Frailty and outcomes in older cancer patients

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4

THE RELEVANCE OF GERIATRIC ASSESSMENT FOR OLDER PATIENTS RECEIVING PALLIATIVE CHEMOTHERAPY

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ABSTRACT

Objective

No tools accurately discriminate between older patients who are fit and those who are frail to tolerate systemic palliative treatment. This study evaluates whether domains of geriatric assessment (GA) are associated with increased risk of chemotherapy intolerance in patients who were considered fit to start palliative chemotherapy after clinical evaluation by their treating clinician.

Methods

This prospective multicenter study included patients ≥70 years who started first line palliative systemic treatment. Before treatment initiation, patients completed GA including Activities of Daily Life (ADL), Instrumental Activities of Daily Life (IADL), Mini-Mental State Examination (MMSE), Mini Nutritional Assessment (MNA), Geriatric Depression Scale (GDS-15) and the Timed Up and Go Test (TUGT). Primary endpoint was treatment modification, defined as inability to complete the first three sessions of systemic treatment as planned. Secondary endpoint was treatment related toxicity ≥ grade 3 (CTCAE Version 4). The association between GA and endpoints were assessed using univariable and multivariable logistic regression analysis.

Results

Ninety-nine patients with median age of 77 (+/- 8) years underwent GA. 48% of the patients required treatment modification and grade 3 toxicity occurred in 53% of patients. One or more geriatric impairments were present in 71% of patients and 32% of patients were frail in two or more domains. Only TUGT was associated with treatment modifications (OR 2.9 [95% CI 1.3-6.5]) and grade 3 toxicities (OR 2.8 [95% CI 1.2-6.3]).

Conclusion

Frailty was common in older patients who were considered fit to receive palliative chemotherapy. Treatment modification was necessary in half of the patients. Only TUGT was significantly associated with treatment modifications and grade 3 chemotherapy toxicities.

INTRODUCTION

Due to an improved life expectancy, physicians will see an increasing number of older patients with malignant disease.[1] In the past decades, substantial progress has been made in the treatment of cancer. However, it is unclear whether all age groups benefit from these improvements due to exclusion of older patients in clinical trials. Less than 10% of the patients with cancer aged ≥ 75 years were enrolled in clinical trials. [2] In the setting of geriatric oncology, research suggests that frail older patients have an increased risk of chemotherapy toxicity, which can severely impact quality of life.[3]

Currently, physicians often use clinical judgement to recommend palliative chemotherapy, because a short clinical tool to identify patients at risks of treatment toxicity is not widely used. Frailty may be hard to detect by clinical judgment, and conversely most oncologists consider very few patients as frail. Oncologists need an objective and validated clinical tool to discriminate between fit and frail older patients in palliative setting to avoid chemotherapeutic major adverse events that severely impact the quality of life, or that withhold patients from the beneficial effects of chemotherapy due to treatment modifications. This may be especially relevant for older patients who are treated in the palliative setting, as quality of life may be considered more important than length of life.

International guidelines recommend that clinicians take geriatric assessment (GA) results into account when recommending chemotherapy in older patients.[4] GA has been developed to discriminate between fit and frail older patients by providing information on physical function, comorbidity, nutrition and cognition. Previous studies have shown the additional value of a comprehensive GA for the identification of patients who are at risk of chemotherapy intolerance in combined palliative and curative setting.[3] However, a comprehensive GA is a time-consuming method (as it may take up to an hour of more per patient). A short GA may improve its applicability in daily clinical practice, but it remains unclear which frailty characteristics are the most predisposing for adverse events. In addition, the use of GA in palliative setting is poorly investigated and weighing risks from benefits from chemotherapeutic treatment is likely different in palliative patients compared to patients who are treated in the curative setting.[4] A predictive (screening) model in which geriatric oncologic frailty can be assessed may help to discriminate between patients who will benefit of chemotherapeutic treatment in daily clinical practice. Furthermore, it may help guide the implementation of health interventions that aim to optimize pre-chemotherapeutic condition.

This study evaluates whether domains of a geriatric assessment are associated with increased risk of chemotherapy intolerance within the first three cycles of chemotherapy in patients who were considered fit to start palliative chemotherapy after clinical evaluation by their treating physician.

