

# Treatment decisions and outcomes in geriatric oncology

Inez C. van Walree





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# **Treatment decisions and outcomes in geriatric oncology**

## **Behandelbeslissingen en uitkomsten in de geriatrische oncologie**

(met een samenvatting in het Nederlands)

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*"We cannot direct the winds, but we can adjust the sails"*

Bron: Bertha Calloway, historian.





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# Chapter 1

Introduction and outline of thesis

## INTRODUCTION

### **Ageing of the population**

The Western population is ageing rapidly: the number of people aged 80 years or older is projected to triple from 143 million in 2019 to 426 million in 2050.<sup>1</sup> In the Netherlands, people aged 80 years currently have a remaining life expectancy of approximately eight to ten years and this will continue to increase the following decades.<sup>2</sup> However, this longevity comes at the price of an increase in the prevalence of (chronic) diseases in older adults.

### **Ageing and cancer**

Cancer is an example of a disease disproportionately affecting older adults: 30% of the people with cancer are aged 75 years or older while only 13% of Dutch inhabitants currently belong to this age group.<sup>3,4</sup> There is a discrepancy between the prevalence of cancer among older people on the one hand and knowledge about treatment choices, course of treatment and outcomes for this age group on the other hand. This knowledge gap may be due to several reasons. Firstly, older patients are underrepresented in cancer clinical trials.<sup>5</sup> Secondly, ageing is a heterogeneous process, which stresses the clinical need to identify ageing-related physiologic changes and comorbid conditions as both factors may affect course of treatment and outcomes.<sup>6</sup> Therefore, study results generated in a younger, more healthy population cannot be extrapolated to the general older patient with cancer. Lastly, older patients' treatment priorities may differ from those of their younger counterparts. For example, older patients may be less willing to trade off quality of life for prolongation of life.<sup>7</sup> As a consequence of these factors, optimal treatment for older patients with cancer is thus largely unknown, and often, specific guideline treatment recommendations are lacking for these patients.

### **Geriatric assessment and frailty screening tools**

To aid physicians in treatment decision-making and to distinguish fit from frail patients, a geriatric assessment can be performed. A geriatric assessment is a systematic evaluation of a patient's health status using validated tools that assess specific domains which are commonly impaired in older patients, including functional status, comorbidity, cognition, social status/support, and nutritional status.<sup>8</sup> Geriatric assessment can aid in uncovering previously unrecognized health issues. This is relevant because the majority of older patients with cancer have at least one and often multiple impairments in geriatric domains.<sup>9</sup> Moreover, outcomes of geriatric assessment are independently associated with survival, course of treatment, health care utilisation, functional dependence and quality of life.<sup>10</sup>

However, it may not be feasible to perform geriatric assessment in all older patients with cancer. Currently, physician's clinical judgment is frequently used to estimate a patient's

frailty level. Yet it is unknown whether this is an accurate method to identify frailty in older patients with cancer. An alternative is to use a two-step approach, starting with a screening tool to identify potentially frail patients who will benefit from geriatric assessment. The G8 is an example of a commonly used frailty screening tool. However, data on the use of the G8—including associations of the G8 with clinical outcomes such as survival, course of treatment, and quality of life—have not yet been systematically reviewed.

### **Treatment choices and outcomes in older patients with cancer**

Results from research other than clinical trials show that there are disparities in cancer treatment and outcomes according to age.<sup>11–15</sup> Older patients are less likely to receive treatment in accordance with the treatment guidelines and frequently receive less aggressive treatment.<sup>13–17</sup> This may represent appropriate trade-off in frail older patients, for whom standard treatment could be overly harmful given their limited reserves. For example, older patients are more likely to experience treatment-related adverse events such as chemotherapy toxicity, surgical complications, hospitalisations, and death.<sup>18–21</sup> On the other hand, there is also a risk that fit older patients are undertreated if treatment choices are based on chronological age alone. Therefore, many questions regarding treatment choices and outcomes in older patients with cancer remain and more data on these outcomes are required.

### **Patient-reported outcomes**

To determine the efficacy of new treatments for cancer, the most frequently used outcomes are survival, disease-free survival or response rate. However, older patients may value other outcomes—such as quality of life and maintenance of functional independence—as more important.<sup>22,23</sup> To meet this demand, cancer research has increasingly studied patient-reported outcomes (PROs).<sup>24</sup> PROs include data that can be obtained only directly from the patient and examples include symptoms that are not observable for others (such as fatigue, depression or sleeping disorders) or the impact of the tumour or treatment on the patient's daily functioning and health-related quality of life (HRQoL).<sup>25</sup> Earlier studies on PROs in older patients with cancer, particularly in patients with gynaecological cancer, yielded conflicting results or did not provide longitudinal follow-up.<sup>26–28</sup> Therefore, more evidence on these outcomes is needed to optimally inform older patients about their prospects during and after cancer treatment.

## AIMS AND OUTLINE OF THIS THESIS

Many questions regarding treatment and outcomes of older patients with cancer remain to be answered. This thesis aims to provide answers to some of these questions and comprises three parts:

In **Part I** we focus on frailty assessment in older patients with cancer. We assess the correlation between clinical judgment and geriatric assessment and we review the G8 screening tool. In addition, we study the agreement of newly developed patient-reported version of the G8 with the original G8. **Part II** focuses on treatment choices, course of treatment and reasons for guideline non-adherence in older patients with (ovarian) cancer. In **Part III**, we study the use and results of patient-reported outcomes and health-care utilisation in patients with (gynaecological) cancer.

**Part I** consists of three chapters: in **Chapter 2** we prospectively evaluate correlations between clinical judgment for frailty of the cancer specialist, the general practitioner, and patient's self-assessment as well as the correlation between clinical judgment and geriatric assessment. In **Chapter 3**, the use of the G8 screening tool is systematically reviewed focusing not only on its diagnostic accuracy to identify frailty, but also on the association between the G8 and clinical outcomes such as survival, course of treatment and patient-reported outcomes. In **Chapter 4**, we assess the agreement between a newly developed patient-reported version of the G8 and the original G8 in both older patients with cancer as well as in geriatric patients without cancer.

In **Part II**, current treatment practice and reasons for guideline non-adherence in older patients with cancer are evaluated. A comparison of treatment choices and course of treatment in younger and older patients with ovarian cancer diagnosed at the Diaconessenhuis Utrecht between 2010 and 2015 is described in **Chapter 5**. In **Chapter 6** a nation-wide, population-based age-stratified analysis is performed on treatment patterns and reasons for guideline non-adherence in patients with advanced stage ovarian cancer. **Chapter 7** describes how frequently the oldest old patients with cancer (80 years and older) diagnosed at the Diaconessenhuis Utrecht complete their chemotherapy according to plan.

**Part III** addresses patient-reported outcomes in older patients with (gynaecological) cancer. In **Chapter 8**, we describe healthcare utilisation in the last three months of life among patients treated with palliative chemotherapy at the Diaconessenhuis Utrecht. In **Chapter 9**, we perform a cross-sectional analysis of health-related quality of life (HRQoL) in long-term survivors of ovarian cancers, comparing HRQoL of younger and older women (< 70 versus  $\geq$  70 years). **Chapter 10** is a longitudinal analysis of HRQoL of patients with

endometrial cancer, in which we assess whether chronological age or comorbidity burden is more strongly associated with changes in HRQoL over time.

Finally, **Part IV** consists of a general discussion with an interpretation of the potential implications of our findings for clinical practice and future research (**Chapter 11**), and a summary on the main findings of this thesis (**Chapter 12 and 13**).

## REFERENCES

1. United Nations. Global issues, Ageing. Accessed date: 18 March 2020. Available at: <https://www.un.org/en/sections/issues-depth/ageing/>.
2. CBS StatLine. Levensverwachting; geslacht, leeftijd (per jaar en periode van vijf jaren), Accessed Date: 18 March 2020 (in Dutch).
3. Volksgezondheidszorg.info, Kanker, Cijfers & Context, Huidige situatie. Accessed date: 18 March 2020 (in Dutch). Available at: <https://www.volksgezondheidszorg.info/onderwerp/kanker/cijfers-context/huidige-situatie#!node-aantal-nieuwe-gevallen-van-kanker>.
4. CBS StatLine. Bevolking; geslacht, leeftijd en burgerlijke staat, 1 januari. Accessed date: 18 March 2020 (in Dutch). Available at: <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/7461bev/table?ts=1558432491453>.
5. Le Saux, O. *et al.* Changes in the use of end points in clinical trials for elderly cancer patients over time. *Ann. Oncol.* **28**, 2606–2611 (2017).
6. Cailliet, P. *et al.* Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. *Clin. Interv. Aging* **9**, 1645–60 (2014).
7. Fried, T. R., Bradley, E. H., Towle, V. R. & Allore, H. Understanding the Treatment Preferences of Seriously Ill Patients. *N. Engl. J. Med.* **346**, 1061–1066 (2002).
8. Wildiers, H. *et al.* International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. *J. Clin. Oncol.* **32**, 2595–2603 (2014).
9. Soubeyran, P. *et al.* Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. *PLoS One* **9**, e115060 (2014).
10. Mohile, S. G. *et al.* Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J. Clin. Oncol.* JCO.2018.78.868 (2018). doi:10.1200/JCO.2018.78.8687
11. Zeng, C. *et al.* Disparities by Race, Age, and Sex in the Improvement of Survival for Major Cancers: Results From the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program in the United States, 1990 to 2010. *JAMA Oncol.* **1**, 88–96 (2015).
12. Nipp, R. *et al.* Disparities in cancer outcomes across age, sex, and race/ethnicity among patients with pancreatic cancer. *Cancer Med.* **7**, 525–535 (2018).
13. Schulkes, K. J. G. *et al.* Multidisciplinary decision-making regarding chemotherapy for lung cancer patients-An age-based comparison. *Eur. J. Cancer Care (Engl.)* **27**, e12768 (2018).
14. Schiphorst, A. H. W., Verweij, N. M., Pronk, A. & Hamaker, M. E. Age-Related Guideline Adherence and Outcome in Low Rectal Cancer. *Dis. Colon Rectum* **57**, 967–975 (2014).
15. Sarasqueta, C. *et al.* Impact of age on the use of adjuvant treatments in patients undergoing surgery for colorectal cancer: patients with stage III colon or stage II/III rectal cancer. *BMC Cancer* **19**, 735 (2019).
16. Jansen, L. *et al.* Age-specific administration of chemotherapy and long-term quality of life in stage II and III colorectal cancer patients: a population-based prospective cohort. *Oncologist* **16**, 1741–51 (2011).



17. Jordan, S. *et al.* Patterns of chemotherapy treatment for women with invasive epithelial ovarian cancer – A population-based study. *Gynecol. Oncol.* **129**, 310–317 (2013).
18. Hurria, A. *et al.* Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J. Clin. Oncol.* **29**, 3457–3465 (2011).
19. Moore, K. N. *et al.* Adjuvant chemotherapy for the ‘oldest old’ ovarian cancer patients: can we anticipate toxicity-related treatment failure in a vulnerable population? *Cancer* **115**, 1472–1480 (2009).
20. Mahdi, H., Wiechert, A., Lockhart, D. & Rose, P. G. Impact of Age on 30-Day Mortality and Morbidity in Patients Undergoing Surgery for Ovarian Cancer. *Int. J. Gynecol. Cancer* **25**, 1216–1223 (2015).
21. Abdel-Rahman, O. & Ahmed, O. Predictors of toxicity-related hospitalization in four randomized studies of 5-fluorouracil-based chemotherapy in metastatic colorectal cancer. *Int. J. Colorectal Dis.* **34**, 675–680 (2019).
22. Wedding, U., Pientka, L. & Höffken, K. Quality-of-life in elderly patients with cancer: A short review. *Eur. J. Cancer* **43**, 2203–2210 (2007).
23. Akishita, M. *et al.* Priorities of Health Care Outcomes for the Elderly. *J. Am. Med. Dir. Assoc.* **14**, 479–484 (2013).
24. Mierzynska, J. *et al.* Prognostic value of patient-reported outcomes from international randomized clinical trials on cancer: a systematic review. *Lancet Oncol.* **20**, e685–e698 (2019).
25. Deshpande, P., Sudeepthi, B. I., Rajan, S. & Abdul Nazir, C. Patient-reported outcomes: A new era in clinical research. *Perspect. Clin. Res.* **2**, 137 (2011).
26. Decoster, L. *et al.* Health related quality of life in older patients with solid tumors and prognostic factors for decline. *J. Geriatr. Oncol.* (2019). doi:10.1016/j.jgo.2019.03.018
27. Kornblith, A. B. *et al.* Long-term psychosocial adjustment of older vs younger survivors of breast and endometrial cancer. *Psychooncology*. **16**, 895–903 (2007).
28. von Gruenigen, V. E., Gil, K. M., Frasure, H. E., Jenison, E. L. & Hopkins, M. P. The impact of obesity and age on quality of life in gynecologic surgery. *Am. J. Obstet. Gynecol.* **193**, 1369–1375 (2005).



# PART I

Frailty assessment in older patients with cancer



# Chapter 2

## Clinical judgment versus geriatric assessment for frailty in older patients with cancer

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## **ABSTRACT**

### **Background**

Geriatric assessment (GA) is an appropriate method for identifying frailty in older patients with cancer, but a shorter instrument may be easier to use in clinical practice. Clinical judgment is always available and requires no investments in time or resources. The purpose of this study was to assess correlations between clinical judgment for frailty of the cancer specialist, the general practitioner and patient's self-assessment, and the correlation between clinical judgment and GA.

### **Methods**

This was a dual-center inception cohort study of patients with cancer aged  $\geq 70$  years starting curative or first-line palliative chemotherapy. GA included the following domains: (instrumental) activities of daily living, nutrition, mobility, cognition, mood, and polypharmacy. Clinical judgment for frailty was rated on a scale from 0 to 10 (0=not frail, 10=frail). Correlation was tested using Kendall's tau-b correlation coefficient.

### **Results**

Of all 55 patients, 76% had  $\geq 2$  geriatric impairments. Median clinical judgment frailty score was 3 (range 1-10 for cancer specialist and patient and range 0-10 for general practitioner) and did not vary much according to the number of impaired geriatric domains (ranging from 2 for 0-1 impaired domains to 4 for  $\geq 3$  impaired domains). Correlations between mutual clinical judgment scores and between clinical judgment and GA were negligible or low.

### **Conclusion**

Correlations between clinical judgment scores and between clinical judgment and GA were poor. Most patients with multiple geriatric impairments had low 'subjective' frailty scores. Other frailty assessments, such as frailty screening tools or GA, should be considered in addition to clinical judgment when selecting older patients for potential treatment with chemotherapy

## INTRODUCTION

Cancer is primarily a disease of older people. In the Netherlands, currently half of all patients newly diagnosed with cancer are aged 70 years of age or older.<sup>1</sup> Due to the ongoing aging of Western societies, this number is expected to increase in the following decades.

Treatment-decision making for older patients with cancer is complex. Firstly, these patients form a heterogeneous group regarding their health status: they have varying degrees of comorbidity, functional impairments, geriatric syndromes, and social support systems. Secondly, older patients are at increased risk of treatment-related adverse outcomes such as functional dependence and reduced quality of life.<sup>2,3</sup> Finally, older patients and those with comorbidity are significantly under-represented in clinical trials.<sup>4</sup> Consequently, optimal treatment for these patients is largely unknown and treatment guidelines do not always provide recommendations specific to this population. Therefore, physicians need effective tools to distinguish fit older patients who may tolerate standard treatment, from those who are frail and will likely benefit most from an adapted treatment regimen.

Frailty is a state of increased vulnerability due to decreased physiologic reserve caused by the accumulation of aging processes across multiple organ systems.<sup>5</sup> While frailty is age-related, it does not necessarily coincide with age in a linear fashion. More than half of all older patients with cancer have pre-frailty or frailty and these patients are at increased risk of adverse events.<sup>6</sup> The gold standard for assessing frailty is a geriatric assessment (GA), which is a multidimensional assessment of a patient's health status across somatic, psychosocial, and functional domains.<sup>7</sup>

Frailty can be overtly present but impairment can also be more subtle, in which case it will require specific inquiry or assessment to be noted. Various observers may pick up on different issues depending on their perspective and the timing and setting in which a patient is evaluated. The purpose of our study was to assess correlations between clinical judgment for frailty of the cancer specialist (oncologist/haematologist), the general practitioner and patient's self-assessment, and the correlation between clinical judgment and GA.

## METHODS

### Study design and patient collection

This inception cohort study was performed in two teaching hospitals in the Netherlands, the Diaconessenhuis Utrecht and the Haga Hospital (The Hague). Between July 2018 and October 2019, all consecutive patients with cancer aged  $\geq 70$  years who were to receive

chemotherapy with curative intent or first-line palliative treatment for a solid tumour or lymphomas were eligible for inclusion. Patients were included prior to the start of chemotherapy at the oncology hematology day care service, at the outpatient clinic, or during hospitalisation. Patients were excluded if informed consent was not provided or if they had insufficient understanding of the Dutch language. The study was approved by the medical ethics review boards of both participating hospitals and written informed consent was obtained from all patients prior to enrollment.

### Data collection

For each patient, baseline demographic data were collected from the medical file by the primary investigator and during the GA, which included age at treatment, sex, educational level, living situation, comorbidity according to the Charlson Comorbidity Index (CCI, the items on tumor and metastatic disease due to the current tumour were excluded), body mass index (BMI), the Eastern Cooperative Oncology Group performance score (ECOG PS), cancer type, stage of disease, and planned chemotherapy treatment.

### Geriatric assessment

GA was performed at the geriatric outpatient clinic or oncology department by either a specialized geriatric nurse or one of the investigators who were both trained in geriatrics. GA consisted of validated questionnaires or a structured assessment of the following seven domains (Table 1): activities of daily living (ADL; Katz-6),<sup>8</sup> instrumental ADL (Lawton and Brody),<sup>9</sup> nutrition (mini nutritional assessment short-form, MNA-SF),<sup>10</sup> mobility (4-meter walking test and falls in the previous 6 months), cognition, polypharmacy ( $\geq 5$  drugs), and mood. Cognition was assessed with the 6-item cognitive impairment test

**Table 1.** Content of geriatric assessment.

Domain	Test	Range	Cut-off	Source	Impairment <sup>a</sup>
ADL	Katz-scale	0-12	$\geq 2$	Patient	15% (n= 8)
IADL	Lawton & Brody	0-24	$\geq 3$	Patient	60% (n= 33)
Nutrition	MNA-SF	0-14	$< 12$	Patient	75% (n= 41)
Mobility <sup>b</sup>	4 meter walking test Falls in past 6 months		$< 0.8$ m/s $\geq 1$	Patient	36% (n= 20)
Cognition <sup>c</sup>	6-CIT	0-28	$\geq 8$	Patient	35% (n= 19)
	Clock	0-14	$\leq 10$		
Mood <sup>d</sup>	GDS-15	0-15	$\geq 5$	Patient	16% (n= 9)
Polypharmacy	Number of drugs		$\geq 5$	Chart	46% (n= 25)

<sup>a</sup> Impairment: proportion of patients who scored below/above the cut-off value.

<sup>b</sup> Mobility was impaired if either the 4 meter walking test was  $< 0.8$  m/s or there was  $\geq 1$  fall in the past 6 months.

<sup>c</sup> Cognition was impaired if either the 6-CIT or the Clock drawing test was abnormal.

<sup>d</sup> Mood was assessed in a two-step approach. Firstly, the PHQ-2 was completed. Only if the PHQ-2 score was abnormal, GDS was completed.

(i)ADL= (instrumental) activities of daily living; MNA-SF = Mini Nutritional Assessment Short Form; 6-CIT = 6-Cognitive Impairment Test; PHQ-2 = Patient Health Questionnaire-2; GDS = Geriatric Depression Scale.



(6-CIT)<sup>11</sup> and the clock drawing test, and was considered impaired if one of the two or both were abnormal.<sup>12</sup> Mood was assessed with the patient health questionnaire-2 (PHQ-2)<sup>13</sup> and, in case of an abnormal score, the geriatric depression scale-15 (GDS-15)<sup>14</sup> was completed. The outcome of GA was composed by the sum of impairments in the seven geriatric domains: thus, a minimum score of zero points and a maximum of seven points could be obtained.

### **Clinical judgment**

Prior to the start of chemotherapy, the patient, cancer specialist (oncologist/hematologist), and general practitioner were asked to indicate how frail they thought the patient currently was. Frailty was rated on a numeric rating scale from zero to ten, wherein zero indicated not frail at all and ten indicated most frail. The patient was asked to answer this question prior to GA. The general practitioner and the cancer specialist were blinded for the outcome of GA as well as for the frailty estimates from the others. Treatment decisions were made prior to inclusion.

### **Statistical analysis**

Sociodemographic and clinical characteristics, as well as GA domains, were presented as median (range or interquartile range) or frequencies and proportions. To assess the relationship between clinical judgment scores and clinical judgment and GA, we generated scatterplots and we calculated correlation coefficients. Correlations were tested using Kendall's tau-b correlation coefficient, using clinical judgment and GA as a continuous variable (clinical judgment scores ranging from 0 to 10 and GA from 0 to 7). Kendall's tau is the correlation test of choice to measure the strength of the association between two non-parametric variables in case of a small sample size.<sup>15</sup> Correlation coefficients were interpreted as follows: 0.00-0.30 negligible correlation; 0.30 – 0.50 low correlation; 0.50 – 0.70 moderate correlation; 0.70 – 0.90 high correlation; 0.90 – 1.0 very high correlation.<sup>16</sup>

Data analysis was performed in SPSS Statistics version 23.0. A two-tailed P-value smaller than 0.05 was considered statistically significant.

## **RESULTS**

### **Patient characteristics**

From July 2018 to October 2019, 60 patients were eligible for inclusion of whom five patients did not agree to participate. Therefore, 55 patients were considered for the present study. Median age of the patients was 74 years (range 70-95 years) and 40% were female (Table 2). Most common diagnoses were lung cancer (n= 20; 36%), prostate cancer (n= 13; 24%) and hematological malignancies (n= 10; 18%). Most patients were treated

**Table 2.** Patient characteristics, N (%).

Characteristics	Total (n = 55)
Age, median (range)	74 (70 – 95)
Sex	
Female	22 (40)
Male	33 (60)
Educational level <sup>a</sup>	
High	26 (47)
Medium	21 (38)
Low	8 (15)
Missing	0
Marital status <sup>b</sup>	
Partner	36 (66)
No partner	19 (34)
Missing	0
BMI	
< 19	2 (4)
19-23	11 (20)
> 23	42 (76)
Missing	0
CCI	
0-1	37 (67)
≥ 2	18 (33)
Missing	0
ECOG PS	
0-1	29 (88)
≥ 2	4 (12)
Missing	22
Tumour type	
Lung cancer	20 (36)
Prostate cancer	13 (24)
Breast cancer	4 (7)
Hematological malignancy	10 (18)
Other <sup>c</sup>	8 (15)
Missing	0
Cancer stage	
Stage 1-2	3 (6)
Stage 3-4	49 (94)
Missing	3
Setting	
Curative	19 (35)
Palliative	36 (66)
Missing	0

<sup>a</sup> Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.

<sup>b</sup> Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited. <sup>c</sup> Other tumour types included bladder cancer (n= 1), adenocarcinoma of unknown primary site (n= 1), gastric cancer (n= 1), biliary tract cancer (n= 1), ovarian cancer (n= 1), colon cancer (n= 1) urothelial cell carcinoma (n= 1) and unknown primary tumour (n= 1).

BMI = body mass index; CCI = Charlson Comorbidity Index; ECOG PS = Eastern Cooperative Oncology Group Performance Status.

with palliative intent (66%) and had an ECOG PS of 0 or 1 (88%). One-third had a CCI-score of  $\geq 2$ .

### Geriatric assessment outcomes

The prevalence of geriatric impairments was high: risk of malnutrition was found in 75%, IADL impairments in 60%, and polypharmacy in 46% of the patients (Table 1). Overall, the median number of geriatric impairments was 2 (range 0-6): 24% of patients had no or one impairment, 27% had two, and 49% had three or more.

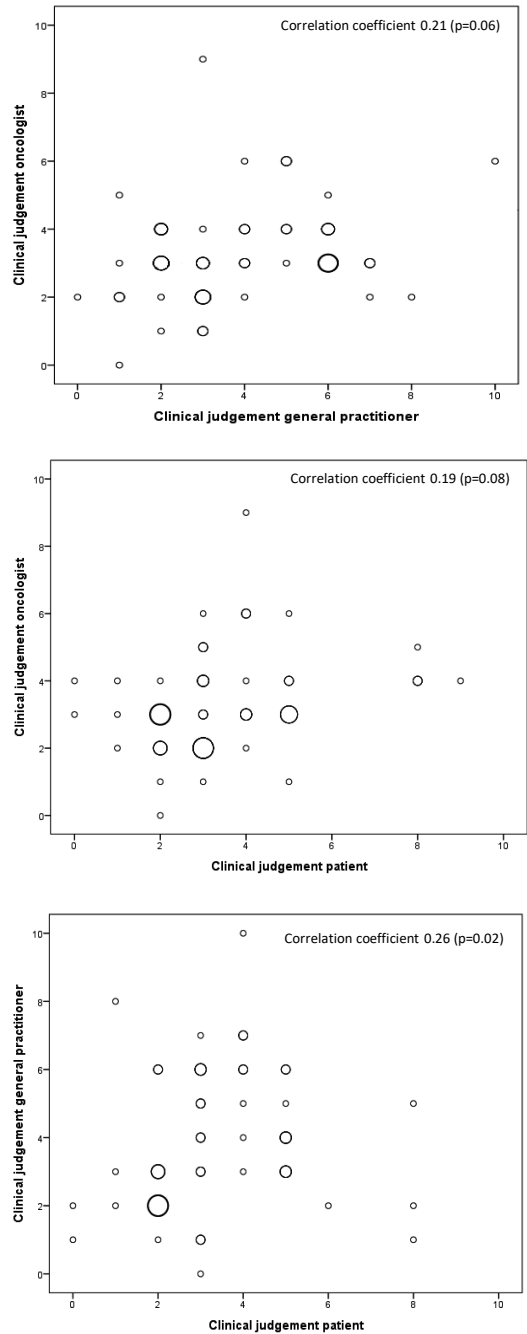
### Clinical judgment outcomes

Clinical judgment scores of the cancer specialist, the general practitioner, and the patient were available for respectively 54, 52, and 55 patients. For all patients, at least two clinical judgment scores were available. All assessors scored the patients as relatively fit with a median frailty score of 3 for all three assessors (interquartile range respectively 2-4 for the cancer specialist, 2-6 for the general practitioner and 2-5 for the patient).

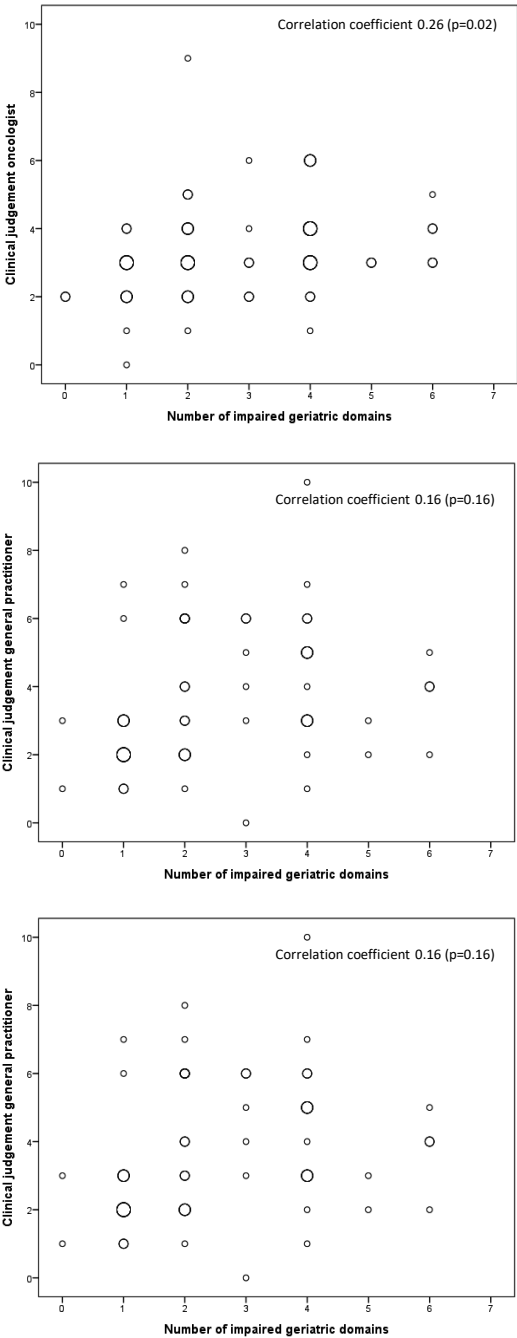
All three scatterplots display a weak positive association between clinical judgment scores: as the assessor's score increases, the score from another assessor also tends to increase (Figure 1A-C). For individual patients, the differences between clinical judgment scores from different assessors were large. This difference ranged from -6 to 6 between the scores of the general practitioner and the cancer specialist, meaning that in extremis, the general practitioner scored the patient six points more frail than the cancer specialist, but at the other end scored the patient six points more fit. These ranges were from -7 to 7 between the general practitioner and the patient, and from -5 to 5 between the patient and the cancer specialist. Correlation coefficients between clinical judgment scores were all negligible and only the correlation between the cancer specialist and the patient was statistically significant ( $p=0.02$ , Figure 1A-C).

### Relationship between clinical judgment and GA

The association between clinical judgment scores and GA was weak as well (Figure 2A-C). Thus, as the number of geriatric impairments increased, patients generally were scored slightly higher (i.e. more frail). However, clinical judgment scores did not show much variation across the total number of impaired geriatric domains and all scores were  $\leq 5$  (Table 3). For example, patients with  $\geq 3$  impaired geriatric domains (representing significant impairment) still had low frailty scores (3 for the cancer specialist and 4 for the general practitioner and patient). The correlation between the cancer specialist's clinical judgment and GA was 0.26, which was statistically significant ( $p=0.02$ ) but of negligible clinical relevance (Figure 2A-C). The correlation between the patient and GA was also statistically significant ( $p<0.01$ ) but of low clinical relevance. The correlation between the general practitioner and GA was 0.16 and was negligible.



**Figure 1.** Correlations between clinical judgment scores of the cancer specialist and the general practitioner (1A), the cancer specialist and the patient (1B) and the general practitioner and the patient (1C). Significance of circle size: twice the same score = size 8; three times the same score = size 10; four times the same score = size 12; five times the same score = size 15; six times the same score = size 18; seven times the same score = size 21.



**Figure 2.** Correlations between clinical judgment score of the cancer specialist and geriatric assessment (2A), of the general practitioner and geriatric assessment (2B) and of the patient and geriatric assessment (2C). Significance of circle size: twice the same score = size 8; three times the same score = size 10; four times the same score = size 12; five times the same score = size 15; six times the same score = size 18; seven times the same score = size 21.

**Table 3.** Clinical judgment scores (median, range) according to specific geriatric domains and according to the total number of impaired geriatric domains.

	Clinical judgment cancer specialist	Clinical judgment general practitioner	Clinical judgment patient
ADL impaired	4 (2 – 6)	3.5 (2 – 10)	4 (2 – 8)
IADL impaired	3 (1 – 9)	4 (1 – 10)	4 (0 – 9)
Nutrition impaired	3 (0 – 9)	4 (0 – 8)	3 (0 – 9)
Mobility impaired	3.5 (1 – 6)	4 (2 – 10)	4 (1 – 8)
Cognition impaired	3 (1 – 5)	4.5 (1 – 8)	3 (0 – 8)
Mood impaired	3 (1 – 4)	3 (1 – 7)	5 (0 – 9)
Polypharmacy present	3 (1 – 6)	4 (0 – 10)	3 (0 – 9)
0-1 impaired domains	2 (0 – 4)	2 (1 – 7)	2 (0 – 5)
2 impaired domains	3 (1 – 9)	4 (1 – 8)	3 (1 – 8)
≥ 3 impaired domains	3 (1 – 6)	4 (0 – 10)	4 (0 – 9)

(I)ADL = (instrumental) activities of daily living.

Cancer specialists tended to score patients with ADL impairments as more frail compared to other impairments (median frailty score 4), while general practitioners appeared to give greatest weight to impaired cognition (median frailty score 4.5) and to impaired mood (median frailty score 5).

## DISCUSSION

In this study we assessed the correlation between clinical judgment of frailty by the cancer specialist, the general practitioner and the patient, and the correlation between clinical judgment and GA. Our main finding is that all of these correlations were negligible or low. Although the majority of patients had multiple geriatric impairments, median clinical judgment frailty scores were low. Consequently, navigating solely on clinical judgment for identification of potentially frail patients could result in missing patients with relevant geriatric impairment.

Traditionally, the Karnofsky or ECOG PS are used to assess functional status and to decide whether a patient can start chemotherapy. Nevertheless, these scales were validated in younger patients and do not address the heterogeneity in the aging process. Indeed, several studies have shown that multiple geriatric impairments can be present in patients with good performance status, and that GA or GA tools add information to performance status in older patients with cancer.<sup>17,18</sup> Unfortunately, we could not analyze whether there was a correlation between ECOG PS and frailty assessment due to too many missing values for ECOG PS. However, performance status is one dimensional and focusses primarily on

physical functioning. It does not include factors such as psychosocial functioning and nutritional status which are generally included in a frailty assessment.

Our finding of clinical judgment being more conservative in defining patients as frail than GA is in line with findings from earlier studies that assessed the relationship between the cancer specialist's clinical judgment and GA.<sup>19-22</sup> Only two studies specifically asked cancer specialists to rate their patients' frailty, using a classification of fit, vulnerable, or frail.<sup>19,20</sup> One of these studies found that agreement between cancer specialist's clinical judgment and GA was only fair<sup>19</sup> and the other found poor sensitivity for clinical judgment compared to GA.<sup>20</sup> The other two studies assessed frailty indirectly, according to whether patients received standard or adapted treatment.<sup>21,22</sup> In agreement with our results, they found that GA identified more frail patients than clinical judgment.<sup>19-22</sup> Some studies also found that GA impairment was independently associated with poorer survival, while clinical judgment was not.<sup>19,21</sup> Two additional studies found that the oncologist's clinical judgment was also not predictive of chemotherapy toxicity.<sup>23,24</sup>

To our knowledge, we are the first to assess the correlation between clinical judgment of three different assessors in older patients with cancer. In addition, only few studies compared clinical judgment of the general practitioner and patient self-assessment to GA. One study in older patients in primary care (not specifically with cancer) compared several frailty instruments, including the general practitioner's clinical judgment and the patient's self-rated health, to two reference standards (Fried's frailty criteria and clinical judgment of a multidisciplinary expert panel).<sup>25</sup> This study demonstrated that both assessors had good discriminative ability to identify frailty, but also found only fair to moderate kappa values for frailty scores compared to the reference standards.<sup>25</sup>

We hypothesized that self-assessment of frailty could be valuable because of patient's self-knowledge; patients generally know all aspects of their health status, that is physical, social, psychological, and spiritual well-being. All these aspects may influence clinical outcomes. A recent study evaluated the association between self-perceived age and geriatric domain impairments in older patients with cancer.<sup>26</sup> They found that patients who reported feeling the same or older than their chronological age were more likely to experience poor health as captured by GA. Patients in this study thus appeared to be able to estimate their biological age as this was associated with geriatric impairments. This self-perceived biological age might serve as a proxy for frailty. In addition, a study performed in primary care found good diagnostic accuracy for patient's self-rated health to detect frailty.<sup>25</sup>

Although we found better clinical relevance for the correlation between frailty based on clinical judgment and GA for patient self-assessment compared to that of the other two

assessors, clinical relevance was still low. More studies are needed to elucidate whether patient's self-assessment of frailty is associated with GA impairments and with clinical outcomes such as survival or quality of life.

A reason why clinical judgment scores were poorly correlated with GA may be that the assessors rate frailty differently than GA. One study demonstrated that cancer specialists emphasize cancer-related factors such as tumor type and disease stage as well as ECOG PS.<sup>19</sup> On the other hand, GA focus is broader and assesses other factors as well. Consequently, GA will identify more patients as being frail than clinical judgment. In addition, all patients in our study were judged fit enough by the cancer specialists to receive chemotherapy. After this decision, it is unlikely that cancer specialists give their patients a high frailty score. Indeed, cancer specialists scored only 15% of the patients a frailty score of  $\geq 5$ . The fact that 76% of our patients had  $\geq 2$  impaired geriatric domains leads to the question of whether the cancer specialist's judgment that the patients were fit enough to receive chemotherapy was perhaps overly optimistic and may have resulted in overtreatment. On the other hand, given the heterogeneity of the study population and of the different chemotherapy regimens, not all chemotherapy can be considered equivalent and frail patients may have received dose reductions or a more tolerant regimen. The impact of the variability in frailty assessment across multiple assessors and between clinical judgment and geriatric assessment should be subject to future research. More specifically, outcomes between patients in whom clinical judgment of frailty agreed with GA versus patients in whom there was disagreement, should be compared. In addition, future follow-up data on the course of chemotherapy and the patient's ability to complete chemotherapy according to the initial plan will help differentiate between these possible interpretations of the difference in frailty assessment.

Because only a minority of patients had high frailty scores, our results suggest that cancer specialists and general practitioners might benefit from education and awareness to identify frailty in older patients with cancer. We found that cancer specialists and general practitioners scored patients with ADL impairments and cognitive impairment as more frail compared to other impairments. Nevertheless, differences in frailty scores between specific impaired domains were very small (varying maximally 1.5 points on a scale from 0 to 10). Impairments in mood and cognition may be easily overlooked when these domains are not specifically addressed. Although these domains can be assessed with short frailty screening tools, such as the G8,<sup>27</sup> GA systematically assesses these different domains and often finds impairments that would have been missed with regular assessment.<sup>20,28</sup> In 2018, the American Society of Clinical Oncology published a guideline with the recommendation that all patients aged 65 years and older receiving chemotherapy should receive a GA.<sup>29</sup> However, prospective studies are required to investigate if GA followed by



targeted interventions is able to improve prognosis, course of treatment, and quality of life.

Strengths of our study include it being the first published study to test clinical judgment of multiple assessors. In addition, our GA included the main recommended domains and these domains were assessed with validated tests.<sup>29,30</sup> Finally, patients answered the frailty question before GA and cancer specialists and general practitioners were blinded to GA outcomes so that this information did not influence their scores. Our study also has some limitations. First, sample size is limited. However, it is unlikely that a greater sample size would have resulted in better correlation between clinical judgment scores and GA. Second, frailty based on clinical judgment was rated on a numeric rating scale, but this scale has not been validated for this purpose. Furthermore, no numerical anchors were provided. There currently is no consensus on the definition and diagnosis of frailty.<sup>5</sup> However, in the Netherlands people are accustomed to expressing feelings or thoughts intuitively on such a scale since childhood. All hospitals use this method to evaluate a patient's pain intensity. Furthermore, our method has been used in one prior study that has demonstrated that this scale has good diagnostic accuracy to assess frailty.<sup>25</sup> While some earlier studies used a threefold category (fit, intermediate, and frail), we think the numeric scale may better reflect the continuum of the frailty spectrum. Third, as no demographic information from the physicians was systematically registered, we were not able to compare working experience in relation to frailty assessment. Because both participating hospitals already have much experience in geriatric oncology, it is unlikely that better correlations would be found in other hospitals.

## Conclusion

This study in older patients with cancer shows that the correlation between clinical judgment and GA in identifying frailty was poor. Although most patients had multiple geriatric impairments, clinical judgment generally assessed patients as quite fit, and this was similar for cancer specialists, general practitioners, and the patients themselves. Therefore, other frailty assessments, such as frailty screening tools or GA, should be considered in addition to clinical judgment when selecting older patients with cancer for potential treatment with chemotherapy. Nevertheless, future research in a larger study population is necessary and should also assess whether clinical judgment is able to predict clinical outcomes such as chemotherapy completion and survival.

## REFERENCES

1. Cijfers over kanker. Nederlandse Kankerregistratie. [www.cijfersoverkanker.nl](http://www.cijfersoverkanker.nl). Accessed april 1, 2017.
2. Galvin, A. *et al.* Determinants of functional decline in older adults experiencing cancer (the INCAPAC study). *J. Geriatr. Oncol.* **10**, 913–920 (2019).
3. Kent, E. E. *et al.* Health-related quality of life in older adult survivors of selected cancers: Data from the SEER-MHOS linkage. *Cancer* **121**, 758–765 (2015).
4. Hamaker, M. E., Stauder, R. & van Munster, B. C. Exclusion of older patients from ongoing clinical trials for hematological malignancies: an evaluation of the National Institutes of Health Clinical Trial Registry. *Oncologist* **19**, 1069–1075 (2014).
5. Morley, J. E. *et al.* Frailty consensus: a call to action. *J. Am. Med. Dir. Assoc.* **14**, 392–397 (2013).
6. Handforth, C. *et al.* The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **26**, 1091–1101 (2015).
7. Extermann, M. *et al.* Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit. Rev. Oncol. Hematol.* **55**, 241–252 (2005).
8. Katz, S., Ford, A., Moskowitz, R., Jackson, B. & Jaffe, M. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. *JAMA* **185**, 914–919 (1963).
9. Lawton, M. P. & Brody, E. M. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179–186 (1969).
10. Rubenstein, L. Z., Harker, J. O., Salva, A., Guigoz, Y. & Vellas, B. Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF). *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.* **56**, M366–M372 (2001).
11. Brooke, P. & Bullock, R. Validation of a 6 item cognitive impairment test with a view to primary care usage. *Int. J. Geriatr. Psychiatry* **14**, 936–40 (1999).
12. Wolf-Klein, G. P., Silverstone, F. A., Levy, A. P., Brod, M. S. & Breuer, J. Screening for Alzheimer's Disease by Clock Drawing. *J. Am. Geriatr. Soc.* **37**, 730–734 (1989).
13. Kroenke, K., Spitzer, R. L. & Williams, J. B. W. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med. Care* **41**, 1284–92 (2003).
14. Sheikh, J. & Yesavage, J. Geriatric Depression Scale (GDS). Recent evidence and development of a shorter version. *Clin. Gerontol. a Guid. to Assess. Interv.* 165–73. (1986).
15. Arndt, S., Turvey, C. & Andreasen, N. C. Correlating and predicting psychiatric symptom ratings: Spearman's r versus Kendalls tau correlation. *J. Psychiatr. Res.* **33**, 97–104 (1999).
16. Hinkle, D., Wiersma, W. & Jurs, S. *Applied Statistics for the Behavioral Sciences*. (2003).
17. Repetto, L. *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.* **20**, 494–502 (2002).

18. Hurria, A. *et al.* Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. *J. Clin. Oncol.* **34**, 2366–2371 (2016).
19. Kirkhus, L. *et al.* Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. *Br. J. Cancer* **117**, 470–477 (2017).
20. Wedding, U., Koding, D., Pientka, L., Steinmetz, H. T. & Schmitz, S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. *Crit. Rev. Oncol. Hematol.* **64**, 1–9 (2007).
21. Tucci, A. *et al.* A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. *Cancer* **115**, 4547–4553 (2009).
22. Hamaker, M. E., Augschoell, J. & Stauder, R. Clinical judgement and geriatric assessment for predicting prognosis and chemotherapy completion in older patients with a hematological malignancy. *Leuk. Lymphoma* **57**, 2560–7 (2016).
23. Alibhai, S. M. H., Aziz, S., Manokumar, T., Timilshina, N. & Breunis, H. A comparison of the CARG tool, the VES-13, and oncologist judgment in predicting grade 3+ toxicities in men undergoing chemotherapy for metastatic prostate cancer. *J. Geriatr. Oncol.* **8**, 31–36 (2017).
24. Moth, E. B. *et al.* Predicting chemotherapy toxicity in older adults: Comparing the predictive value of the CARG Toxicity Score with oncologists' estimates of toxicity based on clinical judgement. *J. Geriatr. Oncol.* **10**, 202–209 (2019).
25. Sutorius, F. L., Hoogendijk, E. O., Prins, B. A. H. & van Hout, H. P. J. Comparison of 10 single and stepped methods to identify frail older persons in primary care: diagnostic and prognostic accuracy. *BMC Fam. Pract.* **17**, 102 (2016).
26. Loh, K. P. *et al.* Relationships of self-perceived age with geriatric assessment domains in older adults with cancer. *J. Geriatr. Oncol.* (2019). doi:10.1016/j.jgo.2019.12.011
27. van Walree, I. C. *et al.* A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. *J. Geriatr. Oncol.* (2019). doi:10.1016/j.jgo.2019.04.016
28. Extermann, M. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. *Crit. Rev. Oncol. Hematol.* **49**, 69–75 (2004).
29. Mohile, S. G. *et al.* Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J. Clin. Oncol.* **JCO.2018.78.868** (2018). doi:10.1200/JCO.2018.78.8687
30. Wildiers, H. *et al.* International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer. *J. Clin. Oncol.* **32**, 2595–2603 (2014).



# Chapter 3

A systematic review on the association of the G8  
with geriatric assessment, prognosis and course of treatment  
in older patients with cancer

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## **ABSTRACT**

### **Aim**

The aim of this systematic review is to summarise all available data on the use of the G8 screening tool in geriatric oncology, focusing on the diagnostic accuracy of the G8 to predict the presence of impairments on geriatric assessment (GA) and on its association with different clinical outcomes (survival, course of treatment and patient-centred outcomes).

### **Methods**

A systematic search in MEDLINE and EMBASE for studies on the use of the G8 in older patients with cancer.

### **Results**

The literature search identified 8987 reports, of which 54 publications from 46 studies were included (including 18 conference abstracts). 19 studies compared the diagnostic characteristics of the G8 with GA. Median sensitivity and specificity of the G8 for frailty on GA were respectively: 85% and 64%. Out of the 24 studies addressing the association of the G8 with survival, 15 (63%) found the G8 was associated with survival. Six out of fourteen studies (43%) reporting on treatment-related complications found an association between G8 scores and risk of complications. Treatment completion, health care utilisation and patient-centred outcomes were investigated less frequently.

### **Conclusion**

The G8 is a useful diagnostic tool to identify older patients with cancer who require full GA and is associated with survival and treatment-related complications. Future prospective studies should investigate whether the G8 is predictive for other relevant clinical outcomes such as treatment completion and patient-centred outcomes.

## INTRODUCTION

Oncologists are confronted with an increasing population of older patients with cancer for whom treatment decisions are needed. Decision-making for these patients is complex and forms a challenge for treating physicians. Because of a scarcity of evidence from large randomized controlled trials, there are limited data on the feasibility and outcomes of different treatment modalities for this population.<sup>1–3</sup> Treatment goals may also be different because older patients with cancer often value maintenance or improvement of quality of life (QOL) over an increase in overall survival.<sup>4,5</sup> In addition, they form a heterogeneous population with major differences for functional and cognitive status as well as for the presence of comorbidities and polypharmacy.<sup>6</sup> As a result, older patients' benefit from treatment can differ and especially those with comorbidity or functional impairments are at risk of adverse health outcomes.

In order to identify fit from unfit patients and to tailor oncologic treatment, some form of geriatric assessment (GA) is increasingly being incorporated in oncologic care, to evaluate the overall health status of an older patient.<sup>7</sup> The majority of older patients with cancer have at least one and often multiple impairments in GA domains, which are frequently undetected with a standard oncologic evaluation. These impairments are associated with increased risk of treatment-related complications, a decline in functioning or QOL and poorer survival.<sup>8</sup> However, not all older patients with cancer require a complete GA and GA is also resource-consuming. Therefore, a two-step approach, starting with a screening tool to identify those older patients with cancer who will benefit from full GA, has been recommended by the International Society of Geriatric Oncology (SIOG).<sup>7</sup>

The G8 was the first such screening tool specifically designed for older patients with cancer.<sup>9</sup> It consists of eight items covering multiple GA domains (Table 1). Seven items are derived from the original 18-item mini nutritional assessment questionnaire (MNA<sup>10</sup>; appetite changes, weight loss, mobility, neuropsychological problems, body mass index, medication and self-reported health) and one item concerns the patient's age. Overall, the G8 score ranges from 0 (heavily impaired) to 17 (not at all impaired), with a cut-off for potential frailty of  $\leq 14$ . The G8 is easy and quick to administer (median time five minutes) and its diagnostic accuracy has been validated in large independent cohorts.<sup>11,12</sup> Two systematic reviews concluded that the G8 was one of the most robust screening tools currently available.<sup>13,14</sup>

Although originally designed to identify those potentially frail older patients who may benefit from GA,<sup>9,11</sup> the association of the G8 with clinical outcomes such as treatment complications, physical functioning after treatment and survival has also been studied.<sup>12,15</sup> A review published in 2015 reported on the results of four studies relating the G8 to clinical

**Table 1.** The original G8 screening tool.

Items	Possible responses (score)
1. Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake
2. Weight loss during the last 3 months?	0 = weight loss > 3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss
3. Mobility?	0 = bed or chair bound 1 = able to get out of bed/chair but does not go out 2 = goes out
4. Neuropsychological problems?	0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems
5. Body mass index (BMI)? (weight in kilograms) / (height in square metres)	0 = BMI <19 1 = BMI 19 to <21 2 = BMI 21 to <23 3 = BMI ≥23
6. Takes more than three prescription drugs per day?	0 = yes 1 = no
7. In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good 0.5 = does not know 1.0 = as good 2.0 = better
8. Age	0 = >85 1 = 80-85 2 = <80
Total score 0-17	Cut-off ≤ 14: potentially frail

outcomes.<sup>14</sup> However, the primary aim of this review was not to provide an extensive overview on the association of screening tools with clinical outcomes because it only included studies that reported on the use of screening tools for detection of impairments on GA. Studies reporting on the association with clinical outcomes specifically could thus have been missed. In addition, after the publication of this review, many studies have been published on the association of the G8 and clinical outcomes. Therefore, the aim of the present systematic review is to summarise all currently available data on the use of the G8, focusing on both the comparison of the G8 with GA as well as its association with clinical outcome measures.

## MATERIALS AND METHODS

### Search strategy and selection criteria

Our aim was to identify all studies that investigated the G8 screening tool in relation to full GA and clinical outcomes in patients with cancer, independent of age, cancer type or stage of disease.



The following search was performed on July 20<sup>th</sup> 2018, in both MEDLINE and EMBASE: (((((((neoplasms[MeSH Terms]) OR neoplasm\*[tiab]) OR cancer\*[tiab]) OR tumour\*[tiab]) OR tumor\*[tiab]) OR oncolog\*[tiab]) OR malignan\*[tiab])) AND (((“geriatric 8”[tiab]) OR G8[tiab]) OR (geriatric assessment[MeSH Terms]) OR (geriatric[tiab] AND assessment\*[tiab]) OR ((frailty[MeSH Terms]) OR frail\*[tiab]))). A date range was applied, because the first publication on the G8 was published in May 2008 as a meeting abstract,<sup>16</sup> no limits in age or language were applied.

For this systematic review, we included studies evaluating the original eight-item G8 or a modified version derived from the original G8. Studies were considered eligible if they evaluated the performance of the G8 in older patients with cancer, in relation to the two main outcome measures. The first outcome measure was the diagnostic accuracy of the G8 compared with GA. The second outcome measure was the association of the G8 with clinical outcomes, including prognosis (survival), the course of treatment (toxicity or treatment-related complications, serious adverse events, treatment completion and health care utilisation) and patient-centred outcome measures (functioning and quality of life). If outcome data were only available for patients considered frail based on G8, but not for those considered fit (or the reverse), these studies were excluded.

The titles and abstracts of all studies retrieved by the search were assessed by one reviewer (lvW) to determine which warranted further examination. All potentially relevant articles were subsequently screened as full text. If only an abstract was available, an effort was made to find the final report of the study by searching EMBASE and MEDLINE using the names of first, second and/or final authors as well as key words from the title. If multiple publications were available from one study, only the primary study was included (with the largest patient population or with the most relevant results), except when the other manuscripts contained relevant outcomes that were not included in the primary publication.

Finally, references of included studies were cross-referenced to retrieve any additional relevant citations.

### **Data extraction**

For each eligible study, data regarding study design and results were independently extracted by two authors (lvW and ES). Items that were extracted were the study population (age, sex, cancer type), method of patient selection, the treatment to be received, the content of the GA, the G8's diagnostic accuracy for frailty compared to GA, and clinical outcomes (survival, course of treatment and patient-centred outcomes).

### Quality assessment

The methodological quality of each of the studies was assessed independently by two reviewers (IvW and ES), using the Newcastle-Ottawa scale adapted to this subject (Appendix 1a). Disagreements among the reviewers were discussed during a consensus meeting and in case of persisting disagreement, the assistance of a third reviewer (MH) was sought.

### Data synthesis and analysis

We summarised the study results to describe our main outcomes of interest. If necessary, percentages were calculated of patients with an impaired G8 or GA. Moreover, sensitivity, specificity, positive and negative predictive values and relative risks were calculated, based on the results reported in the study. Due to the expected heterogeneity in the study populations, a formal meta-analysis was not considered feasible.

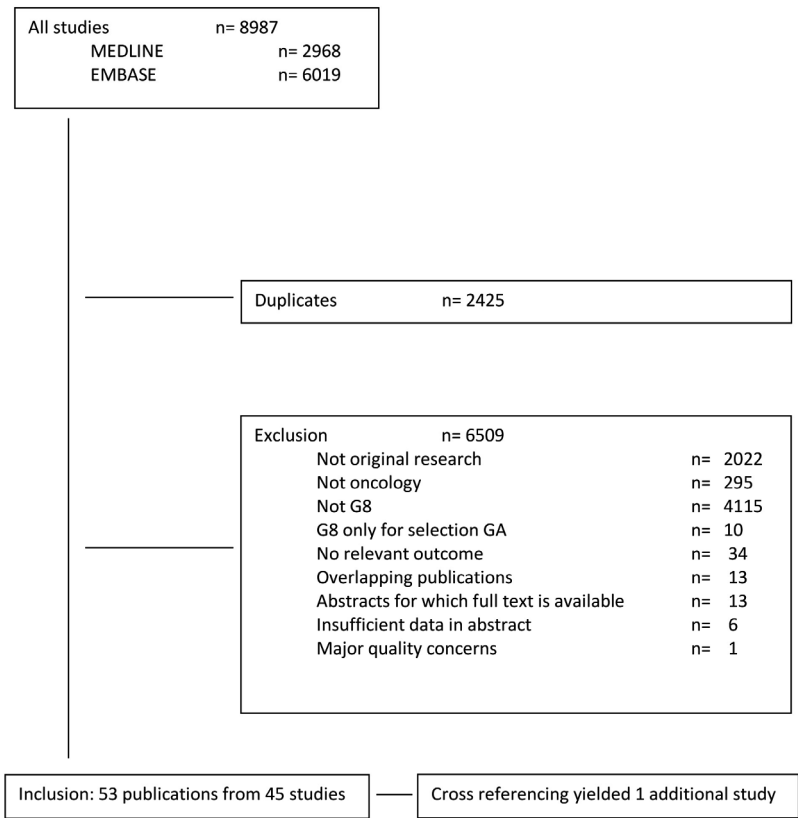
## RESULTS

### Study characteristics

The literature search yielded 8987 citations (2968 from MEDLINE and 6019 from EMBASE), of which 2425 were duplicates and 6509 were excluded for other reasons (Figure 1). Of note, one potentially relevant study was excluded because of quality concerns, including contradictory outcomes and unclear content of the GA.<sup>17</sup> Cross-referencing yielded one additional study.<sup>18</sup> Ultimately, 54 publications from 46 studies were included for this review,<sup>9,11,12,18-68</sup> of which 18 were conference abstracts.<sup>18,19,21,22,26,27,36,37,40,42,44,46,49,53,54,56,59,63</sup>

The characteristics of these 46 studies are summarised in Table 2. The first publications were from 2012<sup>9,18,33,55</sup> and the majority of studies (74%) were published in the past four years. Median sample size was 143 patients (range 27-1435) and median age of the included patients ranged from 65 to 82 years. Study populations were heterogeneous, with 43% focusing on patients with various cancer types.<sup>9,11,12,18-21,25,30,32,36-39,41,42,47,51,55,57,59,62,64,65</sup> Two studies specifically mentioned they also included hospitalized patients,<sup>26,44,45</sup> while one study included hospitalized patients only.<sup>33,34</sup> Seventeen studies evaluated patients receiving various treatment regimens,<sup>11,12,19,22,23,25,26,29,31,37,38,42,44,45,48-50,52,53,57</sup> eleven focused on patients receiving chemotherapy,<sup>9,18,20,21,27,28,30,33,34,36,43,66,67</sup> five on radio(chemo) therapy,<sup>24,47,51,54-56</sup> six on surgery,<sup>35,40,41,46,58,59,61</sup> one on targeted therapy<sup>32</sup> and one on allogeneic stem-cell transplantation.<sup>39</sup> For five studies, the treatment was unknown.<sup>60,62-65</sup>

For outcomes, 19 studies addressed the comparison of the diagnostic accuracy of the G8 compared to GA.<sup>9,11,12,22,34,37-39,41,43,44,50,51,53,55,60,64,65,67</sup> 24 studies described the association of the G8 with survival,<sup>11,12,20,22,24-26,28,31,34,39,42,48,49,52,54,56,57,60,19,61,63,66,67</sup> 17 studies reported on the association of the G8 with course of treatment,<sup>18-20,23,29,30,33,35,36,40,46,47,49,52,56,58,59,61</sup> and four



**Figure 1.** Search results and study selection.  
Abbreviations: GA = geriatric assessment.

studies addressed the association between the G8 and patient-centred outcomes.<sup>12,27,29,42,54</sup> According to the G8, the median prevalence of frailty was 70% (range 20-100%).

