Frailty and quality of life in older adults with cancer

Ellen R.M. Scheepers

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CHAPTER 1

Introduction and outline of thesis

INTRODUCTION

Ageing and cancer

Over the past century, the age structure of the worldwide population has changed. Particular in high income countries, the fertility rate has decreased and the life expectancy has increased.[1] Thanks to medical advances, global health is improving and many diseases have become chronic. As a result, the proportion of older people increased and people die at an older age.[1] Due to this double ageing process, the number of people older than 80 years worldwide is expected to triple from 143 million in 2019 up to 426 million in 2050.[2] In the Netherlands, a similar pattern is observed: compared to 2020, two to three times as many people aged 80 years or older are expected in 2050 (Figure 1).[3]

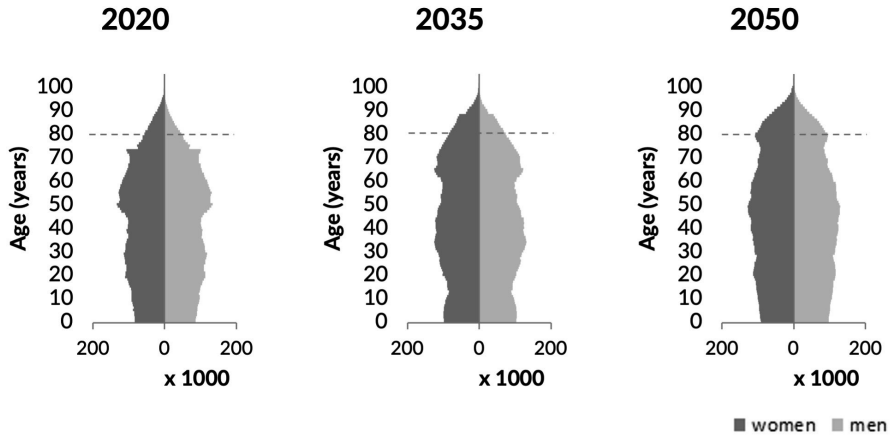

Figure 1. Age structure of the Dutch population in 2020,2035 and 2050.[3]

As a result of these demographic changes, the prevalence of diseases which already predominantly affect older patients will increase. Cancer has the second largest disease burden in the world after cardiovascular diseases and predominantly affects older individuals.[4] In the Netherlands, one third of all patients with cancer is aged 75 years and older and 40% is aged between 60 and 75 years at diagnosis.[5] Due to the expected demographic changes, these proportions are expected to rise during the upcoming decades.[6]

Treatment decisions in older patients with cancer

In older patients with cancer, the treatment decision-making process can be challenging. First of all, as ageing is a unique process, older patients form a highly heterogeneous population. In addition to genetic predisposition, life style factors, intercurrent and chronic diseases will affect the physical and psychological reserves during a life time. Moreover, large differences are observed in functional status as well as social support system. Consequently, life expectancy will vary from person to person. The median life expectancy of an 80 year old man for example is 8 years, but the lowest 25th percentile lives only 5 years, whereas the top 25th percentile can still live for 12 years (Figure 2).[7] Due to this variation in health

status, the benefit and harms of cancer treatment can differ. Patients with comorbidity or less physical or psychological reserve are at increased risk of adverse health outcomes after cancer treatment, such as functional dependence and loss of quality of life.[8,9]

