Hb <8.5 mmol/L was used.
Data are hazard ratios (with the accompanying 95% confidence intervals) with *p*-values by Cox regression analysis. Adjusted model: age and comorbidity.

Table 5

Differences between baseline and second assessment of MMSE and GFI in patients treated with at least 4 cycles of chemotherapy (n=21)

	At baseline		2e assessment		Mean change	SE	*p*-value*
	Median	IQR	Median	IQR			
MMSE	29	27-30	29	27-30	0.30	0.70	0.67
GFI	2	1-4	3	2-6	0.86	0.55	0.14
physical part	1.00	1.00-3.00	2.00	1.00-3.00	0.71	0.35	0.05
psychosocial part	1.00	1.00-2.00	1.00	0.00-2.50	0.19	0.32	0.56

IQR indicates interquartile range; SE, standard error.
*: *p*-value from *t*-test for paired samples.
physical part: (instrumental) activities of everyday living (ADL and IADL elements).
psychosocial part: memory, mood and anxiety.

Figure 1. Flow diagram of the study

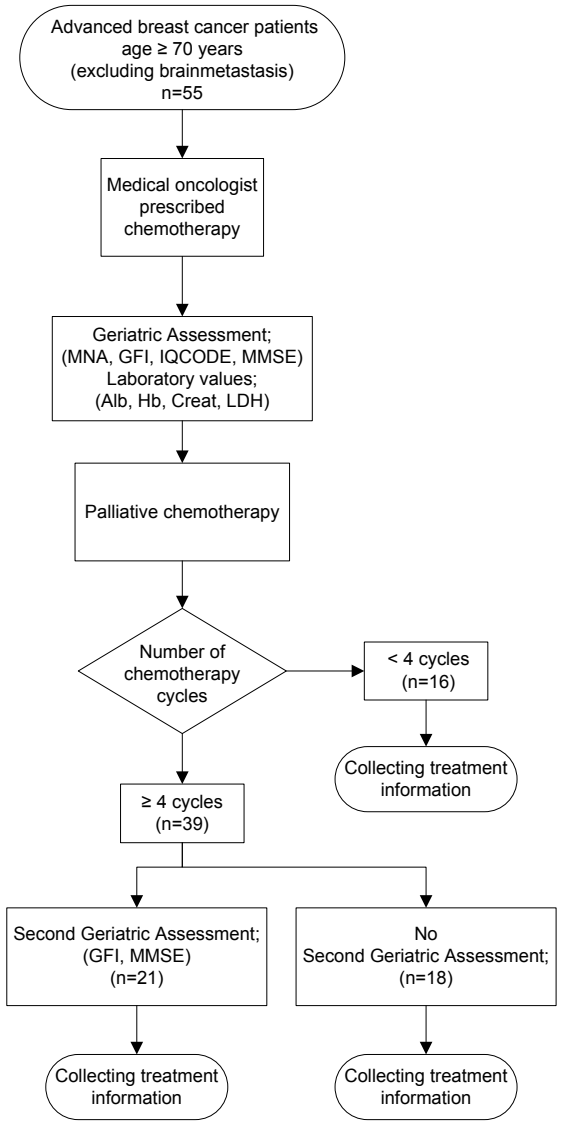
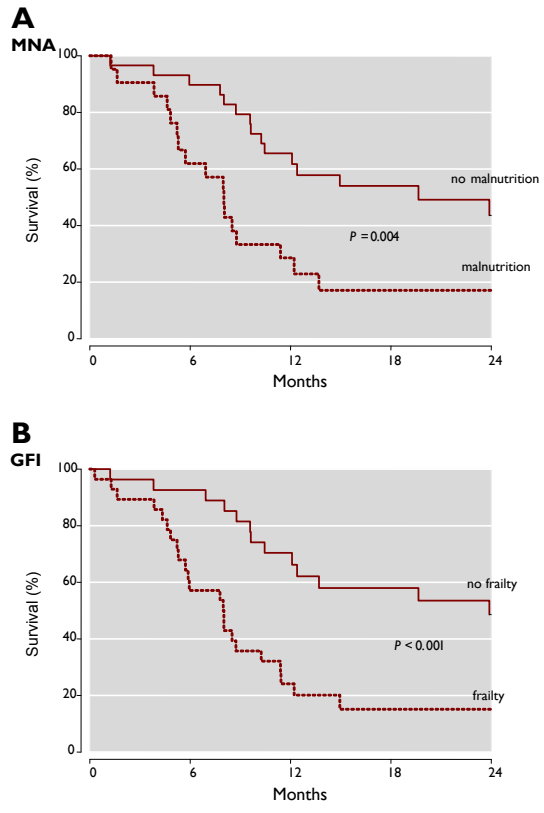


Figure 2.
Kaplan–Meier curves of overall survival in patients with advanced breast cancer according to categories of [A] Mini Nutritional Assessment (MNA) and [B] Groningen Frailty Indicator (GFI). *p*-values by log-rank tests. MNA data was missing for 2 patients at baseline, whereas there were no missing data for the GFI



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Chapter

4

Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy

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Abstract

Introduction: In general, geriatric assessment (GA) provides the combined information on comorbidity and functional, nutritional and psychosocial status and may be predictive for mortality outcome of cancer patients. The impact of geriatric assessment on the outcome of older patients with colorectal cancer treated with chemotherapy is largely unknown.

Methods: In a prospective study, 143 patients with colorectal cancer who were 70 years and older were assessed before chemotherapy by Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State Examination (MMSE).

Results: Fifty-four (38%) patients received adjuvant chemotherapy and 89 (62%) patients received palliative chemotherapy. Malnutrition and frailty were prevalent in 39 (27%, assessed by MNA) and 34 (24%, by GFI) patients, respectively; whereas cognitive impairment was prevalent in 19 (13%, by IQCODE) and 11 (8%, by MMSE) patients, respectively. In patients with palliative chemotherapy, poor MNA scores were associated with receiving less than 4 cycles of chemotherapy ***(p*** = 0.008). Poor MNA and GFI scores were associated with increased hazard ratios (HRs) for mortality for patients with palliative chemotherapy: HR = 2.76 (95% confidence interval [CI]: 1.60-4.77; p < 0.001) and HR = 2.72 (95% CI: 1.58–4.69; p < 0.001), respectively, after adjustment for several clinical parameters.

Conclusions: Malnutrition and frailty were strongly associated with an increased mortality risk in patients who underwent palliative chemotherapy. Furthermore, a poor score on MNA was predictive for less tolerance of chemotherapy. Our findings may help the oncologist in future decision making and advice for elderly patients with colorectal cancer.

Introduction

Colorectal cancer is one of the most frequent types of cancer in Western countries, and the incidence and mortality of patients increases with age. In the Netherlands, 54% of patients diagnosed with colorectal cancer and 66% of patients

who died of colorectal cancer were above 70 years of age [1]. These data are almost similar to data from the United States [2]. In the past two decades, patients with colorectal cancer showed a substantial improvement in survival, which has been attributed largely to the increased administration of chemotherapy. However, this increased survival – and the increased use of chemotherapy – was less pronounced in elderly patients in comparison with younger patients [3–5]. The process of aging is associated with a loss of functional reserve of multiple organ systems, increased prevalence of chronic diseases and enhanced susceptibility to stress [6]. This process occurs at a different pace in individuals resulting in a large heterogeneity within the elderly patients with cancer group. For elderly patients, cancer treatments should be adapted to life expectancy and the increased risk of toxicity. Therefore, 'functional age' rather than chronological age is important for cancer treatment planning. Geriatric Assessment (GA) may be a useful tool in the management and follow-up of elderly patients with cancer. A GA provides the combined objective and subjective information on comorbidity, nutrition, cognition, functional and psychosocial status [6, 7]. Previous studies showed that several GA domains were associated with poor treatment tolerance and poor survival, independent of age and stage of disease [8, 9]. However, studies of GA in cohorts comprising of only patients with colorectal cancer are scarce [10]. In the present study, we have performed a GA in 143 patients with colorectal cancer aged 70 years and above, with the aim to assess its predictive value for tolerance and feasibility of treatment with adjuvant and palliative chemotherapy.

Patients and Methods

Patients

Between May 2004 and February 2010, four hospitals in the western part of the Netherlands participated in a geriatric oncology study. Because of time needed for training of personnel in the technique of GA, the hospitals started at different time points. Patients of 70 years of age and older and regarded eligible for chemotherapy treatment by their medical oncologist, were prospectively included. Common eligibility criteria used by medical oncologists included adequate performance status by Eastern Cooperative Oncology Group (ECOG 0-3), sufficient organ function and absence of severe comorbidity. For the current study we selected all patients (n = 143) diagnosed with colorectal cancer and treated with chemotherapy. Of these, 60 patients (42%) were also included in a previous analysis with several types of cancer combined [11]. According to the Dutch

national evidence-based guidelines for colon cancer, adjuvant chemotherapy is recommended for patients with colon cancer with lymph node metastases (stage III) and for patients with high risk stage II colon cancer [12]. Patients with colon and rectal cancer with distant metastases usually received chemotherapy with palliative intent and at least four cycles of chemotherapy were considered to be necessary to reach the palliative goal of treatment. Whether the administration of chemotherapy was 'adjuvant' or 'palliative' was left to the discretion of the oncologist.

Geriatric Assessment (GA) and Clinical Data

A GA was performed by specially trained nurses before the start of chemotherapy treatment. The used tests with their accompanying cut-off points have been described previously [11]. In brief (Table 1):

- Mini Nutritional Assessment (MNA) [13], makes it possible to identify patients at risk for malnutrition, before severe changes in weight or albumin levels occur [14];
- Groningen Frailty Indicator (GFI) [15] screens on physical, cognitive, social and emotional items (see Appendix);
- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [16], screens for cognitive decline by interviewing family members or care givers, for which we used the short Dutch translation IQCODE-N [17];
- Mini Mental State Examination (MMSE) [18] is considered to be a screening test for detecting current cognitive dysfunction.

Patients completing at least four cycles of chemotherapy were assessed a second time using the GFI and MMSE at the end of chemotherapy or at six months after the start of chemotherapy. The number of comorbidities and number of regularly used medications, performance status according to the Eastern Cooperative Oncology Group (ECOG) and laboratory values (serum-albumin, -creatinine, -lactate dehydrogenase (LDH) and hemoglobin before start of chemotherapy) were collected from the medical records of patients, as well as chemotherapy regimen, number of cycles, toxicity and mortality. Comorbidity was recorded according to the Charlson Index [19]. The vital status of patients was cross-checked with the municipal registry at the end of the data collection period.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and chi-square tests were used to compare subgroups. Continuous variables were presented as means ± standard deviations (SD) and subgroups were compared by unpaired t-tests. In the right-skewed LDH-values, a log-transformation was performed before analyses. Chi-square and Fisher Exact tests were used to analyze the associations between dichotomized GA-variables and receiving more or less than four chemotherapy cycles. In multivariate logistic regression analyses these associations were adjusted for sex, age, number of co-morbidities and laboratory values (hemoglobin, serum-creatinine and LDH levels). Patients receiving adjuvant chemotherapy and those receiving palliative chemotherapy treatment were analysed separately. Changes in GA-scores over time (before chemotherapy and after at least four cycles) were analysed using the paired sample t-test. Survival probabilities were estimated using Kaplan Meier curves and the log-rank test was used to test for differences in survival rates among subgroups of GA. Cox proportional hazard analyses were used to estimate hazard ratios for mortality for each of the four GA tests, adjusted for sex, age, number of co-morbidities and laboratory values (hemoglobin, serum-creatinine and LDH). The analyses were repeated for adjustment on performance status, number of medications and albumin values, because of a larger number of missing values for these variables. A final Cox proportional hazard analysis was performed to assess independent mortality risks for the MNA and GFI scores. A p-value less than 0.05 was considered significant. SPSS 17.0 for Windows® (SPSS inc. Chicago, IL) was used for statistical analyses.

Results

Patient and Tumour Characteristics

Baseline characteristics of all 143 elderly patients with colorectal cancer are shown in Table 2. The mean age was 75 years (range 70-92), 12% of patients were 80 years and older. Forty-nine percent of patients had multiple comorbidities (mean = 1.6 ± 1.3). Most common were hypertension (35%), cardiac diseases (30%), chronic obstructive pulmonary disease (COPD) (22%), diabetes mellitus (20%), vascular diseases (17%), and previous malignancies (13%). With respect to polypharmacy, 50% of patients used four or more kinds of medication (mean = 3.7 ± 2.8). According to the ECOG functional score, at least one-fifth of patients were functionally restricted. However, a functional performance score was not documented in 11% of patient records. Seventeen percent of patients had a diagnosis of rectal cancer. Fifty-four patients (38%) received chemotherapy with

curative intent (adjuvant: stage II-III), of whom 96% were patients with colon cancer. Another eighty-nine patients with colorectal cancer (62%) were treated with palliative intent (synchronous or metachronous distant metastases). Baseline characteristics of adjuvant or palliatively treated patients were significantly different with respect to sex, hemoglobin- and LDH-values.

Geriatric Assessment

Assessment showed that 28% of patients were at risk for malnutrition or malnourished (measured by MNA). Frailty, measured by the GFI, was present in 24% of patients, 13% of patients were suspect for cognitive decline (IQ-code), and 8% had serious cognitive dysfunction (measured by MMSE). Of patients with palliative chemotherapy, 33% were at risk for malnutrition, versus 20% of patients with adjuvant chemotherapy (p = 0.10) (Table 1).

Chemotherapy Treatment

The majority of elderly patients received poly-chemotherapy, mainly capecitabine-oxaliplatin (CapOx; 39%) or fluorouracil-leucovorin-oxaliplatin (FOLFOX4; 13%). Forty-two percent of patients received mono-chemotherapy, either capecitabine (36%) or fluorouracil-leucovorin (6%). Of adjuvant treated patients, 48% received poly-chemotherapy, compared to 64% of palliatively treated patients (p = 0.06). In addition, 20% of palliatively treated patients received bevacizumab. Mean number of chemotherapy cycles was 6.2 (±4.4, range 1-29), and were similar for adjuvant and palliatively treated patients (6.2 and 6.3, respectively; p = 0.41). Seventy-three percent of patients received four or more cycles of chemotherapy. Fifteen percent of patients received their chemotherapy according to protocol. Deviations of protocol included a lower dose or medication change (16%), a delay and/or discontinuation of chemotherapy (47%) or both (37%). The majority of patients (78%) experienced one or more toxicities due to their chemotherapy. Most important toxicities were (poly)neuropathy (29%), diarrhoea (23%), and fatigue (14%). Patients treated with adjuvant chemotherapy seemed to experience slightly more haematological toxicities (9%) than patients treated with palliative intent (2%; p = 0.06). In palliatively treated patients, patients at risk of malnutrition or who were malnourished (MNA < 24) less frequently completed four or more cycles of chemotherapy than well nourished patients (p = 0.008; Table 3). This finding persisted after adjustment for age, sex, number of co-morbidities and laboratory values (odds ratio [OR] for ≥4 vs <4 cycles = 0.29, 95% Confidence Interval [CI]: 0.11-0.81). In 62 patients, a second assessment of MMSE and GFI was performed. Compared to baseline scores, there was a significant deterioration in GFI-scores in patients receiving palliative chemotherapy (mean change-0.86; standard error [SE] 0.32; p = 0.01). When we sub-classified GFI in a physical- and psychosocial part, deterioration was found in the physical part (p = 0.001) but not in the psychosocial part (p = 0.85).

Risk of Mortality

During a median follow-up of 15 months (range 0.5-62) a total of 76 patients (53%) died. Among patients receiving palliative chemotherapy, those with poor MNA- and GFI-scores showed significantly higher hazard ratios (HRs) of mortality (p-values <0.001; Table 4). The median survival difference for the MNA (well nourished vs. malnourished) and GFI (not frail vs. frail) was 9 and 10 months, respectively (Fig. 1). The increased risk of mortality for palliatively treated patients with poor baseline MNA- and GFI-scores persisted after adjustment for age, sex, number of comorbidities, and laboratory values of hemoglobin, creatinine and LDH (hazard ratio [HR] = 2.76, 95% CI: 1.60-4.77 and HR = 2.72, 95% CI: 1.58-4.69, respectively; Table 4). In sensitivity analyses, in which we additionally adjusted for performance status, numbers of medications and serum albumin, results remained similar (data not shown). In a multivariate model with both MNA and GFI, the risk of mortality was significant for patients with poor baseline MNA-scores (HR = 2.54, 95% CI: 1.49-4.33), and borderline significant for patients with poor GFI-scores (HR = 1.66, 95% CI: 0.94-2.94). No interaction effect was found (i.e. MNA*GFI: p for interaction 0.40).

Discussion

Our study reports the results of GA in 143 patients aged 70 years and older with colorectal cancer who received chemotherapy with either adjuvant or palliative intent. We found that in palliatively treated patients, poor MNA scores were associated with less tolerance of chemotherapy, and GFI-test scores of physical functioning deteriorated over time. Furthermore, poor baseline scores on MNA and GFI were associated with an increased mortality risk in case of chemotherapy with palliative intent. This tumour specific analysis with a larger number of elderly patients with colorectal cancer extends our previous findings among patients with different kinds of tumours combined [11]. Comorbidity, disability and geriatric syndromes were found prevalent in many elderly patients with colorectal cancer [20]. In two recent studies, various geriatric assessment variables were identified to be associated with severe chemotherapy toxicity [21, 22], independ-

ent from laboratory test values, patient, tumour and treatment characteristics. Common predictive geriatric parameters seem to encompass decreased physical activity, social activity and nutrition status. In a previous study, activities of daily living (ADL) impairment and malnutrition were also independently associated with changes of the cancer treatment plan [23]. With increasing age, comorbidities and general aspects of ageing increase the risk of toxicities of chemotherapy and competing causes of death gain importance. The majority of elderly patients may benefit from chemotherapy treatment, but therapeutic margins are small in many of them, and require a careful evaluation of biological and clinical markers of aging, aggressiveness of the tumour, the biological and psychosocial costs of treatment and its perception by the patient [24]. The administration of chemotherapy increases survival in the elderly in the same way as in younger patients [25, 26] and there is no evidence that the susceptibility of colon cancer to chemotherapy differs in younger and older patients [27]. However, scientific evidence from prospective clinical trials taking into account the heterogeneity of elderly patients with colorectal cancer is scarce [10, 28] and therefore our knowledge of the performance of the appropriate therapeutic strategies in this age group is often severely limited [10]. Chronological age as an indicator for health risks in the elderly is not a very sensitive and specific risk marker. The concept of frailty may be more valuable [29]. A geriatric screening should distinguish between fit and frail patients, of which the first group of patients should receive standard adult chemotherapy treatment [26, 27, 30, 31] while the latter may require a more in-depth evaluation of their functional reserve and a tailored chemotherapy treatment plan [9, 32, 33].

In two recent studies of the prognostic value of GA in elderly patients with cancer, nutritional status was found to be predictive of early mortality and overall survival in multivariate models [34,35]. The prevalence of (or risk of) malnutrition in our study was almost similar to an overview of 7 studies with 2798 community dwelling elderly persons assessed by MNA (29%, range 15%–44%) [13]. Our study showed that malnutrition was associated with poor tolerance of chemotherapy and increased mortality in elderly patients with colorectal cancer treated with palliative intent. Adjustment for several clinical parameters did not alter these results. Compared to frailty (by GFI), malnutrition seemed to be the stronger predictor of mortality. More research is needed in palliatively treated patients concerning the relation between nutritional status, tumour behaviour, the type of chemotherapy and mortality. Furthermore, in malnourished patients it is unclear whether they benefit more from palliative chemotherapy than from comprehensive palliative care. In adjuvant treated patients, the number of patients appeared too small to show significant associations.

In our study physical and psychosocial frailty (assessed by GFI) was associated with an about 2.5 times increased mortality risk in patients treated with palliative intent. In addition, especially the physical aspects (ADL and instrumental activities of daily living [IADL] variables) showed a clear decline after at least four cycles of chemotherapy. This probably shows that tolerance to chemotherapy plays an important role for elderly patients with colorectal cancer. A loss of (instrumental) activities of everyday living may have a great impact on their quality of life. Therefore, in future studies of GA a more sensitive ADL/IADL test may be used to assess a possible decline of physical functioning [36, 37].

The MMSE and IQCODE did not differentiate between patients who underwent less than four cycles of chemotherapy or four or more cycles and did not clearly predict mortality. Moreover, we found no decline in the MMSE-scores after at least four cycles of chemotherapy. This is in agreement with a meta-analysis of 16 studies in which small to moderate but non-significant negative effects of chemotherapy were found in various domains of cognitive function [38]. There are some limitations that need to be discussed. First, the patients in our study underwent GA after the oncologist decided they were eligible for receiving chemotherapy, which may have introduced some selection bias. The assessed patients may have relatively better GA-scores. Compared to an Asian study in an outpatient geriatric oncology clinic, our study comprised of few patients with ECOG ≥ 2 [35]. Furthermore, population-based studies showed that the proportion of elderly patients who received chemotherapy was lower in patients with stage III colon cancer than in patients with colorectal cancer with distant metastases [4, 5]. Therefore, selection bias may be more apparent in elderly patients with adjuvant chemotherapy. Despite this bias, we consider our findings as valid and informative. Even after selection by oncologists, the GA revealed considerable frailty as assessed with the GFI and MNA. Second, our finding of the increased risk of mortality associated with higher levels of frailty at baseline may be partly explained by residual confounding factors like alcohol consumption, smoking and socio-economic status. Furthermore, we did not screen for geriatric syndromes like depression, delirium, incontinence, falls, dizziness and syncope as was done by others [9], and unfortunately serum albumin values and performance status were lacking in one-tenth of our patients. However, contrary to most studies of GA our patient group was homogeneous with respect to tumour type and we performed analyses separately in adjuvant and palliatively treated patients. Third, the decline in GA test results was likely underestimated. To minimize the bur-

den of testing, only patients who completed at least four cycles of chemotherapy were re-assessed with GFI and MMSE. However, many patients who received four or more chemotherapy cycles refused to complete a second assessment and patients with better GA scores were more likely to remain included, leading to some attrition bias. Furthermore, the course of the nutritional status of our patients during chemotherapy treatment was not assessed. At last, MNA as well as GFI were independently associated with an increased mortality risk. However, MNA and GFI correlated moderately (Sr = 0.43), suggesting that the tests showed some construct overlap and therefore partially identified the same group of frail patients. However, the ECOG-performance status also showed correlation with inferior scores for MNA and GFI. Nevertheless, with MNA and GFI more in depth information is gathered than is obtained with ECOG performance score, thereby augmenting the possibilities to interfere with care for the elder patient [39].