In addition, three studies assessed the diagnostic performance of two modified versions of the G8 compared to GA<sup>44,53,68</sup> and one publication addressed the prognostic value of one of the modified G8 versions.<sup>45</sup>

**Quality assessment**

The results of the quality assessment can be found in Figure 2. Detailed results per publication are listed in Appendix 1b. The overall quality of the studies was good. In two studies there was a high risk of bias because there was more than 10% missing data for the G8.<sup>18,38</sup> In another study the description of the method of geriatric evaluation was insufficient with a high risk of bias as a consequence.<sup>50</sup> Duration of follow-up was not mentioned in fifteen publications.<sup>18,19,21,25,28,30,32,36,47,49,52,58,59,62,63</sup> Five publications had loss to follow-up rates over 10%,<sup>12,27,29,42,54</sup> while another 22 publications did not provide sufficient information to assess adequacy of follow-up.<sup>18,19,21,24,25,28,30–33,36,37,46,48,49,52,56–60,62</sup>

Table 2. Included studies.

Publication	Study method			Patients			Outcome						
	Publication year(s)	Abstract (A) or Full text (F)	Study population	Patient selection	Treatment	Number of patients*	% male	Age in years (median, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Agemi <sup>19</sup>	2015	A	Lung cancer	All patients aged ≥ 70 years candidate for oncological treatment	Various	101	81	79 (70-95)	82		X	X	
Aparicio <sup>20</sup>	2018	F	Metastatic colorectal cancer	Untreated patients aged ≥ 75 years who completed geriatric questionnaires	CT (± TT)	96	55	80 (75-91)	81		X	X	
Aydin <sup>21</sup>	2016	A	Acute myeloid leukemia	Consecutive, newly diagnosed referrals aged > 60 years	CT	69	?	?	?		X		
Baitar <sup>22,23</sup>	2013 2014	F F	Various cancer types	Age ≥ 65 years, newly diagnosed cancer or recurrent disease	Various	170	54	77 (66-97)	76	X	X	X	
Bellera <sup>9,27</sup>	2012 2015	F A	Various cancer types	Patients aged ≥ 70 years scheduled to receive first-line chemotherapy	CT	339	59	77 (70-99)	82	X	X		X
Bonomo <sup>24</sup>	2017	F	Head and neck cancer	Age ≥ 65 years, unsuitable for curatively intended concurrent CTR or high-dose RT by clinical judgement	RT	36	58	78 (65-91)	100		X		
Bononi <sup>25</sup>	2013	A	Various cancer types	Unselected outpatients aged > 70 years	Various	530	50	?	69		X		
Boulahssass <sup>26</sup>	2018	F	Various cancer types	Consecutive patients aged > 70 years, outpatient or hospitalised	Various	1050	40	82 (70-100)	86		X		
Cvetkovic <sup>28</sup>	2017	A	Indolent B-cell lymphoma	Consecutive patients aged ≥ 65 years fulfilling criteria for treatment	CT	89	51	75 (65-88)	?		X		
Decoster <sup>29</sup>	2017	F	Colorectal cancer	Age ≥ 70 years, newly diagnosed cancer or cancer progression/relapse	Various	193	62	77 (70-89)	?			X	X
Decoster <sup>30</sup>	2018	F	Metastatic colorectal cancer	Age ≥ 70 years, suitable for first-line chemotherapy	CT	248	62	77 (69-91)	81		X	X	

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Publication		Study method		Patients			Outcome						
Author	Publication year(s)	Abstract (A) or full text (F)	Study population	Patient selection	Treatment	Number of patients*	% male	Age in years (median, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Denewet <sup>31</sup>	2016	F	Various cancer types	Age ≥ 70 years with new cancer diagnosis or disease progression	Various	205	53	79 (70-93)	86		X		
Dimopoulos <sup>32</sup>	2016	A	Multipel myeloma	Consecutive, unselected patients aged ≥ 65 years	TT	144	55	76 (66-92)	?		X		
Dubruille <sup>33,34</sup>	2012	F	Haematological cancers	Consecutive, inpatients aged ≥ 65 years, fit enough for chemotherapy	CT	90	57	74 (65-89)	72	X	X	X	
Fagard <sup>35</sup>	2017	F	Colorectal cancer	Patients aged ≥ 70 years planned for surgery	Surgery	190	55	77 (70-97)	61			X	
Gangopadhyay <sup>36</sup>	2018	F	Various cancer types	Patients aged > 65 years who completed CTR	CTR	219	42	78 (65-89)	?			X	
Hamaker <sup>37</sup>	2014	F	Haematological cancers	Consecutive, newly diagnosed patients aged ≥ 67 years	Various	108	53	78 (67-99)	61	X	X		
Hentschel <sup>38</sup>	2016	F	Various cancer types	Consecutive patients aged ≥ 63 years referred to a tertiary cancer centre	Various	63	62	73 (63-93)	75	X			
Holmes <sup>39</sup>	2014	F	Haematological cancers	Patients eligible for allo-HCT aged ≥ 60 years	allo-HCT	50	70	65 (60-73)	56	X			
Kaibori <sup>40</sup>	2016	F	Hepatocellular carcinoma	Consecutive patients scheduled for liver resection aged ≥ 70 years	Surgery	71	73	77 (70-89)	55		X	X	
Kenig <sup>41</sup>	2015	F	Solid abdominal tumors	Consecutive patients ≥ 65 years in need of surgery under general anesthesia	Surgery	135	47	75 (65-92)	85	X			
Kenis <sup>42,42</sup>	2014	F	Various cancer types	Patients aged ≥ 70 years at diagnosis or at disease progression/relapse	Various	937	37	76 (70-95)	74	X	X	X	X
Kim <sup>43</sup>	2017	A	Various cancer types	Patients receiving first-line chemotherapy aged ≥ 70 years	CT	301	?	75 (70-93)	88	X			

Publication		Study method		Patients			Outcome						
Author	Publication year(s)	Abstract (A) or full text (F)	Study population	Patient selection	Treatment	Number of patients*	% male	Age in years (median, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Martinez-Tapia <sup>44,45</sup>	2017	F	Various cancer types	Consecutive newly diagnosed in- and outpatients aged ≥ 70 years	Various	1333	52	80 (IQR 76-84)	84	X	X		
	2016	F											
Matsushita <sup>46</sup>	2018	A	High-risk prostate cancer	Patients aged ≥ 75 years	Surgery	41	100	77 (IQR 76-79)	39			X	
Middelburg <sup>47</sup>	2017	F	Various cancer types	Patients irradiated with curative intent aged ≥ 65 years	RT or CRT	380	52	72 (65-96)	44			X	
Molina-Garrido <sup>48</sup>	2013	A	Various cancer types	Patients aged ≥ 70 years	Various	202	62	80	?		X		
Neve <sup>49</sup>	2016	F	Head and neck cancer	Aged ≥ 65 years with a primary malignancy	Various	35	63	74 (65-93)	49			X	
Ogawa <sup>50</sup>	2015	A	Lung cancer	Patients with various stages of lung cancer prior to treatment	Various	154	69	> 70 years	60	X			
Osborne <sup>51</sup>	2017	F	Localised prostate cancer	Patients aged ≥ 70 years planned to receive RT with radical intent	RT	156	100	74 (70-84)	23	X			
Osorio <sup>52</sup>	2016	A	Breast cancer	Consecutive patients aged ≥ 70 years	Various	92	1	78 (70-94)	?			X	
Pamoukdjian <sup>53</sup>	2017	F	Various cancer types	Consecutive outpatients aged ≥ 65 years	Various	252	45	81 (SD 6)	88	X			
Potte <sup>154,55</sup>	2015	F	Head and neck cancer	Consecutive patients aged ≥ 65 years eligible for curative therapy	RT or CRT	100	86	72 (65-86)	69	X	X	X	X
	2012	F											
Runzer-Colmenares <sup>56</sup>	2017	F	Various cancer types	Older patients receiving RT with curative treatment intent	RT	181	100	78 (SD 5)	20			X	
Schulkes <sup>57</sup>	2017	F	Lung cancer	All patients aged ≥ 70 years	Various	142	62	77 (73-82)	70		X		
Silvestri <sup>58,59</sup>	2018	A	Kidney cancer	Patients aged ≥ 70 years prior to surgery	Surgery	162	46	77 (SD 6)	60		X	X	
Smets <sup>60</sup>	2014	F	Various cancer types	Patients aged ≥ 70 years, recently diagnosed with a solid tumor	?	108	35	76 (70-88)	60	X			

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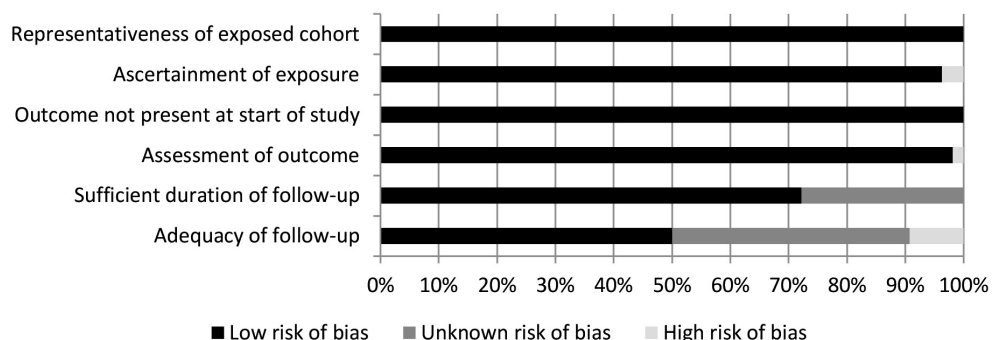
Publication	Study method			Patients		Outcome							
Author	Publication year(s)	Abstract (A) or Full text (F)	Study population	Patient selection	Treatment	Number of patients*	% male	Age in years (median, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Soubeyran <sup>11,68</sup>	2014	F	Various cancer types	Age ≥ 70 years, before first-line treatment or between two steps of a first-line treatment sequence	Various	1435	30	78 (70-98)	68	X	X		
	2016	F											
Souwer <sup>61</sup>	2018	F	Colorectal cancer	Patients aged > 70 years receiving non-elective surgery for stage I-III CRC	Surgery	137	55	78 (IQR 75-83)	50		X	X	
Stauder <sup>62</sup>	2015	A	Haematological cancers	At initial diagnosis, age cut-off unclear	?	64	56	79	?		X		
Stokoe <sup>18</sup>	2012	A	Various cancer types	Patients aged ≥ 65 years	CT	165	?	71 (65-84)	?			X	
Takahashi <sup>63</sup>	2017	F	Various cancer types	Patients aged ≥ 70 years	?	264	66	75 (70-91)	83		X		
Velghe <sup>64</sup>	2014	F	Haematological cancers	Newly diagnosed patients aged ≥ 70 years referred to a tertiary hospital	?	50	50	76 (70-87)	76	X			
Von Saint-George <sup>65</sup>	2016	A	Various cancer types	All patients aged ≥ 70 years	?	50	?	?	41	X			
Wildiers <sup>66</sup>	2018	F	Metastatic breast cancer	Patients aged ≥ 70 years, or frail patients aged ≥ 60 years, with life expectancy > 12 weeks and performance status according to WHO-scale of 0-3	CT (± HT)	79	0	77	70		X		
Yokom <sup>67</sup>	2018	F	Various cancer types	Patients starting systemic therapy aged ≥ 70 years	CT	27	71	74 (70-92)	64	X			

\* Shown patient number is the number for which analysis with the G8 were possible

? not reported

Allo-HCT = allogeneic stem cell transplantation; CT = chemotherapy; CRT = chemo(radio)therapy; HT = hormonal therapy; IQR = interquartile range; RT = radiotherapy; SD = standard deviation; TT = targeted therapy; WHO = World Health Organisation.

Note: if details regarding the G8 cut-off used in the study were lacking (n= 6; all but one conference abstracts), we presumed that the validated cut-off of ≤ 14 was used.



**Figure 2.** Outcome of the quality assessment. Details are reported in Appendix 1a (quality assessment questionnaire) and 1b (assessment per study).

Of the 24 studies reporting on the association of the G8 with survival, fourteen studies specifically mentioned the sociodemographic and/or clinical characteristics survival analyses were adjusted for<sup>16,20,26,30,32,34,37,40,45,48,54,57,63,66</sup> and seven performed multivariate analysis but did not report for which covariates they adjusted.<sup>12,19,21,24,25,28,31</sup> For another two studies it was unclear whether they performed univariate or multivariate analysis<sup>59,62</sup> and one study only did an univariate analysis.<sup>61</sup>

### Diagnostic accuracy of the original G8 versus GA

For the 19 studies assessing the G8 in relation to GA,<sup>9,11,12,22,34,37–39,41,43,44,50,51,53,55,60,64,65,67</sup> Table 3 shows the content of this assessment and Figure 3 demonstrates the relationship between sensitivity and false-positives for the different studies. GA varied from five to nine geriatric domains with a median of seven. Eighteen out of 19 studies (95%) assessed functional status (ADL and/or iADL),<sup>9,11,12,28,31–33,35,37,38,45,47,50,55,58,59,62,64</sup> and seventeen out of 19 studies (89%) assessed mood<sup>9,11,12,28,31–33,35,37,38,47,50,55,58,59,62,64</sup> and nutrition.<sup>9,11,12,28,31–33,35,37,38,47,50,55,58,59,62,64</sup> Cognition ( $n = 16$ , 84%),<sup>9,11,12,28,31–33,35,37,38,47,50,55,58,62,64</sup> mobility and/or falls ( $n = 15$ , 79%)<sup>9,11,28,31–33,35,37,38,45,47,50,58,59,62,64</sup> and comorbidity ( $n = 14$ , 74%)<sup>9,11,12,28,33,35,38,47,50,55,58,59,62,64</sup> were also commonly included while polypharmacy ( $n = 6$ , 32%),<sup>(9,11,12,28,33,35,38,47,50,55,58,59,62,64)</sup> social support ( $n = 6$ , 32%)<sup>12,22,37,39,51,67</sup> and fatigue ( $n = 1$ , 5%)<sup>34</sup> were less frequently included.

Frailty based on GA was defined as the presence of one or more geriatric conditions in six studies<sup>9,11,44,51,53,64</sup> and two or more in twelve studies.<sup>12,22,34,37–39,41,43,50,55,60,67</sup> For one study,<sup>65</sup> the cut-off used to define frailty was not mentioned. Study populations showed a wide variation in the prevalence of frailty as diagnosed by GA; a median of 73% patients was considered frail (range 31–94%, Table 3). In studies using the cut-off of  $\geq 1$ , the prevalence of frailty ranged from 31% to 94%, and in studies using a cut-off of  $\geq 2$ , the range was 32% to 80%.

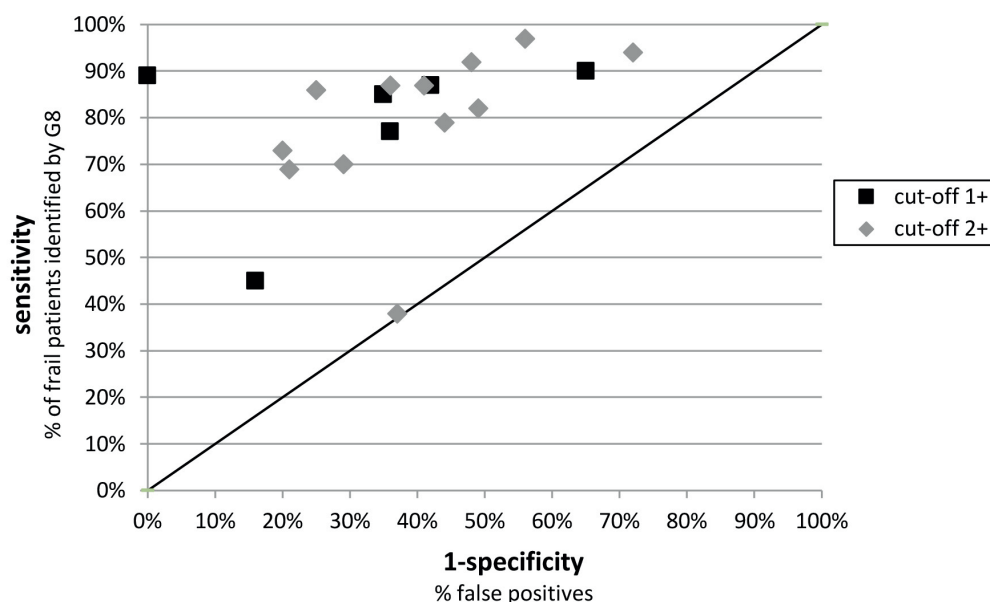


**Table 3.** Diagnostic performance of the original G8 compared to a geriatric assessment.

Study	Number of domains in GA	Domains in GA	n=	cut-off GA impaired	% frail on G8	% frail on GA	SE (%)	SP (%)	PPV (%)	NPV (%)
Von Saint-George <sup>65</sup>	6	mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	?	41	31	74	74	86	56
Bellera <sup>9</sup>	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	339	1+	82	94	85	65	97	21
Marínez-Tapia <sup>44</sup>	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	729	1+	81	87	87	58	93	41
Osborne <sup>51</sup>	5	ADL, iADL, mobility/falls, social support, polypharmacy	156	1+	23	31	45	84	55	78
Pamoukdjian <sup>33</sup>	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	252	1+	88	94	90	35	95	19
Soubeyran <sup>11</sup>	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	1435	1+	68	80	77	64	90	40
Velghe <sup>64</sup>	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	1+	76	88	89	100	100	55
Baitar <sup>22</sup>	8	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, comorbidity	170	2+	76	64	92	52	78	78
Dubruille <sup>34</sup>	9	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity, polypharmacy, fatigue	90	2+	72	80	79	56	88	40
Hamaker <sup>37</sup>	8	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, polypharmacy	108	2+	61	70	69	79	89	50
Hentschel <sup>38</sup>	6	cognition, mood, iADL, nutrition, mobility/falls, polypharmacy	63	2+	75	36	38	63	37	64
Holmes <sup>39</sup>	9	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, comorbidity, polypharmacy	50	2+	56	66	70	71	83	55
Kenig <sup>41</sup>	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	135	2+	85	73	97	44	83	84
Kenis <sup>12</sup>	7	cognition, mood, ADL, iADL, nutrition, social support, comorbidity	937	2+	74	74	87	59	86	61
Kim <sup>43</sup>	6	cognition, mood, ADL, iADL, nutrition, mobility/falls	301	2+	88	73	94	28	79	60
Ogawa <sup>50</sup>	?	Unclear	154	2+	60	32	82	51	44	86
Pottel <sup>55</sup>	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	2+	67	69	86	75	88	71
Smets <sup>60</sup>	6	cognition, mood, ADL, iADL, nutrition, comorbidity	108	2+	60	48	87	64	69	84
Yokom <sup>67</sup>	8	cognition, mood, iADL, nutrition, mobility/falls, social support, comorbidity, polypharmacy	27	2+	64	79	73	80	94	40

? = not reported

ADL = activities of daily living; iADL = instrumental activities of daily living; GA = geriatric assessment; NPV = negative predictive value; PPV = positive predictive value; SE = sensitivity; SP = specificity.



**Figure 3.** Sensitivity and 1-specificity of the original G8 for frailty on geriatric assessment (GA) based on the presence of one or more (cut-off 1+) or two or more (cut-off 2+) geriatric conditions on GA for the different studies.

The sensitivity of the G8 to detect potential frailty ranged from 38% to 97% with a median of 85% (Table 3). The specificity was lower, with a median of 64% (range 28%-100%). Thus, the G8 yielded 15% false-negative results, meaning potentially frail patients were incorrectly identified as fit and 36% false-positive, i.e. fit patients identified as potentially frail. Positive and negative predictive value ranged from 37% to 100% and from 19% to 86% respectively (with medians of 86% and 56% respectively). There did not seem to be a difference in performance of the G8 comparing the cut-off of 1 or more impaired domains versus 2 or more impaired domains; for studies using a cut-off of  $\geq 1$  to define frailty on GA, median sensitivity and specificity were 85% and 65% respectively (range 45%-90% and 35%-100%), while for studies using a cut-off of  $\geq 2$ , median sensitivity and specificity were 84% and 61% respectively (range 38%-97% and 28%-80%).

### Association between the original G8 and clinical outcomes

Fifteen out of 24 studies addressing survival found that frailty based on the G8 was associated with a higher risk of mortality (63%, Table 4).<sup>11,12,19-21,24-26,28,30-32,34,37,40,45,48,54,57,59,61-63,66</sup>

An association between the G8 and survival was found in four out of eight studies addressing patients receiving chemotherapy and/or radiotherapy (50%)<sup>20,21,24,28,30,34,54,66</sup> and none of the three studies on surgery.<sup>40,58,61</sup> Eleven out of thirteen studies in patients receiving varying treatments found an association between frailty on the G8 and survival (85%).<sup>11,12,19,25,26,31,32,37,45,48,57,62,63</sup> Details of differences between patients considered frail

versus fit according to the G8 with regards to overall survival and progression-free survival are listed in Table 4.

Fourteen studies addressed chemotherapy toxicity or treatment-related complications<sup>18,19,23,29,30,33,35,36,40,46,47,56,58,61</sup> and six of these found that a low G8 score was associated with the occurrence of toxicity or treatment-related complications (43%).<sup>18,36,40,46,56,58</sup> One additional study addressed a composite endpoint including safety and efficacy, and found a positive association in the univariate analysis, which was no longer significant after correcting for potential confounders.<sup>20</sup> All three studies separately reporting toxicity rates for fit and frail patients based on the G8 found significantly higher rates of chemotherapy- and/or radiotherapy-related toxicity in the latter, with relative risks varying from 1.4 to 11.3.<sup>18,47,56</sup> In four studies on the incidence of post-operative complications, relative risks for complications for potentially frail patients compared to fit patients ranged from 1.1 to 14.7; differences were significant in three out of four studies.<sup>35,40,58,61</sup> Four studies reported on treatment completion<sup>19,30,47,52</sup> and none found an association between low G8 scores and non-completion. Of the four studies evaluating the association between the G8 and health care utilisation,<sup>40,49,59,61</sup> only one study<sup>40</sup> (25%) found that a G8 score < 14 was associated with a longer median postoperative hospital stay.

Four studies addressed patient-centred outcomes, including functional decline ( $n=3$ )<sup>12,27,29,42</sup> and quality of life ( $n=1$ ).<sup>54</sup> Three studies found that a G8 score  $\leq 14$  was independently associated with either functional decline<sup>12,27,42</sup> or lower QoL (75%)<sup>48</sup> while the fourth study did not find an association.<sup>29</sup>

### Performance of modified G8 versions

Two modified G8 versions were evaluated in three studies to assess its diagnostic performance compared to GA.<sup>44,53,68</sup> One of these studies investigated a modified G8 containing six items that independently predicted impaired GA: weight loss, neuropsychological problems, polypharmacy, self-rated health, performance status and a history of heart failure or coronary artery disease.<sup>44</sup> This modified G8, with a cut-off of  $\geq 6$  of 35 points for potential frailty, outperformed the original G8 with sensitivity of 89.2% vs 87.2%, specificity of 79.0% vs 57.7%, positive predictive value of 96.5% vs 93.1% and negative predictive value of 52.8% vs 40.9% for the modified G8 and original G8 respectively. In a first external validation of this modified G8 sensitivity and specificity were 89.3% and 64.7% respectively.<sup>53</sup> In addition, an impaired score on this modified G8 was independently associated with poorer 1- and 3-years survival.<sup>45</sup>

The second modified G8 replaced the item on neuropsychological problems in the original G8 by a 4-item iADL score.<sup>68</sup> This modified G8 used the same cut-off value for potential

**Table 4.** Associations between the original G8 and treatment-related toxicity or complications and between the original G8 and survival.

Publication		Study design		Outcome				
Author		Study population	Type of cancer treatment	n=	Me(d)ian Follow-up	Toxicity or complications	Survival	Comparison of survival frail vs fit*
Aydin <sup>21</sup>		Acute myeloid leukemia	CT	85	?		+ / ++	
Cvetkovic <sup>28</sup>		Indolent B-cel lymphoma	CT	89	?		+ / ++	
Decoster <sup>30</sup>		Metastatic colorectal cancer	CT	252	2-3 months	+ / —	+ / —	PFS 8.7 vs 11.4 months
Dubruille <sup>34</sup>		Haematological cancers	CT	90	?	-	-	
Stokoe <sup>18</sup>		Various cancer types	CT	165	?	+		
Aparicio <sup>20</sup>		Metastatic colorectal cancer	CT (± TT)	102	20.4 months		-	
Wildiers <sup>66</sup>		Metastatic breast cancer	CT (± HT)	80	20.7 months		+ / ++	6-month OS 88% vs 100% 12-month OS 67% vs 100%
Baitar <sup>23</sup>		Various cancer types	CT or CRT	85	1 month	- / —		
Gangopadhyay <sup>36</sup>		Various cancer types	CRT	219	?	+ / ++		
Bonomo <sup>24</sup>		Head and neck cancer	RT	37	13 months		+ / —	
Runzer-Colmenares <sup>56</sup>		Various cancer types	RT	181	10.2 months	+ / ++		
Middelburg <sup>47</sup>		Various cancer types	RT or CRT	409	?	+ / —		
Potte <sup>154</sup>		Head and neck cancer	RT or CRT	100	?		+ / ++	36-month OS 36% vs 70%
Fagard <sup>35</sup>		Colorectal cancer	Surgery	190	?	+ / —		
Kaibori <sup>40</sup>		Hepatocellular carcinoma	Surgery	71	> 6 months after hepatectomy	+ / ++	-	
Matsushita <sup>46</sup>		High-risk prostate cancer	Surgery	41	?	+ / ++		
Silvestri <sup>58,59</sup>		Kidney cancer	Surgery	162	40.6 months	+	-	1-month OS 96% vs 96% 6-month OS 94% vs 96%
Souwer <sup>61</sup>		Colorectal cancer	Surgery	139	At least 6 months	-	-	

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Dimopoulos <sup>32</sup>	Multipel myeloma	TT	144	?		+ / ++
Stauder <sup>62</sup>	Haematological cancers	?	64	?		+
Takahashi <sup>63</sup>	Various cancer types	?	264	?		+ / ++
Agemi <sup>19</sup>	Lung cancer	Various	101	?	-	+ / ++
Bononi <sup>25</sup>	Various cancer types	Various	530	?		+ / ++
Bouhassass <sup>26</sup>	Various cancer types	Various	1050	3.3 months		+ / —
Decoster <sup>29</sup>	Colorectal cancer	Various	193	2-3 months	- / —	
Denewet <sup>31</sup>	Various cancer types	Various	205	?		+ / ++
Hamaker <sup>37</sup>	Haematological cancers	Various	108	33.6 months		+ / ++
Kenis <sup>12</sup>	Various cancer types	Various	937	19 months		+ / ++
Martinez-Tapia <sup>45</sup>	Various cancer types	Various	1333	26.5 months		+ / ++
Molina-Garrido <sup>48</sup>	Various cancer types	Various	202	7.2 months		? / —
Schulkes <sup>57</sup>	Lung cancer	Various	142	16.1 months		+ / ++
Soubeyran <sup>11</sup>	Various cancer types	Various	1167	12.4 months		+ / ++

\* Bold value indicates *P*-value ≤ 0.05

† In patients receiving standard treatment

# Percentages estimated from figure

? = not reported; — = no association on univariate analysis, multivariate analysis including G8 in model not performed or unclear whether not finding an association was the result of univariate or multivariate analysis; + = association on univariate analysis, multivariate analysis including G8 in model not performed or unclear whether finding an association was the result of univariate or multivariate analysis; - / — = no association on univariate or multivariate analysis; + / — = association on univariate analysis, no association on multivariate analysis; + / ++ = association on multivariate analysis.

CT = chemotherapy; CRT = chemo(radio)therapy; HT = hormonal therapy; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; TT = targeted therapy.

frailty as the original G8 ( $\leq 14$ ). Sensitivity of the iADL-modified G8 was not different from that of the original G8 (77% vs 77%) but its specificity was significantly higher (67% vs 64% for the original G8,  $p < 0.05$ ).

## DISCUSSION

This systematic review of 46 studies on the performance of the G8 shows that, although the G8 was originally developed as a screening tool to detect vulnerable older patients with cancer who may benefit from more elaborate GA, many studies also evaluated its association with survival and treatment-related complications. We found a good sensitivity for the G8 compared to GA to detect potentially frail patients. In addition, almost two-thirds of the studies that assessed the association of the G8 with survival and 43% of the studies on treatment-related complications found that low G8 scores were associated with poorer outcomes. Evidence on treatment completion, health care utilisation and patient-centred outcomes was limited, but a trend towards more functional decline and poorer QoL in patients with low G8 scores was observed while an association between frailty based on G8 and treatment completion or health care utilisation was not found.

This systematic review has some limitations. First, some of the included studies have not been published in full text reports (yet), which limited the amount of available data on the execution and results of the study. Furthermore, study populations were heterogeneous, investigating different levels in frailty status, a wide range of cancer types, stages and treatment modalities, thus hampering extrapolation of these results to individual oncology practice. In addition, the content of the GA differed considerably between studies, as did the cut-off value that was used to define frailty. This is likely the consequence of the current lack of consensus on the definition of frailty.<sup>69</sup> The definition that is used will influence the prevalence of frailty in a study population and similarly the diagnostic performance of the G8 in predicting potential frailty. Moreover, the scales and instruments used to assess the different domains differed as well. This also means that a formal meta-analysis could not be performed. Importantly, not all studies evaluating the association of the G8 with clinical outcome measures reported the direction or size of the effect nor was it always clear how outcome measures were defined. Furthermore, many studies only showed data for included patients receiving the treatment in question but did not report specifically on the preceding patient selection. Thus, it was not possible to assess generalizability of study results. Despite these limitations, this systematic review provides a valuable overview of all currently available evidence on the use of the G8 and shows that it may be used to aid physicians' treatment decision making in older patients with cancer by identifying potentially frail patients and those who are at increased risk for adverse clinical outcomes.

The high sensitivity of the G8 compared to a more elaborate GA is in line with results from two earlier systematic reviews that compared the diagnostic performance of the various available screening tools in older patients with cancer.<sup>13,14</sup> Both concluded that, compared to other frailty screening tools, the G8 was among the most sensitive and most frequently studied. Our review included fifteen studies that were published after these prior reviews, but median sensitivity and specificity of the G8 were not very different to what those reviewers found: sensitivity of 87%<sup>13</sup> and 86%,<sup>14</sup> and specificity of 61%<sup>13</sup> and 60%<sup>14</sup> respectively.

It can be argued that the performance of the G8 compared to GA is not perfect; specificity and negative predictive value of the G8 were moderate to poor, presumably because of the high prevalence of frailty in older patients with cancer (on average 73% of the patients were frail on GA). To improve the diagnostic performance of the G8 and to rationalise the use of medical resources, several studies evaluated a modified version of the G8.<sup>44,53,68</sup> These modified versions had higher specificity than the original G8 without compromising on sensitivity. However, only one study evaluated the prognostic value of the modified G8 for survival and studies on other important outcome measures are currently lacking.<sup>45</sup>

To our knowledge, we are the first to provide a comprehensive systematic review on the association of the G8 with different clinical outcomes. It is remarkable that, even in a wide variety of tumour types, treatments and settings, a screening tool as short and easy to administer as the G8 is associated with several of these outcomes. This is a major strength of this screening tool, and our review confirms this association. While three out of four studies on patient-centred outcomes found an independent association between functional decline or QoL and the G8, more studies are needed to strengthen this finding. Furthermore, the association of the G8 with health care utilisation and treatment completion should also be more thoroughly investigated. However, given its shortness, it seems a lot to expect the G8 to refine prognosis, goal of care discussions, tailored treatment and advanced care planning. Therefore, the G8 cannot replace full GA or clinical judgement but is useful in a two-step approach followed by GA for potentially frail patients.

## Conclusion

This systematic review shows that the G8 screening tool has been widely studied in older patients with cancer. The G8 may help physicians make informed treatment decisions by identifying patients who require full GA and because a low G8 score is associated with survival and treatment-related complications. Future prospective studies should evaluate whether the G8 predicts course of treatment and patient-centred outcomes.

## REFERENCES

1. Hamaker ME, Stauder R, van Munster BC. Exclusion of older patients from ongoing clinical trials for hematological malignancies: an evaluation of the National Institutes of Health Clinical Trial Registry. *Oncologist*. 2014;19(10):1069-75. doi:10.1634/theoncologist.2014-0093
2. Schulkes KJG, Nguyen C, van den Bos F, van Elden LJR, Hamaker ME. Selection of Patients in Ongoing Clinical Trials on Lung Cancer. *Lung*. 2016;194:967-74. doi:10.1007/s00408-016-9943-7
3. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of Patients 65 Years of Age or Older in Cancer-Treatment Trials. *N Engl J Med*. 1999;341(27):2061-7. doi:10.1056/NEJM199912303412706
4. Wedding U, Pientka L, Höffken K. Quality-of-life in elderly patients with cancer: A short review. *Eur J Cancer*. 2007;43(15):2203-10. doi:10.1016/j.ejca.2007.06.001
5. Soto Perez de Celis E, Li D, Sun C-L, Kim H, Twardowski P, Fakih M, et al. Patient-defined goals and preferences among older adults with cancer starting chemotherapy (CT). *J Clin Oncol*. 2018;36.
6. 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(13):3377-86. doi:10.1002/cncr.26646
7. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz J-P, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol*. 2005;55(3):241-52. doi:10.1016/j.critrevonc.2005.06.003
8. 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(22):2326-47. doi:10.1200/JCO.2018.78.8687
9. Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol Off J Eur Soc Med Oncol*. 2012;23(8):2166-72. doi:10.1093/annonc/mdr587
10. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*. 1999;15(2):116-22. <http://www.ncbi.nlm.nih.gov/pubmed/9990575>
11. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. *PLoS One*. 2014;9(12):e115060. doi:10.1371/journal.pone.0115060
12. Kenis C, Decoster L, Van Puyvelde K, De Grève J, Conings G, Milisen K, et al. Performance of Two Geriatric Screening Tools in Older Patients With Cancer. *J Clin Oncol*. 2014;32(1):19-26. doi:10.1200/JCO.2013.51.1345



13. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol.* 2012;13(10):e437-44. doi:10.1016/S1470-2045(12)70259-0
14. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. *Ann Oncol.* 2015;26(2):288-300. doi:10.1093/annonc/mdl210
15. Kenis C, Decoster L, Bastin J, Bode H, Van Puyvelde K, De Grève J, et al. Functional decline in older patients with cancer receiving chemotherapy: A multicenter prospective study. *J Geriatr Oncol.* 2017;8(3):196-205. doi:10.1016/j.jgo.2017.02.010
16. Soubeyran, P, Bellera, C, Goyard, D, Heitz, H, Cure H, Rousselot H, et al. Validation of G8 screening tool in geriatric oncology: The ONCODAGE project. *J Clin Oncol.* 2011;29:9001
17. Luce S, De Breucker S, van Gossum A, Demols A, Mekinda Z, Ena G, et al. How to identify older patients with cancer who should benefit from comprehensive geriatric assessment? *J Geriatr Oncol.* 2012;3(4):351-8. doi:10.1016/j.jgo.2012.06.003
18. Stokoe J, Pearce J, Sinha R, Ring A. G8 and VES-13 scores predict chemotherapy toxicity in older patients with cancer. *J Geriatr Oncol.* 2012:S33-S102.
19. Agemi Y, Miyazaki K, Misumi Y, Sato A, Ishii M, Nakamura Y, et al. Prospective evaluation of the G8 and dementia screening scores (DSS) for frailty in elderly patients (pts) with lung cancer. *J Clin Oncol.* 2015;33(15):Supplement 1.
20. Aparicio T, Bouché O, Francois E, Retornaz F, Barbier E, Taieb J, et al. Geriatric analysis from PRODIGE 20 randomized phase II trial evaluating bevacizumab + chemotherapy versus chemotherapy alone in older patients with untreated metastatic colorectal cancer. *Eur J Cancer.* 2018;97:16-24. doi:10.1016/j.ejca.2018.03.030 LK -
21. Aydin S, Audisio E, D'Arda S, Allione B, Nicolino B, Busca A, et al. Defining frailty of elderly patients with acute myeloid leukemia at diagnosis. *Haematologica.* 2016;101(Supplement):384-5
22. Baitar A, Van Fraeyenhove F, Vandebroek A, De Droogh E, Galdermans D, Mebis J, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. *J Geriatr Oncol.* 2013;4(1):32-8. doi:10.1016/j.jgo.2012.08.001
23. Baitar A, Van Fraeyenhove F, Vandebroek A, De Droogh E, Galdermans D, Mebis J, et al. Geriatric screening results and the association with severe treatment toxicity after the first cycle of (radio)chemotherapy. *J Geriatr Oncol.* 2014;5(2):179-84. doi:10.1016/j.jgo.2013.12.004
24. Bonomo P, Desideri I, Loi M, Lo Russo M, Olmetto E, Maragna V, et al. Elderly patients affected by head and neck squamous cell carcinoma unfit for standard curative treatment: Is de-intensified, hypofractionated radiotherapy a feasible strategy? *Oral Oncol.* 2017;74:142-7. doi:10.1016/j.oraloncology.2017.10.004
25. Bononi A, Inno A, Borghi M, Tesi P, Barile C, Crepaldi G, et al. The prognostic value of rapid screening tests (RST) in geriatric assessment of patients with cancer over 70. *J Clin Oncol.* 2013;31(15):Supplement 1

26. Boulahssass R, Gonfrier S, Ferrero J-M, Sanchez M, Mari V, Moranne O, et al. Predicting early death in older adults with cancer. *Eur J Cancer*. 2018;100:65-74. doi:10.1016/j.ejca.2018.04.013
27. Chakiba C, Bellera C, Fonck M, Blanc J, Ceccaldi J, Imbert Y, et al. Functional decline during first-line chemotherapy in elderly patients can be predicted by abnormal G8 score and performance status. *J Clin Oncol*. 2015;33(15):Supplement 1
28. Cvetkovic Z, Novkovic A, Djumic Z, Bibic T, Ivanovic A, Milutinovic N. Prognostic value of G8 screening tool in patients with indolent B-Cell lymphoproliferative neoplasms - A single centre experience. *Haematologica*. 2017;102:749
29. Decoster L, Vanacker L, Kenis C, Prenen H, Van Cutsem E, Van der Auwera J, et al. Relevance of Geriatric Assessment in Older Patients With Colorectal Cancer. *Clin Colorectal Cancer*. 2017;16(3):e221-9. doi:10.1016/j.clcc.2016.07.010
30. Decoster L, Kenis C, Naessens B, Houbier G, De Man M, Lambrecht G, et al. Integrating geriatric assessment in the first line chemotherapy treatment in older patients with metastatic colorectal cancer: Results of a prospective observational cohort study (AVAPLUS). *J Geriatr Oncol*. 2018;9(2):93-101. doi:10.1016/j.jgo.2017.10.002
31. Denewet N, De Breucker S, Luce S, Kennes B, Higuët S, Pepersack T. Comprehensive geriatric assessment and comorbidities predict survival in geriatric oncology. *Acta Clin Belg*. 2016;71(4):206-13. doi:10.1080/17843286.2016.1153816
32. Dimopoulos M, Gavriatopoulou M, Roussou M, Fotiou D, Ziogas D, Migkou M, et al. Prospective evaluation of geriatric assessment tools in real-world, unselected, elderly patients with symptomatic myeloma. *Haematologica*. 2016;101:259
33. Dubruille S, Maerevoet M, Roos M, Vandenbossche S, Meuleman N, Libert Y, et al. G8 or multimodal geriatric assessment (MGA) for the screening of older patients with malignant hemopathies ? *Haematologica*. 2012;97:34-5
34. Dubruille S, Libert Y, Roos M, Vandenbossche S, Collard A, Meuleman N, et al. Identification of clinical parameters predictive of one-year survival using two geriatric tools in clinically fit older patients with hematological malignancies: Major impact of cognition. *J Geriatr Oncol*. 2015;6(5):362-9. doi:10.1016/j.jgo.2015.07.006
35. Fagard K, Casaer J, Wolthuis A, Flamaing J, Milisen K, Lobelle J-P, et al. Value of geriatric screening and assessment in predicting postoperative complications in patients older than 70 years undergoing surgery for colorectal cancer. *J Geriatr Oncol*. 2017;8(5):320-7. doi:10.1016/j.jgo.2017.07.008
36. Gangopadhyay A. Predictors of chemoradiation related febrile neutropenia prophylaxis in older adults - Experience from a limited resource setting. *Rep Pract Oncol Radiother*. 2018;23(3):228-31. doi:10.1016/j.rpor.2018.02.004
37. Hamaker ME, Mitrovic M, Stauder R. The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. *Ann Hematol*. 2014;93(6):1031-40. doi:10.1007/s00277-013-2001-0
38. Hentschel L, Rentsch A, Lenz F, Hornemann B, Schmitt J, Baumann M, et al. A Questionnaire Study to Assess the Value of the Vulnerable Elders Survey, G8, and Predictors of Toxicity-

- ty as Screening Tools for Frailty and Toxicity in Geriatric Cancer Patients. *Oncol Res Treat.* 2016;39(4):210-6. doi:10.1159/000445365
39. Holmes HM, Des Bordes JKA, Kebriaei P, Yennu S, Champlin RE, Giralt S, et al. Optimal screening for geriatric assessment in older allogeneic hematopoietic cell transplantation candidates. *J Geriatr Oncol.* 2014;5(4):422-30. doi:10.1016/j.jgo.2014.04.004
40. Kaibori M, Ishizaki M, Matsui K, Iida H, Inoue K, Nagashima F, et al. Geriatric assessment as a predictor of postoperative complications in elderly patients with hepatocellular carcinoma. *Langenbeck's Arch Surg.* 2016;401(2):205-14. doi:10.1007/s00423-016-1388-1
41. Kenig J, Zychiewicz B, Olszewska U, Richter P. Screening for frailty among older patients with cancer that qualify for abdominal surgery. *J Geriatr Oncol.* 2015;6(1):52-9. doi:10.1016/j.jgo.2014.09.179
42. Vande Walle N, Kenis C, Heeren P, Van Puyvelde K, Decoster L, Beyer I, et al. Fall predictors in older cancer patients: a multicenter prospective study. *BMC Geriatr.* 2014;14:135. doi:10.1186/1471-2318-14-135
43. Kim JW, Kim HS, Lee Y-G, Hwang IG, Song H-S, Koh S-J, et al. Prospective validation of a novel geriatric screening tool, the Korean cancer study group geriatric score (KG)-7, in older patients with advanced cancer undergoing 1st line palliative chemotherapy. *J Clin Oncol.* 2017;35(15)
44. Martinez-Tapia C, Canoui-Poitaine F, Bastuji-Garin S, Soubeyran P, Mathoulin-Pelissier S, Tournigand C, et al. Optimizing the G8 Screening Tool for Older Patients With Cancer: Diagnostic Performance and Validation of a Six-Item Version. *Oncologist.* 2016;21(2):188-95. doi:10.1634/theoncologist.2015-0326
45. Martinez-Tapia C, Paillaud E, Liuu E, Tournigand C, Ibrahim R, Fossey-Diaz V, et al. Prognostic value of the G8 and modified-G8 screening tools for multidimensional health problems in older patients with cancer. *Eur J Cancer.* 2017;83:211-9. doi:10.1016/j.ejca.2017.06.027
46. Matsushita K, Sandhu J, Horie S, Endo F, Shimbo M, Narimoto K, et al. The role of G8 screening tool in the assessment of surgical outcome of elderly patients ([ 75 y.o.) with high-risk prostate cancer: A pilot study. *J Urol.* 2018;199(4):e198
47. Middelburg JG, Mast ME, de Kroon M, Jobsen JJ, Rozema T, Maas H, et al. Timed Get Up and Go Test and Geriatric 8 Scores and the Association With (Chemo-)Radiation Therapy Noncompliance and Acute Toxicity in Elderly Cancer Patients. *Int J Radiat Oncol Biol Phys.* 2017;98(4):843-9. doi:10.1016/j.ijrobp.2017.01.211
48. Molina-Garrido M, Mora-Rufete A. Frailty screening questionnaires and their role as predictors of survival in elderly cancer patients: ONCOFRAGIL project. Preliminary results. *Eur Geriatr Med.* 2013;4:S88-9. doi:10.1016/j.eurger.2013.07.289
49. Neve M, Jameson MB, Govender S, Hartopeanu C. Impact of geriatric assessment on the management of older adults with head and neck cancer: A pilot study. *J Geriatr Oncol.* 2016;7(6):457-62. doi:10.1016/j.jgo.2016.05.006
50. Ogawa A, Nagashima F, Hamaguchi T. Evaluation of the G8 screening tools for frailty in older patients with cancer. *Ann Oncol.* 2015;26:vii119. doi:10.1093/annonc/mdv472.59

51. Osborne GEC, Appleyard SA, Gilbert DC, Jones CI, Lorimer C, Villanueva M, et al. Comprehensive Geriatric Assessment in Men Aged 70 Years or Older with Localised Prostate Cancer Undergoing Radical Radiotherapy. *Clin Oncol*. 2017;29(9):609-16. doi:10.1016/j.clon.2017.05.003
52. Osorio F, Urbano J, Barradas A, Magalhães A, Fougo J. Value of geriatric screening tools in the prediction of undertreatment in older patients with breast cancer. *Eur J Cancer*. 2016;57:S146-7
53. Pamoukdjian F, Canoui-Poitaine F, Longelin-Lombard C, Aparicio T, Ganne N, Wind P, et al. Diagnostic performance of gait speed, G8 and G8 modified indices to screen for vulnerability in older cancer patients: the prospective PF-EC cohort study. *Oncotarget*. 2017;8(31):50393-402. doi:10.18632/oncotarget.17361
54. Pottel L, Lycke M, Boterberg T, Pottel H, Goethals L, Duprez F, et al. G-8 indicates overall and quality-adjusted survival in older head and neck cancer patients treated with curative radiochemotherapy. *BMC Cancer*. 2015;15(1). doi:10.1186/s12885-015-1800-1
55. Pottel L, Boterberg T, Pottel H, Goethals L, Duprez F, Rottey S, et al. Determination of an adequate screening tool for identification of vulnerable elderly head and neck cancer patients treated with radio(chemo)therapy. *J Geriatr Oncol*. 2012;3(1):24-32. doi:10.1016/j.jgo.2011.11.006
56. Runzer-Colmenares FM, Urrunaga-Pastor D, Aguirre LG, Reategui-Rivera CM, Parodi JF, Taype-Rondan A. Frailty and vulnerability as predictors of radiotoxicity in older adults: A longitudinal study in Peru. *Med Clin (Barc)*. 2017;149(8):325-30. doi:10.1016/j.medcli.2017.02.022
57. Schulkes KJG, Souwer ETD, van Elden LJR, Codrington H, van der Sar-van der Brugge S, Lammers J-WJ, et al. Prognostic Value of Geriatric 8 and Identification of Seniors at Risk for Hospitalized Patients Screening Tools for Patients With Lung Cancer. *Clin Lung Cancer*. 2017;18(6):660-6.e1. doi:10.1016/j.clcc.2017.02.006
58. Silvestri T, Pavan N, Boschian R, Di Cosmo G, De Concilio B, Celia A, et al. A multicentre analysis of the role of the g8 screening tool in the assessment of PERI-operative and functional outcome in elderly patients with kidney tumours. *J Urol*. 2018;199(4):e782
59. Boschian R, Pavan N, Verzotti E, Silvestri T, Traunero F, Liguori G, et al. Predictive value of G8 screening tool in elderly population undergoing radical cystectomy: Preliminary evaluation. *Anticancer Res*. 2018;38(4):2542
60. Smets IHGJ, Kempen GIJM, Janssen-Heijnen MLG, Deckx L, Buntinx FJVM, van den Akker M. Four screening instruments for frailty in older patients with and without cancer: a diagnostic study. *BMC Geriatr*. 2014;14(1):26. doi:10.1186/1471-2318-14-26
61. Souwer ETD, Verweij NM, van den Bos F, Bastiaannet E, Slangen RME, Steup WH, et al. Risk stratification for surgical outcomes in older colorectal cancer patients using ISAR-HP and G8 screening tools. *J Geriatr Oncol*. 2018;9(2):110-4. doi:10.1016/j.jgo.2017.09.003
62. Stauder R, Spross J, Augschöll J. Geriatric assessment defines impairments and clinical outcome in myelodysplastic syndromes. *Leuk Res*. 2015;39:S65
63. Takahashi M, Takahashi M, Komine K, Yamada H, Kasahara Y, Chikamatsu S, et al. The G8 screening tool enhances prognostic value to ECOG performance status in elderly cancer patients: A retrospective, single institutional study. *PLoS One*. 2017;12(6). doi:10.1371/journal.pone.0179694

64. Velghe A, Petrovic M, De Buyser S, Demuynck R, Noens L. Validation of the G8 screening tool in older patients with aggressive haematological malignancies. *Eur J Oncol Nurs*. 2014;18(6):645-8. doi:10.1016/j.ejon.2014.05.006
65. Von Saint-George T, Schaich M. Do G8-screening-results correlate with results of advanced geriatric-oncologic-assessments? *Oncol Res Treat*. 2016;39:284. doi:10.1159/000449050
66. Wildiers H, Tryfonidis K, Dal Lago L, Vuylsteke P, Curigliano G, Waters S, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. *Lancet Oncol*. 2018;19(3):323-36. doi:10.1016/S1470-2045(18)30083-4
67. Yokom DW, Alibhai SMH, Sattar S, Krzyzanowska MK, Puts MTE. Geriatric oncology screening tools for CGA-based interventions: results from a phase II study of geriatric assessment and management for older adults with cancer. *J Geriatr Oncol*. 2018;9(6):683-6. doi:10.1016/j.jgo.2018.03.001
68. Petit-Monéger A, Rainfray M, Soubeyran P, Bellera CA, Mathoulin-Pélissier S. Detection of frailty in elderly cancer patients: Improvement of the G8 screening test. *J Geriatr Oncol*. 2016;7(2):99-107. doi:10.1016/j.jgo.2016.01.004
69. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. *J Gerontol A Biol Sci Med Sci*. 2013;68(1):62-7. doi:10.1093/gerona/gls119

**Appendix 1a.** Quality assessment, based on the Newcastle-Ottawa Scale.

<b>Selection</b>	1. Representativeness of the exposed cohort	+ truly representative of the average older cancer patient + somewhat representative of the average older cancer patient - selected group of users ? no description of the derivation of the cohort
	2. Ascertainment of exposure	+ G8 taken in all patients - G8 not taken in all patients (> 10% missings)
	3. Demonstration that outcomes of interest (comparison G8 with GA and/or clinical outcomes) were not present at start of study	+ yes - no
<b>Outcome</b>	1. Assessment of outcome (comparison G8 with GA and/or clinical outcomes)	+ clear description of method of assessment* - unclear description of method of assessment ? no description
	2. Was follow-up long enough for outcome to occur? Comparison G8 with GA: always Chemotherapy toxicity: end of treatment Postoperative morbidity: 30 days Treatment completion: end of treatment Survival: 6 months <sup>†</sup> Health care utilisation: 30 days Physical functioning/quality of life: 3 months	+ yes - no ? not mentioned
	3. Adequacy of follow-up of cohorts <sup>†</sup>	+ complete follow-up: all subjects accounted for + subjects lost to follow-up unlikely to introduce bias: loss to follow-up less than 10% - follow-up rate less than 90% ? no statement

GA= geriatric assessment

\* It was judged that survival data with a follow-up time shorter than 6 months, excluding treatment-related mortality, were not relevant to clinical practice

<sup>†</sup> Comparison G8 with GA as outcome of interest: clearly defined which domains of GA were evaluated and/or which questionnaire were used

**Appendix 1b.** Quality assessment of included studies.

Publication	Selection		Outcome			
Author	Representativeness of exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Agemi <sup>19</sup>	+	+	+	+	?	?
Aparicio <sup>20</sup>	+	+	+	+	+	+
Aydin <sup>21</sup>	+	+	+	+	?	?
Baitar <sup>22,23</sup>	+	+	+	+	+	+
Bellera <sup>9</sup>	+	+	+	+	+	+
Bellera <sup>27</sup>	+	+	+	+	+	-
Bonomo <sup>24</sup>	+	+	+	+	+	?
Bononi <sup>25</sup>	+	+	+	+	?	?
Boulahssass <sup>26</sup>	+	+	+	+	+	+
Cvetkovic <sup>28</sup>	+	+	+	+	?	?
Decoster <sup>29</sup>	+	+	+	+	+	-
Decoster <sup>30</sup>	+	+	+	+	?	?
Denewet <sup>31</sup>	+	+	+	+	+	?
Dimopoulos <sup>32</sup>	+	+	+	+	?	?
Dubruille <sup>34</sup>	+	+	+	+	+	+
Dubruille <sup>33</sup>	+	+	+	+	+	?
Fagard <sup>35</sup>	+	+	+	+	+	+
Gangopadhyay <sup>36</sup>	+	+	+	+	?	?
Hamaker <sup>37</sup>	+	+	+	+	+	?
Hentschel <sup>38</sup>	+	-	+	+	+	+
Holmes <sup>39</sup>	+	+	+	+	+	+
Kaibori <sup>40</sup>	+	+	+	+	+	+
Kenig <sup>41</sup>	+	+	+	+	+	+
Kenis <sup>12,42</sup>	+	+	+	+	+	-
Kim <sup>43</sup>	+	+	+	+	+	+
Martinez-Tapia <sup>44,45</sup>	+	+	+	+	+	+
Matsushita <sup>46</sup>	+	+	+	+	+	?
Middelburg <sup>47</sup>	+	+	+	+	?	+
Molina-Garrido <sup>48</sup>	+	+	+	+	+	?
Neve <sup>49</sup>	+	+	+	+	?	?
Ogawa <sup>50</sup>	+	+	+	-	+	+

*Continue*

*Continued*

Publication	Selection		Outcome			
	Representativeness of exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Osborne <sup>51</sup>	+	+	+	+	+	+
Osorio <sup>52</sup>	+	+	+	+	?	?
Pamoukdjian <sup>53</sup>	+	+	+	+	+	+
Pottel <sup>54</sup>	+	+	+	+	+	-
Pottel <sup>55</sup>	+	+	+	+	+	+
Runzer-Colmenares <sup>56</sup>	+	+	+	+	+	?
Schulkes <sup>57</sup>	+	+	+	+	+	?
Silvestri <sup>58,59</sup>	+	+	+	+	?	?
Smets <sup>60</sup>	+	+	+	+	+	?
Soubeyran <sup>11,68</sup>	+	+	+	+	+	+
Souwer <sup>61</sup>	+	+	+	+	+	+
Stauder <sup>62</sup>	+	+	+	+	?	?
Stokoe <sup>18</sup>	+	-	+	+	?	?
Takahashi <sup>63</sup>	+	+	+	+	?	+
Velghe <sup>64</sup>	+	+	+	+	+	+
Von Saint-George <sup>65</sup>	+	+	+	+	+	+
Wildiers <sup>66</sup>	+	+	+	+	+	+
Yokom <sup>67</sup>	+	+	+	+	+	+







# Chapter 4

## Development of a self-reported version of the G8 screening tool

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## **ABSTRACT**

### **Introduction**

The G8 is a widely used frailty screening tool in patients with cancer that was designed to be completed by healthcare professionals. A patient-reported version would enable a broader application. Aim of this study was to develop a self-reported version of the G8 and to assess its agreement with the original G8.

### **Methods**

A self-reported version of the G8 was developed with the aid of communication specialists. Patients aged  $\geq 70$  years from two different study populations were included: 1. Patients with cancer and 2. Patients visiting the geriatric outpatient clinic. The original G8 was completed by an oncology nurse or clinical research assistant and patients completed the self-reported G8. Patients were blinded to results of the original G8. Kappas were calculated to measure the agreement between the self-reported and original G8 for both the individual items as well as for the cut-off for potential frailty ( $\leq 14$ ).

### **Results**

161 patients participated, of whom 104 had cancer (65%). Patients with cancer more frequently completed all items than geriatric patients (all items completed in 94% versus 72%,  $p < 0.001$ ). The agreement for potential frailty was substantial for patients with cancer (Kappa 0.63) and poor for geriatric patients (Kappa 0.05).

### **Conclusion**

Completion of the self-reported G8 is feasible and agreement of its outcome with the original G8 outcome is sufficient for patients with cancer but not for geriatric patients. The self-reported G8 may therefore be a useful alternative to the original G8 in older patients with cancer.

## INTRODUCTION

The G8 screening tool was developed to screen for the presence of frailty in older patients with cancer.<sup>1</sup> It is derived from the mini-nutritional assessment (MNA) and was designed to be completed by oncology nurses, clinical research assistants or physicians. The ONCODAGE prospective cohort study validated the G8.<sup>2</sup> This French multicenter study evaluated the G8 in 1435 older patients receiving first-line treatment for various cancers; median age was 78 years and more than half of the patients had breast cancer. Kappas for agreement between the G8 individual item scores and scores from the corresponding items on the MNA varied from 0.96 for age to 0.36 for neuropsychological problems. The Kappa for abnormal outcome was 0.65.

Two systematic reviews on frailty screening tools in this patient population have concluded that the G8 is one of the most sensitive and robust tools currently available.<sup>3,4</sup> Moreover, a recent review summarizing all available evidence for the G8 shows that the G8 is not only a useful tool to identify potentially frail patients who require a geriatric assessment (GA), but that, despite heterogeneity in tumour type, treatment and settings, its outcomes are associated with mortality and course of treatment as well.<sup>5</sup> This is a remarkable finding for a screening tool as short and simple to administer as the G8, which consists of eight questions and takes less than five minutes to complete.

The use of frailty screening tools in routine oncology practice is suboptimal, despite recommendations from multiple guidelines. A recent study analysed barriers to the implementation of the G8 in clinical practice and found, among others, that nurses and oncologists believe other tasks are of higher priority than administering the G8.<sup>6</sup> A patient-reported version of the G8 could overcome this issue and could also facilitate a more widespread use of this tool because patients are increasingly being asked to complete health-related questionnaires at home. A patient-reported G8 could provide valuable baseline and longitudinal data on the impact of cancer treatment on a patient's functional status. Therefore, the aim of this study was to develop a self-reported version of the G8 and to assess its agreement with the original G8.

