Journal of Geriatric Oncology 11 (2020) 488–495

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

The impact of comprehensive geriatric assessment for optimal treatment of older patients with cancer: A randomized parallel-group clinical trial

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ARTICLE INFO

Article history:
Received 8 April 2019
Received in revised form 27 May 2019
Accepted 26 June 2019
Available online 3 July 2019

Keywords:
Older patient
Cancer
Gynecological cancer
Urological cancer
Lung cancer
Comprehensive geriatric assessment
Treatment decision
Randomized controlled trial

ABSTRACT

Objectives: The aim was to investigate if oncologic treatment decision based on G8 screening followed by comprehensive geriatric assessment (CGA) and a multidisciplinary team conference in patients with G8 ≤ 14 was better than treatment decision based on standard assessment. ClinicalTrials.gov Identifier: NCT02671994.
Materials and Methods: From January 2016 to June 2018, 96 patients with cancer, aged ≥70 years, were included. Patients were randomized to treatment decision based on the oncologist's clinical judgement (control) or based on screening with G8. If G8 > 14 treatment decision was made as in the control group and if G8 ≤ 14, patients were referred to CGA including intervention as needed and treatment decision after a multidisciplinary team conference (MDT).
Results: The study was closed early. 47 patients were randomized to the control group and 49 to the intervention group; 28 had a G8 ≤ 14, 24 of whom attended CGA. In the intervention group 48% completed treatment as planned compared to 54% in the control group ($p = .208$). Thirty-eight percent experienced grade 3–4 toxicity in the control group compared with only 20% in the intervention group ($p = .055$). Median overall survival (OS) was 14.2 months in the control group and 19.1 months in the intervention group ($p = .911$). Median progression-free survival (PFS) was 9.0 months in the control group and 7.8 months for the intervention group ($p = .838$).
Conclusion: Treatment decision based on G8 screening followed by CGA had no impact on completion rate of planned oncologic treatment, OS or PFS, but resulted in a borderline significant lower incidence of grade 3–4 toxicity.

1. Introduction

The number of older patients with cancer is increasing due to the aging of the population. Aging is associated with a progressive decline in the functional reserve of many organ systems and increased incidence of multimorbidity, including cancer [1–3]. The prevalence of comorbidity in older patients with cancer varies from 36 to 94% [4–7] Comorbidity impacts survival, stage at diagnosis and risk of chemotherapy-related toxicity [4–7]. In newly diagnosed patients with cancer, the prevalence of polypharmacy is 35%–80% [8,9]. Polypharmacy increases the risk of adverse drug events, drug-drug interactions, hospitalizations, potentially inappropriate medications, and mortality [10,11]. Older patients with cancer have increased risk of toxicity to chemotherapy with a reported incidence of grade 3–5 toxicity of 53–64% in patients aged ≥70 years [12–14]. Chronological age does not necessarily reflect physiological age, and older patients are often excluded from clinical trials creating a knowledge gap with limited evidence to guide treatment decisions in this population [15].

Oncologic treatment decisions are usually based on performance status (PS), such as Karnofsky PS (KPS) or Eastern Cooperative Oncology Group PS (ECOG PS) and the oncologist's judgement [16,17]. These tools have been shown to be insufficient in assessing functional status in older patients with cancer [18,19].

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https://doi.org/10.1016/j.jgo.2019.06.019

In geriatric medicine, comprehensive geriatric assessment (CGA) is "a multidimensional and usually interdisciplinary diagnostic process designed to determine a frail older person's medical condition, mental health, functional capacity, and social circumstances. The purpose is to plan and carry out a holistic plan for treatment, rehabilitation, support and long term follow up." [20] A keystone in CGA is the assessment by a specialist in geriatric medicine and the implementation of interventions as needed.

Both the American Society of Clinical Oncology (ASCO) and the International Society of Geriatric Oncology (SIOG) recommend a CGA in the evaluation of older patients and the Geriatric-8 (G8) as a screening tool [21,22]. Only a few randomized controlled trials (RCTs) have investigated the role of CGA in older patients with cancer [23–25].

The aim of this study was to investigate if oncologic treatment decision based on G8 screening followed by CGA and a multidisciplinary team conference (MDT) in patients with G8 < 14 is superior to standard treatment decision based on the oncologist's clinical judgement in older patients with cancer.

2. Materials and Methods

This was a single-center randomized controlled open study including older patients with cancer, who were evaluated for chemotherapy or targeted therapy. Collection and storage of data was approved by The Regional Committees on Health Research Ethics for Southern Denmark (Journal number: S-20150093 CSF) and the Danish Data Protection Agency (Journal number: 15/20250). ClinicalTrials.gov Identifier: NCT02671994.

2.1. Study Population

Inclusion criteria were, 1) age ≥ 70 years, 2) a diagnosis of gynecological cancer (ovarian (ICD-10 codes C56–57, C48), endometrial cancer (C54–55)), urological cancer (prostate (C61), bladder (C65–57), kidney cancer (C64)), or non-small cell lung cancer (NSCLC (C34)), 3) starting chemotherapy or targeted therapy (tyrosine kinase inhibitor) for primary or recurrent disease, 4) able to understand/speak Danish, and 5) able to give informed consent. Exclusion criteria were a previous cancer diagnosis other than recurrence of the current cancer disease (carcinoma in situ of the cervix and non-melanoma skin cancer were allowed) and either surgery or curative intended radiation therapy within the last four weeks prior to inclusion (local radiotherapy of isolated lesions for palliative intent was allowed prior to and during the study).