Our findings may help to better identify those patients with colorectal cancer with poor prognosis, which is of clinical importance for counselling, psychosocial support, and management of elderly patients receiving chemotherapy for colorectal cancer. Specific and timely nutritional interventions may improve nutritional status, tolerability of chemotherapy and survival in some elderly patients, which is also suggested by other investigators [34].

Conclusion

In conclusion, poor scores for MNA and GFI were independently associated with increased hazard ratios for mortality, and poor MNA-scores were predictive for a less than planned number of chemotherapy cycles in palliatively treated patients.

Table 1 – Characteristics and scores of the geriatric assessment.

Geriatric Assessment		Adjuvant Chemotherapy n = 54	Palliative Chemotherapy n = 89	
	Scale	**Mean (SD)**	**Mean (SD)**	**p-value**
MNA[$]	0-14 pts (S) 0-16 pts (A)	11.3 (2.6)	11.5 (2.3)	0.71
GFI	0-15	2.3 (1.9)	2.6 (2.1)	0.31
IQCODE	1-5	3.1 (0.3)	3.1 (0.2)	0.10
MMSE	0-30	28.3 (2.5)	28.3 (2.0)	0.58
	Subgroup with impaired Geriatric Assessment scores (cut-off points)	**n (%)**	**n (%)**	**p-value**
MNA[$]	17-23.5 pts: At risk of malnutrition, or, < 17 pts: Malnourished	10 (20)	29 (33)	0.10
GFI	≥ 4 pts: Frail	11 (20)	23 (26)	0.46
IQCODE	> 3.31 pts: Cognitive Decline	6 (11)	13 (15)	0.53
MMSE	≤ 24 pts: Cognitive Dysfunction	5 (9)	6 (7)	0.60

Abbreviations: MNA, Mini Nutritional Assessment, a stepwise test: when the score in the screening section (S) is less than 12 points, indicating the possibility of malnutrition, the assessment section (A) is filled in; IQCODE, Informant Questionnaire on Cognitive Decline; GFI, Groningen Frailty Indicator; MMSE, Mini Mental State Examination; SD, standard deviation; pts, points.
$ excluding n = 6 (4%) missing values.

Table 2 – Baseline characteristics of 143 patients with colorectal cancer.

	Total N = 143 (%)	Adjuvant N = 54 (%)	Palliative N = 89 (%)	p-value
Sex – No. (%)				0.02
male	84 (59)	25 (46)	59 (66)	
Female	59 (41)	29 (54)	30 (34)	
Age – No. (%)				0.28
70-74 years	68 (48)	29 (54)	39 (44)	
75-79 years	57 (40)	21 (39)	36 (40)	
≥ 80 years	18 (12)	4 (7)	14 (16)	
ECOG Performance Status – No. (%)				0.15#
0	98 (69)	38 (84)	60 (73)	
1	26 (18)	7 (16)	19 (23)	
2 +	3 (2)	0	3 (4)	
Unknown	16 (11)	9 (-)	7 (-)	
No. of Comorbid Organ Systems – No. (%)				0.66
0	31 (22)	12 (22)	19 (21)	
1	42 (29)	18 (33)	24 (27)	
2 +	70 (49)	24 (44)	46 (52)	
Number of Medications – No. (%)				0.65#
0	20 (14)	9 (18)	11 (12)	
1-3	49 (34)	18 (35)	31 (35)	
4 +	71 (50)	24 (47)	47 (53)	
Unknown	3 (2)	3 (-)	0	
Tumour Location – No. (%)				0.001
Colon	119 (83)	52 (96)	67 (75)	
Rectum	24 (17)	2 (4)	22 (25)	
Albumin (g/L)$ – Mean ± SD	37.1 ± 9.9	37.2 ± 6.9	37.1 ± 11.5	0.18
Hemoglobin (Hb, mmol/L) – Mean ± SD	7.6 ± 0.87	7.4 ± 0.79	7.7 ± 0.89	0.02
Creatinine (µmol/L) – Mean ± SD	87.2 ± 22.0	86.7 ± 17.5	87.5 ± 24.6	0.64
LDH (U/L)& – Median (P25-P75)	319 (208-402)	239 (174-367)	357 (250-489)	< 0.001

Data are presented as numbers and percentages. ECOG denotes Eastern Cooperative Oncology Group. LDH denotes lactate dehydrogenase.

excluding category 'unknown'; $ excluding n = 17 (12%) missing values; & excluding n = 2 (1%) missing values.

Table 3 – Comparison of geriatric assessment scores according to receiving less than four versus four or more cycles of chemotherapy in patients with colorectal cancer.

Test	Adjuvant Chemotherapy (n = 54)				Palliative Chemotherapy (n = 89)			
	Total N=54 (%)	<4 cycles N=13 (%)	≥4 cycles N=41 (%)	p-value	Total N = 89 (%)	< 4 cycles N = 26 (%)	< 4 cycles N = 63 (%)	p-value
MNA				0.42				0.008$
Well Nourished	40 (80)	9 (69)	31 (84)		58 (67)	12 (46)	46 (75)	
(Risk of) Malnutrition	10 (20)	4 (31)	6 (16)		29 (33)	14 (54)	15 (25)	
Unknown	4				2			
GFI				0.26				0.23$
Not Frail	43 (80)	12 (92)	31 (76)		66 (74)	17 (65)	49 (78)	
(Risk of) Frailty	11 (20)	1 (8)	10 (24)		23 (26)	9 (35)	14 (22)	
IQCODE				0.32				0.51
Normal Risk	48 (89)	13 (100)	35 (85)		75 (85)	20 (80)	55 (87)	
Cognitive Decline	6 (11)	0	6 (15)		13 (15)	5 (20)	8 (13)	
Unknown					1			
MMSE				0.08				1.00
Normal	49 (91)	10 (77)	49 (95)		82 (93)	24 (92)	58 (93)	
Cognitive Dysfunction	5 (9)	3 (23)	2 (5)		6 (7)	2 (8)	4 (7)	
Unknown	-				1			

Data are presented as numbers and percentages.

$ p-values by Pearson chi-squared test, all other p-values by Fisher Exact tests.

Table 4 – Association between baseline geriatric assessment scores and survival in patients with colorectal cancer.

Test		Adjuvant Chemotherapy (n = 54)				Palliative Chemotherapy (n = 89)			
		n	Crude	p-value	Adjusted	n	Crude	p-value	Adjusted	p-value
MNA				0.89				<0.001		<0.001
Well Nourished		40	Ref		Ref	58	Ref		Ref	
(Risk of) Malnutrition		10	0.90 (0.19-4.23)		1.04 (0.20-5.25)	29	2.95 (1.79-4.85)		2.76 (1.60-4.77)	
GFI				0.35				0.001		<0.001
Not Frail		43	Ref		Ref	66	Ref		Ref	
(Risk of) Frailty		11	0.37 (0.05-2.94)		0.38 (0.05-3.08)	23	2.38 (1.41-4.02)		2.72 (1.58-4.69)	
IQCODE				0.45				0.30		0.24
Normal Risk		48	Ref		Ref	75	Ref		Ref	
Cognitive Decline		6	-			13	1.14 (0.74-2.71)		1.51 (0.76-3.02)	
MMSE				0.11				0.38		0.39
Normal		49	Ref		Ref	82	Ref		Ref	
Cognitive Dysfunction		5	3.68 (0.70-15.54)		3.98 (0.76-20.93)	6	1.54 (0.62-3.85)		1.51 (0.59-3.85)	

Hazard ratios and p-values by Cox proportional hazard analysis adjusted for age, sex, number of co-morbidities and laboratory value's (hemoglobin, creatinine, LDH).

Figure 1.

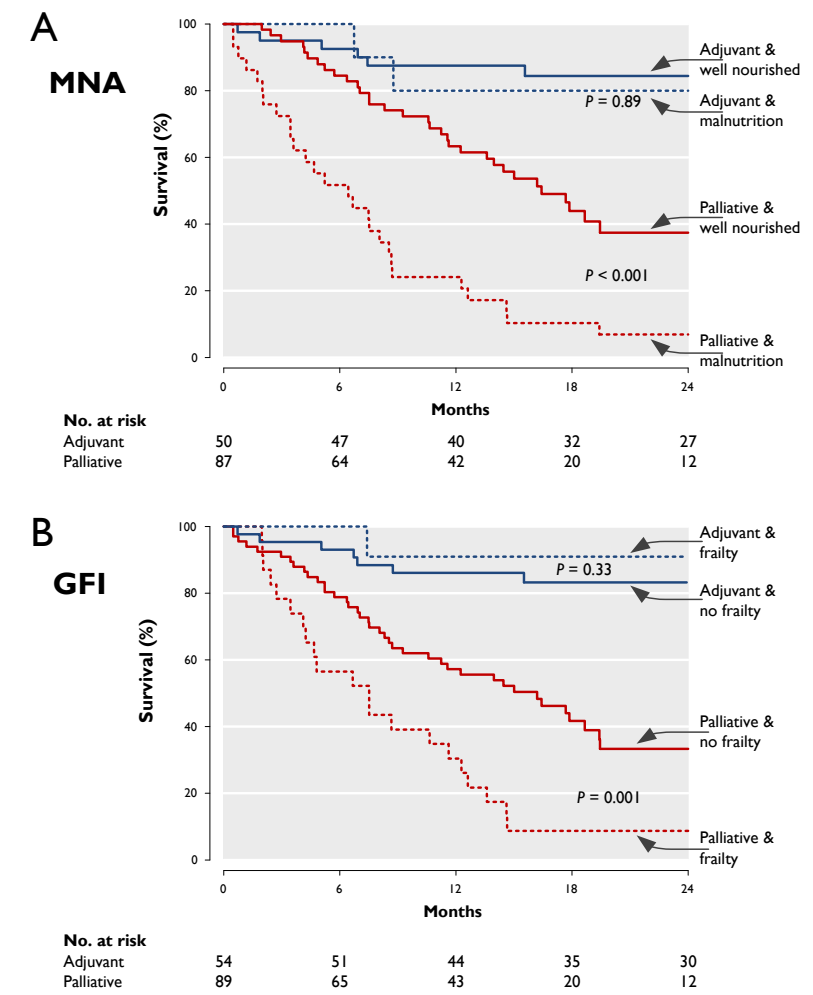

Fig. 1 – Kaplan–Meier curves of overall survival in 143 patients with colorectal cancer according to categories of [A] Mini Nutritional Assessment (MNA) and [B] Groningen Frailty Indicator (GFI). P-values by log-rank tests separately for patients undergoing adjuvant/curative chemotherapy (n = 54) and palliative chemotherapy (n = 89). MNA data was missing for 7 patients at baseline, whereas there were no missing data for the GFI.

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Chapter

5

Prognostic significance of geriatric assessment in combination with laboratory parameters in elderly patients with aggressive non-Hodgkin lymphoma

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Abstract

The age-adjusted International Prognostic Index (IPI) is an important prognostic factor for patients with non-Hodgkin lymphoma (NHL). We investigated whether a geriatric assessment (GA) is of additional prognostic value in NHL. In this prospective cohort study of 44 patients aged 70 years or older with NHL receiving R-CHOP, a GA was administrated before the start of chemotherapy. GA was composed of Mini Nutritional Assessment (MNA), Groningen Frailty Indicator (GFI), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Mini Mental State Examination (MMSE) and levels of albumin, creatinine, lactate-dehydrogenase (LDH) and hemoglobin. Multivariate analyses were performed using logistic regression and the cox regression model. After adjustment for sex, age, comorbidity and univariate laboratory values with $p \leq 0.1$, abnormal MNA and GFI scores and low hemoglobin level were associated with not being able to complete the intended chemotherapy: odds ratio (OR) 8.29 (95% confidence interval [CI]: 1.24-55.6; p = 0.03), 9.17 (95% CI: 1.51-55.8; p = 0.02) and 5.41 (95% CI: 0.99-29.8; p = 0.05), respectively. Adjusted for sex, age, comorbidity, age-adjusted IPI and univariate laboratory values with $p \leq 0.1$, frailty by GFI and low hemoglobin were associated with worse survival with hazard ratio (HR) of mortality of 2.55 (95% CI: 1.07-6.10; p = 0.04) and 4.90 (95% CI: 1.76-13.7; p = 0.002), respectively. We conclude that (risk of) malnutrition, measured with the MNA, frailty, measured with the GFI, and low hemoglobin level had additional predictive value for early treatment withdrawal, and GFI and hemoglobin were, independent of the age-adjusted IPI, predictive for an increased mortality risk.

Introduction

Non-Hodgkin lymphomas (NHL) form the largest group of malignancies (40-50%) within the range of hemato-oncological diseases [1, 2]. The median ages of diagnosis and death are 66 and 75 years, respectively [3, 4]. Aggressive B-cell NHL is the most common lymphoid tissue neoplasm in adults and occurs frequently in elderly patients [5]. The incidence steadily increases with age [6].

Since the 1970s the first generation chemotherapy regimen with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) remains the best available treatment after comparison with second generation regimens, as was shown in a randomized trial of patients with advanced stage aggressive B-cell NHL [7]. Rituximab has been added to the standard treatment since more than ten years (R-CHOP) [8]. In patients over 80 years old a reduced dose of CHOP with rituximab (R-miniCHOP) has been suggested as new standard treatment [9].

The process of aging is associated with increasing functional impairment and increasing comorbidity [10] and age is a well-established prognostic factor for NHL. In 1993, the International NHL Prognostic Factors Project developed the International Prognostic Index (IPI) with the risk factors age, stage, performance status, lactate dehydrogenase (LDH) and extranodal sites of disease. The age-adjusted IPI, originally developed for patients of 60 years and younger but also shown to be applicable for older age groups, is defined by the risk factors stage, performance status and LDH [11].

A comprehensive geriatric assessment (GA) can be a useful tool in the management and follow-up of elderly patients [12-14]. A comprehensive GA provides information on the functional status of older cancer patients with the combined objective and subjective information on comorbidity, functional-, nutritional-, and psychosocial status. Several studies have been published underscoring the usefulness of some form of GA [9, 15-18]. Application of GA in a cohort of 143 patients with NHL demonstrated the importance of instrumental activity of daily living (IADL) score and comorbidity as prognostic variables for survival [18]. The R-miniCHOP study showed that a decreased serum albumin was an important risk factor for survival [9] and this was also found in a study among NHL patients over 90 years of age [19]. In a cohort of 348 elderly patients, among whom 105 patients with non-Hodgkin lymphoma, male sex, advanced stage, poor MNA score and a prolonged timed get up and go (GUG) test were associated with a higher risk of mortality [16]. Tailored treatment based on GA identified three groups in a study of 91 elderly patients with diffuse large B-cell lymphoma (DLBCL): fit patients, patients with comorbidity, and frail patients. The overall survival of fit patients was significant better in comparison with the other two groups [17]. Finally, in a study of 100 elderly NHL patients, three subgroups could be characterized by GA: fit, unfit and frail. They received R-CHOP mitigated in dose and drugs according to co-morbidity, activities of daily living (ADL) and IADL scores, resulting in manageable toxicity and excellent outcome [15].

The aim of the present prospective study is to investigate the prognostic value of GA in addition to the age-adjusted IPI for patients aged 70 years and older diagnosed with non-Hodgkin lymphoma and treated with R-CHOP.

Patients and Methods

Study design

This prospective cohort study involved patients aged 70 years or older (n = 90) with non-Hodgkin lymphoma who were considered fit to be treated with chemotherapy by their hematologist. Patients were recruited between May 2004 and February 2010 from three general and one university hospital. To investigate a homogeneous patient population we selected all patients with DLBCL and follicular lymphoma grade III who were treated with R-CHOP (n = 44). The excluded 46 patients (of whom 12 patients with DLBCL) who were treated with other schemes than the R-CHOP regimen were comparable for the following baseline characteristics compared to the included patients: male gender (53% vs 43%; P = 0.39), age (mean = 77 yr vs 78 yr, P = 0.48), Karnofsky Index (median = 0, vs median = 0; p = 0.56), age-adjusted IPI of 2 to 3 (55% vs 46%; p = 0.47) and 2 or more comorbidities (53% vs 46%; p = 0.82), see figure 1. We included follicular lymphoma grade III patients, because usually these patients receive the same treatment regimens as patients with DLBCL, resulting in improved survival [20, 21]. One patient was assessed twice, at the first manifestation of DLBCL and at a relapse three-and-a-half years later. In the survival analysis only data on the first manifestation was used (n = 43). Ten patients were included in a previous analysis with several types of cancer combined [22].

Geriatric Assessment

Before participating in the study, informed consent was obtained. At baseline, the patients were prospectively assessed by trained nurses using the following tests: Mini Nutritional Assessment (MNA) [23], Groningen Frailty Indicator (GFI) [24], Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [25], and Mini Mental State Examination (MMSE) [26]. There were data missing for MNA (n = 2), but these could be reliable categorized based on the available data. The GFI, IQCODE, MMSE and MNA tests were pragmatically selected for performing a GA with a minimum of overlap between the domains and a maximum of 45 minutes to complete the interview. The MNA combines anthropometric measures with risk factors for malnutrition (disease, mental health and functional dependency, ingestive behaviour and subjective health) [27]. The MNA is a stepwise test and is comprised of two sections. First, there is the screening section (6 items). When the score is less than 12 points, indicating the possibility of malnutrition, the assessment section (12 items) is filled in. The GFI has been developed as a simple screening instrument for frailty and a case finder for elderly patients who would benefit from integrated (geriatric) care. The GFI consists of items on physical, cognitive, social and emotional functioning with a maximum score of 15 points. Patients scoring 4 or more points are considered to be frail (appendix). The IQCODE screens for cognitive decline over the last 10 years by interviewing family members or care givers, for which we used the short Dutch translation IQCODE-N [28]. The 16 items are rated on 5-point Likert scales, ranging from much improved to much worsened, and the average score is used in the analyses. In clinical settings, a cut-off score of 3.31 reasonably balances between sensitivity and specificity on the outcome of cognitive decline with higher scores indicating poorer cognition. The MMSE has been tested extensively and is considered to be a standard test for current cognitive function. Sensitivity of the MMSE for cognitive dysfunction is 88%, the specificity is 93% [29]. The cut-off point for poor cognition is 24 points or less. If indicated by the test results, a dietician or a geriatrician was consulted because of the importance of corrective action [30].

Laboratory values and other variables

Laboratory assessment before start of chemotherapy included serum albumin (cut-off < 35g/L); hemoglobin (cut-off < 6.8 mmol/L); creatinine (cut-off ≥ 100 µmol/L) and LDH (cut-off ≥ 250 U/L). These laboratory values were recorded retrospectively from the medical files by a trained registrar. Co-morbidity was registered by Charlson's comorbidity scoring system [31]. Another way of registration for comorbidity is possible with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), but we did not choose for this system because it is more time consuming. Of course, we did not count NHL as comorbidity to calculate the Charlson comorbidity index, because NHL was the index disease. Performance status was registered by the scoring system ECOG/WHO or Karnofsky (KI) [32, 33]. Toxicity of chemotherapy in patients with early treatment withdrawal was retrospectively retrieved from the medical files and was scored according to the Common Terminology Criteria of Adverse Events (CTCAE) v. 4.03 [34].

Treatment and follow-up

According to current guidelines, patients with stage I (Ann Arbor stage [35]) were planned to be treated with at least three cycles of R-CHOP and patients with stages II-IV at least six cycles (according to scheme). When less than the number of cycles according to scheme were administered, this was considered as early treatment withdrawal.

The duration of follow-up was defined as the time between the date of the first GA until 1st January 2013 or the date of death. Vital status was checked with the nationwide population registries network at the end of the study period. These registries provide complete coverage of all deceased Dutch citizens. The cause of death was retrospectively retrieved from the medical files. Repeated assessment by GFI and MMSE was scheduled at the end of chemotherapy or at six months after start of chemotherapy.

Statistical analysis

Categorical variables are presented as numbers with percentages, chi-square tests were used to compare subgroups. We dichotomized stage in stage I and stage II-IV. Because of the small numbers of patients with an age-adjusted IPI of low risk and high risk we dichotomized the age-adjusted IPI in two categories: 0 and 1 risk factor (n = 24) versus 2 and 3 risk factors (n = 20). We also dichotomized MNA, GFI, IQ-code, MMSE, albumin, hemoglobin, creatinine and LDH according to the given cut-off scores.

To assess the association between GA scores and early treatment withdrawal, odds ratios (ORs) with 95% confidence intervals (CI) with p-values were estimated by univariate- and multivariate logistic regression analysis. Survival probabilities were estimated using Kaplan Meier curves and the log-rank test was used to test for differences in survival rates among subgroups of MNA, GFI, serum albumin, hemoglobin, serum creatinine, serum LDH and age-adjusted IPI. Association between baseline geriatric assessment scores and survival were estimated by hazard ratios (HRs) by univariate- and multivariate Cox proportional hazard analysis. Multivariate logistic regression models were adjusted for sex, age, comorbidity and univariate laboratory values with $p \leq 0.1$. The multivariate Cox regression models were adjusted for sex, age, comorbidity, age-adjusted IPI and univariate laboratory values with $p \leq 0.1$. Changes in GA-scores over time were analysed using the paired sample t-test. A p-value lower than 0.05 was considered significant. IBM-SPSS statistics 21 for Windows® (IBM-SPSS inc. Chicago, IL.) was used for statistical analyses.