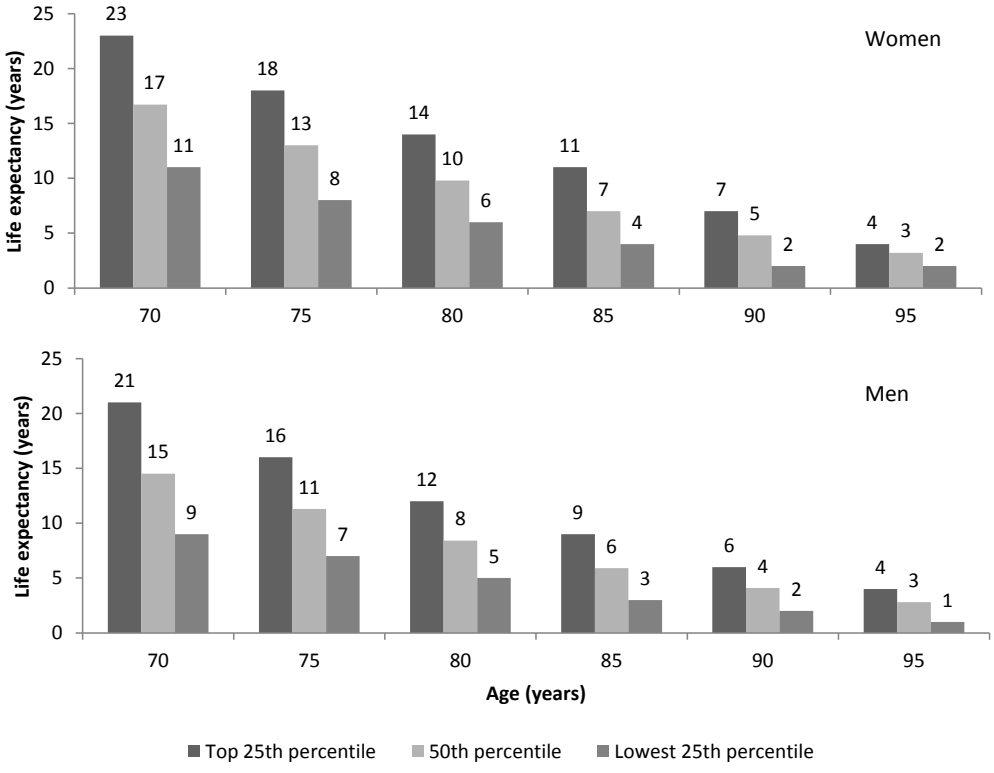

Figure 2. Upper, middle, and lower quartiles of life expectancy for women and men at selected ages. Adapted data from the Life Tables of the United States 2017. [7,10]

Another complicating factor in the treatment decision-making process is the fact that older patients with cancer and especially those with comorbidities are frequently excluded from clinical trials.[11,12] Hence, evidence regarding efficacy and safety of cancer treatment for younger or fit patients may not be applicable to older patients. Consequently, treatment guidelines cannot provide recommendations to this older population and optimal treatment for these patients has not fully been elucidated. In addition, treatment goals of older patients may differ from younger patients with cancer. Older patients are less willing to accept toxicity for additional survival benefit,[13] particularly when oncological treatment could potentially have a negative impact on functioning or quality of life.[14,15] Therefore, it can be challenging to tailor cancer care in older patients. 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

The assessment of a patient's ability to tolerate the available treatment options may help in tailoring cancer care and is often assessed by the level of frailty. Over the years, several definitions of frailty have been formulated.[16] In general, frailty is a consequence of the ageing process and is characterized by a decline in functioning across multiple domains (physical, psychological, social) accompanied by an increased vulnerability to stressors. It exists alongside age, comorbidity or disease characteristics and it is a dynamic state which needs a multidimensional approach and might have various implications in different scenarios.[17] Various methods are developed to assess the level of frailty.[18] In daily practice, treatment decisions are frequently made based on clinical judgment whereas a comprehensive geriatric assessment is considered as the 'golden standard' to assess the level of frailty. This systematic assessment tries to determine patient's health status focussing on somatic, psychological, functional and social domains. However, performing a comprehensive geriatric assessment in all older patients with cancer seems not always feasible and necessary before cancer treatment decision making. Therefore, frailty screening tools are developed. One of the frailty screening tools frequently used in oncology is the Geriatric8 (G8). This frailty screening tool may be used to identify those patients in need of a comprehensive geriatric assessment. Evidence concerning the diagnostic and predictive value of these methods is limited, especially regarding the accuracy of clinical judgment.