2.2. Endpoints

The primary endpoint was the rate of completion of oncologic treatment as scheduled (number of planned courses) without premature termination due to unacceptable toxicity, progression of disease, or death. Patients, who received treatment until progression, were followed for a maximum of 6 months during treatment. A maximum of 1 dose reduction and/or a maximum of 14 days of dose delay were allowed.

Secondary endpoints

- Rate of severe (grade 3–4 toxicity (National Cancer Common Terminology Criteria for Adverse Events (CTCAE) version 4).
- Time from randomization to start of treatment
- Progression-free survival (PFS) defined as time from randomization to disease progression or death.
- Overall survival (OS) defined as time from randomization to death.

2.3. Study Procedures and Intervention

Eligible patients were randomized 1:1 to intervention versus control using block randomization with random blocks of four and six with stratification for cancer diagnosis (gynecological versus urological versus lung cancer), and prior chemotherapy and/or radiation (yes/no). The protocol was amended to include patients with lung cancer 12 months after study initiation.

All patients had an ECOG PS score.

For patients in the control group a treatment decision was based on the oncologist's clinical judgement.

Participants in the invention group were screened with the G8. In patients with G8 > 14, treatment decision was based on the oncologist's clinical judgement. Patients with G8 ≤ 14 were referred to the Department of Geriatric Medicine, OUH for CGA including assessment of comorbidity, polypharmacy, nutrition, and physical, cognitive and social function. Activities of daily living (ADL) was assessed by the Barthel-20 Index, where a score of 20 was normal, and decreasing scores indicated increasing disability [26]. Muscle strength was assessed by the 30 s chair stand test (30s CST) with scores <10 indicating high risk for falls and hand grip strength test with strength <21 kg for men and < 15 kg for women considered abnormal [27,28]. The Charlson Comorbidity Index (CCI) was used to assess comorbidity with score 0–1 indicating no/mild comorbidity, score 2–3 indicating moderate comorbidity, and score ≥ 4 indicating severe comorbidity [29]. Cognitive function was screened with Orientation-Memory-Concentration (OMC) (score > 24: normal/minimal impairment, score 18–24: minimal/moderate impairment, score 8–17: moderate/severe impairment, score 0–7: severe impairment) [30]. Nutrition was assessed by a modified nutrition assessment, where scores ≤6 indicated risk of malnutrition [31]. Polypharmacy was assessed in accordance with the Screening Tool of Older Person's Prescriptions and Screening Tool to Alert Doctors to Right Treatment (STOPP-START) criteria, and numbers of changes within ATC groups were recorded [32]. The extent and need for social support was clarified by geriatric nurses.

2.4. Data Collection

Patient baseline characteristics were collected by nurses and physicians. ECOG PS was assessed by an oncologist, who also performed the G8 screening for patients in the intervention group. CGA data on morbidities and medications were obtained by geriatricians, and functional data by geriatric nurses. Results of MDT were recorded by the treating oncologist.

All patients were monitored for death and progression until March 15, 2019 or death.

Data on toxicities were recorded at every visit using the National Cancer Common Terminology Criteria for Adverse Events CTCAE version 4, according to standard care. Furthermore, hospital admissions because of toxicity were considered as at least grade 3 toxicity (severe toxicity). The worst grade of toxicity during treatment was recorded.

Quality of life (QoL) was assessed at baseline using the EQ-5D-5 L questionnaire [33–35].

2.5. Statistical Analysis

Descriptive patient characteristics as well as outcomes were reported as counts with proportions for categorical measures and as medians with ranges or means with standard deviations (SD) for numerical measures. Difference in proportions was tested by Chi-square test or Fisher's exact test, depending on the number of counts) and differences in numerical data were tested by median test for age and Wilcoxon rank-sum test for other numerical variables. Progression-free survival was estimated from time of randomization to time of disease progression or death, and overall survival from the time of randomization to death of any cause, censoring at end of follow-up March 15th, 2019 by the Kaplan-Meier method comparing groups with log-rank test. Furthermore, hazard ratios (HR) were estimated by Cox regression analyses, both crude and adjusted for age, sex, ECOG PS, diagnosis group and line of treatment. All analyses were carried out in

Stata 15, and p-values below 0.05 were considered statistically significant. The study was planned to include 182 patients to obtain a power of 80% with an expected increase in treatment completion rate from 60% to 80%.

3. Results

From January 2016 to June 2018, 114 patients were included. The study was closed after inclusion of 50% of the patients according to the prospectively calculated patient sample. An interim analysis of the primary effect parameter after inclusion of 110 patients showed that a numerically higher (but nonsignificant) number of patients in the control group than in the intervention group fulfilled the criteria for effect (see below). Therefore we concluded that it would be unrealistic to obtain a 20% difference in favor of the intervention arm if the study was continued to include patients as originally planned.

The patient flow is shown in Fig. 1. Of the 114 patients, 59 were randomized to the control group and 55 to the intervention group. Eighteen patients were excluded (see CONSORT diagram, Fig. 1). Patient characteristics were well-balanced between the two groups, with the exception of median age, where patients in the control group were slightly older (Table 1). The majority of the patients had ECOG PS 0–1 and were treatment-naive. The diagnoses were predominately prostate (37% in the intervention group and 28% in the control group) and ovarian cancer (31% in the intervention group and 34% in the control group). Patients in the intervention group were not delayed in start of treatment compared to the control group. In the intervention group, 28 patients had a G8 score ≤ 14, and 24 completed CGA. Four patients were not referred to CGA.