Results

Characteristics and scores of the geriatric assessment are shown in table 1. The mean score (± SDs) of the MNA screening was 10.5 ± 2.6 and for the MNA assessment 13.6 ± 1.8. The mean scores of GFI, IQCODE and MMSE were 3.10 ± 0.14, 3.6 ± 2.7 and 27.7 ± 1.9 respectively.

Table 2 shows the baseline characteristics of the 44 patients treated with R-CHOP chemotherapy, of whom 43% were men. The mean age was 78 years (range 70–86), 46% were 80 years or older. The majority of patients either belonged to the low-intermediate risk category of the age-adjusted IPI (one risk factor) or to the high-intermediate risk category (two risk factors). No co-morbidities were documented in 11 (22%) patients. Most patients had diffuse large B-cell lymphoma (91%). The median follow-up was 46 months (range 0–101).

At baseline, 15 patients (34%) were at risk for malnutrition or were malnourished and 19 patients (43%) had a GFI score of four or more points. Albumin was low in 14 (32%) patients and low hemoglobin was seen in 11 (25%) patients. There were only a few patients with cognitive impairment by IQ-CODE and MMSE, 11% and 5% respectively. Creatinine and LDH were elevated in 13 (30%) and 38 (86%) patients respectively (Table 3).

Thirty-two (73%) patients received chemotherapy according to the protocol. Twelve (27%) patients failed to complete the intended number of chemotherapy cycles: 11 with stage II-IV and 1 with stage I. The most important reasons for early withdrawal were toxicity of chemotherapy (50% of cases), insufficient response, worsening of comorbidity and general condition.

Table 4 shows the association between geriatric assessment scores and laboratory variables for early treatment withdrawal. In the univariate analysis poor MNA and GFI scores, and a decreased value of hemoglobin were associated with early treatment withdrawal. In multivariate analysis, after adjustment for sex, age, comorbidity and univariate laboratory values with $p \leq 0.1$, poor MNA and GFI scores and low hemoglobin level maintained association with early treatment withdrawal: ORs 8.29 (95% CI: 1.24-55.6; p = 0.03), 9.17 (95% CI: 1.51-55.8; p = 0.02) and 5.41 (95% CI: 0.99-29.8; p = 0.05), respectively. According to the CTCAE, half of the patients with early treatment withdrawal (n = 12) had hematological toxicity grade 3 to 4. All 12 patients suffered from nonhematological toxicities such as mucositis, lung infection, depression, renal insufficiency, bad condition, atrial flutter, dysphagia, nausea, colonic- or gastric hemorrhage, and sepsis, see table 5. In a separate analysis, also adjusting for MNA and GFI, the MNA was no longer significantly associated with early treatment withdrawal, possibly reflecting that impaired nutritional status results in frailty (data not shown).

With respect to survival, 28 (65%) patients had died at the date of last follow-up. The Kaplan-Meier curves for survival, according to predefined cut-off scores, are shown in figure 2. Patients with abnormal MNA and GFI score, low

hemoglobin and elevated creatinine showed a significantly higher mortality risk. In univariate Cox regression analysis the age-adjusted IPI with 2-3 risk factors versus 0-1 risk factor showed a HR of 1.57 (95% CI: 0.74-3.31; p=0.24). In multivariate analysis (adjusted for sex, age, comorbidity, univariate laboratory values with $p \leq 0.1$ and age-adjusted IPI) abnormal GFI score and low hemoglobin predicted for mortality with HRs of 2.55 (95% CI: 1.07-6.10; p = 0.04) and 4.90 (95% CI: 1.76-13.7; p = 0.002), respectively, shown in table 6.

Most common cause of death was progression of NHL (50%). Four patients (15%) died because of toxicity of chemotherapy. Other causes were cardiovascular problems (12%), infectious problems (12%) or unknown (11%).

GFI and MMSE were repeated in only 13 patients at the end or 6 months after the start of chemotherapy; therefore meaningful analyses could not be performed.

Discussion

This prospective cohort study demonstrates that early treatment withdrawal after start of R-CHOP was associated with poor scores for MNA and GFI, and decreased levels of hemoglobin at the start of chemo-immunotherapy. An abnormal score for GFI and decreased level of hemoglobin were significantly associated with the risk of death, both in univariate and multivariate analyses. As the number of patients with cognitive impairment, measured by IQ-code and MMSE, was limited, no meaningful analyses could be performed in this regard.

It is important to realize that in this cohort of patients the hematologist decided to treat the patient with systemic therapy before GA was performed. The patients were considered fit enough for treatment with R-CHOP on clinical grounds. This probably explains the low number of patients with cognitive dysfunction as assessed by MMSE and IQ-CODE. The hematologist quite likely selected on the absence of obvious cognitive problems. Nevertheless, GA revealed considerable shortcomings in the test results of MNA and GFI, respectively in 34 and 43% of the patients. It is well accepted nowadays that a GA provides additional information to judgment by performance status and is predictive for the functional outcome in the elderly patient with cancer [12, 14].

Poor scores for MNA, GFI and anemia were associated with early withdrawal of systemic chemotherapy (inability to be treated according to scheme) and this pertains especially for the GFI and anemia. Most probably a poor score with MNA also reflects frailty. The GFI, a 15-items questionnaire (9 on physical functioning and 6 on psychosocial functioning), is an indicator for frailty, exemplified for example by a decline in self-management abilities [36]. Alternatively, the ADL and IADL questionnaires could be used. However, GFI also reflects nourishment, cognition, feelings of anxiety and depression. When frailty, defined by GFI or ADL/IADL, results in the inability to receive optimal chemo-immunotherapy, reduced survival can be expected as has been demonstrated in several studies [9, 15, 17, 37, 38). Shortcomings in IADL have been demonstrated to result in increased hematologic toxicity [39], overall grade 3-5 toxicity [40], early functional decline [41] and shorter survival [18]. The predictive model of Hurria et al on grade 3-5 toxicity also identified anemia as a risk factor [40] and moreover, anemia is part of the FLIPI risk score, albeit this score has been developed for follicular lymphomas [42, 43]. The present study showed that early treatment withdrawal was associated with toxicity of the R-CHOP regimen in 50% of the cases. Early withdrawal of systemic chemotherapy could be responsible for the reduced survival in this patients category, as also has been demonstrated in the analysis of a population-based cohort of patients aged 75 years or older with DLBCL [44]. Finally, shortcomings in MNA was found a risk factor for non-hematologic toxicity [39] as well as for early death [16].

To date, the most important prognostic value for survival is obtained by using the age-adjusted IPI [11], even in the present era in which a lot of immune-histochemical biomarkers have been investigated for additional prognostic significance [45]. Fine-tuning of the application of the IPI in the post rituximab era resulted in the so-called R-IPI [46] and for patients older than 70 years of age the E-IPI has been demonstrated to give more discriminative power in the low and low-intermediate risk groups [47]. Nevertheless, in other patient cohorts the standard IPI remained a valid predictor of outcome [48]. Others showed the absolute lymphocyte count to be an independent risk factor besides the R-IPI, ALC/R-IPI [49], or the comorbidity [50]. Especially in elderly patients, of whom the majority is not entered into clinical trials [51], population-based data [44] may provide additional insights for proper treatment decisions in this fast growing number of patients, as has been shown for comorbidity and IPI [50]. Therefore, the present study emphasizes the importance of a GA by showing that frailty by the GFI and low hemoglobin were predictive for the risk of early withdrawal of R-CHOP and mortality of patients over 70 years of age treated with R-CHOP. Notably, almost half of the patients (46%) in our study were 80 years or older and the median follow-up was 46 months, thereby augmenting the value of the data for elderly patients.

Some limitations have to be taken into account. Firstly, the cohort is small,

resulting in relatively wide confidence intervals. Secondly, a limited number of tests were selected to perform a GA, striving for a minimum need of time and a minimum of overlapping items between tests. We did not assess the response criteria standardized by Cheson [52], and therefore we could not analyze whether GA predicted for response. Thirdly, the selected patients underwent a GA after they were considered to be fit to undergo chemotherapy by their hematologist, thereby introducing selection bias. Despite these limitations the GA results revealed some interesting associations with early withdrawal of chemotherapy and mortality.

In conclusion, we found additional prognostic factors. MNA, GFI and hemoglobin were associated with early treatment withdrawal and GFI and hemoglobin were, independent of the age-adjusted IPI, predictive for an increased mortality risk. Further research in larger cohorts of elderly patients with non-Hodgkin lymphoma is needed for proper fine-tuning of prognostic factors besides the well known IPI. The value of GA to identify risk factors, suitable and elderly patients confined, is demonstrated with this study and practical judgment alone falls short in this regard. Whether appropriate interventions, based on identified risk factors by GA, can result in better outcome of treatment, should be investigated in future prospective studies. So far, the identification of GA-associated risk factors should be helpful for caution in the management strategy of the hematologist.

Table 1. Domains and measures of the Geriatric Assessment

Domain	Measure	No. of items	Description	Range of scores	Mean (SD)	Min-Max
Nutrition	MNA	6 (screening) 12 (assessment)	Identify patients at risk for malnutrition	0-14 (S) 0-16 (A) (higher score: better nutritional state)	10.5 (2.6) 13.6 (1.8)	4-14 9-16
Cognition	IQCODE	16	Screens for cognitive decline over the last 10 years by interviewing family members or care givers	1-5 (lower score: less cognitive decline)	3.10 (0.14)	3.00-3.63
	MMSE	20	Screens for cognitive dysfunction	0-30 (Higher score: better cognitive function)	27.7 (1.9)	23-30
Frailty	GFI	15	Screens for deterioration on physical, cognitive, and psycho-social items	0-15 (Higher score: more frailty)	3.6 (2.7)	0-11

Abbreviations: MNA, Mini Nutritional Assessment, a stepwise test: when the score in the screening section (S) is less than 12 points, indicating the possibility of malnutrition, the assessment section (A) is completed. With the assessment section, a total score of 24-30 points is indicative of being well-nourished, 17-23.5 points for being at risk of malnutrition, and a score of less than 17 points for being malnourished.; IQCODE, Informant Questionnaire on Cognitive Decline, ranging from much improved to much worsened, and the average score is used in the analyses; GFI, Groningen Frailty Indicator, with a maximum score of 15 points. Patients scoring 4 or more points are considered to be frail. MMSE, Mini Mental State Examination, where the cut-off point for poor cognition is 24 points or less. SD, standard deviation.

Table 2 Baseline characteristics of patients with NHL receiving R-CHOP regimen (n=44)*

	n (%)
Sex	
Male	19 (43)
Female	25 (57)
Age	
70-74 years	8 (18)
75-79 years	16 (36)
≥ 80 years	20 (46)
WHO-performance / Karnofski Index	
0 - (KI 90-100%)	31 (71)
1 - (KI 70-80%)	10 (23)
≥2 - (KI 30-60%)	3 (6)
Age-adjusted IPI	
0 - Low risk	3 (7)
1 - Low-intermediate risk	21 (47)
2 - High-intermediate risk	18 (41)
3 - High risk	2 (5)
Comorbidity (Charlson index)	
0	11 (25)
1	12 (27)
≥ 2	20 (46)
Unknown	1 (2)
Malignancy	
Diffuse large B-cell lymphoma (DLBCL)	40 (91)
Follicular lymphoma grade III	4 (9)
Stage	
Stage I	11 (25)
Stage II	11 (25)
Stage III	10 (23)
Stage IV	12 (27)

*One patient presented with stage I and three-and-a-half years later with stage II DLBCL and thus was registered twice.

Table 3. Abnormal baseline geriatric and laboratory assessment results (n=44)

Test	n (%)
MNA (Risk of) malnutrition*	15(34)
GFI (risk of) frailty (>4 points)	19 (43)
IQ-code Cognitive decline** (<3.31 points))	5 (11)
MMSE Cognitive dysfunction (<24 points)	2 (5)
Albumin Low (<35g/l)	14 (32)
Hemoglobin Low (<6.8mmol/L)	11 (25)
Creatinine Elevated (≥100 µmol/L)	13 (30)
LDH Elevated (≥250 U/L)	38 (86)

*:(Risk of) malnutrition defined as a score of ≤ 11 on the MNA screening section or less than 24 pts on the assessment section.
** (n=43).

Table 4. Geriatric and laboratory assessment scores according to failure to complete R-CHOP regimens (n=44)

	Chemotherapy					
	Completed n (%)	Not completed n (%)	**Univariate Analysis** odds ratio (95% CI)	**p-value**	**Multivariate Analysis*** odds ratio (95% CI)	**p-value**
MNA						
Well nourished	25 (78)	4 (33)				
(Risk of) malnutrition	7 (22)	8 (67)	7.14 (1.65-30.9)	0.008	8.29 (1.24-55.6)	0.03
GFI						
Not frail	22 (69)	3 (25)				
(Risk of) frailty	10 (31)	9 (75)	6.60 (1.47-29.7)	0.01	9.17 (1.51-55.8)	0.02
Albumin						
Normal	23 (72)	7 (58)				
Low (<35g/l)	9 (28)	5 (42)	1.83 (0.46-7.27)	0.39		
Hemoglobin						
Normal	27 (84)	6 (50)				
Low (<6.8 mmol/L)	5 (16)	6 (50)	5.40 (1.23-23.7)	0.03	5.41 (0.99-29.8)	0.05
Creatinine						
Normal	23 (72)	8 (67)				
Elevated (≥100 µmol/L)	9 (28)	4 (33)	1.28 (0.31-5.32)	0.74		
LDH						
Normal	3 (9)	3 (25)				
Elevated (≥250 U/L)	29 (91)	9 (75)	0.31 (0.05-1.82)	0.19		

Odds ratios were calculated using logistic regression.
Completed: **s**tage I number of cycles ≥ 3; stage II, III and IV number of cycles ≥ 6.
*Adjusted for sex, age, comorbidity and univariate laboratory values with p ≤ 0.1.
The MMSE and IQ-CODE were not taken into account due to the low variability in scores.

Table 5. Treatment related adverse events of 12 patients with early treatment withdrawal.

Toxicity type*	Grade 3-5	Grade 3	Grade 4	Grade 5
	no (%)	no (%)	no (%)	no (%)
Hematologic				
Leukocytopenia	5 (42)	4 (25)	1 (8)	
Anemia	2 (17)	2 (17)		
Trombocytopenia	2 (17)	1 (8)	1 (8)	
Nonhematologic				
Mucositis	2 (17)	2 (17)		
Lung infection	3 (25)			3 (25)
Renal insufficiency	1 (8)	1 (8)		
General condition (fragility)	1 (8)			1 (8)
Atrial flutter	1 (8)	1 (8)		
Dysphagia	1 (8)	1 (8)		
Nausea	2 (17)	2 (17)		
Colonic hemorrhage	1 (8)		1 (8)	
Gastric hemorrhage	1 (8)			1 (8)
Sepsis	3 (25)	1 (8)		2 (17)
Ileus	1 (8)	1 (8)		

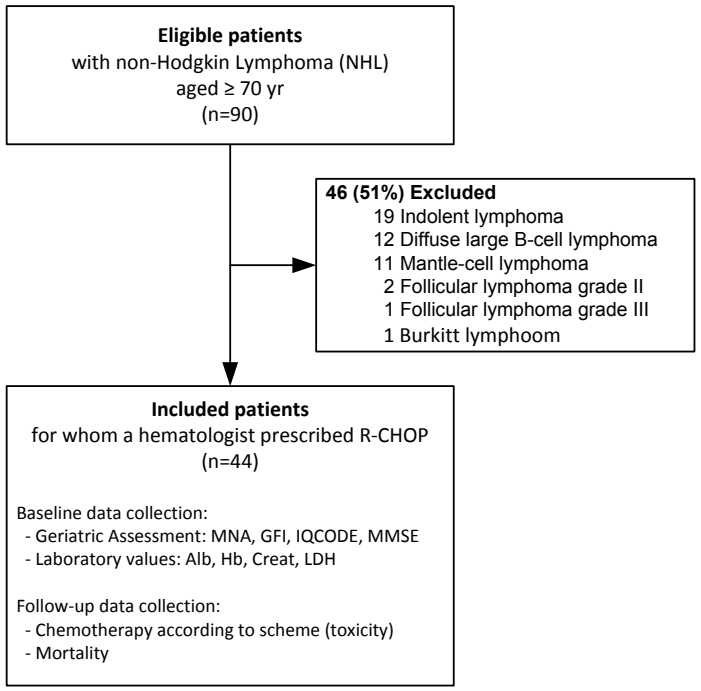
* According to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (34)

Table 6. Geriatric and laboratory assessments in relation to all cause mortality in patients with NHL treated with R-CHOP chemotherapy (n=43*)

	Alive n (%)	**Deceased** n (%)	**Univariate Analysis** hazard ratio (95%CI)	**p-value**	**Multivariate Analysis**** hazard ratio (95%CI)	**p-value**
MNA						
Well nourished	12 (80)	16 (57)				
(Risk of) malnutrition	3 (20)	12 (43)	2.11 (0.98-4.54)	0.056	1.46 (0.56-3.78)	0.44
GFI						
Not frail	11 (73)	13 (46)				
(risk of) frailty	4 (27)	15(54)	2.39 (1.11-5.14)	0.03	2.55 (1.07-6.10)	0.04
Albumin						
Normal	11 (73)	19 (68)				
Low (<35g/l)	4 (27)	9 (32)	1.83 (0.81-4.16)	0.15		
Hemoglobin						
Normal	14 (93)	18 (64)				
Low (<6.8 mmol/L)	1 (7)	10 (36)	2.45 (1.12-5.37)	0.03	4.90 (1.76-13.7)	0.002
Creatinine						
Normal	12 (80)	19 (68)				
Elevated (≥100 µmol/L)	3 (20	9 (32)	2.23 (0.98-5.12)	0.057	1.84 (0.70-4.86)	0.22
LDH						
Normal	3 (20)	3 (11)				
Elevated (≥250 U/L)	12 (80)	25(89)	0.92 (0.27-3.11)	0.90		
IPI						
Low risk + Low-intermediate risk	9 (60) 6 (40)	14 (50) 14 (50)	1.57 (0.74-3.31)	0.24		
High-intermediate risk + High risk						

HRs were calculated using Cox regression analysis.
* One patient was registered twice because of a relapse after three-and-a-half years, only the first assessment was used in the survival analysis.
** Adjusted for sex, age, comorbidity, age-adjusted IPI and univariate laboratory values with p ≤ 0.1.

Figure 1. Flow-diagram of the study



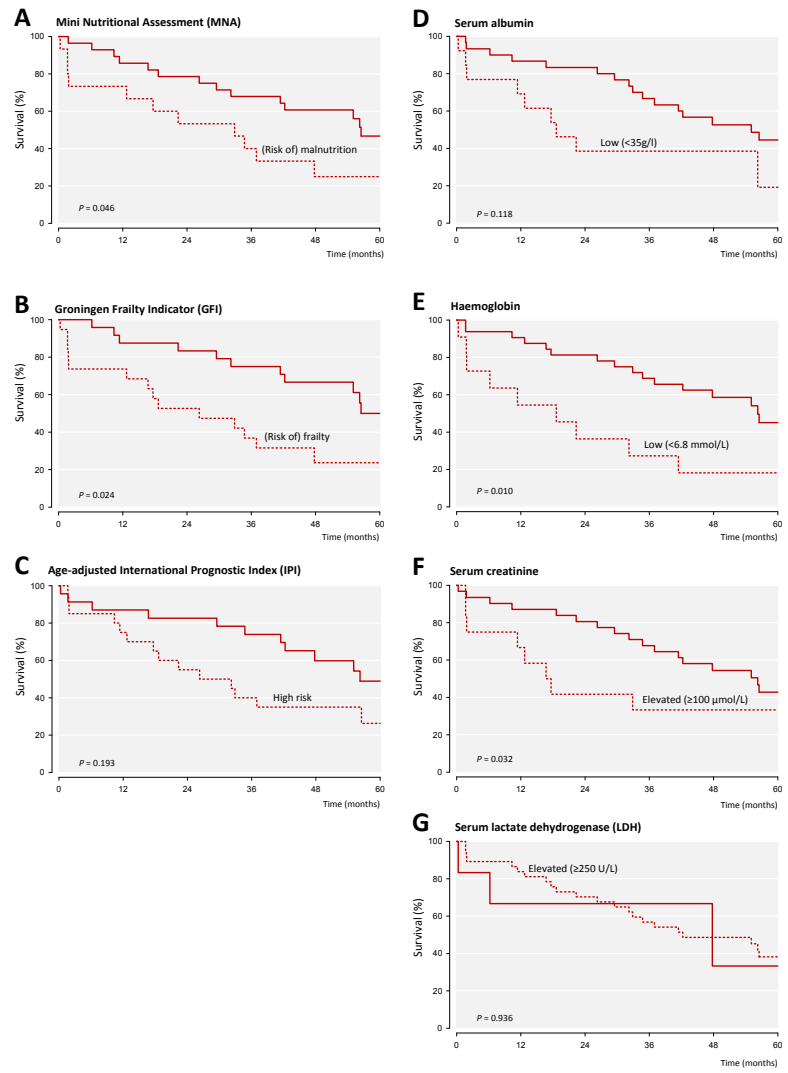


Figure 2.
Kaplan–Meier curves of overall survival during up to 60 months (i.e. 4 yr, until 31 December 2012) follow-up in patients with NHL according to categories of: [A] MNA, [B] GFI, [C] age-adjusted IPI, [D] albumin, [E] hemoglobin, [F] creatinine, and [G] LDH.
P-values by log-rank tests.