METHOD

Patients

This prospective multicenter study included patients between November 2012 and September 2014 in the St. Antonius Hospital Nieuwegein and the Tergooi Hospital Hilversum in The Netherlands. Patients were eligible for participation if they were aged ≥ 70 years and diagnosed with metastatic cancer for whom first line palliative chemotherapy was prescribed by an experienced (≥5 years) medical oncologist or hematologist. In addition, also patients with non-Hodgkin lymphoma and multiple myeloma receiving chemotherapy (with or without targeted therapy) were eligible for participation. Because of older age, patients with multiple myeloma were considered ineligible for stem cell transplantation.

Other inclusion criteria was an understanding of Dutch language due to the use of Dutch questionnaires. Patients with metastases in the central nervous system were excluded from this study. Patients diagnosed with breast or colorectal cancer could have received previous chemotherapy (neoadjuvant or adjuvant) if >6 months before study participation. This study was approved by the Medical Research Ethics Committees United (MEC-U) in Nieuwegein. All patients provided written informed consent in accordance with the Declaration of Helsinki.

Geriatric assessment

Before initiating the systemic treatment, all patients were prospectively assessed using a GA that consisted of 6 preselected geriatric assessments. The elements of the GA were chosen based on previously validated, standardized, mostly survey-based measures, testing several geriatric domains. The cognitive domain included the questionnaire Mini-Mental State Examination (MMSE). Depressive symptoms were assessed using the 15 item Geriatric Depression Scale (GDS-15). Physical functioning was assessed using the Activities of Daily Life (ADL) and the Instrumental Activities of Daily Life (IADL) questionnaires. The IADL assesses independent living skills. These skills are considered more complex than the basic activities of daily living. To assess nutritional status, the Mini Nutritional Assessment (MNA) was used. The Timed Up and Go Test (TUGT) evaluates gait and balance and requires a person to stand up, walk 3 meters, turn, walk back and sit down. Polypharmacy was defined as the use of ≥4 drugs per day. All GA measures were completed by a nurse practitioner or a member of the research team and did not require a specialized training background for administration. The treating physician was not aware of the results of the GA and it did not affect treatment decisions or interventions. All elements of the used GA have predefined cut off points for frailty. (Table 2)

Endpoints

The primary endpoint (treatment modification) was defined as the inability to complete the first three sessions of chemotherapy as planned. This included any early discontinuation of treatment, dose reduction or dose delay (≥5 days) based on reported toxicities as graded by de National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[5] Treatment discontinuations due to death from any cause or disease progression were not considered treatment modifications due to CTCAE toxicity, and were therefore not included in the primary endpoint. The cutoff point of three cycles of chemotherapy was chosen because in daily clinical practice the response of chemotherapy is most commonly evaluated after three cycles. The secondary endpoint was treatment related toxicity ≥ grade 3.

Statistical analysis

Patient characteristics were described in means ± standard deviation (SD) for continuous variables if normally distributed, medians and interquartile range (IQR) if not normally distributed, and percentages or numbers for categorical or ordinal variables. To test for differences between mono versus combination chemotherapy and the primary and secondary endpoints, we used a Chi-square test. Furthermore, we used the Chi-square test to analyze the cumulative effect of geriatric impairments on primary and secondary outcome. Subsequently, we assessed the relation between treatment modification and grade 3 toxicity in a univariable logistic regression analysis. The geriatric assessments that reached a P-value less than 0.1 were further examined in a multivariable logistic regression model with clinically relevant, empirically chosen confounders including age at inclusion continuously, sex (male / female) and type of cancer (solid versus hematological). Unadjusted and adjusted Odds Ratios (OR) were calculated with corresponding 95% confidence intervals (95% CI).

Finally, because patients with hematological malignancies may have a different prognosis compared to patients with solid metastasized malignancies, chemotherapeutic treatment considerations may be different. Different treatments may lead to different toxicity profiles and different risks of treatment modifications, which may potentially impact on the relation between GA and outcomes. To investigate potential differences in the relation between GA and outcomes between patients with hematologic and non-hematologic malignancies, we repeated the previous analyses including only the group of patients with solid metastasized malignancies. The group of hematologic malignancies (n=18) was considered too small to conduct a subgroup analysis.