Table 2 shows the results of the CGA. The most common comorbidities were diabetes without complications (n = 7) and myocardial infarction (n = 5). The five most common ATC groups that were adjusted were analgesic drugs (opioids), drugs for constipation, nutritional agents, and urological drugs (drugs used in prostate hyperplasia).

Seventy-one percent of the patients only had one visit to the Geriatric Clinic, but for 75% of the patients a health intervention was implemented. The most common intervention concerned changes in medications, most frequently as new prescriptions (33%) (8/24), deprescriptions in 29% (7/24) and dose changes in 30% (7/24). All interventions are shown in Table 3.

A total of 94 patients were scheduled to start oncologic treatment. Eighty-eight were to start chemotherapy (42 in the control group and

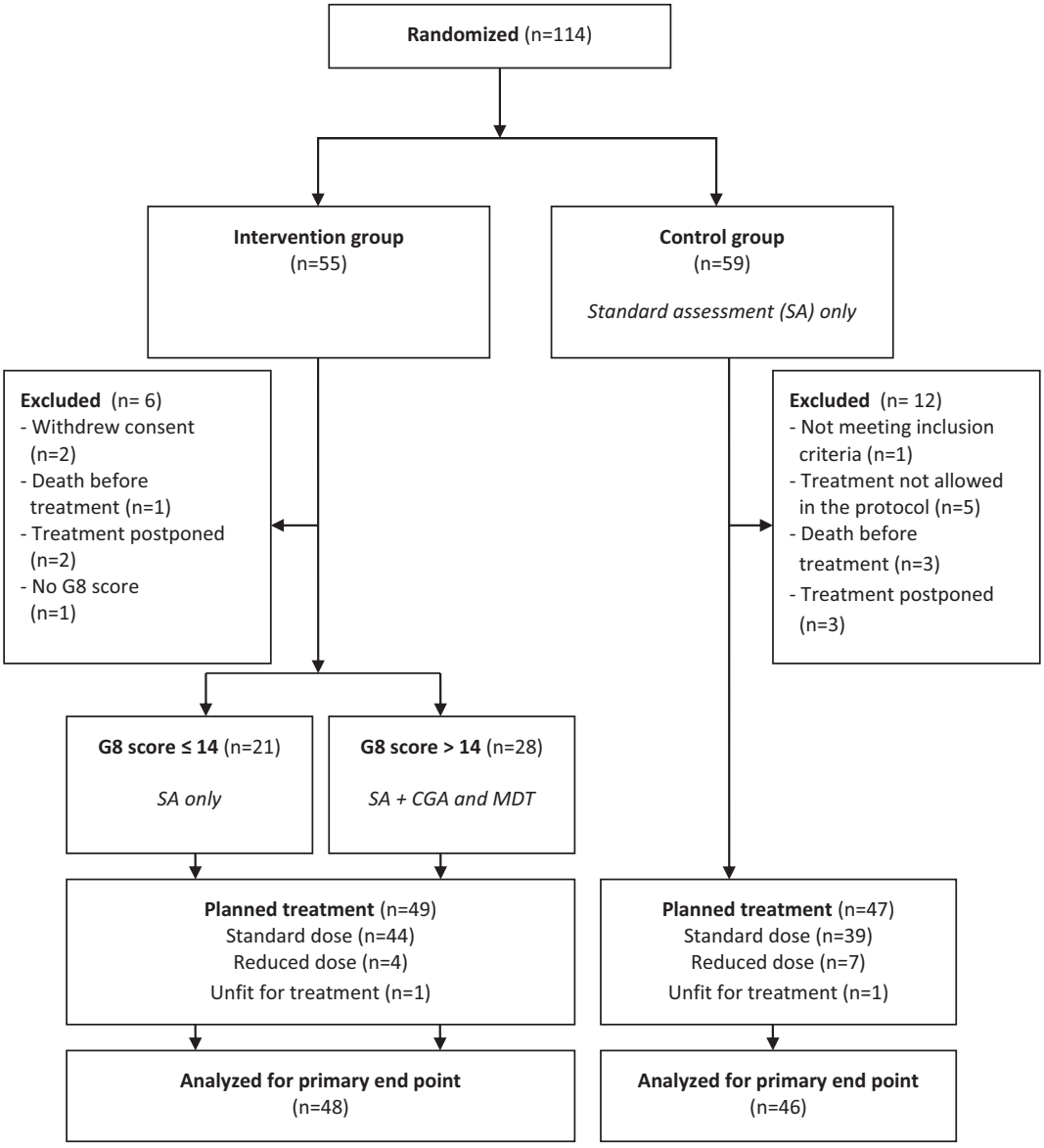

Fig. 1. Consort flow diagram.

Table 1
Patient characteristics.