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Chapter

Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the Elderly

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Abstract

Background: Comprehensive geriatric assessment (CGA) is a multidimensional method to detect frailty in elderly patients. Time saving could be accomplished by identifying those individual items that classify elderly cancer patients at risk for feasibility of chemotherapy and for mortality.

Material and methods: Patients older than 70 years of age were assessed before the first chemotherapy administration. Geriatric assessment (GA) consisted of the Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State Examination (MMSE). Predictive individual items for feasibility of chemotherapy and mortality were entered in the multivariable logistic regression and Cox-regression models, and a three-item sum scale was constructed: the Geriatric Prognostic Index (GPI).

Results: The 494 patients had a median age of 75 years (range 70-92 years). The majority of the patients had malignancies of the digestive tract (41.7%) followed by haematological tumors (22.3%). Three items of the MNA ('psychological distress or acute disease in the past three months', 'neuropsychological problems' and 'using > 3 prescript drugs') independently predicted for feasibility of chemotherapy. Two items of the MNA and one of the GFI ('declining food intake in past 3 months', 'using >3 prescript drugs', and 'dependence in shopping') independently predicted for mortality. In comparison with patients without any positive item on the three-item GPI, patients with one, two or three positive items had hazard ratios (HRs) of 1.58, 2.32, and 5.58, respectively (all $p < 0.001$).

Conclusions: With only three items of the MNA, feasibility of chemotherapy can be predicted. The three-item GPI may help to identify elderly cancer patients at elevated risk for mortality.

Background

The majority of persons with cancer is older than 65 years of age, and 70% of cancer mortality occurs in this age cohort [1]. As a result of demographic changes, the demand for care and treatment of older people with cancer will strongly increase in the coming decades.

Comprehensive geriatric assessment (CGA) is a multidimensional method to provide objective information on comorbidity, functional status, social support, polypharmacy, nutritional- and psychosocial status [2]. As geriatric problems increase sharply after 70 years of age in cancer patients, the guidelines of the International Society of Geriatric Oncology (SIOG) recommend that all patients with cancer and an age above 70 years should undergo some form of GA [3]. However, to conduct a full CGA is time consuming and associated with high costs. Therefore, a two-step approach could be a pragmatic alternative by using a brief screening tool. Well known examples of screening tools are formed by abbreviated CGA (aCGA) [4], Vulnerable Elders Survey (VES-13) [5], the Geriatric 8 (G8) [6], Groningen Frailty Indicator (GFI) [7], Flemish version of the Triage Risk Screening Tool (fTRST) [8] and others [9]. Nevertheless, further time saving might be accomplished by identifying the essential items of such screening tools. For example, this has been shown to be applicable for the Mini Nutritional Assessment (MNA) [10]. The study of osteoporotic fractures (SOF) index was developed from frequently cited physiologic domains in the frailty literature [11, 12] and appeared accurate in comparison with CGA for the detection of frailty in cancer patients [13]. The geriatric vulnerability score (GVS) appeared applicable for elderly patients with advanced ovarian cancer treated with carboplatin [14].

The present cohort of elderly cancer patients, collected in the region of the Comprehensive Cancer Center West in the Netherlands, offered the opportunity to analyze and determine which elements of the chosen geriatric screening program were independently predictive for feasibility of chemotherapy and mortality.

Material and methods

Patients older than 70 years of age with various types of cancer (N = 520) were prospectively assessed before chemotherapy administration with either curative or palliative intent. The decision for treatment with chemotherapy had already been made by the treating (hemato)-oncologist on clinical grounds. The patients had been considered to be fit enough to receive chemotherapy. The collection of data was accomplished between May 2004 and February 2010 in three general and one university hospital: the hospital of the Reinier de Graaf Groep in Delft, Groene Hart hospital in Gouda, Haga hospital in The Hague, and the Leiden University Medical Center in Leiden. After February 2010 no more funding was available for data management, thus prohibiting further inclusion of patients in

this prospective registration cohort. We excluded 25 patients because they did not start with chemotherapy and one patient because of age.

GA consisted of the MNA, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), GFI and Mini Mental State Examination (MMSE). These tests were selected for performing a GA with a minimum of overlap between the domains, and a maximum duration of 45 minutes to complete the interview. The tests have been described in detail previously [15]. The appendices provide details on these tests. Patients scoring 4 or more points on the GFI were considered to have a moderate to severe frailty. The IQCODE screens for cognitive decline over the last 10 years by interviewing family members or caregivers. We used the short 16 items Dutch translation IQCODE-N [16]. The MMSE has been tested extensively and is considered to be a standard test for current cognitive function.

Feasibility of chemotherapy was defined by the inability to complete the intended number of cycles of chemotherapy: at least four cycles. This number was arbitrarily chosen as a surrogate endpoint, realizing that four cycles cannot be considered as the standard number of cycles. It was considered likely, that if at least four cycles could be administered, then patients could be treated with the intended total dose of chemotherapy. The small group of patients with aggressive non-Hodgkin lymphoma stage I who were treated with the intended number of three cycles of chemo(-immuno)therapy and involved field radiotherapy, were grouped under the heading of four or more cycles of chemotherapy.

The duration of the follow-up was defined as the difference between the date of the first GA and 1st January 2013 or the date of death. Vital status and last follow-up date were recorded from the patient's medical record. If indicated by the test results, a dietician or a geriatrician was consulted.

Statistical analysis

To identify the most relevant individual items of the MNA, GFI, IQ-CODE and MMSE, every single item was dichotomized. Details are given in addendum 1.

Categorical variables are presented as numbers with percentages and continuous variables as medians with their range. Logistic regression analysis and Cox regression analysis on (items of) the MNA, GFI, IQCODE and MMSE for the prediction of feasibility of chemotherapy and mortality obtained odds ratios (ORs) and hazard ratios (HRs), respectively. To avoid type I errors in multiple testing, a p-value < 0.01 was considered statistically significant. All multivariable models were adjusted for sex, age, purpose of treatment, and type of malignancy.

Those questionnaires of the MNA, GFI, IQCODE and MMSE that independently predicted for feasibility of chemotherapy or mortality ($p < 0.01$) were used in further analyses with the dichotomized composite items. When individual items were predictive for feasibility of chemotherapy and mortality ($p<0.01$), these were included in multivariable logistic regression and Cox-regression models. Forward stepwise procedures were used in both the logistic and Cox regression models, with an entry criterion of $p<0.01$ and the removal criterion of $p>0.10$. As sensitivity analysis, the variable selection procedures were rerun using backward stepwise selection. Subsequently, the independent predictive items for mortality were summed, and this sum score was analyzed using the multivariable adjusted Cox regression model. In stratified analyses, the predictors for mortality were tested separately in the palliative treated and adjuvant/curative treated groups. The models were internally validated by calculating c-statistics, which are measures for the discriminative performance of the models, using bootstrapping to take into account that the models were developed and validated on the same data [17]. For logistic regression the c-statistic is equal to the area under the curve of a ROC curve. Statistical tests and analyses were performed using SPSS 21 for Windows® (SPSS inc. Chicago, IL. USA) and R 3.1.0 [18] using package rms (Regression Modeling Strategies) [19].

Results

A total of 494 patients with various types of cancer were evaluated. Table 1 shows the baseline characteristics of the patients.

The scores of the GA are shown in table 2. Roughly one-third of the patients showed shortcomings with the MNA and the GFI, and some 10% of the patients had cognitive problems. In total 353 patients were treated with four or more cycles of chemotherapy, of whom 61% were treated with full dose and 39% with an adapted dose. A total of 141 patients (29%) could not complete at least four cycles of chemotherapy. In this group, 69% of the patients were treated with full dose, and 31% received an adapted dose (a decision of the treating oncologist). The reasons for early treatment withdrawal were complications of chemotherapy (50%), deteriorating general condition (11%), ineffectiveness of chemotherapy (10%), worsening comorbidity (2%) and others (27%). Addendum 2 gives information on applied chemotherapy regimens. Of course, this shows a large variety in this cohort of patients.

The median follow-up was 17 months (range 1-101) for all patients, and 61

months (range 44-101) for the 99 survivors. The most common cause of death was cancer progression (84.0%). Other causes were treatment related (3.1%), cardiovascular mortality (2.3%), or unknown causes (10.6%).

The effect of the MNA, GFI, IQCODE and MMSE on feasibility of chemotherapy and mortality are given in table 3. Patients with adverse scores on the MNA and GFI had a higher odds to stop chemotherapy before the 4th cycle with ORs of 2.21 (95% confidence interval [CI]: 1.48-3.31; $p < 0.001$) and 1.71 (95% CI: 1.13-2.58; $p = 0.01$), respectively. After adjusting for gender, age, purpose of treatment and type of malignancy only the MNA was significantly related to feasibility with a p value < 0.01: OR 2.30 (95% CI: 1.48-3.58; $p < 0.001$). The MNA remained a significant predictor after additional adjustment for GFI (OR 2.12 (95% CI: 1.33-3.39; $p = 0.002$). With respect to mortality, an adverse score for MNA and GFI was associated with increased HRs for mortality of 1.68 (95% CI: 1.37-2.06; $p < 0.001$) and 1.47 (95% CI: 1.19-1.82; $p < 0.001$), respectively. After adjustment for gender, age, purpose of treatment and type of malignancy, these HRs remained significant (1.86; 95% CI: 1.48-2.34; $p < 0.001$; and 1.77; 95% CI: 1.41-2.22; $p < 0.001$, respectively).

Table 4 shows the univariable significant individual items (with $p < 0.01$) of MNA for feasibility of chemotherapy and of the GFI and MNA for mortality. In the stepwise selection procedure, three items of the MNA independently predicted feasibility ['psychological distress' (MNA-D), 'neuropsychological problems' (MNA-E) and 'using > 3 prescript drugs' (MNA-H)], with ORs of 2.10 (95% CI: 1.31-3.38; $p = 0.002$), 3.44 (95% CI: 1.50-7.90; $p = 0.004$) and 1.96 (95% CI: 1.27-3.03; $p = 0.002$), respectively. Two items of the MNA ['declining food intake in past 3 months' (MNA-A) and 'using > 3 prescript drugs' (MNA-H)] and one item of the GFI ['dependence in shopping' (GFI-Q1)] independently predicted for mortality, with HRs of 1.82 (95% CI: 1.47-2.24; $p < 0.001$), 1.38 (95% CI: 1.12-1.71; $p = 0.003$) and 1.77 (95% CI: 1.31-2.40; $p < 0.001$), respectively. In sensitivity analyses a backward stepwise selection procedure resulted in the same three items. Table 5 shows the c-statistic of the different models. For mortality the outcome increased from 0.66 to 0.70 when adding MNA(A), MNA(H) and GFI(Q1) to the model. This indicates that these three dichotomous variables gave additional predictive value to the model. Similarly, the items MNA(D), MNA(E), and MNA(H) added predictive value to the outcome variable feasibility, increasing the c-statistic from 0.61 to 0.69.

A sum score, the Geriatric Prognostic Index (GPI), was constructed using the three items with increased HRs for mortality. With one positive item the HR was 1.58 (95% CI: 1.24-2.02; $p < 0.001$), with two positive items 2.32 (95% CI: 1.76-3.06; $p < 0.001$), and with all three items 5.58 (95% CI: 3.48-8.61; $p < 0.001$), in comparison with no positive item. The median survival with the GPI was 2.26 years with score 0, 1.34 years with score 1, 0.95 years with score 2 and 0.56 years with score 3 (figure 1).

The effect of the three predictive items for mortality was studied separately in the palliative (N = 288) and adjuvant/curative (N = 206) treated patients. The three items (MNA-A, MNA-H and GFI-Q1) remained significant in the palliative treated group with HRs of 2.02 (95% CI: 1.54-2.65; $p < 0.001$), 1.54 (95% CI: 1.19-2.00; $p = 0.001$) and 1.89 (95% CI: 1.30-2.74; $p = 0.001$), respectively. In the adjuvant/curative treated group the GFI-Q1 remained associated with mortality (HR 2.22 [95% CI: 1.28-3.83; $p = 0.004$]), but the effect of MNA-A and MNA-H was smaller (HR 1.31 [95% CI: 0.90-1.93; $p = 0.17$] and 1.30 [95% CI: 0.89-1.92; $p = 0.18$], respectively).

Discussion

In this study among 494 elderly cancer patients the result of the MNA test was predictive for the risk of premature discontinuation of chemotherapy. Furthermore, a three-item Geriatric Prognostic Index (GPI) was constructed, that predicted for mortality. It has to be stressed that these 494 patients were considered to be fit for treatment with chemotherapy before the GA was performed.

CGA is an evidence-based method to evaluate deficits and frailty in elderly cancer patients [3]. This diagnostic tool provides information for the process leading up to the treatment plan and may recognize previously unaddressed problems, creating opportunities to improve functional status and resources of old cancer patients [3]. It may even contribute to prolonged survival and may help to weigh the benefits against the risks of chemotherapy and identify patients that may be too frail to profit from this demanding form of treatment [3].

Already, the literature of geriatric oncology highlighted scoring systems for the toxicity of chemotherapy [20, 21]. Hurria *et al.* identified three risk strata for grade 3-5 toxicity, with 11 risk factors [21], while the CRASH score of Extermann *et al.* identified four risk factors for hematologic and nonhematologic toxicity each, discerning four risk categories for grade 4 hematologic toxicity and grade 3-4 nonhematologic toxicity [20]. Hoppe *et al.* identified depression and dependence for instrumental activity of daily living (IADL) as risk factors for early functional decline during chemotherapy [22]. The GVS showed increased toxicity with three or more risk factors of albumin, lymphocyte count, and scores of

Activity of Daily Living (ADL), IADL and Hospital Anxiety and Depression Scale, for patients with advanced ovarian cancer and treatment with carboplatin [14]. The present study concentrated on the inability to complete at least four cycles of chemotherapy and showed that in the case of (risk of) malnutrition by MNA the chance not to complete chemotherapy increased more than two-fold. The large variety of chemotherapy regimens, shown in addendum 2, precluded analyses of specific schedules. However, for all schedules given adequate dose intensity is essential, whether it is given for palliative or curative reasons. The reasons for early treatment withdrawal in our study form common reasons in general oncology practice to decide on stopping chemotherapy. And of course it is legitimate to ask the question, whether one should have started chemotherapy at all, when this only results in toxicity and early treatment withdrawal [2, 3, 23, 24].

Others concentrated in their research on risk factors for mortality [24, 25]. Kanesvaran *et al.* developed a Clinical Scoring System (CSS) in an Asian population, consisting of the factors age, albumin, ECOG performance status, depression, stage of disease and nutritional index. A nomogram predicted overall survival rate [25]. Soubeyran *et al.* identified male gender, advanced stage, poor MNA and decreased mobility as risk factors for early death [24]. The GVS showed significantly worse survival with the same risk factors as shown for toxicity [14]. As previously shown in a smaller cohort [15], the present study identified poor MNA and poor GFI as risk factors for mortality. In general, CGA contains components that predict for mortality [23]. These data show the importance of the nutritional status and frailty score as part of pre-treatment assessment to select patients who might benefit from interventions.

Screening tests have been developed to help for the identification of frailty and select the patients who might benefit from extensive CGA [9]. However, screening tools still contain 5 - 15 items [4, 8], which may lead to a barrier against broad usage in clinical care. Many health workers aim for a balance between optimal health-care and a minimal burden to patients and caregivers [5, 6]. To improve pretreatment assessment it is not always necessary to complete a full version of a (self-reported) questionnaire. The aCGA used seven of 16 ADL/IADL items for detection of shortcomings [4]. The three-item SOF index showed a sensitivity and specificity of 89.0 and 81.1, respectively, for the detection of disabilities in comparison with CGA [13]. The GVS score was developed for elderly patients with advanced ovarian cancer and treatment with carboplatin [14].

Regarding feasibility of chemotherapy, this study shows that three items of the MNA were predictive in multivariable analysis: “psychological stress or acute disease in the past three months”, “neuro psychological problems” and “using more than three prescript drugs”. These items seem comparable with items used by Hurria et al: “decreased social activity because of physical/emotional health, limited at least sometimes” and “taking medications with some help/unable” [21]. Depression was one of the risk factors for early functional decline, as shown by Hoppe et al [22], and was also a risk factor of the GVS [14]. The MNA-score as a whole was one of the risk factors for nonhematologic toxicity, identified with the CRASH score [20].

The present study introduces the GPI as instrument for the prediction of mortality. Two items of the MNA (MNA-A and MNA-H) and one item of GFI (GFI-Q1) proved to be highly predictive for mortality. In comparison with no positive items the patients with all three items positive showed a HR for mortality of 5.58 (95% CI 3.48-8.61; $p < 0.001$). This holds especially for the palliative treated patients. The GPI cannot be compared with the SOF index [13], which has not been correlated with mortality, nor with the CSS [25] (developed in an Asian population), nor with the GVS [14] (tumor- and treatment specific score). The GPI concentrates on decreased food intake, polypharmacy and dependence in shopping. Poor score of MNA was identified as risk factor of early death by Soubeyran et al, but this study was not analyzed which factor(s) of the MNA contributed mostly [24]. Dependence in shopping was also identified by others as important risk factor for detection of disabilities [4].

The GPI could support the use of chemotherapy in patients with score 0-1, whereas a more thorough CGA would be warranted for those patients scoring 2 (median survival in this cohort almost one year) and the use of chemotherapy should be questioned in patients with score 3 (median survival of only six months). A potential form of bias exists for MNA-H, due to the fact that all patients with a normal screening score on the MNA were given score 1 (see appendix). Therefore the GPI should be validated in an independent study population of elderly cancer patients.

Some limitations have to be mentioned. First, a variety of cancer types were included. However, we adjusted for cancer type in our multivariable models. Another source of heterogeneity may have been the fact that different chemotherapy regimens were given of which not all were given in the full doses. Second, the selected patients underwent a GA after they were considered to be fit to undergo chemotherapy by their oncologist, thereby introducing selection bias. Nevertheless, considerable shortcomings appeared to be present at baseline regarding GFI and MNA. Third, we tested the individual items of the MNA, GFI, IQCODE and MMSE resulting in a three-item GPI. Type I errors occurs in multiple testing and therefore we selected only individual items that were predictive in crude models with a p

value < 0.01 and in forward stepwise regression models with an entry criterion of p < 0.01. Fourth, models were developed and validated on the same dataset. The GPI therefore needs to be validated in future studies of elderly cancer patients. A strength of the study is that we did analyze separately the adjuvant/curatively and the palliatively treated patients for the effect of the GPI on mortality.

In conclusion, our results show that a poor MNA score was predictive for not completing four cycles of chemotherapy and poor MNA- and GFI scores were predictive for mortality of elderly patients with various types of cancer. 'Psychological stress', 'neuropsychological problems' and 'number of drugs taken' were predictive items of MNA for feasibility of chemotherapy. 'Declining food intake', 'number of drugs taken' and 'dependence in shopping' were the three predictive items for a higher risk of mortality, resulting in the GPI. Hazard ratios for mortality increased linearly with sum scores increasing from 0 to 3 points. The GPI can help to identify the elderly patient at increased risk for mortality, who beforehand is considered to be fit enough to receive treatment with chemotherapy.

Table 1. Baseline characteristics of 494 elderly cancer patients.

	Median	*N* (%)
Age	75 (70-92)	
70-74 years		237 (48.0)
75-79 years		170 (34.4)
≥ 80 years		87 (17.6)
Male gender		246 (49.9)
Type of malignancy:		
Upper digestive tract		64 (13.0)
Lower digestive tract		142 (28.7)
Haematological		110 (22.3)
Breast		61 (12.3)
Gynaecological		38 (7.7)
Prostate		29 (5.9)
Lung		21 (4.3)
Urinary tract		11 (2.2)
Other		18 (3.6)
Purpose of treatment:		
Adjuvant/ curative		206 (41.7)
Palliative		288 (58.3)

Table 2. Results of the geriatric assessments of 494 elderly cancer patients.

Test	Score	*N* (%)
MNA*	well nourished	316 (64.5)
	(risk of) malnutrition *	174 (35.5)
	unknown	4
GFI	< 4 pts	344 (69.8)
	≥ 4 pts	149 (30.2)
	unknown	1
IQCODE	≤ 3.30 pts	418 (87.1)
	> 3.30 pts	62 (12.9)
	unknown	14
MMSE	> 24 pts	445 (91.0)
	≤ 24 pts	44 (9.0)
	unknown	5

*(Risk of) malnutrition defined as a score of ≤ 11 on the MNA screening section or less than 24 pts on the assessment section (see appendix).

Table 3. Outcome of geriatric assessment of MNA (*N*=490), GFI (*N*=493), IQCODE (*N*=480) and MMSE (*N*=489) for feasibility of chemotherapy and overall mortality in elderly cancer patients.