Patient related outcomes

In addition to information concerning efficacy and safety of cancer treatment, particularly older patients prefer counselling regarding the impact of cancer treatment on patient related outcomes. Patient related outcomes cover a range of health outcomes such as symptoms, functional limitations, quality of life and patient satisfaction.[19] The need for gathering knowledge concerning the impact of cancer treatment on patient related outcomes is also emphasized by multiple international organisations.[20–22] However, data regarding patient related outcomes in geriatric oncology is still limited.

AIMS AND OUTLINE OF THE THESIS

Although the knowledge in geriatric oncology increases, many questions regarding the treatment decision-making process for older patients with cancer remain to be answered in order to improve tailored made cancer care. This thesis will try to provide answers to some of these questions.

This thesis comprises two parts. **Part I** focuses on various methods for frailty assessment, while **Part II** evaluates treatment patterns and patient related outcomes in older patients with cancer.

Part I consists of four chapters: in **Chapter 2** the relevance of performing a geriatric assessment in older patients with a haematological malignancy is systematically reviewed.

The accuracy of clinical judgment to identify frailty compared to the G8 frailty screening tool and geriatric assessment is prospectively evaluated in **Chapter 3**. The use of the G8 frailty screening tool including its value to identify frailty and predict clinical outcomes such as survival, course of treatment and patient related outcomes is reviewed in **Chapter 4**. In **Chapter 5**, the association between the G8 frailty screening tool and treatment choices in older patients with primary localized breast cancer is assessed.

In **part II**, we focus on current cancer treatment choices for older cancer patients and study patient related outcomes. **Chapter 6** describes treatment patterns and reasons for non-guideline adherence in patients with colorectal cancer. **Chapter 7** analyses the study objectives of clinical trials and whether the inclusion of patient related outcomes has changed over the years. The impact of surgery and adjuvant chemotherapy on quality of life in patients with colon cancer is assessed in **Chapter 8** and **Chapter 9**. **Chapter 8** focuses on changes in quality of life at group-level versus individual-level whereas **Chapter 9** addresses the resilience of quality of life in these patients with colon cancer. In **Chapter 10**, we study the predictors of perceived social support in patients with gynaecological cancer.

The final part of this thesis consists of a general discussion (**Chapter 11**) interpreting our findings, discussing their potential implications for clinical practice and addressing future perspectives.