	Control group (N = 47)	Intervention group (N = 49)	P-value
Age (years)			
Median	76.8	73.9	0.008
Range	70–84	70–87	
Sex			
Female	23 (49%)	23 (47%)	0.845
Male	24 (51%)	26 (53%)	
Eastern Cooperative Oncology Group Performance Status (ECOG PS)			
0	17 (36%)	21 (43%)	0.343
1	22 (47%)	18 (37%)	
2	8 (17%)	7 (14%)	
3	0	3 (6%)	
Line of treatment			
1st	25 (54%)	29 (60%)	0.537
2nd	9 (20%)	8 (17%)	
3rd	9 (20%)	5 (10%)	
4th	3 (7%)	4 (8%)	
5th	0	2 (4%)	
Diagnosis			
Urological cancer	24 (51%)	25 (51%)	0.812
Prostate cancer	13 (28%)	18 (37%)	
Bladder cancer	7 (15%)	5 (10%)	
Kidney cancer	4 (9%)	2 (4%)	
Gynecological cancer	19 (40%)	20 (41%)	
Ovarian cancer	16 (34%)	15 (31%)	
Endometrial cancer	3 (6%)	5 (10%)	
Lung cancer, NSCLC	4 (9%)	4 (8%)	
EQ-5D health index score	0.79 (0.73;	0.78 (0.74;	0.545
Mean (95% CI)	0.85)	0.82)	
VAS score	74 (67;	71 (64; 77)	0.389
Mean (95% CI)	81)		
Time to treatment	10.4	8.8 (6.8)	0.886
Days (mean (SD))	(10.3)		

NSCLC: non-small cell lung cancer, VAS: Visual Analogue Scale.

Table 2
Results of the different domains of the comprehensive geriatric assessment N = 24).

Functional status	
Barthel-20 Index[1] (median (IQR))	20 (18.5; 20)
Normal (score = 20)	15 (63%)
Minimal disability (score 18–19)	6 (25%)
Moderate/severe disability (score < 18)	3 (13%)
30s CST[2] (median (IQR))	10 (8; 13)
Normal (score ≥ 10)	12 (50%)
Abnormal (score 1–9)	11 (46%)
Unknown	1 (4%)
Handgrip strength test[a]	
Female	
Abnormal, right hand	2 (20%)
Abnormal, left hand	2 (20%)
Male	
Abnormal, right hand	0 (0%)
Abnormal, left hand	0 (0%)
Comorbidity	
CCI	
None/mild comorbidity (score 0–1)	11 (46%)
Moderate comorbidity (score 2–3)	7 (29%)
Severe comorbidity (score ≥ 4)	6 (25%)
Cognition	
OMC (median (IQR))	26 (24; 28)
Normal/minimal impairment (score > 24)	13 (54%)
Minimal/moderate impairment (score 18–24)	8 (33%)
Moderate/severe impairment (score 8–17)	3 (13%)
Severe impairment (score 0–7)	0
Nutrition	
MNA	
Normal (score > 6)	7 (29%)
Risk of malnutrition (score ≤ 6)	17 (71%)

30s CST: 30 s Chair Stand Test, CCI: Charlson Comorbidity Index, OMC: Orientation-Memory-Concentration, MNA: Mini Nutritional Assessment.
[a] Strength <21 kg for men and < 15 kg for women considered abnormal [3].

46 in the intervention group), while 6 were scheduled to start targeted therapy (4 in the control group and 2 in the intervention group). Targeted therapy consisted of TKI-inhibitors for patients with kidney cancer.

In the control group, 39 (83%) of the patients were planned to start standard dose oncologic treatment and 7 (15%) in a reduced dose, while 1 (2%) was evaluated unfit for treatment (Table 4). In the intervention group, 44 (90%) of the patients were planned to start standard dose oncologic treatment. Twenty-one of these patients had a G8 score of >14, while 28 had a G8 score G8 ≤ 14. 5 (10%) patients were not considered eligible for treatment in standard dose at the MDT; four received treatment in a reduced dose, while one was unfit for treatment. Reasons included comorbidity (1), impaired nutritional status (2), impaired functional status (3) and/or impaired cognition (1), low hemoglobin (1), or social situation (1). Some patients had more than one reason.

In the control group, 25 patients (54%) completed treatment as planned without premature termination and a maximum of 1 dose reduction and/or a maximum of 14 days of dose delay (primary effect parameter) as compared to 23 patients (48%) in the intervention group (p = .533). In the control group, 23 patients (59%), who started treatment in standard dose continued treatment in a 100% dose throughout their course of treatment, whereas 12 (31%) had one dose reduction. In the control group, five patients (71%), who started treatment in a reduced dose did not experience additional dose reductions, while two (29%) did. In the intervention group, 31 patients (70%), who started treatment in standard dose did not experience dose reductions, and 13 (30%) had one dose reduction. The four patients in the intervention group, who started treatment in a reduced dose, did not experience additional dose reductions. Only patients in the control group experienced >1 dose reduction and/or dose delay >14 days (Table 2). Premature termination of planned treatment was predominantly caused by unacceptable toxicity.

Eighty-six patients (95%) experienced toxicity, 44 (98%) in the control group, and 41 (92%) in the intervention group (Table 5). Most of the patients experienced grade 1–2 toxicity – 60% in the control group and 72% in the intervention group. Overall, the most common toxicities were fatigue, peripheral sensory neuropathy, nausea and diarrhea. None of the patients experienced grade 5 toxicity. Grade 3–4 was experienced by 17 (38%) in the control group as compared to 9 (20%) in the intervention group (p = .055) (Table 3). Most of the severe toxicities were recorded during hospitalizations. The most common severe toxicities were febrile neutropenia, anemia, fatigue and various infections.