## METHODS

A self-reported version of the original G8 was developed in Dutch language with the aid of communication specialists (Appendix 1a and 1b, self-reported G8 shown in English).

Patients aged 70 years and older from two different study populations were included to assess agreement between the newly developed self-reported G8 and the original G8. The first cohort consisted of consecutive patients diagnosed with cancer seen at the outpatient

clinic of two large teaching hospitals in the Netherlands, the Diaconessenhuis in Utrecht and the Haga Hospital in The Hague. For these patients, the original G8 was already part of routine care at intake and administered by oncology nurses or a clinical research assistant trained for the tool completion. The self-reported version was completed at a subsequent visit to the out-patient clinic. Patients were blinded to results of the original G8. Completion of both screening tools was always prior to the start of cancer treatment and time span between both questionnaires was never more than four weeks. To assess the agreement among frail older patients as well, the second cohort consisted of consecutive general geriatric patients visiting the diagnostic day centre at the department of geriatric medicine of the Diaconessenhuis. While the G8 is not routinely administered in this patient population, the MNA short-form (MNA-SF) is part of routine care and is completed for all new patients. Only the G8 item self-rated health is not part of the MNA-SF and could not be extracted for these geriatric patients. To allow us to assess agreement of geriatric patients' cut-off scores for potential frailty on both questionnaires, their answer to this item on the self-reported G8 was used to calculate their cut-off score for the original G8.

All patients signed informed consent before completing the self-reported version of the G8 while waiting for the doctor's appointment; help from family members was permitted if needed. Patients were excluded in case of insufficient understanding of the Dutch language.

The medical ethics committee reviewed the research protocol and provided a written statement that this study was exempt from full ethical review.

### **Statistical analysis**

For all items of the original G8 we calculated the number of patients from the total group who did not achieve the maximum number of points and referred to this as "suboptimal score". Feasibility of the self-reported G8 was assessed based on missing values for the items.

The agreement between the original and self-reported G8 was tested using the Kappa agreement statistic<sup>7</sup> and using percentages of identical scores. The agreement was assessed for the total group and for the oncological and geriatric patients separately. Kappas and 95% confidence intervals were calculated for all individual items (except for the item self-rated health for geriatric patients) as well as for the cut-off for potential frailty of both tools ( $\leq 14$ ).<sup>1</sup> Kappa values were interpreted as follows: Kappa  $\leq 0.20$ , poor agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81-1.00, almost perfect agreement.<sup>8</sup> Kappas were also compared to the scores derived from the ONCODAGE study.<sup>2</sup> In case of missing values for

any of the items, the score for the cut-off potential frailty was only calculated if the missing item could not change this outcome (i.e. from fit to potentially frail and vice versa).

For all items of the original G8 except for the item self-assessed health we calculated the number of patients from the total group who did not achieve the maximum number of points (referred to as suboptimal score).

All analyses were performed in SPSS Statistics version 24.0.

## RESULTS

4

A cohort of 161 patients was included of whom 65% were patients with cancer (n= 104) and the remaining were geriatric patients who visited the diagnostic day centre (35%; n= 57). Patients with cancer were included between August 2017 and April 2019 and geriatric patients between July 2017 and August 2017. Of all patients, 42% were aged 80 years or older (n= 68); geriatric patients were more frequently  $\geq 80$  years of age than those with cancer (68% versus 28% respectively,  $p < 0.001$ ). 34% of all patients were male (n= 54). No patients were excluded due to a language barrier.

Of the patients with cancer, 45 were diagnosed with breast cancer (43%), 26 with colorectal cancer (25%), 20 with lung cancer (19%), 6 with prostate cancer (6%), 6 with non-Hodgkin lymphoma (6%) and 1 with gastric cancer (1%). For the geriatric patients, reasons to attend the geriatric day centre included cognitive screening (n= 39; 68%), fall analysis or walking disorder (n= 15; 26%), malaise (n= 6; 11%) and other (n= 1; 2%). Multiple reasons were possible per patient.

For the total group, the original G8 total score ranged from 5 to 17, with a median of 13; 67% of patients was potentially frail (score  $\leq 14$ ). Regarding the individual items of the original G8, suboptimal scores were most common for the items self-rated health and medication use (suboptimal scores in 73% and 63% respectively), were moderately common for the items age, body mass index, weight loss and appetite changes (suboptimal scores in 42%, 37%, 34% and 27% respectively) and unusual for the item mobility (suboptimal score in 6%). The median of the self-reported G8 was 13.5 (range 7 – 17) with 69% of patients having a score of 14 or lower. For 5 patients, the cut-off score for potential frailty could not be calculated due to the fact that the patients would change from fit to potentially frail depending on the answer to missing items.

The oncologic cohort was significantly fitter than the geriatric cohort. Using the original G8, 60% was potentially frail versus 86% of the geriatric patients; for the self-reported G8 this was 60% and 91% respectively, both  $p < 0.001$ ).

**Feasibility**

Feasibility was generally good except for the question on neuropsychological problems (missing  $n=6$ , 4%) and on length and weight (missing  $n=11$ , 7%, Table 1). Three patients did not complete the item self-reported health (2%). In addition, for both weight loss and medication use there was one missing (1%).

Patients with cancer more frequently completed all items than geriatric patients (94% versus 72%,  $p < 0.001$ ). Patients with a score  $\leq 14$  on the original G8 less frequently completed the self-reported G8 compared to patients with a normal score on the original G8 (85% versus 98%,  $p = 0.02$ ).

**Reproducibility**

When investigating the agreement between the original and self-reported G8 for all patients, agreement varied between fair for neuropsychological problems (Kappa 0.35) and almost perfect for age (Kappa 0.96, Table 1). The agreement for potential frailty (score  $\leq 14$ ) was moderate (Kappa 0.56). Percentages of identical scores ranged from 73% for appetite changes and weight loss to 98% for patient's age. 68% of the total scores differed  $\leq 1$  point.

For patients with cancer, the agreement between both tools for the individual items was better than for the total group: the item neuropsychological problems was the only one with fair agreement (Kappa 0.36). Agreement for medication use and self-rated health were moderate (Kappas of 0.50 and 0.46 respectively), while the other items' agreement ranged between substantial and almost perfect (Table 1). Kappa for potential frailty was 0.63. Identical scores ranged from 61% for self-rated health to 98% for mobility. 71% of the total scores varied  $\leq 1$  point. Compared to the ONCODAGE cohort, four items had higher Kappa (appetite changes, weight loss, mobility, and self-rated health), three had lower Kappa (body mass index, medication use, and age) and for one item Kappas were identical (neuropsychological problems, Table 1).

When focusing on geriatric patients, the agreement between both instruments was poor; only Kappas for medication use and age were  $> 0.40$ . For geriatric patients, Kappa for potential frailty was 0.05. Percentages of identical scores ranged from 56% for weight loss and appetite changes to 100% for age and 61% of the total scores differed  $\leq 1$  point.

**DISCUSSION**

This study in 161 older patients with and without a cancer diagnosis measured the agreement between the original G8 completed by a healthcare professional and a newly developed, patient-reported version of the G8. Kappa for potential frailty (score  $\leq 14$ ) on



**Table 1.** Reproducibility of the self-reported G8 compared to the original G8.

Items (self-reported) G8	Kappas (95% CI) total population (n= 161)	Identical scores total population	Kappas (95% CI) patients with cancer (n= 104)	Identical scores patients with cancer	Kappas (95% CI) geriatric patients (n= 57)	Identical scores geriatric patients	Kappas (95% CI) ONCODAGE cohort (n= 1429)
Appetite changes Missing	0.45 (0.31;0.58) 0	73%	0.62 (0.47;0.77) 0	83%	0.16 (-0.08;0.40) 0	56%	0.56 (0.52;0.61)
Weight loss Missing	0.53 (0.42;0.64) 1	73%	0.69 (0.56;0.81) 1	83%	0.22 (0.04;0.41) 0	56%	0.65 (0.61;0.68)
Mobility Missing	0.53 (0.29;0.77) 0	93%	0.83 (0.59;1.06) 0	98%	0.25 (-0.07;0.57) 0	84%	0.56 (0.51;0.61)
Neuropsychological problems Missing	0.35 (0.20;0.50) 6	76%	0.36 (0.12;0.59) 3	86%	0.19 (-0.04;0.42) 3	57%	0.36 (0.31;0.41)
Body mass index Missing	0.56 (0.42;0.69) 11	81%	0.65 (0.49;0.81) 2	85%	0.39 (0.17;0.61) 9	71%	0.81 (0.77;0.84)
Medication Missing	0.60 (0.47;0.72) 1	80%	0.50 (0.34;0.67) 0	75%	0.75 (0.57;0.93) 1	89%	0.74 (0.70;0.78)
Self-rated health* Missing	NA 0	NA	0.46 (0.33;0.58) 0	61%	NA	NA	0.38 (0.35;0.42)
Patient's age Missing	0.96 (0.92;1.00) 0	98%	0.91 (0.83;0.99) 0	96%	1.0 (1.00;1.00) 0	100%	0.96 (0.95;0.97)
Cut-off potential frailty (score ≤ 14) Missing	0.56 (0.41;0.70) 5	81%	0.63 (0.47;0.78) 3	82%	0.05 (-0.24;0.33) 2	80%	0.65 (0.61;0.70)

For geriatric patients' original G8 total score, answers to the item self-rated health from the self-reported G8 were used.

\* NA = item not available. Geriatric patients filled out the MNA-SF instead of the original G8 and the question concerning self-rated health is not included in this questionnaire.

95% CI = 95% confidence interval.

both instruments was substantial for older patients with cancer and poor for geriatric patients without cancer. Kappas for the individual items were generally better for patients with cancer than for geriatric patients, especially for the items change in appetite, weight loss, mobility and body mass index (all Kappa > 0.6 for patients with cancer). In older patients with cancer, the self-reported G8 could thus provide an alternative to the original G8.

Most of the screening tools or geriatric parameters currently available for the screening of vulnerability in older patients with cancer were designed to be completed by healthcare workers. There are only few studies that compared the agreement of a healthcare provider-completed instrument with that of a patient-completed screening instrument.<sup>9</sup> The ONCODAGE study validated the original G8 in a large population of older patients with cancer and calculated Kappas for the G8 compared to the MNA.<sup>2</sup> Although Kappas obtained in our study are not perfect, they are comparable with Kappas yielded in this study that lead to widespread implementation of the original G8 in clinical practice. The low reproducibility observed for the questions neuropsychological problems and self-rated health was also encountered in the ONCODAGE study.

Beforehand, we expected better agreement for the individual items of the original G8 and the self-reported G8, because most of the original items require input from the patient and/or are objective. However, we found mostly moderate reproducibility for patients with cancer and poor for geriatric patients. One explanation for this could be the interval between administration of the original G8 and the self-reported G8, which could be up to four weeks. It is possible that in this time span age or health status changed or patients received new diagnoses affecting their answers. In addition, for patients with cancer, total scores on both measurements were close to the cut-off for potential frailty of 14 points, making it more likely for small changes to significantly affect overall score. The fact that 71% of total scores for patients with cancer differed  $\leq 1$  point may support this hypothesis. The agreement for some of the items may also have been poor mainly because the majority of patients gave the same answer; high rates of the same score negatively influences the Kappa. For example, the number of identical answers for the item neuropsychological problems in patients with cancer and for the item mobility in the total group were rather high (86% and 97% respectively) while Kappas were only 0.36 and 0.53 respectively. Finally, Kappas can also be influenced by the number of options per item; Kappa values are smaller when there are fewer options per item because of an increased risk of change agreement. The most likely explanation for the difference in reproducibility between cancer patients and geriatric patients is that geriatric patients, who were older, are generally more frail as well and may have reduced cognitive ability affecting their capacity to reliably complete the questions on their own. For these patients, agreement between

the original G8 and self-reported G8 was poor. Hence, other self-reported questionnaires, such as the vulnerable elders survey-13 (VES-13), are possibly a better choice.

Although reproducibility was not perfect, our results indicate that the self-reported G8 can be used in older patients with cancer. Completing the self-reported G8 was feasible for almost all these patients. In addition, comparison of the original and self-reported G8 demonstrated that 82% of these patients had identical outcomes for potential frailty on both questionnaires. Besides being useful in clinical practice as a frailty screening tool for older patients with cancer, the self-reported G8 may also be implemented in scientific research for these patients. Patient-reported outcomes are increasingly being used as primary or secondary (composite) end-points in clinical trials. Adding a short and easy instrument such as the self-reported G8 to other questionnaires may provide valuable baseline data as well as longitudinal data on the impact of cancer treatment on patient's vitality and frailty; aspects generally not taken into account by current large trials.

A strength of our study is that, to our knowledge, we are one of the first to provide a comparison of the reproducibility of two versions of a screening tool, one completed by a healthcare professional and the other by the patient. We assessed the agreement between the two questionnaires in a heterogeneous population, including both geriatric patients as well as patients with different types of tumours. While on the one hand this is a strength, the heterogeneity may also have negatively impacted the validity of the instrument. This study also has some other limitations. Firstly, time span between the original and self-reported G8 was up to four weeks. This may mean that our results underestimate true agreement between both questionnaires. Secondly, the interval between administration of the instruments varied between patients, as the second measurement coincided with a visit to the outpatient clinic. In addition, we assessed feasibility of the self-reported G8 based on missing values, although more factors determine feasibility. Furthermore, we did not capture information on how many patients required caregiver assistance to complete the self-reported G8. Finally, we demonstrated agreement between the self-reported G8 and the original G8, but not with other outcome measures. The association of the self-reported G8 with outcomes like GA, mortality, course of treatment and patient-reported outcomes may be addressed by future research.

## Conclusion

We have developed a self-reported version of G8 that can be used in older patients with cancer but not in geriatric patients. For older patients with cancer, agreement with the original G8 is substantial and the self-reported G8 could be an alternative to the original G8.

## REFERENCES

1. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann. Oncol.* 2012;**23**(8):2166–72. doi:10.1093/annonc/mdr587
2. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. *PLoS One.* 2014;9(12):e115060. doi:10.1371/journal.pone.0115060
3. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol.* 2012;13(10):e437–44. doi:10.1016/S1470-2045(12)70259-0
4. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. *Ann Oncol.* 2015;26(2):288–300. doi:10.1093/annonc/mdu210
5. van Walree IC, Scheepers E, van Huis-Tanja LH, Emmelot-Vonk MH, Bellera C, Soubeyran P, et al. A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. *J. Geriatr. Oncol.* 2019. Epub ahead of print. doi:10.1016/j.jgo.2019.04.016
6. Gulasingam P, Hag R, Mascarenhas Johnson A, Togo E, Moore J, Straus SE, et al. Using Implementation Science to Promote the Use of the G8 Screening Tool in Geriatric Oncology. *J. Am. Geriatr. Soc.* 2019;67(5):898–904. doi:10.1111/jgs.15920
7. Cohen A. A coefficient of agreement for nominal scales. *Educ. Psychol. Meas.* 1960;20:37–46.
8. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.
9. Huhmann MB, Perez V, Alexander DD, Thomas DR. A self-completed nutrition screening tool for community-dwelling older adults with high reliability: a comparison study. *J. Nutr. Health Aging* 2013;**17**:339–44. doi:10.1007/s12603-013-0015-x

**Appendix 1a.** Original G8.

Items	Possible responses (score)
1. Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake
2. Weight loss during the last 3 months?	0 = weight loss > 3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss
3. Mobility?	0 = bed or chair bound 1 = able to get out of bed/chair but does not go out 2 = goes out
4. Neuropsychological problems?	0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems
5. Body mass index (BMI)? (weight in kilograms) / (height in square metres)	0 = BMI <19 1 = BMI 19 to <21 2 = BMI 21 to <23 3 = BMI ≥23
6. Takes more than three prescription drugs per day?	0 = yes 1 = no
7. In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good 0.5 = does not know 1.0 = as good 2.0 = better
8. Age	0 = >85 1 = 80-85 2 = <80
Total score 0-17	Cut-off ≤ 14: potentially frail

**Appendix 1b.** Self-reported G8.

Items	Possible responses (score)
1. This question is about the past 3 months. Did you start eating less during that period?	<input type="checkbox"/> I did not eat less <input type="checkbox"/> I started to eat a little less <input type="checkbox"/> I started to eat much less
2. How much weight have you lost in the last 3 months?	<input type="checkbox"/> I did not lose weight <input type="checkbox"/> I lost between 0 and 2 kg <input type="checkbox"/> I lost 3 kg or more <input type="checkbox"/> I do not know if I have lost weight
3. How well are you moving?	<input type="checkbox"/> I go out independently <input type="checkbox"/> I can get out of my bed or chair myself but I do not go outside myself <input type="checkbox"/> I cannot get out of my bed or chair myself
4. Do you have psychological (mental) problems? Explanation: examples of psychological problems are depression or forgetfulness	<input type="checkbox"/> I do not have psychological problems <input type="checkbox"/> I am a bit forgetful or depressed <input type="checkbox"/> I am seriously forgetful or depressed
5. Do you take any medication?	<input type="checkbox"/> No <input type="checkbox"/> Yes, one to three <input type="checkbox"/> Yes, more than three
6. Do you think you are healthier or less healthy than most people your age?	<input type="checkbox"/> I am less healthy <input type="checkbox"/> I am as healthy <input type="checkbox"/> I am healthier <input type="checkbox"/> I do not know
7. How old are you?	<input type="checkbox"/> I am not yet 80 years old <input type="checkbox"/> I am 80 to 85 years old <input type="checkbox"/> I am 86 years or older
8. How tall are you?	.... centimetre
9. How much do you weigh?	.... kilograms







# PART II

Treatment choices, course of treatment and reasons for guideline non-adherence in older patients with cancer



# Chapter 5

Treatment decision-making in elderly women with  
ovarian cancer: an age-based comparison

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## **ABSTRACT**

### **Objective**

To investigate treatment choices and outcomes in women with ovarian cancer, comparing elderly ( $\geq 75$  years) and younger patients ( $< 75$  years).

### **Methods**

Single-center retrospective analysis of patients diagnosed with ovarian cancer between 2010 and 2015. The initial treatment plan and course of treatment were extracted from medical files.

### **Results**

Of 128 included patients, 34% were aged  $\geq 75$  years. The initial treatment plan consisted of the combination of cytoreductive surgery (CRS) and platinum-based doublet chemotherapy (i.e. standard treatment) in only 10% of the elderly patients with an indication for this treatment. 5% of these patients completed this treatment without adaptations (compared to 85% and 48% respectively in younger patients). 38% of the elderly patients with an indication for CRS and chemotherapy received best supportive care (BSC) only. Patient preference was an important reason to withhold standard treatment. Surgery- and chemotherapy-related complications and hospital admissions did not differ between groups. Median survival was lower in the elderly ( $p = 0.002$ ) and in patients receiving BSC ( $p < 0.001$ ).

### **Conclusion**

Elderly patients were less frequently treated in accordance with the treatment guideline. To select those older patients who may benefit from (adapted) treatment is challenging. Future studies should evaluate determinants associated with treatment completion to improve outcomes in this vulnerable population.

## INTRODUCTION

Ovarian cancer is the leading cause of death from gynecological cancer in the Western world.<sup>1</sup> In the Netherlands, approximately 1300 patients are diagnosed with ovarian cancer every year and 28% are older than 75 years.<sup>2</sup> Due to non-specific symptoms, 80% present with advanced disease.<sup>3</sup>

For early-stage disease, treatment consists of surgery only. The standard treatment of advanced ovarian cancer involves comprehensive cytoreductive surgery (CRS) and six cycles of combination chemotherapy. This treatment can be burdensome, especially for the elderly. Postoperative morbidity and chemotherapy toxicity are often increased in these patients and are associated with higher long-term excess mortality rates.<sup>4,5</sup> In addition, they are more likely to receive adapted treatment compared to younger patients.<sup>6-9</sup>

Nevertheless, the optimal treatment for elderly patients with ovarian cancer is unknown. It is unclear whether they are currently undertreated or if adapted treatment is an appropriate adjustment to a state of increased vulnerability. These patients form a heterogeneous population regarding comorbidity, functional capacity and geriatric syndromes.<sup>10</sup> Many trials on ovarian cancer do not reflect real-life outcomes, because elderly patients and those with comorbidity are often excluded. Although some studies have evaluated treatment regimens specifically in the elderly,<sup>11-17</sup> adequate interpretation of these data also requires knowledge about the morbidity, functional outcomes and mortality of the untreated elderly population. Unfortunately, this information is often unavailable. Moreover, reasons why these patients receive an adapted treatment have not been investigated yet, while knowledge about this decision-making process may influence treatment choices strongly. As a result, many questions regarding the treatment of ovarian cancer in the elderly remain.

To offer physicians some guidance for treatment decision-making, our knowledge regarding present treatment choices and course of treatment in current clinical practice needs to be extended. We therefore aimed to analyze these outcomes in older ( $\geq 75$  years) and younger patients ( $< 75$  years) with newly diagnosed ovarian cancer.

## METHODS

This retrospective cohort study included all women newly diagnosed with ovarian cancer between January 2010 and December 2015 in the Diaconessenhuis in Utrecht, The Netherlands. The National Cancer Registry (NCR) was used to identify cases. This is a nationwide registry that contains information on tumor characteristics and initial treatment from over 95% of newly diagnosed malignancies in the Netherlands.<sup>18</sup> Data

is retrieved from a national pathology database supplemented by data from medical records, collected by trained registry personnel. Follow-up status is available through linkage of the NCR data with municipal population registries.

For all identified cases, patient and tumor characteristics were collected from the medical file. Patient characteristics included: age at diagnosis, living situation and marital status, prior medical history assessed using the Charlson comorbidity index (CCI; a score of  $\geq 1$  indicates the presence of comorbidity influencing ten-year mortality risk),<sup>19</sup> performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, nutritional status documented with the Malnutrition Universal Screening Tool (MUST; a score of  $\geq 1$  indicates a risk of malnutrition), the presence of polypharmacy (use of  $\geq 5$  different medications) and functionality regarding independence in activities of daily living and instrumental activities of daily living (ADL/iADL). Tumor characteristics included: date of oncological diagnosis, FIGO classification, histology and grade.

Subsequently, the initial treatment plan was extracted from the medical file, including type of chemotherapy regimen if any, as well as whether the patient was intended to receive surgery. When patients did not receive any oncologic treatment but only supportive measures, this was defined as receiving best supportive care (BSC). We assessed whether or not the initial treatment plan was discussed in the multidisciplinary cancer team (MDT) meeting. The initial plan was compared to the current Dutch guideline to examine whether there was a deviation from treatment recommended in the guideline.<sup>20</sup> An overview of guideline recommendations can be found in the Appendix. Both neoadjuvant and adjuvant chemotherapy regimens were considered as standard care. Adaptations from guideline-recommended chemotherapy were classified as primary adjustments when changes were made prior to the first treatment cycle. Reasons to deviate from guideline-recommended care were retrieved and subdivided in the following categories: comorbidity, physical condition, age, patient preference and other reasons. Reasons for an adapted chemotherapy regimen and reasons to refrain from surgery were combined.

Next, we evaluated the course of treatment and whether patients received treatment according to their initial treatment plan. For surgery this included whether the patient received surgery, as well as postoperative course and complications. For chemotherapy we determined whether secondary adaptations—consisting of dose reductions, delay in cycles, switch to monotherapy or reduced number of cycles—had occurred. Death unrelated to treatment, stopped treatment because of progressive disease and chemotherapy dose escalation were classified as treatment finished according to initial plan unless other secondary adaptations were implemented. Reasons for secondary treatment adjustments were assessed and classified as patient preference, toxicity, deterioration of physical condition and other reasons.

Follow-up data were retrieved from the records. Mortality was determined using the Municipal Data Registry. Survival time was defined as time from first hospital visit to death from any cause or until the end of follow-up. Length of follow-up was truncated at 48 months.

The medical ethics committee reviewed the research protocol and provided a written statement that this study was exempt from full ethical review given its retrospective nature.

### Statistical analysis

All analyses were performed using SPSS Statistics version 24.0. Patients were divided into two groups according to age: the first group consisted of patients younger than 75 years of age and the second group of patients aged 75 years and older. Patients were also divided into three groups according to received treatment: 1. patients receiving and completing standard treatment, 2. patients receiving adapted treatment, and 3. patients receiving BSC only. For comparisons between groups, the chi-square test was used for nominal and ordinal variables; the ANOVA test was used for continuous variables. Overall survival was estimated using the Kaplan-Meier method with a log-rank analysis. A two-sided  $p$ -value  $< 0.05$  was considered statistically significant.

## RESULTS

### Patient selection and baseline characteristics

Between 2010 and 2015, 132 women were diagnosed with ovarian cancer at the Diaconessenhuis. Four patients were excluded from further analysis because they were treated elsewhere. Therefore, 128 patients were included in this study. Baseline characteristics for patients  $< 75$  years and  $\geq 75$  years are shown in Table 1.

The median age at diagnosis was 67 years (range 31-94); 34% of the patients ( $n=44$ ) were 75 years of age or over. 82% ( $n=105$ ) were diagnosed with FIGO stage IIb-IV. In elderly patients, comorbidity was more prevalent (39% versus 20%;  $p = 0.03$ ) and they were more often ADL or iADL dependent than younger patients (50% versus 5%;  $p < 0.001$ , Table 1). Elderly patients were less frequently discussed in the MDT meeting (64% versus 87%;  $p = 0.002$ ).

### Treatment in younger patients ( $< 75$ years)

Figure 1 shows course of treatment for both younger and elderly patients. According to the guideline, treatment with surgery only was indicated in thirteen younger patients. All these patients received surgery. Peri- or postoperative complications occurred in six patients, including medical infections ( $n=2$ ), surgical infections ( $n=2$ ), perioperative organ

**Table 1.** Patient characteristics per age group.

		<b>All patients (n= 128)</b>	<b>&lt; 75 years (n= 84)</b>	<b>≥ 75 years (n= 44)</b>	<b>p-value**</b>
<b>Median age in years (range)</b>		67 (range 31 – 94)			
<b>Stage of disease</b>	* FIGO I-IIa	23 (18%)	19 (23%)	4 (9%)	0.06
	* FIGO IIB-IV	105 (82%)	65 (77%)	40 (91%)	
<b>Tumor morphology</b>	* Serous	72 (56%)	51 (61%)	21 (48%)	0.16
	* Other	56 (44%)	33 (39%)	23 (52%)	
<b>ECOG score</b>	* 0–1	37 (29%)	29 (35%)	8 (18%)	<b>0.003</b>
	* 2–4	3 (2%)	0 (0%)	3 (7%)	
	* Unknown	88 (69%)	55 (65%)	33 (75%)	
<b>CCI score</b>	* 0	94 (73%)	67 (80%)	27 (61%)	<b>0.03</b>
	* ≥ 1	34 (27%)	17 (20%)	17 (39%)	
<b>Polypharmacy</b>	* No	106 (83%)	75 (89%)	31 (70%)	<b>0.007</b>
	* Yes	22 (17%)	9 (11%)	13 (30%)	
<b>ADL/iADL dependency</b>	* Independent	72 (56%)	55 (65%)	17 (39%)	<b>&lt; 0.001</b>
	* iADL dependent	9 (7%)	1 (1%)	8 (18%)	
	* ADL + iADL dependent	17 (13%)	3 (4%)	14 (32%)	
	* Unknown	30 (23%)	25 (30%)	5 (11%)	
<b>Living situation</b>	* Community-dwelling	112 (88%)	72 (86%)	40 (91%)	0.27
	* Nursing home	3 (2%)	1 (1%)	2 (5%)	
	* Unknown	13 (10%)	11 (13%)	2 (5%)	
<b>Marital status</b>	* Alone	57 (45%)	28 (33%)	29 (66%)	<b>0.001</b>
	* Together	59 (46%)	47 (56%)	12 (27%)	
	* Unknown	12 (9%)	9 (11%)	3 (7%)	
<b>Risk of poor nutrition (MUST)</b>	* No risk	44 (34%)	28 (33%)	16 (36%)	0.87
	* Average/high risk	34 (27%)	21 (25%)	13 (30%)	
	* Unknown	50 (39%)	35 (42%)	15 (34%)	
<b>Patient discussed at MDT meeting</b>	* Yes	101 (79%)	73 (87%)	28 (64%)	<b>0.002</b>
	* No	27 (21%)	11 (13%)	16 (36%)	

\* Bold data indicate  $p$ -value < 0.05.

# Unknown values were not included (eg. were assigned as missing value) when calculating  $p$ -value ADL = Activities of Daily Living; iADL = instrumental Activities of Daily Living; CCI = Charlson Comorbidity Index; ECOG = Eastern Cooperative Oncology Group Scale of Performance Status; FIGO = The International Federation of Gynecology and Obstetrics classification; MDT = multidisciplinary cancer team; MUST = Malnutrition Universal Screening Tool.

injury (n=2), ileus (n=1) and blood loss requiring transfusion (n=1). Some patients had multiple complications.

Tumor characteristics for the remaining 71 patients < 75 years mandated treatment with CRS and (neo)adjuvant combination chemotherapy (Figure 1). 97% (n=69) were referred to the medical oncologist. One patient died before referral and for one patient referral was not effectuated.

In patients with an indication for CRS and chemotherapy, this treatment was chosen in 60 out of 71 patients (85%, Figure 1). Of these patients, 34 (57%) completed treatment



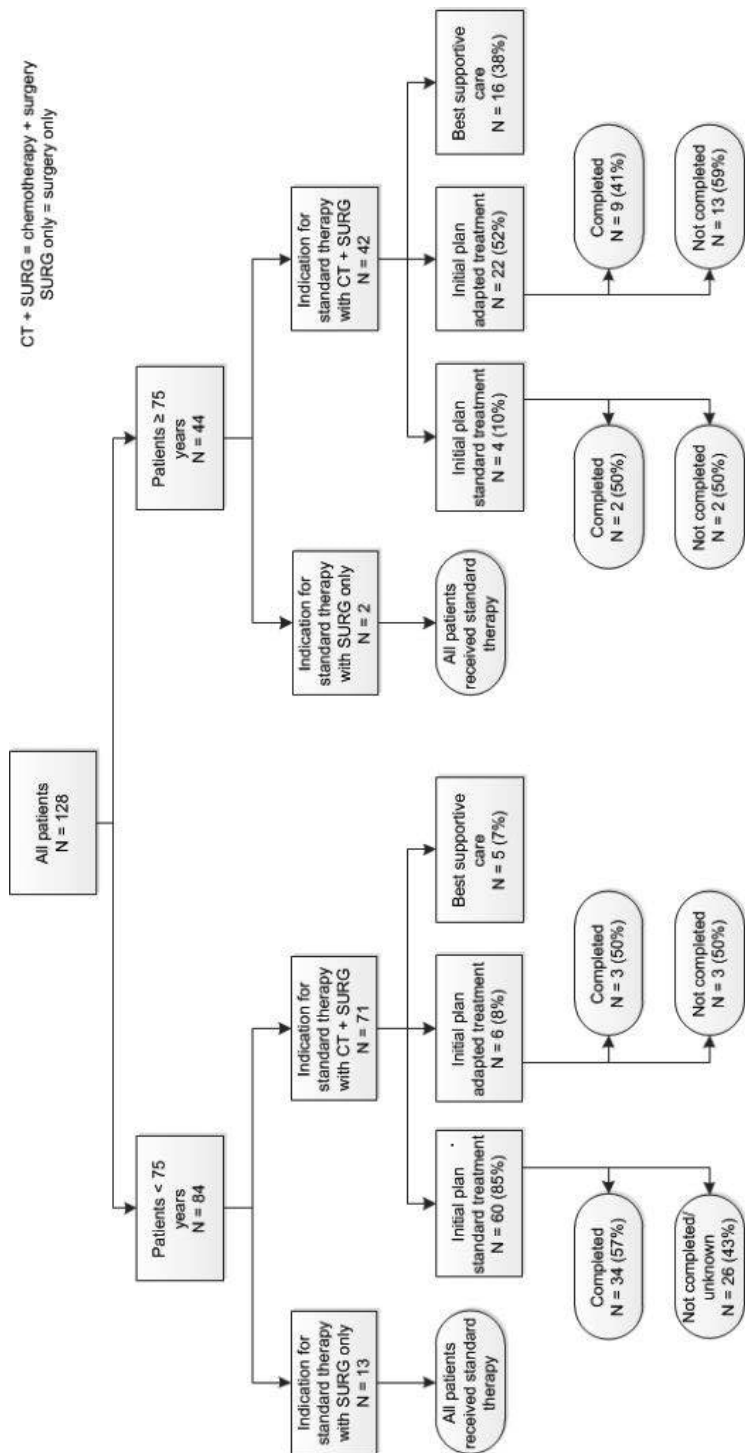


Figure 1. Course of treatment in all patients.

without any adjustments and in 26 patients (43%) secondary treatment adaptations were required (n=19) or course of treatment was partially unknown due to treatment elsewhere (n=7). Of the six patients receiving an adapted initial treatment plan (8%), three completed this plan without secondary adjustments. Five patients (7%) received BSC only.

Reasons for a non-standard treatment plan were mostly patient preference (n=5) and physical condition (n=5, Table 2). The primary reason why the intended treatment was not completed was toxicity (n=17).

Complications of treatment and treatment adaptations for patients with an indication for both CRS and chemotherapy are presented in Table 3. Of the patients receiving chemotherapy, 5% received primary chemotherapy adaptations and secondary adjustments were necessary in 38%. Peri- or postoperative complications occurred in 43% (n=26), including perioperative blood loss requiring blood transfusion (n=12), medical infections (n=9) and postoperative ileus (n=6). Three patients died during treatment. One patient died due to neutropenic sepsis after receiving one cycle of chemotherapy. Two patients suddenly died during treatment without any clear underlying treatment-related cause.

**Table 2.** Reasons for primary or secondary adapted treatment in patients with an indication for both cytoreductive surgery and chemotherapy\*.

	< 75 years (n= 71)	≥ 75 years (n= 42)
<b>Reasons for primary adapted treatment*</b>		
Patient preference	5	13
Physical condition	5	15
Age	0	11
Comorbidity	0	4
Other <sup>#</sup>	3	15
<b>Reasons for secondary adapted treatment*</b>		
Toxicity	17	8
Patient preference	2	4
Deterioration of physical condition	1	5
Other <sup>#</sup>	3	3
<b>Patients who received standard treatment (no reason applicable)</b>	34	2

\* Multiple reasons were possible for each patient. Reasons for adjusted chemotherapy regimen and refraining from CRS were combined and counted once when reasons were the same

<sup>#</sup> Other reasons consisted of prognosis, (new) comorbidity, lung metastases, died before treatment and unclear

**Table 3.** Complications and adaptations of treatment in patients with an indication for both cytoreductive surgery and chemotherapy.

	<b>Total (n= 113)</b>	<b>&lt; 75 years (n= 71)</b>	<b>≥ 75 years (n= 42)</b>	<b>p-value*</b>
<b>Surgery</b>	79 (70%)	61 (86%)	18 (43%)	<b>&lt; 0.001</b>
<i>Type of surgery</i>				
* Primary cytoreductive surgery	45 (57%)	34 (56%)	11 (61%)	
* Interval debulking	34 (43%)	27 (44%)	7 (39%)	0.69
<i>Debulking status</i>				
* Complete or optimal	60 (76%)	47 (77%)	13 (72%)	
* Incomplete	16 (20%)	11 (18%)	5 (28%)	0.45
* Unknown	3 (4%)	3 (5%)	0 (0%)	
<i>Complications of surgery</i>	34 (43%)	26 (43%)	8 (44%)	0.93
<b>Chemotherapy*</b>	80 (75%) <sup>#</sup>	58 (89%) <sup>#</sup>	22 (52%)	<b>&lt; 0.001</b>
<i>Primary chemotherapy adaptations</i>	22 (28%)	3 (5%)	19 (86%)	<b>&lt; 0.001</b>
* Primary dose reduction	16 (20%)	1 (2%)	15 (68%)	<b>&lt; 0.001</b>
* Monotherapy carboplatin	17 (21%)	3 (5%)	14 (64%)	<b>&lt; 0.001</b>
<i>Secondary chemotherapy adaptations</i>	36 (45%)	22 (38%)	14 (64%)	<b>0.04</b>
* Secondary dose reduction	18 (23%)	11 (19%)	7 (32%)	0.22
* Switch to monotherapy	5 (6%)	3 (5%)	2 (9%)	0.52
* Reduced number of cycles	13 (16%)	5 (9%)	8 (36%)	<b>0.003</b>
* Delay between cycles	22 (28%)	13 (22%)	9 (41%)	0.10
<b>Best supportive care only</b>	21 (19%)	5 (7%)	16 (38%)	<b>&lt; 0.001</b>
<i>Complications of chemotherapy requiring secondary adaptations</i>	25 (31%)	17 (29%)	8 (36%)	0.54
<i>Unforeseen hospital admissions during chemotherapy</i>	16 (20%)	12 (21%)	4 (18%)	0.83

\* Bold data indicate p-value &lt; 0.05.

<sup>#</sup> 6 younger patients in whom course of chemotherapy was (partly) unknown were excluded from this analysis

Ultimately, received treatment in younger patients with an indication for both CRS and chemotherapy consisted of standard treatment in 48% (n=34), adapted treatment in 35% (n=25), BSC in 7% (n=5) and unknown in 10% (n=7).

### Treatment in elderly patients (≥ 75 years)

According to the guideline, treatment with surgery only was indicated in only two patients (Figure 1). Both had successful surgery and did not experience any complications.

In the remaining 42 patients, the guideline mandated treatment with CRS and (neo) adjuvant combination chemotherapy. Only 29 patients (69%) were referred to the medical oncologist. In ten out of 42 patients (24%) the MDT or treating physician decided that no chemotherapy was to be offered. Three patients were not referred despite this being recommended in the MDT meeting (reason unknown). Six older patients (14%) underwent a specific geriatric evaluation as part of the work-up for treatment. Another seven had been seen by a geriatrician in the year prior to treatment but did not undergo a specific pre-treatment geriatric oncology evaluation.

Treatment in accordance with the guideline was selected in only four out of 42 patients (10%, Figure 1), of which two completed this treatment without adjustments. Of the 22 patients (52%) with an adapted initial treatment plan, 9 completed this plan without further adaptations. The remaining thirteen patients required secondary adjustments. Sixteen elderly patients received BSC only (38%).

Main reasons for primary adjustments to the treatment plan were physical condition (n=15), patient preference (n=13) and age (n=11, Table 2). Most important reasons why patients did not complete the initial treatment plan were toxicity (n=8), deterioration of physical condition (n=5) and patient preference (n=4). One patient died during treatment because of abdominal sepsis due to complications of surgery.

Primary adaptations in chemotherapy were implemented in 86% of the patients and 64% required secondary adjustments (Table 3). Peri- or postoperative complications occurred in eight patients (44%); perioperative blood loss requiring blood transfusion (n=5) and medical infections (n=4) were the most common.

The final received treatment in elderly patients with an indication for both CRS and chemotherapy consisted of adapted treatment in 57% (n=24), BSC in 38% (n=16) and standard treatment in 5% (n=2).

### **Comparison of treatment strategy and complications according to age group**

Elderly patients were referred to a medical oncologist significantly less often compared to younger patients (69% and 97% respectively;  $p < 0.001$ ). Elderly women did not receive NACT more frequently than younger women (39% and 44% respectively;  $p = 0.69$ ). Primary adjustments in chemotherapy were significantly more frequent in elderly patients compared to younger patients, both for dose reduction (68% versus 2%;  $p < 0.001$ ) and for receiving carboplatin monotherapy (64% versus 5%;  $p < 0.001$ , Table 2). In addition, they received BSC as primary treatment more frequently than younger patients (38% versus 7%;  $p < 0.001$ ). Regarding secondary adaptations, discontinuation rates were significantly higher in elderly women (36% versus 9%;  $p = 0.003$ ).

Unforeseen hospital admissions were present in sixteen (20%) of the 80 patients who received chemotherapy; in 21% of younger patients and in 18% of older patients ( $p = 0.83$ ). Primary reasons for hospital admissions, regardless of age, were infections (n=6) and gastrointestinal problems (n=4).

### **Overall survival**

Median survival in patients with an indication for CRS and chemotherapy was 5.5 months (95% confidence interval (CI) 0.0-16.6) for elderly patients, significantly shorter than in

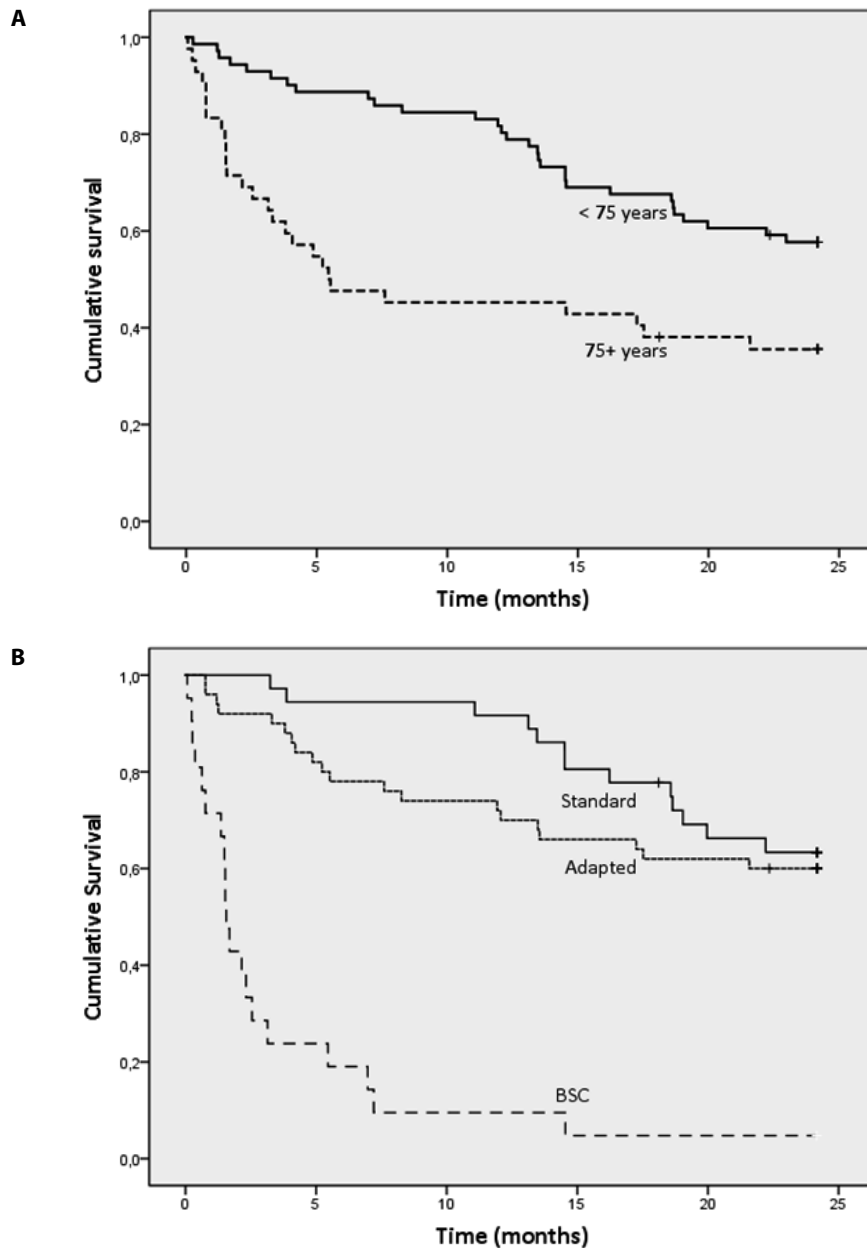
younger patients, where median survival was not reached ( $p = 0.002$ ; Figure 2a). Median survival was 1.6 months in the BSC group (95% CI 1.3-1.8), versus not reached in patients receiving standard or adapted treatment ( $p < 0.001$ ; Figure 2b). In patients who received standard treatment, median survival was not significantly different from those receiving adapted treatment ( $p = 0.80$ ). Analyses stratified according to age group did not show significant survival differences in patients receiving standard or adapted treatment either (data not shown).

## DISCUSSION

In this study of 128 patients with newly diagnosed ovarian cancer, we compared treatment decisions and course of treatment in younger ( $< 75$  years) and elderly ( $\geq 75$  years) patients. Ultimately, only two out of 42 (5%) elderly patients eligible for standard treatment, consisting of CRS with combination chemotherapy based on the current national treatment guideline, received and completed this treatment without any adaptations. In contrast, 34 out of 71 (48%) younger patients completed this treatment without any adjustments. In elderly patients, both an adapted initial treatment plan and BSC were chosen significantly more often (in 52% and 38%) than in younger patients (8% and 7%). Chemotherapy- and surgery-related complication rates and unforeseen hospital admission rates were similar for both age groups. Not surprisingly, overall survival was worse in elderly patients and in those receiving BSC, while there was no difference in survival of patients receiving standard or adapted treatment.

Others have evaluated chemotherapy treatment patterns comparing younger and elderly women with ovarian cancer and their results are in line with our findings. They report that older patients receive standard treatment less frequently,<sup>8,14,21</sup> are less likely to complete treatment<sup>11-14</sup> and more commonly experience treatment-related morbidity.<sup>4,5</sup> In contrast to our study, none of these investigations evaluated the reasons for an initially adapted treatment regimen.

Our results demonstrated that patient preference was an important reason to withhold standard treatment in elderly patients. In a survey among 93 oncologists on chemotherapy decision-making in older cancer patients, patient preference was one of the most influential factors.<sup>22</sup> Patient preference concerning treatment options is mainly based on the information provided by the treating physician and patients' choice of treatment depends largely on their physicians' recommendation.<sup>23</sup> Patients thus need to be extensively informed about the completion and complication rates of treatment of ovarian cancer in current practice to make an informed and shared decision. However, our study shows that the elderly were less frequently referred to a medical oncologist. Hence, they may have received insufficient information to make an informed decision. In prior



**Figure 2 (A).** Kaplan-Meier plot of overall survival in patients with advanced stage disease with an indication for both cytoreductive surgery and chemotherapy ( $n = 113$ ) aged younger than 75 years and 75 years or older. Time in months after diagnosis. **(B)** Kaplan-Meier plot of overall survival in patients with advanced stage disease with an indication for both cytoreductive surgery and chemotherapy ( $n = 107^*$ ) in patients who did receive and completed standard treatment compared to those who received adapted treatment or who received best supportive care (BSC). Time in months after diagnosis.

research addressing the patients' experience regarding the oncologic treatment decision-making process, patients with ovarian cancer did not describe this as shared, but instead described an interaction that was directed mainly by the physician.<sup>24</sup> Since the perception of decisional control is associated with a greater patient satisfaction and better quality of life<sup>25,26</sup> and patients want to be involved in treatment decisions,<sup>27,28</sup> shared decision-making should be strived for as much as possible.

Unexpectedly, we found no survival advantage in patients receiving standard treatment compared to those receiving adapted treatment. We hypothesized that this finding might be explained by poor survival only in older patients. However, survival for younger patients receiving standard or adapted treatment was also not statistically different. Potentially, this lack of benefit could be due to sample size issues.

Most of our patients with an indication for both CRS and chemotherapy received primary and/or secondary treatment adaptations; BSC was selected for nearly one-fifth of all patients and it was the delivered treatment in 38% of the elderly patients. Indeed, a recently performed nation-wide analysis from the Netherlands among older women with advanced stage ovarian cancer demonstrated that, over the last twelve years, the proportion of elderly patients receiving any oncologic treatment has decreased.<sup>29</sup> Whilst our results may suggest an appropriate selection of those older patients unfit for any oncologic treatment, conclusions should be drawn cautiously as chronological age itself was commonly mentioned as a reason to refrain from standard treatment. As a consequence, elderly patients may be at risk for undertreatment. On the other hand, they could be overtreated when receiving standard treatment. As biological age increases and physiologic reserve declines, elderly patients are less likely to complete oncologic treatment and suffer poorer clinical outcomes and more functional decline due to this treatment. For these patients, BSC might be a suitable alternative provided that patient selection is adequately performed.

To avoid basing treatment decisions solely on patients' chronological age and to incorporate patient preference in the decision-making process, a geriatric assessment may be performed. Its use has been recommended by the International Society of Geriatric Oncology and the fifth Ovarian Cancer Consensus Conference.<sup>30,31</sup> It has been successful in uncovering previously unrecognized health issues as well as predicting treatment tolerance and survival both in the general oncologic population,<sup>32</sup> and in patients with ovarian cancer.<sup>15,33</sup> In our MDT meeting, there is currently no geriatrician present and only a minority of the older patients in our cohort underwent a geriatric evaluation as part of their pre-treatment work-up. Incorporating a geriatric assessment in the multidisciplinary decision-making process helps in individualizing the treatment decision-making process and may improve older patients' outcomes. In addition, elderly patients need to be

included in clinical trials and cohorts more frequently and patient-related outcomes, frailty measures or some form of geriatric assessment should be included. Several such trials are currently ongoing,<sup>34,35</sup> aiming to assess the value of geriatric assessment or screening tools in decision-making. Outcomes of these trials may guide the treatment decision-making process in elderly patients with ovarian cancer.

This study has some limitations. Firstly, due to its retrospective design, there is potential bias in data collection. We were not able to capture the nuances and details of what was discussed in the MDT meeting or in the conversation with the treating physician and consequently, could not provide comprehensive information on the treatment decision-making process. In addition, we considered both primary cytoreductive surgery followed by adjuvant chemotherapy as well as NACT as standard of care. Unfortunately, our patient groups were too small to investigate differences in outcomes based on the chosen treatment modality (NACT or primary cytoreductive surgery) according to age. Chemotherapy toxicity could not easily be graded according to standardized measurements such as the National Cancer Institute Common Toxicity Criteria. Therefore, we only included those chemotherapy side effects leading to secondary treatment adaptations. The fact that this is a single-center study with a small sample size may limit generalizability of our results. Despite these weaknesses, our study underscores the complexity of cancer care for elderly patients with ovarian cancer, has identified opportunities for improvements and may provide information on how to counsel elderly patients with ovarian cancer regarding treatment decisions.

## **Conclusion**

Elderly patients with ovarian cancer were less frequently treated in accordance with the current treatment guideline compared to younger patients and commonly received adapted treatment or BSC only. Patient preference was an important reason to refrain from standard treatment in the elderly. However, it was unclear whether these women were sufficiently informed regarding treatment outcomes. To predict which older patients may benefit from oncologic treatment is difficult. A geriatric assessment may support treatment decision-making and future prospective trials evaluating determinants associated with treatment completion are urgently needed to improve outcomes in this vulnerable population.



## REFERENCES

1. Oberaigner W, Minicozzi P, Bielska-Lasota M, et al. Survival for ovarian cancer in Europe: the across-country variation did not shrink in the past decade. *Acta Oncol* 2012; 51: 441–453.
2. Cijfers over kanker. Nederlandse Kankerregistratie [Web site]. Available at: <http://www.cijfersoverkanker.nl>. Accessed April 1, 2017.
3. Prat J. Ovarian, fallopian tube and peritoneal cancer staging: Rationale and explanation of new FIGO staging 2013. *Best Pract. Res. Clin. Obstet. Gynaecol* 2015; 29: 858–869.
4. Mahdi H, Wiechert A, Lockhart D, et al. Impact of Age on 30-Day Mortality and Morbidity in Patients Undergoing Surgery for Ovarian Cancer. *Int. J. Gynecol. Cancer* 2015; 25: 1216–1223.
5. Moore KN, Reid MS, Fonq DN, et al. Ovarian cancer in the octogenarian: Does the paradigm of aggressive cytoreductive surgery and chemotherapy still apply? *Gynecol. Oncol* 2008; 110: 133–139.
6. Giuliani J, Drudi F. Ovarian cancer in elderly patients: a difference in treatment based on age? *Arch. Gynecol. Obstet* 2012; 286: 1545–1548.
7. Ben-Ami I, Vaknin Z, Schneider D, et al. Perioperative morbidity and mortality of gynecological oncologic surgery in elderly women. *Int. J. Gynecol. Cancer* 2006;16: 452–457.
8. Moore KN, Frank SG, Alward EK, et al. Adjuvant chemotherapy for the ‘oldest old’ ovarian cancer patients: can we anticipate toxicity-related treatment failure in a vulnerable population? *Cancer* 2009; 115: 1472–1480.
9. Efstathiou E, Dimopoulos MA, Bozas G, et al. Advanced epithelial ovarian cancer in the elderly: chemotherapy tolerance and outcome. *Anticancer Res* 2007;27: 611–617.
10. Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit. Rev. Oncol. Hematol* 2005;55: 241–252.
11. Sabatier R, Calderon B jr, Lambaudie E, et al. Prognostic factors for ovarian epithelial cancer in the elderly: a case-control study. *Int. J. Gynecol. Cancer* 2015;25: 815–822.
12. Ferrero A, Fuso L, Tripodi E, et al. Ovarian Cancer in Elderly Patients: Patterns of Care and Treatment Outcomes According to Age and Modified Frailty Index. *Int. J. Gynecol. Cancer* 2017;27: 1863–1871.
13. Fourcadier E, Trétarre B, Gras-Aygon C, et al. Under-treatment of elderly patients with ovarian cancer: a population based study. *BMC Cancer* 2015;15: 937.
14. Kievit SB, Smorenburg CH, Hamaker ME, et al. Treatment patterns in elderly women with ovarian cancer: single center experience in the Netherlands. *Eur. J. Gynaecol. Oncol* 2017;38: 680–684.
15. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Ann. Oncol* 2005;16: 1795–1800.

16. Sharma S, Driscoll D, Odunsi K, et al. Safety and efficacy of cytoreductive surgery for epithelial ovarian cancer in elderly and high-risk surgical patients. *Am. J. Obstet. Gynecol* 2005;193: 2077–2082.
17. Hilpert F, du Bois A, Greimel ER, et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged  $\geq 70$  years with advanced ovarian cancer—a study by the AGO OVAR Germany. *Ann. Oncol* 2007;18: 282–287.
18. Cijfers over kanker. Nederlandse Kankerregistratie [Web site]. Available at: <http://www.cijfersoverkanker.nl>. Accessed September 19, 2017.
19. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis* 1987;40: 373–383.
20. Richtlijnen oncologische zorg [Web site]. Available at: <http://www.oncoline.nl/ovariumcarcinoom>. Accessed April 1, 2017.
21. Walters CL, Schneider KE, Whitworth JM, et al. Perioperative Morbidity and Mortality in Octogenarians With Ovarian Cancer. *Int. J. Gynecol. Cancer* 2013;23:1006–1009.
22. Moth EB, Kiely BE, Naganathan V et al. How do oncologists make decisions about chemotherapy for their older patients with cancer? A survey of Australian oncologists. *Support. Care Cancer* 2018;26: 451–460.
23. Puts MT, Tapscott B, Fitch M, et al. A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. *Cancer Treat. Rev* 2015;41: 197–215.
24. Elit L, Charles C, Gold I, et al. Women's perceptions about treatment decision making for ovarian cancer. *Gynecol. Oncol* 2003;88: 89–95.
25. Mandelblatt J, Kreling B, Figueiredo M, et al. What is the impact of shared decision making on treatment and outcomes for older women with breast cancer? *J. Clin. Oncol* 2006;24: 4908–4913.
26. Andersen MR, Sweet E, Lowe KA, et al. Involvement in decision-making about treatment and ovarian cancer survivor quality of life. *Gynecol. Oncol* 2012;124: 465–470.
27. Elkin EB, Kim SH, Casper ES, et al. Desire for information and involvement in treatment decisions: elderly cancer patients' preferences and their physicians' perceptions. *J. Clin. Oncol* 2007;25: 5275–5280.
28. Politi MC, Dizon DS, Frosch DL, et al. Importance of clarifying patients' desired role in shared decision making to match their level of engagement with their preferences. *BMJ* 2013;347: f7066.
29. Schuurman MS, Kruitwagen RFPM, Portielje JEA, et al. Treatment and outcome of elderly patients with advanced stage ovarian cancer: A nationwide analysis. *Gynecol. Oncol* 2018;149: 270–274.
30. McGee J, Bookman M, Harter P, et al. Fifth Ovarian Cancer Consensus Conference: individualized therapy and patient factors. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol* 2017;28: 702–710.
31. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J. Clin. Oncol* 2014;32: 2595–2603.

32. Hamaker ME, Schiphorst AH, ten Bokkel Huinink D, et al. The effect of a geriatric evaluation on treatment decisions for older cancer patients-a systematic review. *Acta Oncol* 2014;53: 289–296.
33. Tinquaut F, Freyer G, Chauvin F, et al. Prognostic factors for overall survival in elderly patients with advanced ovarian cancer treated with chemotherapy: Results of a pooled analysis of three GINECO phase II trials. *Gynecol. Oncol* 2016;143: 22–26.
34. EWOC-1 Trial: carboplatin +/- paclitaxel in vulnerable elderly patients with stage III-IV advanced ovarian cancer (EWOC-1). [Web site]. Available at: <https://clinicaltrials.gov/ct2/show/NCT02001272>. Accessed May 25, 2018.
35. Geriatric screening in the treatment of elderly patients with ovarian carcinoma (GERSOC). [Web site]. Available at: <https://www.zonmw.nl/nl/onderzoek-resultaten/doelmatigheidsonderzoek/programmas/project-detail/doelmatigheidsonderzoek/geriatric-screening-in-the-treatment-of-elderly-patients-with-ovarian-carcinoma-gersoc/>. Accessed May 25, 2018.