RESULTS

Patient, tumor and treatment characteristics

Between 2012 and 2014, a total of 99 patients were included. The median age was 77 (IQR 8) years and 34% was octogenarian. Two-thirds of the patients were male. A minority of patients (14%) were restricted in daily activities (ECOG ≥ 2). Almost all patients lived at home (94%) and the majority together with a partner (70%). The most common tumor types were colorectal (21%), urogenital (19%) and Non-Hodgkin Lymphoma(NHL) or Multiple Myeloma(MM) (18%). Most patients received combination chemotherapy (62%) and six patients started with an upfront dose reduction of chemotherapy. Combination therapy included: taxane-based chemotherapy (20%) was the most frequently prescribed therapy after platinum based (18%) and anthracycline (11%) based chemotherapy. Baseline characteristics are depicted in Table 1.

Geriatric assessment

Table 2 shows the results of the GA prior to the chemotherapy. All enrolled patients participated in the GA. One or more geriatric impairments were present in 71% of patients and 32% patients were frail in two or more domains. Eleven subjects were not able to carry out the TUGT, due to various reasons and were considered physically impaired. A slow gait speed, cognitive impairment and risk of malnutrition were the most commonly observed impairments and occurred in 52%, 14% and 15% of patients respectively. The median score of the TUGT was 10.5 (7.4) seconds, and 52% of the patients were considered impaired. The median score of the ADL was 6 (IQR 1), and 9% of patients required assistance during simple daily living activities such as feeding and dressing, and 8% of the patients required help with instrumental activities of daily life. Few patients were considered cognitively impaired (14%) and 9% of patients scored high on the GDS-15 questionnaire. Malnutrition occurred in 15.2% of the older patients.

Treatment modifications

In total, 47 of the 99 patients (48%) required one or more treatment modifications during the first three cycles of chemotherapy. 18 patients received a dose reduction (18%), 21 patients required a delay in chemotherapy administration (21%) and 21 patients discontinued treatment (21%) (Figure 1).

Table 1. Baseline table of patients receiving palliative chemotherapy (n=99).

Characteristics	Total patients (%)
Age, median (IQR)	77 (IQR 8)
Sex - male	62 (63)
St. Antonius hospital	62 (63)
Tergooi hospital	37 (37)
ECOG performance score	
0	44 (44)
1	41 (41)
2	12 (12)
3	2 (2)
BMI, mean (±SD)	26 (±4)
Underweight (<18.5)	3 (3)
Normal (18.5-25)	47 (48)
Overweight (25-30)	37 (37)
Obese(≥30)	12 (12)
Type of malignancy	
Colorectal cancer	21 (21)
Urogenital cancer	19 (19)
Hematological cancer	18 (18)
Gynecological cancer	13 (13)
Upper gastrointestinal cancer	11 (11)
Lung cancer	11 (11)
Breast cancer	5 (5)
Melanoma	1 (1)
Type chemotherapy	
Mono	37 (37)
Combination	62 (63)
Adaptive chemotherapy schedule at baseline	6 (6)
Polypharmacy ≥4	67 (68)
Living with partner	68 (69)
Living at home	96 (97)

Abbreviations: IQR, Interquartile Range; ECOG, Eastern Cooperative Oncology Group; SD, Standard Deviation; BMI, Body Mass Index; GI, Gastrointestinal

Most patients required a dose reduction after the first cycle (11/18, 61%) and the most common causes for dose reductions were diarrhea (5/18, 28%), malaise (4/18, 22%) and neutropenic fever (4/18, 22%). Most of the patients discontinued the chemotherapy after the first cycle (15/21, 71%), most frequently due to malaise (7/21, 33%), diarrhea

(5/21, 24%) and neutropenic fever (2/21, 10%). Chemotherapy delay (median 10 (IQR 8) days) was most frequently observed after cycle 3 (14/21, 67%) and most frequently caused by neutropenia (5/21, 24%), infections (4/21, 19%) and diarrhea (3/21, 14%). There was no significant difference between patients receiving mono versus combination chemotherapy and the risk of dose reductions (p=0.14), delay (p=0.34) or treatment discontinuations (p=0.11).

Table 2. GA specifics and outcomes according to all patients (n=99).

