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Chapter

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

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3



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 time limit 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 pos-

sible 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 caregivers, 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 $\pm$ 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 $< 35\text{g/L}$); hemoglobin (cutoff $< 7.5\text{mmol/L}$); creatinine (cutoff $\geq 100\text{ }\mu\text{mol/L}$) and LDH (cutoff $\geq 250\text{ U/L}$). 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

Table 1 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 (range 70–88). 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
	<i>n</i>	%
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

	≥4 cycles (n=39) n (%)	<4 cycles (n=16) n (%)	All patients (n=55)			
			Crude odds ratio	p	Adjusted odds ratio	p
Geriatric assessment:						
<i>MNA:</i>						
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
<i>GFI:</i>						
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
<i>IQCODE:</i>						
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
<i>MMSE:</i>						
no cognitive decline > 24	33 (87)	16 (100)				
cognitive dysfunction ≤ 24	5 (13)	0 (0)	–		–	
Laboratory tests:						
<i>Albumin:</i>						
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
<i>Hemoglobin:</i>						
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
<i>Creatinine:</i>						
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
<i>LDH:</i>						
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:					
<i>MNA:</i>					
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
<i>GFI:</i>					
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
<i>IQCODE:</i>					
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
<i>MMSE:</i>					
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:					
<i>Albumin:</i>					
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
<i>Hemoglobin:</i>					
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
<i>Creatinine:</i>					
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
<i>LDH:</i>					
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		2° 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

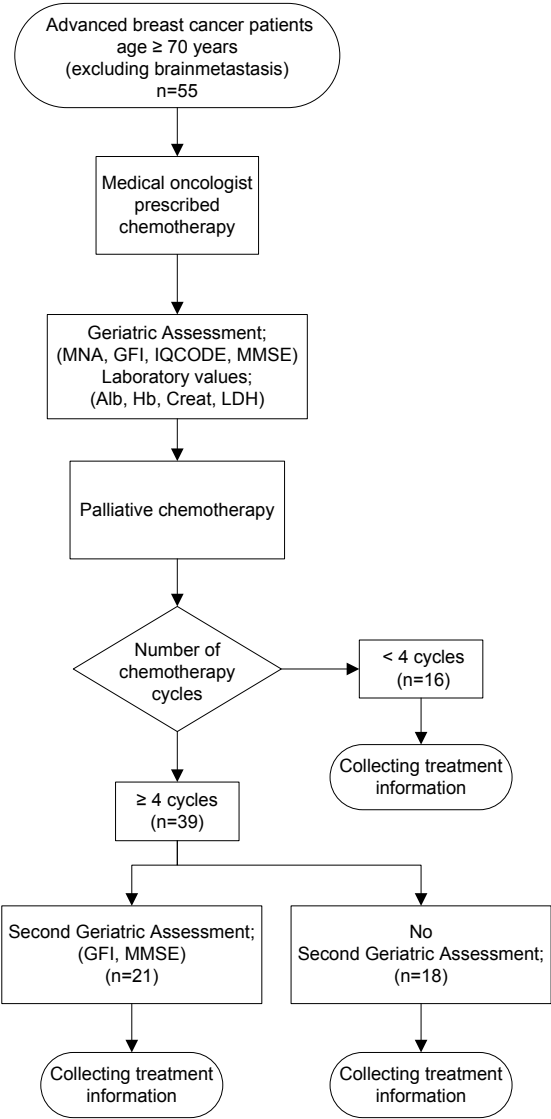
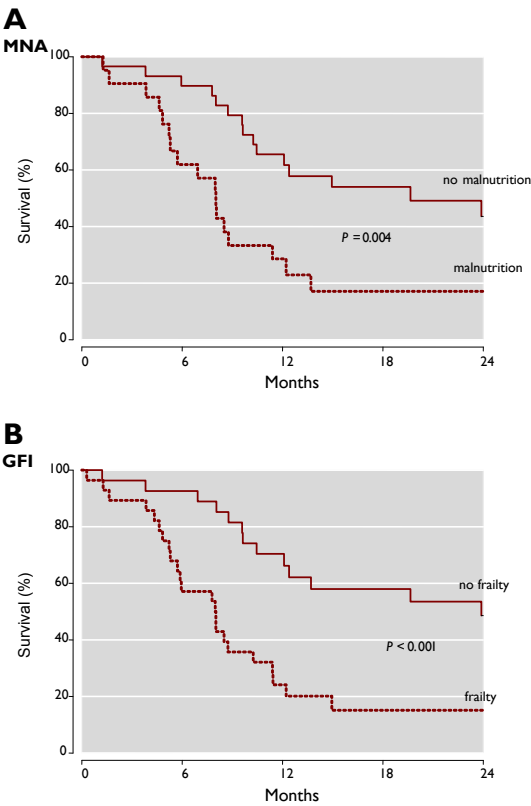


Figure 2. Kaplan–Meier curves of overall survival in patients with advanced breast cancer according to categories of [A] Mini Nutritional Assessment (MNA) and [B] Groningen Frailty Indicator (GFI). *p*-values by log-rank tests. MNA data was missing for 2 patients at baseline, whereas there were no missing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



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