**Appendix.** Summary of the Dutch guideline for treatment of women with ovarian cancer according to tumor stage.

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<b>FIGO stage I-IIa*</b>	Surgery only
<b>FIGO stage IIb-IV</b>	CRS in combination with platinum-based doublet chemotherapy <sup>#</sup>

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\*When tumor grading is poor (grade III), the addition of chemotherapy might be considered.

<sup>#</sup>Consisting of six cycles of carboplatin AUC 6 and paclitaxel 175 mg/m<sup>2</sup>.

AUC = Area Under the Curve; CRS = cytoreductive surgery; FIGO = The International Federation of Gynecology and Obstetrics classification.





# Chapter 6

Reasons for guideline non-adherence in older and younger women with advanced stage ovarian cancer

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## **ABSTRACT**

### **Objective**

This study aims to assess the reasons for guideline non-adherence in women with advanced stage ovarian cancer and whether these reasons differ according to age.

### **Methods**

All women diagnosed with advanced stage ovarian cancer, International Federation of Gynecology and Obstetrics (FIGO) IIb-IV, between 2015 and 2018 were selected from the Netherlands Cancer Registry. Treatment patterns and reasons for guideline non-adherence were analyzed according to age groups.

### **Results**

4210 women were included, of whom 34%, 33%, 26%, and 8% were aged <65, 65-75, 75-85, and ≥85 years respectively. With advancing age, less women received guideline-adherent treatment (decreasing from 70% to 2% in women aged <65 and ≥85 years respectively) and more women received best supportive care only (ranging from 4% to 69% in women aged <65 and ≥85 years respectively). The most prevalent reasons for guideline non-adherence differed according to age and included patient preference in older women, and functional status and extent of disease in younger women.

### **Conclusion**

Most older women did not receive guideline-adherent care and patient preference was the most common reason for this decision. This knowledge provides insight in the current treatment decision-making process and highlights the importance of eliciting patient treatment preferences. Further prospective research is necessary to study the underlying motivation for women to decline guideline care and the extent to which shared decision-making influences treatment choice.



## INTRODUCTION

Ovarian cancer affects mostly older women; median age at diagnosis is 63 years and in the Netherlands currently 45% of these women are aged 70 years and older at diagnosis.<sup>1,2</sup> Because of the imminent aging of western societies, the number of older women with ovarian cancer is expected to increase. Compared to their younger counterparts, older women more frequently present with advanced stage disease and have poorer prognosis. For example, almost two-thirds of the women aged  $\geq 75$  and older present with distant cancer compared to 39% of women aged  $< 50$  years and 5-year survival is 16% in these older women compared to 43% in women  $< 50$  years.<sup>3</sup>

Upfront debulking surgery followed by six cycles of platinum-based chemotherapy is the treatment of choice for women with advanced stage disease in whom complete resection appears feasible.<sup>4</sup> Neoadjuvant chemotherapy followed by interval debulking surgery is a good alternative when the likelihood of achieving a complete resection is low or for those with a high perioperative risk profile, both of which are more common in older women.<sup>5</sup>

Nevertheless, many women with ovarian cancer, especially older women, do not receive guideline-adherent treatment.<sup>6-12</sup> Knowledge on age-related differences in treatment patterns and underlying reasons for non-adherence may identify factors to improve insight in the shared decision-making and treatment decision-making process. Currently, few studies have assessed the reasons for guideline non-adherence amongst different age groups.<sup>13-15</sup> This nationwide population-based analysis aims to compare treatment patterns and reasons for guideline non-adherence in women with advanced stage ovarian cancer according to age.

## METHODS

### Data collection

The Netherlands cancer registry (NCR) contains data on tumor and treatment characteristics from over 95% of newly diagnosed malignancies in the Netherlands.<sup>2</sup> Primary source of notification of the NCR is the automated nationwide pathological archive, supplemented by additional sources, such as the national registry of hospital discharge diagnoses and multidisciplinary team reports. After notification, trained registry administrators routinely extract required information on diagnosis, initial treatment, patient- and tumor characteristics in all hospitals in the Netherlands. Since 2015, the NCR records the main reason for withholding oncological treatment and since 2017, reasons for not receiving surgery after chemotherapy or not receiving chemotherapy after debulking are also collected.

**Patient selection**

Between January 2015 and September 2018, all women newly diagnosed with advanced stage epithelial ovarian cancer, including peritoneal and fallopian tube carcinoma, or patients diagnosed with ovarian cancer with an unspecified morphology were extracted from the NCR database. Disease stage was based on pathological stage information, supplemented by clinical stage information if pathological stage was unavailable or unknown.<sup>16</sup> Advanced stage disease was defined as FIGO classification IIB or higher<sup>17</sup> as formulated by the International Federation of Gynecology and Obstetrics (FIGO) staging system 2009. Patients diagnosed on autopsy (n=10) were excluded.

**Data abstraction**

Clinical registry data included patient, tumor and treatment characteristics. Patient characteristics included age at diagnosis, socioeconomic status, and comorbid conditions including the Charlson Comorbidity Index (CCI).<sup>18</sup> 12% (181) Socioeconomic status was based on four-digit postal code of the residence area of the patient, combining aggregated individual fiscal data on the economic value of the home and household incomes and was categorized into low, medium or high.<sup>19</sup> The CCI was only available for the years 2015-2017 because data on comorbidity were not collected in all hospitals for 2018. Tumor characteristics included tumor stage, histologic subtype, morphology and year of diagnosis.

Treatment characteristics included use of multidisciplinary team consultation, initial treatment received and course of treatment. Reported initial treatment was classified as surgery in combination with chemotherapy (irrespective of the order), chemotherapy only, surgical resection only, other oncological treatment (e.g. hormonal treatment or radiotherapy), or best supportive care only. For patients receiving chemotherapy, we extracted type of chemotherapy and whether patients had received  $\geq 3$  cycles or not. This cut-off was chosen because the NCR only records information on the number of cycles of the first course of chemotherapy. In case of neoadjuvant chemotherapy, we had no information on adjuvant chemotherapy post-debulking. Because, according to the National treatment guidelines, three cycles is the standard for neoadjuvant chemotherapy, we decided to use a cut-off of three. We defined guideline-adherent treatment as a combination of debulking surgery and  $\geq 3$  cycles platinum-based doublet chemotherapy.

In the NCR, for women receiving best supportive care only and for women not receiving surgery after primary chemotherapy or not receiving chemotherapy after surgery, the primary reason for these treatment choices is extracted from clinical records by the registry administrators; these are classified as one of nine predefined options: comorbidity, functional status, social context, old age, short life expectancy, patient preference, extensive disease, other, and unknown. Only one reason per person is registered. Since

2015, the NCR started recording the primary reason for choosing best supportive care only; thus, these data were evaluable for the entire study period. From 2017 onwards, the NCR also records the primary reason for not receiving surgery after chemotherapy or not receiving chemotherapy after surgery.

### Statistical analyses

Patients were divided into four age-categories: <65 years, 65-75 years, 75-85 years, and ≥85 years. We used one-way ANOVA for continuous, normally distributed data, the Mann-Whitney U Test for continuous non-normally distributed data, and chi-square tests for categorical variables to describe sociodemographics, clinical characteristics, treatment patterns and reasons for non-standard treatment stratified according to age. All analyses were executed using IBM SPSS Statistics version 23.0. A two-sided P-value of <0.05 was considered statistically significant.

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## RESULTS

### Patient characteristics

Between 1 January 2015 and December 2018, 4210 patients were diagnosed with advanced stage epithelial ovarian cancer or advanced stage ovarian cancer with unspecified morphology in the Netherlands. Mean age at diagnosis was 68.4 years (SD 12.2). Of these patients, 34% were aged <65 years (n=1436), 33% between 65 and 75 years (n=1372), 26% between 75 and 85 years (n=1080) and 8% were older than 85 years (n=322, Table 1). CCI was significantly higher in older patients (CCI ≥3 in 10% vs 2% of patients <65 and ≥85 years,  $p<0.001$ ). Most common comorbidities were cerebrovascular disease (58%), heart disease (28%), and diabetes mellitus (19%), all of which were more prevalent in patients aged ≥85 years (all  $p<0.001$ ). In addition, disease characteristics were less favourable in older women (Table 1). Serous ovarian cancer was the most common histological subtype (70%) and most women had poorly differentiated disease (86%). Of women aged ≥85 years, 10% were not discussed at a multidisciplinary team meeting, compared to 2% in all other age groups ( $p<0.001$ ). In addition, for over half of these women aged ≥85 years (55%) it was unknown whether they were discussed at such a meeting.

### Treatment patterns according to age

Of all 4210 women, 60% received a combination of surgery and chemotherapy (n=2520), 4% received surgery only (n=168), 18% received chemotherapy only (n=735), 1% received other treatment (n=58, for example hormonal therapy or radiotherapy), and 17% received best supportive care only (n=729, Figure 1). Best supportive care only was selected in 4% (n=55), 11% (n=149), 28% (n=304), and 69% of women aged respectively <65, 65-75, 75-85, and ≥85 years ( $p<0.001$ ). Of the women who were not discussed in a multidisciplinary

**Table 1.** Sociodemographic and clinical characteristics of women with advanced stage ovarian cancer stratified by age, N (%).

	<b>Total (n = 4210)</b>	<b>&lt; 65 years (n = 1436)</b>	<b>65-75 years (n = 1372)</b>	<b>75-85 years (n = 1080)</b>	<b>≥ 85 years (n = 322)</b>	<b>P-value</b>
Socioeconomic status						
Low	1269 (30)	440 (31)	381 (28)	339 (31)	109 (34)	0.1
Medium	1672 (40)	542 (38)	570 (42)	433 (40)	127 (39)	
High	1269 (30)	454 (32)	421 (31)	308 (29)	86 (27)	
CCI†						
0	1762 (62)	738 (75)	570 (59)	365 (52)	89 (43)	<b>&lt;0.001</b>
1-2	926 (32)	218 (22)	334 (35)	276 (39)	98 (47)	
≥ 3	174 (6)	24 (2)	61 (6)	68 (10)	21 (10)	
Unknown	354	119	83	105	47	
Type of comorbidity‡						
Heart disease	538 (28)	62 (13)	170 (25)	206 (36)	100 (55)	<b>&lt;0.001</b>
Cerebrovascular disease	1100 (58)	198 (43)	413 (60)	367 (65)	122 (67)	<b>&lt;0.001</b>
Diabetes mellitus	359 (19)	60 (13)	124 (18)	138 (24)	37 (20)	<b>&lt;0.001</b>
Lung disease	281 (15)	75 (16)	99 (15)	91 (16)	16 (9)	0.08
Neurological	309 (16)	57 (12)	107 (16)	106 (19)	39 (21)	<b>&lt;0.01</b>
Gastrointestinal	320 (17)	89 (19)	103 (15)	95 (17)	33 (18)	0.33
Urological disease	105 (6)	20 (4)	32 (5)	38 (7)	15 (8)	0.1
Thrombosis	173 (9)	52 (11)	72 (11)	41 (7)	8 (4)	<b>0.01</b>
Muscular	83 (4)	24 (5)	29 (4)	22 (4)	8 (4)	0.79
Endocrine	265 (14)	70 (15)	99 (15)	73 (13)	23 (13)	0.69
Infectious	22 (1)	4 (1)	5 (1)	12 (2)	1 (1)	0.09
Histologic subtype						
Serous	2927 (70)	1072 (75)	1058 (77)	690 (64)	107 (33)	<b>&lt;0.001</b>
Other	1283 (30)	364 (25)	314 (23)	390 (36)	215 (67)	
FIGO stage at diagnosis						
IIB-IIC	286 (7)	146 (10)	77 (6)	49 (5)	14 (5)	<b>&lt;0.001</b>
IIIA-IIIC	2477 (60)	823 (58)	843 (62)	643 (61)	168 (57)	
IV	1367 (33)	447 (32)	439 (32)	369 (35)	112 (38)	
Unknown	80	20	13	19	28	
Multidisciplinary team meeting						
Yes	2774 (98)	1007 (99)	962 (99)	674 (97)	131 (90)	<b>&lt;0.001</b>
No	59 (2)	8 (1)	14 (1)	22 (3)	15 (10)	
Unknown	1377	421	396	384	176	

Bold data indicate P-value <0.05.

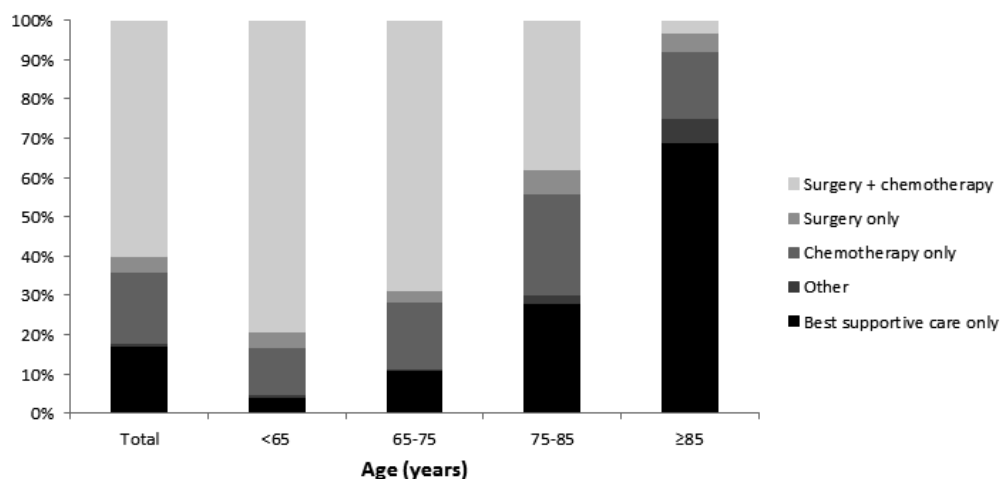
† CCI was available for women diagnosed between 2015 and 2017 (n= 3216).

‡ 1901 women were diagnosed with ≥1 of these specific comorbidities between 2015 and 2017.

CCI = Charlson Comorbidity Index; FIGO = International Federation of Gynecology and Obstetrics.

team meeting, only 22% received a combination of surgery and chemotherapy (13 out of 59) and most received best supportive care only (63%; n= 37).

Detailed treatment characteristics are shown in Table 2. Older women received surgery significantly less frequently than younger women (decreasing from 84% in women aged <65 years to 8% in those ≥85 years,  $p<0.001$ ). Incomplete debulking was more common in older women (26% in women ≥85 years vs 8% in women <65 years,  $p<0.01$ ). Use of chemotherapy decreased with age, ranging from 92% in those aged <65 to 20% among



**Figure 1.** Treatment patterns in women with advanced stage ovarian cancer according to age.

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the oldest group ( $p<0.001$ ). Platinum-doublet chemotherapy was the most common chemotherapy regimen in women up to 85 years of age while carboplatin monotherapy was the most frequently applied regimen in women aged  $\geq 85$  years ( $p<0.001$ ).

Compared to the other age groups, women aged 85 years or older completed  $\geq 3$  chemotherapy cycles significantly less frequently (93% vs 77% of women aged  $<65$  year and  $\geq 85$  years respectively,  $p<0.001$ ). Of all women, 52% received guideline-adherent treatment (i.e. debulking in combination with  $\geq 3$  cycles of platinum-doublet chemotherapy, Table 2). The proportion of women receiving guideline care declined rapidly in women aged  $\geq 75$  years: 70% and 62% of the women  $<65$  and between 65-75 years received optimal treatment, compared to 31% and 2% of the women aged 75-85 and  $\geq 85$  years ( $p<0.001$ ).

### Reasons to choose best supportive care only

Reasons for offering best supportive care only were recorded for 721 out of 729 women. The most frequently mentioned were patient preference (43%) and functional status (28%, Table 3). Patient preference was more commonly recorded as reason in older women (ranging from 24% in those  $<65$  years to 49% in women aged  $\geq 85$  years,  $p<0.01$ ). In contrast, functional status was the most recorded reason in younger women (35% in women aged  $<65$  years), but rates did not differ significantly across age groups ( $p=0.11$ ).

### Reasons for not receiving surgery after primary chemotherapy

Table 4 lists commonly documented reasons for omitting surgery after chemotherapy (these data were only available for women diagnosed in 2017 and 2018). These included extent of disease (40%), particularly in younger women for whom this represented the

**Table 2.** Treatment details for women with advanced stage ovarian cancer stratified by age, N (%).

	<b>Total (n = 4210)</b>	<b>&lt; 65 (n = 1436)</b>	<b>65-75 (n = 1372)</b>	<b>75-85 (n = 1080)</b>	<b>≥ 85 (n = 322)</b>	<b>P-value</b>
Surgery	2688 (64)	1205 (84)	980 (71)	477 (44)	26 (8)	<b>&lt;0.001</b>
Type of surgery						
Primary cytoreductive surgery	856 (32)	450 (37)	268 (27)	127 (27)	11 (42)	<b>&lt;0.001</b>
Interval debulking	1659 (62)	666 (55)	665 (68)	319 (67)	9 (35)	
Other surgery	173 (6)	89 (7)	47 (5)	31 (7)	6 (23)	
Outcome of debulking						
Complete or optimal	2252 (91)	1015 (92)	833 (91)	390 (89)	14 (74)	<b>&lt;0.01</b>
Incomplete	223 (9)	83 (8)	85 (9)	50 (11)	5 (26)	
Debulking outcome unknown	40	18	15	6	1	
Chemotherapy	3255 (77)	1314 (92)	1182 (86)	695 (64)	64 (20)	<b>&lt;0.001</b>
Type of chemotherapy†						
Platinum-doublet	2965 (91)	1277 (97)	1135 (96)	531 (76)	22 (34)	<b>&lt;0.001</b>
Carboplatin monotherapy	259 (8)	17 (1)	37 (3)	163 (24)	42 (66)	
Other	30 (1)	19 (2)	10 (1)	1 (0)	0 (0)	
≥ 3 cycles chemotherapy‡	2897 (91)	1204 (93)	1057 (91)	587 (87)	49 (77)	
Guideline-adherent treatment^	2199 (52)	1008 (70)	849 (62)	335 (31)	7 (2)	<b>&lt;0.001</b>

Bold data indicate P-value <0.05.

† Type of chemotherapy was unknown in one woman.

‡ Of the women who had received chemotherapy. This number was unknown in 59 women.

^ Treatment in accordance with the guideline was defined as debulking surgery in combination with ≥3 cycles of platinum-based doublet chemotherapy.

reason for approximately two-thirds of treatment decisions (68%, compared to 36%, 30%, and 14% in women between 65-75, 75-85, and ≥85 years,  $p < 0.01$ ). Functional status and patient preference were the second and third most common reasons (18% and 17% respectively) of which the latter became more frequent with increased age (7%, 8%, 28%, and 14% in women aged respectively <65, 65-75, 75-85, and ≥85 years,  $p = 0.03$ ).

### Reasons for not receiving chemotherapy after surgery

Reasons for not receiving chemotherapy after surgery were recorded in 70 women of whom only three were aged ≥85 years (Table 5). The most commonly recorded reason was patient preference (34%), and this rate increased with advancing age (18%, 35%, 39%, and 100% in women aged respectively <65, 65-75, 75-85, and ≥85 years,  $p = 0.04$ ).

## DISCUSSION

This population-based study among 4210 women with advanced stage ovarian cancer has analyzed treatment patterns and reasons for guideline non-adherence according to age and finds that, compared to younger women, older women less frequently receive a combination of surgery and chemotherapy and more frequently receive best supportive care only. The main reason for withholding guideline-adherent care in older women is patient preference, while in younger women functional status and extent of disease are the most common reasons.

**Table 3.** Reasons for best supportive care only in 729 women with advanced stage ovarian cancer stratified by age, N (%).

	<b>Total (n = 729)</b>	<b>&lt; 65 years (n = 55)</b>	<b>65-75 years (n = 149)</b>	<b>75-85 years (n = 303)</b>	<b>≥ 85 years (n = 222)</b>
Comorbidity	29 (4)	5 (9)	8 (5)	8 (3)	8 (4)
Functional status	207 (28)	19 (35)	48 (32)	90 (30)	50 (23)
Old age	11 (2)	0 (0)	0 (0)	1 (0)	10 (5)
Short life expectancy	41 (6)	7 (13)	9 (6)	13 (4)	12 (5)
Patient preference	313 (43)	13 (24)	58 (39)	133 (44)	109 (49)
Extensive disease	67 (9)	5 (9)	13 (9)	29 (10)	20 (9)
Other	53 (7)	5 (9)	11 (7)	27 (9)	10 (5)
Unknown	8 (1)	1 (2)	2 (1)	2 (1)	3 (1)

**Table 4.** Reasons for not receiving surgery after primary chemotherapy in 127 women with advanced stage ovarian cancer stratified by age, N (%).

	<b>Total (n = 127)</b>	<b>&lt; 65 years (n = 31)</b>	<b>65-75 years (n = 36)</b>	<b>75-85 years (n = 53)</b>	<b>≥ 85 years (n = 7)</b>
Comorbidity	7 (6)	2 (7)	4 (11)	1 (2)	0 (0)
Functional status	23 (18)	2 (7)	8 (22)	11 (21)	2 (29)
Old age	1 (1)	0 (0)	0 (0)	1 (2)	0 (0)
Short life expectancy	8 (6)	1 (3)	3 (8)	4 (8)	0 (0)
Patient preference	21 (17)	2 (7)	3 (8)	15 (28)	1 (14)
Extensive disease	51 (40)	21 (68)	13 (36)	16 (30)	1 (14)
Other	15 (12)	3 (10)	5 (14)	5 (9)	2 (29)
Unknown	1 (1)	0 (0)	0 (0)	0 (0)	1 (14)

**Table 5.** Reasons for not receiving chemotherapy after surgery in 70 women with advanced stage ovarian cancer stratified by age, N (%).

	<b>Total (n = 70)</b>	<b>&lt; 65 years (n = 22)</b>	<b>65-75 years (n = 17)</b>	<b>75-85 years (n = 28)</b>	<b>≥ 85 years (n = 3)</b>
Comorbidity	1 (1)	1 (5)	0 (0)	0 (0)	0 (0)
Functional status	12 (17)	2 (9)	3 (18)	7 (25)	0 (0)
Old age	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Short life expectancy	5 (7)	2 (9)	2 (12)	1 (4)	0 (0)
Patient preference	24 (34)	4 (18)	6 (35)	11 (39)	3 (100)
Extensive disease	10 (14)	4 (18)	2 (12)	4 (14)	0 (0)
Other	17 (23)	9 (41)	4 (24)	4 (14)	0 (0)
Unknown	1 (1)	0 (0)	0 (0)	1 (4)	0 (0)

Approximately half of the women in our study received treatment in accordance with the National guidelines. This is well in the range of findings from earlier population-based studies in which percentages for guideline-adherent care varied between 24% and 79%.<sup>6–12</sup> Similar to what we have observed, these studies reported a declining rate of guideline adherence with increasing age.<sup>10,11</sup> To our knowledge, we are the first to address treatment patterns specifically in women aged 85 years and older. In our study, best supportive care was much more common in these women (69%) compared to women aged between 75 and 85 years (28%). One prior study did evaluate treatment patterns in women aged  $\geq 80$  years and found that the proportion receiving best supportive care only had increased from 38% between 2002 and 2004 to 50% between 2011 and 2013.<sup>20</sup>

Very few other studies in women with ovarian cancer have investigated reasons to deviate from guideline care and whether these reasons differed according to age.<sup>13–15</sup> A small retrospective single center study found that failure to complete chemotherapy was the most common reason for guideline non-adherent treatment, primarily due to poor tolerance of chemotherapy and comorbidities.<sup>14</sup> Compared to our study, they reported patient preference less frequently as reason to decline adjuvant chemotherapy (34% vs 3% respectively).<sup>14</sup> However, this study did not compare reasons according to age and was performed in a tertiary hospital in the United States. Therefore, differences in study setting and patient characteristics may explain our different results. In agreement with our findings, two smaller studies, both conducted in the Netherlands, found patient preference to be the main reason for withholding oncological treatment in older women and identified functional status as the most common reason in younger women.<sup>13,15</sup>

Many factors may influence older patients' decision to decline standard oncological treatment.<sup>21</sup> Unfortunately, we do not know *why* older women frequently chose this option. A first explanation may be that the information regarding treatment options was different compared to younger women. Perhaps physicians were more hesitant to mention standard treatment to older women because of fear of significant treatment side-effects in these women. A second explanation could be that older patients generally are less willing to undergo burdensome treatment that implies a long recovery period and the potential risk of becoming functional dependent.<sup>22</sup> Younger patients often are more determined to undergo aggressive treatment in exchange for small survival benefit and patient preference may be less frequently recorded as a reason to withhold standard treatment in these women.

Because patient preference concerning treatment options is mainly based on the information provided by the treating physician and patients' treatment choice depends largely on their trust in and recommendation of their physician,<sup>21</sup> an effective patient-physician relationship as well as comprehensive information on possible treatments are



crucial for the patient to make an informed and shared decision. Nevertheless, several studies found that physicians spend less time with and less often involve their older patients in the treatment decision-making process.<sup>23,24</sup> Unfortunately, we do not know the details of the information that was provided to patients in our study. Future prospective studies should evaluate the underlying motivation for younger and older patients to decline guideline care and the extent to which shared decision-making influences treatment choice. Direct observation of interactions within the patient-physician dyad could be helpful in understanding the patterns of shared decision-making and designing interventions to improve shared-decision making.

Another interesting finding of our study is that women aged  $\geq 85$  years were less frequently discussed in a multidisciplinary team meeting. Of the women who were not discussed in a multidisciplinary team meeting, only 22% received a combination of both surgery and chemotherapy. Given the complexity of treatment decisions in this heterogeneous population, a multidisciplinary view on treatment options might be especially relevant for these women. In addition, inclusion of a geriatrician in the multidisciplinary team meeting can be an effective method to improve patient-centered care for older patients with cancer. Currently, the available information at these meetings is mainly disease-oriented and patient-centered information is often lacking. The presence of a geriatrician can help to focus on factors such as comorbidity, remaining functional capacity and resilience as well. These factors are at least as important as disease specific factors in the assessment whether a patient is capable to tolerate treatment.

Strengths of this study include analysis on a nationwide population-based level and a subgroup analysis of women aged 85 years and older. Furthermore, to our knowledge this is the first large study to provide reasons for choosing best supportive care only as well as reasons for not receiving surgery after chemotherapy or not receiving chemotherapy after surgery. Patient preference was the most common reason for guideline non-adherent care in older women. This information provides insight in the current treatment decision-making process and highlights the importance of eliciting patient treatment preferences. Several limitations need to be taken into account when interpreting our results. Firstly, the assessment of reasons to withhold guideline care may be susceptible to interpretation; the administrator only extracted the primary reason for non-guideline treatment, while in real life often a combination of interrelated reasons may play a role in the decision-making process. However, this assessment was performed by trained and experienced administrators and was subject to strict quality control. Indeed, a prior study performed in patients with pancreatic cancer demonstrated that this procedure was reliable.<sup>25</sup> Secondly, because reasons for non-standard treatment were extracted from the medical files, it is likely that some nuances and considerations of the treatment decision-making process discussed during the conversation with the physician or during the multidisciplinary team meeting

may have been missed. Thirdly, patient numbers for reasons not receiving chemotherapy after surgery or not receiving surgery after chemotherapy were small, especially for women aged  $\geq 85$  years old. Therefore, it is difficult to draw firm conclusions from these results. Fourthly, we defined guideline-adherent care as debulking in combination with  $\geq 3$  cycles of platinum-doublet chemotherapy. According to the guideline, a total number of six cycles is defined as the standard number of cycles. Unfortunately, the NCR only registers the number of cycles in the first consecutive period of chemotherapy. Therefore, if a patient received both neoadjuvant and adjuvant chemotherapy, the NCR only records the number of cycles given neoadjuvantly. Finally, given the observational design of our study, information on important patient characteristics, such as educational level, physical functioning, cognitive status, frailty and other geriatric parameters were not available and data on patient-reported outcomes such as quality of life and independence were also lacking. Despite these caveats, our results provide valuable information on age-related differences in current treatment patterns and reasons for guideline non-adherence in women with advanced stage ovarian cancer.

## **Conclusion**

Most older women with advanced stage ovarian cancer do not receive guideline-adherent care and patient preference is the most common reason for this decision, while in younger women functional status and extent of disease are the main reasons for guideline non-adherence. This knowledge provides insight in the current treatment decision-making process and underlines the importance of eliciting patient treatment preferences. Further prospective research should focus on the underlying motivation for women to decline guideline care and the extent to which shared decision-making influences treatment choice.

## REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER\* Explorer. Ovary cancer: recent trends in SEER incidence rates 2000–2016 by age. Available at: <https://seer.cancer.gov/explorer/application.php>. (Accessed: 26th November 2019)
2. Nederlandse Kankerregistratie, beheerd door IKNL. Eierstokkanker: Incidentie en sterfte. Available at: [www.cijfersoverkanker.nl](http://www.cijfersoverkanker.nl). (Accessed: 26th November 2019)
3. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER\* Explorer. Ovary cancer 5-year SEER relative survival rates 2009–2015 by age. Available at: <https://seer.cancer.gov/explorer/application.php>. (Accessed: 26th November 2019)
4. Colombo, N. *et al.* ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumors and recurrent disease†. *Ann. Oncol.* **30**, 672–705 (2019).
5. Wright, A. A. *et al.* Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *J. Clin. Oncol.* **34**, 3460–3473 (2016).
6. Warren, J. L. *et al.* Trends in the receipt of guideline care and survival for women with ovarian cancer: A population-based study. *Gynecol. Oncol.* **145**, 486–492 (2017).
7. Bristow, R. E., Chang, J., Ziogas, A. & Anton-Culver, H. Adherence to Treatment Guidelines for Ovarian Cancer as a Measure of Quality Care. *Obstet. Gynecol.* **121**, 1226–1234 (2013).
8. Lin, J. J., Egorova, N., Franco, R., Prasad-Hayes, M. & Bickell, N. A. Ovarian Cancer Treatment and Survival Trends Among Women Older Than 65 Years of Age in the United States, 1995–2008. *Obstet. Gynecol.* **127**, 81–89 (2016).
9. Harlan, L. C., Clegg, L. X. & Trimble, E. L. Trends in surgery and chemotherapy for women diagnosed with ovarian cancer in the United States. *J. Clin. Oncol.* **21**, 3488–94 (2003).
10. Fourcadier, E. *et al.* Under-treatment of elderly patients with ovarian cancer: a population based study. *BMC Cancer* **15**, 937 (2015).
11. Maas, H. A. A. M., Kruitwagen, R. F. P. M., Lemmens, V. E. P. P., Goey, S. H. & Janssen-Heijnen, M. L. G. The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study. *Gynecol. Oncol.* **97**, 104–109 (2005).
12. Hodeib, M. *et al.* Socioeconomic status as a predictor of adherence to treatment guidelines for early-stage ovarian cancer. *Gynecol. Oncol.* **138**, 121–127 (2015).
13. van Walree, I. C. *et al.* Treatment decision-making in elderly women with ovarian cancer: an age-based comparison. *Int. J. Gynecol. Cancer* **29**, 158–165 (2019).
14. Erickson, B. K., Martin, J. Y., Shah, M. M., Straughn, J. M. & Leath, C. A. Reasons for failure to deliver National Comprehensive Cancer Network (NCCN)-adherent care in the treatment of epithelial ovarian cancer at an NCCN cancer center. *Gynecol. Oncol.* **133**, 142–146 (2014).
15. Zijlstra, M. *et al.* Treatment patterns and associated factors in patients with advanced epithelial ovarian cancer: a population-based study. *Int. J. Gynecol. Cancer* **29**, 1032–1037 (2019).

16. Prat, J. & FIGO Committee on Gynecologic Oncology. Staging Classification for Cancer of the Ovary, Fallopian Tube, and Peritoneum: Abridged Republication of Guidelines From the International Federation of Gynecology and Obstetrics (FIGO). *Obstet. Gynecol.* **126**, 171–4 (2015).
17. Oncoline. Epithelial Ovarian Cancer. Available at: <https://www.oncoline.nl/ovariumcarcinoom>. (Accessed: 7th May 2018)
18. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**, 373–83 (1987).
19. Duin, C. & Keij, I. Sociaal-economische status indicator OP postcode niveau. *Maandstat. van Bevolk.* **50**, 32–5 (2002).
20. Schuurman, M. S. *et al.* Treatment and outcome of elderly patients with advanced stage ovarian cancer: A nationwide analysis. *Gynecol. Oncol.* **149**, 270–274 (2018).
21. Puts, M. T. E. *et al.* A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. *Cancer Treat. Rev.* **41**, 197–215 (2015).
22. Wedding, U., Pientka, L. & Höffken, K. Quality-of-life in elderly patients with cancer: A short review. *Eur. J. Cancer* **43**, 2203–2210 (2007).
23. Keeler, E. B., Solomon, D. H., Beck, J. C., Mendenhall, R. C. & Kane, R. L. Effect of Patient Age on Duration of Medical Encounters With Physicians. *Med. Care* **20**, 1101–1108 (1982).
24. Gaston, C. M. & Mitchell, G. Information giving and decision-making in patients with advanced cancer: a systematic review. *Soc. Sci. Med.* **61**, 2252–64 (2005).
25. Zijlstra, M. *et al.* Patient characteristics and treatment considerations in pancreatic cancer: a population based study in the Netherlands. *Acta Oncol.* **57**, 1185–1191 (2018).





# Chapter 7

## Chemotherapy in the oldest old: choices and outcomes

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## **ABSTRACT**

### **Objective**

Treatment decision-making in older patients with cancer is difficult due to a paucity of data evaluating chemotherapy tolerability in this population. We investigated the feasibility of chemotherapy in the oldest old.

### **Methods**

Single-center retrospective analysis of patients aged  $\geq 80$  years initiating chemotherapy for one of five common solid malignancies or non-Hodgkin lymphoma between 2010 and 2016. Treatment plan and course were extracted from medical files. Primary outcome was whether chemotherapy was completed according to plan, defined as a calculated relative dose intensity (RDI)  $\geq 85\%$ .

### **Results**

104 patients receiving 129 chemotherapy lines were included. Median age at diagnosis was 82 years (range 80-94 years). Most patients (64%) received palliative intent chemotherapy. Primary and secondary chemotherapy adaptations were implemented in 63% and 65% of the cases and hospitalisation occurred in a quarter. 52% of all cases completed chemotherapy according to plan.

### **Conclusion**

Almost half of the chemotherapy regimens started in the oldest old were not completed according to plan, despite frequently implemented upfront adaptations. The decision to start chemotherapy in these patients should be carefully considered. To improve decision-making in current practice, there is a need for the implementation of validated tools assessing chemotherapy feasibility in these patients.



## INTRODUCTION

Cancer is primarily a disease of the older patient<sup>1</sup> and is the second leading cause of death globally.<sup>2</sup> People over the age of 80 constitute one of the fastest growing segments of the general population.<sup>3</sup> Consequently, the number of older patients with cancer is increasing and oncologists will be faced with decision-making regarding chemotherapy for octogenarians more frequently.

Treatment of the oldest old patients with chemotherapy is complex due to significant heterogeneity in physiological reserves, comorbidity, functional capacity, and the presence of geriatric syndromes.<sup>4</sup> Older patients are less likely to receive chemotherapy compared to younger patients.<sup>5–9</sup> Benefits such as increased survival and symptom reduction in order to improve or maintain quality of life should be carefully weighed against chemotherapy-related toxicity and subsequent potential loss of independence. For older patients, quality of life is often of greater importance than prolongation of life.<sup>10</sup> The challenge is to differentiate between the more fit older patients who may benefit from standard treatment and the unfit or frail older patients who may benefit from adapted treatment or best supportive care only. This is a field of active research and optimising the selection procedure is currently a high priority.

The most consistent determinant influencing older patients' decision to accept or decline chemotherapy is their oncologist's recommendation.<sup>11</sup> Therefore, physicians need to be able to optimally inform their patients regarding all aspects of chemotherapy. However, since older patients and those with comorbidity are frequently excluded from clinical trials,<sup>12</sup> scientific data on chemotherapy course and outcomes are lacking for the oldest old. Even in trials specifically designed for older patients, inclusion of patients aged 80+ may be as low as 3%.<sup>13</sup> Consequently, the optimal treatment for octogenarians with an indication for chemotherapy is currently unknown, and often, specific recommendations are lacking in guidelines.

Therefore, we investigated the feasibility and tolerability of chemotherapy in a cohort of patients aged 80 years or older. Primarily, we assessed whether chemotherapy was completed according to plan.

## METHODS

### Study design and population

For this analysis, patients treated between October 2010 and December 2016 were retrospectively selected from the hospital administration data of the Diaconessenhuis Utrecht, a large teaching hospital in the Netherlands. Patients were considered eligible

if they were aged 80 years or older at the start of a new line of chemotherapy for one of five solid cancer types common in the older patient—lung cancer, breast cancer, colorectal cancer, gynecological malignancies, and prostate cancer – or for various types of B-non-Hodgkin lymphoma. Patients with both curative and palliative treatment intent were considered eligible. When a patient received multiple lines of chemotherapy, these lines were analysed separately. Patients were excluded if they only received hormonal or targeted therapy without chemotherapy.

**Data collection: clinical characteristics**

For all selected patients, patient, tumor, and treatment characteristics were collected. Patient characteristics included: date of birth, gender, living situation and marital status, prior medical history (assessed using the Charlson comorbidity index (CCI)),<sup>14</sup> performance status according to the Eastern Cooperative Oncology Group (ECOG) scale,<sup>15</sup> nutritional status documented with the malnutrition universal screening tool (MUST; a score of  $\geq 1$  indicates a risk of malnutrition),<sup>16</sup> the presence of polypharmacy (use of  $\geq 5$  different medications), and functionality regarding independence in activities of daily living and instrumental activities of daily living (ADL/iADL).<sup>17,18</sup> ADL and iADL are routinely assessed during chemotherapy intake. For iADL, questions on shopping, food preparation, housekeeping and medication were available. If one or more of the items was impaired it was scored as ADL and/or iADL dependent. Tumor characteristics included: type of cancer, date of oncological diagnosis, disease stage, and whether it concerned a primary or recurrent tumor.

**Determining initial chemotherapy plan**

Subsequently, data regarding chemotherapy were collected. Type and line of chemotherapy, treatment goal (curative or palliative), and the first and last date of chemotherapy (defined as the last day of the last known cycle or on the day further treatment was cancelled) were recorded. If the same chemotherapy regimen was reintroduced within 3 months after cessation of a treatment, this was considered as the same treatment line. If chemotherapy was interrupted for three months or more, reintroduction of the same chemotherapy regimen was considered as a new treatment line. For each line of chemotherapy, the treatment plan was extracted from the medical file. This plan was compared to the current (Dutch) guidelines to examine if there was a deviation from treatment recommended in the guidelines (Appendix 1a and 1b).

We distinguished two types of guidelines, based on the presence or absence of treatment recommendations specifically for older or unfit patients. We then formulated five groups based on whether the guidelines mentioned treatment recommendations specifically for older or unfit patients, or not (Appendix 1c). If only standard recommendations were available, without any recommendations specifically for older or unfit patients, the

treatment plan was compared with these standard recommendations and the plan could consist of standard treatment or non-guideline based adapted treatment. If a guideline also contained alternative recommendations specifically for those older or unfit, we first evaluated whether the treatment plan was in accordance with the standard guideline recommendations as for younger or fit patients, and if not, whether it was corresponding with the alternative recommendations for older or unfit patients. Those plans neither in accordance with standard or alternative guideline recommendations, were considered as non-guideline based adapted treatment plans. Some guidelines did not mention recommendations in case of recurrent disease and cases for which this was true were excluded from analyses involving the treatment plan.

Adaptations were classified as primary adaptations when changes were made upfront, prior to the first treatment cycle. Possible primary adjustments included dose reductions, changes in chemotherapeutic drug(s) used, omission of targeted therapy (in patients with metastatic colorectal cancer), and sequential instead of concurrent chemoradiation (in patients with lung cancer). Reasons to choose adapted treatment instead of standard or alternative treatment were retrieved from the medical file. Reasons to deviate from guideline-recommended treatment were classified as: comorbidity, physical condition, patient preference, age, lack of expected benefit, or unclear if not recorded.

### **Assessing course of treatment**

Next, we evaluated the course of treatment and whether patients received treatment according to their initial treatment plan. Here, we combined the two groups in which the treatment plan consisted of standard treatment and we also combined the two groups in which the treatment plan consisted of non-guideline based adapted treatment (Appendix 1c). We determined whether secondary adaptations—consisting of dose reductions, delay in cycles, changes in chemotherapeutic drug administered, reduced number of cycles, or increased time interval between each cycle—had occurred. If patients died due to a cause other than treatment-related death, treatment was stopped because of progressive disease, or in case of chemotherapy dose escalation, this was noted as treatment finished according to initial plan unless other secondary adaptations were implemented. Delay in chemotherapy administration was defined as a delay of seven days or more. Reasons for secondary treatment adjustments were assessed and classified as patient preference, toxicity, deterioration of physical condition, other, and unclear. Toxicity was only recorded when it resulted in a secondary adjustment of chemotherapy. Death due to treatment and hospitalisations were also noted. Only unplanned hospital stays of more than 24 hours during chemotherapy were recorded as hospitalisation.

**Outcome measures**

Primary outcome was the percentage of chemotherapy regimens completed according to the treatment plan. To determine whether a case completed chemotherapy according to plan, the relative dose intensity (RDI) was calculated by comparing the planned dose intensity with the dose intensity actually received by the patient. The formula for calculating the RDI is depicted in Figure 1. The RDI takes into account all secondary treatment adjustments. An RDI of 85% or higher was considered as successfully completed treatment according to plan. When combination therapy was administered, RDI was calculated for each drug and the average of those RDI's was used. Secondary objectives included hospitalisation rates and the number of primary and secondary adjustments to chemotherapy.

The medical ethics committee reviewed the research protocol and provided a written statement that this study was exempt from full ethical review given its retrospective nature.

**Statistical analysis**

All analyses were performed in SPSS Statistics version 24.0. P-values smaller than 0.05 were considered statistically significant. For comparisons between groups (standard, alternative, and non-guideline based adapted treatment plan), the chi-square test was used for nominal and ordinal variables; the Anova test was used for continuous variables. For calculations with patient characteristics, the total number of patients (n= 104) was used and for analyses considering treatment outcomes, the total number of treatment lines (hereinafter referred to as cases, n= 129) was used, unless stated differently. In addition, baseline characteristics and course of treatment of cases receiving first-line chemotherapy (curative or palliative, n= 93) were compared with those receiving second-line chemotherapy or higher (n= 36).

**RESULTS****Patient and tumor characteristics**

Between October 2010 and December 2016, 104 patients of 80 years or older initiated a (new) line of chemotherapy for one of five solid malignancies or non-Hodgkin lymphoma. Baseline characteristics are shown in Table 1. The median age at diagnosis was 82 years (range 80-94 years). The majority of patients were female (n= 66, 64%), were ADL and iADL independent (57%), and were community-dwelling (92%). ECOG PS was available in 44% of patients and of these half had a PS of 1 or higher. Charlson Comorbidity Index was  $\geq 1$  in 53% of patients (n= 55, range 0-8). Polypharmacy was present in 46% and 17% had a MUST-score of  $\geq 1$  indicating a risk of malnutrition (in 56% of patients the MUST-score was unknown). Of all patients, 36% had non-Hodgkin lymphoma (n= 37), 18% colorectal

**First step: standard or reference DI of each drug separately**

$$\frac{\text{Planned full dose of drug per cycle (mg/m}^2\text{)}}{\text{Planned number of weeks in cycle (week)}}$$

**Second step: actual DI of each drug**

$$\frac{\text{Total dose of drug actually received by the patient}^1 \text{ (mg/m}^2\text{)}}{\text{Total number of weeks actually needed to receive total dose}^{2,3,4} \text{ (week)}}$$

**Third step: RDI of each drug**

$$\frac{\text{Actual DI of each drug (mg/m}^2\text{)}}{\text{Standard DI of each drug (week)}}$$

**Fourth step: average RDI of multiple regimens**

$$\frac{\text{Sum of RDI of each drug}}{\text{Number of different drugs}}$$

**Figure 1. Calculation of the relative dose intensity (RDI)\***

Abbreviations: DI = dose intensity; RDI = relative dose intensity.

\* The RDI takes into account all secondary adjustments: dose reductions, delay in cycles, changes in chemotherapeutic drug administered, reduced number of cycles or increased time interval between each cycle.

<sup>1</sup> If treatment was continued after receiving the planned number of chemotherapy cycles, only the initially planned number of cycles was included.

<sup>2</sup> If treatment was continued after receiving the planned number of cycles, only the number of weeks needed to receive the initially planned number of cycles was included.

<sup>3</sup> In case of treatment discontinuation due to progressive disease or if patients died due to a cause other than treatment-related death, the number of weeks since the start of treatment until the day of discontinuation was included.

<sup>4</sup> In case of interval debulking surgery, the number of weeks that the treatment was interrupted due to surgery was excluded.

**Figure 1.** Calculation of the relative dose intensity (RDI).

cancer (n= 19), 17% ovarian cancer (n= 18), 17% lung cancer (NSCLC n= 10, SCLC n= 8), 10% breast cancer (n= 10), and 2% prostate cancer (n= 2); 54% had stage IV disease.

**Initial chemotherapy plan**

The 104 individual patients received 129 lines of chemotherapy. Almost two-thirds of patients (64%) were treated with palliative intent. First-line palliative treatment (43%) was the most common treatment line (Table 1). Of the patients with solid tumors, 63% received single-agent chemotherapy. The most commonly used chemotherapy agents or regimens were carboplatin (n= 18), capecitabine (n= 16), and (adjusted) R-CHOP or R-mini-CHOP (n= 19).

**Table 1.** Baseline characteristics of patients, tumor types and stage distribution.

		<b>All patients (n = 104)</b>
Age in years, median (range)		82 (80-94)
Gender, <i>n</i> (%)	* Male	38 (36)
	* Female	66 (64)
CCI score, <i>n</i> (%)	* 0	49 (47)
	* ≥ 1	55 (53)
ECOG performance status, <i>n</i> (%)	* 0	23 (22)
	* ≥ 1	23 (22)
	* Not reported	58 (56)
ADL/iADL dependency, <i>n</i> (%)	* ADL and iADL independent	59 (57)
	* ADL and/or iADL dependent	29 (28)
	* Not reported	16 (15)
Risk of poor nutrition (MUST), <i>n</i> (%)	* No risk	28 (27)
	* Average/high risk	18 (17)
	* Unknown	58 (56)
Polypharmacy, <i>n</i> (%)	* No	56 (54)
	* Yes	48 (46)
Living situation, <i>n</i> (%)	* Community-dwelling	96 (92)
	* Nursing home	3 (3)
	* Not reported	5 (5)
Marital status, <i>n</i> (%)	* Together	49 (47)
	* Alone	50 (48)
	* Unknown	5 (5)
Tumor type, <i>n</i> (%)	* Colorectal cancer	19 (18)
	* Breast cancer	10 (10)
	* Lung cancer	18 (17)
	* Ovarian cancer	18 (17)
	* Prostate cancer	2 (2)
	* Non-Hodgkin lymphoma	37 (36)
Cancer stage, <i>n</i> (%)	* Stage I	4 (4)
	* Stage II	8 (8)
	* Stage III	33 (32)
	* Stage IV	56 (54)
	* Not applicable	3 (3)
Treatment goal, <i>n</i> (%)	* Curative	37 (36)
	* Palliative	67 (64)
Primary or recurrent tumor, <i>n</i> (%)	* Primary	78 (75)
	* Recurrent	26 (25)
Treatment line <sup>a</sup> , <i>n</i> (%)	* First-line curative	37 (29)
	* First-line palliative	56 (43)
	* Second-line palliative	26 (20)
	* Third-line palliative	8 (6)
	* Fourth-line palliative	2 (2)
Single agent <sup>b</sup> , <i>n</i> (%)		42 (63)

Abbreviations: ADL = activities of daily living; CCI = Charlson comorbidity index; ECOG-PS = Eastern Cooperative Oncology Group Scale of Performance Status; MUST = malnutrition universal screening tool.

<sup>a</sup> Shown number (n) is of all chemotherapy lines (n= 129) instead of all patients (n= 104)

<sup>b</sup> Patients with a diagnosis of non-Hodgkin lymphoma were excluded (n= 37)

Treatment plan details are shown in Table 2. For 59 cases (46%), only standard guideline recommendations were available. Of these, treatment plan was in accordance with standard treatment in nine cases (15%), while the plan consisted of non-guideline based adapted treatment in the remaining 50. For 66 cases (51%), alternative guideline recommendations for older or unfit patients were available. Treatment plan consisted of standard treatment as in young and/or fit patients, alternative treatment, and non-guideline based adapted treatment in 6 (9%), 32 (48%), and 28 (42%) cases respectively. For four cases (3%, all recurrent disease), the associated guideline did not mention any treatment recommendations.

Primary chemotherapy adaptations consisted of dose reductions ( $n = 50$ , 39%), changes in chemotherapeutic drugs administered ( $n = 49$ , 38%), omission of targeted therapy ( $n = 5$  out of the 15 chemotherapy regimens for metastatic colorectal cancer with an indication for targeted therapy) and/or sequential instead of concurrent chemoradiation ( $n = 9$  out of the 9 regimens for lung cancer with an indication for chemoradiation, Table 3).

When reasons to choose for an adapted treatment were mentioned, the most frequently encountered reasons were age ( $n = 16$ ), comorbidity ( $n = 10$ ), and physical condition ( $n = 8$ , Table 4).

### Course of treatment

Chemotherapy was completed according to the treatment plan – indicated by an RDI  $\geq 85\%$  – in 52% of all cases ( $n = 67$ ); RDI ranged from 6% to 150%. Chemotherapy completion rates were not significantly different between cases where standard, alternative, or non-guideline based adapted treatment was chosen ( $p = 0.59$ , Figure 2).

In 84 of 129 cases secondary adaptations were required (65%, Table 3); nonetheless, 23 of these did achieve an RDI  $\geq 85$ . Secondary adjustments consisted most frequently of not completing all planned chemotherapy cycles ( $n = 50$ ; 39%), delay between cycles ( $n = 49$ ,

**Table 2.** Chemotherapy treatment plan details.

	<b>Total (n = 129)</b>
Guideline contains recommendations for young and/or fit patients only	59 (46%)
Standard treatment plan	9 (15%)
Non-guideline based adapted treatment plan	50 (85%)
Guideline contains alternative recommendations for older or unfit patients	66 (51%)
Standard treatment plan as in young and/or fit patients	6 (9%)
Alternative treatment plan for older or unfit patients	32 (48%)
Non-guideline based adapted treatment plan	28 (42%)
Guideline contains no treatment recommendations	4 (3%)

**Table 3.** Primary and secondary chemotherapy adaptations.

	Total (n = 129)
Primary chemotherapy adaptations <sup>a</sup>	79 (63%)
* Primary dose reductions <sup>a</sup>	50 (40%)
* Change in chemotherapeutic drug <sup>a</sup>	49 (39%)
* Omission of targeted therapy <sup>b</sup>	5 (33%)
* Sequential instead of concurrent chemoradiation <sup>c</sup>	9 (100%)
Secondary chemotherapy adaptations	84 (65%)
* Secondary dose reductions	36 (28%)
* Interval	9 (7%)
* Change in chemotherapeutic drug	9 (7%)
* Interruption of cycle	4 (3%)
* Delay between cycles	49 (38%)
* Reduced number of cycles	50 (39%)

<sup>a</sup> Four cases that received chemotherapy for recurrent disease were not taken into account because the associated guidelines did not mention treatment recommendations for recurrent disease

<sup>b</sup> In case of metastatic colorectal cancer with an indication for targeted therapy (n = 15)

<sup>c</sup> In case of lung cancer with an indication for chemoradiation (n = 9)

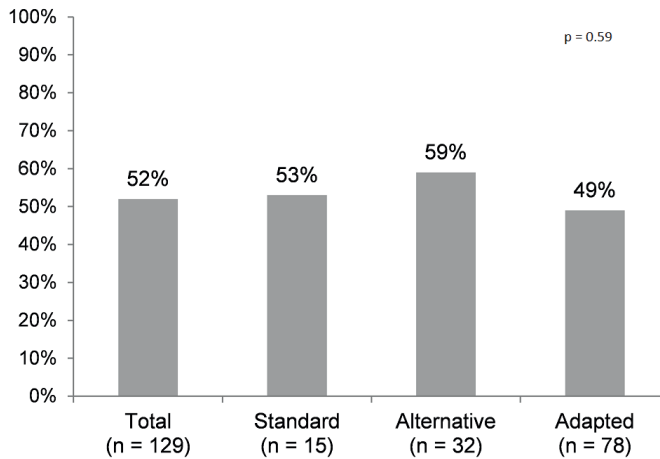
**Table 4.** Reasons for primary or secondary adapted chemotherapy treatment.

	Total (n = 129)
Reasons for primary adapted treatment <sup>a,b</sup>	
* Age	16
* Physical condition	8
* Comorbidity	10
* Patient preference	1
* Not reported	50
Reasons for secondary adapted treatment <sup>b</sup>	
* Toxicity	68
* Patient preference	14
* Deterioration of physical condition	18
* Other	16
* Not reported	4

<sup>a</sup> Four cases that received chemotherapy for recurrent disease were not taken into account because the associated guidelines did not mention treatment recommendations for recurrent disease

<sup>b</sup> Multiple reasons were possible per patient

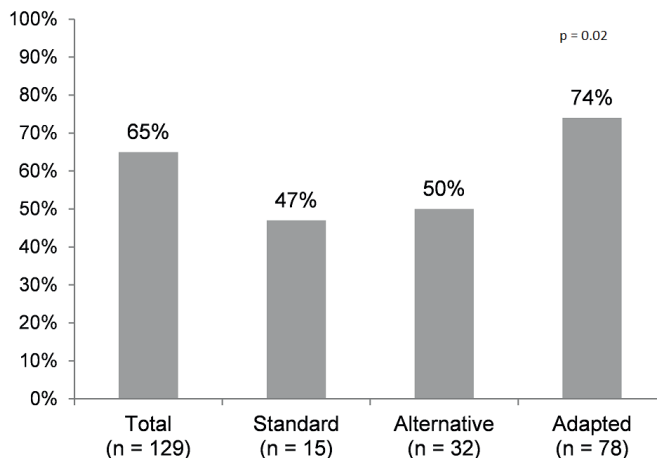




**Figure 2.** Rates of chemotherapy regimens completed according to plan (defined as a relative dose intensity  $\geq 85\%$ ), stratified according to treatment plan.

38%), and dose reductions (n= 36, 28%). Secondary adaptations occurred more frequently in cases with primary chemotherapy adaptations than in those consisting of standard or alternative treatment (74%, 47%, and 50% respectively,  $p = 0.02$ , Figure 3).

The most frequent reason why the intended treatment was not completed according to plan was toxicity (n= 68, 53%, Table 4). This manifested primarily as haematological toxicity (n= 22) and infectious complications (n= 15) or as constitutional symptoms (n= 20). Toxicity rates did not differ among groups ( $p = 0.58$ ). Other frequently encountered reasons for secondary adaptations were patient preference (n= 14) and a deterioration of

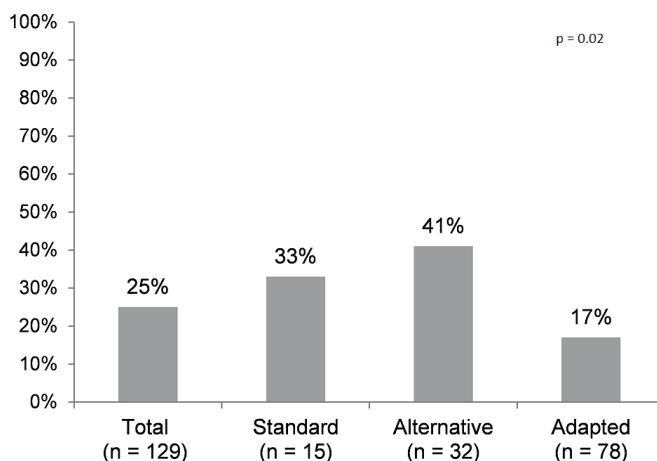


**Figure 3.** Rates of secondary chemotherapy adaptations stratified according to treatment plan.

physical condition (n= 18). Four patients died due to chemotherapeutic-related infection. Another patient died during treatment because of an ischemic cerebral stroke.

In 25% of the cases one or more unplanned hospital admissions were required, with a median length of stay of 10 days (range 2-23 days). The most common reason for hospital admission was infection (n= 17). Hospital admissions occurred significantly less often in cases with an adapted treatment plan than in cases where treatment plan consisted of standard or alternative treatment (17%, 33%, and 41% respectively,  $p = 0.02$ . Figure 4).

Primary and secondary outcomes were not different for patients receiving first-line chemotherapy compared to patients receiving second-line or higher chemotherapy (Appendix 1d).



**Figure 4.** Hospitalisation rates stratified according to treatment plan.

## DISCUSSION

### Main findings

Although the oldest old represent a growing population evaluated in medical oncology clinics, there is a paucity of data on chemotherapy tolerability and feasibility in this age group. Therefore, we set out to assess these properties in patients aged 80 years or older starting chemotherapy. We found that in more than 60% of the cases upfront chemotherapy adaptations were implemented. Despite these primary treatment adjustments, secondary treatment adaptations (65%) and hospitalisations (25%) were common. Half of the chemotherapy lines started in octogenarians and nonagenarians were finished according to plan (defined as an RDI  $\geq 85\%$ ). The rate of successfully completed treatments was not affected by whether the initial treatment plan consisted of standard, alternative, or non-guideline based adapted treatment.

### Comparison with prior research

We defined our primary outcome—chemotherapy finished according to the treatment plan—by assessing the RDI, as this is an objective method to quantify treatment completion that takes into account all secondary chemotherapy adaptations. A high RDI is associated with favorable outcomes.<sup>19–21</sup> Although an RDI  $\geq 85\%$  was achieved in 52% of the cases, the range of the RDI varied widely between 6% and 150%. Presumably, this range reflects the varying degrees of frailty in our population. It also demonstrates the difficulty of selecting older patients suitable for chemotherapy and of achieving the optimal dose intensity in these patients.