Questionnaire or test	Score range	Cut off point for frailty	Median (25^{th}, 75^{th})	Number of frail patients (%)
ADL	0-6	≤4	5 (5, 6)	9 (9)
IADL	0-14	≤7	13 (11, 14)	8 (8)
GDS-15	0-15	≥6	2 (1, 4)	9 (9)
TUGT	0-inf	≥10	10 (8, 15)	41 (41)
MMSE	0-30	≤24	28 (26, 29)	14 (14)
MNA	0-30	≤17	20 (18, 24)	15 (15)

Abbreviations: ADL, Activities of Daily Life; IADL, Instrumental Activities of Daily Life; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment; GDS-15, Geriatric Depression Scale; TUGT, Timed Up and Go Test.

Table 3 shows the number of patients who were considered impaired per each individual GA test, the number of treatment modifications, and the association between GA and treatment modifications. Most patients who were considered impaired on any of the GA tests required a treatment modifications, except for patients who were considered impaired by the MMSE test (43% of the impaired patients and 48% of the non-impaired patients required a treatment modification). In the univariable logistic regression analysis, the TUGT was the only significant factor associated with treatment modifications (OR 2.9 [95% CI 1.3-6.5], p=0.01). The TUGT remained significantly associated for treatment modifications (OR 3.1 [1.3-7.2], p=0.01) after correcting for the potential confounders of age, sex and type of tumor (data not shown). No significant associations among the other geriatric assessments were found. By repeating the previous analyses, including only the patients with solid tumors, we did not find any important differences in the relation between GA and treatment modifications compared to the total group of patients. (Supplementary Table 1)

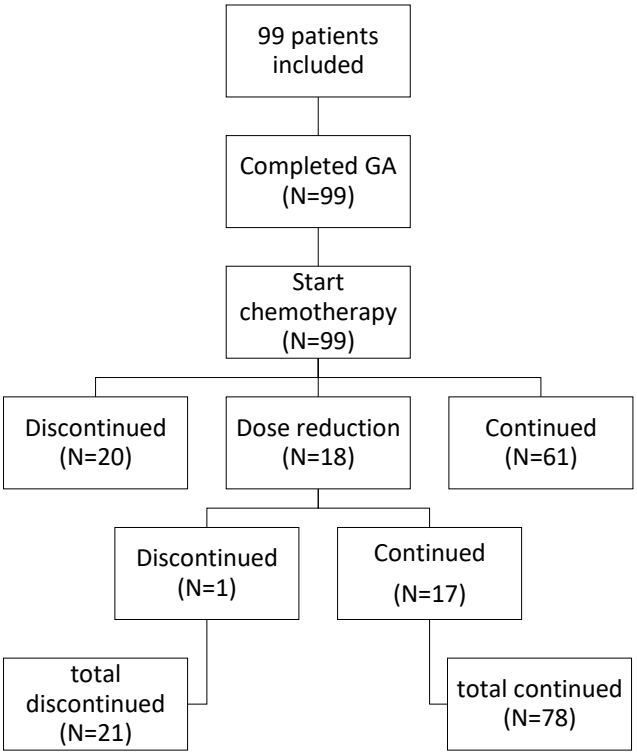

Figure 1. Flow chart of included patients and chemotherapy administration(n=99).

Finally, the proportion of patients who required a treatment modification was not associated with an increasing number of impaired GA (p=0.556). (Figure 2) Of the patients without geriatric impairments, 38% required a treatment modification, while in patients with 1, 2 of 3+ geriatric impairments grade 3 toxicity was reported in 47%, 55% and 59% respectively.

Grade ≥3 toxicity

Grade 3 toxicity occurred in 53 patients (54%) (Table 4). Grade 4 and 5 toxicities were not observed. Most patients (89%) who experienced a grade 3 toxicity required a treatment modification. Grade 3 hematologic and non-hematologic toxicity occurred in 14% and 40% of patients, respectively. The most common grade 3 toxicities were diarrhea (25%), neutropenia (23%) and (neutropenic) infection (21%). Among the 6 patients who started with an upfront dose reduction, grade 3 toxicity occurred in 3 patients (50%) due to hematological toxicities.