The median follow-up was 14.1 months (95% CI: 11.7–17.7). Median OS was 14.2 months (95% CI: 11.6-not reached) in the control group and 19.1 months (95% CI: 11.8-not reached) in the intervention group

Table 3
Implemented interventions based on the comprehensive geriatric assessment (N = 24).

Referrals to other departments/examinations/general practitioner/other	
Examinations (x-ray of thorax, measurement of peripheral or orthostatic blood pressure, DXA scan)	8
Assessment of physical function by physical therapist	4
Rehabilitation plan by physician	2
Prepared rehabilitation plan for municipal training	2
General practitioner	4
Other	2
Nutritional interventions	
Rehydration	1
Dietary counselling	4
Nutritional preparations	4[b]
Social situation	
Increased aid at home (personal care, practical aid, management of medication, food arrangement)	6 (11)[a]

[a] Number of patients (number of times)
[b] Changes within categories of Anatomical Therapeutic Chemical (ATC) Classification System.

Table 4
Oncologic treatment and primary endpoint.

	All patients N = 96	Control group N = 47	Intervention group N = 49	P-value
Planned treatment at standard dose	83 (86%)	39 (83%)	44 (90%) G8 > 14: 21 G8 ≤ 14: 23	0.672
Planned treatment at reduced dose	11 (11%)	7 (15%)	4 (8%) G8 > 14: 0 G8 ≤ 14: 4	
Unfit for treatment	2 (2%)	1 (2%)	1 (2%) G8 > 14: 0 G8 ≤ 14: 1	
Premature treatment termination	43 (45%)	18 (39%)	25 (51%)	0.208
Reasons for premature treatment termination		Unacceptable toxicity (11) Disease progression (5) Death (1) Other complication (2)	Unacceptable toxicity (15) Disease progression (8) Death (1) Other complication (3) No reason specified (2)	
At least one dose reduction	31 (33%)	18 (39%)	13 (27%)	0.214
> 1 dose reduction	4 (4%)	4 (9%)	0	0.054
Dose delay >14 days	2 (2%)	2 (4%)	0	0.237

Three patients (all in the control group had): premature termination + > 1 dose reduction, premature termination + dose delay >14 days, respectively, more than one dose reduction + dose delay >14 days.

(p = .911). Crude HR was 0.97 (95% CI: 0.57–1.65) (p = .911), and HR adjusted for age, sex, ECOG PS, diagnosis group and line of treatment was 1.24 (95% CI: 0.68–2.24) (p = .484). Median PFS was 9.0 months (95% CI: 7.3–10.5) in the control group and 7.8 months (95% CI: 6.4–9.3) for the intervention group (p = .838). Fig. 2 shows the Kaplan-Meier curves for OS and PFS for the two groups.

4. Discussion

To our knowledge, this study represents one of the largest randomized trials examining the significance of CGA in older patients with cancer. In addition, it is the first RCT to examine the effect of CGA in older patients with cancer with G8 ≤ 14, followed by an MDT, on oncologic treatment decision and outcomes.

The study demonstrated that implementation of CGA in the management of older patients with cancer was feasible, and referral for CGA did not delay start of treatment. The intervention did not lead to a higher completion rate of planned oncologic treatment as compared to the control group. However, only patients in the control group (n = 4) needed more than one dose reduction and experienced dose delay >14 days. There was a borderline significant tendency of a greater proportion of patients in the control group experiencing severe toxicity (grade 3–4) than in the intervention group. The intervention did not influence OS or PFS.

Corre et al. conducted a RCT in patients aged ≥70 years with advanced NSCLC and ECOG PS of 0–2, in which treatment allocation was based on GA, and found no difference in treatment-failure free survival (TFFS), progression-free survival (PFS), overall survival (OS) or grade 3–4 toxicity, but a reduction in all-grade toxicity and fewer treatment failures due to toxicity were observed in the GA arm [23]. Our results are in accordance with this regarding grade 3–4 toxicity, although we only found a near significant reduction. Contrary to the findings by Corre et al., we did not find a difference in treatment failures. However, our study differs from the study by Corre et al. First of all, even though the

Table 5
Treatment-related toxicity.