A handful of prior studies have assessed the feasibility and tolerability of chemotherapy in the oldest old, using the rate of dose modifications and treatment discontinuation due to toxicity as primary outcomes.<sup>22–24</sup> In one study of 420 patients aged 80 years or older with an indication for palliative first-line chemotherapy for solid tumors, only 24% of these patients received chemotherapy.<sup>22</sup> Despite 78% of patients in their cohort receiving monotherapy and 59% having an upfront dose reduction, over half of these highly selected patients experienced toxicity necessitating treatment modifications, and only 17% completed the planned course of chemotherapy while almost one-third of the patients required one or more hospitalisations. In another study in 318 patients aged 80 years and older initiating chemotherapy for malignant solid tumors, upfront dose reductions were implemented in 41% of cases.<sup>23</sup> In the course of treatment, 52% of cases required secondary dose reduction, omission or delay, and hospitalisation occurred in 32%. In total, 32% of the patients finished chemotherapy without receiving secondary adaptations. Compared to these findings, we observed an equal toxicity rate (53%) and a lower hospitalisation rate (25%) in our cohort. Contrarily, in our study, primary and secondary chemotherapy adaptations were more frequently implemented (63% and 65% respectively), and the number of chemotherapy regimens completed according to plan was higher (52%). Differences in guideline recommendations, patient population, and treatment setting may be partially responsible for these contrasting findings.

Prior studies comparing chemotherapy feasibility in older ( $\geq 70$  years) with younger patients yielded conflicting results; some studies found lower feasibility rates for older patients,<sup>25–28</sup> whereas others suggest similar feasibility rates across age groups.<sup>29–31</sup> In addition, multiple prospective studies evaluated course of chemotherapy specifically in older patients with cancer.<sup>32–35</sup> Primary and secondary adaptation rates (9% to 67% and 0% to 69% respectively) as well as completion rates (9% to 90%) vary widely between studies, due to differences in definitions, study populations and treatment regimens.<sup>27,28,31–34</sup> Although this limits the comparability to our results, overall it can be said that treatment adaptations were more common in our oldest old population compared to both patients aged 70 years and older as well as compared to younger patients.

**Implications for clinical practice and research**

Primary chemotherapy adaptations are commonly implemented in older patients with cancer with the intention to prevent deleterious effects of this treatment. However, when so many patients receive a modified chemotherapy regimen and nevertheless are unable to complete this treatment, the question is whether chemotherapy is feasible in the oldest old, and whether regimens with secondary adaptations superimposed on primary adaptations are still effective or should be omitted altogether; in our study, nearly three-quarters of the 79 primary adapted chemotherapy regimens required secondary adaptations. Exposing vulnerable older patients to a burdensome chemotherapy treatment may be undesirable. Most older patients value independent functioning and quality of life over quantity of life.<sup>36,37</sup> However, in light of the potential for increased care dependence<sup>38</sup> and hospitalisations<sup>39</sup> due to chemotherapy, this preference appears to be insufficiently taken into consideration. There is an urgent need for studies evaluating optimal treatment strategies and patient-related outcome measures in the oldest old with cancer to improve quality of care for these patients. Until then, in selected older patients, best supportive care may be a reasonable alternative to chemotherapy and should be discussed with these patients and their caregivers.

To aid chemotherapy decision-making in older patients with cancer, prediction scores and models have been developed to assess the risk of toxicity and chemotherapy feasibility for these patients. Geriatric impairments were shown to predict chemotherapy feasibility<sup>32–35</sup> and two recently developed prediction tools for grade III or higher chemotherapy-related toxicity also include multiple geriatric parameters.<sup>40,41</sup> In particular, nutritional status, IADL impairment, cognition and mobility have shown an association with toxicity and treatment completion.<sup>33,40–44</sup> For a more elaborate examination of the feasibility of chemotherapy, a geriatric assessment (GA) may be performed, which helps to differentiate between fit older adults for whom standard treatment may be achievable and frail older adults for whom chemotherapy should be adapted or omitted.<sup>45</sup> While often stated as a time-consuming and infeasible process, the total time actually required by the health care provider is little.<sup>46</sup> Additionally, the issues GA uncovers influence treatment decision-making and course of treatment because it predicts not only treatment-related complications and survival but also appears to improve treatment tolerance and completion.<sup>47</sup>

Although the implementation of a screening tool or GA is recommended by guidelines, its integration into clinical practice is currently hampered because of the time investment required to perform a GA and because there is a shortage of trained clinical staff.<sup>48,49</sup> Therefore, recently, the American Society of Clinical Oncology published a guideline to facilitate this implementation by providing a practical overview of which geriatric tools should be assessed and by giving recommendations for management of common age-

related conditions.<sup>50</sup> This guideline recommends that a GA should be performed in all older patients with cancer aged 65 years and older receiving chemotherapy.

### **Strengths and limitations**

In this study, we describe a selected patient population; only those patients who started chemotherapy were included and we could not compare this group with those patients (probably less fit) in whom chemotherapy was not given, or who were never referred to the medical oncologist. Our patients had relatively few comorbidities and functioning was generally unimpaired. Hence, our results cannot be extrapolated to all octogenarians with cancer and must be interpreted carefully. However, we have shown that even in a selected sample of relatively fit older patients with cancer, chemotherapy was commonly unfeasible and outcomes are unlikely to be more favorable in the “general” oldest old with cancer.

Strengths of our study include the thorough description regarding the primary treatment plan and the course of chemotherapy in the oldest old. In addition, we used an objective method to measure our primary outcome, the relative dose intensity. One limitation is that we did not objectify patients’ response to chemotherapy and consequently information regarding treatment effectiveness is lacking. Another potential drawback is the method we used to define standard, alternative, or adapted treatment. This was defined based upon the recommendations of the applicable (Dutch) guidelines but current insights and recommendations from international guidelines may be different. Some guidelines did not mention specific recommendations in case of recurrent disease and some did not provide treatment recommendations specifically for older patients. To deal with this heterogeneity, those regimens for which guideline recommendations were lacking were excluded from analysis and we used clear definitions for standard, alternative, or adapted treatment. Given the retrospective nature of our study, we were unable to grade chemotherapy toxicity according to standardised measurements, and to collect data regarding the impact of chemotherapy on quality of life and symptom burden. Since hospital admission and treatment discontinuation are solid endpoints, we are confident that severe toxicity was sufficiently taken into consideration. Despite these limitations, our outcomes may aid oncologists in informing their oldest old patients about chemotherapy outcomes on more evidence-based grounds because currently, guidelines are often lacking chemotherapy recommendations specifically for older or unfit patients. Luckily, trials and cohorts excluding older patients with cancer solely based on their age are becoming fewer in number and hopefully, guidelines can provide chemotherapy recommendations for older or unfit patients of all cancer types in the near future.

## **Conclusion**

In a selected sample of relatively fit patients aged 80 years or older with cancer, almost half of the chemotherapy regimens were not completed according to the initial plan, despite frequently implemented primary treatment adaptations. The decision to treat these patients with chemotherapy should be carefully considered. To aid decision-making, future research should focus on patient-reported outcomes and the implementation of prediction models or screening tools assessing the feasibility of chemotherapy in the oldest old.

## REFERENCES

1. Cancer incidence by age. Available at: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero>. (Accessed: 23rd March 2018)
2. WHO Cancer Fact sheet. Available at: <http://www.who.int/mediacentre/factsheets/fs297/en/>. (Accessed: 26th March 2018)
3. CBS Statline. Bevolking; geslacht, leeftijd en burgerlijke staat. Available at: <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/7461bev/table?dl=5052>. (Accessed: 23rd March 2018)
4. Extermann, M. *et al.* Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit. Rev. Oncol. Hematol.* **55**, 241–252 (2005).
5. Jansen, L. *et al.* Age-specific administration of chemotherapy and long-term quality of life in stage II and III colorectal cancer patients: a population-based prospective cohort. *Oncologist* **16**, 1741–51 (2011).
6. Lissbrant, I. F., Garmo, H., Widmark, A. & Stattin, P. Population-based study on use of chemotherapy in men with castration resistant prostate cancer. *Acta Oncol. (Madr)*. **52**, 1593–1601 (2013).
7. Jordan, S. *et al.* Patterns of chemotherapy treatment for women with invasive epithelial ovarian cancer – A population-based study. *Gynecol. Oncol.* **129**, 310–317 (2013).
8. Schonberg, M. A. *et al.* Breast Cancer Among the Oldest Old: Tumor Characteristics, Treatment Choices, and Survival. *J. Clin. Oncol.* **28**, 2038–2045 (2010).
9. Ramsey, S. D., Howlader, N., Etzioni, R. D. & Donato, B. Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: evidence from surveillance, epidemiology and end results-Medicare. *J. Clin. Oncol.* **22**, 4971–8 (2004).
10. Wedding, U., Koding, D., Pientka, L., Steinmetz, H. T. & Schmitz, S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. *Crit. Rev. Oncol. Hematol.* **64**, 1–9 (2007).
11. Puts, M. T. E. *et al.* A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. *Cancer Treat. Rev.* **41**, 197–215 (2015).
12. van Bekkum, M. L., van Munster, B. C., Thunnissen, P. L. M., Smorenburg, C. H. & Hamaker, M. E. Current palliative chemotherapy trials in the elderly neglect patient-centred outcome measures. *J. Geriatr. Oncol.* **6**, 15–22 (2015).
13. Gridelli, C. *et al.* Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J. Natl. Cancer Inst.* **95**, 362–72 (2003).
14. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**, 373–83 (1987).
15. Oken, M. M. *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am. J. Clin. Oncol.* **5**, 649–55 (1982).

16. Elia, M. Screening for malnutrition: a multidisciplinary responsibility. Development and use of the Malnutrition Universal Screening Tool (MUST) for adults. Malnutrition advisory group (MAG), a standing committee of BAPEN. (2003).
17. Katz, S., Ford, A., Moskowitz, R., Jackson, B. & Jaffe, M. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. *JAMA* **185**, 914–919 (1963).
18. Lawton, M. P. & Brody, E. M. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179–186 (1969).
19. Hirakawa, T. *et al.* Importance of maintaining the relative dose intensity of CHOP-like regimens combined with rituximab in patients with diffuse large B-cell lymphoma. *Ann. Hematol.* **89**, 897–904 (2010).
20. Ben-David, Y., Rosen, B., Franssen, E., Einarson, T. & Szyfer, I. Meta-analysis comparing cisplatin total dose intensity and survival. *Gynecol. Oncol.* **59**, 93–101 (1995).
21. Gianni, A. M. & Piccart, M. J. Optimising chemotherapy dose density and dose intensity. new strategies to improve outcomes in adjuvant therapy for breast cancer. *Eur. J. Cancer* **36 Suppl 1**, S1-3 (2000).
22. Ip, E. *et al.* Use of palliative chemotherapy in patients aged 80 years and over with incurable cancer: experience at three Sydney cancer centres. *Intern. Med. J.* **47**, 75–81 (2017).
23. Sud, S., Lai, P., Zhang, T., Clemons, M. & Wheatley-Price, P. Chemotherapy in the oldest old: The feasibility of delivering cytotoxic therapy to patients 80 years old and older. *J. Geriatr. Oncol.* **6**, 395–400 (2015).
24. Pentheroudakis, G. *et al.* Palliative chemotherapy in elderly patients with common metastatic malignancies: A Hellenic Cooperative Oncology Group registry analysis of management, outcome and clinical benefit predictors. *Crit. Rev. Oncol. Hematol.* **66**, 237–247 (2008).
25. Moore, K. N. *et al.* Adjuvant chemotherapy for the 'oldest old' ovarian cancer patients: can we anticipate toxicity-related treatment failure in a vulnerable population? *Cancer* **115**, 1472–1480 (2009).
26. Muss, H. B. *et al.* Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J. Clin. Oncol.* **25**, 3699–704 (2007).
27. Hamaker, M. E. *et al.* Multidisciplinary decision-making on chemotherapy for colorectal cancer: an age-based comparison. *J. Geriatr. Oncol.* **6**, 225–32 (2015).
28. Schulkes, K. J. G. *et al.* Multidisciplinary decision-making regarding chemotherapy for lung cancer patients-An age-based comparison. *Eur. J. Cancer Care (Engl)*. **27**, e12768 (2018).
29. Blanchard, E. M. *et al.* Comparison of Platinum-Based Chemotherapy in Patients Older and Younger than 70 Years: An Analysis of Southwest Oncology Group Trials 9308 and 9509. *J. Thorac. Oncol.* **6**, 115–120 (2011).
30. Folprecht, G. *et al.* Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. *J. Clin. Oncol.* **26**, 1443–51 (2008).



31. Berger, A. K. *et al.* Palliative chemotherapy for pancreatic adenocarcinoma: a retrospective cohort analysis of efficacy and toxicity of the FOLFIRINOX regimen focusing on the older patient. *BMC Gastroenterol.* **17**, 143 (2017).
32. Aaldriks, A. A. *et al.* Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. *Acta Oncol. (Madr)*. **55**, 15–23 (2016).
33. Aparicio, T. *et al.* Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. *J. Clin. Oncol.* **31**, 1464–70 (2013).
34. von Gruenigen, V. E. *et al.* Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer – An NRG oncology/Gynecologic Oncology Group study. *Gynecol. Oncol.* **144**, 459–467 (2017).
35. Soubeyran, P. *et al.* Predictors of Early Death Risk in Older Patients Treated With First-Line Chemotherapy for Cancer. *J. Clin. Oncol.* **30**, 1829–1834 (2012).
36. Akishita, M. *et al.* Priorities of Health Care Outcomes for the Elderly. *J. Am. Med. Dir. Assoc.* **14**, 479–484 (2013).
37. Fried, T. R., Bradley, E. H., Towle, V. R. & Allore, H. Understanding the Treatment Preferences of Seriously Ill Patients. *N. Engl. J. Med.* **346**, 1061–1066 (2002).
38. Kenis, C. *et al.* Functional decline in older patients with cancer receiving chemotherapy: A multicenter prospective study. *J. Geriatr. Oncol.* **8**, 196–205 (2017).
39. O'Neill, C. B. *et al.* ReCAP: Hospitalizations in Older Adults With Advanced Cancer: The Role of Chemotherapy. *J. Oncol. Pract.* **12**, 151–152 (2016).
40. Hurria, A. *et al.* Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. *J. Clin. Oncol.* **34**, 2366–2371 (2016).
41. Extermann, M. *et al.* Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* **118**, 3377–3386 (2012).
42. Hoppe, S. *et al.* Functional decline in older patients with cancer receiving first-line chemotherapy. *J. Clin. Oncol.* **31**, 3877–82 (2013).
43. Owusu, C., Margevicius, S., Schluchter, M., Koroukian, S. M. & Berger, N. A. Short Physical Performance Battery, usual gait speed, grip strength and Vulnerable Elders Survey each predict functional decline among older women with breast cancer. *J. Geriatr. Oncol.* **8**, 356–362 (2017).
44. Falandry, C. *et al.* Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial. *Ann. Oncol.* **24**, 2808–13 (2013).
45. Puts, M. T. E. *et al.* Use of geriatric assessment for older adults in the oncology setting: a systematic review. *J. Natl. Cancer Inst.* **104**, 1133–1163 (2012).
46. Hamaker, M. E., Wildes, T. M. & Rostoft, S. Time to Stop Saying Geriatric Assessment Is Too Time Consuming. *J. Clin. Oncol.* **35**, 2871–2874 (2017).

47. Hamaker, M. E. *et al.* The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients – A systematic review. *J. Geriatr. Oncol.* **9**, 430–440 (2018).
48. Versteeg, K. S., Konings, I. R., Lagaay, A. M., van de Loosdrecht, A. A. & Verheul, H. M. W. Prediction of treatment-related toxicity and outcome with geriatric assessment in elderly patients with solid malignancies treated with chemotherapy: a systematic review. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **25**, 1914–8 (2014).
49. Puts, M. T. E. *et al.* An update on a systematic review of the use of geriatric assessment for older adults in oncology. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **25**, 307–15 (2014).
50. Mohile, S. G. *et al.* Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J. Clin. Oncol.* JCO.2018.78.868 (2018). doi:10.1200/JCO.2018.78.8687



**Appendix 1a.** Summary of Dutch guideline recommendations for chemotherapy treatment of the relevant solid tumors according to tumor stage.\*

<b>Tumor</b>	<b>Stage</b>	<b>Standard treatment for young and fit patients</b>	<b>Alternative treatment for older and/or unfit patients</b>
Ovarian cancer	FIGO stage IIb-IV <sup>1</sup>	6 cycles of carboplatin AUC 6 day 1 q3w + paclitaxel 175 mg/m <sup>2</sup> day 1 q3w	No recommendations in the guideline
	Recurrent disease <sup>2</sup>	Therapy-free interval ≥ 6 months: reintroduction of first-line chemotherapy Therapy-free interval < 6 months: etoposide (at least 4 cycles 50 mg/m <sup>2</sup> days 1-21 q4w) <i>OR</i> topotecan <i>OR</i> liposomal doxorubicin <i>OR</i> gemcitabine <i>OR</i> weekly platinum combination therapy	No recommendations in the guideline
SCLC	Stage I-III	Concurrent chemoradiation therapy: 4 cycles of cisplatin 60 mg/m <sup>2</sup> day 1 q3w + etoposide 120 mg/m <sup>2</sup> /day days 1-3 q3w	Consider sequential chemoradiation: 4 cycles of cisplatin 80 mg/m <sup>2</sup> day 1 q3w + etoposide 100 mg/m <sup>2</sup> /day days 1-3 q3w <i>OR</i> 4 cycles of carboplatin AUC 5 day 1 q3w + etoposide 120 mg/m <sup>2</sup> /day days 1-3 q3w
	Stage IV	Palliative chemotherapy: 4-6 cycles of cisplatin 80 mg/m <sup>2</sup> day 1 q3w + etoposide 100 mg/m <sup>2</sup> /day days 1-3 q3w <i>OR</i> carboplatin AUC 5 day 1 q3w + etoposide 120 mg/m <sup>2</sup> /day days 1-3 q3w	No recommendations in the guideline
	Recurrent disease	Therapy-free interval ≥ 3 months (sensitive): reintroduction of first-line chemotherapy Therapy-free interval < 3 months (resistant): start second-line chemotherapy (e.g. topotecan)	Therapy-free interval ≥ 3 months (sensitive): topotecan Therapy-free interval < 3 months (resistant): consider to withhold chemotherapy in unfit patients

*Continue*

Continued

Tumor	Stage	Standard treatment for young and fit patients	Alternative treatment for older and/or unfit patients
NSCLC	Stage IB-II	Adjuvant chemotherapy <sup>3,4</sup> with cisplatin-containing regimen: e.g. 4 cycles of cisplatin 75 mg/m <sup>2</sup> day 1 q3w + pemetrexed 500 mg/m <sup>2</sup> day 1 q3w <i>OR</i> cisplatin 80 mg/m <sup>2</sup> day 1 q3w + gemcitabine 1250 mg/m <sup>2</sup> days 1 + 8 q3w	No recommendations in the guideline
	Stage III	Concurrent chemoradiation <sup>5</sup> with cisplatin-containing regimen: e.g. 3-4 cycles of cisplatin 60 mg/m <sup>2</sup> day 1 q3w + etoposide 120 mg/m <sup>2</sup> /day days 1-3 q3w	Concurrent chemoradiation with platinum-based doublet chemotherapy (e.g. carboplatin may be chosen instead of cisplatin; carboplatin AUC 5 day 1 q3w + etoposide 120 mg/m <sup>2</sup> /day days 1-3 q3w) <i>OR</i> sequential chemoradiation <sup>2</sup> : 3-4 cycles of cisplatin 75 mg/m <sup>2</sup> day 1 q3w <i>OR</i> carboplatin AUC 5 day 1 q3w in combination with pemetrexed 500 mg/m <sup>2</sup> day 1 q3w <i>OR</i> 3-4 cycles of cisplatin 80 mg/m <sup>2</sup> day 1 q3w <i>OR</i> carboplatin AUC 5 day 1 q3w in combination with gemcitabine 1250 mg/m <sup>2</sup> days 1 and 8 q3w
	Stage IV	TKI <sup>6</sup> <i>OR</i> palliative chemotherapy <sup>4</sup> : platinum-based doublet chemotherapy, e.g. 4 cycles of cisplatin 75 mg/m <sup>2</sup> day 1 q3w + pemetrexed 500 mg/m <sup>2</sup> day 1 q3w <i>OR</i> cisplatin 80 mg/m <sup>2</sup> day 1 q3w <i>OR</i> carboplatin AUC 5 day 1 q3w in combination with gemcitabine 1250 mg/m <sup>2</sup> days 1 and 8 q3w	Platinum-based doublet chemotherapy (e.g. carboplatin may be chosen instead of cisplatin also in case of non-squamous cell carcinoma); 4 cycles of carboplatin AUC 5 day 1 q3w with gemcitabine 1250 mg/m <sup>2</sup> days 1 and 8 q3w <i>OR</i> pemetrexed 500 mg/m <sup>2</sup> day 1 q3w <i>OR</i> monotherapy with gemcitabine, vinorelbine or taxanes
Colorectal cancer	Recurrent disease	No treatment recommended in the guideline	No recommendations in the guideline
	Stage IV <sup>7</sup>	6 cycles of CAPOX-B (capecitabine 2dd 1000 mg/m <sup>2</sup> days 1-14 q3w + oxaliplatin 130 mg/m <sup>2</sup> day 1 q3w + bevacizumab 7.5mg/m <sup>2</sup> d1 q3w) <i>OR</i> 9 two-weekly cycles of FOLFOX-B (two-weekly 5FU, oxaliplatin and bevacizumab)	Fluoropyrimidine (5-FU 425 mg/m <sup>2</sup> day 1 q1w during 3 months <i>OR</i> 6 cycles of capecitabine 2dd 1250 mg/m <sup>2</sup> days 1-14 q3w) in combination with bevacizumab <i>OR</i> consider a fluoropyrimidine- and oxaliplatin-containing schedule with primary dose reductions in combination with bevacizumab
	Recurrent/ progressive <sup>8</sup>	6 cycles of irinotecan monotherapy (350 mg/m <sup>2</sup> day 1 q3w, 180 mg/m <sup>2</sup> day 1 q2w or 80 mg/m <sup>2</sup> /time days 1-8-15 q4w) <i>OR</i> 18 weeks of combination therapy (capecitabine or 5-FU 2800 mg/m <sup>2</sup> day 1 q2w + irinotecan 350 mg/m <sup>2</sup> day 1 q3w, 180 mg/m <sup>2</sup> q2w or 80 mg/m <sup>2</sup> /time days 1-8-15 q4w) <i>OR</i> 6 cycles of fluoropyrimidine (capecitabine 2dd 1000 mg/m <sup>2</sup> days 1-14 q3w or 5-FU) + oxaliplatin 130 mg/m <sup>2</sup> day 1 q3w	No recommendations in the guideline

Continue

Continued

Tumor	Stage	Standard treatment for young and fit patients	Alternative treatment for older and/or unfit patients
Breast cancer <sup>a</sup>	Metastatic disease or locally unresectable	AC-containing schedule (e.g. FAC, FEC, AC, EC) and/or taxanes (6 cycles of paclitaxel 80 mg/m <sup>2</sup> day 1 q1w or 175 mg/m <sup>2</sup> day 1 q3w or docetaxel) OR 6 cycles of capecitabine monotherapy (2dd 1250 mg/m <sup>2</sup> days 1-14 days q3w) - HER-2 overexpression: HER-2 blockade	Capecitabine (2dd 1250 mg/m <sup>2</sup> days 1-14 days q3w). No other specific treatment recommendations mentioned in the guideline
	Recurrent/progressive <sup>a</sup>	No specific treatment recommended in the guideline	No recommendations in the guideline
Prostate cancer <sup>a</sup>	Stage IV, pre-docetaxel	6 cycles of docetaxel 75 mg/m <sup>2</sup> day 1 q3w	No recommendations in the guideline
	Stage IV, post-docetaxel	6 cycles of cabazitaxel 25 mg/m <sup>2</sup> day 1 q3w	No recommendations in the guideline

Abbreviations: FIGO = The international Federation of gynaecology and obstetrics classification; HER-2 = human epidermal growth factor receptor 2; (N)SCLC = (non) small cell lung cancer; TKI = tyrosine kinase inhibitor.

Chemotherapy abbreviations/explanations: 5-FU = 5-fluorouracil; AC = adriamycine (doxorubicine), cyclophosphamide; CAPOX-B = capecitabine, oxaliplatin, bevacizumab; EC = epirubicine, cyclophosphamide; FAC = 5-fluorouracil, adriamycine, cyclophosphamide; FEC = 5-fluorouracil, epirubicine, cyclophosphamide; fluoropyrimidine = capecitabine or 5-fluorouracil; FOLFOX-B = 5-fluorouracil, oxaliplatin, bevacizumab;

\* Two different types of guideline recommendations were distinguished based on whether the guideline mentioned treatment recommendations specifically for older and/or unfit patients or not. 1 = Standard treatment: only standard guideline recommendations were available and recommendations for older and/or unfit patients were not mentioned. 2 = Alternative treatment: besides standard recommendations, guideline recommendations for older and/or unfit patients were also available. Relevant guidelines at the time of data collection were used; hence, recommendations may deviate from current treatment recommendations. Only treatment for those tumors and tumor stages represented in the database is shown. When the specific chemotherapy agent-as recommended by the guidelines-was not applicable in the study, dosages of this agent are not shown.

<sup>1</sup> Both neoadjuvant and adjuvant regimens were considered as standard care

<sup>2</sup> In case of recurrent disease, treatment continuation until disease progression or unacceptable toxicity was considered as standard treatment

<sup>3</sup> In patients with stage IB disease, chemotherapy can be given in case the tumor is > 4 centimetres

<sup>4</sup> In case of squamous cell carcinoma gemcitabine is the additional chemotherapy agent of choice, whereas in case of non-squamous cell carcinoma pemetrexed is the additional chemotherapy agent of choice. In patients with stage IV NSCLC and histological subtype non-squamous cell carcinoma, carboplatin with paclitaxel and bevacizumab may be considered as well.

<sup>5</sup> Nationwide consensus regarding the specific chemotherapy regimen and optimal radiation scheme is lacking

<sup>6</sup> Targeted therapy with TKI is indicated if mutation in EGFR or ALK is found

<sup>7</sup> When first-line treatment consisted of capecitabine + bevacizumab, and oxaliplatin was given as second-line treatment, this was also considered as standard treatment

<sup>8</sup> After previous chemotherapy

<sup>9</sup> Hormonal therapy or androgen deprivation therapy were not taken into account.

**Overview of the (Dutch) guidelines or protocols:**

Ovarian cancer: <https://www.oncoline.nl/ovariumcarcinoom>

SCLC: <https://www.oncoline.nl/kleincellig-longcarcinoom>

NSCLC: <https://www.oncoline.nl/niet-kleincellig-longcarcinoom>

Colorectal cancer: <https://www.oncoline.nl/colorectaalcarcinoom>

Breast cancer: <https://heelkunde.nl/sites/heelkunde.nl/files/richtlijnen-definitief/Mammacarcinoom2012.pdf>

Prostate cancer: <https://www.oncoline.nl/prostaatacarcinoom>

CLL: [https://www.hematologienederland.nl/sites/default/files/richtlijn-cll-hovon\\_20170607\\_def\\_0.pdf](https://www.hematologienederland.nl/sites/default/files/richtlijn-cll-hovon_20170607_def_0.pdf)

Waldenstrom: [https://www.hematologienederland.nl/sites/default/files/MW\\_ntvh\\_2012.pdf](https://www.hematologienederland.nl/sites/default/files/MW_ntvh_2012.pdf)

Marginale zone lymfoom: <http://www.bloodjournal.org/content/127/17/2064?sso-checked=true>

Ref ALCL: <http://www.esmo.org/Guidelines/Haematological-Malignancies/Peripheral-T-Cell-Lymphomas>

Burkitt: <https://webshare.iprova.nl/8n3s7sl1ltfng85n/Document.aspx?websharedocumentid=3efb4595-6585-4a5f-8a12-2c5d6aac14f2>

DLBCL: [http://www.hovon.nl/upload/File/Richtlijnen\\_BehAdv/DLBCL%20HOVON%20website%20augustus%20%202018%20clean.pdf](http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/DLBCL%20HOVON%20website%20augustus%20%202018%20clean.pdf)

DLBCL: [http://www.hovon.nl/upload/File/Richtlijnen\\_BehAdv/DLBCL%20HOVON%20website%20augustus%20%202018%20clean.pdf](http://www.hovon.nl/upload/File/Richtlijnen_BehAdv/DLBCL%20HOVON%20website%20augustus%20%202018%20clean.pdf)

MCL: Hovon 75: [http://www.hovon.nl/trials/trials-by-type/nhl.html?action=showstudie&studie\\_id=7&categorie\\_id=1](http://www.hovon.nl/trials/trials-by-type/nhl.html?action=showstudie&studie_id=7&categorie_id=1)

MCL: Hovon 75: [http://www.hovon.nl/trials/trials-by-type/nhl.html?action=showstudie&studie\\_id=7&categorie\\_id=1](http://www.hovon.nl/trials/trials-by-type/nhl.html?action=showstudie&studie_id=7&categorie_id=1)

**Appendix 1b.** Summary of guideline recommendations for chemotherapy treatment of the various types of non-Hodgkin lymphoma.\*

Type NHL	Stage	Standard treatment for young and fit patients	Alternative treatment for older and/or unfit patients
CLL/SCLL	Active/symptomatic disease <sup>1</sup>	<i>del(11p)/p53</i> mutation: ibrutinib No <i>del(11p)/p53</i> mutation: 6 cycles of R-FC	<i>del(11p)/p53</i> mutation: ibrutinib No <i>del(11p)/p53</i> mutation: R-Chlorambucil <sup>2</sup> OR 6 cycles of R-bendamustine (Rituximab 375 mg/m <sup>2</sup> + bendamustine 90 mg/m <sup>2</sup> days 1-2 q4w) Repeat first line treatment OR ibrutinib OR R-bendamustine OR R-chlorambucil <sup>2</sup>
Waldenström's macroglobulinaemia	Recurrent/refractory disease	Repeat first line treatment OR R-bendamustine OR allo-SCT	
	Active/symptomatic disease <sup>1</sup>	6-8 cycles of DRC OR 4-6 cycles of R-FC	6-8 cycles of DRC OR 4-6 cycles of R-FC OR 6 cycles of R-bendamustine (Rituximab 375 mg/m <sup>2</sup> + bendamustine 90 mg/m <sup>2</sup> days 1-2 q4w) OR R-chlorambucil <sup>2</sup> OR 4 cycles of Rituximab monotherapy Repeat first line treatment OR bortezomib OR R-bendamustine
	Recurrent/refractory disease	Repeat first line treatment OR bortezomib OR R-bendamustine OR auto-SCT	
DLBCL	II-IV	6 three-weekly cycles of R-CHOP: Rituximab 375 mg/m <sup>2</sup> day 1, cyclophosphamide 750 mg/m <sup>2</sup> day 1, doxorubicine 50 mg/m <sup>2</sup> day 1, vincristine 1.4 mg/m <sup>2</sup> (max 2 mg) day 1 and prednisone 100 mg days 1-5, followed by 2 cycles of Rituximab monotherapy	6 three-weekly cycles of R-mini-CHOP followed by 2 cycles of Rituximab OR 4-6 four-weekly cycles of R-PECC R-mini-CHOP: Rituximab 375 mg/m <sup>2</sup> day 1, doxorubicine 25 mg/m <sup>2</sup> day 1, vincristine 1 mg day 1, cyclophosphamide 400 mg/m <sup>2</sup> day 1, prednisone 40 mg/m <sup>2</sup> days 1-5 R-PECC: Rituximab 375 mg/m <sup>2</sup> day 1, etoposide 100 mg/m <sup>2</sup> days 1-5, chlorambucil 8 mg/m <sup>2</sup> days 1-5, lomustine 80 mg/m <sup>2</sup> day 1, prednisone 40 mg/m <sup>2</sup> days 1-5 4-6 four-weekly cycles of R-PECC: see DLBCL stage II-IV for dosages (alternative)
MCL	Recurrent/refractory disease	R-DHAP, R-VIM, R-DHAP followed by BEAM and auto-SCT	
	II-IV	3 cycles of R-CHOP followed by 2 cycles of R-high dose cytarabine (alternating or sequential) followed by BEAM and auto-SCT	8 cycles of R-CHOP followed by Rituximab maintenance therapy for a maximum of 2 years OR R-chlorambucil <sup>2</sup> OR R-bendamustine R-CHOP: Rituximab 375 mg/m <sup>2</sup> day 1, cyclophosphamide 750 mg/m <sup>2</sup> day 1, doxorubicine 50 mg/m <sup>2</sup> day 1, vincristine 1.4 mg/m <sup>2</sup> (max 2 mg) day 1 and prednisone 100 mg days 1-5 R-bendamustine: Rituximab 375 mg/m <sup>2</sup> + bendamustine 90 mg/m <sup>2</sup> days 1-2 q4w No recommendations in the guideline
	Recurrent/refractory disease	No recommendations in the guideline	
Burkitt lymphoma	IIA	High risk: combination of alternately 2 cycles of dose-modified R-CODOX-M and 2 cycles of dose-modified R-IVAC followed by 8 cycles of Rituximab	No recommendations in the guideline

Continue



*Continued*

ALCL	Stage IA, ALK-disease <sup>1</sup>	3 cycles of CHOEP and involved-field radiation therapy	No recommendations in the guideline
Nodal marginal zone lymphoma	Active/symptomatic disease <sup>1</sup>	8 three-weekly cycles of R-CVP: Rituximab 375 mg/m <sup>2</sup> day 1, cyclophosphamide 750 mg/m <sup>2</sup> day 1, vincristine 1.4 mg/m <sup>2</sup> (max 2 mg) day 1 and prednisone 40 mg/m <sup>2</sup> days 1-5	8 three-weekly cycles of R-CVP: Rituximab 375 mg/m <sup>2</sup> day 1, cyclophosphamide 750 mg/m <sup>2</sup> day 1, vincristine 1.4 mg/m <sup>2</sup> (max 2 mg) day 1 and prednisone 40 mg/m <sup>2</sup> days 1-5 OR R-chlorambucil <sup>2</sup> OR Rituximab monotherapy

ALCL = anaplastic lymphoma kinase negative; ALK = anaplastic lymphoma kinase; allo-SCT = allogeneic stem-cell transplantation; auto-SCT = autologous stem-cell transplantation; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; SCLL = small cell lymphocytic lymphoma.

Chemotherapy abbreviations: anti-CD20 monoclonal antibody = Rituximab, Obinutuzumab or Ofatumumab; BEAM = carmustine, etoposide, cytarabine, melphalan; CODOX-M = cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate; CHOEP = cyclophosphamide, etoposide, doxorubicin, vincristine, prednisone; DRC = dexamethasone, Rituximab, cyclophosphamide; IVAC = ifosfamide, cytarabine, etoposide and intrathecal methotrexate; R-CHOP = Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CP = Rituximab, cyclophosphamide, prednisone; R-CVP = Rituximab, cyclophosphamide, vincristine, etoposide, chlorambucil, lomustine, prednisone. R-VIM = Rituximab, etoposide, ifosfamide, fludarabine, cyclophosphamide; R-PECC = Rituximab, etoposide, chlorambucil, lomustine, prednisone. R-VIM = Rituximab, etoposide, ifosfamide, methotrexate.

\* Two different types of guideline recommendations were distinguished based on whether the guideline mentioned treatment recommendations specifically for older and/or unfit patients or not. 1 = Standard treatment: only standard guideline recommendations were available and recommendations for older and/or unfit patients were not mentioned. 2 = Alternative treatment: besides standard recommendations, guideline recommendations for older and/or unfit patients were also available. Relevant guidelines at the time of data collection were used; hence, recommendations may deviate from current treatment recommendations. Only treatment for non-Hodgkin-lymphomas and NHL-stages represented in the database is shown. When the specific chemotherapy agent-as recommended by the guidelines-was not applicable in the study, dosages of this agent are not shown.

<sup>1</sup>Treatment is started in case of active/symptomatic disease

<sup>2</sup>Various treatment regimens for chlorambucil are accepted: chlorambucil 10 mg/m<sup>2</sup> days 1-7 q4w, chlorambucil 0.1-0.15 mg/kg/day daily until maximal response or treatment for 1 year, chlorambucil 10 mg days 1-14 q4w, chlorambucil 0.4 mg/kg days 1-14 q4w, chlorambucil 20 mg days 1-5 q4w, chlorambucil 0.5 mg/kg days 1 and 15 q4w.

**Appendix 1c.** Grouping according to whether the guideline mentioned recommendations for older and/or unfit patients or not.

Guideline contains recommendations only for young and fit patients	Guideline contains recommendations for older and/or unfit patients	Analyzed as
Group 1: Standard	Group 3: Standard	Standard
	Group 4: Alternative	Alternative
Group 2: Adapted	Group 5: Adapted	Adapted

5 groups were formulated based on whether the guideline mentioned treatment recommendations specifically for older or unfit patients, or not. If only standard recommendations were available, without any recommendations specifically for older or unfit patients, the treatment plan was compared with these standard recommendations and the plan could consist of standard treatment (group 1) or non-guideline based adapted treatment (group 2). If a guideline also contained alternative recommendations specifically for those older or unfit, we first evaluated whether the treatment plan was in accordance with the standard guideline recommendations as for younger or fit patients (group 3), and if not, whether it was corresponding with the alternative recommendations for older or unfit patients (group 4). Those plans neither in accordance with standard or alternative guideline recommendations, were considered as non-guideline based adapted treatment plans (group 5).

**Appendix 1d.** Baseline characteristics and course of treatment of cases receiving first-line chemotherapy (either curative or palliative) compared to cases receiving second-line or higher chemotherapy.

		First-line chemotherapy (n = 93)	Second-line or higher chemotherapy (n = 36)	p-value*
Age in years, median		83.1	82.5	
Gender, n (%)	* Male	34 (37)	7 (19)	
	* Female	59 (63)	29 (81)	
CCI score, n (%)	* 0	43 (40)	21 (58)	
	* $\geq 1$	53 (57)	15 (42)	
ECOG performance status	* 0	21 (23)	2 (6)	
	* $\geq 1$	22 (24)	4 (11)	
	* Not reported	50 (54)	30 (83)	
ADL/iADL dependency, n (%)	* ADL and iADL independent	54 (58)	12 (33)	
	* ADL and/or iADL dependent	27 (29)	8 (22)	
	* Not reported	12 (13)	16 (44)	
Risk of poor nutrition (MUST), n (%)	* No risk	29 (31)	4 (11)	
	* Average/high risk	17 (18)	5 (14)	
	* Unknown	47 (51)	27 (75)	
Polypharmacy, n (%)	* No	45 (48)	23 (64)	
	* Yes	48 (52)	13 (36)	
Living situation, n (%)	* Community-dwelling	86 (93)	31 (86)	
	* Nursing home	4 (4)	0 (0)	
	* Not reported	3 (3)	5 (14)	
Marital status, n (%)	* Together	45 (48)	18 (50)	
	* Alone	46 (50)	12 (33)	
	* Unknown	2 (2)	6 (17)	
Tumor type, n (%)	* Colorectal cancer	16 (17)	15 (42)	
	* Breast cancer	10 (11)	2 (6)	
	* Lung cancer	17 (19)	1 (3)	
	* Ovarian cancer	20 (22)	6 (17)	
	* Prostate cancer	2 (2)	1 (3)	
	* Non-Hodgkin lymphoma	28 (30)	11 (31)	
Primary chemotherapy adaptations, n (%)		55 (59)	24 (75)	0.11
	* Primary dose reductions	34 (37)	0.18	0.18
	* Change in chemotherapeutic drug	33 (36)	0.15	0.15
Secondary chemotherapy adaptations, n (%)		58 (62)	26 (72)	0.29
	* Secondary dose reductions	25 (27)	0.68	0.68
	* Interval	5 (5)	0.25	0.25
	* Change in chemotherapeutic drug	8 (9)	0.24	0.24
	* Delay between cycles	35 (38)	0.90	0.90
	* Reduced number of cycles	33 (36)	0.22	0.22
Hospitalisation, n (%)		25 (27)	7 (19)	0.38
Chemotherapy-related toxicity, n (%)		48 (52)	20 (56)	0.69
Chemotherapy completed according to plan (RDI $\geq 85\%$ )		49 (53)	18 (50)	0.78

\* p-values only shown for primary and secondary outcomes.



# PART III

Patient-reported outcomes in older patients with cancer



# Chapter 8

Chemotherapy and healthcare utilization near the end of life in  
patients with cancer

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## **ABSTRACT**

### **Introduction**

The quality of medical care delivered to cancer patients near the end of life is a significant issue. Previous studies have defined several areas suggestive of aggressive cancer treatment as potentially representing poor quality care. The primary objective of current analysis was to examine chemotherapy and health care utilization in the last three months of life among cancer patients that received palliative chemotherapy.

### **Methods**

Patients were selected from the hospital administration database of the Diaconessenhuis Utrecht, the Netherlands. Patient characteristics, chemotherapy and healthcare utilization were extracted from the medical files.

### **Results**

604 patients were included for analysis (median age: 64 years). For 300 patients (50%) chemotherapy was given in the last three months (CT+). For 76% (n=229) of CT+patients unplanned hospital admissions were made in these last three months, compared to 44% (n=133) of CT–patients ( $p<0.001$ ). Visits to the Emergency Room in last three months were made by 67% (n=202) of CT+patients compared to 43% (n=132) of CT–patients ( $p<0.001$ ). Of CT+patients, 29% (n=87) died in the hospital compared to 8% (n=24) of CT–patients ( $p<0.001$ ).

### **Conclusion**

Half of the patients that received palliative chemotherapy were treated with chemotherapy in the last three months of life. Healthcare consumption was significantly higher in patients who received chemotherapy in the last three months of life. Being able to inform our patients about these aspects of treatment can help to optimize both the quality of life and the quality of dying in patients with cancer.



## INTRODUCTION

Many issues faced at the end of life by patients dying of cancer will be similar, regardless of their initial type of cancer.<sup>1</sup> Previous studies have defined several areas suggestive of overly aggressive cancer treatment and potentially representing poor quality care, including use of chemotherapy in the last period before death, use of treatment resulting in high rates of emergency room (ER) visits, hospitalization or intensive care units (ICU), admission for terminal patients and underuse of hospice services.<sup>2-4</sup> Quality of medical care delivered to cancer patients near the end of life is therefore of significant concern.

Trends over time suggest that the utilization of aggressive cancer care near the end of life is increasing, without rendering significant benefits in terms of disease control, quality of life or survival.<sup>5</sup> Possible explanations are the expanding range of chemotherapeutic options, increasing optimism amongst cancer specialists, anecdotal experiences of late-line treatment success, higher expectations and demands from patients and their families and also the complexities of truthfully communicating a patient's poor prognosis whilst not wanting to take away hope.<sup>1,5</sup>

Reversely, interventions aimed at improving quality of care at the end of life, such as offering palliative care early in a disease trajectory when cure is not an option, have been shown to result in significant improvement in quality of life.<sup>6</sup> In some cases, such as in a large randomized trial of metastatic lung cancer patients, the improvements caused by advanced care planning were similar to what can be expected among patients who have a response to cisplatin-based chemotherapy. In addition to improved quality of life, these patients received less aggressive end-of-life care and even experienced longer survival.<sup>6</sup>

In this time of increasingly sophisticated anti-cancer treatments and subsequently mounting health care costs, judicious use of treatment options and tailor-made care is of paramount importance. A first step in improving the quality of care provided at the end of life for patients diagnosed and treated for cancer is to become aware of our own treatment practices. Therefore, the primary objective of this audit was to examine the use of chemotherapy in the last three months of life among cancer patients treated with palliative chemotherapy at the Diaconessenhuis Utrecht, the Netherlands. Secondary outcome measures included healthcare utilization during the last three months of life.

## METHODS

This audit was performed in the Diaconessenhuis Utrecht – a large teaching hospital in the Netherlands. We selected all patients who had received chemotherapy with a

palliative intent for a solid malignancy between February 2011 and August 2015 and were deceased at the time of analysis, from the Diaconessenhuis hospital administration data. Patients were excluded if they only received topical chemotherapy (for example intravesical in bladder malignancies). Patients were also excluded if they were (partially) treated elsewhere, because this resulted in missing data regarding healthcare utilization, including chemotherapy, in the last three months of life.

Patients were classified as CT+ if they received palliative chemotherapy in the last three months of life and as CT- if they did not.

For all patients, the following data were collected from the medical charts: date of birth, sex, diagnosis, date of (palliative) diagnosis, last known date of chemotherapy, date and location of death, details about known healthcare utilization (data about admission to hospital or the ICU and ER-visits) in the last three months of life. In addition, for CT+ patients we also collected data on comorbidity (assessed using the Charlson comorbidity index<sup>7</sup> (CCI)), Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the time of initiation of last line of treatment, first date of chemotherapy, last known date of chemotherapy, and the type and treatment line of chemotherapy.

The medical ethics committee reviewed the research protocol and provided a written statement that this study was exempt from full ethical review given its retrospective nature.

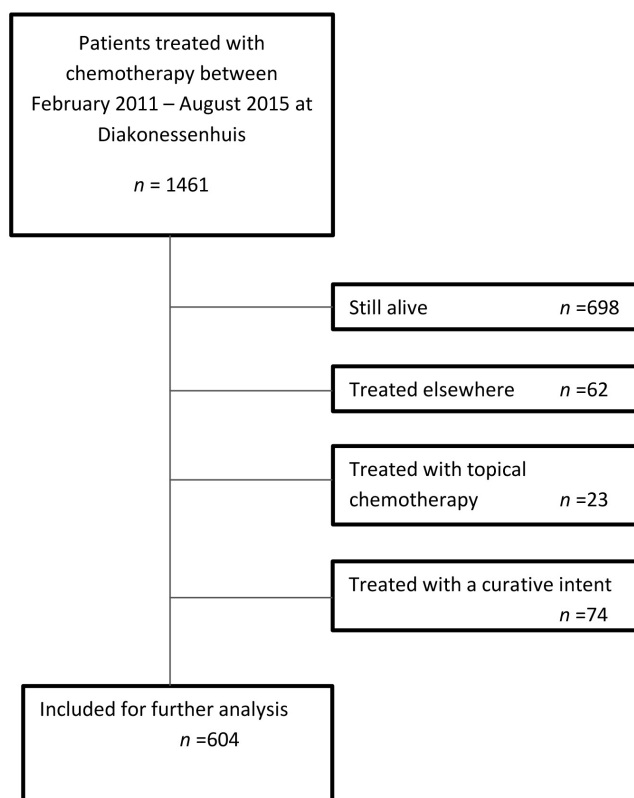
### **Statistical analysis**

All analyses were performed in SPSS Statistics version 23.0. A p-value smaller than 0.05 was considered statistically significant. For comparisons between groups, the chi-square test was used for nominal and ordinal variables, and the ANOVA test was used for continuous variables. Subgroup analyses were performed according to primary diagnosis: lung cancer, colorectal cancer, breast cancer, malignancies of upper gastro-intestinal tract (GI), including malignancies of the esophagus, gastric cancer, cholangiocarcinoma and pancreas carcinoma and the remaining diagnoses were grouped together ('other').

## **RESULTS**

### **Patient selection**

A total of 1461 individual patients were treated with palliative chemotherapy in our hospital between February 2011 and August 2015 and therefore selected from the hospital administration data. The patient selection is depicted in Figure 1: 698 patients were still alive and therefore excluded; their diagnoses can be viewed in the Appendix. Sixty-two patients were excluded because they were treated elsewhere and another 97 patients



**Figure 1.** Patient selection.

because they were treated with a curative intent ( $n=74$ ) or received topical chemotherapy only ( $n=23$ ). Ultimately, 604 patients were selected for further analyses.

### Baseline characteristics

The 604 included patients received palliative chemotherapy for a wide range of diagnoses (Table 1). The most frequent diagnoses were lung cancer (38.6%;  $n=233$ ), colorectal cancer (24.2%;  $n=146$ ), breast cancer (14.1%;  $n=85$ ) and malignancies of the upper GI tract (8.6%;  $n=52$ ). The remaining 14.6% ( $n=88$ ) were treated for other malignancies: ovarian ( $n=32$ ), prostate ( $n=25$ ), urothelium ( $n=20$ ), endometrial ( $n=4$ ), adenocarcinoma of unknown primary (ACUP ( $n=6$ )) or angiosarcoma ( $n=1$ ).

Half of all included patients ( $n=300$ ) received chemotherapy in the last three months of life (CT+). Patients who did not receive chemotherapy in the last three months of life (CT-;  $n=304$ ) had a median time between death and the last chemotherapy of 170 days (IQR 25-75: 123 – 278), compared to a median of 39 days for the CT+patients (IQR 25- 75: 21- 63 days) (Table 2).

**Table 1.** Diagnoses.

Type of malignancy	n (total n=604)	% of total (n= 604)
Lung	233	38.6
Colorectal	146	24.2
Breast	85	14.1
Upper gastro-intestinal tract*	52	8.6
Other**	88	14.6

\*Upper gastro-intestinal tract: cholangio, gastric, pancreatic, esophagus

\*\*Ovarian, prostate, urothelium, adenocarcinoma of unknown primary, endometrial, angiosarcoma

**Table 2** Baseline characteristics.

	All patients	CT + *	CT – **	p-value	
Number of patients (%)					
-	Total	604	300	304	0.17
-	Lung	233	111	122	
-	Colorectal	146	68	78	
-	Breast	85	50	35	
-	Upper GI	52	31	21	
-	Other	88	40	48	
Median age at diagnosis in years (IQR25-75)					
-	Total	63.8 (56.5 – 70.6)	63.5 (56.5 – 70.1)	64.7 (56.3 – 71.4)	0.17
-	Lung	65.3 (58.9 – 72.0)	65.2 (58.5 – 72.1)	65.4 (59.0– 72.0)	0.84
-	Colorectal	64.8 (57.1 – 71.4)	63.8 (55.0 – 70.2)	66.5 (58.8 – 73.7)	0.28
-	Breast	57.4 (48.8 – 64.9)	59.4 (56.5 – 64.7)	53.7 (48.9 – 65.5)	0.59
-	Upper GI	61.7 (50.8 – 68.0)	61.4 (50.8 – 69.3)	2.0 (50.5 – 67.9)	0.90
-	Other	64.0 (58.7 – 70.8)	62.8 (59.3 – 68.4)	67.8 (56.3 – 72.4)	0.37
Median time between primary diagnosis and death in days (IQR25-75)					
-	Total	454 (215 – 1087)	346.5 (119 – 846)	595 (323 – 1157)	<0.001
-	Lung	260 (137 – 451)	127 (73 – 315)	377.5 (250 – 551)	0.04
-	Colorectal	642 (358 – 1126)	424.5 (207 – 839)	843.5 (543 – 1512)	<0.001
-	Breast	1930 (1032 – 4170)	1823.5 (833 – 3985)	1932 (1156 – 5208)	0.59
-	Upper GI	225 (110 – 403)	162 (80 – 307)	401 (260 – 563)	<0.001
-	Other	822 (400 – 1662)	673 (169 – 1498)	1039 (490 – 1888)	0.04

*Continue*

*Continued*

	<b>All patients</b>	<b>CT + *</b>	<b>CT – **</b>	<b>p-value</b>
Median time between last chemotherapy and death in days (IQR25-75)				
- Total	91 (39 – 170)	39 (21-63)	170 (123-278)	<b>&lt;0.001</b>
- Lung	99 (38 – 180)	37 (18 – 63)	170 (127 – 271)	<b>&lt;0.001</b>
- Colorectal	99 (40 – 177)	36.5 (20 – 62)	170 (127 – 235)	<b>&lt;0.001</b>
- Breast	75 (29 – 140)	35 (14 – 63)	169 (119 – 295)	<b>&lt;0.001</b>
- Upper GI	69 (39 – 123)	43 (28 – 63)	144 (111 – 264)	<b>&lt;0.001</b>
- Other	99 (51 – 216)	46 (30 – 68)	173 (125 – 342)	<b>&lt;0.001</b>
Patients for whom last course was first line chemotherapeutic treatment				
- Total		161 (53.7)		
- Lung		75 (67.6)		
- Colorectal		22 (32.4)		
- Breast		16 (32.0)		
- Upper GI		25 (81.0)		
- Other		21 (52.5)		

Bold values indicate significance at  $p < 0.05$

Single numbers displayed between brackets represent percentages (%), other numbers: IQR25-75: interquartile ranges 25<sup>th</sup> and 75<sup>th</sup> percentile

\*CT+ (chemotherapy) Patients that received palliative chemotherapy in the last three months of life

\*\*CT– Patients that did not receive chemotherapy in the last three months of life

GI = gastrointestinal

Out of all patients treated with chemotherapy for lung cancer (n=233), 47.6% (n=111) were treated with chemotherapy in the last three months of life (CT+ lung cancer patients). This was 46.6% for colorectal cancer patients (n=68), 58.8% for breast cancer (n=50), 59.6% for upper GI tract malignancies and 45.4% for other malignancies (n=40). There was no significant difference between these subgroups ( $p=0.17$ ).

The median age of all included patients was 63.8 years (IQR25 -75: 56.5-70.6) and did not differ significantly between CT+ patients (median 63.5 years) and CT– patients (median 64.7 years,  $p=0.17$ ). Among the subgroups, the median age did not differ significantly between CT+ and CT– patients (Table 2).

For CT+ patients, the ECOG PS at the time of initiation of the last line of chemotherapy was not recorded in 40.7%. Of the patients for whom ECOG was documented, 61% had an ECOG PS of 0, 30% had an ECOG PS 1, 7% had an ECOG PS 2, and 3% ECOG PS4, respectively. The Charlson Comorbidity Index at this time was  $\geq 1$  for 36.3% (n=109) and the remaining 64% had a CCI of 0.

The median time between diagnosis and death was 454 days; this was significantly lower in the CT+ patients compared to the CT- patients with medians of 345 days and 595 days, respectively ( $p<0.001$ ). The median time between diagnosis and death ranged from 260 days (IQR25-75: 137-451) for lung cancer patients to 1930 days (IQR25-75: 1032-4170) for breast cancer patients. The CT+ patients had a significantly shorter time period between diagnosis and death in all subgroups, although this difference was not statistically significant for breast cancer patients.

For 53.7% of the CT+ patients, the last course of chemotherapy consisted of first line treatment. This percentage was 67.6% for lung cancer, 32.4% for colorectal cancer patients, and 48.4 % for upper GI tract malignancies. For CT+ breast cancer patients, the last course of chemotherapy was first line treatment for 31% of the patients, second line for 20%, third line for 16% and fourth line for 12%.

### **Healthcare utilization in the last 90 days of life**

For the total group, unplanned hospital admissions in the last three months of life were made for 362 out of 604 patients (59.9%). (Table 3) This percentage was significantly higher for CT+ patients than for CT- patients (76.3%  $n = 229$  versus 43.8%  $n = 113$ ), ( $p<0.001$ ). For CT+ patients this ranged from 68.0% for breast cancer patients to 84.6% of lung cancer patients. For CT- patients this ranged from 28.2% (colorectal cancer) to 53.3% (lung cancer).

Visits to the Emergency Room in the last three months of life were made by 55.3% of the total group ( $n=334$ ), significantly more often by CT+ patients (67.3%;  $n=202$ ) compared to CT- patients (43.4%;  $n=132$ ) ( $p<0.001$ ). In the subgroups, this ranged from 28.6% in CT- breast cancer patients to 79.3% in CT+ lung cancer patients (Table 3).

### **End of life/ Place of death**

The place of death was unknown for 33.5% ( $n=203$ ) of all patients. Of the remaining, 217 patients died at home (35.9%), comprising 28.0% of the CT+ patients ( $n=84$ ) and 43.8% of the CT- patients ( $n=133$ ) (Table 3). Of all included patients, 18.4% died in hospital ( $n=111$ ), and this occurred significantly more often in CT+ patients (29.0%;  $n=87$ ) compared to CT- patients (7.9%;  $n=24$ ) ( $p<0.001$ ). The percentages were similar among all subgroups. In addition, 12.2% ( $n=74$ ) of the patients died in a hospice. There was no statistical difference between admission in a hospice or unknown place of death between CT+ and CT- patients.