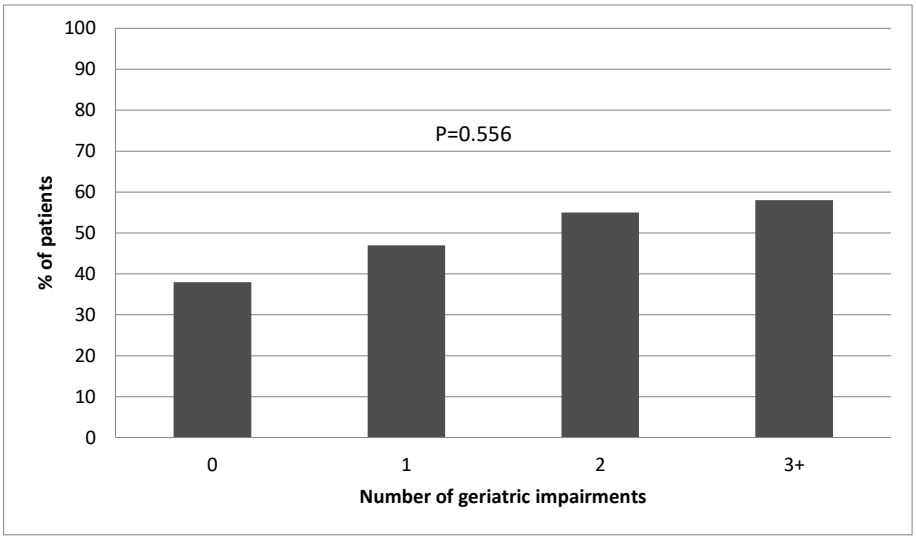

Figure 2. Association between number of impaired geriatric assessments and percentages of patients with treatment modifications.

Twenty-eight patients (28%) with an adverse event were admitted to the hospital, with a mean time of hospitalization of 7.8 days (+/-SD 2.3) The most frequent reasons for hospitalization were diarrhea and neutropenic fever. Three patients developed a delirium.

The association between individual GA tests and grade 3 toxicity are depicted in Table 4. Patients with an impaired GA test experienced more often a grade 3 toxicity compared to patients with a normal GA test, except for the patients with an impaired MMSE: 43% of the impaired patients versus 53% of the non-impaired patients experienced toxicity. In the univariable analysis, again only the TUGT was significantly associated with treatment related grade 3 toxicity (OR 2.8 [95% CI 1.2-6.3], p=0.01). After correction for confounders, the TUGT (2.8 [95% CI 1.3-7.2]), p=0.01) remained significantly associated with the occurrence of grade 3 toxicity. Finally, the subgroup analysis in which only patients with solid tumors were included did not show differences in the relation to GA and the occurrence of grade 3 toxicity compared to the total group of patients. (Supplementary Table 1)

Table 3. Association between GA and treatment modification/grade 3 toxicity (n=99).

Geriatric assessment	Patients with treatment modification/total patients (n (%))	Treatment modification OR (95% CI)
ADL		
Impaired	6/9 (67)	2.4 (0.6-10.2)
Independent	41/90 (45)	1.0
IADL		
Impaired	6/8 (75)	3.7 (0.7-19.1)
Independent	41/91 (45)	1.0
GDS-15		
Impaired	6/9 (67)	2.4 (0.6-10.2)
Independent	41/90 (45)	1.0
TUGT		
Impaired	31/52 (60)	2.9 (1.3-6.5)
Independent	16/47 (34)	1.0
MMSE		
Impaired	6/14 (43)	0.8 (0.3-2.5)
Independent	41/85 (48)	1.0
MNA		
Impaired	9/15 (60)	1.8 (0.6-5.6)
Independent	38/84 (40)	1.0

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; ADL, Activities of Daily Life; IADL, Instrumental Activities of Daily Life; MMSE, Mini-Mental State Examination;

Table 4. Treatment related grade 3 toxicity (n=53).

Grade 3 toxicity	Patients (%)
Non-hematological (n=39)	
Diarrhea	13 (25)
Malaise	12 (23)
Infection	6 (11)
Neutropenic infection	5 (9)
Ileus	1 (2)
Allergic reaction	1 (2)
Sensory neuropathy	1 (2)
Hematological (n=14)	
Neutropenia	8 (15)
Anemia	3 (6)
Thrombocytopenia	3 (6)

P-value	Patients with grade 3 toxicity/ total patients (n (%))	Grade 3 toxicity OR (95% CI)	P-value
0.24			0.41
	6/9 (67)	1.8 (0.4-7.8)	
	47/90 (52)	1.0	
0.12			0.12
	6/8 (75)	0.9 (0.7-1.0)	
	47/91 (51)	1.0	
0.24			0.23
	6/9 (67)	1.1 (0.9-1.3)	
	47/90 (52)	1.0	
0.01			0.01
	34/52 (65)	2.8 (1.2-6.3)	
	19/47 (40)	1.0	
0.70			0.29
	8/14 (43)	0.9 (0.8-1.0)	
	45/85 (53)	1.0	
0.30			0.10
	9/15 (60)	0.9 (0.8-1.0)	
	44/84 (52)	1.0	

MNA, Mini Nutritional Assessment; GDS-15, Geriatric Depression Scale; TUGT, Timed Up and Go Test.