Feasibility	*N*=353 ≥ 4 cycles; *n* (%)	*N*=141 < 4 cycles; *n* (%)	Univariable Analysis; odds ratio (95% CI)	P-value	Multivariable Analysis*; odds ratio (95% CI)	P-value
MNA						
Well nourished	245 (69.8)	71 (51.1)	ref		ref	
(Risk of) malnutrition	106 (30.2)	68 (48.9)	2.21 (1.48-3.31)	<0.001	2.30 (1.48-3.58)	<0.001
GFI						
Not frail	258 (73.1)	86 (61.4)	ref		ref	
(risk of) frailty	95 (26.9)	54 (38.6)	1.71 (1.13-2.58)	0.01	1.68 (1.08-2.62)	0.02
IQCODE						
Normal risk	300 (87.0)	118 (87.4)	ref			
Cognitive decline	45 (13.0)	17 (12.6)	0.96 (0.53-1.75)	0.90	–	
MMSE						
No cognitive dysfunction	322 (92.3)	123 (87.9)	ref			
Cognitive dysfunction	27 (7.7)	17 (12.1)	1.65 (0.87-3.13)	0.13	–	
Mortality	**Alive; *N* (%)**	**Deceased; *N* (%)**	**Univariable Analysis; hazard ratio (95% CI)**	**P-value**	**Multivariable Analysis*; hazard ratio (95% CI)**	**P-value**
MNA						
Well nourished	75 (76.5)	241 (61.5)	ref		ref	
(Risk of) malnutrition	23 (23.5)	151 (38.5)	1.68 (1.37-2.06)	<0.001	1.86 (1.48-2.34)	<0.001
GFI						
Not frail	75 (76.5)	269 (68.1)	ref		ref	
(risk of) frailty	23 (23.5)	126 (31.9)	1.47 (1.19-1.82)	<0.001	1.77 (1.41-2.22)	<0.001
IQCODE						
Normal risk	86 (88.7)	332 (86.7)	ref			
Cognitive decline	11(1.3)	51 (13.3)	1.12 (0.83-1.50)	0.46	–	
MMSE						
No cognitive dysfunction	90 (92.8)	355 (90.6)	ref			
Cognitive dysfunction	7 (7.2)	37 (9.4)	1.36 (0.97-1.91)	0.08	–	

Hazard and odds ratios (with 95% confidence intervals [CI]) were calculated using either Cox regression or logistic regression analysis.
* Adjusted for sex, age, purpose of treatment, type of malignancy.

Table 4. Independent effects of MNA and GFI items for feasibility of chemotherapy and overall mortality in 494 elderly cancer patients.

Feasibility	Present *N* (%)	≥ 4 cycles; %	< 4 cycles; %	Univariable Analysis; odds ratio (95% CI)	P-value	Multivariable Analysis; odds ratio (95% CI)	P-value
MNA							
Declining food intake in past 3 months (A)*	217 (44.2%)	39.3%	56.4%	2.00 (1.34-3.00)	0.001	–	–
Weight loss in past 3 months (B)	179 (36.5%)	32.3%	47.1%	1.88 (1.26-2.80)	0.002	–	–
Psychological stress or acute disease in past 3 months (D)	120 (24.4%)	19.7%	36.4%	2.34 (1.52-3.61)	< 0.001	2.10 (1.31-3.38)	0.002
Dementia or depression (E)	35 (7.1%)	4.6%	13.6%	3.29 (1.64-6.60)	0.001	3.44 (1.50-7.90)	0.004
Using > 3 prescript drugs (H)	181 (36.6%)	31.7%	48.9%	2.06 (1.38-3.07)	< 0.001	1.96 (1.27-3.03)	0.002
Self view of nutritional status (O)	99 (20.0%)	17.0%	27.7%	1.87 (1.18-2.96)	0.008	–	–
Poor self-rated health (P)	129 (26.1%)	22.1%	36.2%	2.00 (1.31-3.06)	0.001	–	–
Mortality	**Present *N* (%)**	**Alive; %**	**Deceased; %**	**Univariable Analysis; hazard ratio (95% CI)**	**P-value**	**MultivariableAnalysis; hazard ratio (95% CI)**	**P-value**
MNA							
Declining food intake in past 3 months (A)	217 (44.2%)	32.7%	47.1%	1.63 (1.33-1.98)	< 0.001	1.82 (1.47-2.24)	< 0.001
Psychological stress or acute disease in past 3 months (D)	120 (24.4%)	14.3%	27.0%	1.38 (1.11-1.73)	0.004	–	–
Using > 3 prescript drugs (H)	181 (36.6%)	24.2%	39.7%	1.58 (1.29-1.94)	< 0.001	1.38 (1.12-1.71)	0.003
Declining protein intake (K)	90 (18.2%)	12.1%	19.7%	1.49 (1.16-1.91)	0.002	–	–
Intake ≤ 5 cups of fluid per day (M)	35 (7.1%)	2.0%	8.4%	1.76 (1.23-2.52)	0.002	–	–
Self-rated nutritional problems (N)	99 (20.0%)	11.1%	22.3%	1.81 (1.42-2.30)	< 0.001	–	–
Poor self-rated health (P)	129 (26.1%)	18.2%	28.1%	1.62 (1.30-2.02)	< 0.001	–	–
GFI							
Dependence in shopping (Q1)	59 (12.0%)	4.1%	13.9%	2.02 (1.51-2.69)	< 0.001	1.77 (1.31-2.40)	< 0.001
Dependence in (un)dressing (Q3)	12 (2.4%)	0.0%	3.0%	2.34 (1.31-4.16)	0.004	–	–
Poor self-rated physical fitness (Q5)	196 (39.8%)	29.6%	42.3%	1.42 (1.16-1.74)	0.001	–	–
Weight loss in past 6 months (Q8)	191 (38.7%)	32.7%	40.3%	1.38 (1.13-1.69)	0.002	–	–

Hazard and odds ratios (with 95% confidence intervals [CI]) were calculated using either Cox regression or logistic regression analysis. Independent predictors in a multivariable Cox-regression model using a stepwise procedure with an entry criterion of p<0.01 , while adjusted for sex, age, purpose of treatment, and type of malignancy.
* A: Item A of MNA, Q5: question 5 of GFI.

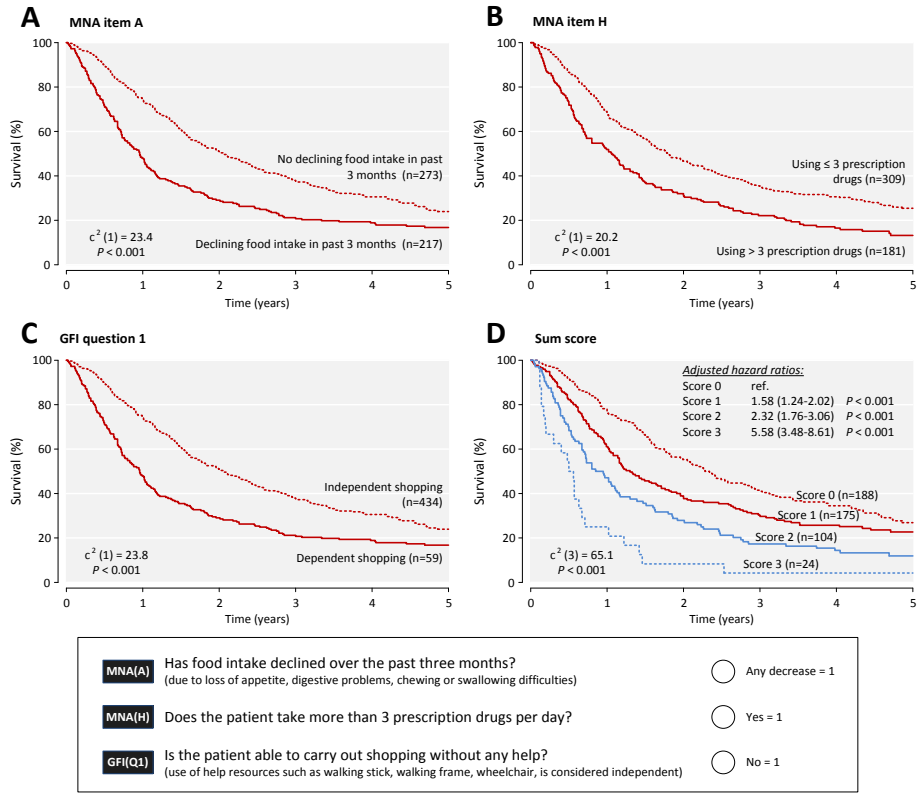
Table 5.

C-statistic coefficients of the different additional models for feasibility of chemotherapy and mortality.

Model	Feasibility	Mortality
Gender, age, purpose of treatment, and type of malignancy	0.61	0.66
MNA + GFI, dichotomized	0.65	0.69
MNA-D + MNA-E + MNA-H	0.69	--
MNA-A + MNA-H + GFI-Q1	--	0.70
GPI score	--	0.70

MNA-A: Declining food intake in past 3 months; MNA-D: Psychological stress or acute disease in past 3 months;
MNA-E: Dementia or depression; MNA-H: Using > 3 prescript drugs; GFI-Q1: Dependence in shopping.

Figure 1



Kaplan–Meier curves of overall survival in 494 elderly patients with various types of cancer according to: [A] MNA item A, [B] MNA item H, [C] GFI question 1 and [D] sum score of these three items. P-values by log-rank tests.

Addendum 1.

Dichotomized items of the screening tests.

With MNA the individual items were dichotomized as follows;
- item A: score 0/1 vs score 2
- item B: score 0/1 vs score 2/3
- item C: score 0/1 vs score 2
- item E: score 0/1 vs score 2
- item F: score 0/1/2 vs score 3
- item J: score 0 vs score 1/2
- item K: score 0.0/0.5 vs score 1.0
- item M: score 0.0/0.5 vs score 1.0
- item N: score 0/1 vs score 2
- item O: score 0/1 vs score 2
- item P: score 0.0/0.5 vs score 1.0/2.0
- item Q: score 0.0/0.5 vs score 1.0

The cut-off score for the items of the IQ-CODE was between 'nothing changed' and 'worse'.

The cut-off score for the items of the MMSE according to Small et al.* were;
- 'immediate memory': ≥ 2 points,
- 'serial sevens': ≥ 3 points,
- 'delayed memory': ≥ 2 points
- 'follow commands': ≥ 2 points,

* From: Small, B.J. et al., *Mini-Mental State Examination item scores as predictors of Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. J Gerontol A Biol Sci Med Sci, 1997. 52(5): p. M299-304.*

Addendum 2
Chemotherapy of malignancies

Type of malignancy	Chemotherapy	N (%)
Upper digestive tract (N=64)	Platina combination therapy	47 (73.5)
	Gemcitabine	13 (20.3)
	Capecitabine	2 (3.1)
	Platina mono therapy	2 (3.1)
Lower digestive tract (N=142)	5-fluoropyrimidine combination therapy	82 (57.8)
	5-fluoropyrimidine mono therapy	54 (38.0)
	Irinotecan mono therapy	4 (2.8)
	Platina combination therapy	2 (1.4)
Haematological (N=110)	Combination chemotherapy (mostly rituximab, cyclophosphamide, hydroxydaunomycin, oncovin, prednisone (R-CHOP))	82 (74.5)
	Multiple myeloma directed therapies (vincristin-adriamycin-dexamethasone (VAD), bortezomib and combinations, melphalan and combinations)	18 (16.4)
	Mono therapy (chloorambucil, fludarabine, methotrexate, decitabine, rituximab)	10 (9.1)
Breast (N=61)	Capecitabine mono therapy	16 (26.1)
	Anthracycline mono therapy	9 (14.8)
	Anthracycline combination therapy	9 (14.8)
	Paclitaxel	6 (9.8)
	Docetaxel	3 (4.9)
	Taxane combination therapy	4 (6.6)
	CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil)	4 (6.6)
	Vinorelbine	4 (6.6)
	Anthracyclines + Taxane	4 (6.6)
	Herceptin	1 (1.6)
	Gemcitabine	1 (1.6)
Gynaecological (N=38)	Platina combination therapy	25 (65.8)
	Platina mono therapy	12 (31.6)
	Melphalan	1 (2.6)
Prostate (N=29)	Docetaxel	28 (96.6)
	Mitoxantrone	1 (3.4)
Lung (N=21)	Platina combination therapy	17 (81)
	CDE (cyclophosphamide, doxorubicin, etoposide)	4 (19)
Urinary tract (N=11)	Platina combination therapy	8 (72.7)
	M-VAC (methotrexate, vinblastin, adriamycin, cisplatin)	2 (18.2)
	Platina mono therapy	1 (9.1)

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Chapter

Summary and general discussion
Samenvatting en algemene discussie

7

Summary and general discussion

The decision to treat elderly patients with cancer aged 70 years or older with chemotherapy is generally based on clinical judgment of the clinician, in combination with the evidence obtained from clinical studies performed in younger age groups. This clinical judgment often falls short to characterize the actual condition of the elderly in full details. The instrument of geriatric assessment (GA) might be helpful to detect these hidden shortcomings and may aid clinical decision making with regard to the feasibility of treatment with chemotherapy and prediction of survival in the elderly patients with cancer. This thesis is the result of clinical research on certain elements of GA that might be useful for routine daily oncology practice, in order to select the proper patients and improve the outcome of treatment with chemotherapy.

Summary

Chapter 2 describes the role of GA on 202 patients with a mean age of 77 years (range 71-92 years), all treated at the Reinier de Graaf hospital in Delft. The majority were women (55%), and most of the patients had colorectal cancer (30%) followed by haematological malignancies (18%) and breast cancer (17%). The GA consisted of the Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Index (GFI) and Mini Mental State Examination (MMSE). Furthermore, among 51 patients the assessment by MMSE and GFI was repeated after at least four cycles of chemotherapy or at six months after start of treatment with the aim to assess the impact of the given chemotherapy. At baseline, adversities were detected in 33% of patients on the MNA, in 37% on the GFI, in 10% on the MMSE and in 15% on the IQCODE. The percentage of patients who could not complete at least four cycles of chemotherapy was significantly different in comparison with patients who underwent four or more cycles with respect to the average scores on the MNA and MMSE ($p = 0.001$ and $p = 0.04$, respectively). The mortality rate after the start of chemotherapy was higher for patients with low (vs. high) MNA scores and high (vs. low) GFI scores, with hazard ratios (HRs) of 2.19 (95% confidence interval [CI]: 1.42-3.39; $p < 0.001$) and 1.80 (95% CI: 1.17-2.78; $p = 0.007$), respectively. After adjustment for sex, age, purpose of chemotherapy and type of malignancy, the increased HRs for mortality persisted. The post-chemotherapy evaluation by GFI and MMSE showed a significant deterioration for the MMSE ($p = 0.041$) but not for the GFI ($p = 0.476$). In conclusion, inferior test results of MNA, and for a lesser extent of the MMSE, were predictive for the inability to complete 4 cycles of chemotherapy, while patients with unfavourable MNA and GFI scores showed increased mortality rates.

Chapter 3 concentrates on the results of the outcome of GA in 55 patients with breast cancer, who had a mean age of 76 years (range 70–88 years, 20% were older than 80 years). Apart from the above mentioned GA, also the results of laboratory tests at baseline for serum albumin, haemoglobin, creatinine and lactate dehydrogenase (LDH) were taken into consideration in relation to the outcome of palliative chemotherapy. Twenty-one patients underwent post-chemotherapy evaluation by GFI and MMSE. Abnormal test results were present in 42% patients for MNA, 51% for GFI, 18% for IQCODE and 9% for MMSE. Laboratory tests were abnormal in 13%, 33%, 78% and 84% of the patients, respectively for creatinin, albumin, haemoglobin and LDH. Besides the inverse correlation of MNA and GFI ($r = -0.43$; $P < 0.001$) and the inverse correlation of IQCODE and MMSE ($r = -0.36$; $P = 0.01$), no significant correlations between the GA tests results and laboratory tests results were found. However, disability according to WHO-performance status was correlated with an inferior test result of MNA ($r = -0.28$, $p = 0.04$) and GFI ($r = 0.38$, $p = 0.004$).

There was no significant difference between the number of patients ($n = 39$) who underwent at least 4 cycles of chemotherapy compared to patients who underwent less than 4 cycles ($n = 16$) with regard to GA and laboratory parameters (neither after adjusting for age, comorbidity and WHO performance status). Inferior MNA and GFI scores were associated with increased mortality, with HRs of 3.05 (95% CI: 1.44–6.45; $p = 0.004$) and 3.40 (95% CI: 1.62–7.10; $p = 0.001$), respectively. When MNA and GFI were combined in one multivariate Cox regression model, both GA parameters independently contributed to early mortality ($p = 0.04$ for MNA and $p = 0.02$ for GFI). The median survival difference between normal versus abnormal MNA (well nourished vs. malnourished) and normal versus abnormal GFI (not frail vs. frail) was more than 12 months for both tests. The post-chemotherapy evaluation by GFI and MMSE showed worsening of the physical aspects of the GFI ($p = 0.05$). **In conclusion**, neither GA tests nor laboratory tests were predictive for the chance to complete chemotherapy in this cohort of patients. However, abnormal baseline results of MNA and/or GFI were strongly associated with an increased mortality risk, which could not be demonstrated for abnormal laboratory tests.

The analysis of the role of GA in 143 patients with colorectal cancer for its predictive value on the feasibility of treatment with chemotherapy and survival, separately for patients treated with adjuvant intent ($n = 54$) or palliative intent ($n = 89$), is described in **Chapter 4**. Mean age was 75 years (range 70-92 years),

12% of patients were 80 years and older, 59% were men. At baseline, 28% of the patients showed abnormalities on the MNA, 24% on the GFI, 13% on the IQCODE and 8% on the MMSE. The mean scores of the GA tests were not significantly different between adjuvant and palliatively treated patients. Mean number of chemotherapy cycles was similar for adjuvant and palliatively treated patients (6.3 and 6.2, respectively; p = 0.41). With respect to the probability of receiving less than four cycles of chemotherapy, only the result of the MNA test was significantly predictive (p = 0.008) and only for palliatively treated patients. This finding persisted after adjusting for age, sex, number of co-morbidities and laboratory values. Patients with poor MNA- and GFI-scores had a higher risk of mortality with HRs of 2.95 (95% CI: 1.79-4.85; p < 0.001) and 2.38 (95% CI: 1.41-4.02; p = 0.001), respectively, again only when treated in palliative setting. This persisted after adjustment for age, sex, number of comorbidities, and laboratory values of haemoglobin, creatinine and LDH (HRs 2.76 and 2.72, both p<0.001, respectively). In addition, adjusting for performance status, number of medications and serum albumin showed similar results in sensitivity analyses. The median survival differences between normal versus abnormal MNA test (i.e. well nourished vs. malnourished) and between normal versus abnormal GFI test (i.e. not frail vs. frail) were 9 and 10 months, respectively. Longitudinal follow-up by GFI and MMSE tests showed significant deterioration in GFI scores, especially of the physical elements limited to the palliatively treated group. **In conclusion**, poor MNA scores were predictive for the chance to receive less than four cycles of chemotherapy, and poor scores for MNA and GFI showed independently increased HRs for mortality for palliatively treated patients only.

Chapter 5 describes the prognostic value of the used GA in relation to the age-adjusted IPI for patients with a mean age of 78 years (range 70-86 years; n = 44) diagnosed with aggressive non-Hodgkin lymphoma (91% had diffuse large B-cell lymphoma (DLBCL)) and treatment with R-CHOP. Fifty-seven percent were women and 46% were 80 years or older. The majority of patients either belonged to the low-intermediate risk category of the age-adjusted IPI (one risk factor, n = 21) or to the high-intermediate risk category (two risk factors, n = 18). At baseline, 34% of the patients showed shortcomings on the MNA, 43% on the GFI, 11% on the IQCODE and 5% on the MMSE. Laboratory tests showed low albumin in 32%, low haemoglobin in 25%, elevated creatinine in 30% and elevated LDH in 86% of the patients. Abnormal results of the MNA and GFI tests, and low haemoglobin levels were associated with not being able to complete the intended chemotherapy, adjusted for sex, age, comorbidity and univariate laboratory values with p ≤ 0.1 (odds ratio 8.29, 9.17 and 5.41, respectively). With respect

to survival probabilities, frailty by abnormal GFI and low haemoglobin showed increased HRs for mortality, 2.55 and 4.90 respectively (adjusted for sex, age, comorbidity, age-adjusted IPI and univariate laboratory values with p < 0.10). **In conclusion,** this cohort of patients with aggressive NHL showed, that (risk of) malnutrition, measured with the MNA, frailty, measured with the GFI, and low haemoglobin level were predictive for early treatment withdrawal, and abnormal GFI and haemoglobin were, independent of the age-adjusted IPI, predictive for an increased mortality risk.

A detailed analysis on the question, which elements of the chosen geriatric screening program were independently predictive for feasibility of chemotherapy and mortality in the whole cohort of 494 patients forms the subject of **Chapter 6.** Men and women were almost equally divided. The mean age was 75 years (range 70-92 years). Most of the patients had cancer of the lower digestive tract (29%), followed by haematological malignancies (22%), upper digestive tract cancers (13%) and breast cancer (12%). Fifty-eight percent of the patients were treated with palliative intent. The GA showed shortcomings on the MNA in 36%, on the GFI in 30%, on the IQCODE in 13% and on the MMSE in 9% of the patients. In multivariable adjusted models, the MNA proved to be predictive for feasibility of chemotherapy with an odds ratio of 2.30 (95% CI: 1.48-3.58; p<0.001). With respect to survival, abnormal tests for MNA and GFI were independently predictive for mortality with HRs of 1.86 (95% CI: 1.48-2.34; p<0.001) and 1.77 (95% CI: 1.41-2.22; p<0.001), respectively. Concerning the individual items of the MNA and the GFI, three items of the MNA were predictive for feasibility of chemotherapy: 'psychological distress and/or acute disease in the past three months', 'dementia or depression' and 'using >3 prescript drugs' with odds ratios of 2.10, 3.44 and 1.96, respectively. Two items of the MNA and one item of the GFI: 'declining food intake in past 3 months', 'using >3 prescript drugs', and 'dependent shopping', were independently predictive for mortality with HRs of 1.82, 1.38 and 1.77, respectively. Subsequently, the independent predictive items for mortality were summed, and this sum score was analyzed using the multivariable adjusted Cox regression model. In comparison with patients without any positive item, patients with one, two or three positive item showed HRs for mortality of 1.58, 2.32 and 5.58, respectively. This sum score was called the Geriatric Prognostic Index (GPI). The median survival by application of the GPI was 2.26 years with score 0, 1.34 years with score 1, 0.95 years with score 2 and 0.56 years with score 3. **In conclusion**, a poor MNA score was predictive for not completing four cycles of chemotherapy (feasibility of chemotherapy), while poor MNA and GFI scores were predictive for an increased risk for mortality in this cohort of 494

patients with a variety of malignancies and treatments. The GPI can help to identify the elderly patient at increased risk for mortality. This instrument offers the oncologist an opportunity for fine-tuning of the treatment plan. We would like to advice that patients scoring 0-1 can be offered chemotherapy, a more thorough CGA might be of help for patients scoring 2, and the use of chemotherapy is questionable in patients scoring 3 points.