	All patients (N = 94)	Control group (N = 46)	Intervention group (N = 48)	P-value	Missing
Worst toxicity experienced (including hospitalizations)					
Grade 0	5 (5%)	1 (2%)	4 (9%)		3
Grade 1–2	60 (66%)	27 (60%)	33 (72%)		
Grade 3–4 (incl. hosp)	26 (29%)	17 (38%)	9 (20%)	0.055	
Hospitalization experienced	23 (24%)	15 (33%)	8 (17%)	0.072	0
Febrile neutropenia (grade 1–4)	1 (1%)	1 (2%)	0	0.494	9
Febrile neutropenia (grade 3–4)	1 (1%)	1 (2%)	0	0.494	
Nausea (grade 1–4)	31 (36%)	16 (36%)	15 (35%)	0.885	7
Nausea (grade 3–4)	1 (1%)	0	1 (2%)	0.494	
Vomiting (grade 1–4)	8 (9%)	5 (11%)	3 (7%)	0.713	7
Vomiting (grade 3–4)	0	0	0	NA	
Diarrhea (grade 1–4)	25 (29%)	14 (33%)	11 (26%)	0.476	8
Diarrhea (grade 3–4)	0	0	0	NA	
Fatigue (grade 1–4)	78 (91%)	41 (95%)	37 (86%)	0.265	8
Fatigue (grade 3–4)	4 (5%)	2 (5%)	2 (5%)	1.000	
Peripheral sensory neuropathy (grade 1–4)	30 (35%)	18 (43%)	12 (28%)	0.149	9
Peripheral sensory neuropathy (grade 3–4)	1 (1%)	0	1 (2%)	1.000	
Hand-Foot Syndrome (grade 1–4)	23 (28%)	15 (37%)	8 (19%)	0.074	11
Hand-Foot Syndrome (grade 3–4)	1 (1%)	1 (2%)	0	0.494	
Discoloration of nail (grade 1–4)	10 (14%)	5 (14%)	5 (15%)	0.882	25
Discoloration of nail (grade 3–4)	0	0	0	NA	
Loss of nail (grade 1–4)	2 (3%)	2 (6%)	0	0.493	26
Loss of nail (grade 3–4)	0	0	0	NA	
Other (grade 1–4)	35[a] (37%)	17 (37%)	18 (38%)		0
Other (grade 3–4)	4	2 (5%)	2 (5%)		

[a] Three of these patients have two different other toxicities.

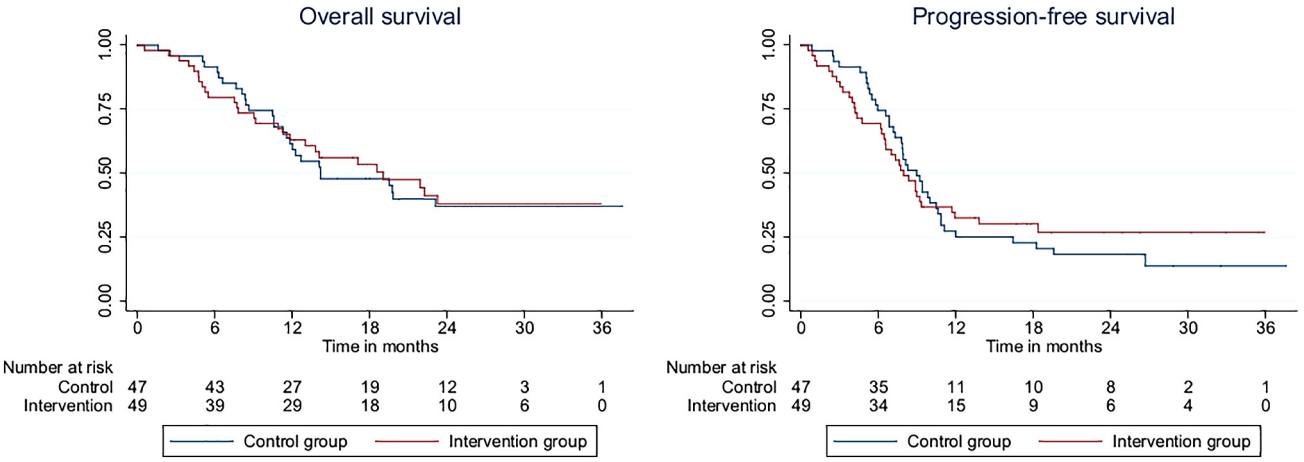

Fig. 2. Overall survival (OS) and progression-free survival (PFS).

authors refer to the assessment in their study as a CGA, it is in fact a GA, as detection of problems was not met with specific interventions. CGA entails that the diagnostic process/assessment by a geriatrician is followed by relevant interventions to optimize the health status of the patient [22]. It is reasonable to assume that implementing relevant interventions based on an assessment with the purpose of optimizing general health status affects outcomes differently than the assessment alone.

Secondly, Corre et al. included a more uniform population in terms of diagnosis. Even though, the diagnoses were evenly distributed between our two groups, the pooling of patients with different cancer diagnoses that vary in characteristics such as cause, treatment and prognosis may potentially reduce the total effect of the intervention. Finally, the treatment allocation in the Corre study was completely pre-specified in both the control group (based on PS and age) and in the intervention group (based on GA). Our design allowed for a more individual selection of treatment at the discretion of the oncologist.

A non-randomized study in patients aged ≥70 years compared an observational group with an intervention group, where high-risk patients underwent a CGA. They found that patients in the intervention group were more likely to complete oncologic treatment as planned and needed fewer treatment modifications. A nonsignificant trend towards less grade 3+ toxicity rate was also found in the intervention group [36]. The latter finding is in line with our study. Although Kalsi et al. found an effect of CGA on completion of treatment as planned, it is important to notice that 33.8% achieved this in the intervention group vs. 11.4% in the control group, which must be considered as relatively small proportions of the populations. Differences in study populations, as they included a large proportion of patients with GI cancer, may also account for the different findings. Furthermore, they used the CGA-GOLD questionnaire to select high risk patients, whereas we used the G8 screening tool. As these methods comprise different approaches for selecting high risk/frail patients, it is natural that this can cause a difference in the populations undergoing CGA's in the two studies.