DISCUSSION

The present study analyzes the association between GA and chemotherapy intolerance in older patients receiving first line palliative systemic treatment for both solid and hematologic malignancies. Our data show that half of the patients who were considered fit to start palliative systemic chemotherapy required treatment modifications and/or experienced grade 3 treatment related toxicity during the first three cycles of treatment. Of all investigated geriatric domains, only an impaired TUGT was significant associated with a three times increased risk of chemotherapy intolerance in patients who are considered fit to start chemotherapy.

Despite multiple studies that investigated the predictive value of GA for mortality, studies on the predictive value of GA for chemotherapeutic intolerance are limited. [3] [4] The first, of Aaldriks and colleagues, investigated the predictive value of GA for treatment modification in a heterogenic population, in which 55% of the 202 included patients were treated in the palliative setting.[6] Impaired MNA in this study was associated with an increased probability of treatment modification. Two other studies, both in patients with metastatic ovarian carcinoma, found that better functional, quality of life and social activity scores were associated with a greater likelihood of completing four cycles of chemotherapy.[7] [8]

Two studies developed and externally validated predictive models for chemotherapy toxicity.[9] [10] Both studies included patients treated in both the curative and palliative setting. The CARG (Cancer and Aging Research Group) developed a "chemotherapy toxicity calculator," which is a risk score consisting of 11 items, taking less than 5 minutes to complete.[9] In this study the TUGT was also significantly associated with the occurrence of grade 3 to 5 toxicity. In another study including 187 older patients with various types of malignancies stage 1-4, the CRASH score (Chemotherapy Risk Assessment Scale for High-age Patients i.e. 70 years or older) was developed.[10] In this study results from several GA tools were combined to predict severe toxicity, including functional, nutritional and cognition tools, taking up to 20 to 30 minutes to complete. They observed an association with IADL, MNA and the occurrence of toxicity. Additional predictors in this study for toxicity were hemoglobin, creatinine clearance, albumin, self-rated health, ECOG performance and chemotoxicity score (i.e. a score to rate the likelihood of experiencing toxicity based on the intensity of treatment). Three other studies investigated the association between GA and chemotherapy toxicity in more homogeneous patients populations with either advanced colorectal, breast or lung cancer.[11] [12] [13] In these studies IADL and MMSE were considered most strongly related with toxicities.

In contrast to the CRASH score and the later 2 studies, we did not find a relation between toxicity and IADL or MMSE scores, which may be explained by the low number of patients with an impaired test in our study, or because the CRASH score used a very strict cut off point for frailty in the MMSE questionnaire of <30 rather than the more commonly used cut-off point of 24. Finally, all these studies, except the CARG study, did not include the TUGT or other functional tests, which was the test that was most strongly related with grade 3 toxicity in our study. The observed high risk of treatment modifications and grade 3 toxicities is comparable to the risk that were observed in several other studies. [2] [3] [4]

Frailty is caused by the cumulative decline across multiple organs systems and resulting in a decreaed resistance to stressors such as chemotherapy. This suggests that the accumulation of geriatric impairments may results in higher risks of chemotherapy intolerance, which was also observed in several previous studies.[14] In contrast, we only observed a numerical, but non-significant, association between the number of geriatric impairments and treatment modifications.

Frailty may be hard to detect by clinical judgment, and conversely most oncologists consider very few patients as frail.[15] The current standard of functional status assessment by using the ECOG performance score has been shown to poorly predict functional impairment in older patients. A GA can detect health problems that may be associated with unfavorable outcomes, which may otherwise go unrevealed. For example this may be relevant for the need for assistance in daily functioning or malnutrition, as a large study of 1820 patients showed that 51.2% of patients, who suffer from unknown geriatric problems, primarily suffered from impaired physical functioning (40.1%) and malnutrition (37.6%).[16] These are both geriatric domains that are easily assessed by MNA and ADL questionnaires, and also potentially modifiable by interventions which may optimize patient's condition.