General discussion

In the Netherlands, the life expectancy for men increased from 76 years to 79 years and for women from 81 years to 83 years during the decade 2000-2010. In this decade, the chance for a 65 years old man to reach the age of 80 years increased from 52% to 63% and for a woman from 71% to 75%. For a large part, this may be explained by declining cancer deaths, as the incidence and mortality of patients with cancer increases with age. Sixty percent of all cancers and 70% of cancer mortality is found above 65 years of age [1]. Therefore, adult oncologists are, in fact, geriatric oncologists [2]. The estimated life expectancy and how treatment might affect function and quality of life is of utmost importance, as stated recently by Hyman Muss in an interview for the ASCO Post [3]. There are several tools to predict the life expectancy of elders [3-6]. An example of an online tool for the estimated life expectancy is given by ePrognosis [3, 7, 8]. However, these tools have not yet been studied and validated specifically within the oncology population, and they should be explored in uniform cancer populations [9]. Nevertheless, by using the information of ePrognosis, one aspect for fine-tuning of the treatment plan can be covered. To cover other aspects, a geriatric-focused assessment is mandatory in order to avoid both undertreatment and excessive toxicity of the treatment plan [2]. Because of the heterogeneity in the aging process, a cut-off score of age for the use of geriatric assessment before (and during!) treatment of the elderly patients with cancer is not well defined [9]. However, the prevalence of age-related changes (e.g. dementia, decline of visual and hearing function, congestive heart failure etc.) increases sharply after 70 years of age [10, 11] and therefore we used a cut-off score of ≥ 70 years. An international expert panel reached consensus, that GA should be performed in patients of 70 years and over, and in younger patients with special issues or concerns [12].

The International Society of Geriatric Oncology (SIOG) formulated a consensus statement on the role for geriatric assessment in older patients with cancer [9]. The consensus concentrated on the answers for seven questions, in short: 1. What is the rationale for GA? 2. What extra information is given by GA?

3. Will GA predict complications? 4. What is the impact of GA on overall survival? 5. What is the impact of GA on treatment decisions? 6. What should be covered by GA? and 7. How should GA be organized and implemented? [9]. An extensive review of the literature provided answers on these questions. GA can detect relevant health care problems in older patients with cancer that are under- or unrecognized with a standard history and physical examination [13], and which elements have significant effects on complications of treatment [14-17], change of treatment plan [18, 19] and survival outcomes [20-22]. The domains that should be covered by GA comprise: demography and social status, comorbidity, functional status, cognition, depression, nutrition, fatigue, polypharmacy, and prevalent geriatric syndromes [9]. An international expert panel considered functional status, comorbidity and cognition as the most important domains [12]. A recent survey among haematologists in the Netherlands showed, that in daily practice geriatric assessments are rarely carried out, and that especially comorbidity and shortcomings with ADL are considered important for the decision to treat with curative intent or not [23]. Furthermore, cardiovascular comorbidity, cognitive disorders (especially dementia) and untreated depression formed common reasons for dose-reductions in advance or palliative treatment only, especially in the over-eighties [24].

An instrument mentioned by the SIOG-consensus is the MNA, which measures nutritional status in a broad sense. The MNA screens on eighteen items, of which eleven items are directly related to nutrition while seven items cover other aspects of well-being: two items on IADL, three items on comorbidity, one item on polypharmacy and one item on psychological health. Roughly one-third of the patients included in our studies showed shortcomings on the MNA (ranging from 28 to 42%). In case of such shortcomings, risks were increased for not completing four cycles of chemotherapy (except for 55 patients with breast cancer) as well as for overall mortality. The Eastern Cooperative Oncology Group found weight loss before the start of chemotherapy to have a negative impact on survival in a group of 3047 patients [25]. More recent studies confirmed the meaning of the nutritional status for mortality [20, 21]. An example that gives support for the MNA to predict the risk of severe non-hematologic toxicity after chemotherapy in older patients is shown with the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH-score) [15]. This thesis, together with several reports in the literature, underscores the importance of the MNA as a risk profiling tool before chemotherapy is offered to the older patient with cancer, both with respect to toxicity and mortality risk.

The GFI is an instrument considered to assess frailty and contains two ADL items, two IADL items, one on polypharmacy, cognition and nutrition each, three physical fitness items, and five psycosocial items. The GFI may aid as a case finder for elderly patients who would benefit from integrated (geriatric) care [26]. As a screening test for frailty the GFI has been tested in elderly patients both without cancer [26, 27] and with cancer [27-30]. The threshold for frail vs. non-frail is ≥ 4 points. However, in patients with cancer a cut-off value of ≥ 3 points seems more sensitive for the detection of frailty in comparison with a full comprehensive geriatric assessment [28]. Abnormal scores of the GFI (≥ 4 points) were identified in 30% of the patients investigated in the studies of this thesis (ranging from 24 to 51% for the different cohorts). Patients with shortcomings showed a higher risk for mortality after start of treatment with chemotherapy. Similarly, an elevated risk of mortality was found in patients after surgery for gastric cancer [30]. Thus, the studies in this thesis emphasize the importance of the GFI to identify elderly patients at increased risk for mortality after the start of chemotherapy. A more detailed comprehensive geriatric assessment with the help of a geriatrician might be helpful for these patients, in order to identify frailty as precise as possible. Further studies should explore whether intervention aimed at specific domains of frailty and malnutrition may help to improve outcome.

The MMSE is often used to screen for cognitive problems in elderly patients with cancer. Screening for cognition is also mentioned as an important domain by consensus panels [9, 12]. The patients in the studies of this thesis showed cognitive problems in 5-10% on the MMSE and 11-18% on the IQCODE. Some of the analyses reported in this thesis showed a correlation with the risk of mortality, but these relationships were generally less strong than the relationships with the above mentioned GFI and MNA. Only the cohort study described in Chapter 2, showed statistically significant association between a low MMSE score and the risk of not completing the intended chemotherapy. Moreover, the MMSE worsened significantly during chemotherapy in this cohort. It has to be stressed, that the patients underwent screening after the decision for the start of chemotherapy had been made by their (hemato-)oncologist, which choice would most likely be affected by overt symptoms of cognitive dysfunction. As included patients were therefore unlikely to have obvious cognitive problems, our findings may be prone to some selection bias. Nevertheless, a previous study also found evidence for an abnormal MMSE test to be predictive of non-hematologic toxicity in the CRASH score [15]. Findings therefore suggest that patients with cognitive impairment may require a modification of their treatment regimen or increased supervision during their treatment [31, 32].

One might suppose that patients who have been treated with chemotherapy before, would show more signs of frailty and therefore would have a worse prognosis in comparison with patients without previous chemotherapy. Among the 494 patients with various types of cancer described in chapter six, there were 74 patients who had already received chemotherapy before inclusion in the protocol comprising geriatric assessment. The groups of 420 and 74 patients did not differ significantly with respect to age-groups and gender. However, significantly more patients were treated with curative intent in the group of 420 patients who did not receive any chemotherapy in the past versus the group who did receive chemotherapy before (46% versus 20%, $p < 0.001$). This may explain that Cox regression analysis showed an increased HR for mortality of 1.35 (95% confidence interval: 1.03-1.75; $p = 0.03$) in the previous chemotherapy group. Anyhow, the percentages of patients with an adverse score for GA at baseline were not significantly different among the two groups, as shown in table 1. Moreover, previous chemotherapy was not an effect modifier for the predictive effect of the GPI on mortality ($p=0.44$ for interaction term), as shown in table 2. From this analysis we conclude that there was no significant difference in the GPI as a predictor for mortality, whether or not chemotherapy was given previously.

Table 1. Base-line characteristics according to previous chemotherapy in 494 patients.

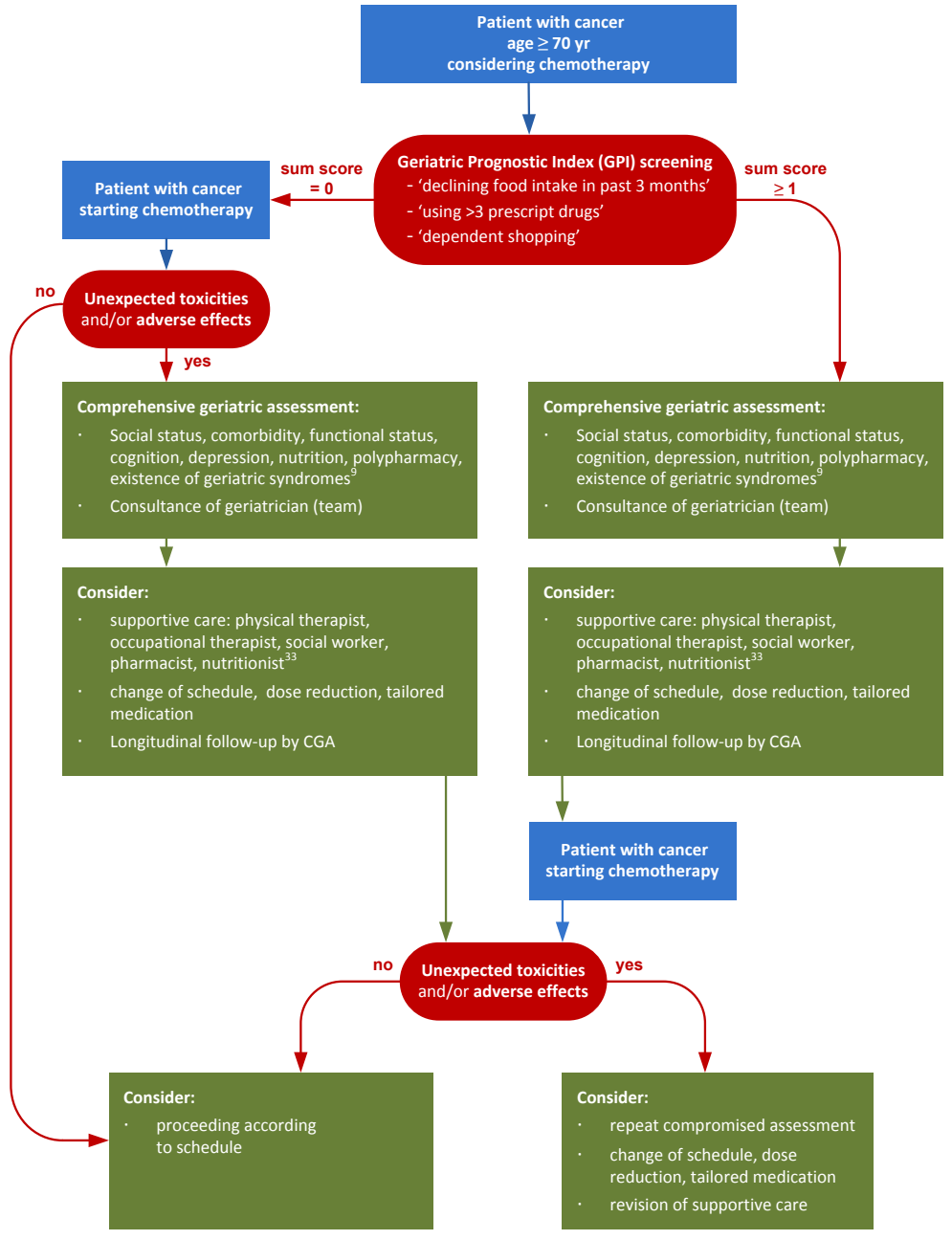
	No previous chemotherapy (n=420)	**Previous chemotherapy** (n=74)	**p-value**
Male gender	213 (50.7%)	33 (44.6%)	0.33
Age groups:			
70-74 yr	200 (47.6%)	37 (50.0%)	0.67
75-79 yr	145 (34.5%)	25 (33.8%)	
≥ 80 yr	75 (17.9%)	12 (16.2%)	
Curative intent	191 (45.5%)	15 (20.3%)	< 0.001
Adverse base-line score of GA			
MNA	153 (36.8%)	21 (28.4%)	0.16
GFI	131 (31.3%)	18 (24.3%)	0.23
IQCODE	52 (12.6%)	10 (14.7%)	0.64
MMSE	40 (9.6%)	4 (5.5%)	0.26

Table 2. Risk of mortality in relation to the GPI score according to previous chemotherapy.

GPI score	Median survival (months)	Adjusted hazard ratios (CI)	P-Value for trend	P-value for interaction
No Previous Chemotherapy (n=420)				
Score 0 (n=154)	29	Ref.	< 0.001	0.44
Score 1 (n=152)	15	1.58 (1.21-2.08)		
Score 2 (n=90)	10	2.40 (1.76-3.24)		
Score 3 (n=21)	5	5.20 (3.18-8.49)		
Previous Chemotherapy (n=74)				
Score 0 (n=34)	16	Ref.	0.09	
Score 1 (n=23)	14	1.04 (0.54-2.01)		
Score 2 (n=14)	9	1.39 (0.69-2.81)		
Score 3 (n=3)	7	7.60 (1.94-29.7)		

Hazard ratios (with 95% confidence intervals [CI]) were calculated using Cox regression analysis, and models were adjusted for sex, age, purpose of treatment, and type of malignancy.

Flowchart



Our in-depth analysis that included all items of the MNA and the GFI on the risk for mortality after the start of chemotherapy identified two items of the MNA and one item of the GFI as independent risk factors. On the basis of these three items the Geriatric Prognostic Index (GPI) was constructed to help the medical (hemato-)oncologist in identifying the elderly patient with cancer at increased risk for mortality before chemotherapy is started. Just by asking the following three questions important prognostic information may be uncovered: 'declining food intake in past 3 months', 'using > 3 prescript drugs', and 'dependence in shopping'. In case of a high score, a more elaborate comprehensive geriatric assessment by a geriatrician is warranted to tailor a more detailed treatment plan before chemotherapy should be considered. The meaning of these findings and recommendations for clinical practice should be investigated in future research. However, so far these recommendations are only applicable for patients of whom the clinician decided for treatment with chemotherapy on clinical grounds and furthermore, need to be validated in other cohorts.

How should the knowledge, obtained by a geriatric assessment in clinical oncology be incorporated into clinical practice? In the ideal situation the elderly patient's needs are covered by a geriatric oncologist. However, both the fields of geriatrics and oncology are evolving rapidly and therefore, in practice, cooperative actions of oncologists (trained in the basic principles of geriatrics) and geriatricians (trained in applying cancer-specific geriatric assessments) will be necessary to optimize the care for the elderly with cancer [33]. This can be accomplished in so-called geriatric oncology units or by a geriatric consultation team (GCT) [9, 33]. The advantage of the model with a GCT is, that the direct relationship between the patient and the oncologist is not interrupted and that the onco-geriatric team is available for guidance if further geriatric-related issues occur. A possible disadvantage might be the organization for longitudinal follow-up of geriatric issues [9]. GCT's (consisting of a geriatrician and geriatrics-trained nurse practitioner or physician's assistant) should be embedded into an existing oncology clinic, and should participate actively in a multidisciplinary team [9, 33]. Recently, the role of the pharmacist in the multidisciplinary team was advised to further explore the potential adverse effects of polypharmacy, complex drug-drug interactions, and potentially inappropriate medication [34].

Mohile et al defined four goals for research in geriatric oncology [35]:

1. Incorporate geriatric assessment tools into clinical trials that predict adverse outcomes for older adults with cancer.
2. Test the ability of a geriatric assessment model of care for improving outcomes of older cancer patients.
3. Understand the impact of oncology therapeutics in the general population of older cancer patients.
4. Identify and test interventions to improve symptoms and maintain quality of life of older cancer patients.

The clinical research described in this thesis focused on the roles of the MNA and the GFI, both for feasibility of treatment with chemotherapy and as predictors for overall survival. Whether intervention strategies, after having identified specific shortcomings, will lead to better outcomes and will help to maintain quality of life, form challenging questions that still need to be resolved. On the basis of the results described in this thesis and in view of the current literature, we propose the following recommendations as is depicted in the flow chart below when chemotherapy is considered in an elderly patient with cancer.

The elderly patients with cancer, increasing rapidly in numbers in the coming decades, deserve nothing less than an optimal inventory of coexisting geriatric problems which predict the feasibility of certain therapeutic strategies, of which chemotherapy is an important part. Furthermore, this gives a better insight in the overall life expectancy in order to choose the proper treatment-plan without the risk of over- or under treatment [2]. Elderly-specific studies on intervention strategies, based on GA, to improve the outcome of treatment should be developed and the elderly should be encouraged to participate herein. These kind of studies have been performed in younger age groups with positive outcome for an exercise related program in breast cancer patients [36] and, currently, a study protocol on the effect of physical exercise in elderly breast cancer survivors is running in the Netherlands (the Climb Every Mountain study) [37]. Thus, the research is evolving, although much effort still lies ahead in the coming decade on the development of tumor-specific studies. The studies of this thesis can be used for background information, upon which these developments can be built. We hope that this thesis may contribute to the development of standardized instruments and may help to let the GA become part of routine care in the elderly oncology patient. The use of computerized measurements may facilitate this incorporation.

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Samenvatting en algemene discussie

Het besluit om patiënten met kanker van 70 jaar en ouder te behandelen met chemotherapie is grotendeels gebaseerd op het klinische oordeel van de behandelend arts, welke in belangrijke mate gebaseerd is op wetenschappelijk onderzoek van jongere patiëntengroepen. Het klinische oordeel schiet vaak te kort om gedetailleerd de actuele conditie van de oudere patiënt te typeren. Het instrument geriatrisch assessment (GA) kan helpen om verborgen problemen op te sporen en de besluitvorming met betrekking tot de haalbaarheid van de behandeling met chemotherapie en de overleving van de oudere patiënt met kanker te onderbouwen. Dit proefschrift is het resultaat van onderzoek met de gekozen onderdelen van het GA die van belang zouden kunnen zijn in de oncologische praktijk van alledag, teneinde de uitkomst van de behandeling met chemotherapie te verbeteren.

Samenvatting

Hoofdstuk 2 beschrijft de rol van het GA bij 202 patiënten met een gemiddelde leeftijd van 77 jaar (met een spreiding van 71-92 jaar) die allen behandeld werden in het Reinier de Graafgasthuis in Delft. De meerderheid was vrouw (55%) en de meesten hadden darmkanker (30%) gevolgd door hematologische maligniteiten (18%) en borstkanker (17%). Het GA bestond uit de 'Mini Nutritional Assessment' (MNA), 'Informant Questionnaire on Cognitive Decline in the Elderly' (IQCODE), 'Groningen Frailty Index' (GFI) en 'Mini Mental State Examination' (MMSE). Bovendien werden bij 51 patiënten de MMSE en de GFI herhaald na tenminste 4 kuren of 6 maanden na de start van de chemotherapie met het doel de gevolgen van de chemotherapie op de testscores te kunnen beoordelen. Voor aanvang van de chemotherapie werden de volgende percentages tekortkomingen geregistreerd: met de MNA bij 33% van de patiënten, met de GFI bij 37%, met de MMSE bij 10%, en met de IQCODE bij 15%. Het percentage van de patiënten die 4 kuren niet konden afmaken verschilde significant van de groep die wel 4 of meer kuren hadden gekregen ten aanzien van de gemiddelde uitkomsten van de MNA ($p = 0.001$) en MMSE ($p = 0.04$). Het sterftecijfer na de start van de chemotherapie was verhoogd bij patiënten met een lage (versus hoge) MNA score en een hoge (versus lage) GFI score, met 'hazard ratios' (HRs) van respectievelijk 2.19 (95% 'confidence' interval [CI]: 1.42-3.39; $p < 0.001$) en 1.80 (95% CI: 1.17-2.78; $p = 0.007$). De verhoogde HR's persisteerden na correctie voor geslacht, leeftijd, doel van de chemotherapie en soort maligniteit. De evaluatie van de MMSE en GFI na de chemotherapie liet een significante verslechtering zien

bij de MMSE (p = 0.04), maar niet bij de GFI (p = 0.48). **Samenvattend** bleken slechtere resultaten bij de MNA, en in mindere mate met de MMSE, voorspellend voor het niet afronden van tenminste 4 chemotherapiekuren, terwijl patiënten met tekortkomingen met de MNA en GFI een verhoogd sterfterisico lieten zien.