A recent study by Magnuson et al. comparing a usual care arm and an intervention arm with GA and intervention recommendations to oncologists found no significant differences in GA measures, grade 3–5 toxicity, hospitalizations, dose reductions, dose delays, early treatment discontinuation, or hospice enrollments. Furthermore, there was no notable difference in anticipated toxicity according to the Cancer and Aging Research Group (CARG) tool and observed toxicity in the two arms [24]. This is more in line with our findings. Their study population was more similar to ours, as they included patients aged ≥70 years, stage III-IV solid tumors and with a diagnosis of GI-, gynecologic- or lung cancer. They also concluded that it was feasible to conduct CGA in a timely manner in older patients with cancer, as is the case in our study.

We found a lower incidence of severe toxicity in this population compared to what has previously been reported in older cancer populations receiving chemotherapy [12–14]. This may be explained by the fact that the vast majority of our patients in both the intervention arm and in the control arm had a good PS, which is known to be associated with lower risk of chemotherapy-related toxicity [13,22].

Even though the majority of our population only experienced grade 1–2 toxicity, unacceptable toxicity was the main reason for discontinuing treatment. This indicates that some grade 2 toxicities may also be significant in older patients with cancer [12].

This study has some strengths. It showed that it is feasible to implement CGA without treatment delay, and the fact that CGA was performed by geriatricians with implementation of relevant geriatric interventions is also a strength. Overall, studies with geriatrician-delivered CGA interventions in older patients with cancer have been rare, especially RCTs. Most studies so far have focused on GA rather than CGA, where certain GA elements such as impairments regarding IADL, cognitive function, physical functional and nutritional status have been associated to higher risk of chemotherapy-related toxicity [12,13,21,22]. We tried to account for the heterogeneity of the population in terms of cancer diagnosis and treatment line by stratification of the randomization and adjustment in the survival analysis, rather than subgroup analysis. The patients in our study had a relatively high median age, and inclusion was not restricted by an upper age limit. Even though some studies operate with cut-offs for CGA, these are not well-defined [37–41]. Therefore, our study avoided the use of constructed cut-offs and instead opted for the development of an individual, personalized care and treatment plan for each patient.

Unfortunately, we did not manage to include the scheduled number of patients. We did not find an effect of CGA on completion of oncologic treatment as planned. It is possible that a larger study would have been able to disclose more differences between the two study groups. Recording of initial treatment plan was not performed in this study, but this would have facilitated an evaluation of, whether CGA and MDT were able to affect treatment decision. A review of 35 studies has shown that geriatric evaluation (geriatric consultation, a multidisciplinary geriatric evaluation, or a GA) is able to affect oncologic treatment decision, leading to modification of initial treatment plan in a median of 28% of patients, mainly an alteration of the treatment plan to a less aggressive option [42].

This study had an overweight of patients in good health condition. In this context, it is important to be aware of the steps necessary to reach enrollment in the study. First of all, there is the referral from the general practitioner to the surgical department. The GPs might not refer the oldest and most frail patients for further diagnostic processes and treatment. A surgical department might reach a similar conclusion and

decide against further referral to the department of oncology. Another factor of importance is the reluctance of some frail patients to be referred – but as already described, physicians' attitude is a significant factor in the decision-making process of patient treatment, so how information is presented to these patients is essential [43]. It may still be an obstacle to transform from an approach based on chronological age to one based on physiological age. This means that in studies, where recruitment takes place in an oncological department, the study population may not reflect the older cancer population in general. The heterogeneity of the population may also comprise a limitation, as it can dilute the effect of the intervention, when patients with different cancers that entail different prognoses and different treatment regimens are assessed together.

The decision to exclude patients, who had radiotherapy or surgery <4 weeks before inclusion, was made to make the population as comparable as possible, as it was assumed that undergoing these treatment modalities closely up to inclusion would affect the general health status of the patients and, thus, reflect CGA outcome. CGA in older patients with cancer with G8 ≤ 14 and subsequent final oncologic treatment decision at an MDT did not significantly improve the completion rate of planned treatment as compared to oncologic treatment decision based on the oncologist's clinical judgement. However, it might reduce the incidence of severe toxicity. Further research is needed to clarify the place for CGA in the treatment decision in older patients with cancer.

Declarations of Competing Interests

None of the authors have any conflicts of interest.

Author Contributions

Conception and design (SN, LM, TLJ, JH), data collection (SN, LM, TLJ, JH, SJ, AK, LD), analysis and interpretation of data (SN, LM, TLJ, JH, SM), manuscript writing (the manuscript was drafted by SN and modified by SN, LM, TLJ, LD, AK, SJ, SM, JH), approval of the final manuscript (SN, LM, TLJ, LD, AK, SJ, JH, SM).

Acknowledgements and Funding

We would like to thank the Danish Cancer Society [grant number R90-A6232] and The Velux Foundation [grant number 9631] for funding this study. The sponsors did not have any role in the study design, the collection and analysis of data; in the interpretation of results; in the writing of the report; or in the decision to submit the article for publication.