REFERENCES

1. Ritchie H, Roser M. Our World in Data, Age structure [Internet]. [cited 2020 Apr 28]. Available from: https://ourworldindata.org/age-structure
2. United Nations. Global issues, Ageing [Internet]. [cited 2021 Apr 28]. Available from: https://www.un.org/en/global-issues/ageing
3. Centraal bureau statistiek [Internet]. [cited 2020 Aug 15]. Available from: https://opendata.cbs.nl/#/CBS/nl/
4. Roser M, Ritchie H. Our world in data - Burden of disease [Internet]. [cited 2021 Oct 13]. Available from: https://ourworldindata.org/burden-of-disease
5. Integraal Kankercentrum Nederland (IKNL). Aantal nieuwe kankerpatiënten in 2020 gedaald door coronacrisis, eerste daling in dertig jaar [Internet]. [cited 2021 Apr 28]. Available from: https://iknl.nl/persberichten/aantal-nieuwe-kankerpatienten-in-2020-gedaald-door
6. Pilleron S, Soto-Perez-de-Celis E, Vignat J, Ferlay J, Soerjomataram I, Bray F, et al. Estimated global cancer incidence in the oldest adults in 2018 and projections to 2050. Int J Cancer. 2021;148(3):601–8.
7. Walter LC, Schonberg MA. Screening mammography in older women: A review. JAMA - J Am Med Assoc. 2014;311(13):1336–47.
8. Galvin A, Helmer C, Coureau G, Amadeo B, Rainfray M, Soubeyran P, et al. Determinants of functional decline in older adults experiencing cancer (the INCAPAC study). J Geriatr Oncol. 2019;10(6):913–20.
9. Kent EE, Ambs A, Mitchell SA, Clauser SB, Smith AW, Hays RD. Health-related quality of life in older adult survivors of selected cancers: Data from the SEER-MHOS linkage. Cancer. 2015;121(5):758–65.
10. National Center for Health Statistics. Life tables from the United States [Internet]. 2017 [cited 2021 Jun 10]. Available from: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/NVSR/68_07/
11. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: Known problem, little progress. J Clin Oncol. 2012;30(17):2036–8.
12. 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.
13. Hurria A, Mohile SG, Dale W. Research Priorities in Geriatric Oncology: Addressing the Needs of an Aging Population. JNCCN J Natl Compr Cancer Netw. 2012;10(2):286–8.
14. Pallis AG, Ring A, Fortpied C, Penninckx B, van Nes MC, Wedding U, et al. Eortc workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. Ann Oncol. 2011;22(8):1922–6.
15. Van Leeuwen KM, Van Loon MS, Van Nes FA, Bosmans JE, De Veti HCW, Ket JCF, et al. What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):1–39.
16. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. Nurs Outlook. 2010;58(2):76–86.
17. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365–75.
18. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, 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):241–25.
19. McKenna SP. Measuring patient-reported outcomes: Moving beyond misplaced common sense to hard science. BMC Med. 2011;9(86).
20. Calvert M, Brundage M, Jacobsen PB, Schünemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: Implications for clinical trials and practice. Health Qual Life Outcomes. 2013;11:184.
21. OECD. Recommendations to OECD ministers of health from the high level reflection group on the future of health statistics [Internet]. 2017. Available from: https://www.oecd.org/els/health-systems/Recommendations-from-high-level-reflection-group-on-the-future-of-health-statistics.pdf
22. IHCOM. International Consortium for Health Outcomes Measurement [Internet]. [cited 2020 Nov 25]. Available from: https://www.ichom.org/

PART I

FRAILTY IN OLDER PATIENTS WITH CANCER

CHAPTER
2

Geriatric assessment in older patients with a haematological malignancy: a systematic review

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ABSTRACT

Background

The aim of this systematic review is to give an update of all currently available evidence of the relevance of a geriatric assessment in treatment of older patients with haematological malignancies.

Methods

A systematic search in MEDLINE and EMBASE was performed to find studies in which a geriatric assessment was used to detect impaired geriatric domains or to address the association between geriatric assessment and survival or clinical outcome measures.

Results

The literature search included 4629 reports, of which 54 publications from 44 studies were included. 73% of the studies were published in the last five years. Median age of patients was 73 (range 58-86) and 71% had a good WHO performance status. The median prevalence of geriatric impairments varies between 17% to 68%, even in patients with a good WHO performance status. Polypharmacy, nutritional status and instrumental activities of daily living were most frequently impaired. Whereas several geriatric impairments and frailty (based on a frailty screening tool or summarised geriatric assessment score) were predictive for a shorter overall survival, WHO performance status lost its predictive value in most studies. The association between geriatric impairments with treatment-related toxicity varies, with a trend towards a higher risk for (non-)haematological toxicity in frail patients. During follow up, frailty seems to be associated with treatment non-completion, especially when patients are malnourished. Patients with a good physical capacity had a shorter hospital stay and reduced hospitalization rate.

Conclusion

Geriatric assessment, even in patients with a good performance status, can detect impaired geriatric domains and these impairments may be predictive for mortality. Moreover, geriatric impairments suggest a higher risk of treatment-related toxicity, treatment non-completion and using health care services. Before starting treatment in older patients with haematological malignancies a geriatric assessment should be considered.