Hoofdstuk 3 concentreert zich op de resultaten van de uitkomst van het GA bij 55 patiënten met borstkanker met een gemiddelde leeftijd van 76 jaar (met een spreiding van 70-88 jaar en van wie 20% ouder dan 80 jaar was). Naast de hierboven genoemde GA testen zijn ook de uitgangswaarden van serum albumine, hemoglobine, creatinine en lactaat dehydrogenase (LDH) in beschouwing genomen in relatie tot de uitkomst van palliatieve chemotherapie. Bij 21 patiënten werd de MMSE en de GFI herhaald na tenminste 4 kuren of 6 maanden na de start van de chemotherapie. Met de MNA waren afwijkende testresultaten aanwezig bij 42% van de patiënten, met de GFI bij 51%, met de IQCODE bij 18% en met de MMSE bij 9%. Afwijkende laboratoriumtesten van creatinine, albumine, hemoglobine en LDH waren aanwezig bij respectievelijk 13%, 33%, 78% en 84% van de patiënten. Behalve de inverse correlatie tussen de MNA en GFI (r = -0.43; p < 0.001) en tussen de IQCODE en MMSE (r = -0.36; p = 0.01), werden er geen significante correlaties tussen de GA- en laboratoriumtesten gevonden. Echter, een verminderde 'WHO-performance status' (PS) was wel gecorreleerd met slechtere uitkomsten van de MNA (r = -0.28, p = 0.04) en GFI (r = 0.38, p = 0.004). Er waren geen statistisch significante verschillen tussen het aantal patiënten (n = 39) die ten minste 4 kuren kregen vergeleken met de patiënten (n = 16) die minder dan 4 kuren kregen met betrekking tot het GA en de laboratorium parameters (ook niet na correctie voor leeftijd, comorbiditeit en PS). Slechtere MNA en GFI uitkomsten waren geassocieerd met een verhoogde mortaliteit met HRs van respectievelijk 3.05 (95% CI: 1.44–6.45; p = 0.004) en 3.40 (95% CI: 1.62–7.10; p = 0.001). Wanneer de MNA en de GFI werden gecombineerd in één multivariabel Cox-regressie model, hadden beide GA-parameters een onafhankelijke bijdrage (p = 0.04 voor de MNA en p = 0.02 voor de GFI). Het verschil van de mediane overleving met de MNA (normaal versus (kans op) ondervoeding) en de GFI (niet kwetsbaar versus kwetsbaar) was meer dan 12 maanden voor beide testen. De evaluatie van de MMSE en GFI na de chemotherapie liet een verslechtering zien van de fysieke aspecten van de GFI (p = 0.05). **Samenvattend** bleken noch de GA-testen, noch de laboratoriumtesten voorspellend te zijn voor de kans om de chemotherapie af te ronden in dit patiëntencohort. Echter, abnormale uitgangswaarden van de MNA en/of GFI verhoogden het mortaliteitsrisico, terwijl dit niet kon worden aangetoond voor abnormale laboratoriumtesten.

De analyse van de rol van het GA bij 143 patiënten met darmkanker voor de voorspellende waarde van de haalbaarheid van de behandeling met chemotherapie en voor de overleving, afzonderlijk voor adjuvant (n = 54) en palliatief (n = 89) behandelde patiënten wordt beschreven in **hoofdstuk 4.** De gemiddelde leeftijd was 75 jaar (met een spreiding van 70-92 jaar van wie 12% ouder was dan 80 jaar). Voor aanvang van de chemotherapie werden tekortkomingen geconstateerd bij 28% van de patiënten met de MNA, bij 24% met de GFI, bij 13% met de IQCODE en bij 8% met de MMSE. De gemiddelde scores van de GA testen waren niet significant verschillend tussen de adjuvant en de palliatief behandelde patiënten. Het gemiddelde aantal chemotherapie cycli was gelijk voor de adjuvant en de palliatief behandelde patiënten, respectievelijk 6.3 en 6.2 (p = 0.41). Ten aanzien van de mogelijkheid om minder dan 4 chemotherapie cycli te krijgen bleek alleen het resultaat van de MNA significant voorspellend (p = 0.008), en wel alleen voor de palliatief behandelde patiënten. Deze bevinding persisteerde na correctie voor leeftijd, geslacht, aantal comorbiditeiten en laboratorium waarden. Patiënten met een slechte MNA- en GFI-score hadden een hoger mortaliteitsrisico met HRs van respectievelijk 2.95 (95% CI: 1.79-4.85; p < 0.001) en 2.38 (95% CI: 1.41-4.02; p = 0.001), wederom alleen in de palliatief behandelde groep. Dit bleef ook zo na multivariabele adjustering (HRs van respectievelijk 2.76 en 2.72, beide p < 0.001). Na additioneel geadjusteerd te hebben voor PS, aantal medicamenten en serum albumine lieten sensitiviteits-analyses soortgelijke uitkomsten zien. Het verschil in mediane overleving met de MNA (normaal versus (kans op) ondervoeding) en de GFI (niet kwetsbaar versus kwetsbaar) was respectievelijk 9 en 10 maanden. Longitudinaal vervolgonderzoek met de GFI en MMSE liet alleen een in de palliatief behandelde patiënten een significante achteruitgang zien in de GFI score, en wel met betrekking tot de fysieke aspecten van de GFI. **Samenvattend** bleek een slechte MNA scores voorspellend te zijn voor de kans op minder dan 4 cycli chemotherapie en slechte scores van de MNA en GFI toonden, onafhankelijk van elkaar, toegenomen HR's voor sterfte, alleen in de palliatief behandelde groep.

Hoofdstuk 5 beschrijft de prognostische waarde van het gebruikte GA in relatie tot de 'age-adjusted-International Prognostic Index' (age-adjusted-IPI) bij patiënten met een gemiddelde leeftijd van 78 jaar (met een spreiding van 70-86 jaar; n = 44) gediagnosticeerd met agressief non-Hodgkin lymfoom (NHL). Van hen had 91% een diffuus grootcellig B-cel lymfoom (DLBCL) en allen waren behandeld met R-CHOP. De meerderheid van de patiënten behoorde of tot de laag-intermediaire risico groep (1 risico factor, n = 21) of tot de hoog-intermediaire risico groep (2 risico factoren, n = 18). Voor aanvang van de chemotherapie werden tekortkomingen geconstateerd bij 34% van de patiënten met de MNA, bij

43% met de GFI, bij 11% met de IQCODE en bij 5% met de MMSE. Laboratorium testen toonden laag albumine bij 32% van de patiënten, laag hemoglobine bij 25%, verhoogd creatinine bij 30%, en verhoogd LDH bij 86%.

Afwijkende resultaten van de MNA en GFI en een laag hemoglobine waren geassocieerd met het niet afronden van de voorgenomen chemotherapie, in multivariabele modellen (odds ratio van respectievelijk 8.29, 9.17 en 5.41). Een afwijkende GFI en een laag hemoglobine lieten een onafhankelijk verhoogd risico op mortaliteit zien met HRs van respectievelijk 2.55 en 4.90. **Samenvattend** liet dit cohort van patiënten met agressief NHL zien dat (de kans op) ondervoeding, gemeten met de MNA, kwetsbaarheid, gemeten met de GFI, en een verlaagd hemoglobine voorspellend waren voor voortijdig staken van de behandeling en een afwijkende GFI en hemoglobine waren, onafhankelijk van de 'age-adjusted-IPI', voorspellend voor een verhoogd mortaliteitsrisico.

Een gedetailleerde analyse van de vraag, welke onderdelen van het gekozen geriatrisch screenings programma onafhankelijk voorspellend waren voor de haalbaarheid van chemotherapie en welke voor mortaliteit in het gehele cohort van 494 patiënten, vormt het onderwerp van **hoofdstuk 6.** Mannen en vrouwen waren zo goed als gelijk verdeeld. De gemiddelde leeftijd was 75 jaar (met een spreiding van 70-92 jaar). De meeste patiënten hadden maligniteiten van de lage tractus digestivus (29%), gevolgd door hematologische maligniteiten (22%), hoge tractus digestivus maligniteiten (13%) en borstkanker (12%). Achtenvijftig procent van de patiënten werd behandeld met palliatieve intentie. Het GA liet tekortkomingen zien bij 36% van de patiënten met de MNA, bij 30% met de GFI, bij 13% met de IQCODE, en bij 9% met de MMSE. In multivariabele, gecorrigeerde modellen bleek de MNA voorspellend voor de haalbaarheid van chemotherapie met een odds ratio van 2.30 (95% CI: 1.48-3.58; $p < 0.001$). Ten aanzien van de overleving waren afwijkende testuitslagen van de MNA en GFI onafhankelijk voorspellend voor mortaliteit met HRs van respectievelijk 1.86 (95% CI: 1.48-2.34; $p < 0.001$) en 1.77 (95% CI: 1.41-2.22; $p < 0.001$). Met betrekking tot de individuele items van de MNA en GFI bleken drie items van de MNA onafhankelijk voorspellend voor de haalbaarheid van chemotherapie: 'mentale stress en/of acute ziekte in de afgelopen drie maanden', 'dementie of depressie', en 'dagelijks meer dan drie voorgeschreven medicijnen' met een odds ratio van respectievelijk 2.10, 3.44 en 1.96. Twee items van de MNA ('verminderde eetlust in de afgelopen drie maanden' en 'dagelijks meer dan drie voorgeschreven medicijnen') en één item van de GFI ('afhankelijkheid voor boodschappen doen') waren onafhankelijk voorspellend voor mortaliteit met HRs van respectievelijk 1.82, 1.38 and 1.77. Vervolgens werden de onafhankelijk voorspellende items samengenomen en werd de score geanalyseerd door middel van een multivariabel gecorrigeerd Cox regressie-model. In vergelijking met patiënten zonder één enkel positief item lieten de patiënten met één, twee of drie positieve items HR's zien van respectievelijk 1.58, 2.32 en 5.58. Deze score werd de 'Geriatric Prognostic Index' (GPI) genoemd. De mediane overleving met toepassing van de GPI was 2.26 jaar met score 0, 1.34 jaar met score 1, 0.95 jaar met score 2 en 0.56 jaar met score 3. **Samenvattend** bleek een slechte MNA-score voorspellend voor de haalbaarheid van chemotherapie, terwijl slechte MNA- en GFI- scores voorspellend waren voor mortaliteit in dit cohort van 494 patiënten met een verscheidenheid aan maligniteiten en behandelingen. De GPI kan behulpzaam zijn om oudere patiënten te identificeren met een verhoogd mortaliteitsrisico. Dit instrument biedt de oncoloog de mogelijkheid om het behandelplan af te stellen op de noden van de patiënt. We zouden willen adviseren om patiënten met een score van 0-1 standaard chemotherapie aan te bieden, terwijl een uitgebreider GA van nut kan zijn bij een score van 2. Het is discutabel of chemotherapie aangeboden moet worden bij een score van 3.

Algemene discussie

In Nederland is de levensverwachting in de jaren 2000-2010 voor mannen gestegen van 76 jaar naar 79 jaar en voor vrouwen van 81 jaar naar 83 jaar. De kans om 80 jaar te worden voor een 65-jarige man laat in dit decennium een stijging zien van 52% naar 63% en voor een vrouw van 71% naar 75%. Voor een groot gedeelte is dit te verklaren door een daling van de sterfte ten gevolge van kanker, immers, met stijgende leeftijd nemen de incidentie en de mortaliteit ten gevolge van kanker toe. Zestig procent van alle kankers en 70% van de mortaliteit ten gevolge van kanker wordt gezien na de leeftijd van 65 jaar [1]. Daarom zijn oncologen in feite geriater-oncologen [2]. De geschatte levensverwachting en de wijze waarop de behandeling het functioneren en de kwaliteit van leven beïnvloedt, is uitermate belangrijk, zoals benadrukt door Hyman Muss in een interview voor de ASCO Post [3].

Er zijn verschillende hulpmiddelen om de levensverwachting van ouderen te schatten [3-6]. Een voorbeeld van een 'online' hulpmiddel voor de geschatte levensverwachting betreft 'ePrognosis' [3, 7, 8]. Echter, dergelijke hulpmiddelen zijn nog niet bestudeerd binnen de oncologische populatie en behoren verder te worden onderzocht per tumorsoort [9]. Desalniettemin, door gebruik te maken van de informatie van ePrognosis kan één aspect voor een goed afgestemd behandelplan worden meegenomen. Voor het wegen van andere aspecten is een

geriatrisch georiënteerde beoordeling vereist, teneinde onderbehandeling en bovenmatige toxiciteit van het behandelplan te vermijden [2]. Vanwege de heterogeniteit van het verouderingsproces is een afkapwaarde voor de leeftijd, vanaf welke een geriatrische beoordeling ('geriatric assessment' (GA)) moet worden gebruikt vóór (en tijdens!) de behandeling van de oudere patiënt met kanker niet goed gedefinieerd [9]. Echter, de prevalentie van leeftijdsgebonden aandoeningen (zoals dementie, achteruitgang van visus en gehoor, hartfalen, etc.) stijgt fors na de leeftijd van 70 jaar [10, 11] en daarom gebruikten wij deze afkapwaarde. Een internationaal panel van deskundigen kwam ook tot consensus, dat GA uitgevoerd moet worden bij patiënten van zeventig jaar en ouder, alsmede bij jongere patiënten met speciale problemen of zorgvragen [12].

De 'International Society of Geriatric Oncology' (SIOG) formuleerde consensus over de rol van het GA bij oudere patiënten met kanker [9]. De consensus concentreerde zich op de antwoorden van zeven vragen, in het kort: "1. Wat is de rationale voor het GA? 2. Welke extra informatie wordt verstrekt door het GA? 3. Kan het GA complicaties voorspellen? 4. Wat betekent het voor de totale overleving? 5. Wat betekent het voor de besluitvorming van de behandeling? 6. Wat moet meegenomen worden bij het GA? en 7. Hoe moet het GA georganiseerd en geïmplementeerd worden?" [9]. Een uitgebreid overzicht van de literatuur geeft antwoorden op deze vragen. GA kan bij oudere patiënten met kanker relevante gezondheidsproblemen vaststellen die niet onderkend of niet herkend zijn bij standaard anamnese en lichamelijk onderzoek [13] en die significante effecten hebben op complicaties van de behandeling [14-17], wijziging van het behandelplan [18, 19] en uitkomst van de overleving [20-22]. De domeinen die meegenomen behoren te worden bij het GA omvatten: demografische en sociale status, comorbiditeit, functionele status, cognitie, depressie, voeding, vermoeidheid, polyfarmacie en bestaande geriatrische syndromen [9]. Een internationaal panel van deskundigen beschouwde functionele status, comorbiditeit en cognitie als de meest belangrijke domeinen [12]. Een enquête onder Nederlandse hematologen liet zien, dat in de dagelijkse praktijk GA's zelden worden uitgevoerd en dat met name comorbiditeit en tekortkomingen bij de ADL van belang werden geacht ten aanzien van de intentie om wel of niet curatief te behandelen [23]. Bovendien vormden cardiovasculaire comorbiditeit, cognitieve stoornissen (vooral dementie) en onbehandelde depressie veel voorkomende redenen om op voorhand dosis-reductie toe te passen of alleen palliatief te behandelen, met name bij 80-plussers [24].

Eén van de instrumenten, aangegeven in de SIOG consensus, betreft de

MNA, waarmee de voedingsstatus in brede zin gemeten wordt. De MNA screent op achttien items, waarvan elf items direct gerelateerd zijn aan voeding en zeven items aan andere aspecten van welzijn: twee items over IADL, drie items over comorbiditeit , één item over polyfarmacie, en één item over psychische gezondheid. Ongeveer een derde van de patiënten (variërend van 28% tot 42%) in onze studies lieten tekortkomingen zien bij de MNA. Bij zulke tekortkomingen was er een verhoogd risico zowel om vier chemotherapie cycli niet af te maken (met uitzondering van 55 patiënten met borstkanker) als voor de totale sterfte. De 'Eastern Cooperative Oncology Group' vond in een groep van 3047,patiënten, dat gewichtsverlies voor de start van de chemotherapie een negatief effect had op de overleving [25]. Recentere studies bevestigden het belang van de voedingsstatus met betrekking tot mortaliteit [20, 21]. Een voorbeeld, dat steun geeft aan de MNA als voorspellende factor voor het risico van ernstige niet-hematologische toxiciteit na chemotherapie bij oudere patiënten, betreft de 'Chemotherapy Risk Assessment Scale voor High-Age Patients (CRASH-score)' [15]. Al met al ondersteunt dit proefschrift, samen met verscheidene rapportages in de literatuur, het belang van de MNA als risicoprofiel voor chemotherapie bij de oudere patiënt met kanker, zowel voor wat betreft toxiciteit als mortaliteit.

De GFI is een instrument met het doel kwetsbaarheid te beoordelen en bevat twee items over de ADL, twee items over de IADL, één item over respectievelijk polyfarmacie, cognitie en voeding, drie items over fysieke fitheid, en vijf psychosociale items. De GFI kan helpen bij het identificeren van oudere patiënten die zouden kunnen profiteren van geïntegreerde (geriatrische) zorg [26]. De GFI is als screenings instrument voor kwetsbaarheid getest bij oudere patiënten, zowel zonder [26, 27] als met kanker [27-30]. De drempelwaarde voor kwetsbaar versus niet-kwetsbaar is ≥ 4 punten. Echter, bij patiënten met kanker lijkt een afkapwaarde van ≥ 3 punten gevoeliger voor de detectie van kwetsbaarheid in vergelijking met een volledig uitgevoerd CGA [28]. Tekortkomingen met de GFI (≥ 4 punten) werden gevonden in 30% van de patiënten in de studies van dit proefschrift (variërend van 24% tot 51% in de verschillende cohorten). Patiënten met tekortkomingen vertoonden een verhoogd risico op mortaliteit na aanvang van de behandeling met chemotherapie. Evenzo werd er een verhoogd sterfte-risico gevonden na operatie bij patiënten met maagkanker [30]. Aldus benadrukken de studies in dit proefschrift het belang van de GFI om oudere patiënten met een verhoogd risico op mortaliteit te identificeren na de start van de chemotherapie. Een gedetailleerd CGA, met behulp van een geriater, kan nuttig zijn voor deze patiënten om kwetsbaarheid zo precies mogelijk te identificeren. Vervolgstudies

moeten onderzoeken of interventie, gericht op specifieke domeinen van kwetsbaarheid en ondervoeding, kunnen helpen bij het verbeteren van de uitkomsten.

De MMSE wordt vaak gebruikt voor de screening op cognitieve problemen bij oudere patiënten met kanker. Screening van cognitie wordt ook genoemd als belangrijk domein door de consensus-panels [9, 12]. De patiënten in de studies van dit proefschrift lieten cognitieve problemen zien in 5%-10% met de MMSE en in 11%-18% met de IQCODE. Sommige van de gerapporteerde analyses in dit proefschrift laten een correlatie zien met het sterfterisico, maar deze relaties waren minder sterk en minder consistent dan de relaties met de hiervoor genoemde GFI en MNA. Alleen de beschreven cohort-studie van hoofdstuk 2 laat een significante associatie zien tussen een lage MMSE-score en het risico om de beoogde chemotherapie niet af te maken. Bovendien was er een significante verslechtering geobserveerd met de MMSE tijdens chemotherapie in dit cohort. Het moet worden benadrukt dat de patiënten de screening ondergingen nadat de beslissing was genomen om te starten met chemotherapie door hun (hemato-) oncoloog. Hierbij is het waarschijnlijk dat de keuze werd beïnvloed door duidelijke symptomen van cognitieve dysfunctie. Omdat het onwaarschijnlijk geacht werd dat de geïncludeerde patiënten duidelijke cognitieve problemen hadden, kunnen onze bevindingen beïnvloed zijn door selectie bias. Desalniettemin werden er in een eerdere studie ook aanwijzingen gevonden dat een afwijkende MMSE-test voorspellend was voor niet-hematologische toxiciteit in de CRASH score [15]. Deze bevindingen suggereren dan ook dat patiënten met cognitieve achteruitgang baat kunnen hebben bij aanpassing van hun behandelplan of een intensiever toezicht tijdens de behandeling [31, 32].

Men kan veronderstellen dat patiënten, die eerder met chemotherapie zijn behandeld meer tekenen van kwetsbaarheid tonen en daarom een slechtere prognose hebben, in vergelijking met patiënten die niet eerder met chemotherapie zijn behandeld. Onder de in hoofdstuk 6 beschreven 494 patiënten met een verscheidenheid aan kanker bevonden zich 74 patiënten, die chemotherapie hadden gehad vóór deelname aan het protocol met GA. De groepen van 420 en 74 patiënten verschilden niet significant met betrekking tot leeftijdscohorten en geslacht. Echter, in de groep van 420 patiënten zonder eerdere chemotherapie werden significant vaker patiënten in opzet curatief behandeld, in vergelijking met de groep waarin eerder chemotherapie was toegediend (41% versus 20%, $p < 0.001$). Dit kan de verklaring zijn dat Cox regressie analyse een verhoogde HR voor mortaliteit liet zien van 1.35 (95% BI: 1.03-1.75; $p = 0.03$) in de groep die eerder met chemotherapie was behandeld. Hoe dan ook, het aandeel van patiënten met een afwijkende uitgangsscore van GA verschilde niet significant tussen de twee groepen, zie tabel 1. Bovendien bleek eerdere chemotherapie niet van invloed op de voorspellende waarde van de GPI voor mortaliteit ($p = 0.44$ voor interactie), zie tabel 2. Concluderend: er was geen significant verschil voor de GPI als risicofactor voor mortaliteit, of nu wel of niet eerder chemotherapie was gegeven.

Tabel 1. Kenmerken van de 494 patienten in relatie tot eerdere chemotherapie.