**Table 3.** Healthcare utilization in the last 3 months of life.

		Unplanned hospital admissions	Visits ER	Death in hospital	Death at home
Total (n=604)		362 (59.9)	334 (55.3)	111 (18.4)	217 (35.9)
	CT+*	229 (76.3)	202 (67.3)	87 (29)	84 (28)
	CT–**	133 (43.8)	132 (43.4)	24 (7.9)	133 (43.8)
	p-value	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Lung (n=233)		160 (68.7)	156 (67.0)	50 (21.5)	93 (39.9)
	CT+	95 (85.6)	88 (79.3)	34 (30.6)	30 (27.0)
	CT–	65 (53.3)	68 (55.7)	16 (13.1)	63 (51.6)
	p-value	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Colorectal (n=146)		72 (49.3)	62 (42.5)	26 (17.8)	50 (34.2)
	CT+	50 (73.5)	38 (55.9)	22 (32.4)	19 (27.9)
	CT–	22 (28.2)	24 (30.8)	4 (5.1)	31 (37.9)
	p-value	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Breast (n=85)		45 (52.9)	38 (45.2)	16 (18.8)	34 (40.0)
	CT+	34 (68.0)	28 (57.1)	14 (28.0)	17 (34.0)
	CT–	11 (31.4)	10 (28.6)	2 (5.7)	17 (48.6)
	p-value	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.05</b>	<b>0.05</b>
Upper GI (n=52)		34 (65.4)	32 (61.5)	8 (15.4)	16 (30.8)
	CT+	23 (74.2)	23 (74.2)	8 (25.8)	9 (29.0)
	CT–	11 (52.4)	9 (42.9)	0 (0)	7 (33.0)
	p-value	0.11	<b>0.02</b>	n.a.	<b>0.02</b>
Other (n=88)		51 (58)	46 (52.3)	11 (12.5)	24 (11.1)
	CT+	27 (67.5)	26 (62.5)	9 (22.5)	9 (22.5)
	CT–	24 (50.0)	21 (43.8)	2 (4.2)	15 (31.3)
	p-value	0.106	0.08	0.07	0.07

Bold values indicate significance at  $p < 0.05$

Numbers displayed between brackets represent percentages (%)

\*CT+ (chemotherapy) Patients that received palliative chemotherapy in the last three months of life

\*\*CT– Patients that did not receive chemotherapy in the last three months of life

ER = emergency room; GI = gastro-intestinal

## DISCUSSION

We found that as many as half of the patients received chemotherapy in the last three months of life in this audit on chemotherapy and healthcare utilization among patients receiving palliative chemotherapy. For patients treated for breast cancer or for malignancies of the upper GI tracts this was even higher, reaching up to 60%. In CT+ patients, the last course of chemotherapy was first line treatment in 54% and the median time between the initiation of the last line of chemotherapy and death was 39 days. More than half of patients had unplanned hospital admissions and visited the ER in the last three months of life. Both occurred significantly more often in CT+ patients than in CT- patients and this finding was consistent among all predefined subgroups. In addition, we found that the risk of dying in the hospital was significantly higher for CT+ patients.

There is a long-held perception of death resulting from treatment failure rather than disease progression and as a result, initiation or continuation of treatment is the 'the default option' for patients presenting to emergency departments or other places of the hospital.<sup>3,8,9</sup> On the other hand, chemotherapy and healthcare utilization in the last three months of life have both been suggested as determinants of overly aggressive or poor quality end-of-life care.<sup>2-4</sup> In the course of disease, clinicians, patients and their caregivers must continually weigh the potential benefits of treatment against their negative effects and find the balance between hope and realism.

Our study shows that the use of chemotherapy in the last three months of life is high. However, it is difficult to place these results into clinical perspective and to determine if this does indeed represent suboptimal cancer care. Because of the retrospective nature of our study, we are not informed about details leading to the decision to start or to continue chemotherapy in individual patients. Legitimate reasons for starting chemotherapy late in the disease trajectory do exist; for instance, the aim of chemotherapy might have been to treat specific symptoms and thereby improve quality of life.<sup>3,10</sup>

As demonstrated in a large randomized controlled trial in metastatic lung cancer patients, early integration of palliative care with standard oncologic care resulted in less aggressive treatment at the end of life and clinically meaningful improvements in quality of life and mood.<sup>6</sup> However, most remarkably, early integration of palliative care prolonged survival by two months, despite patients receiving less chemotherapy. A possible explanation for this finding seems to be in line with earlier data that showed that a lower quality of life and depressed mood are associated with shorter survival among patients with metastatic non-small-cell lung cancer.<sup>11,12</sup> Early integration of palliative care will also lead to well-timed advance care planning and allow patients and their caregivers to express their preferences and concerns regarding the end of life.<sup>13,14</sup>



Our study has several limitations. Firstly, our results are only descriptive and therefore it is difficult to determine whether or not individual treatment decisions should be considered overly aggressive or non-beneficial. Second, our study has a single-center study design. Despite the fact that dilemmas regarding cancer treatments in a palliative setting are universal, the opinions and preconceptions of individual physicians may have an impact on treatment decisions. In addition, intercultural differences, as for example informing the patient about the disease status, are not universal.<sup>15,16</sup> Therefore, a similar audit in another center might yield different results.

Nevertheless, our findings are in line with prior research, which has shown that treatment towards the end of life is becoming more aggressive over time.<sup>1</sup> One review demonstrated that the prevalence of non-beneficial treatment at the end-of-life in cancer patients ranged from 33% to 38%.<sup>3</sup> Reported rates of the start of chemotherapy at the end of life ranged from 8.8% within fourteen days of death<sup>17</sup> to 76% within six weeks of death.<sup>18</sup> Due to differences in healthcare systems around the world, data about healthcare utilization (e.g. emergency department visits or unplanned hospitalization), are more difficult to compare. One study reported that up to 48% of advanced lung cancer patients visited the emergency ward within 30 days preceding death.<sup>19</sup> In an Australian study, up to 74% of the cancer patients made unplanned hospital visits in the six months after chemotherapeutic treatment.<sup>20</sup>

In addition to healthcare utilization at the end of life, place of death should be regarded as an essential goal in end-of-life care.<sup>21</sup> Most people prefer to stay at home in the last phase of life.<sup>22</sup> Yet, a survey among Dutch general practitioners revealed that potentially 25% of the hospital admissions could have been avoided.<sup>23</sup> Our data show that receiving chemotherapy near the end of life is associated with a lower chance of dying at home. Similarly, one study found that more than half of the patients whose death was expected, were transferred from home to a hospital in the last three months of life.<sup>24,25</sup>

Given the palliative treatment intent, it is important to be able to inform our patients about other aspects of treatment, as for example the likelihood of requiring emergency hospital admission or the impact it will have on quality of life, physical functioning and care dependency. However, at the moment these patient-centered outcome measures (PROMs) are only incorporated into a minority of the ongoing clinical trials.<sup>26</sup> In addition, a recent study showed that 57% of phase III clinical trials for solid malignancies with a poor prognosis did not include quality of life as a study objective.<sup>27</sup> Of the trials that did, these results were omitted in 50% of full text publications or only presented as a single sentence statement.<sup>27</sup>

This analysis was performed as a first step in improving the quality of care our center offers cancer patients in the last phase of life. As a next step, efforts need to be made to more routinely incorporate advance care planning for patients in the palliative treatment setting, particularly as they near the end of life. One important issue is that it is not simple to recognize when the last three months or the final of life has started. No validated tools currently exist to aid clinicians in this process. Additionally, it will be helpful if better predictors for therapeutic response are available. This could be an important line of future research.

### **Conclusion**

In this retrospective study, half of all cancer patients treated with chemotherapy with a palliative intent received chemotherapy in the last three months of life. Use of healthcare, including unplanned hospital admissions and ER visits was high among all patients, but significantly higher for patients receiving chemotherapy in the last three months than for those who did not. Additionally, the risk of dying in the hospital was higher for CT+ patients, whereas CT- patients more often died at home. For diseases with a poor prognosis we need to inform our patients about these aspects of treatment as well. Although it is difficult to generalize our results, we have made a first step to give insight in these often overlooked aspects of treatment. Expanding research on which treatments may be non-beneficial in the last phase of life can contribute to improving both quality of life and quality of death in patients suffering from cancer.

## REFERENCES

1. Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? *J Clin Oncol.* 2008;26(23):3860-3866. doi:10.1200/JCO.2007.15.8253.
2. Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. *J Clin Oncol.* 2003;21(6):1133-1138.
3. Cardona-Morrell M, Kim J, Turner RM, Anstey M, Mitchell IA, Hillman K. Non-beneficial treatments in hospital at the end of life: a systematic review on extent of the problem. *Int J Qual Health Care.* June 2016. doi:10.1093/intqhc/mzw060.
4. De Korte-Verhoef MC, Pasman HRW, Schweitzer BPM, Francke AL, Onwuteaka-Philipsen BD, Deliens L. How could hospitalisations at the end of life have been avoided? A qualitative retrospective study of the perspectives of general practitioners, nurses and family carers. *PLoS One.* 2015;10(3):e0118971. doi:10.1371/journal.pone.0118971.
5. van den Berg JW, Venema G, Uil S, Kloosterziel C. Chemo wordt te lang doorgezet. *Med Contact (Bussum).* 2013;39:1974-1975.
6. Temel JS, Greer JA, Muzikansky A et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363:733-742.
7. Charlson ME, Pompei KL, Ales CR, Mackenzie A. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373-383.
8. Darmon M, Azoulay E. Critical care management of cancer patients: cause for optimism and need for objectivity. *Curr Opin Oncol.* 2009;21(4):318-326. doi:10.1097/CCO.0b013e32832b68b6.
9. Palda VA, Bowman KW, McLean RF, Chapman MG. "Futile" care: do we provide it? Why? A semistructured, Canada-wide survey of intensive care unit doctors and nurses. *J Crit Care.* 2005;20(3):207-213. doi:10.1016/j.jcrc.2005.05.006.
10. Matsuyama, R, Reddy, S, Smith T. Why do patients choose chemotherapy near the end of life? A review of the perspective of those facing death from cancer. *J Clin Oncol.* 2006;24:3490-3496.
11. Maione P, Perrone, Gallo C, Manzione L, Vito Piantedosi F, Barbera S, Cigolari S RF. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly s. *J Clin Oncol.* 2005;23(28):6865-6872.
12. Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. *J Clin Oncol.* 2009;27(34):5816-5822. doi:10.1200/JCO.2009.23.7420.
13. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. *N Engl J Med.* 2012;367(17):1616-1625. doi:10.1056/NEJMoa1204410.
14. Mack JW, Walling A, Dy S, et al. Patient beliefs that chemotherapy may be curative and care received at the end of life among patients with metastatic lung and colorectal cancer. *Cancer.* 2015;121(11):1891-1897. doi:10.1002/cncr.29250.

15. Collis E, Sleeman KE. Do patients need to know they are terminally ill? Yes. *BMJ*. 2013;346:f2589.
16. Blackhall LJ. Do patients need to know they are terminally ill? No. *BMJ*. 2013;346:f2560.
17. von Gruenigen V, Daly B, Gibbons H, Hutchins J, Green A. Indicators of survival duration in ovarian cancer and implications for aggressiveness of care. *Cancer*. 2008;112(10):2221-2227. doi:10.1002/cncr.23391.
18. Nevadunsky NS, Spoozak L, Gordon S, Rivera E, Harris K, Goldberg GL. End-of-life care of women with gynecologic malignancies: a pilot study. *Int J Gynecol Cancer*. 2013;23(3):546-552. doi:10.1097/IGC.0b013e3182842efa.
19. Temel JS, McCannon J, Greer JA, et al. Aggressiveness of care in a prospective cohort of patients with advanced NSCLC. *Cancer*. 2008;113(4):826-833. doi:10.1002/cncr.23620.
20. McKenzie H, Hayes L, White K, et al. Chemotherapy outpatients' unplanned presentations to hospital: a retrospective study. *Support care cancer Off J Multinatl Assoc Support Care Cancer*. 2011;19(7):963-969. doi:10.1007/s00520-010-0913-y.
21. Kinoshita H, Maeda I, Morita T, et al. Place of death and the differences in patient quality of death and dying and caregiver burden. *J Clin Oncol*. 2015;33(4):357-363. doi:10.1200/JCO.2014.55.7355.
22. Gomes B, Higginson IJ, Calanzani N, et al. Preferences for place of death if faced with advanced cancer: a population survey in England, Flanders, Germany, Italy, the Netherlands, Portugal and Spain. *Ann Oncol*. 2012;23(8):2006-2015. doi:10.1093/annonc/mdr602.
23. De Korte-Verhoef MC, Pasman HRW, Schweitzer BP, Francke AL, Onwuteaka-Philipsen BD, Deliens L. General practitioners' perspectives on the avoidability of hospitalizations at the end of life: A mixed-method study. *Palliat Med*. 2014;28(7):949-958. doi:10.1177/0269216314528742.
24. Abarshi E, Echteld M, Van den Block L, Donker G, Deliens L, Onwuteaka-Philipsen B. Transitions between care settings at the end of life in the Netherlands: results from a nationwide study. *Palliat Med*. 2010;24(2):166-174. doi:10.1177/0269216309351381.
25. Pivodic L, Pardon K, Miccinesi G, et al. Hospitalisations at the end of life in four European countries: a population-based study via epidemiological surveillance networks. *J Epidemiol Community Health*. 2016;70(5):430-436. doi:10.1136/jech-2015-206073.
26. Schulkes KJG, Nguyen C, van den Bos F, Hamaker ME, van Elden LJR. Patient-Centered Outcome Measures in Lung Cancer Trials. *Lung*. June 2016. doi:10.1007/s00408-016-9903-2.
27. Hamaker ME, Schulkes KJ, ten Bokkel Huinink D, van Munster BC, van Huis LH, van den Bos F. Evaluation and reporting of quality of life outcomes in phase III chemotherapy trials for poor prognosis malignancies. *Qual Life Res*. 2016:1-7. doi:10.1007/s11136-016-1360-0.

**Appendix.** Type of malignancy of patients treated with chemotherapy (curative or palliative intent) at Diaconessenhuis Utrecht not deceased.

Type of malignancy	n (%)
Lung	63 (9)
Colorectal	157 (22.5)
Mamma	418 (59.8)
Ovarian	29 (4.1)
Prostate	11 (1.6)
Urothelium	4 (0.6)
Pancreas	2 (0.3)
Gastric	8 (1.1)
Esophagus	4 (0.6)
Endometrium	2 (0.3)



# Chapter 9

Older ovarian cancer survivors report lower long-term health-related quality of life than younger survivors: a study from the population-based profiles registry

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## **ABSTRACT**

### **Objective**

To assess long-term differences in health-related quality of life (HRQoL) of older ovarian cancer survivors compared to both an age-matched normative population and to younger survivors. In addition, the differential effect of chemotherapy on HRQoL between older and younger survivors was compared.

### **Methods**

Ovarian cancer survivors (n= 348) diagnosed between 2000 and 2010, as registered by the Dutch population-based Eindhoven Cancer Registry, were invited to complete the EORTC QLQ-C30 HRQoL questionnaire in 2012. HRQoL outcomes of survivors were compared with an age-matched normative population and older survivors ( $\geq 70$  years) were compared with younger survivors.

### **Results**

The questionnaire was returned by 191 ovarian cancer survivors (55%), 31% were aged  $\geq 70$  years (n= 59). Compared to the normative population, survivors  $\geq 70$  years scored lower on global health status and all functioning subscales except emotional functioning, and they reported more symptoms. Survivors aged  $< 70$  years only reported worse physical and cognitive functioning in comparison with the normative population. Most differences were of medium to small clinical relevance. Age appeared to moderate the effect of chemotherapy on HRQoL. Older survivors who had received chemotherapy experienced better physical functioning and less pain and insomnia while the opposite was found in younger survivors.

### **Conclusion**

In comparison with an age-matched normative population, older ovarian cancer survivors report lower HRQoL scores than younger survivors. As this represents a selection of long-term survivors, future research should focus on the trajectory of HRQoL from diagnosis throughout treatment and follow-up to identify which factors are related to worse HRQoL in the entire older ovarian cancer population and whether timely interventions are able to improve HRQoL.



## INTRODUCTION

Ovarian cancer is primarily a disease of the elderly and in the Netherlands, more than one third of ovarian cancer patients are aged 70 years or older at diagnosis,<sup>1</sup> and this proportion is growing.<sup>2</sup> Most patients present with advanced-stage disease and have a poor prognosis, with five-year survival rates of less than 15% in patients aged 75 years or older.<sup>3</sup>

The majority of patients with ovarian cancer are treated with cytoreductive surgery and combination chemotherapy,<sup>4</sup> which is an extensive treatment. In early stage disease, treatment consists of surgery; adjuvant chemotherapy is offered when there are unfavorable tumor characteristics<sup>4</sup> and to patients in whom the staging procedure was suboptimal, which occurs more often in elderly patients.<sup>5</sup>

Health-related quality of life (HRQoL) of women with ovarian cancer is seriously impaired by both the diagnosis as well as the extensive treatment.<sup>6,7</sup> With the growing number of older ovarian cancer survivors, data on long-term HRQoL are highly relevant. Multiple organizations have recommended the use of HRQoL as a primary outcome measure in studies on patients with (ovarian) cancer<sup>8–11</sup> but long-term data on these outcomes are largely missing for older patients. Answers to questions such as “How long can I keep living in my own house?” and “Will my cognitive functioning be maintained after treatment?” may be at least as important to older cancer patients as actual long-term survival.<sup>12,13</sup> The scarce research on age and HRQoL in ovarian cancer shows inconsistent results<sup>6,14–18</sup> and in all these studies, the relation between age and HRQoL was not the primary study outcome.

One of the most characteristic aspects of ageing is the failure to maintain homeostasis when challenged by stressors such as disease or treatment, due to diminished physiological reserves.<sup>19</sup> In addition, because of age-related changes in pharmacokinetics and pharmacodynamics<sup>20</sup> and thus a risk of larger lingering side-effects in older women, chemotherapy may disproportionately affect HRQoL of older survivors. Only one prospective study evaluated older patients' chemotherapy tolerance and found that both functioning and quality of life were associated with completion of four cycles of chemotherapy.<sup>21</sup> However, the moderating effect of age on the impact of chemotherapy on HRQoL of older and younger ovarian cancer survivors has not been investigated yet. In addition, studies that assessed long-term functioning and symptoms in older ovarian cancer survivors compared to an age-matched general population are currently lacking, while this comparison may be more relevant than comparisons with their younger counterpart.

Therefore, the aims of the present study were to assess long-term differences in HRQoL of older ovarian cancer survivors compared to both an age-matched normative population and to younger ovarian cancer survivors. In addition, the effect of chemotherapy on HRQoL of older and younger ovarian cancer survivors was compared. We hypothesized older survivors' HRQoL to be worse than that of both the normative population and younger survivors and that older survivors' HRQoL is more negatively affected by chemotherapy than HRQoL of younger survivors.

## **METHODS**

### **Setting, participants and data collection**

For this study, data of a cross-sectional, population-based survey among ovarian cancer survivors were used. Details of the data collection have been reported previously.<sup>22</sup> In short, all women diagnosed with ovarian cancer between 2000 and 2010, as registered in the Southern region of the Netherlands Cancer Registry (NCR), were eligible for participation ( $n = 1147$ ). Patients were excluded if they died prior to the start of the study or if their address was unverifiable. Of the 348 eligible ovarian cancer survivors, 191 completed the questionnaire (55%). Respondents and non-respondents did not differ on baseline characteristics (age, years since diagnosis, tumor stage, treatment and socio-economic status).<sup>22</sup>

Patient-reported outcomes were collected in 2012. Ovarian cancer survivors received a letter from their (ex)-attending specialist and a paper questionnaire. Data collection was performed within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship), which is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a population-based cohort of cancer survivors.<sup>23</sup> Ethical approval for the study was obtained from the Medical Ethics Committee of the St. Elisabeth Hospital, Tilburg, the Netherlands.

### **Normative population**

Socio-demographic and HRQoL data of the normative population were obtained from CentERpanel; an online household panel representative of the Dutch population in the Netherlands.<sup>24</sup> Details of the annual data collection are described elsewhere.<sup>25</sup> In total, data of 1883 cancer-free respondents  $\geq 18$  years were available. Of this sample, a random 5-years age-matched normative sample was selected, reflecting the distribution of the ovarian cancer survivors in this study, resulting in 264 respondents.

### **Clinical and sociodemographic characteristics**

Clinical and sociodemographic information was obtained from the NCR (i.e., date of birth, date of diagnosis, tumor stage, tumor grade, primary treatment and socio-economic

status).<sup>26</sup> Comorbidity at the time of the study was assessed with the adapted Self-administered Comorbidity Questionnaire.<sup>27</sup>

### **Health-related quality of life**

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) was used to assess HRQoL.<sup>28</sup> This questionnaire contains five functional scales regarding physical, role, cognitive, emotional and social functioning and a global health status scale. In addition, it comprises symptom scales on fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial problems. Each item is scored on a 4-point Likert scale ranging from 1: *not at all*, to 4: *very much*. All scale scores were linearly transformed to a 0-100 score.<sup>29</sup> Higher scores on the functioning scales and global health status/QoL represent better HRQoL, while higher scores on the symptom scales indicate worse HRQoL.

### **Statistical analyses**

Ovarian cancer survivors and the normative population were divided into groups according to age: < 70 years and  $\geq$  70 years of age at time of the survey. To describe sociodemographics and clinical characteristics, stratified according to age group, we used independent samples t-tests for continuous and chi-square tests for categorical variables.

To compare differences in HRQoL levels between ovarian cancer survivors and the normative population (similar age groups), multivariable linear regression analyses were performed. These analyses were adjusted for the following a priori defined confounders: number of comorbidities (as continuous variable), educational level (high = university or higher education; medium = vocational training; low = primary or secondary education or less) and partner status (partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited). In addition, multivariable linear regression analyses were conducted to compare HRQoL of both age groups of ovarian cancer survivors adjusted for the time since diagnosis, number of comorbidities, educational level, partner status and treatment received (chemotherapy yes/no; all but one of the survivors received surgery). Due to missing values on one or more dependent or independent variables across the different regression analyses, between four to twelve patients were not included in each regression analysis.

Linear regression analysis was performed to assess the moderating effect of age on the association between chemotherapy and HRQoL outcomes. To assess the moderating effect of age, an interaction term of chemotherapy and age was included, and all a priori-selected covariates (i.e. time since diagnosis, number of comorbidities, educational level, partner status and treatment received) were added to the model. Dependent variables were the HRQoL functioning and symptom scales of the QLQ-C30. For outcome scales

where the interaction term of chemotherapy and age was statistically significant, stratified analyses for the two age groups were carried out.

Clinically important differences (CID) were determined based upon published guidelines for the EORTC QLQ-C30.<sup>30</sup> A large difference is defined as one representing unequivocal clinical relevance, a medium difference as likely to be clinically relevant but to a lesser extent, a small difference to be subtle but nevertheless clinically relevant and a trivial difference as circumstances unlikely to have any clinical relevance. For emotional functioning there is no CID available, and therefor Norman's rule of thumb was used to assess clinical relevance. Norman's rule of thumb states that a difference between groups of half a SD or more can be regarded clinically relevant.<sup>31</sup>

All analyses were performed using IBM SPSS Statistics version 23.0. A two-sided p-value < 0.05 was considered significant, while for the moderation analysis a p-value < 0.1 was considered significant.<sup>32</sup>

## RESULTS

### Sample characteristics

The mean age of the 191 ovarian cancer survivors who responded to the questionnaire was 64 years; 59 were aged  $\geq 70$  years at the time of the survey (31%, Table 1). Women were diagnosed with ovarian cancer on average 6 years before completing the questionnaire (range 2 – 12 years). Two-thirds were diagnosed with early-stage disease (64%). All but one received surgery, while 131 (69%) received chemotherapy. The normative population consisted of 264 controls.

### Comparison of baseline characteristics among ovarian cancer survivors and the normative population

Older ovarian cancer survivors more often did not have a partner (56% versus 27% respectively;  $p < 0.01$ ; Table 1) and had lower educational levels (64% versus 37% respectively low educational level;  $p < 0.01$ ) compared to younger survivors.

The normative population had a higher educational level compared to the ovarian cancer survivors ( $p < 0.01$ ).

### Comparison of HRQoL between ovarian cancer survivors and the normative population

Ovarian cancer survivors aged < 70 years reported significantly worse physical and cognitive functioning compared to the normative population (Table 2; Figure 1A). These differences were of small clinical relevance. Emotional and social functioning were not

**Table 1.** Sociodemographic and clinical characteristics of the study population, N (%).

	Survivors < 70 (n = 132)	Norm < 70 (n = 181)	P-value*	Survivors ≥ 70 (n = 59)	Norm ≥ 70 (n = 83)	P-value*	P-value survivors*
Age at time of survey (mean, SD)	58.5 (8.4)	58.2 (8.1)	0.75	77.3 (5.3)	76.0 (4.4)	0.10	
Educational level†							
High	29 (22)	64 (35)		5 (9)	27 (33)		
Medium	53 (41)	20 (11)	<b>&lt; 0.01</b>	15 (27)	3 (4)	<b>&lt; 0.01</b>	<b>&lt; 0.01</b>
Low	48 (37)	97 (54)		35 (64)	53 (64)		
Missing	2	0		4	0		
Marital status‡							
Partner	95 (73)	134 (74)	0.85	25 (44)	42 (51)	0.43	<b>&lt; 0.01</b>
No partner	35 (27)	47 (26)		32 (56)	41 (49)		
Missing	2	0		2	0		
Number of comorbidities							
0	37 (29)	48 (27)		10 (17)	6 (7)		
1	34 (26)	43 (24)		18 (31)	19 (23)		
≥ 2	59 (45)	89 (49)	0.78	31 (53)	58 (70)	0.07	0.24
Missing	2	1		0	0		
Years since diagnosis (mean, SD)	6.1 (3.2)			6.4 (3.2)			0.48
FIGO stage at diagnosis							
I	83 (63)			32 (54)			
II	13 (10)			9 (15)			0.72
III	30 (23)			14 (24)			
IV	5 (3)			3 (5)			
Missing	0			0			
Treatment							
Chemotherapy only	1 (1)			0 (0)			
Surgery only	42 (32)			18 (31)			0.78
Chemotherapy + surgery	89 (67)			41 (70)			
Missing	0			0			

\* Bold data indicate P-value < 0.05

† Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.

‡ Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited.

**Table 2.** Mean score (SD) on the EORTC QLQ-C30 functioning and symptom scales of ovarian cancer survivors and the normative population according to age. Multivariable regression analysis with HRQoL as dependent variable and age as independent variable.

EORTC QLQ-C30 scales	Survivors < 70 (n = 132)	Survivors ≥ 70 (n = 59)	Norm < 70 (n = 181)	Norm ≥ 70 (n = 83)	Survivors vs norm < 70 β (95% CI)	P-value	CID*	Survivors vs norm ≥ 70 β (95% CI)	P-value	CID*	Survivors < 70 vs survivors ≥ 70 β (95% CI)	P-value	CID*
Physical functioning	83.3 (20.4)	70.2 (23.5)	88.5 (15.8)	75.7 (20.8)	-5.6 (-9.0;-2.2)	<0.01	small	-11.1 (-18.1;-4.1)	<0.01	small	-11.0 (-17.6;-4.5)	<0.01	small
Role functioning	81.2 (24.8)	68.8 (33.3)	86.4 (22.3)	80.3 (24.3)	-5.5 (-10.1;-0.9)	0.02	trivial	-19.4 (-28.5;-10.2)	<0.01	medium	-12.4 (-21.2;-3.5)	<0.01	small
Emotional functioning	83.1 (20.6)	82.4 (20.0)	84.5 (17.6)	86.9 (15.8)	-1.0 (-5.1;-3.0)	0.62	no	-6.6 (-12.9;-0.2)	0.04	no	-2.0 (-8.7;4.9)	0.57	no
Cognitive functioning	84.9 (20.0)	84.2 (22.6)	90.3 (15.9)	91.0 (13.6)	-5.5 (-9.3;-1.6)	<0.01	small	-9.1 (-15.5;-2.8)	<0.01	medium	0.7 (-6.4;7.9)	0.84	trivial
Social functioning	87.5 (19.7)	86.1 (22.9)	91.1 (17.8)	92.0 (14.3)	-3.3 (-7.3;0.8)	0.11	trivial	-10.4 (-16.6;-4.3)	<0.01	small	-2.9 (-9.9;4.3)	0.44	trivial
Global health status	77.8 (16.8)	70.5 (21.9)	76.7 (16.8)	72.7 (17.3)	1.4 (-1.9;4.8)	0.39	trivial	-6.9 (-12.8;-0.9)	0.02	small	-7.2 (-12.8;-1.7)	0.01	small
Fatigue	22.1 (23.2)	31.1 (28.5)	19.4 (20.3)	24.1 (21.4)	2.7 (-1.7;7.0)	0.23	trivial	13.6 (5.7;21.4)	<0.01	medium	8.9 (1.0;16.8)	0.03	small
Nausea / vomiting	4.3 (12.1)	8.5 (20.5)	4.4 (12.4)	3.8 (13.4)	-0.4 (-3.0;2.3)	0.78	trivial	6.1 (0.3;11.9)	0.04	small	3.0 (-2.1;8.1)	0.25	small
Pain	19.4 (26.1)	25.4 (30.7)	20.3 (24.2)	27.5 (28.6)	-1.1 (-5.6;3.5)	0.65	trivial	5.8 (-3.3;14.9)	0.21	trivial	5.5 (-2.9;13.9)	0.20	trivial
Dyspnoea	10.4 (21.9)	21.0 (31.3)	8.3 (17.2)	11.3 (21.0)	1.8 (-2.4;5.9)	0.40	trivial	15.8 (7.0;24.6)	<0.01	large	10.9 (2.6;19.2)	0.01	medium
Insomnia	25.4 (29.0)	29.7 (34.4)	22.4 (27.9)	21.3 (26.8)	3.2 (-2.8;9.1)	0.30	trivial	9.7 (-0.7;20.1)	0.07	small	0.6 (-9.7;10.9)	0.91	trivial
Appetite loss	3.8 (10.6)	15.2 (30.6)	3.2 (13.0)	3.2 (9.9)	0.37 (-2.3;3.0)	0.79	trivial	13.4 (6.5;20.4)	<0.01	small	9.8 (3.7;15.9)	<0.01	small

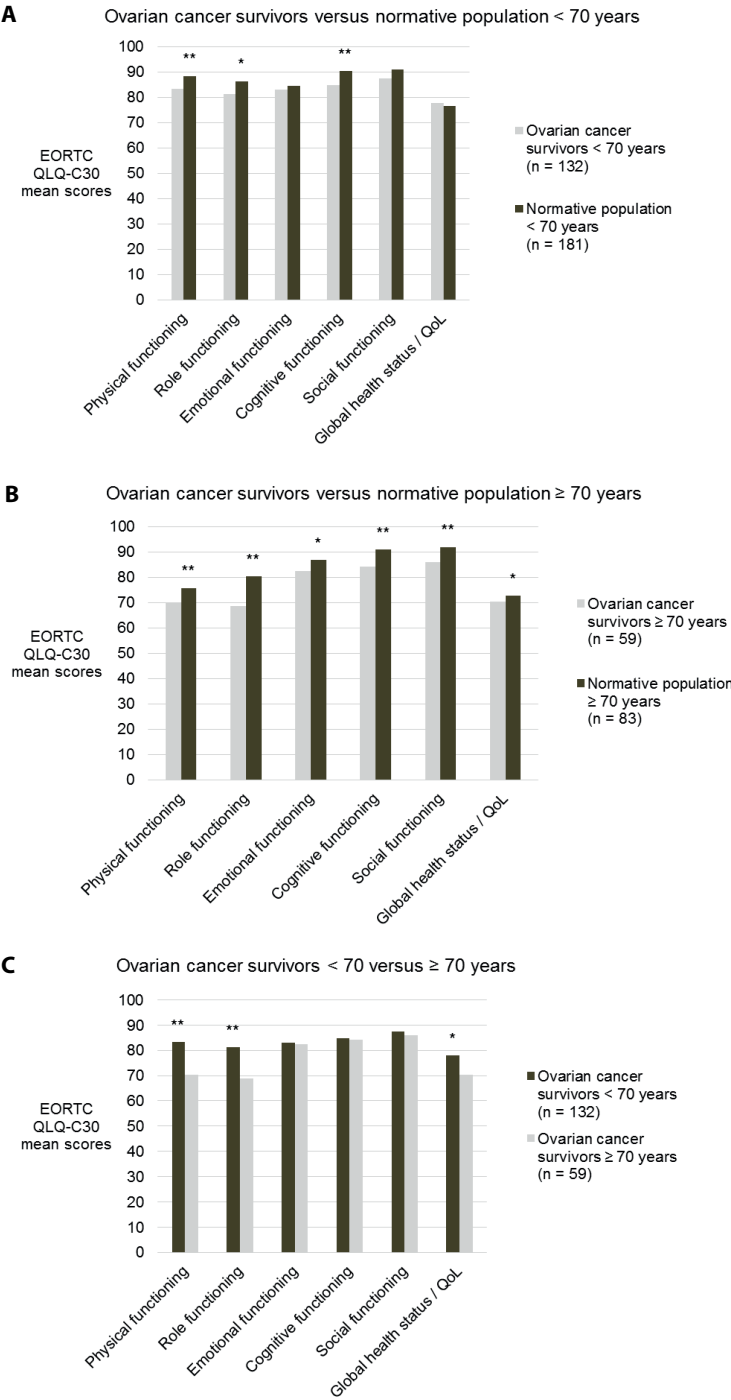
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Constipation	11.4 (21.3)	16.4 (24.7)	6.9 (17.2)	12.1 (18.5)	3.8 (-0.3;7.8)	0.07	trivial	7.0 (-0.7;14.7)	0.07	small	6.4 (-1.0;13.9)	0.09	small
Diarrhea	6.3 (18.0)	6.0 (19.2)	3.5 (11.4)	3.2 (11.2)	2.4 (-0.6;5.3)	0.11	trivial	3.7 (-1.7;9.1)	0.17	trivial	-1.6 (-7.3;4.3)	0.61	trivial
Financial problems	7.4 (19.5)	6.1 (15.8)	4.3 (15.8)	3.6 (13.8)	3.3 (-0.6;7.2)	0.11	small	4.1 (-1.3;9.5)	0.14	small	-1.6 (-8.2;5.0)	0.63	trivial

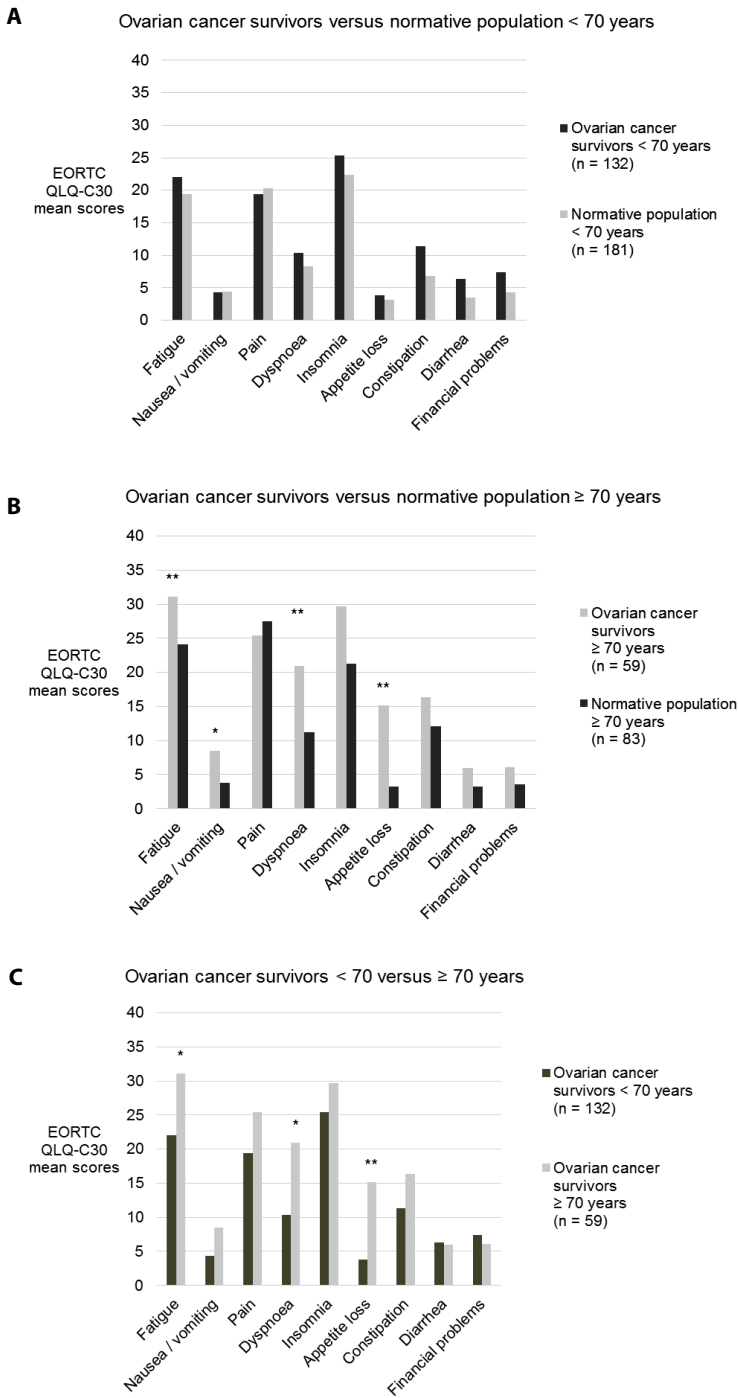
2nd–5th column show crude means and standard deviations (SD). From the 6th column to the end: multivariable regression analysis with EORTC-QLQ-C30 functioning domains or symptoms as dependent variable and age as dichotomous independent variable, adjusted for covariates. A higher score on the functioning scales and global health status means better functioning and quality of life, whereas a higher score on the symptom scales means more complaints. Unstandardized betas ( $\beta$ ), confidence intervals (95% CI) and P-values are reported.

\*Legend for clinically important difference (CID): large = a difference representing unequivocal clinical relevance; medium = a difference likely to be clinically relevant but to a lesser extent; small = a subtle but nevertheless clinically relevant difference; trivial = a difference unlikely to have any clinical relevance. For emotional functioning, no CID is available and Norman's rule of thumb was used to assess clinical relevance. Norman's rule of thumb states that a difference between groups of half a SD or more can be regarded clinically relevant. Bold value indicate CID of small or higher in combination with P-value  $\leq 0.05$ ; CID = clinically important difference; HRQoL = health-related quality of life; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.



**Figure 1.** Differences in EORTC QLQ-C30 mean functioning and global health scores between **A.** ovarian cancer survivors and the normative population < 70 years; **B.** ovarian cancer survivors and the normative population ≥ 70 years; **C.** ovarian cancer survivors aged < 70 years and ≥ 70 years.





**Figure 2.** Differences in EORTC QLQ-C30 mean symptom scores between **A.** ovarian cancer survivors and the normative population < 70 years; **B.** ovarian cancer survivors and the normative population ≥ 70 years; **C.** ovarian cancer survivors aged < 70 years and ≥ 70 years.

significantly different compared to the normative population, nor were the QLQ-C30 symptom scales (Table 2; Figure 2A).

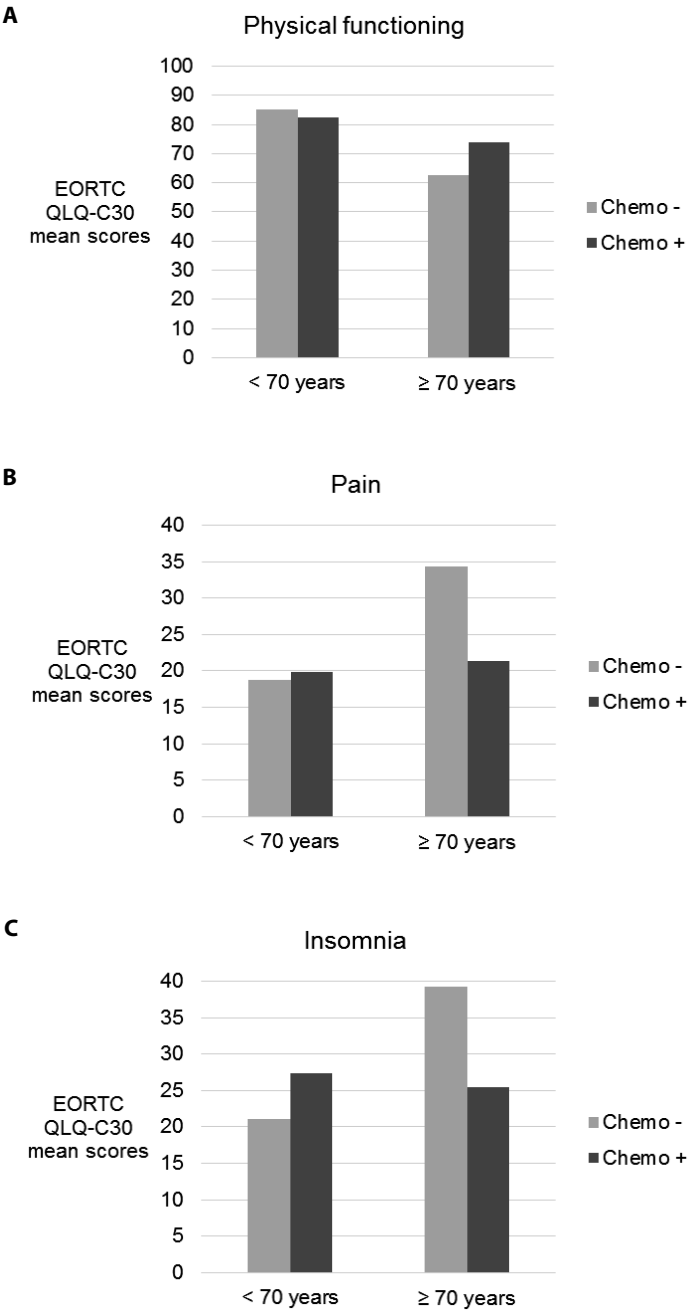
Considering women aged  $\geq 70$  years, compared to the normative population, ovarian cancer survivors reported significantly lower levels on global health status as well as all functioning subscales except emotional functioning (Table 2; Figure 1B). The differences in cognitive and role functioning were of medium clinical relevance, while the others were of small clinical relevance. Among the QLQ-C30 symptom scales, the following were scored significantly worse in the ovarian cancer survivors: fatigue, nausea/vomiting, dyspnea, and appetite loss (Table 2; Figure 2B). There was a trend towards statistical significance for insomnia and diarrhea which were both reported more often in the ovarian cancer survivors. The clinical relevance of the differences was large for dyspnea, medium for fatigue and small for other symptoms.

### **Comparison of HRQoL between younger and older ovarian cancer survivors**

In comparison with younger survivors, older survivors reported significantly poorer physical and role functioning and a lower global health status (Table 2; Figure 1C). These three differences were of small clinical relevance. Emotional, social and cognitive functioning were comparable between both groups. Considering the symptom scales, older survivors scored worse on fatigue, dyspnea and appetite loss (Table 2; Figure 2C). The clinical relevance of these differences was medium for dyspnea and small for fatigue and appetite loss.

### **Differential association between chemotherapy treatment and HRQoL between younger and older ovarian cancer survivors**

There was a significant interaction between chemotherapy and age for physical functioning, pain and insomnia, while the other scales did not differ between women who received chemotherapy and those who did not (data not shown). Stratified multilevel linear regression analyses subsequently showed that older survivors who had received chemotherapy ( $n=41$ ) experienced better physical functioning and less pain and insomnia compared to older survivors who had not received chemotherapy ( $n=18$ ; Figure 3A-C). The clinical relevance for differences in physical functioning and pain were small and for insomnia medium. In younger survivors who had received chemotherapy ( $n=90$ ), physical functioning and pain were scored slightly worse compared to those who had not received chemotherapy ( $n=42$ ) and those that had received chemotherapy experienced more insomnia (Table 3, Figure 3A-C). The clinical relevance for differences in physical functioning and pain were trivial and was small for insomnia.



**Figure 3.** Moderation of the association between chemotherapy and HRQoL by age for  
**A.** physical functioning;  
**B.** pain;  
**C.** insomnia

## DISCUSSION

We analyzed HRQoL in 191 ovarian cancer survivors at an average of six years after diagnosis and found that compared to a normative population, older survivors scored worse on global health status and all functioning domains except emotional functioning, and they reported more symptoms. Younger survivors only scored worse on physical and cognitive functioning. In addition, compared to their younger counterparts, physical and role functioning were rated poorer by older survivors and they reported a lower global health status and more symptoms. The majority of these differences were of medium to small clinical relevance. Lastly, although the number of patients was small, age appeared to moderate the effect of chemotherapy on HRQoL; in contrast to our hypothesis, older survivors who had received chemotherapy experienced better physical functioning and less pain and insomnia while the opposite was seen for younger survivors who had received chemotherapy.

Earlier studies evaluating HRQoL in ovarian cancer survivors—without age-specific analyses—yielded conflicting results.<sup>7,33–36</sup> Most observed rather good post-treatment HRQoL, showing similar or better mental and physical HRQoL scores in comparison with norms for the general population.<sup>33–35</sup> However, poor HRQoL in ovarian cancer survivors has also been reported, with observations of persistent mental and somatic morbidity in this population.<sup>6,7</sup> Survivors suffered from cognitive and social impairments and reported lingering symptoms of fatigue, pain and neuropathy.<sup>6,7</sup> None but one of these studies<sup>7</sup> used an age-matched normative control population for comparison.

Studies in different types of malignancies did compare HRQoL outcomes of cancer survivors with an age-matched normative population.<sup>37–39</sup> Similar to our results, older survivors experienced more functional limitations compared to a normative population. However, while in our study the difference in HRQoL compared to the normative population was greater for older survivors than for younger survivors, most of these studies reported an opposite effect. It was suggested that this greater impact of the disease and its treatment for younger patients was due to higher work-related and social demands. On the other hand, it is also possible that older patients received less aggressive treatment than younger patients, and that this explains the difference in impact. There is no clear explanation for the higher impact for older than for younger patients in our study compared to prior studies. As we do not have detailed information on the treatment regimens the patients received, we cannot assess whether this may explain differences in the impact of HRQoL.

Only a handful of prior studies assessed whether cancer and its treatment have different consequences for older than for younger ovarian cancer survivors. None of these studies

primarily assessed the association of age with HRQoL outcomes, nor did they use an age-matched normative population. Furthermore, these studies differed from our study in that they used a lower age cutoff and mostly other questionnaires to assess HRQoL, such as the SF-36 and the FACT-O, and survivors were generally more recently diagnosed with ovarian cancer. On the one hand, they found that older age was associated with poorer physical functioning one-year post-diagnosis<sup>14</sup> and that older survivors reported worse symptoms of fatigue on average 16 months post-treatment.<sup>6</sup> However, others did not find age to be predictive of HRQoL or symptoms<sup>16,18</sup> or reported that older age predicted better physical and emotional wellbeing during chemotherapy.<sup>17</sup>

Although many studies have investigated HRQoL in cancer survivors, we were – to the best of our knowledge – the first to compare the HRQoL of older and younger ovarian cancer survivors with an age-matched normative population. As hypothesized, we found that older ovarian cancer survivors experienced poorer HRQoL than their younger counterparts. Effect sizes were clinically relevant, albeit of medium to small difference, except for a difference of large clinical relevance for dyspnea in older survivors compared to the normative population. An explanation for our findings may be the decreased physiological reserve of older ovarian cancer survivors. Ageing in general is associated with a decrease in physiological reserve and deconditioning due to a gradual deterioration of organ function.<sup>19</sup> Although many age-related changes might not be relevant under normal conditions, they may become apparent when the individual is faced with stressors, such as the diagnosis and treatment of ovarian cancer. HRQoL of older ovarian cancer survivors thus might be more affected by this disease and its lingering treatment' sequelae than HRQoL of younger survivors.

Contrary to what we expected, HRQoL of our older survivors seemed not to be negatively affected by chemotherapy. These findings need to be interpreted with caution due to a risk of selection bias. The older survivors participating in our study reflect a selected population of healthier older women; they were considered to be fit enough to receive a burdensome treatment and they were still alive six years (range 2-12 years) after treatment. Unfit older patients may have received less aggressive chemotherapy regimens or best supportive care only and detriments in HRQoL are presumably underestimated as those patients who deceased before the start of the study will tend to have poorer HRQoL and more symptoms than those surviving longer. Other studies demonstrated that long-term side effects of chemotherapy negatively affect HRQoL.<sup>40</sup> The most important contributing factors to deterioration of HRQoL among patients receiving chemotherapy were peripheral neuropathy, a more negative attitude towards sickness and a poorer financial situation.<sup>40</sup>

One of the strengths of this study is that it is the first to report on the association of age with long-term HRQoL in ovarian cancer survivors using an age-matched norm population

for the comparisons. Also, this study was performed in a population-based setting instead of a hospital-based setting and this improves the generalizability of our results. Limitations include that our findings apply to long-term survivors only and are therefore not representative of the entire population of older ovarian cancer patients. Indeed, most of our patients had early-stage disease while ovarian cancer is normally diagnosed at advanced stage disease. In addition, as the mean age of our cohort was 64 years, we have no information on HRQoL in the oldest old and our results cannot be extrapolated to them. Because of this age composition, we chose to use the somewhat arbitrary cut-off of 70 years rather than a higher cut-off, as this would result in too few older patients to make valid comparisons between groups. In addition, there is a risk of selection bias of both ovarian cancer survivors and normative respondents as it has been demonstrated that non-respondents have poorer HRQoL.<sup>41</sup> Lastly, we lack detailed information on the exact primary treatment and the response to this treatment, and whether the survivors were disease free or received any treatment at the time of the questionnaire, although these treatment and disease characteristics may have influenced HRQoL outcomes.

We found that long-lasting deficits in functioning and symptoms are prevalent particularly in older ovarian cancer survivors. Accordingly, patients should receive information regarding HRQoL outcomes to manage their expectations. The items most clinically affected were physical and cognitive functioning and, among older survivors also, dyspnea and fatigue. This is important as these are areas that may be amenable to targeted interventions, such as counseling, psychosocial support, physical therapy and symptom management, with the aim of stabilizing or improving HRQoL. Ovarian cancer survivors with lingering sequelae may benefit from supportive care. Future research should identify which predictors are related to worse HRQoL in older survivors and whether targeted interventions are able to improve their HRQoL.

### **Conclusion**

In comparison with an age-matched normative population, older ovarian cancer survivors report lower long-term HRQoL scores than younger survivors. Future research could focus on patients with advanced-stage disease as well and should identify which predictors are related to worse HRQoL in older survivors and whether timely interventions are able to improve their HRQoL.

## REFERENCES

1. Netherlands Comprehensive Cancer Organisation (IKNL). Werkwijze [in Dutch]. <http://www.cijfersoverkanker.nl/werkwijze-13.html> [Accessed 19 September 2017]
2. Cijfers over kanker. Nederlandse Kankerregistratie [in Dutch]. [www.cijfersoverkanker.nl](http://www.cijfersoverkanker.nl). [Accessed April 1st, 2017]
3. Surveillance, Epidemiology, and End Results (SEER) Explorer Application. <https://seer.cancer.gov/explorer/application.php>. [Accessed April 6, 2018]
4. Oncoline. Epitheliaal ovariumcarcinoom [in Dutch]. <https://www.oncoline.nl/ovariumcarcinoom>. [Accessed May 7, 2018]
5. Dumas L, Ring A, Butler J, Kalsi T, Harari D, Banerjee S. Improving outcomes for older women with gynaecological malignancies. *Cancer Treat Rev*. 2016;50:99-108. doi:10.1016/j.ctrv.2016.08.007
6. Stavraka C, Ford A, Ghaem-Maghami S, et al. A study of symptoms described by ovarian cancer survivors. *Gynecol Oncol*. 2012;125(1):59-64. doi:10.1016/j.ygyno.2011.12.421
7. Liavaag AH, Dørum A, Fosså SD, Tropé C, Dahl AA. Controlled study of fatigue, quality of life, and somatic and mental morbidity in epithelial ovarian cancer survivors: how lucky are the lucky ones? *J Clin Oncol*. 2007;25(15):2049-2056. doi:10.1200/JCO.2006.09.1769
8. Quality of life and clinical trials. *Lancet (London, England)*. 1995;346(8966):1-2. <http://www.ncbi.nlm.nih.gov/pubmed/7603136>. [Accessed May 3, 2018]
9. Speight J, Barendse SM. FDA guidance on patient reported outcomes. *BMJ*. 2010;340(jun21):c2921-c2921. doi:10.1136/bmj.c2921
10. International Society of Geriatric Oncology (SIOG). <http://www.siog.org/content/siog-guidelines>. [Accessed May 3, 2018]
11. Joly F, Hilpert F, Okamoto A, Stuart G, Ochiai K, Friedlander M. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: Recommendations on incorporating patient-reported outcomes in clinical trials in epithelial ovarian cancer. *Eur J Cancer*. 2017;78:133-138. doi:10.1016/j.ejca.2017.03.019
12. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the Treatment Preferences of Seriously Ill Patients. *N Engl J Med*. 2002;346(14):1061-1066. doi:10.1056/NEJMsa012528
13. Akishita M, Ishii S, Kojima T, et al. Priorities of Health Care Outcomes for the Elderly. *J Am Med Dir Assoc*. 2013;14(7):479-484. doi:10.1016/j.jamda.2013.01.009
14. Zhou Y, Irwin ML, Ferrucci LM, et al. Health-related quality of life in ovarian cancer survivors: Results from the American Cancer Society's Study of Cancer Survivors — I. *Gynecol Oncol*. 2016;141(3):543-549. doi:10.1016/j.ygyno.2016.04.006
15. Stewart DE, Wong F, Duff S, Melancon CH, Cheung AM. "What Doesn't Kill You Makes You Stronger": An Ovarian Cancer Survivor Survey. *Gynecol Oncol*. 2001;83(3):537-542. doi:10.1006/gy.2001.6437
16. Matulonis UA, Kornblith A, Lee H, et al. Long-term adjustment of early-stage ovarian cancer survivors. *Int J Gynecol Cancer*. 2008;18(6):1183-1193. doi:10.1111/j.1525-1438.2007.01167.x

17. Le T, Leis A, Pahwa P, et al. Quality of life evaluations in patients with ovarian cancer during chemotherapy treatment. *Gynecol Oncol.* 2004;92(3):839-844. doi:10.1016/j.ygyno.2003.11.034
18. Holzner B, Kemmler G, Meraner V, et al. Fatigue in ovarian carcinoma patients. *Cancer.* 2003;97(6):1564-1572. doi:10.1002/cncr.11253
19. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. *Lancet Oncol.* 2018;19(6):e305-e316. doi:10.1016/S1470-2045(18)30348-6
20. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *Br J Clin Pharmacol.* 2004. doi:10.1046/j.1365-2125.2003.02007.x
21. von Gruenigen VE, Huang HQ, Beumer JH, et al. Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer—An NRG oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 2017;144(3):459-467. doi:10.1016/j.ygyno.2016.11.033
22. Ezendam NPM, Pijlman B, Bhugwandass C, et al. Chemotherapy-induced peripheral neuropathy and its impact on health-related quality of life among ovarian cancer survivors: results from the population-based PROFILES registry. *Gynecol Oncol.* 2014;135(3):510-517. doi:10.1016/j.ygyno.2014.09.016
23. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: Scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer.* 2011;47(14):2188-2194. doi:10.1016/j.ejca.2011.04.034
24. centERpanel. [www.website.centerpanel.nl](http://www.website.centerpanel.nl)
25. van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer.* 2011;47(5):667-675. doi:10.1016/j.ejca.2010.11.004
26. van Duin C, Keij I. Sociaal-economische status indicator op postcodeniveau. In: *Maandstatistiek van de Bevolking.* ; 2002:32-35
27. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum.* 2003;49(2):156-163. doi:10.1002/art.10993
28. Niezgoda HE, Pater J. A validation study of the domains of the core EORTC quality of life questionnaire. *Qual Life Res.* 1993;2(5):319-325.
29. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. On behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.* <http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf>
30. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol.* 2011;29(1):89-96. doi:10.1200/JCO.2010.28.0107



31. Norman GR, Sloan JA, Wyrwich KW. Interpretation of Changes in Health-related Quality of Life. *Med Care*. 2003;41(5):582-592. doi:10.1097/01.MLR.0000062554.74615.4C
32. Twisk J. *Applied Multilevel Analysis*. Cambridge: Cambridge University Press.; 2006
33. Wenzel LB, Donnelly JP, Fowler JM, et al. Resilience, reflection, and residual stress in ovarian cancer survivorship: a gynecologic oncology group study. *Psychooncology*. 11(2):142-153. <http://www.ncbi.nlm.nih.gov/pubmed/11921330>
34. Kornblith AB, Mirabeau-Beale K, Lee H, et al. Long-Term Adjustment of Survivors of Ovarian Cancer Treated for Advanced-Stage Disease. *J Psychosoc Oncol*. 2010;28(5):451-469. doi:10.1080/07347332.2010.498458
35. Lutgendorf SK, Shinn E, Carter J, et al. Quality of life among long-term survivors of advanced stage ovarian cancer: A cross-sectional approach. *Gynecol Oncol*. 2017;146(1):101-108. doi:10.1016/j.ygyno.2017.05.008
36. Mirabeau-Beale KL, Kornblith AB, Penson RT, et al. Comparison of the quality of life of early and advanced stage ovarian cancer survivors. *Gynecol Oncol*. 2009;114(2):353-359. doi:10.1016/j.ygyno.2009.05.009
37. Van Der Poel MWM, Oerlemans S, Schouten HC, et al. Quality of life more impaired in younger than in older diffuse large B cell lymphoma survivors compared to a normative population: A study from the population-based PROFILES registry. *Ann Hematol*. 2014. doi:10.1007/s00277-013-1980-1
38. van der Poel MWM, Oerlemans S, Schouten HC, van de Poll-Franse L V. Elderly multiple myeloma patients experience less deterioration in health-related quality of life than younger patients compared to a normative population: a study from the population-based PROFILES registry. *Ann Hematol*. 2015. doi:10.1007/s00277-014-2264-0
39. Verweij NM, Bonhof CS, Schiphorst AHW, et al. Quality of life in elderly patients with an osteomy—a study from the population-based PROFILES registry. *Color Dis*. 2018;20(4):O92-O102. doi:10.1111/codi.13989
40. Bhugwandass CS, Pijnenborg JMA, Pijlman B, Ezendam NPM. Effect of chemotherapy on health-related quality of life among early-stage ovarian cancer survivors: a study from the population-based PROFILES registry. *Curr Oncol*. 2016;23(6):556. doi:10.3747/co.23.3243
41. de Rooij BH, Ezendam NPM, Mols F, et al. Cancer survivors not participating in observational patient-reported outcome studies have a lower survival compared to participants: the population-based PROFILES registry. *Qual Life Res*. August 2018. doi:10.1007/s11136-018-1979-0



# Chapter 10

Do age and comorbidity impair recovery during two years after treatment for endometrial cancer?