INTRODUCTION

Due to increasing life expectancy and ageing of the population, there is a growing number of older patients with cancer, including patients with a haematological malignancy. Worldwide, haematological malignancies account for approximately 9% of all cancers and are the fourth most frequently diagnosed cancer.[1] Today, 60% of these patients are older than 65 years and this proportion will increase in the future.[2,3]

Over the last decades, treatment options for haematological malignancies have been in progress. For example, the initial treatment of patients with multiple myeloma changed from cytotoxic chemotherapeutics to better-tolerated agents such as immuno-modulatory drugs or monoclonal antibodies.[4] Moreover, the proportion of older patients with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) undergoing haematopoietic stem cell transplantation (HCT) has risen, partly due to expansion of age limits.[5,6]

However, it can be difficult to deliver optimal cancer treatment tailored to individual needs of an older patient, particularly as older patients are frequently excluded from clinical trials.[7] Older patients represent a heterogeneous population due to large differences in comorbidity, functional capacity and psychological and physical reserves. As a result, the benefit of treatment can differ and patients with comorbidity or geriatric impairments are particularly at risk of adverse health outcomes. Choosing the optimal treatment for these patients is a challenge.

Therefore, it is recommended to assess the level of frailty of older patients.[8] Frailty is a biological syndrome which can exist alongside age, comorbidity or disease characteristics. Over the years, numerous definitions of frailty were formulated and still, there is no consensus on this definition.[9] Generally, there are two commonly used approaches to define frailty. The first defines frailty based on phenotypic criteria including reduced grip strength, walking speed, physical capacity, level of energy and weight loss. Patients are considered frail if three or more criteria are present.[10] The second approach proposes a frailty index which is an accumulation of patient's deficits. These deficits consists of physical or cognitive symptoms, functional impairments, abnormal laboratory values and comorbidities.[11,12] In daily practice, frailty is a dynamic state which needs a multidimensional approach and might have various implications in different scenarios.

An appropriate method to assess the level of frailty of older patients is a geriatric assessment.[8,13] This consists of a systematic assessment of an older patient's health status focussing on somatic, psychological, functional and social domains. To detect geriatric impairments in these domains, different tools can be used.[14] Moreover, frailty screening tools were developed in order to identify older patients who require a full geriatric assessment.[15] Nowadays, some form of geriatric assessment is increasingly incorporated in haemato-oncologic care to customize haemato-oncologic treatment.[16]

In 2014, we published a systematic review on the value of performing a geriatric assessment in older patients with a haematological malignancy, demonstrating that a geriatric assessment can detect multiple health issues and has predictive value for clinical outcome in older patients with a haematological malignancy.[17] However, evidence was limited, especially regarding clinical outcomes such as treatment-related toxicity, treatment completion or physical functioning after treatment. Since then, many new studies have been published on this subject. Therefore, the aim of this present systematic review is to give an update of all currently available data on the association between geriatric impairments and haematological cancer related outcomes.

METHODS

Search strategy and article selection

Our aim was to identify studies concerning patients with a haematological malignancy in which a geriatric assessment was used to detect geriatric impairments or which address the association between baseline geriatric assessment and outcome.

Geriatric assessment was defined as an assessment composed of at least two of the following domains: cognitive function, mood, nutritional status, activities of daily living (ADL), instrumental activities of daily living (IADL), polypharmacy (using five or more drugs), objectively measured physical capacity (for instance, gait speed, hand grip strength or balance tests), social support and frailty (assessed with a frailty screening tool or by summarising the geriatric assessment). As prior medical history/comorbidity and performance status are a routine part of the haematological work-up, these were not counted as domains of the geriatric assessment for this particular systematic review. For outcomes, the following items were defined: prevalence of geriatric impairments, change in oncologic treatment plan, toxicity of chemotherapy, health care utilisation, physical functioning after treatment, quality of life after treatment and mortality.