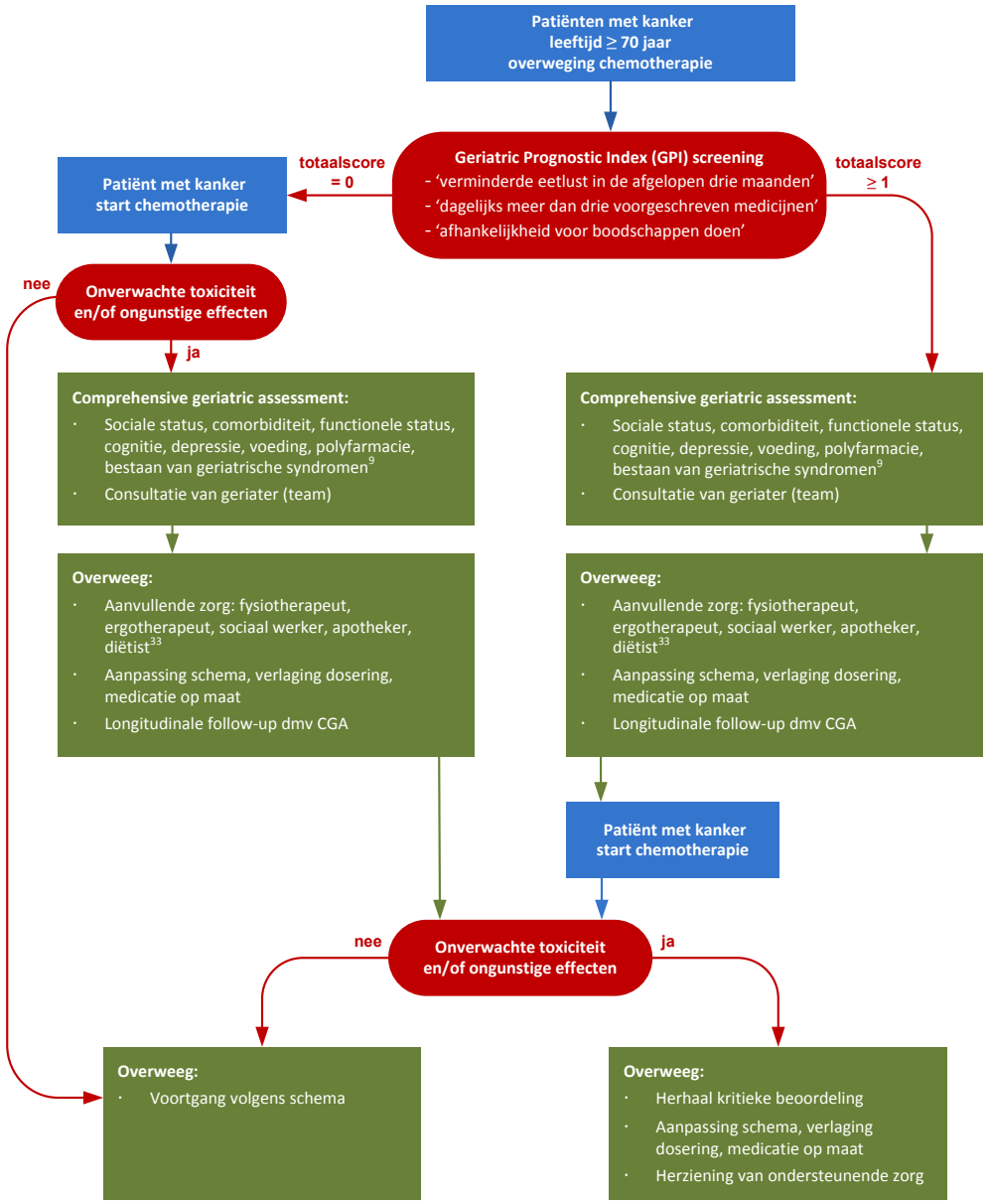
	Geen eerdere chemotherapie (n=420)	**Eerder chemotherapie** (n=74)	**p-waarde**
Mannelijk geslacht	213 (50.7%)	33 (44.6%)	0.33
Leeftijdsgroepen:			
70-74 jr	200 (47.6%)	37 (50.0%)	0.67
75-79 jr	145 (34.5%)	25 (33.8%)	
≥ 80 jr	75 (17.9%)	12 (16.2%)	
In opzet curatieve behandeling	191 (45.5%)	15 (20.3%)	< 0.001
Afwijkende uitgangsscore GA:			
MNA	153 (36.8%)	21 (28.4%)	0.16
GFI	131 (31.3%)	18 (24.3%)	0.23
IQCODE	52 (12.6%)	10 (14.7%)	0.64
MMSE	40 (9.6%)	4 (5.5%)	0.26

Tabel 2. Mortaliteitsrisico voor de GPI score in relatie tot eerdere chemotherapie.

GPI score	**Mediane overleving (maanden)**	**Gecorrigeerde hazard ratios (BI)**	**P-waarde voor trend**	**P-waarde voor interaktie**
Geen eerdere chemotherapie (n=420)				
0 punten (n=154)	29	Ref.	< 0.001	0.44
1 punt (n=152)	15	1.58 (1.21-2.08)		
2 punten (n=90)	10	2.40 (1.76-3.24)		
3 punten (n=21)	5	5.20 (3.18-8.49)		
Eerder chemotherapie (n=74)				
0 punten (n=34)	16	Ref.	0.09	
1 punt (n=23)	14	1.04 (0.54-2.01)		
2 punten (n=14)	9	1.39 (0.69-2.81)		
3 punten (n=3)	7	7.60 (1.94-29.7)		

Hazard ratios (met 95% BI) zijn berekend dmv Cox regressie analyse, en de modellen werden gecorrigeerd voor geslacht, leeftijd, doel van de behandeling en soort maligniteit.

Stroomdiagram



In onze gedetailleerde analyse, waarbij alle items werden meegenomen van de MNA en de GFI met betrekking tot het sterfterisico na de start met chemotherapie, werden twee items van de MNA en één item van de GFI als onafhankelijke risico factor geïdentificeerd. Op basis van deze drie items werd de 'Geriatric Prognostic Index (GPI)' samengesteld om de drukbezette (hemato-)oncoloog te helpen bij het identificeren van de oudere patiënt met kanker met een verhoogd sterfterisico. Alleen al door het stellen van de volgende drie vragen kan belangrijke prognostische informatie worden onthuld: 'Heeft u een verminderde eetlust in de afgelopen drie maanden?', 'Gebruikt u dagelijks meer dan drie voorgeschreven medicijnen?' en 'Bent u afhankelijk van anderen voor boodschappen doen?'. In het geval van een hoge score is een meer uitgebreid CGA geïndiceerd voor het nauwkeurig afstemmen van het behandelplan dat nodig kan zijn bij het streven naar een betere uitkomst. De betekenis van deze bevindingen en adviezen voor de klinische praktijk zal in de toekomst nader onderzocht moeten worden. Echter, momenteel zijn deze aanbevelingen alleen van toepassing bij patiënten voor wie de clinicus behandeling met chemotherapie op klinische gronden wenselijk achtte. Bovendien moeten de bevindingen gevalideerd worden in een ander cohort.

Hoe moet de kennis, tot nu toe verkregen door het GA in de geriatrische oncologie, in de klinische praktijk worden toegepast? In de ideale situatie zal in de behoeften van de oudere patiënt voorzien worden door geriater-oncologen. Echter, zowel het vakgebied van de geriatrie als de oncologie ontwikkelt zich snel en daarom zal, praktisch gesproken, samenwerking van oncologen (getraind in de basisprincipes van de geriatrie) en geriaters (getraind in het toepassen van kanker specifieke GA's) noodzakelijk zijn om de zorg voor ouderen met kanker te optimaliseren [33]. Dit kan worden gerealiseerd op geriatrische oncologie afdelingen of door een geriatrisch consultatie team (GCT) [9, 33]. Het voordeel van het model met een GCT is dat de directe relatie tussen de patiënt en de oncoloog niet wordt verstoord en dat het team beschikbaar is voor begeleiding als later geriatrie-gerelateerde problemen optreden. Een mogelijk nadeel betreft de organisatie voor longitudinaal vervolgen van de geriatrische problemen [9]. Een GCT (bestaande uit een geriater en geriatrisch opgeleide 'nurse practitioner' of 'physician's assistant') zou zelfs kunnen worden ingebed in een bestaande oncologische kliniek en zou actief moeten participeren in een multidisciplinair team [9, 33]. Recent werd de rol voor de apotheker benadrukt binnen het multidisciplinaire team, voor het in kaart brengen van de mogelijk nadelige gevolgen van polyfarmacie, gecompliceerde interacties tussen geneesmiddelen en potentieel ondoelmatige medicatie [34].

Mohile en anderen definieerden vier doelen voor verder onderzoek in geriatrische oncologie [35]:

1. Incorporeer GA instrumenten in klinisch onderzoek die nadelige uitkomsten voorspellen voor de oudere volwassenen met kanker;
2. Onderzoek de mogelijkheid van een GA zorgmodel om de uitkomst van de oudere patiënt met kanker te verbeteren;
3. Verkrijg meer inzicht op de invloed van de oncologische behandeling in de algemene populatie van de oudere patiënt met kanker;
4. Identificeer en onderzoek interventies om de symptomen te verbeteren en de kwaliteit van leven van ouderen patiënten met kanker te behouden.

Het klinisch onderzoek zoals beschreven in dit proefschrift richtte zich op de prognostische rol van de MNA en de GFI, voor zowel de haalbaarheid van de behandeling met chemotherapie als voor de overleving. Of interventie strategieën, na opsporing van specifieke tekortkomingen, zullen resulteren in betere uitkomsten en of deze zullen helpen om de kwaliteit van leven te behouden, zijn uitdagende vragen die nu nog niet zijn beantwoord. Op grond van de in dit proefschrift beschreven resultaten en met in achtneming van de huidige literatuur worden de volgende aanbevelingen voor de behandeling met chemotherapie bij oudere patiënten met kanker in het stroomdiagram weergegeven.

De oudere patiënten met kanker, in aantal snel toenemend de komende decennia, verdienen niets minder dan een optimale inventarisatie van reeds bestaande geriatrische problemen welke nadelige uitkomsten voorspellen en aangepakt moeten worden [2]. Onderzoek naar interventiestrategieën die specifiek gericht zijn op ouderen, op basis van GA, zullen verder ontwikkeld moeten worden om de uitkomst van de behandeling te verbeteren en ouderen moeten worden aangemoedigd om aan deze onderzoeken deel te nemen. Dit type onderzoek werd verricht met positief resultaat door middel van fysieke training bij patiënten met borstkanker in jongere leeftijdsgroepen [36] en momenteel is er een lopend onderzoek naar het effect van fysieke training bij oudere patiënten met borstkanker (de 'Climb Every Mountain'-studie) [37]. De onderzoeken zijn dus in ontwikkeling, maar in het komend decennium zal nog veel inspanning geleverd moeten worden voor het uitvoeren van tumorspecifieke studies. De onderzoeken in dit proefschrift kunnen gebruikt worden als achtergrondinformatie en een eerste stap vormen waarop deze ontwikkelingen gebaseerd kunnen worden. We hopen dat dit proefschrift een bijdrage kan leveren aan het ontwikkelen van gestandaardiseerd instrumentarium en daarmee, dat het GA

een routine onderdeel wordt van de zorg bij de oudere patiënt met kanker. Het toepassen van computer-technologie zal het gebruik van dit instrumentarium vergemakkelijken.

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Appendices

Mini Nutritional Assessment (MNA)*

SCREENING

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake

B Weight loss during the last 3 months
0 = weight loss greater than 3kg (6.6lbs)
1 = does not know
2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs)
3 = no weight loss

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems

F Body Mass Index (BMI) (weight in kg) / (height in m^2)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater

Screening score (subtotal max. 14 points)
12-14 points: Normal nutritional status
8 - 11 points: At risk of malnutrition
0 -7 points: Malnourished

ASSESSMENT (if screening < 12 points)

G Lives independently (not in nursing home or hospital)
1 = yes 0 = no

H Takes more than 3 prescription drugs per day
0 = yes 1 = no

I Pressure sores or skin ulcers
0 = yes 1 = no

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals

K Selected consumption markers for protein intake
• At least one serving of dairy products (milk, cheese, yoghurt) per day
• Two or more servings of legumes or eggs per week
• Meat, fish or poultry every day
0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes

L Consumes two or more servings of fruit or vegetables per day?
0 = no 1 = yes

M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem

P In comparison with other people of the same age, how does the patient consider his / her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 =MAC 21 to 22
1.0 = MAC 22 or greater

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater

Assessment score (max. 16 points)

Total (Screening + Assessment)
24 to 30 points: Normal nutritional status
17 to 23.5 points: At risk of malnutrition
Less than 17 points: Malnourished

(From: Guigoz et.al. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med, 2002. 18(4): p.737-57).

* http://www.mna-elderly.com/forms/MNA_MNenglish.pdf.

Groningen Frailty indicator (GFI)

Mobility
Is the patient able to carry out these tasks single handed without any help? (The use of help resources such as walking stick, walking frame, wheelchair, is considered independent)

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

Physical Fitness

5. What mark does the patient give himself/herself for physical fitness? (scale 0 to 10)

Vision

6. Does the patient experience problems in daily life due to poor vision?

Hearing

7. Does the patient experience problems in daily life due to being hard of hearing?

Nourishment

8. During the last 6 months has the patient lost a lot of weight unwillingly? (3 kg in 1 month or 6 kg in 2 months)

Morbidity

9. Does the patient take 4 or more different types of medicine?

Cognition (Perception)

10. Does the patient have any complaints about his/her memory or is the patient known to have a dementia syndrome?

Psychosocial

11. Does the patient sometimes experience emptiness around him/her?
12. Does the patient sometimes miss people around him/her?
13. Does the patient sometimes feel abandoned?
14. Has the patient recently felt downhearted or sad?
15. Has the patient recently felt nervous or anxious?

Scoring:

Questions 1–4:	Independent = 0; dependent = 1
Question 5:	0–6 = 1; 7–10 = 0
Questions 6–9:	No = 0; yes = 1
Question 10:	No and sometimes = 0; yes = 1
Questions 11–15:	No = 0; sometimes and yes = 1

(From: Slaets JP. Vulnerability in the Elderly: frailty. Med Clin North Am 2006;90:593-601)

Informant questionnaire on cognitive decline in the elderly (IQCODE)

Hoe is mevrouw/meneer, vergeleken met 10 jaar geleden, bij:

		1	2	3	4	5
1.	Feiten herinneren over familie-leden en vrienden, zoals beroepen, verjaardagen of adressen.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
2.	Herinneren wat er pas geleden is gebeurd.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
3.	Gesprekken herinneren van een paar dagen geleden.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
4.	Onthouden van zijn/haar adres en telefoonnummer.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
5.	Onthouden welke dag en maand het is.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
6.	Onthouden waar normaal gesproken ligt.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
7.	weten te vinden dat op z'n gewone plek ligt.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
8.	Omgaan met bekende huishoudelijke apparaten.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
9.	Leren omgaan met nieuwe huishoudelijke apparaten.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
10.	Nieuwe dingen leren in het algemeen.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
11.	Het verhaal kunnen volgen in een boek of op televisie.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
12.	Beslissingen nemen over alledaagse dingen.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
13.	Omgaan met geld voor de boodschappen.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
14.	Geldzaken regelen, zoals het pensioen, bankzaken.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
15.	Andere alledaagse rekenproblemen oplossen, zoals hoe eten er gekocht moet worden, weten wanneer familieleden of vrienden voor het laatst op bezoek zijn geweest.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
16.	Het gezonde verstand gebruiken om te begrijpen wat er gebeurt en de zaken op een rijtje te zetten.	Veel beter	Iets beter	Niet veranderd	Iets slechter	Veel slechter
	Totaal					

(From: Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. Psychological Medicine 1994;24:145-153.

Mini-Mental State Examination (MMSE)

Ik ga u nu enkele vragen stellen en geef u enkele problemen om op te lossen. Wilt u alstublieft uw best doen omzo goed mogelijke antwoorden te geven.

noteer antwoord — score:

1. a. Welk jaar is het?
   b. Welk seizoen is het?
   c. Welke maand van het jaar is het?
   d. Wat is de datum vandaag?
   e. Welke dag van de week is het?

   (0-5) _____

2. a. In welke provincie zijn we nu?
   b. In welke plaats zijn we nu?
   c. In welk ziekenhuis (instelling) zijn we nu?
   d. Wat is de naam van deze afdeling?
   e. Op welke verdieping zijn we nu? (0-5) _____

3. Ik noem nu drie voorwerpen. Wilt u die herhalen nadat ik ze alle drie gezegd heb?
   Onthoud ze want ik vraag u over enkele minuten ze opnieuw te noemen.
   (Noem "appel, sleutel, tafel", neem 1 seconde per woord)(1 punt
   voor elk goed antwoord, herhaal maximaal 5 keer
   tot de patiënt de drie woorden weet) (0-3) _____

4. Wilt u van de 100 zeven aftrekken en van wat overblijft weer zeven aftrekken en zo doorgaan tot ik stop zeg?
   (Herhaal eventueel 3 maal als de persoon stopt, herhaal dezelfde instructie,geef maximaal 1 minuut de tijd) Noteer hier het antwoord.
   of
   Wilt u het woord "'worst" achterstevoren spellen?.
   Noteer hier het antwoord. (0-5) _____

5. Noemt u nogmaals de drie voorwerpen van zojuist.
   (Eén punt voor elk goed antwoord). (0-3) _____

6. Wat is dit? En wat is dat?
   (Wijs een pen en een horloge aan. Eén punt voor elk goed antwoord). (0-2) _____

7. Wilt u de volgende zin herhalen: " Nu eens dit en dan weer dat ".
   (Eén punt als de complete zin goed is) (0-1) _____

8. Wilt u deze woorden lezen en dan doen wat erstaat'?
   (papier met daarop in grote letters: "Sluit uw ogen") (0-1) _____

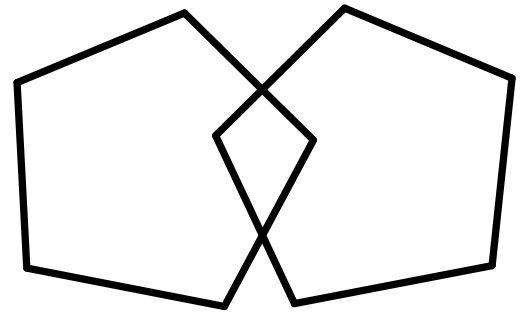
9. Wilt u dit papiertje pakken met uw rechterhand, het dubbelvouwen en het op uw schoot leggen? (Eén punt voor iedere goede handeling). (0-3) _____

10. Wilt u voor mij een volledige zin opschrijven op dit stuk papier? (Eén punt wanneer de zin een onderwerp en een gezegde heeft en betekenis heeft). (0-1) _____

11. Wilt u deze figuur natekenen?
    (Figuur achterop dit papier. Eén punt als figuur geheel correct is nagetekend.
    Er moet een vierhoek te zien zijn tussen de twee vijfhoeken) (0-1) _____

TOTALE TEST SCORE: (0-30) _____

Sluit uw ogen



(from: Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 1975; 12:189-198).

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List of publications

Journals

A.A. Aaldriks, E. Maartense, J.W.R. Nortier, L.G.M. van der Geest, S. le Cessie, B.C. Tanis, J.E.A. Portielje, P. Ypma, E.J. Giltay. *Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the Elderly.* Acta Oncol. 2015 Aug 25:1-9. [Epub ahead of print]

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Other

Abstract

A.A. Aaldriks, E. Maartense, J.W.R. Nortier, L.G.M. van der Geest, S. le Cessie, B.C. Tanis, J.E.A. Portielje, P. Ypma, E.J. Giltay. *Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly (abstract).* 2015 ASCO Annual Meeting Proceedings I.

Oral presentations

A.A. Aaldriks. Voorspellende waarde van geriatrisch assessment bij patiënten ouder dan 70 jaar, behandeld met chemotherapie. Afscheidssymposium van E. Maartense, 25 september 2013, Reiner de Graafgroep, Delft, the Netherlands.

A.A. Aaldriks. CGA's welke en wanneer . Platformbijeenkomst GeriOnNe: Geriatrisch assessment: nog steeds meer vragen dan antwoorden. 29 September 2010, Utrecht, the Netherlands.

A.A. Aaldriks. Voorspellende waarde van geriatrisch assessment bij patiënten ouder dan 70 jaar, behandeld met chemotherapie. 4e Nationale Symposium Kanker bij Ouderen. 11 November 2009, Location De Reehorst, Ede, the Netherlands.

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Poster presentations

A.A. Aaldriks, E. Maartense, J.W.R. Nortier, L.G.M. van der Geest, S. le Cessie, B.C. Tanis, J.E.A. Portielje, P. Ypma, E.J. Giltay. Three components of a Geriatric Screening determine the Geriatric Prognostic Index (GPI) as risk profile before chemotherapy in the Elderly. 14th Meeting of the International Society of Geriatric Oncology SIOG. October 23-25, 2014, Lisboa Congress Centre Praça das Indústrias, Lisboa, Portugal.

A.A. Aaldriks, E.J. Giltay, S. le Cessie, L.G.M. van der Geest, J.E.A. Portielje, B.C. Tanis, J.W.R. Nortier, E. Maartense. The impact of geriatric assessment on the outcome of older breast cancer patients treated with chemotherapy. 11th Meeting of the International Society of Geriatric Oncology. November 3-5, 2011, Pullman Rive Gauche Hotel, Paris, France.

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Ab Aaldriks, Delft september 2015

Curriculum vitae.

Aaldrik Albertus (Ab) Aaldriks werd geboren op 8 januari 1961 te ‘s-Gravenhage. Na de middelbare school is hij begonnen aan een technische opleiding werktuigbouwkunde maar na enkele jaren gestart aan de HBO-V te Voorburg. Na het behalen van het diploma heeft hij enige tijd gewerkt in Maastricht als psychiatrisch verpleegkundige. In 1986 is hij gestart met de opleiding voor verloskundigen in Hasselt (België). Na zijn registratie als verloskundige is hij met Caroline een verloskundige maatschap begonnen in Delft en werkte gedurende 10 jaar als verloskundige tot en met 1999. In 1994 begon hij met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam en behaalde in 2002 zijn artsdiploma. Van 2000 tot 2002 werkte hij als docent anatomie en verloskunde aan het Albeda college in Rotterdam. In 2002 begon hij als arts-assistent gynaecologie in het Reinier de Graafgasthuis. Na een jaar kreeg hij de mogelijkheid om de opleiding tot psychiater te volgen bij GGZ-Delfland. Zijn keuzestage deed hij op de afdeling zwangerschapsgerelateerde psychiatrie bij prof. dr. M. W. Hengeveld in het Erasmus MC. Op 1 oktober 2008 werd hij ingeschreven in het medisch specialisten register als psychiater. Van 1996 tot 2010 was hij lid van het Centraal Tuchtcollege voor de Gezondheidszorg. Momenteel werkt hij als psychiater met als aandachtsgebied ernstig verslaafde zwangeren met psychiatrische problematiek. Ab is getrouwd met Caroline Koetsier en heeft drie zoons, Arno, Timo en Joren. Ab is een zondagskind.