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## **ABSTRACT**

### **Background**

A better understanding of the impact of age and comorbidity on health-related quality of life (HRQoL) may improve treatment decision-making in patients with endometrial cancer. We investigated whether either age or comorbidity is more strongly associated with changes in HRQoL over time.

### **Methods**

Endometrial cancer patients (n= 296) were invited to complete questionnaires after initial treatment and after 6, 12 and 24 months follow-up. Patients were divided into subgroups according to age (<60, 60-75 and  $\geq 75$  years) and according to comorbidity (0, 1, 2 or  $\geq 3$ ). HRQoL was measured with the five EORTC QLQ-C30 functioning scales. Linear mixed models were performed for the different subgroups to assess changes in HRQoL over time. HRQoL was also compared to longitudinal outcomes from an age- and gender-matched normative population.

### **Results**

The first questionnaire was returned by 221 patients (75%) of whom six were excluded due to progressive disease. Changes in HRQoL were mainly associated with cumulative comorbidity burden and not with age. Patients with comorbidity reported deterioration of physical and role functioning between 12 and 24 months. Compared to the normative population, patients initially scored higher on physical and role functioning, but at 24 months outcomes were no longer different.

### **Conclusion**

Cumulative comorbidity burden was more strongly associated with deterioration of HRQoL than patient's age. Therefore, patients with endometrial cancer and multiple comorbid conditions require careful follow-up of HRQoL after treatment.

## INTRODUCTION

The world's population is aging and the number of people aged  $\geq 60$  years is expected to more than double by 2050 and to more than triple by 2100.<sup>1</sup> Inherent to this aging is an increase in comorbidity; currently half of the population aged  $\geq 60$  years has two or more chronic conditions.<sup>2</sup>

Endometrial cancer is a type of cancer that disproportionately affects women above 60 years of age: more than 40% of patients are aged  $\geq 65$  years.<sup>3</sup> It is also associated with high prevalence of comorbid conditions such as diabetes, obesity and cardiovascular disease.<sup>4,5</sup> Various prior studies have found that age above 60 and comorbidity were independently associated with treatment-related morbidity and poorer survival.<sup>6–10</sup> Perhaps more importantly, both factors may also impact health-related quality of life (HRQoL).<sup>11–15</sup> This outcome is of particular interest to patients suffering from cancers with a relatively good prognosis such as endometrial cancer and to older people with cancer, who often give preference to maintenance or improvement of HRQoL rather than an increase in survival.<sup>6,16</sup>

Understanding the evolution of HRQoL during and after treatment can be an important factor in decision-making regarding oncologic treatment. In the limited studies available, having multiple comorbid conditions was associated with poorer HRQoL after treatment.<sup>12,13</sup> Age was also found to be a factor, but the direction of this association varied: one found patients aged  $\geq 65$  years to be at higher risk of poorer outcome,<sup>15</sup> while others reported poorer results for patients under 60 years of age.<sup>14,17</sup> Only one study compared longitudinal HRQoL outcomes of endometrial cancer patients with a normative population but this trial focused on HRQoL stratified by treatment regimen.<sup>18</sup>

Although age and comorbidity are strongly related, they are not synonymous. Given their independent association with clinical outcomes,<sup>6,8,10</sup> they are generally both taken into account for treatment decision-making. Our aim was to identify which of these two characteristics is more strongly associated with changes in HRQoL over time in patients with endometrial cancer. In addition, we assessed changes in HRQoL over time within age and comorbidity subgroups and we compared changes in HRQoL of patients with changes in HRQoL of an age- and gender-matched normative population.

## METHODS

### Design

This study is a secondary analysis of the prospective, cluster randomized ROGY Care trial.<sup>19</sup> In short, this trial studied the effects of usual care versus survivorship care plans (SCP)

on patient-reported outcomes in patients with ovarian and endometrial cancer with 2-year follow-up. In hospitals with usual care, the gynaecologist provided care as usual. In hospitals with SCP care, patients received a document containing information about the diagnosis and treatments, and a follow-up care plan. Primary outcome was defined as patient satisfaction with information provision and care and these results have been described elsewhere.<sup>19,20</sup> SCP were demonstrated not to directly influence HRQoL, allowing us to use the trial data as prospective cohort data.<sup>21</sup> Other details of the ROGY Care trial have been described previously and can be found in the published study protocol.<sup>22</sup> For the current study, only patients with endometrial cancer were selected. The ROGY Care trial has been approved by the medical research ethics committees of all participating centers.

### **Participants and recruitment**

All women from twelve hospitals in the South of the Netherlands newly diagnosed with endometrial cancer between April 2011 and October 2012 were invited to participate by their treating gynaecologist with a letter and informed consent. After consent, follow-up questionnaires were sent after initial treatment and at 6, 12 and 24 months after treatment. Patient exclusion criteria (undergoing palliative care, or unable to complete a Dutch questionnaire) were minimal to maximize generalizability.<sup>23</sup>

### **Study measures**

#### *Clinical data*

Clinical data were obtained from the Netherlands Cancer Registry which routinely collects data on newly diagnosed cancer patients in all hospitals in the Netherlands and included age, socioeconomic status, date of diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage and primary treatment. Other sociodemographic data (e.g., partner status, educational level and employment status) were assessed with the first questionnaire. Data on the presence of a recurrence were retrospectively extracted from the medical records two years after completion of the trial inclusion. Patients with progressive disease at baseline were excluded and data of patients with recurrent disease during follow-up were excluded if a patient was diagnosed with recurrent disease before or within a month after completion of the follow-up questionnaire. For the current analysis only patients were included who filled out the first questionnaire and who completed at least two questionnaires.

#### *Comorbidity data*

Comorbidity was assessed with the adapted self-administered comorbidity questionnaire at each time point.<sup>24</sup> This questionnaire contains thirteen common medical conditions (i.e. heart disease, high blood pressure, lung disease, diabetes mellitus, ulcer or stomach disease, kidney or liver disease, anaemia or other blood disease, cancer, depression,

osteoarthritis/degenerative arthritis, back pain and rheumatoid arthritis) and three optional conditions. For each condition, patients are asked whether they currently have or in the past twelve months had this problem and whether it limited their daily activities. For this analysis, we disregarded high blood pressure as a comorbid condition, because this is considered to be a risk factor more than an actual comorbid condition and we combined the comorbid conditions arthritis and rheumatoid disease into one condition for analyses. The optional medical conditions the patient could report were only taken into account when they limited the patients' daily activities.

Because obesity is associated with lower HRQoL in endometrial cancer patients,<sup>25</sup> but obesity is not accounted for in the self-administered comorbidity questionnaire, we also analysed the influence of body mass index (BMI) on HRQoL. BMI was categorised into BMI <30 and BMI ≥30.

#### *Health-related quality of life*

To assess HRQoL, we used the five functional subscales (physical, role, cognitive, emotional, social) of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (Version 3.0).<sup>26</sup> Items are answered on a 4-point Likert scale ranging from (1) not at all to (4) very much, and subsequently linearly transformed to a 0–100 scale, with higher scores representing better HRQoL.

#### **Normative population**

Next, we compared our findings with longitudinal data obtained from a normative Dutch population. Socio-demographics and HRQoL of the normative population were obtained from CentERpanel; an online household panel representative of the Dutch population in the Netherlands.<sup>27</sup> Panel members were included between 2009 and 2012 and received online questionnaires on HRQoL and self-reported comorbidity annually from the first year since participation until 2013. BMI was not available for the normative population. Details of the data collection have been described before.<sup>28</sup> For the current analysis, participants were eligible if they did not have a history of cancer and if they completed at least two questionnaires. Of this sample, a random 10-year age- and gender matched normative sample was selected, reflecting the distribution of the endometrial cancer patients in this study. Patients were matched 1:1.04 with the normative population.

#### **Statistical analysis**

Both the endometrial cancer patients and normative population were divided into subgroups according to age: <60, 60–75 and ≥75 years at time of the questionnaire. In addition, they were divided into four comorbidity subgroups according to the number of comorbidities at the time of the questionnaire (0, 1, 2 or ≥3 comorbidities).

To describe patients' baseline sociodemographics and clinical characteristics stratified according to age or comorbidity groups, independent samples t-tests or one way ANOVAS were used for continuous variables and chi-square tests or Fisher's exact test were applied for categorical variables at baseline.

Longitudinal linear mixed model analyses were performed with the functioning scales as continuous dependent variables. Time was included as an independent categorical variable (after initial treatment [0] and after 6, 12 and 24 months). A random intercept on the patient-level was included in the model to adjust for intra-dependency between repeated measures.<sup>29</sup> Analyses were adjusted for the following a priori defined confounders: educational level, partner status, radiotherapy, and trial arm. Mixed model analysis handles missing data by using the known values to correct and estimate the unknown values, assuming that data is missing at random.<sup>29</sup> For comorbidity at baseline, we imputed missing values using values from the second questionnaire at 6 months follow-up when available.

First, we included age and number of comorbidities as categorical independent variables in the models. We then included the interaction term of comorbidity and age to evaluate whether older patients with comorbidity had poorer HRQoL than younger patients with comorbidity. Subsequently, to assess whether age or comorbidity had different associations with HRQoL at different points in time, we build models with age, time and the interaction term "age x time" or with comorbidity, time and "comorbidity x time".

Because we found a significant deterioration for physical and role functioning between 12 and 24 months follow-up, we explored whether the following characteristics could account for this deterioration: specific comorbidities present at baseline, receiving treatment at the time of the questionnaire or poor baseline measurements of physical or role functioning (defined as the quartile of patients with the lowest score of physical or role functioning at baseline). To do so we analysed models with interaction terms, consisting of "the characteristic of interest x time at 24 months".

To compare differences in HRQoL between endometrial cancer patients and the normative population (similar age and comorbidity groups), we compared HRQoL at baseline, after one and after two years using multivariable linear regression analyses with HRQoL as dependent variable and patients versus the normative population as independent variables, adjusted for partner status and educational level.

Clinically relevant differences between QLQ-C30 scores were determined using the guideline for interpretation of the QLQ-C30 'between groups'<sup>30</sup> and for interpretation of longitudinal differences between scores the guideline 'within a group'.<sup>31</sup> Clinically relevant



differences were defined as differences of small class size (subtle but nevertheless clinically relevant) or larger. Because a guideline for interpretation of the emotional functioning scale is not available for 'between groups', we used the guideline for role functioning scale instead because this is the strictest one.

All analyses were performed using IBM SPSS Statistics version 23.0. For the baseline and mixed model analyses, a two-sided p-value  $<0.05$  was considered significant. For the multivariable linear regression analyses the level of significance was set at  $p \leq 0.01$ , to guard against false-positive results because of multiple testing.

## RESULTS

### Patients' baseline descriptives

The first questionnaire was returned by 221 of 296 endometrial cancer patients (75%). Six patients were excluded from analyses due to progressive disease at baseline. Overall, 215 patients were included in this analysis. Non-respondents were older and had higher disease stages. Details concerning differences between full respondents and respondents lost to follow-up have been described elsewhere.<sup>12</sup> In short, respondents lost to follow-up were older, less often had a partner and had more comorbidities than patients who completed all questionnaires. Respectively 3, 11 and 4 patients were excluded from analyses at 6, 12 and 24 months due to a recurrence.

Thirty-nine patients were aged  $<60$  years (18%), 128 were aged 60-75 years (60%) and 48 were aged  $\geq 75$  years (22%) (Table 1). Sixty-three (29%), 50 (23%), 49 (23%) and 52 (24%) patients had no, one, two or three or more comorbid conditions respectively (Table 2).

### Association of age and number of comorbidities with HRQoL

Independent of number of comorbidities, a significant difference for age groups was found on social functioning (Table 3). Independent of age, patients with comorbidity scored significantly worse on all functioning outcomes and differences were largest for those with  $\geq 3$  comorbidities.

The interaction term "age x comorbidity" was not statistically significant at any of the time points (data not shown).

### Changes in patients' HRQoL over time by age and comorbidity subgroups

Age was not associated with significant differences in HRQoL over time (Figure 1). Increasing comorbidity burden was associated with a statistically significant and clinically relevant deterioration in physical and role functioning between 12 and 24 months. The other functioning scales remained stable or showed non-significant improvement over time.

**Table 1.** Descriptives of women with endometrial cancer according to age subgroups and comparison with the normative population, N (%).

Endometrial cancer patients					Normative population		Patients versus norm	
	Total (n= 215)	< 60 years (n= 39)	60-75 years (n= 128)	≥ 75 years (n= 48)	P-value	Total (n= 224)	P-value	
Respondent								
6 months follow-up	158 (74)	29 (74)	97 (76)	32 (67)	0.47			
12 months follow-up	146 (68)	28 (72)	91 (71)	27 (56)	0.15			
24 months follow-up	128 (60)	26 (67)	79 (62)	23 (48)	0.15			
Educational level†								
High	23 (11)	5 (13)	17 (14)	1 (2)		68 (31)		
Medium	139 (66)	29 (74)	86 (70)	24 (50)	≤ 0.001	138 (62)	≤ 0.001	
Low	48 (23)	5 (13)	20 (16)	23 (48)		15 (7)		
Missing	5	0	5	0		3		
Marital status‡								
Partner	155 (73)	32 (82)	104 (83)	19 (40)		141 (63)		
No partner	57 (27)	7 (18)	22 (18)	28 (60)	≤ 0.001	83 (37)	0.02	
Missing	3	0	2	1				
BMI								
< 30	115 (54)	21 (54)	68 (54)	26 (55)	0.99			
≥ 30	97 (46)	18 (46)	58 (46)	21 (45)				
Missing	3	0	2	1				
Number of comorbidities								
0	63 (29)	14 (36)	41 (32)	8 (17)		68 (30)		
1	50 (23)	9 (23)	33 (26)	8 (17)	0.09	61 (27)	0.21	
2	49 (23)	6 (15)	28 (22)	15 (31)		34 (15)		
≥ 3	52 (24)	10 (26)	25 (20)	17 (35)		61 (27)		
Missing	1	0	1	0		0		
Tumor stage								
I	183 (88)	34 (92)	110 (88)	39 (87)				
II	6 (3)	1 (3)	5 (4)	0 (0)	0.15			
III	12 (6)	0 (0)	9 (7)	3 (7)				
IV	6 (3)	2 (5)	1 (1)	3 (7)				
Missing	8	2	3	3				

Continue

Continued

Primary treatment									
Surgery	213 (99)	39 (100)	127 (100)	47 (98)	0.18				
Radiotherapy	74 (35)	2 (5)	50 (39)	22 (46)	<b>&lt; 0.001</b>				
Chemotherapy	11 (5)	2 (5)	6 (5)	3 (6)	0.92				
Missing	1	0	1	0					
Individual comorbidities									
Heart disease	25 (12)	2 (5)	9 (7)	14 (29)	<b>&lt; 0.001</b>		22 (10)	0.53	
Cerebrovascular disease	8 (4)	0 (0)	3 (2)	5 (10)	<b>0.02</b>		4 (2)	0.21	
Renal disease	4 (2)	0 (0)	2 (2)	2 (4)	0.34		4 (2)	0.95	
Diabetes mellitus	41 (19)	3 (8)	28 (22)	10 (21)	0.13		21 (9)	<b>&lt; 0.01</b>	
Lung disease	17 (8)	4 (10)	10 (8)	3 (6)	0.79		31 (14)	0.05	
Gastric ulcer	3 (1)	0 (0)	2 (2)	1 (2)	0.69		5 (2)	0.52	
Liver disease	2 (1)	1 (3)	0 (0)	1 (2)	0.22		3 (1)	0.69	
Hematologic disease	13 (6)	6 (15)	5 (4)	2 (4)	<b>0.03</b>		7 (3)	0.14	
Thyroid disease	19 (9)	3 (8)	11 (9)	5 (10)	0.90		18 (8)	0.75	
Depression	17 (8)	3 (8)	9 (7)	5 (10)	0.77		8 (4)	0.05	
Backache	67 (31)	12 (31)	37 (29)	18 (38)	0.57		77 (34)	0.50	
Arthritis/rheumatoid disease	80 (37)	8 (21)	46 (36)	26 (54)	<b>&lt; 0.01</b>		91 (41)	0.49	
Other problem 1*	30 (14)	10 (26)	11 (9)	9 (19)	<b>0.02</b>		34 (15)	0.73	
Other problem 2	12 (6)	5 (4)	3 (6)	3 (6)	0.32		9 (4)	0.44	
Other problem 3	4 (2)	1 (3)	2 (2)	1 (2)	0.92		1 (0)	0.18	
Missing	1		1	0			7		

Bold data indicate P-value < 0.05.

† Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.

‡ Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited.

\* Other problems 1, 2 and 3 are three optional medical conditions the patient can complete manually.

BMI = body mass index; SD = standard deviation.

**Table 2.** Descriptives of women with endometrial cancer according to comorbidity subgroups, N (%).

	<b>No comorbidities (n = 63)</b>	<b>1 comorbidity (n = 50)</b>	<b>2 comorbidities (n = 49)</b>	<b>≥ 3 comorbidities (n = 52)</b>	<b>P-value</b>
Age at time of questionnaire mean (SD)	65.5 (9.0)	66.9 (7.3)	70.0 (9.2)	69.0 (9.6)	<b>0.03</b>
Educational level <sup>†</sup>					<b>&lt; 0.01</b>
High	12 (20)	3 (6)	6 (13)	2 (4)	
Medium	43 (73)	35 (70)	28 (58)	33 (64)	
Low	4 (7)	12 (24)	14 (29)	17 (33)	
Missing	4	0	1	0	
Marital status <sup>‡</sup>					0.52
Partner	47 (77)	35 (70)	38 (78)	34 (67)	
No partner	14 (23)	15 (30)	11 (22)	17 (33)	
Missing	2	0	0	1	
BMI					<b>0.03</b>
< 30	37 (60)	27 (54)	31 (65)	19 (37)	
≥ 30	25 (40)	23 (46)	17 (35)	32 (63)	
Missing	1	0	1	1	
Tumor stage					0.51
I	56 (95)	41 (85)	40 (85)	45 (86)	
II	0 (0)	3 (6)	1 (2)	2 (4)	
III	3 (5)	3 (6)	3 (6)	3 (6)	
IV	0 (0)	1 (2)	3 (6)	2 (4)	
Missing	4	2	2	0	
Primary treatment					0.50
Surgery	62 (98)	49 (98)	49 (100)	52 (100)	
Radiotherapy	18 (29)	21 (42)	19 (39)	15 (29)	
Chemotherapy	2 (3)	1 (2)	3 (6)	5 (10)	
Missing	0	1	0	0	0.30

For one patient, comorbidity data were missing.

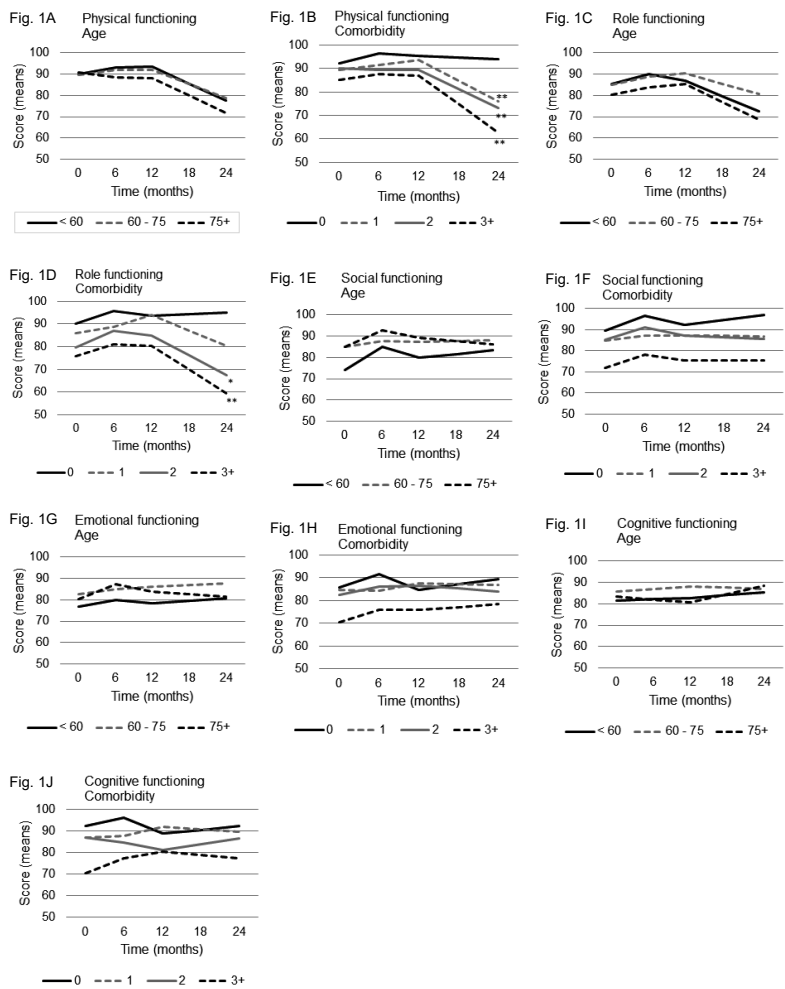
Bold data indicate P-value < 0.05.

† Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.

‡ Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited.

BMI = body mass index; SD = standard deviation.

To find possible explanations for patients' deterioration in physical and role functioning between 12 and 24 months, we assessed whether certain patient (i.e. specific comorbidities, poor baseline physical or role functioning) or treatment characteristics (i.e. receipt of radiotherapy) could be related to this deterioration. No specific comorbidity could explain the deterioration; almost all comorbidities, including obesity, were associated with poorer physical functioning at 24 months (Appendix 1a). Patients in the lowest quartile of baseline role functioning reported a significant and clinically relevant decline in role functioning between 12 and 24 months (Appendix 1b). Poor baseline physical functioning and the receipt of radiotherapy were not associated with physical or role functioning at 24 months.



**Figure 1. Age and comorbidity**  
Mean scores of health-related quality of life over time for different age (b60, 60–75 and ≥75) and comorbidity (0, 1, 2, ≥3) subgroups. A higher scores means better functioning. Y-axis was truncated, actual scores range from 0 to 100. Analyses were adjusted for marital status, educational level and radiotherapy. \* Statistically significant and clinically relevant differences on functioning scores for the interaction term (time and age or time and comorbidity) relative to reference category (age category <60 years or group without comorbidity after initial treatment). \* $p < 0.01$ , \*\* $p < 0.001$ . **1A.** Physical functioning according to age subgroups. **1B.** Physical functioning according to comorbidity subgroups. **1C.** Role functioning according to age subgroups. **1D.** Role functioning according to comorbidity subgroups. **1E.** Social functioning according to age subgroups. **1F.** Social functioning according to comorbidity subgroups. **1G.** Emotional functioning according to age subgroups. **1H.** Emotional functioning according to comorbidity subgroups. **1I.** Cognitive functioning according to age subgroups. **1J.** Cognitive functioning according to comorbidity subgroups.

**Comparisons of endometrial cancer patients and the normative population**

In total, data of 3483 cancer-free respondents were available and 2539 completed at least two questionnaires (73%). After gender and age-matching, 224 respondents were available for the current analysis.

**Table 3.** Associations between patients' age and comorbidity and EORTC QLQ-C30 functioning domains during two-years follow-up after initial treatment in mixed model analysis.

	Physical functioning			Role functioning			Social functioning			Cognitive functioning			Emotional functioning		
	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value
Age															
< 60 (ref)															
60 – 75	0.0	(-3.8;3.8)	1.00	4.2	(-1.2; 9.6)	0.13	6.9	(0.0;13.7)	0.05	4.0	(-2.3;10.3)	0.21	6.1	(0.2;12.1)	0.05
≥ 75	-1.6	(-6.5;3.4)	0.53	-0.8	(-7.9;6.2)	0.82	9.7	(0.93;18.5)	<b>0.03</b>	2.3	(-5.7;10.4)	0.57	4.4	(-3.3;12.1)	0.26
Comorbidity															
0 (ref)															
1	-6.1	(-9.2;-3.0)	<b>&lt; 0.001</b>	-6.3	(-11.0;-1.6)	<b>&lt; 0.01</b>	-4.6	(-9.6;0.5)	0.08	-6.2	(-10.4;-2.0)	<b>&lt; 0.01</b>	-1.5	(-5.5;2.5)	0.48
2	-6.4	(-9.7;-3.1)	<b>&lt; 0.001</b>	-11.4	(-16.4;-6.4)	<b>&lt; 0.001</b>	-5.7	(-11.1;-0.3)	<b>0.04</b>	-7.7	(-12.3;-3.2)	<b>&lt; 0.001</b>	-1.3	(-5.6;3.0)	0.55
≥ 3	-11.3	(-14.9;-7.7)	<b>&lt; 0.001</b>	-18.1	(-23.4;-12.7)	<b>&lt; 0.001</b>	-13.9	(-19.7;-8.0)	<b>&lt; 0.001</b>	-14.0	(-19.0;-9.0)	<b>&lt; 0.001</b>	-8.2	(-13.0;-3.5)	<b>&lt; 0.01</b>

Mixed model analysis with EORTC-QLQ-C30 functioning domains as dependent variable and age and comorbidity as categorical independent variable, adjusted for partner status, educational level, radiotherapy and trial arm. A higher score on the HRQoL functioning scales means better functioning. Unstandardized betas ( $\beta$ ), confidence intervals (95% CI) and P-values are reported.

Bold data indicate a clinically relevant difference in combination with P-value < 0.05.

**Table 4.** Mean scores and differences on the EORTC QLQ-C30 functioning scales of endometrial cancer patients compared to the normative population according to different age subgroups. Multivariable regression analysis with HRQoL as dependent variable and patients versus the normative population as independent variable.

	Mean						Difference		
	Patients			Normative population			Patient score minus norm score		
	< 60 (n = 39)	60-75 (n = 128)	≥ 75 (n = 49)	< 60 (n = 49)	60-75 (n = 126)	≥ 75 (n = 49)	< 60	60-75	≥ 75
Physical functioning									
Baseline	90.1	89.7	90.6	83.7	86.1	74.3	6.4	3.6	<b>16.3<sup>b</sup></b>
12 months	93.4	92.1	88.2	82.9	84.2	71.6	10.5	<b>7.9<sup>b</sup></b>	<b>16.6<sup>b</sup></b>
24 months	77.4	78.8	71.7	81.2	84.4	69.2	-3.8	-5.6	2.5
Change in 2 years	-12.7	-10.9	-18.9	-2.5	-1.7	-5.1	-10.2	-9.2	-13.8
Role functioning									
Baseline	85.3	84.9	80.2	79.3	86.4	78.2	6.0	-1.5	2.0
12 months	87.0	90.2	85.2	81.9	85.4	72.8	5.1	4.8	12.4
24 months	72.4	80.8	68.5	75.4	85.3	68.0	-3.0	-4.5	0.5
Change in 2 years	-12.9	-4.1	-11.7	-3.9	-1.1	-10.2	-9.0	-3.0	-1.5
Emotional functioning									
Baseline	76.9	82.6	80.1	86.6	88.6	89.5	-9.7	-6.0	-9.4
12 months	78.2	86.0	83.6	86.8	87.7	85.5	-8.6	-1.7	-1.9
24 months	80.8	87.5	81.5	85.4	86.8	85.5	-4.6	0.7	-4.0
Change in 2 years	3.9	4.9	1.4	-1.2	-1.8	-4.0	5.1	6.7	-5.4
Cognitive functioning									
Baseline	81.6	85.8	83.3	84.4	92.5	90.8	-2.8	<b>-6.7<sup>a</sup></b>	-7.5
12 months	82.8	88.2	80.6	86.8	92.9	87.8	-4.0	-4.7	-7.2
24 months	85.3	86.8	88.6	84.6	92.8	87.6	0.7	-6.0	1.0
Change in 2 years	3.7	1.0	5.3	0.2	0.3	-3.2	3.5	0.7	8.5
Social functioning									
Baseline	73.9	84.9	85.1	87.1	94.2	93.2	-13.2	<b>-9.3<sup>a</sup></b>	-8.1
12 months	79.9	87.1	89.4	88.5	93.4	85.4	-8.6	-6.3	4.0
24 months	83.3	88.0	86.0	86.7	93.0	84.6	-3.4	-5.0	1.4
Change in 2 years	9.4	3.1	0.9	-0.4	-1.2	-8.6	9.8	4.3	9.5

2nd–9th colom show crude means. From the 10th colom to the end: differences in functioning scores (the score of the normative population minus the score of the patient group, same age groups). P-values were calculated using multivariable regression analysis with EORTC-QLQ-C30 functioning domains at a specific time point as dependent variable and patients versus the normative population as independent variable, adjusted for covariates (partner status and educational level). A higher score on the functioning scales means better functioning.

Bold values represent significant and clinically relevant differences between patients and the normative population from the same age subgroup.

<sup>a</sup> p ≤ 0.01 in combination with clinically relevant difference.

<sup>c</sup> p < 0.001 in combination with clinically relevant difference.

The normative population had a higher educational level and more often had a partner compared to patients (Table 1). At baseline, patients generally reported better physical and role functioning than the normative population, but this was only significant and clinically relevant for patients aged ≥75 years and those with ≥3 comorbidities (Table 4 stratified by age; Table 5 stratified by comorbidity). Emotional, social and cognitive functioning were scored poorer at baseline by patients than by the normative population. At 12 months follow-up, patients still reported better physical and role functioning than the normative

**Table 5.** Mean scores and differences on the EORTC QLQ-C30 functioning scales of endometrial cancer patients compared to the normative population according to different comorbidity subgroups. Multivariable regression analysis with HRQoL as dependent variable and patients versus the normative population as independent variable.

	Mean		Difference									
	Patients		Normative population					Patient score minus norm score				
	0 (n = 63)	1 (n = 50)	2 (n = 49)	≥ 3 (n = 52)	0 (n = 68)	1 (n = 61)	2 (n = 34)	≥ 3 (n = 61)	0	1	2	≥ 3
<b>Physical functioning</b>												
Baseline	92.3	89.6	90.0	85.3	94.8	85.5	80.6	68.7	-2.5	4.1	9.4	<b>16.6<sup>b</sup></b>
12 months	95.4	93.7	89.3	87.1	94.3	86.7	79.7	63.6	1.1	7.0	<b>9.6<sup>a</sup></b>	<b>23.5<sup>b</sup></b>
24 months	94.2	76.2	73.3	62.6	96.2	86.4	75.6	66.1	-2.0	-10.2	-3.5	-3.5
Change in 2 years	1.9	-13.4	-16.7	-22.7	1.4	0.9	-5.0	-2.6	0.5	-14.3	-11.7	-20.1
<b>Role functioning</b>												
Baseline	90.0	85.8	79.6	75.9	97.3	87.4	78.9	65.0	-7.3 <sup>b</sup>	-1.6	0.7	<b>10.9<sup>a</sup></b>
12 months	93.8	93.9	84.8	80.2	96.9	87.2	77.4	64.9	-3.1	6.7	7.4	<b>15.3<sup>a</sup></b>
24 months	95.0	80.4	67.5	59.5	98.6	89.1	74.4	59.4	-3.6	-8.7	-6.9	0.1
Change in 2 years	5.0	-5.4	-12.1	-16.4	1.3	1.7	-4.5	-5.6	3.7	-7.1	-7.6	-10.8
<b>Emotional functioning</b>												
Baseline	85.6	84.6	82.5	70.4	93.4	87.2	90.0	83.1	-7.8 <sup>a</sup>	-2.6	-7.5	<b>-12.7<sup>a</sup></b>
12 months	84.8	87.6	86.5	76.0	92.2	92.0	87.9	76.4	-7.4	-4.4	-1.4	-0.4
24 months	89.4	87.0	84.1	78.3	93.3	90.3	82.3	79.8	-3.9	-3.3	1.8	-1.5
Change in 2 years	3.8	2.4	1.6	7.9	-0.1	3.1	-7.7	-3.3	3.9	-0.7	9.3	11.2
<b>Cognitive functioning</b>												
Baseline	92.2	87.0	86.8	70.5	94.4	94.8	88.2	82.5	-2.2	-7.8 <sup>a</sup>	-1.4	<b>-12.0<sup>a</sup></b>
12 months	89.0	91.9	81.1	80.3	96.7	96.5	91.2	78.4	-7.7 <sup>a</sup>	-4.6	<b>-10.1<sup>a</sup></b>	1.9
24 months	92.2	89.5	86.5	77.4	95.3	94.2	90.6	81.5	-3.1	-4.7	-4.1	-4.1
Change in 2 years	0.0	2.5	-0.3	6.9	0.9	-0.6	2.4	-1.0	-0.9	3.1	-2.7	7.9
<b>Social functioning</b>												
Baseline	89.7	85.0	85.4	72.1	99.3	94.3	92.2	83.1	-9.6 <sup>b</sup>	-9.3 <sup>a</sup>	-6.8	-11.0
12 months	92.4	87.4	87.4	75.3	99.2	94.7	90.3	77.9	-6.8 <sup>b</sup>	-7.3	-2.9	-2.6
24 months	97.2	86.7	85.7	75.6	98.9	94.2	88.5	79.7	-1.7	-7.5	-2.8	-4.1
Change in 2 years	7.5	1.7	0.3	3.5	-0.4	-0.1	-3.7	-3.4	7.9	1.8	4.0	6.9

2nd–9th column show crude means. From the 10th column to the end: differences in functioning scores (the score of the normative population minus the score of the patient group, same comorbidity groups). P-values were calculated using multivariable regression analysis with EORTC-QLQ-C30 functioning domains as dependent variable and patients versus the normative population as independent variable, adjusted for covariates (partner status and educational level). A higher score on the functioning scales means better functioning.

Bold values represent significant and clinically relevant differences between patients and the normative population from the same comorbidity subgroup.

<sup>a</sup>  $p \leq 0.01$  in combination with clinically relevant difference.

<sup>b</sup>  $p < 0.001$  in combination with clinically relevant difference.



population. However, at 24 months, there were no statistically significant or clinically relevant differences in these HRQoL outcomes, due to a significantly greater deterioration of physical and role functioning in year two for patients than for the normative population. In contrast, emotional, cognitive and social functioning (slightly) improved over time in patients, while these outcomes showed some deterioration in the normative population (Tables 4 and 5). Thus, for all functioning outcomes, absolute differences were smaller at 24 months compared to prior measurements.

## DISCUSSION

This longitudinal study analysed HRQoL after initial treatment until 24 months follow-up among 215 patients with endometrial cancer according to age and comorbidity and found that, independent of age, comorbidity was significantly associated with worse scores on all functioning outcomes. Patients experienced clinically relevant deterioration in physical and role functioning between 12 and 24 months that was associated with cumulative comorbidity burden but not with age. No specific comorbidity was discriminatory for this deterioration. Surprisingly, compared to the normative population, patients initially reported higher scores on physical and role functioning. However, after 24 months these differences were no longer significant or clinically relevant because deterioration of physical and role functioning over time was larger for patients than for the normative population.

In line with our findings, various studies have found that, in patients with endometrial cancer or different cancer types, independent of age, comorbidity was associated with poorer HRQoL at baseline or HRQoL deterioration at follow-up.<sup>11–13,32</sup> One previous study from our group reported on the association between changes in HRQoL and clinical and sociodemographic characteristics of patients included in the Rogy Care trial and also described the association between cumulative comorbidity burden and poorer HRQoL.<sup>12</sup> What our study adds to the existing knowledge is a detailed comparison of the association of age and comorbidity with changes in HRQoL and the use of longitudinal data from an age- and gender-matched normative control population for comparison of outcomes. A possible explanation why comorbidity burden and not patient's age was independently associated with deterioration of HRQoL is that, rather than patient's chronological age itself, age-related issues—such as comorbidity and functioning – may be more likely to have impact on HRQoL outcomes.

Only few studies assessed HRQoL longitudinally in patients with endometrial cancer.<sup>12,33–37</sup> Most had small sample sizes,<sup>33,36</sup> either excluded patients with significant comorbidity or did not report on comorbidity,<sup>33–36</sup> or studied the impact of specific treatment modalities on HRQoL rather than the impact of clinical characteristics.<sup>33–37</sup> In contrast to our findings,

these studies mostly found poor functioning after initial treatment with improvement over time.<sup>34,35,37</sup> There is no clear explanation why our finding of a longer-term deterioration of physical and role functioning is different from findings of these studies. In an attempt to explain our results, we performed exploratory analyses for specific comorbidities, baseline functioning and treatment characteristics. However, none of these analyses could fully account for the deterioration of physical and role functioning.

Only one study, the PORTEC-2 trial, compared longitudinal HRQoL outcomes of endometrial cancer patients who were randomized to receive vaginal brachytherapy or external radiotherapy with data from a normative population.<sup>18</sup> This trial found that patients' functioning outcomes were significantly lower after surgery and recovered in the first six months to subsequently reach a plateau within range of the norm. In contrast to our expectations, we found that patients scored higher on physical and role functioning than the normative population at baseline and at 12 months, with scores being comparable at 24 months. Perhaps, our different baseline findings may be partly explained by differences in the proportion of patients receiving laparoscopic hysterectomy because the implementation of laparoscopic hysterectomy increased steeply in the last decade, from 11% in 2006 to 85% in 2015.<sup>38</sup> The PORTEC-2 trial was conducted between 2002 and 2006 and therefore, compared to our cohort, these patients likely received laparotomy more frequently, which is known to have more impact on functioning than hysterectomy.

We have two hypotheses for the deterioration of physical and role functioning in patients with comorbidity at 24 months. Firstly, it may be that due to frequent check-ups and stricter management, comorbidities were better controlled during active treatment than during follow-up. If this is true, consideration should be given to optimising comorbidity management not only during treatment, but also during follow-up. Secondly, patients with cancer often describe a sense of abandonment after treatment, with increased uncertainty, and limited knowledge of what lies ahead.<sup>39</sup> This feeling can negatively impact HRQoL and this could potentially be more pronounced in patients with multiple comorbidities, but we could not find evidence to support this hypothesis.

There are two possible explanations for our finding on physical and role functioning for patients compared to the normative population. On the one hand, the finding may be the result of selection bias; patients participating in our study met inclusion criteria of the original cluster randomized trial (ROGY Care).<sup>19</sup> Although this trial used minimal exclusion criteria (undergoing palliative care or unable to complete a Dutch questionnaire), it is well known that older or frail patients are less likely to participate and to continue to participate in questionnaire studies.<sup>40,41</sup> Our study may represent a cohort of relatively fit women and consequently baseline functioning scores may have been high compared to the normative population. The finding that the number of comorbid conditions did

not differ between patients and the normative population may support this hypothesis because patients with endometrial cancer generally have higher than normal rates of comorbidity.<sup>4</sup> Therefore, our findings should be interpreted with caution and may not be representative for the real-life patient with endometrial cancer. However, our results suggest that these real-life patients who likely have more comorbidities than the patients in our study may experience poorer HRQoL. In case selection bias has occurred, the absence of difference between 12 and 24 months may represent a real deterioration in physical and role functioning over time for this relatively fit study population.

On the other hand, the finding may be explained by the theory of response shift.<sup>42</sup> According to this theory, patients change their internal standards, values and conceptualisation of HRQoL. Functioning could have been better than patients had expected to be functioning after undergoing treatment, resulting in higher initial scores compared to the normative population. This optimism may fade over time, which could explain the comparable outcomes at 24 months. In this case, our findings indicate that the most commonly applied designs to assess HRQoL, i.e. cross-sectional design or measurement at only two time points, may lead to overestimation of HRQoL.

Strengths of this study include the longitudinal design and the comparison with longitudinal data from an age-matched normative population. In addition, the limited exclusion criteria and high response rate improve the generalizability of our results. Another strength is that we excluded patients with progressive disease and that data of patients with recurrent disease were excluded because we wanted to assess HRQoL in a disease-free population. Several limitations should be considered. Firstly, we did not obtain measurements of HRQoL and comorbidity prior to diagnosis, between 12 and 24 months or beyond 24 months. These data would provide a baseline for comparison with subsequent HRQoL measurements over time, would give information on when precisely between 12 and 24 months HRQoL deterioration occurred, and would provide information on long-term HRQoL outcomes. Secondly, questionnaires were completed after initial treatment, but this moment fell during adjuvant or secondary treatment for some patients (n=29), resulting in heterogeneous responses. However, we did not find significant differences between patients who were receiving treatment during the first questionnaire compared to those who did not. Finally, selective loss to follow-up may have caused attrition bias,<sup>43</sup> as patients who were lost to follow-up were on average older and more often had multiple comorbidities. This should be taken into account when interpreting results, as it may be that our findings underestimate the true extent and impact of comorbidities.

Our results emphasise the importance of considering patients cumulative comorbidity burden, and not solely a patient's chronological age, when discussing HRQoL outcomes.

Whether early interventions targeting comorbidity and polypharmacy and life style changes can improve patients' HRQoL has not yet been investigated and may be a subject for further research. Furthermore, clinicians should consider the possibility of a response shift affecting HRQoL after initial treatment. To improve interpretation of the course of HRQoL over time, future research should include a baseline measurement of HRQoL prior to treatment and long-term follow-up, ideally with comparison of data obtained in a normative population.

### **Conclusion**

In women with endometrial cancer cumulative comorbidity burden was more strongly associated with deterioration of HRQoL than patient's age. Compared to a normative population, patients either experience larger deterioration of physical and role functioning or outcomes indicate a response shift after initial treatment with return of HRQoL to levels comparable to the normative population at 24 months. Therefore, patients with endometrial cancer and multiple comorbidities need careful follow-up of HRQoL after treatment.

## REFERENCES

1. United Nations world population ageing report 2015. [https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015\\_Report.pdf](https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf).
2. Barnett, K. *et al.* Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet (London, England)* **380**, 37–43 (2012).
3. National Cancer Institute. Surveillance, Epidemiology and End Results program. Cancer stat facts: uterine cancer. <https://seer.cancer.gov/statfacts/html/corp.html>. Accessed 24-07-2019.
4. Kurnit, K. C., Ward, K. K., McHale, M. T., Saenz, C. C. & Plaxe, S. C. Increased prevalence of comorbid conditions in women with uterine cancer. *Gynecol. Oncol.* **138**, 731–734 (2015).
5. Kitson, S. J. *et al.* The unrecognized burden of cardiovascular risk factors in women newly diagnosed with endometrial cancer: A prospective case control study. *Gynecol. Oncol.* **148**, 154–160 (2018).
6. Binder, P. S. *et al.* Adult Comorbidity Evaluation 27 score as a predictor of survival in endometrial cancer patients. *Am. J. Obstet. Gynecol.* **215**, 766.e1–766.e9 (2016).
7. Boll, D. *et al.* Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995–2008. *Eur. J. Cancer* **47**, 1504–1510 (2011).
8. Noer, M. C., Antonsen, S. L., Ottesen, B., Christensen, I. J. & Høgdall, C. Type I Versus Type II Endometrial Cancer: Differential Impact of Comorbidity. *Int. J. Gynecol. Cancer* **28**, 586–593 (2018).
9. Truong, P. T. *et al.* The effects of age and comorbidity on treatment and outcomes in women with endometrial cancer. *Am. J. Clin. Oncol.* **28**, 157–64 (2005).
10. Wright, J. D. *et al.* Morbidity and mortality of surgery for endometrial cancer in the oldest old. *Am. J. Obstet. Gynecol.* **205**, 66.e1–66.e8 (2011).
11. Cummings, A. *et al.* Comorbidities are associated with poorer quality of life and functioning and worse symptoms in the 5 years following colorectal cancer surgery: Results from the Colorectal Well-being (CREW) cohort study. *Psychooncology*. **27**, 2427–2435 (2018).
12. Zandbergen, N. *et al.* Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis. *Acta Oncol. (Madr)*. **58**, 790–800 (2019).
13. Wang, J.-W. *et al.* Comorbid chronic diseases and their associations with quality of life among gynecological cancer survivors. *BMC Public Health* **15**, 965 (2015).
14. Kornblith, A. B. *et al.* Long-term psychosocial adjustment of older vs younger survivors of breast and endometrial cancer. *Psychooncology*. **16**, 895–903 (2007).
15. von Gruenigen, V. E., Gil, K. M., Frasure, H. E., Jenison, E. L. & Hopkins, M. P. The impact of obesity and age on quality of life in gynecologic surgery. *Am. J. Obstet. Gynecol.* **193**, 1369–1375 (2005).
16. Fried, T. R., Bradley, E. H., Towle, V. R. & Allore, H. Understanding the Treatment Preferences of Seriously Ill Patients. *N. Engl. J. Med.* **346**, 1061–1066 (2002).

17. Rowlands, I. J. *et al.* Predicting positive and negative impacts of cancer among long-term endometrial cancer survivors. *Psychooncology*. **22**, 1963–1971 (2013).
18. Nout, R. A. *et al.* Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. *Eur. J. Cancer* **48**, 1638–48 (2012).
19. Nicolaije, K. A. H. *et al.* Impact of an Automatically Generated Cancer Survivorship Care Plan on Patient-Reported Outcomes in Routine Clinical Practice: Longitudinal Outcomes of a Pragmatic, Cluster Randomized Trial. *J. Clin. Oncol.* **33**, 3550–3559 (2015).
20. de Rooij, B. H. *et al.* Effects of Survivorship Care Plans on patient reported outcomes in ovarian cancer during 2-year follow-up – The ROGY care trial. *Gynecol. Oncol.* **145**, 319–328 (2017).
21. de Rooij, B. H. *et al.* Survivorship care plans have a negative impact on long-term quality of life and anxiety through more threatening illness perceptions in gynecological cancer patients: the ROGY care trial. *Qual. Life Res.* **27**, 1533–1544 (2018).
22. van de Poll-Franse, L. V *et al.* The impact of a cancer Survivorship Care Plan on gynecological cancer patient and health care provider reported outcomes (ROGY Care): study protocol for a pragmatic cluster randomized controlled trial. *Trials* **12**, 256 (2011).
23. Zwarenstein, M. *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* **337**, a2390 (2008).
24. Sangha, O., Stucki, G., Liang, M. H., Fossel, A. H. & Katz, J. N. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum.* **49**, 156–63 (2003).
25. Shisler, R. *et al.* Life after endometrial cancer: A systematic review of patient-reported outcomes. *Gynecol. Oncol.* **148**, 403–413 (2018).
26. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, B. A. O. behalf of the E. Q. of L. G. *The EORTC QLQ-C30 scoring manual. 3rd edition.*
27. centERpanel. Available at: [www.website.centerpanel.nl](http://www.website.centerpanel.nl).
28. Mols, F. *et al.* Reference data of the EORTC QLQ-C30 questionnaire: five consecutive annual assessments of approximately 2000 representative Dutch men and women. *Acta Oncol. (Madr)*. **57**, 1381–1391 (2018).
29. Twisk, J. *Applied multilevel analysis: a practical guide for medical researchers. Cambridge University Press; 2006.* (2006).
30. Cocks, K. *et al.* Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J. Clin. Oncol.* **29**, 89–96 (2011).
31. Cocks, K. *et al.* Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur. J. Cancer* **48**, 1713–1721 (2012).
32. Decoster, L. *et al.* Health related quality of life in older patients with solid tumors and prognostic factors for decline. *J. Geriatr. Oncol.* (2019). doi:10.1016/j.jgo.2019.03.018

33. Le, T. *et al.* Longitudinal Assessments of Quality of Life in Endometrial Cancer Patients: Effect of Surgical Approach and Adjuvant Radiotherapy. *Int. J. Radiat. Oncol.* **75**, 795–802 (2009).
34. Kornblith, A. B. *et al.* Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. *J. Clin. Oncol.* **27**, 5337–42 (2009).
35. Janda, M. *et al.* Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial. *Lancet. Oncol.* **11**, 772–80 (2010).
36. Klee, M. & Machin, D. Health-related quality of life of patients with endometrial cancer who are disease-free following external irradiation. *Acta Oncol.* **40**, 816–24 (2001).
37. de Boer, S. M. *et al.* Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial. *Int. J. Radiat. Oncol. Biol. Phys.* **93**, 797–809 (2015).
38. Wollinga, T. *et al.* Implementation of laparoscopic hysterectomy for endometrial cancer over the past decade. *Gynecol. Surg.* **15**, 7 (2018).
39. Parker, P. A. *et al.* Efficacy of a survivorship-focused consultation versus a time-controlled rehabilitation consultation in patients with lymphoma: A cluster randomized controlled trial. *Cancer* **124**, 4567–4576 (2018).
40. Herrera, A. P. *et al.* Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. *Am. J. Public Health* **100 Suppl 1**, S105-12 (2010).
41. de Rooij, B. H. *et al.* Cancer survivors not participating in observational patient-reported outcome studies have a lower survival compared to participants: the population-based PROFILES registry. *Qual. Life Res.* (2018). doi:10.1007/s11136-018-1979-0
42. Sprangers, M. A. & Schwartz, C. E. Integrating response shift into health-related quality of life research: a theoretical model. *Soc. Sci. Med.* **48**, 1507–15 (1999).
43. Nunan, D., Aronson, J. & Bankhead, C. Catalogue of bias: attrition bias. *BMJ evidence-based Med.* **23**, 21–22 (2018).

**Appendix 1a.** Associations between comorbidities at baseline and physical and role functioning at 24 months follow-up in mixed model analysis.

Specific comorbidity	N =	Physical functioning			Role functioning		
		Crude mean (SD) specific comorbidity not present	Crude mean (SD) specific comorbidity present	P-value interaction term*	Crude mean (SD) specific comorbidity not present	Crude mean (SD) specific comorbidity present	P-value interaction term*
Heart disease	14	79.7 (21.1)	59.5 (19.6)	<b>&lt; 0.001</b>	79.7 (28.7)	57.1 (31.8)	<b>&lt; 0.01</b>
Cerebrovascular disease	4	78.0 (21.7)	58.3 (19.1)	0.08	77.9 (29.7)	44.4 (19.2)	<b>0.03</b>
Diabetes mellitus	20	78.2 (21.0)	73.3 (25.7)	0.56	77.1 (29.1)	76.7 (33.9)	0.96
Pulmonary disease	11	78.1 (22.2)	69.7 (16.7)	0.22	77.5 (30.3)	72.7 (26.1)	0.64
Arthritis/ rheumatoid disease	42	81.2 (20.8)	70.4 (22.2)	<b>&lt; 0.01</b>	82.0 (26.8)	67.9 (33.2)	<b>0.02</b>
Backache	36	83.0 (17.8)	64.6 (24.9)	<b>&lt; 0.001</b>	84.2 (24.4)	61.1 (34.7)	<b>&lt; 0.01</b>
Depression	10	78.3 (21.9)	66.7 (19.6)	<b>0.03</b>	79.4 (28.9)	48.1 (26.9)	<b>0.02</b>
Other problem 1	18	80.1 (19.9)	62.2 (26.3)	<b>&lt; 0.001</b>	81.0 (26.5)	55.6 (37.9)	0.38
Obesity†	56	82.4 (19.3)	72.2 (23.4)	<b>&lt; 0.001</b>	81.6 (27.3)	72.1 (32.4)	<b>0.01</b>

Mixed model analysis with EORTC-QLQ-C30 physical and role functioning domains as dependent variable and specific comorbidities as independent categorical variable, adjusted for covariates (partner status, educational level, radiotherapy, and trial arm). A higher score on the HRQoL functioning scales means better functioning. Crude means and standard deviations (SD) after 24 months follow-up are reported.

N = number of endometrial cancer patients reporting this comorbidity at the last questionnaire (24 months). Bold data indicate a significant interaction term with a P-value < 0.05 in combination with a clinically important difference. \* Interaction term = Time 24 months \* specific comorbidity.

† Obesity: BMI ≥ 30 compared to BMI < 30.



**Appendix 1b.** Exploratory analyses with associations between clinical characteristics at baseline and physical and role functioning at 24 months follow-up in mixed model analysis.

		Physical functioning		Role functioning	
	N =	Crude mean (SD)	P-value*	Crude mean (SD)	P-value*
Radiotherapy no (ref)	84	76.1 (21.9)		77.3 (28.5)	
Radiotherapy yes	33	80.4 (21.8)	0.12	76.3 (33.6)	0.94
No treatment during first questionnaire (ref)	88	76.5 (22.2)		78.0 (30.0)	
Any treatment during first questionnaire	29	79.7 (21.1)	0.02	74.1 (30.7)	0.74
75% best PF baseline (ref)	67	85.4 (15.9)		86.3 (22.5)	
25% worst PF baseline	33	77.6 (18.4)	0.07	77.1 (28.9)	0.16
75% best RF baseline (ref)	52	84.1 (17.3)		88.5 (20.8)	
25% worst RF baseline	35	76.0 (23.8)	0.29	76.0 (30.2)	<b>&lt; 0.001</b>

Mixed model analysis with EORTC-QLQ-C30 physical and role functioning domains as dependent variable and certain clinical characteristics as independent categorical variable, adjusted for covariates (partner status, educational level, radiotherapy, and trial arm). A higher score on the HRQoL functioning scales means better functioning. Crude means and standard deviations (SD) after 24 months follow-up are reported. N = number of endometrial cancer patients for whom these items were available at last follow-up (24 months). Bold data indicate a significant interaction term with a P-value < 0.05 in combination with a clinically important difference. \* Interaction term = Time 24 months \* independent variable.



# PART IV

General discussion and summary



# Chapter 11

General discussion

## GENERAL DISCUSSION

In this thesis on older patients with cancer, we focused on different methods of frailty assessment and current treatment practices and decision-making. In addition, we investigated patient-reported outcomes such as health-related quality of life (HRQoL) and functioning. In this final chapter we will place our results in a broader perspective and discuss some issues and implications of these findings, as well as directions for future research.

### Frailty

Frailty is defined as a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes.<sup>1</sup> Depending on the operationalization, frailty appears to be common in older patients with cancer; a systematic review showed that more than half of older patients with cancer have pre-frailty or frailty.<sup>2</sup> It is important to recognise frailty in patients with cancer because frailty is independently associated with treatment feasibility, complications and increased mortality, as well as with increased risk of physical decline, poor quality of life, and high symptom burden during and following cancer treatment.<sup>2,3</sup> A challenge is that there are no universally accepted operational criteria for frailty, and over 70 different tools have been developed for its identification.<sup>3</sup>

In geriatric medicine, comprehensive geriatric assessment (CGA) is the recommended approach to identify frailty.<sup>4</sup> This approach includes an elaborate clinical, multidisciplinary assessment of an older patient's medical, psychosocial, and functional health. CGA identifies potentially modifiable factors amenable to interventions to maximise independence, social support, cognition, and quality of life while reducing risks for poor outcomes such as delirium, worsening disability, post-operative or chemotherapy-related complications, hospitalisation, and treatment-related mortality.<sup>5,6</sup> Indeed, its outcomes are associated with treatment feasibility, quality of life, functioning, and survival.<sup>7,8</sup> In addition, CGA can be used to assess patient's treatment preferences, values and goals. Its aim is to come to a coordinated and integral care plan for the individual patient and it is also used for intervention and follow-up.

In contrast, in oncology, geriatric assessment (GA) is the most commonly used method to identify frailty.<sup>7</sup> It is important to distinguish between CGA and GA. GA generally includes a questionnaire-based assessment of multiple geriatric domains and can be executed by a health care worker who does not necessarily need to have a background in geriatrics. Its results can help to estimate the risk of treatment-related adverse events.<sup>7</sup> However, unlike CGA, this approach does not evaluate all aspects of frailty and does not use a multidisciplinary evaluation. In addition, GA generally does not consider the patient's

treatment preferences, because there are no questionnaires to assess this, and therefore it is less capable than CGA to establish a patient-tailored treatment plan.

### **Frailty assessment in clinical practice**

Although it has been acknowledged that frailty as identified by (C)GA is the most important risk factor for predicting adverse clinical outcomes in older patients with some specific tumour types,<sup>9</sup> its implementation into routine cancer care has been hampered. Frequently used arguments against the use of (comprehensive) geriatric assessment are that it is time and resource consuming. Therefore, short and easy to use frailty screening tools have been suggested as an alternative.

However, (comprehensive) geriatric assessment has multiple advantages over frailty screening tools. Firstly, it provides information on all relevant domains of ageing while a frailty screening tool generally focusses on only several domains (e.g. functioning and malnutrition). Indeed, we also found that GA often reveals impairments that would have been missed with routine oncological assessment (Chapter 2). Secondly, because (C)GA outcomes are associated with multiple important clinical outcomes such as treatment feasibility, quality of life, functioning, and survival it can help to reach a more informed and patient-tailored treatment decision. Finally, results of a (C)GA can be used for targeted non-oncological interventions prior to treatment such as nutritional or social support and physical therapy, and to individualise oncological treatment.

The argument that a (comprehensive) geriatric assessment is too time and resource consuming is thus ill-founded. It is difficult to understand how it can be easier to start an intensive cancer treatment costing thousands of euros, than to implement the routine use of an assessment that is associated with many important clinical outcomes, including the likelihood of treatment failure or lack of benefit.<sup>10</sup> Moreover, treatment complications are also time and resource consuming and primary prevention of these complications is better than to have to intervene upon their occurrence. Therefore, we think a (comprehensive) geriatric assessment is actually worth the investment in time and resources.

However, due to the above-mentioned arguments, many cancer clinical practices are unable to perform (comprehensive) geriatric assessment in all older patients. Given the importance of creating frailty awareness amongst health care workers and of identifying potentially frail patients, a frailty screening tool should be used in these clinics. An example of a frailty tool that is always available and does not require additional time or resources is clinical judgment. However, navigating solely on clinical judgment for identification of potentially frail patients can result in missing patients with relevant geriatric impairment (Chapter 2).