The following search was performed on March 4th 2019 and updated on January 20th 2020, in both MEDLINE and EMBASE:

((("Hematologic Neoplasms"[Mesh] OR "Leukemia"[Mesh] OR "Lymphoma"[Mesh] OR "Multiple Myeloma"[Mesh] OR "Myelodysplastic Syndromes"[Mesh] OR leukemia[tiab] OR leukaemia[tiab] OR lymphoma*[tiab] OR hodgkin*[tiab] OR non-hodgkin*[tiab] OR (multiple myeloma[tiab]) OR myelodysplas*[tiab] OR (haematolog* AND malignan*[tiab]) OR (hematolog* AND malignan*[tiab]) OR (myeloid[tiab] OR lymphoid[tiab] AND neoplas*[tiab]) OR myeloproliferative[tiab] OR (plasma cell neoplas*[tiab]) OR plasma cell dyscrasia*[tiab] OR (myeloid[tiab] AND sarcoma*[tiab]) OR waldenstrom[tiab] OR myelofibrosis[tiab] OR mastocystosis[tiab] OR (polycyth* AND vera[tiab]) OR (essential AND thrombocyt*[tiab])))) AND (("frailty"[All Fields] OR "Geriatric Assessment"[Mesh] OR frail*[tiab] OR vulnerabl*[tiab] OR geriatricassessment*[tiab] OR geriatric*[tiab])).

No age or language limitations were applied. All search results until 2013 were reviewed previously by Hamaker et al [17]. Therefore, we limited our search to studies published after January 1st 2013. The titles and abstracts of all studies retrieved by the search were assessed by one reviewer (ES) to determine which warranted further examination. All potentially relevant articles were subsequently screened as full text. We excluded studies that did not focus exclusively on haematological malignancies. Finally, references of included studies were cross-referenced to retrieve any additional relevant citations. Eligible studies from all searches (2013, 2019, 2020) were subsequently combined to form the final study selection.

Data extraction

For each eligible study, data regarding study design and results were independently extracted by two authors (ES and AV). Extracted items included the type of study, study population (number of patients, median age, malignancy subtype, stage, treatment) and the content of geriatric assessment. Only validated tools from the geriatric assessment were included. If multiple tools were used to assess one geriatric domain, the result of the most commonly used tool was noted. We registered the prevalence of geriatric impairments, and the reported results on the association between the geriatric assessment and outcome measures. If necessary, study authors were contacted to obtain additional data.

Quality assessment

The methodological quality of each of the studies was assessed independently by two reviewers (ES and AV), using the Newcastle-Ottowa scale adapted to this subject (Appendix 1a and 1b).[18] As our main focus was on older patients with haematological malignancies, we classified studies with a me(di)an age less than 68 years old, or more than one third of the patients younger than 65 years old, as not being fully representative of our target population. Disagreements among the reviewers were discussed during a consensus meeting and in case of persisting disagreement, the assistance of a third reviewer (MH) was enlisted.

Data synthesis and analysis

Due to the heterogeneity in patient populations and study designs with a wide variety in content of geriatric assessments, a meta-analysis was not considered feasible. Therefore, we summarised the study results to describe our main outcomes of interest.

RESULTS

Study characteristics

The literature search yielded 4629 citations (832 from MEDLINE and 3797 from EMBASE), of which 403 were duplicates and 4184 were excluded for other reasons (Appendix 1c). This resulted in 42 eligible publications from 34 studies. Cross-referencing yielded four additional publications. Eight publications from the 2014 review by Hamaker et al.[17] were also eligible. Thus, we ultimately included 54 publications from 44 studies in this review. [19-72]

The characteristics of these 44 studies are summarised in Table 1. 73% were published in the last five years. Median sample size of the studies was 100 (range 25-869), and the me(di)an age of included patients ranged from 58 to 86 years. Eight studies focused on acute myeloid leukaemia and/or myelodysplastic syndromes[19–25,27], two on chronic lymphocytic leukaemia (CLL),[28,29], thirteen on lymphoma,[30–42] seven on multiple myeloma,[42–48] and fifteen studies included various haematological malignancies.[49–63]

The median number of domains addressed in the geriatric assessment was four (range 2-9). These included activities of daily living (ADL) in 30 studies (68%), instrumental ADL (IADL) in 37 (84%), cognition in 29 (66%), mood in 24 (55%) and objectively measure physical capacity in 20 studies (46%). Less commonly assessed were nutritional status (11 studies;25%), social support (8 studies; 18%), polypharmacy (13 studies; 30%) and frailty (8 studies assessed with a frailty screening tool and 17 studies by summarising geriatric assessment; 21% and 39% respectively).