References

[1] Falandry C, Bonnefoy M, Freyer G, Gilson E. Biology of cancer and aging: a complex association with cellular senescence. J Clin Oncol 2014;32:2604–10.
[2] Hansen J. Common cancers in the elderly. Drugs Aging 1998;13:467–78.
[3] Overcash J. Assessing the functional status of older cancer patients in an ambulatory care visit. Healthcare (Basel) 2015;3:846–59.
[4] Jorgensen TL, Hallas J, Friis S, Herrstedt J. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. Br J Cancer 2012;106:1353–60.
[5] Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998;16:1582–7.
[6] Koroukian SM, Murray P, Madigan E. Comorbidity, disability, and geriatric syndromes in elderly cancer patients receiving home health care. J Clin Oncol 2006; 24:2304–10.
[7] Williams GR, Mackenzie A, Magnuson A, Olin R, Chapman A, Mohile S, et al. Comorbidity in older adults with cancer. J Geriatr Oncol 2016;7:249–57.
[8] Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C. Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. J Geriatr Oncol 2012;3:228–37.
[9] Jorgensen TL, Herrstedt J, Friis S, Hallas J. Polypharmacy and drug use in elderly Danish cancer patients during 1996 to 2006. J Geriatr Oncol 2011(3):33–40.
[10] Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, et al. Prevalence and factors associated with polypharmacy in older people with cancer. Support Care Cancer 2014;22:1727–34.
[11] Balducci L, Goetz-Parten D, Steinman MA. Polypharmacy and the management of the older cancer patient. Ann Oncol 2013;24(Suppl. 7):vii36–40.
[12] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457–65.
[13] Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. Cancer 2012;118:3377–86.
[14] Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. J Clin Oncol 2016; 34:2366–71.
[15] Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. J Clin Oncol 2012;30:2036–8.
[16] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 1982;5:649–55.
[17] Peus D, Newcomb N, Hofer S. Appraisal of the Karnofsky performance status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak 2013;13:72.
[18] Jolly TA, Deal AM, Nyrop KA, Williams GR, Pergolotti M, Wood WA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. Oncologist 2015;20:379–85.
[19] Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to eastern cooperative oncology group performance status in elderly cancer patients: an Italian group for geriatric oncology study. J Clin Oncol 2002;20:494–502.
[20] European Geriatric Medicine Society (EuGMS). Comprehensive assessment of the frail older patient. Available from: http://www.eugms.org/fileadmin/user_upload/News_Documents/Publications/Comprehensive_Assessment_of_the_Frail_Older_Patient.pdf; 2017.
[21] Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 2018;36:2326–47.
[22] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32:2595–603.
[23] Corre R, Greillier L, Le Caer H, Audigier-Valette C, Baize N, Berard H, et al. Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non-small-cell lung cancer: the phase III randomized ESOGIA-GFPC-GECP 08-02 study. J Clin Oncol 2016;34:1476–83.
[24] Magnuson A, Lemelman T, Pandya C, Goodman M, Noel M, Tejani M, et al. Geriatric assessment with management intervention in older adults with cancer: a randomized pilot study. Support Care Cancer 2018;26:605–13.
[25] Puts MTE, Sattar S, Kulik M, MacDonald ME, McWatters K, Lee K, et al. A randomized phase II trial of geriatric assessment and management for older cancer patients. Support Care Cancer 2018;26:109–17.
[26] Collin C, Wade DT, Davies S, Horne V. The Barthel ADL index: a reliability study. Int Disabil Stud 1988;10:61–3.
[27] Frederiksen H, Hjelmborg J, Mortensen J, McGue M, Vaupel JW, Christensen K. Age trajectories of grip strength: cross-sectional and longitudinal data among 8,342 Danes aged 46 to 102. Ann Epidemiol 2006;16:554–62.
[28] Csuka M, McCarty DJ. Simple method for measurement of lower extremity muscle strength. Am J Med 1985;78:77–81.
[29] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[30] Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short orientation-memory-concentration test of cognitive impairment. Am J Psychiatry 1983;140:734–9.
[31] Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: the mini nutritional assessment as part of the geriatric evaluation. Nutr Rev 1996;54:S59–65.
[32] O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015;44:213–8.
[33] Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.
[34] Wittrup-Jensen KU, Lauridsen J, Gudex C, Pedersen KM. Generation of a Danish TTO value set for EQ-5D health states. Scand J Public Health 2009;37:459–66.
[35] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.
[36] Kalsi T, Babic-Illman G, Ross PJ, Maisey NR, Hughes S, Fields P, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer 2015;112:1435–44.
[37] Pottel L, Lycke M, Boterberg T, Pottel H, Goethals L, Duprez F, et al. Serial comprehensive geriatric assessment in elderly head and neck cancer patients undergoing curative radiotherapy identifies evolution of multidimensional health problems and is indicative of quality of life. Eur J Cancer Care (Engl) 2014;23:401–12.
[38] Orum M, Gregersen M, Jensen K, Meldgaard P, Damsgaard EMS. Frailty status but not age predicts complications in elderly cancer patients: a follow-up study. Acta Oncol 2018;57:1458–66.
[39] Kirkhus L, Saltyte Benth J, Rostoft S, Gronberg BH, Hjermstad MJ, Selbaek G, et al. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. Br J Cancer 2017;117:470–7.

[40] Smets IH, Kempen GI, Janssen-Heijnen ML, Deckx L, Buntinx FJ, van den Akker M. Four screening instruments for frailty in older patients with and without cancer: a diagnostic study. BMC Geriatr 2014;14:26.
[41] Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015;26:1091–101.
[42] Hamaker ME, Te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - a systematic review. J Geriatr Oncol 2018;9:430–40.
[43] Townsley CA, Naidoo K, Pond GR, Melnick W, Straus SE, Siu LL. Are older cancer patients being referred to oncologists? A mail questionnaire of Ontario primary care practitioners to evaluate their referral patterns. J Clin Oncol 2003;21:4627–35.