Another example of a frailty screening tool is the G8, which is the most robust and frequently studied frailty screening tool in oncology.<sup>11,12</sup> An advantage of this screening tool is that it is not only able to identify potentially frail patients who require CGA, but that a low score is also associated with survival and treatment-related complications (Chapter 3). To facilitate the use of the G8, we developed a patient-reported version and showed that this may be an alternative to the original G8 (Chapter 4). Because the G8 has low sensitivity for cognitive impairment, an additional questionnaire to screen for cognitive impairment, such as the MoCa or the 6-CIT, has been recommended.<sup>13</sup> These screening tests are a good starting point to create frailty awareness and can be used to identify potentially frail patients. These patients can subsequently undergo a limited GA to estimate the level of frailty and the corresponding treatment consequences. We think this GA should at least include comorbidity, polypharmacy, functioning, mobility, nutrition, cognition, mood, delirium risk, and social support system. Subsequently, outcomes of this GA should be discussed in the multidisciplinary team meeting that should include a geriatrician trained in oncology. In case of impairments in multiple geriatric domains, we recommend to perform a full CGA by a multidisciplinary, geriatric team.

### **Challenges of treatment decision-making in older patients with cancer**

As the baby boomer generation ages, the number of older patients with cancer is rising as well. Yet our current medical systems are ill-prepared to care for the most vulnerable patients with cancer. Some clinical trials specifically evaluated treatment regimens in older patients and found that older patients may benefit from “standard” treatment in accordance with guideline recommendations for younger patients. However, these data are often not representative for the older patient seen in routine practice; clinical trials are still hindered by highly restrictive eligibility criteria such as organ-specific and comorbidity-based exclusion criteria and thus include a selected population of very fit older patients.<sup>14,15</sup> Consequently, optimal treatment for individual older patients with cancer is unknown and most treatment guidelines do not provide recommendations specifically for older or frail patients.

To offer physicians some guidance for treatment decision-making in older patients with cancer, we have analysed treatment choices and outcomes in real-life patients. We found that older patients with cancer less frequently received guideline adherent-care than their younger counterparts (Chapter 5-7) and that they were less likely to complete treatment according to plan (Chapter 5 and 7). Despite frequently implemented primary chemotherapy adaptations, secondary adaptations and hospitalisations were common in the oldest old (Chapter 7). In older patients receiving adapted treatment or best supportive care only, patient preference was the most important reason for this decision (Chapter 5 and 6). This suggests that older patients are capable of and willing to participate in treatment decision-making. However, we also found that older patients



were less frequently discussed in a multidisciplinary team meeting (Chapter 6) or referred to a medical oncologist (Chapter 5). In light of the complexity of treatment decisions for this heterogeneous population, it is particularly important to discuss these patients in a multidisciplinary team that preferably involves a geriatrician and also includes information on the patient's overall health status and his or her treatment preferences and goals. In addition, older patients should be able to discuss treatment options and pros and cons with an oncologist in order to make an informed and shared decision.

Nevertheless, all these studies had a retrospective design. Consequently, data on potentially relevant confounders, such as the presence of geriatric syndromes or decreased functional capacity, were not available. Preferably, these studies should be repeated prospectively, with incorporation of baseline frailty and geriatric data. In fact, in our opinion, for any research in older patients with cancer, reporting baseline geriatric data is as important as the tumour-related data or other patient characteristics. Without this information, it is not possible to compare study results or extrapolate their findings to the individual older patient. In addition, prospective studies should also evaluate the underlying motivation to decline guideline treatment and the extent to which shared decision-making influences treatment choice.

Yet our results do provide food for thought. They may lead to questions such as whether oncological treatment is always feasible in the oldest old when so many receive a modified treatment which they are nevertheless unable to complete. Or whether chemotherapy regimens with secondary adaptations superimposed on primary adaptations are still effective or should be omitted altogether. Exposing frail patients to a burdensome oncological treatment may be undesirable because of the potential loss of independence or functioning. Studies suggesting that older patients who do not receive standard treatment are undertreated or even receive inappropriate treatment, insufficiently take into consideration that withholding guideline care may be appropriate for some older patients as valid reasons for guideline non-adherence do exist (Chapter 5 and 6). In addition, these studies often draw their conclusions based on survival benefits from standard treatment and insufficiently consider that, for older patients, independent functioning and quality of life are often as important or more important than prolongation of life.<sup>16,17</sup> We found that many older patients with cancer received best supportive care only (Chapter 5 and 6) and think this may be a reasonable alternative in selected older patients. This is further supported by the finding that patients with a poor prognosis have a high risk of outcomes that represent poor quality of care. Chemotherapy and health care utilisation in the last three months of life is high in these patients and they have an increased chance of dying in the hospital (Chapter 8).

**Outcomes that matter to older patients with cancer**

Ultimately, what matters most to those diagnosed with cancer is to live as long and as good as possible without cancer-related symptoms and to be able to participate in activities that are most important to them. Therefore, besides information on survival and treatment adverse events, information on HRQoL and functioning outcomes during and after treatment should always be provided. After treatment for ovarian cancer, HRQoL may be impaired even up to six years after treatment (Chapter 9). One possible explanation for the finding that older ovarian cancer survivors experienced poorer HRQoL than their younger counterparts could be the decreased physiological reserve or increased comorbidity burden in older patients. Indeed, in a longitudinal study, we found that cumulative comorbidity burden and not a patient's age was independently associated with deterioration of HRQoL (Chapter 10).

Nevertheless, it is important to emphasise that most quality of life questionnaires measure the level of experienced impairment and not the impact or relevance of disability to the patient's daily life. Although our results suggest that older patients and those with higher comorbidity burden experienced poorer HRQoL, it needs to be underlined that the experience of burden is highly dependent on personal values and current quality of life. To our knowledge, very few studies have assessed older patient's personal health goals such as living at home independently, the ability to engage in social activities or to care for a loved one as long as possible. One recently published conference abstract aimed to elicit preferences and priorities among 241 older patients starting chemotherapy.<sup>18</sup> They found that 42% of patients rated other outcomes (function, freedom from pain or symptoms) as more important than survival. In addition, two-thirds of patients considered current HRQoL as equally important or more important than HRQoL at one or five years in the future. Eliciting which outcomes are most important for older patients with cancer may help to improve shared and patient-tailored decision-making. Besides clarifying which outcomes matter most to older patients, it is also important to have more dynamical (i.e. more frequent) measurements of patient-reported outcomes (PROs) to provide a more detailed and realistic view on the recovery trajectory.

**Other strategies to improve outcomes in older patients with cancer***Pre- and rehabilitation*

Given poor treatment feasibility and HRQoL in older compared to younger patients (Chapter 5-7 and Chapter 9), the question is whether these outcomes can be improved by optimising the patient's overall condition. Examples to improve health status are prehabilitation prior to treatment, geriatric co-management during treatment, the use of minimally invasive techniques perioperatively, and rehabilitation after treatment.

Rehabilitation measurements, such as enhanced recovery after surgery (ERAS), have been incorporated in some cancer treatment guidelines<sup>19</sup> but are largely underutilised in clinical practice.<sup>20</sup> Rehabilitation involves (a combination of) physical exercise, psychological and/or nutritional support. It can have beneficial effects on the prevalence of post-treatment complications and can enhance recovery after treatment.<sup>21</sup> However, similar to other fields in medicine, it seems logical that efforts to prevent treatment-related adverse events and deterioration of physical functioning will be more effective.

The aim of prehabilitation is to improve the patient's pre-treatment health status in the period between diagnosis and treatment by means of a multimodal approach using physical exercise training, nutritional interventions, psychological support and/or coaching towards lifestyle changes.<sup>22</sup> Ideally, this improvement would result in faster recovery of physical functioning, less treatment-related adverse events, shorter hospital stays and improved long-term prognosis, as well as in lower direct and indirect healthcare costs.

Although this makes sense theoretically and many studies have been published on this subject in the past decade, scientific evidence demonstrating the value of prehabilitation in older patients with cancer on clinically relevant endpoints is scarce. In the last two years, several systematic reviews have been published focusing on prehabilitation in patients with different tumour types with an indication for surgery.<sup>22–26</sup> Some of the included studies show promising results, such as a reduction in postoperative complications in high-risk older patients undergoing elective major abdominal surgery (75% of whom had cancer),<sup>27</sup> postoperative pain reduction in women undergoing surgery for breast cancer,<sup>28</sup> and significant improvements in physical fitness in patients with various tumour types.<sup>22–24</sup> However, most included trials and studies were of low quality and they were heterogeneous in terms of the content and duration of the prehabilitation intervention program as well as the outcomes that were assessed. In addition, the majority did not include high-risk patients and results thus only apply to healthier older patients. Compliance was often not reported and is likely to be poorer in high-risk (i.e. more frail) patients. Furthermore, the studies did not report anything about the *impact* of postoperative complications (such as the impact on the patient's length of hospital stay, use of resources, or physical functioning) and data on long-term physical functioning, lifestyle changes, quality of life, and cost-effectiveness were not provided. To our knowledge, there are currently no studies assessing the effectiveness of prehabilitation in patients with an indication for chemotherapy.

The absence of a positive effect of prehabilitation on clinical outcomes might be explained by the trajectory of frailty. Because frailty is defined by a *gradual* deterioration of the body systems functioning, the question is whether a relatively short period of pre-treatment

prehabilitation is capable to reverse the frailty process. In addition, as patient compliance is often not reported, poor compliance may be another explanation for the absence of a positive effect. Instead of a prehabilitation program with a duration of a few weeks, it may be more beneficial to advise patients to continuously put effort in improving their exercise capacity (such as walking half an hour every day, supervised if necessary) and to change their life style. Because prehabilitation compliance is likely to be predictive for the compliance in postoperative rehabilitation, this may be a prerequisite for undergoing surgery.

In summary, although some results on the value of prehabilitation in older patients with cancer are promising, there is a need for further high-quality research with a focus on high-risk patients. These studies should measure not only the incidence, but also the impact of postoperative complications and clinical outcomes such as hospital and intensive care admissions, physical functioning and quality of life as well as patient compliance and cost-effectiveness.

In addition to prehabilitation, supportive care during and after cancer treatment may accelerate the recovery trajectory and thus could result in maintenance or improvement of physical functioning and quality of life. Although “standard” perioperative supportive care is well established in current clinical practice, only two studies addressed the additional value of geriatric co-management to further improve post-treatment outcomes.<sup>29,30</sup> One recent retrospective study explored the association between geriatric co-management and 90-day postoperative mortality of 1892 cancer patients aged 75 years and older.<sup>29</sup> They found that 1020 patients (54%) were co-managed by geriatricians and that geriatric co-management was associated with 57% lower risk of 90-day mortality (90-day mortality 3.5% compared to 10.5% in the group receiving standard surgical care, OR = 0.43; 95%CI 0.28-0.67,  $p < 0.001$ ). The other study investigating geriatric co-management, is a prospective, non-randomised study that assessed postoperative outcomes among 42 older women undergoing cytoreductive surgery for advanced stage ovarian cancer.<sup>30</sup> This study found that, despite high rates of geriatric impairments preoperatively (five impairments in >50% of women), rates of 30-day postoperative events were relatively low compared to women treated in the same time period but who did not undergo geriatric evaluation ( $n=40$ ). They found lower rates of unplanned intensive care unit admissions (2% vs 15%) and readmissions (10% vs 15%) in patients receiving geriatric co-management compared to those who did not, but these differences were not statistically significant (likely due to the small sample size). There were no deaths in the geriatric co-management group, while two patients in the control group died. Although both studies show promising results, larger randomised controlled trials are necessary to assess the impact of geriatric co-management on clinical outcomes in older patients with cancer.

Because older patients with cancer frequently experience surgery-related adverse events after extensive radical surgery, minimally invasive techniques such as non-operative treatment or minimally invasive surgery can be used to minimise morbidity. Examples of the first include primary endocrine therapy for breast or prostate cancer, stereotactic radical radiotherapy for non-small cell lung cancer, or chemoradiotherapy for rectal cancer. Examples of the latter are minimally invasive esophagectomy or gastrectomy, both of which were shown to be safe and effective in older patients with cancer.<sup>31,32</sup> Benefits of minimally invasive surgery include less blood loss, shorter recovery time and length of hospital stay, and decreased rates of postoperative infections.<sup>33</sup> Nevertheless, there are currently no data available on the effect of minimally invasive techniques on other important outcomes such as functioning and quality of life.

### *Resilience*

Although frailty is associated with clinical outcomes in older patients with cancer, physicians often observe outcomes they could not predict nor fully understand. Examples are an unexpected recovery of functioning in a patient with multimorbidity and impaired mobility, or an unforeseen worsening of functioning in an older patient who was identified as fit. In other words, outcomes are frequently not in proportion with stressor burden. The concept of physical resilience may explain some of this uncertainty. Resilience can be defined as the physical and mental ability to resist or recover from adverse events of a stressor.<sup>34</sup> Examples of such stressors in older patients with cancer are the cancer diagnosis and oncological treatment. Resilience is not simply the opposite of frailty: if the spectrum of frailty reflects the physiological potential someone has to recover from stressors, resilience applies to the actualisation of that potential.<sup>35,36</sup>

Currently, most well-studied clinical predictors to track the recovery process are static tests of physiological reserves over multiple functioning domains.<sup>36</sup> This means that usually two measurements are conducted to assess an outcome, one before and one after the stressor. Nevertheless, the resulting trajectory does not take into account the high inter-person variability of the physiologic recovery response. Using dynamical rather than static resilience measurements may improve the prediction and management of recovery on the individual patient level.<sup>36</sup> There are several possibilities to measure resilience dynamically.<sup>36</sup> Perhaps the most feasible in frail older patients is to increase the number of measurements around a stressor and to use the natural perturbations from the environment to which a body must respond with micro-recoveries to maintain homeostasis.<sup>36</sup> Examples of such natural perturbations are time series of mood or postural balance. Focusing on these micro-recoveries by using multiple measurements may give an impression of the patient's resilience.

Currently, dynamical data on physical resilience and their relationship with recovery are scarce for older patients with cancer and further longitudinal research is necessary. Outcomes of these studies may help improve treatment decision-making by more accurate and personalised prediction of the recovery trajectory and to adapt oncological treatment. For current clinical practice, it may be useful to check whether the patient has had a recent disease or operation and to ask about the corresponding recovery trajectory.

### **Directions for future research**

In Table 1, recommendations based on findings from this thesis and this discussion are summarised. In addition, in this final topic, we will specifically address opportunities to improve future research in older patients with cancer.

Firstly, older and frail patients need to be included in cancer research more frequently. A logical step would be inclusion in randomised controlled trials. Nevertheless, although this study design generally provides the highest level of evidence, one can question whether this also holds true for older patients. Given the heterogeneity of this population and their underrepresentation in trials, it is difficult to generalise the trial's findings to the individual older patient. In other words, the external validity (i.e. the generalizability of the results to many real-world settings) of this kind of research is limited. There is an increasing interest for obtaining scientific evidence with a focus on the benefits and harms of interventions in real-world, everyday circumstances. This evidence can be performed with observational data capturing routine clinical care through comparative effectiveness research. Examples of this kind of research are large cohort studies or registry studies. Pragmatic clinical trials, which mimic usual clinical practice and use broader eligibility criteria, represent another alternative and have the advantage that they are not subject to biases that may hamper interpretation of cohort or registry studies.<sup>37</sup> Other suitable alternatives include the use of embedded studies that utilise (comprehensive) geriatric assessment measures within larger trials, single arm phase II trials, and trials with a less intensive treatment arm for patients who did not fulfil inclusion criteria of the original trial.

Secondly, there should be more data on the effects of geriatric assessment-based treatment allocation on concrete clinical outcome parameters (such as on treatment tolerability, survival, and quality of life). The only study investigating this issue found that those who were treated on the basis of CGA had a higher rate of treatment completion and less overall toxicity with similar oncological outcomes to the control arm.<sup>38</sup> Further research should focus on relevant oncological and non-oncological outcomes, to understand how a (C)GA can potentially contribute to optimal decision-making. To avoid issues frequently present in prior research, such as heterogeneity in patient population and limited content of GA, these studies should be conducted in single-tumour cohorts and include a broad range of geriatric conditions. This is in line with the finding that frailty

**Table 1.** Recommendations for clinical practice and future research in older patients with cancer.

Topic	Recommendations based on findings of this thesis and discussion
Frailty	<ul style="list-style-type: none"> <li>• Reach agreement on a frailty definition based on (comprehensive) geriatric assessment in older patients with cancer.</li> <li>• In cancer clinical practices where it is infeasible to perform (comprehensive) geriatric assessment in all older patients, start with the G8 and a cognitive screening test such as the MoCa or 6-CIT to identify potentially frail patients who require limited GA. This GA should at least include comorbidity, polypharmacy, functioning, mobility, nutrition, cognition, mood, delirium risk, and social support system. In case of impairments in multiple geriatric domains, perform a full CGA by a multidisciplinary, geriatric team.</li> </ul>
Decision-making	<ul style="list-style-type: none"> <li>• Discuss all older patients with cancer in a multidisciplinary team meeting, preferably in the presence of a geriatrician.</li> <li>• Broaden cancer trial eligibility criteria and use alternatives to randomised controlled trials such as pragmatic trials or prospective cohort studies.</li> <li>• Studies should include baseline geriatric and frailty data.</li> <li>• Prospective studies should be carried out evaluating the underlying motivation to decline guideline care and the extent to which shared decision-making influences treatment choice.</li> <li>• Consider prehabilitation and geriatric co-management in older and frail patients with cancer.</li> <li>• More data are needed on the incidence and impact of post-operative complications and clinical outcomes and cost-effectiveness of prehabilitation.</li> <li>• Consider best supportive care as an option in selected older patients with cancer.</li> <li>• Develop treatment guidelines and recommendations specifically for frail and older patients.</li> </ul>
Patient-reported outcomes	<ul style="list-style-type: none"> <li>• Perform prospective studies that assess the impact and relevance of a cancer diagnosis and treatment on a patient's daily life and studies that evaluate patients' personal health goals.</li> <li>• Study the significance of resilience in older patients with cancer and use dynamical rather than static tests to track the recovery process.</li> <li>• In order to predict outcome to the planned treatment, the physician should check whether the patient has had a recent disease or operation and ask about the corresponding recovery trajectory.</li> <li>• Compare clinical and patient-reported outcomes preferably with those from an age- and gender-matched general population.</li> </ul>

is as least as important or even more important than tumour stage. In addition, future studies should also assess the value of (comprehensive) geriatric assessment in patients receiving new anti-cancer treatments, such as immunotherapy. For these studies applies that if randomisation or stratification according to baseline geriatric parameters is not possible, at least these parameters should be explicitly mentioned in the results.

Thirdly, while patient-reported outcomes are increasingly being used in clinical trials, these outcomes should be the primary endpoint more frequently. Alternatively, they could be used as composite endpoints, which take into account a combination of the tolerability and efficacy of treatment. In addition, more studies are needed to assess the impact and

relevance of cancer diagnosis and treatment on patient's personal lives and to evaluate their life goals and priorities. Study endpoints need to be tailored in order to match those outcomes that are most relevant to older and frail patients, such as independence, physical function, cognition, treatment tolerance, and days spent in good health during treatment. Furthermore, although data on the prevalence of treatment-related morbidity and toxicity are very important, data on the time it took to recover from and the impact on functioning of these adverse events and factors that improve recovery should also receive attention. As said before, resilience, prehabilitation, and geriatric co-management represent important areas for future research in older patients with cancer.

*In conclusion*, treatment decision-making in older patients with cancer remains complex and challenging. In this thesis, we have addressed important aspects of this problem and we may have contributed to the knowledge on frailty assessment, current treatment practices and decision-making, and patient-reported outcomes.



## REFERENCES

1. Clegg, A., Young, J., Iliffe, S., Rikkert, M. O. & Rockwood, K. Frailty in elderly people. *Lancet* 381, 752–762 (2013).
2. Handforth, C. *et al.* The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 26, 1091–1101 (2015).
3. Kirkhus, L. *et al.* Frailty identified by geriatric assessment is associated with poor functioning, high symptom burden and increased risk of physical decline in older cancer patients: Prospective observational study. *Palliat. Med.* 33, 312–322 (2019).
4. Solomon, D. *et al.* Best Paper of the 1980s: National Institutes of Health Consensus Development Conference Statement: Geriatric Assessment Methods for Clinical Decision-Making. *J. Am. Geriatr. Soc.* 51, 1490–1494 (2003).
5. Pilotto, A. *et al.* Three Decades of Comprehensive Geriatric Assessment: Evidence Coming From Different Healthcare Settings and Specific Clinical Conditions. *J. Am. Med. Dir. Assoc.* 18, 192.e1–192.e11 (2017).
6. Huisingh-Scheetz, M. & Walston, J. How should older adults with cancer be evaluated for frailty? *J. Geriatr. Oncol.* 8, 8–15 (2017).
7. Mohile, S. G. *et al.* Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J. Clin. Oncol.* JCO.2018.78.868 (2018). doi:10.1200/JCO.2018.78.8687
8. Stuck A., Siu, A., Wieland, G., Rubenstein, L. & Adams, J. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 342, 1032–1036 (1993).
9. International Society of Geriatric Oncology (SIOG) 2019 oral presentations.
10. Hamaker, M. E., Wildes, T. M. & Rostoft, S. Time to Stop Saying Geriatric Assessment Is Too Time Consuming. *J. Clin. Oncol.* 35, 2871–2874 (2017).
11. Decoster, L. *et al.* Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 26, 288–300 (2015).
12. Hamaker, M. E. *et al.* Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol.* 13, e437–e444 (2012).
13. Portielje, J. E. A., Hamaker, M. E., Maas, H. A. A. M., van Leeuwen, B. L. & van den Bos, F. [American guideline for geriatric oncology; applicable to Dutch clinical practice?]. *Ned. Tijdschr. Geneesk.* 163, (2019).
14. Canoui-Poitaine, F. *et al.* Inclusion of Older Patients with Cancer in Clinical Trials: The SAGE Prospective Multicenter Cohort Survey. *Oncologist* 24, e1351–e1359 (2019).
15. Srikanthan, A. *et al.* Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies. *Cancer Treat. Rev.* 43, 67–73 (2016).
16. Fried, T. R., Bradley, E. H., Towle, V. R. & Allore, H. Understanding the Treatment Preferences of Seriously Ill Patients. *N. Engl. J. Med.* 346, 1061–1066 (2002).

17. Akishita, M. *et al.* Priorities of Health Care Outcomes for the Elderly. *J. Am. Med. Dir. Assoc.* 14, 479–484 (2013).
18. Soto Perez de Celis, E. *et al.* Patient-defined goals and preferences among older adults with cancer starting chemotherapy (CT). *J. Clin. Oncol.* 36, (2018).
19. Richtlijndatabase Federatie Medisch Specialisten (FMS), Colorectaal carcinoom, [https://richtlijndatabase.nl/richtlijn/colorectaal\\_carcinoom\\_crc](https://richtlijndatabase.nl/richtlijn/colorectaal_carcinoom_crc), Accessed date: 18 March 2020 (in Dutch).
20. American Cancer Society. Cancer treatment & survivorship facts & figures 2019-2021. Atlanta: American Cancer Society; 2019.
21. Silver, J. K., Baima, J. & Mayer, R. S. Impairment-driven cancer rehabilitation: an essential component of quality care and survivorship. *CA. Cancer J. Clin.* 63, 295–317 (2013).
22. Thomas, G. *et al.* Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials. *Eur. J. Anaesthesiol.* 36, 933–945 (2019).
23. Yang, A., Sokolof, J. & Gulati, A. The effect of preoperative exercise on upper extremity recovery following breast cancer surgery. *Int. J. Rehabil. Res.* 41, 189–196 (2018).
24. Rosero, I. D. *et al.* Systematic Review and Meta-Analysis of Randomized, Controlled Trials on Preoperative Physical Exercise Interventions in Patients with Non-Small-Cell Lung Cancer. *Cancers (Basel)*. 11, 944 (2019).
25. Tsimopoulou, I. *et al.* Psychological Prehabilitation Before Cancer Surgery: A Systematic Review. *Ann. Surg. Oncol.* 22, 4117–4123 (2015).
26. Schneider, S., Armbrust, R., Spies, C., du Bois, A. & Sehouli, J. Prehabilitation programs and ERAS protocols in gynecological oncology: a comprehensive review. *Arch. Gynecol. Obstet.* 301, 315–326 (2020).
27. Barberan-Garcia, A. *et al.* Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. *Ann. Surg.* 267, 50–56 (2018).
28. Baima, J. *et al.* Teaching of Independent Exercises for Prehabilitation in Breast Cancer. *J. Cancer Educ.* 32, 252–256 (2017).
29. Kim, S. J. Geriatric co-management is associated with reduced 90-day postoperative mortality among patients aged 75+ with cancer. *J. Geriatr. Oncol.* 10, S3-4 (2019).
30. Filippova, O. T. *et al.* Geriatric co-management leads to safely performed cytoreductive surgery in older women with advanced stage ovarian cancer treated at a tertiary care cancer center. *Gynecol. Oncol.* 154, 77–82 (2019).
31. Kwon, I. G. *et al.* Minimally invasive surgery as a treatment option for gastric cancer in the elderly: comparison with open surgery for patients 80 years and older. *Surg. Endosc.* 29, 2321–2330 (2015).
32. Perry, Y., Fernando, H. C., Buenaventura, P. O., Christie, N. A. & Luketich, J. D. Minimally invasive esophagectomy in the elderly. *JSLS J. Soc. Laparoendosc. Surg.* 6, 299–304 (2002).

33. Paul, S., Isaacs, A. J., Treasure, T., Altorki, N. K. & Sedrakyan, A. Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database. *BMJ* 349, g5575 (2014).
34. Whitson, H. E. *et al.* Physical Resilience in Older Adults: Systematic Review and Development of an Emerging Construct. *J. Gerontol. A. Biol. Sci. Med. Sci.* 71, 489–95 (2016).
35. Whitson, H. E. *et al.* Physical Resilience: Not Simply the Opposite of Frailty. *J. Am. Geriatr. Soc.* 66, 1459–1461 (2018).
36. Gijzel, S. M. W. *et al.* Resilience in Clinical Care: Getting a Grip on the Recovery Potential of Older Adults. *J. Am. Geriatr. Soc.* 67, 2650–2657 (2019).
37. Soto-Perez-De-Celis, E. & Lichtman, S. M. Considerations for clinical trial design in older adults with cancer. *Expert Opin. Investig. Drugs* 26, 1099–1102 (2017).
38. Corre, R. *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 ESO GIA-GF-PC-GECP 08-02 Study. *J. Clin. Oncol.* 34, 1476–1483 (2016).



# Chapter 12

Summary

## SUMMARY

Physicians are confronted with an increasing population of older patients with cancer for whom treatment decisions are needed. For these patients, decision-making is complex and involves the delicate balance between under- and overtreatment. Because of poor inclusion in large randomised controlled trials and large heterogeneity in health status and cancer treatment, there is not one standard treatment for older patients with cancer. Older patients' treatment preferences may also differ from those of their younger counterparts; although survival benefit from treatment is an important outcome for most older patients with cancer, they often value other outcomes such as independence and quality of life as equally or more important. Due to these factors, older patients' benefit from oncologic treatment can differ and they benefit most from individualised treatment.

The aim of this thesis was threefold. Firstly, we described several methods of frailty assessment in older patients with cancer, focusing on clinical judgment and on the G8 screening tool (**Part I**). Secondly, current treatment practice in patients with ovarian cancer and the oldest old patients with cancer is evaluated (**Part II**). Thirdly, health-related quality of life (HRQoL), functioning and health-care utilisation of older patients with (gynaecological) cancer is analysed (**Part III**).

In **Part I**, the focus is on different methods to identify potentially frail older patients with cancer. In **Chapter 2**, correlations between clinical judgment for frailty of the cancer specialist, the general practitioner and the patient were assessed in patients undergoing geriatric assessment. We found that correlations between the various clinical judgment scores, and between clinical judgment and geriatric assessment were poor. Most patients with multiple geriatric impairments were clinically assessed as not very frail (median frailty score was three on a scale from zero to ten, where zero indicated not frail at all and ten indicated most frail). We concluded that navigating solely on clinical judgment for identification of potential frailty in older patients with cancer could result in missing patients with relevant geriatric impairments.

Because not all older patients with cancer require an elaborate geriatric assessment, a two-step approach has been recommended by the International Society of Geriatric Oncology (SIOG). With this approach, older patients are screened for potential frailty using a short frailty screening tool and only patients with an impaired score receive full geriatric assessment. The G8 is the most robustly studied screening tool and has been recommended as the screening tool of choice by SIOG. In **Chapter 3** we performed a systematic review and summarized all available evidence on the use of the G8, focusing both on the comparison of G8 with geriatric assessment as well as its association with clinical outcomes (survival, course of treatment and patient-centred outcomes). Our

results suggest that the G8 is not only a useful tool to identify potentially frail patients who may benefit from complete geriatric assessment, but that a low G8 score is also associated with poor survival and treatment-related complications. For other clinical outcomes, there was too little evidence available to draw conclusions. Given the shortness of the G8, it is unlikely that the G8 on its own is able to sufficiently refine prognosis or can be used for goal-of-care discussions, tailored treatment, and advanced care planning. Therefore, we concluded that the G8 cannot replace full geriatric assessment but is useful in a two-step approach followed by geriatric assessment for potentially frail patients.

Because the G8 is a widely used screening tool for older patients with cancer, but is designed to be completed by healthcare professionals, it would be useful to have a patient-reported version. A patient-reported version could facilitate a more widespread use of this tool because there are barriers to implement the G8 in clinical practice. Therefore, in **Chapter 4**, we assessed the agreement of a newly developed patient-reported version of the G8 with the original G8 in 161 older patients with and without a cancer diagnosis. Completing the patient-reported G8 was feasible for almost all patients with cancer and agreement between the two tools was substantial for these patients but poor in geriatric patients without cancer. Although agreement was not perfect, our results demonstrated that the patient-reported version of the G8 may provide an alternative to the original G8 in older patients with cancer.

Although older patients represent the majority of all patients with cancer, evidence on optimal oncological treatment for and outcomes in these patients is scarce. Often, specific recommendations for these patients are lacking in treatment guidelines. In addition, reasons why patients do not receive guideline-adherent care are currently unknown, while knowledge on these reasons may influence the treatment decision-making process. In **Part II**, we investigated current treatment choices and outcomes in patients with gynaecological cancer and in the oldest old with cancer as well as reasons for guideline non-adherent treatment.

In **Chapter 5** we performed a retrospective analysis of the treatment decision-making process in 128 patients diagnosed with ovarian cancer at the Diaconessenhuis Utrecht. We found that only 5% of patients aged 75 years and older with advanced stage ovarian cancer received and completed treatment in accordance with the treatment guideline, while nearly half of the patients aged younger than 75 completed this treatment without requiring adaptations. Furthermore, 38% of the older patients received best supportive care only. Chemotherapy- and surgery-related complication rates and unforeseen hospital admission rates were similar for both age groups. Patient preference was an important reason to refrain from standard treatment in older patients.

To examine these findings on a larger scale, we performed a nation-wide population-based analysis among 4210 women with advanced stage ovarian cancer on treatment patterns and reasons for guideline non-adherence according to age (**Chapter 6**), including an age group of patients aged 85 years and older. In this study we confirmed our finding of the previous chapter that older women, especially the oldest old, much less frequently received guideline-adherent care than their younger counterparts. We also demonstrated that 68% of these women received best supportive care only, compared to 4% of the women aged younger than 65 years of age. The most common reason for guideline non-adherence in older women was patient preference, while functional status and extent of disease were the most important reasons for guideline non-adherence in younger patients.

In **Chapter 7**, we investigated the tolerability and feasibility of chemotherapy in the oldest old patient (e.g. patients aged 80 years and older). Our primary outcome was whether chemotherapy was completed according to plan. We defined this as a calculated relative dose intensity (RDI) of  $\geq 85\%$ . Using the RDI, we compared the planned dose intensity with the dose intensity actually received by the patient. 104 patients were included with a median age of 82 years (range 80-94 years). Almost half of the chemotherapy regimens started in the oldest old were not completed according to plan (48%), despite frequently implemented upfront chemotherapy adaptations (63%). In addition, secondary adaptations and hospitalizations were frequently necessary (in 65% and 25% respectively). The rate of successfully completed chemotherapy was not affected by whether the initial treatment plan consisted of standard, alternative (i.e. guideline contained treatment recommendations specifically for older or unfit patients and these were followed), or non-guideline based adapted treatment. We concluded that because so many patients received a modified chemotherapy regimen but nevertheless were unable to complete this treatment, the question is whether chemotherapy is feasible in the oldest old, and whether regimens with secondary adaptations superimposed on primary adaptations are still effective or should be omitted altogether in selected older patients.

Over the last decades, patient-reported outcomes (PROs) have become a topic of major interest in older patients with cancer. **Part III** of this thesis addressed health-care utilisation in the last three months of life among patients treated with palliative chemotherapy at the Diaconessenhuis Utrecht. In addition, we analysed the use of PROs such as health-related quality of life (HRQoL) and functioning in older patients with endometrial and ovarian cancer.

In **Chapter 8**, we retrospectively assessed potential areas representing poor quality of end-of-life care in patients who had received palliative chemotherapy. Examples of poor quality end-of-life care include starting or continuing chemotherapy in the very last



period of life, and high rates of chemotherapy-related unplanned emergency room visits, hospitalisation, or intensive care unit admissions. Half of the 604 patients analysed received chemotherapy in the last three months of life. Healthcare utilisation and in-hospital-death in the last three months of life were high for all patients, but significantly higher for those patients who received palliative chemotherapy in the last three months of life. These results underline the importance of early integration of palliative care and highlight that, in the course of disease, clinicians, patients and their caregivers must continuously weigh the potential benefits of treatment against their negative effects.

Another important outcome for patients with cancer is the quality of living after oncological treatment. HRQoL of women with ovarian cancer is seriously impaired by both the diagnosis and the extensive treatment but long-term data on this outcome are largely missing, especially for older women. Therefore, we addressed this topic in 191 ovarian cancer survivors on average six years after diagnosis: we compared HRQoL of women with ovarian cancer aged 70 years and older both with an age-matched normative population as well as with their younger counterparts (**Chapter 9**). In addition, we also assessed the differential effect of chemotherapy on HRQoL between older and younger ovarian cancer survivors. We found that older survivors reported poorer HRQoL and more symptoms than both the age-matched normative population and younger survivors. Compared to the normative population, older survivors scored worse on global health status as well as on all functioning scales except emotional functioning. Compared to younger survivors, older survivors rated physical and role functioning poorer and they reported a lower global health status. Our results also suggest that age moderates the effect of chemotherapy on HRQoL. Older survivors who had received chemotherapy experienced better physical functioning and less pain and insomnia while the opposite was found in younger survivors. We concluded that, in comparison with an age-matched normative population, older ovarian cancer survivors report lower HRQoL than younger survivors. Long-lasting deficits in functioning and symptoms were prevalent particularly in older ovarian cancer survivors and these women should receive information regarding HRQoL outcomes to manage their expectations.

Longitudinal analysis of HRQoL may improve the understanding of the evolution of HRQoL during and after treatment and can be an important factor in decision-making regarding oncological treatment. Therefore, in **Chapter 10**, we assessed HRQoL longitudinally at four time points (ranging from after initial treatment to 24 months follow-up) among 215 patients with endometrial cancer and explored whether age or comorbidity was more strongly associated with changes in HRQoL over time. In addition, we compared outcomes with changes in HRQoL of an age- and gender-matched normative population. We found that, independent of age, comorbidity was significantly associated with worse scores on all functioning outcomes. Patients with comorbidity reported deterioration of

physical and role functioning after 12 months. Compared to the normative population, patients initially reported better physical and role functioning. However, at 24 months, differences in these HRQoL outcomes were no longer statistically significant or clinically relevant. There are two possible explanations for this finding: firstly, it is possible that patients experienced larger deterioration of physical and role functioning than the normative population. Secondly, patients' outcomes could indicate a response shift after initial treatment with return of HRQoL to levels comparable to the normative population at 24 months. Results from this study emphasise the importance of considering patients cumulative comorbidity burden, and not solely a patient's chronological age, when discussing HRQoL outcomes.

In **Chapter 11**, the results in this thesis are discussed and placed in a broader perspective. We also provided implications for clinical practice and for future research.

In conclusion, we found that across different tumour types, many oldest old patients do not receive guideline-adherent treatment and do not complete their treatment according to plan. The G8 screening tool may help to identify potentially frail older patients with possible poorer survival and course of treatment. Because many older patients with cancer receive best supportive care only, early integration of palliative care is of utmost importance. Older patients and those with a higher comorbidity burden experienced poorer HRQoL. Our results demonstrate the complexity of treatment decision-making in older patients with cancer and underline the importance of shared-decision making in and patient-tailored treatment for this population.





# Chapter 13

Summary in Dutch – Samenvatting in het Nederlands

## SAMENVATTING IN HET NEDERLANDS

Artsen worden geconfronteerd met een toenemende incidentie van ouderen met kanker die zij behandeladviezen moeten geven. Deze besluitvorming is complex en betreft een delicate balans tussen onder- en overbehandeling. Er bestaat geen “standaard” oncologische behandeling voor ouderen met kanker. Dit komt onder andere doordat zij ondervertegenwoordigd zijn in grote gerandomiseerde studies en er grote variatie bestaat door de heterogeniteit in kankersoorten, behandelingen, gezondheid en kwetsbaarheid. Daarnaast kunnen hun behandelvoorkeuren verschillen ten opzichte van die van jongeren; hoewel overlevingsvoordeel een belangrijke uitkomst is voor de meeste ouderen met kanker, vinden zij andere patiëntgerichte uitkomsten zoals onafhankelijkheid en kwaliteit van leven vaak even belangrijk of belangrijker. Ouderen profiteren daarom het meest van een behandeling op maat.

Het doel van dit proefschrift is driedelig. Allereerst beschrijven we verschillende methoden om kwetsbaarheid vast te stellen bij ouderen met kanker, waarbij we ons richten op de waarde van de klinische blik en het G8 screeningsinstrument (**Deel I**). Ten tweede analyseren we de huidige behandelpraktijk voor zowel vrouwen met eierstokkanker als ook oudste ouderen met kanker (**Deel II**). Tot slot hebben we meerdere patiëntgerichte uitkomsten bestudeerd (**Deel III**).

In **Deel I** ligt de focus op verschillende methoden om potentieel kwetsbare patiënten met kanker te herkennen. In **Hoofdstuk 2** hebben we gekeken naar de correlaties tussen de klinische blik van de oncoloog/hematoloog, de huisarts en de patiënt zelf voor het inschatten van kwetsbaarheid, en naar de correlaties tussen de klinische blik en een geriatrisch assessment. Deze correlaties waren slecht; de meeste patiënten met problemen op meerdere geriatrische domeinen werden middels de klinische blik als niet kwetsbaar beoordeeld. Dit impliceert dat, indien alleen op de klinische blik vertrouwd wordt voor identificatie van potentieel kwetsbare ouderen met kanker, dit kan leiden tot het missen van patiënten met relevante geriatrische problemen.

Omdat niet alle ouderen met kanker een uitgebreid geriatrisch assessment hoeven te ondergaan, beveelt de ‘International Society of Geriatric Oncology’ (SIOG) een twee-staps-methode aan. Hierbij wordt eerst een kort screeningsinstrument gebruikt om potentiële kwetsbaarheid vast te stellen en krijgen alleen patiënten die potentieel kwetsbaar zijn een volledig geriatrisch assessment. De G8 is het meest bestudeerde screeningsinstrument en is de eerste keuze van de SIOG. In **Hoofdstuk 3** hebben we een systematische review uitgevoerd en al het beschikbare bewijs voor het gebruik van de G8 samengevat, waarbij we ons hebben gericht op zowel de vergelijking van de G8 met het geriatrisch assessment, als op de associatie met klinische uitkomsten (namelijk overleving, beloop

van de behandeling en patiëntgerichte uitkomstmaten). Onze resultaten laten zien dat de G8 niet alleen een nuttig instrument is om potentieel kwetsbare patiënten te identificeren die baat kunnen hebben bij een compleet geriatrisch assessment, maar ook dat een lage G8 score geassocieerd is met een slechtere overleving en aan de behandeling gerelateerde complicaties. Voor de overige klinische uitkomsten was te weinig bewijs om conclusies te kunnen trekken. Gezien de beperkte inhoud van de G8 is het echter onwaarschijnlijk dat deze een geriatrisch assessment kan vervangen, maar is de G8 nuttig als eerste stap gevolgd door een geriatrisch assessment voor potentieel kwetsbare patiënten.

Er zijn echter barrières om de G8 in de klinische praktijk te implementeren. De G8 is ontworpen voor afname door een hulpverlener. Een door de patiënt zelf ingevulde (patiënt-gerapporteerde) versie zou makkelijker en meer gebruikt kunnen worden. Daarom hebben we de overeenstemming tussen een door ons ontwikkelde patiënt-gerapporteerde versie van de G8 en de originele G8 beoordeeld in 161 oudere patiënten met en zonder kanker (**Hoofdstuk 4**). Hoewel de overeenstemming tussen de twee instrumenten slecht was voor geriatrische patiënten zonder kanker, was deze substantieel voor ouderen met kanker. Voor deze groep is de patiënt-gerapporteerde G8 daarom een alternatief voor de originele G8.

Ondanks het feit dat ouderen de meerderheid van alle patiënten met kanker vormen, is het bewijs voor de optimale oncologische behandeling van deze patiënten schaars. Vaak bevatten behandelrichtlijnen geen specifieke aanbevelingen voor deze groep. Daarnaast zijn de redenen waarom patiënten niet behandeld worden volgens de richtlijn momenteel onbekend, terwijl kennis over deze redenen het besluitvormingsproces kan beïnvloeden. In **Deel II** hebben we de huidige behandelkeuzes en uitkomsten onderzocht voor vrouwen met gynaecologische tumoren en voor de oudste ouderen met kanker (namelijk 80 jaar en ouder). Ook hebben wij gekeken naar redenen om af te wijken van de behandelrichtlijnen.

In **Hoofdstuk 5** hebben we een retrospectieve analyse verricht naar het besluitvormingsproces bij 128 vrouwen met eierstokkanker gediagnosticeerd in het Diaconessenhuis Utrecht. We vonden dat slechts 5% van de vrouwen van 75 jaar en ouder met vergevorderde eierstokkanker een behandeling volgens de richtlijn kregen voltooide, terwijl vrijwel de helft van de vrouwen jonger dan 75 jaar deze behandeling volbracht zonder aanpassingen. Verder kreeg 38% van de oudere vrouwen alleen ‘best supportive care’. Het aantal chemotherapie- en operatie-gerelateerde complicaties en onvoorziene ziekenhuisopnames was gelijk in beide groepen. Voor oudere vrouwen was de voorkeur van de patiënt een belangrijke reden om af te zien van de standaardbehandeling.

Om deze bevindingen op grotere schaal te bestuderen, hebben we een landelijke, populatie-gebaseerde analyse verricht naar behandelpatronen en redenen om af te zien van de richtlijn onder 4210 vrouwen met een vergevorderd stadium eierstokkanker (**Hoofdstuk 6**). Deze analyse was gestratificeerd op basis van leeftijd en bevatte tevens een groep vrouwen van 85 jaar en ouder. In deze studie worden onze bevinding uit het vorige hoofdstuk bevestigd, namelijk dat oudere vrouwen veel minder vaak volgens de richtlijn worden behandeld dan jongere vrouwen. We vonden ook dat 68% van de vrouwen van 85 jaar en ouder alleen 'best supportive care' kreeg, ten opzichte van 4% van de vrouwen onder de 65 jaar. Bij ouderen was de meest voorkomende reden om af te wijken van de richtlijn opnieuw de voorkeur van de patiënt, terwijl functionele status en uitbreidbaarheid van de ziekte de belangrijkste redenen waren voor jongeren.

In **Hoofdstuk 7** hebben we de tolerantie en haalbaarheid van chemotherapie voor de oudste ouderen onderzocht. Onze primaire uitkomst was of zij de chemotherapie voltooiden volgens plan. 'Volgens plan' werd gedefinieerd als een berekende relatieve dosisintensiteit van de chemotherapie van 85% of meer. Hiermee konden we de geplande dosisintensiteit vergelijken met de dosisintensiteit die de patiënt daadwerkelijk had gekregen. We hebben 104 patiënten geïncludeerd met een mediane leeftijd van 82 jaar (range 80 tot 94 jaar). Vrijwel de helft van de gestarte chemotherapieschema's werd niet voltooid volgens plan (48%), ondanks dat bijna tweederde van de chemotherapieschema's vóór start van de behandeling was aangepast (een primaire aanpassing). Daarnaast kwamen secundaire aanpassingen (een verdere aanpassing van de chemotherapie om die minder zwaar te maken) en ziekenhuisopnames vaak voor (respectievelijk 65% en 25%). Het percentage succesvol voltooide behandelingen werd niet beïnvloed door of de initiële behandeling bestond uit standaard, alternatieve of een niet op de richtlijn gebaseerde behandeling. Een alternatieve behandeling hield in dat de richtlijn alternatieve behandelopties voor oudere of niet fitte patiënten bevatte en dat deze werden gevolgd. Wij concludeerden dat het te bediscussiëren valt of chemotherapieschema's met secundaire aanpassingen bovenop primaire aanpassingen nog effectief zijn of achterwege gelaten moeten worden in geselecteerde oudere patiënten. Daarnaast is het de vraag of—omdat zoveel patiënten een primair aangepaste behandeling kregen maar desondanks de behandeling niet voltooiden volgens plan—behandeling met chemotherapie haalbaar is voor de oudste ouderen.

Gedurende de laatste decennia is er meer belangstelling gekomen voor patiëntgerapporteerde uitkomsten in studies onder ouderen met kanker. In **Deel III** van dit proefschrift hebben we gekeken naar het gebruik van gezondheidszorg gedurende de laatste drie maanden van het leven onder patiënten die behandeld werden met palliatieve chemotherapie. Daarnaast hebben we het gebruik van patiëntgerapporteerde uitkomsten



zoals gezondheidsgerelateerde kwaliteit van leven en functioneren geanalyseerd onder oudere vrouwen met baarmoeder- en eierstokkanker.

In **Hoofdstuk 8** hebben we een retrospectieve analyse verricht naar potentiële factoren die kunnen duiden op een slechte kwaliteit van zorg in de laatste levensfase van patiënten die palliatieve chemotherapie kregen. Voorbeelden van slechte kwaliteit van zorg in de laatste levensfase zijn het starten of continueren van chemotherapie in de allerlaatste periode van het leven, chemotherapie-gerelateerde spoedeisende hulp bezoeken en ziekenhuis- of intensive care opnames. De helft van de 604 patiënten kreeg chemotherapie in de laatste drie maanden van het leven. De cijfers voor gezondheidszorgconsumptie en sterfte in het ziekenhuis in de laatste drie maanden van het leven waren hoog voor alle patiënten. Maar dit gold vooral voor patiënten die palliatieve chemotherapie kregen in de laatste drie maanden van hun leven. Deze resultaten onderstrepen het belang van vroege integratie van palliatieve zorg.

Een andere belangrijke uitkomst voor patiënten met kanker is de kwaliteit van leven na een oncologische behandeling. De diagnose kanker en de uitgebreide behandeling tasten de gezondheidsgerelateerde kwaliteit van leven van vrouwen met eierstokkanker ernstig aan. Lange-termijn data over deze uitkomst ontbreken echter, met name voor ouderen. Daarom hebben wij dit onderwerp bestudeerd onder 191 vrouwen met eierstokkanker gemiddeld zes jaar na de diagnose. Hiervoor hebben we de gezondheidsgerelateerde kwaliteit van leven van overlevenden na eierstokkanker van 70 jaar en ouder vergeleken met die van zowel een op leeftijd gematchte normatieve populatie (zonder eierstokkanker) als met die van overlevenden jonger dan 70 jaar (**Hoofdstuk 9**). Daarnaast hebben we gekeken of het effect van chemotherapie op kwaliteit van leven tussen oudere en jongere overlevenden verschillend is. We vonden dat oudere overlevenden een slechtere gezondheidsgerelateerde kwaliteit van leven en meer symptomen rapporteerden dan zowel de leeftijdsgematchte normatieve populatie zonder eierstokkanker en dan de jongere overlevenden. In vergelijking met de normatieve populatie, scoorden oudere overlevenden slechter op globale gezondheid en op alle functioneringsschalen behalve emotioneel functioneren. In vergelijking met jongere overlevenden, beoordeelden oudere overlevenden fysiek en rol functioneren slechter en rapporteerden zij slechtere scores voor globale gezondheid. Onze resultaten suggereren ook dat leeftijd een modererende factor is wat betreft het effect van chemotherapie op gezondheidsgerelateerde kwaliteit van leven. In tegenstelling tot wat we verwachtten ervoeren oudere overlevenden die chemotherapie hadden gehad beter fysiek functioneren en minder pijn en slapeloosheid en vonden wij het tegenovergestelde voor jongere overlevenden. Dit resultaat kan beïnvloed zijn door het optreden van selectiebias of door het feit dat ouderen mogelijk minder zware chemotherapieschema's hebben gehad. We concludeerden dat, in vergelijking met een op leeftijd gematchte normatieve populatie, oudere overlevenden

van eierstokkanker slechtere gezondheidsgerelateerde kwaliteit van leven rapporteren dan jongere overlevenden. Daarnaast kwamen langdurige gebreken in functioneren en kanker-gerelateerde symptomen vaak voor met name bij oudere overlevenden van eierstokkanker. Deze vrouwen zouden informatie moeten ontvangen over mogelijke gezondheids-gerelateerde uitkomsten om hun verwachtingen te sturen.

Resultaten van longitudinale analyses kunnen helpen ons begrip te vergroten over het beloop van kwaliteit van leven gedurende en na een oncologische behandeling. Deze resultaten zijn ook belangrijk om het gezamenlijke besluitvormingsproces te verbeteren. Daarom hebben wij, in **Hoofdstuk 10**, gezondheidsgerelateerde kwaliteit van leven longitudinaal geanalyseerd op vier tijdstippen (variërend van na de initiële behandeling tot na 24 maanden follow-up). In dit onderzoek onder 215 vrouwen met baarmoederkanker onderzochten wij of leeftijd of comorbiditeit sterker geassocieerd is met veranderingen in gezondheidsgerelateerde kwaliteit van leven over de tijd. Daarnaast hebben we deze uitkomsten vergeleken met die van een naar leeftijd en geslacht gematchte normatieve populatie zonder baarmoederkanker. We vonden dat, onafhankelijk van leeftijd, comorbiditeit significant geassocieerd was met slechtere scores voor alle functioneringsuitkomsten. Patiënten met meerdere comorbiditeiten rapporteerden verslechtering van fysiek en rol functioneren na 12 maanden. In vergelijking met de normatieve populatie rapporteerden patiënten initieel betere scores voor fysiek en rol functioneren, maar na 24 maanden waren deze verschillen niet langer statistisch significant of klinisch relevant. Er zijn twee mogelijke verklaringen voor deze laatste bevinding: allereerst is het mogelijk dat patiënten een grotere achteruitgang in fysiek en rol functioneren ervoeren dan de normatieve populatie. Ten tweede kan het zijn dat de patiëntuitkomsten passen bij een 'response shift' na de initiële behandeling, waarbij de scores vervolgens afnemen tot waardes vergelijkbaar met die van de normatieve populatie na 24 maanden. Onze resultaten benadrukken het belang van het meewegen van cumulatieve comorbiditeit en niet alleen de chronologische leeftijd van de patiënt bij het bespreken van mogelijke uitkomsten van gezondheidsgerelateerde kwaliteit van leven.

In **Hoofdstuk 11** worden de resultaten van dit proefschrift bediscussieerd en in een breder perspectief geplaatst. Ook bespreken we implicaties voor de klinische praktijk en voor toekomstig onderzoek.

Samenvattend blijkt uit de studies in dit proefschrift dat veel oudere patiënten met kanker niet volgens de huidige richtlijnen worden behandeld en dat zij de ingezette behandeling vaak ook niet volgens plan voltooien. De G8 kan helpen om potentieel kwetsbare patiënten met een mogelijk risico op een slechtere overleving en beloop van de behandeling te identificeren. Omdat veel oudere patiënten met kanker alleen 'best

supportive care' krijgen, is vroegtijdige integratie van palliatieve zorg erg belangrijk. Oudere patiënten en patiënten met meerdere comorbiditeiten hebben een hoger risico op slecht ervaren gezondheidsgerelateerde kwaliteit van leven. Onze resultaten geven de complexiteit omtrent de besluitvorming voor ouderen met kanker weer en onderstrepen het belang van gezamenlijke besluitvorming en een geïndividualiseerde behandeling voor deze populatie.



# APPENDICES

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List of publications

Acknowledgements in Dutch – Dankwoord

Curriculum Vitae

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## List of publications

Clinical judgment versus geriatric assessment for frailty in older patients with cancer.  
**van Walree IC**, Scheepers ERM, van den Bos F, van Huis-Tanja LH, Emmelot-Vonk MH, Hamaker ME.

J Geriatr Oncol 2020. Jun 21:S1879-4068(19)31670-4.

doi: 10.1016/j.jgo.2020.05.011 (epub ahead of print)

Reasons for guideline non-adherence in older and younger women with advanced stage ovarian cancer.

**van Walree IC**, Bretveld R, van Huis-Tanja LH, Louwers JA, Emmelot-Vonk MH, Hamaker ME.

Gynecol Oncol. 2020 Mar 11. pii: S0090-8258(20)30221-3.

doi: 10.1016/j.ygyno.2020.03.005 (epub ahead of print)

Do age and comorbidity impair recovery during two years after treatment for endometrial cancer? **van Walree IC**, Hamaker ME, de Rooij BH, Boll D, van Huis-Tanja LH, Emmelot-Vonk MH, Ezendam NPM.

J Geriatr Oncol 2020. Mar 10 pii: S1879-4068(19)30480-1.

doi: 10.1016/j.jgo.2020.02.012 (epub ahead of print)

Cytokines and chemokines are detectable in swivel-derived exhaled breath condensate (SEBC): a pilot study in mechanically ventilated patients.

van der Zee P, **van Walree IC**, Fijen JW, van Houte AJ, van Velzen-Blad H, Rijkers G, Gommers D, Endeman H.

Dis Markers. 2020; jan 11;2020:2696317

Development of a self-reported version of the G8 screening tool.

**van Walree IC**, Vondeling AM, Vink GR, van Huis-Tanja LH, Emmelot-Vonk MH, Bellera C, Soubeyran P, Hamaker ME.

J Geriatr Oncol. 2019;10(6):926-30

A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer.

**van Walree IC**, Scheepers E, van Huis-Tanja LH, Emmelot-Vonk MH, Bellera C, Soubeyran P, Hamaker ME.

J Geriatr Oncol. 2019;10(6):847-58

Chemotherapy in the oldest old: Choices and outcomes.



**van Walree IC**, van Breukelen ELG, Thielen N, van Rens MTM, van Huis-Tanja LH, Hamaker ME.

Eur J Cancer Care. 2019;28(4):e13049

Older ovarian cancer survivors report lower long-term health-related quality of life than younger survivors: a study from the population-based profiles registry.

**van Walree IC**, Hamaker ME, van de Poll-Franse LV, Vos MC, Boll D, van Huis-Tanja LH, Ezendam NPM.

Gynecol Oncol. 2019;153(2):391-398

Treatment decision-making in elderly women with ovarian cancer: an age-based comparison.

**van Walree IC**, van Soolingen NJ, Hamaker ME, Smorenburg CH, Louwers JA, van Huis-Tanja LH.

Int J Gynecol Cancer. 2019;29:158-165

Chemotherapy and healthcare utilization near the end of life in patients with cancer. Schulkes KJG,

**van Walree IC**, van Elden LJR, van den Bos F, van Huis-Tanja LH, Ten Bokkel Huinink D, Hamaker ME.

Eur J Cancer Care 2018;27(2):e12796

Late-onset inflammatory bowel disease in the very elderly.

**van Walree IC**, van Tuyl SA, Hamaker ME.

Neth J Med. 2015;73(1):4-9

Alterations in exhaled breath metabolite-mixtures in two rat models of lipopolysaccharide-induced lung injury.

Bos LD, **van Walree IC**, Kolk AH, Janssen HG, Sterk PJ, Schultz MJ.

J Appl Physiol. 2013;115(10):1487-95

Pattern of cytokines and chemokines in exhaled breath condensate is related to the characteristics of mechanical ventilation.

**van Walree IC**, van Houte A, van Velzen-Blad H, Rijkers G, Endeman H.

Crit Care. 2011;15(suppl 1):144

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## Curriculum Vitae

Inez van Walree was born in Utrecht, the Netherlands, on February 29<sup>th</sup> 1988 and is thus a leap-year baby. When she was ten years old, she moved to Breda. After graduating from the Gymnasium Breda in 2006, she moved to Utrecht again and started as a medical student at the Utrecht University. During her medical training she performed research on acute respiratory distress syndrome at the Intensive Care Unit (ICU) of the Diaconessenhuis Utrecht and afterwards on the ICU of the Academic Medical Center Amsterdam. During her study she made several long journeys and did, among others, an internship in obstetrics-gynecology in Surinam. She completed her medical training in 2014 and started as a junior doctor internal medicine at the Diaconessenhuis Utrecht with the idea to become an oncologist. Accidentally, she came into contact with geriatric medicine as she was placed at the geriatric department in Zeist. During this period, she published her first article together with Marije Hamaker on inflammatory bowel disease in older patients. She liked geriatric medicine so much that she decided to start as a junior doctor at the geriatric department of the Jeroen Bosch Hospital at 's-Hertogenbosch. After half a year, she became a resident in geriatric medicine (AIOS). During her two years of internal medicine at the Meander medical center Amersfoort, she remained interested in oncology. Therefore, she contacted Marije Hamaker again. One thing led to another and a new research project was born. In July 2017, she started with her PhD at the Department of Internal Medicine and Geriatric Medicine at the Diaconessenhuis Utrecht under supervision of Dr. Marije Hamaker, Dr. Lieke van Huis-Tanja and Prof. dr. Mariëtte Emmelot-Vonk. In January 2020, she resumed her residency in geriatric medicine at the Jeroen Bosch Hospital. She lives with her partner Michiel and their three children, Pip, Siem and Loek.







*"We cannot direct the winds,  
but we can adjust the sails"*