The prevalence of geriatric impairments was assessed in all studies (100%). The association between geriatric impairments and mortality was addressed 33 studies (75%), treatment-related toxicity in ten studies (23%), treatment completion in five (11%) and health care utilisation in seven studies (16%). No studies assessed the association of geriatric impairments on physical functioning or quality of life after treatment.

Quality assessment

The results of the quality assessment can be found in Figure 1. Detailed results per study are listed in Appendix 1b. The overall quality of the studies was good. Nine studies included a significant proportion of younger patients (i.e. median age less than 68 years old, or more than one third of the patients younger than 65 years old);[22,27,41,43,46,48,50,58,59] these studies were assessed as not being fully representative of the target cohort of the average older patients with a haematological malignancy. Similarly, eight studies focused on a very specific treatment[20,23,24,31,51,55,56,60] which we considered as not fully representative of our target population. Overall, the duration of follow up was sufficient but in nine studies the follow up rate was less than 90%[24,30,46] or the adequacy of follow up was not reported.[27,32,33,56,57,62] There were no other quality concerns.

Prevalence of geriatric impairments

The prevalence of geriatric impairments is shown in Table 2. The most commonly reported issues were polypharmacy (in a median of 51% of patients; range 17-80%), risk of malnutrition (median 44%; range 27-82%) and IADL impairments (median 37%; range 3-85%). Less common were impaired physical capacity (median 27%; range 3-80%), ADL impairments (median 18%; range 4-67%), symptoms of depression (median 25%; range 10-94%), and cognitive impairment (median 17%; range 0-44%). Four studies that addressed social support showed impairment in a median of 20% (range 7-54%). The median proportion of patients seen as frail based on a frailty screening tool was 68% (range 25-76%). The median proportion of patients screened as frail based on summarised geriatric assessment score was

45% (range 10-88%).

Overall, the median proportion of patients with at least one geriatric impairment was 51% (range 9-82%). By comparison, the median proportion of patients with a WHO performance status of 2 or higher was only 29% (range 1-91%). Even in studies in which the median age of patients was ≤65 years old, or a small proportion of patients had a poor WHO performance status, geriatric impairments were quite common. For example, in one study, 93% of included patients had a WHO performance status of 0-1; nonetheless, 45% of patients had impairments in IADL, 39% in physical capacity and 25% were frail based on a frailty screening tool (Table 2).[49]

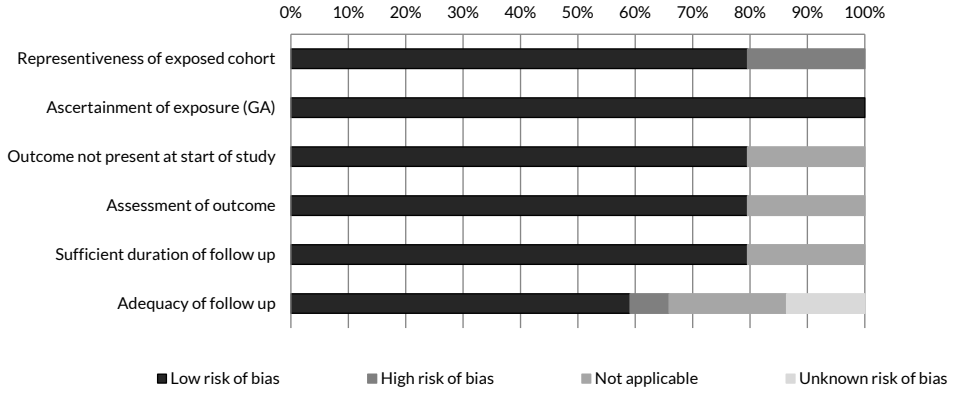


Figure 1. Outcome of the quality assessment.
Details are reported in Appendix 1a (quality assessment questionnaire) and Appendix 1b (assessment per study).