In this study we included a heterogeneous study population, consisting of patients with different types of tumors, who received different palliative systemic treatment regimens, rather than patients suffering from a certain type of tumor. The reason for including a heterogeneous study population is that we wanted to determine whether there are common factors of vulnerability for treatment modifications and severe toxicities in a broad range of older patients who are treated for their cancer, as this may improve its ability for all oncologists to use it in daily clinical practice. However, the heterogeneity in the patient population and chemotherapy treatments may also lead to different types of toxicity and therefore different risks of treatment modification. However, our subgroup analysis in patients with solid tumors did not reveal any important differences in the

relation between GA and outcomes. Another limitation is the relative small sample size, which may impact the significance of associations between GA components and outcomes. Finally, we have no data on characteristics of patients who were eligible for study inclusion but declined participation. As frail patients are more likely to decline study participation, there is a possibility that we included a patient population with favourable prognosis, i.e. only patients with good clinical condition, which may impact the generalizability of our results.

As pointed out by the international guidelines, evidence is increasing for the use of GA to aid physicians in daily clinical practice in several ways: by identifying impairments, clarifying patients priorities, predicting survival and toxicity risk, establishing a pretreatment baseline, and developing GA guided interventions. All these elements may influence treatment decisions (i.e. upfront dose adjustments) and help to guide in shared decision making.[4 17] This also implies that although the majority of the individual GA test were not significantly associated with treatment modifications or grade 3 toxicity, a GA can still be relevant for the before mentioned purposes.

Finally, an important next step would be to investigate whether future intervention studies that aim to improve geriatric domains also have the potential to decrease the risk of chemotherapy toxicity and improve treatment tolerance.

In conclusion, frailty was common in patients with metastatic cancer who were considered fit to receive palliative chemotherapy. Treatment modification was necessary in half of the patients. The TUGT was significantly associated with treatment modifications and grade 3 toxicities.

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SUPPLEMENTARY TABLE

Supplementary Table 1. Association between GA and treatment modifications/grade 3 toxicity in patients with solid cancer (n=81).

Geriatric assessment	Patients with treatment modification/total patients (n (%))	Treatment modification OR (95% CI)
ADL		
Impaired	3/5 (60)	0.5 (0.0-7.0)
Independent	36/76 (47)	1.0
IADL		
Impaired	4/6 (67)	2.7 (0.3-27.9)
Independent	35/75 (47)	1.0
GDS-15		
Impaired	5/7 (71)	2.7 (0.4-16.8)
Independent	34/74 (46)	1.0
TUGT		
Impaired	26/42 (62)	3.2 (1.2-8.2)*
Independent	13/39 (33)	1.0
MMSE		
Impaired	6/12 (50)	0.8 (0.2-3.3)
Independent	33/69 (48)	1.0
MNA		
Impaired	7/12 (58)	1.3 (0.3-5.4)
Independent	32/69 (46)	1.0

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; ADL, Activities of Daily Life; IADL, Instrumental Activities of Daily Life; MMSE, Mini-Mental State Examination; MNA, Mini Nutritional Assessment; GDS-15, Geriatric Depression Scale; TUGT, Timed Up and Go Test.

P-value	Patients with grade 3 toxicity/ total patients (n (%))	Grade 3 toxicity OR (95%)	P-value
0.57			0.63
	3/5 (60)	0.5 (0.1-6.8)	
	41/76 (54)	1.0	
0.34			0.57
	4/6 (67)	1.9 (0.2-16.5)	
	40/75 (53)	1.0	
0.30			0.93
	4/7 (57)	0.9 (0.2-5.2)	
	40/74 (54)	1.0	
0.02			0.03
	18/42 (43)	2.9 (1.1-7.2)**	
	16/39 (41)	1.0	
0.70			0.95
	7/12 (58)	0.9 (0.2-4.0)	
	37/69 (54)	1.0	
0.68			0.46
	8/12 (67)	1.7 (0.4-7.0)	
	36/69 (52)	1.0	

*Adjusted (age/gender) OR 3.4 (95% CI [1.4-8.9], p=0.02)

**Adjusted (age/gender) OR 2.8 (95% CI [1.2-7.1], p=0.00)