Association between geriatric impairments and mortality

The association of geriatric impairments with mortality was addressed in 33 studies (Table 3). In univariate analysis, 27 out of 29 studies (93%) showed a significant association between at least one geriatric impairment and mortality. The association between a specific geriatric domain and mortality varied between 0-74%. Polypharmacy was assessed in only two studies and showed no association. For all other geriatric domains except mood, nutritional status and social support, at least 50% of the studies reported a univariate association between impairment and mortality. IADL, ADL, impaired physical capacity and cognition were most frequently associated with mortality (in 74%, 67%, 63% and 55% of the studies, respectively). In multivariable analyses, ADL, IADL, impaired physical capacity and cognition remained associated with mortality (in 40%, 62%, 50% and 50% of the studies, respectively). Moreover, at least 75% of all studies which assessed frailty (assessed with a frailty screening tool or by summarising the geriatric assessment), demonstrated this to be associated with mortality in multivariable analyses.

Risk factors for mortality commonly used in haemato-oncology such as age, WHO performance status and comorbidity were also associated with mortality in univariate analysis (respectively in 79%, 63% and 64% of the studies). However, in multivariable analyses, this association was no longer present for WHO performance status; age and comorbidity retained its association with mortality in 43% and 47% of the studies, respectively.

Association of geriatric impairments with treatment-related toxicity

Ten studies assessed geriatric impairments in relation to treatment-related toxicity.[28,29,32–34,37,45,48,55,59] Four out of six studies in which frailty (based on a summarised geriatric assessment score) was assessed, reported an association between frailty and treatment-related toxicity.[33,34,45,48] This included haematological toxicity in one study,[33] non-haematological toxicity in two studies[45,48] and overall toxicity in one study.[34] One study showed an association specifically between impaired IADL and treatment-related infections in CLL patients.[28] In studies in which patients with various haematological malignancies were included, associations between physical capacity[55] or cognition[59] and treatment-related toxicity were demonstrated. No other associations between frailty (based on a summarised geriatric assessment score) or individual geriatric domains and treatment-related toxicity were found in these ten studies.

Association of geriatric impairments with treatment completion

The association of geriatric impairments on the ability to complete the proposed treatment was studied in five studies.[25,32,36,38,45] Four out of five studies found an association between geriatric impairments and treatment completion. In comparison to fit patients, the risk of treatment non-completion was significantly higher in frail patients (based on summarised geriatric assessment score or frailty screeningtool).[25,36,38,45] Three studies showed a significant association between a specifically geriatric domain and treatment non-completion: in two studies which included patients with non-hodgkin lymphoma, malnutrition was associated with treatment non-completion.[36,38] Another study in which patients with AML or MDS were included, showed an association between impaired iADL, impaired physical capacity or cognitive impairment and treatment non-completion. In this study, no other geriatric impairments or clinical characteristics such as comorbidity or WHO performance status were not associated with treatment non-completion.[25]

Association of geriatric impairments with health care utilisation

The association of geriatric impairments on health care utilisation was addressed in seven studies.[32,46,53,55,57,59,62] Six out of these studies showed an association between geriatric impairments and health care utilisation. In four studies impaired physical capacity was associated with increased use of health care.[46,55,57,62] In patients with various haematological malignancies, other geriatric impairments, such as ADL,[62] iADL,[53] cognition[59] and mood[46] were also associated with health care utilisation. In one study with DLBCL patients, no association between frailty (assessed by summarised geriatric assessment score) and unplanned admissions was found.[32]

DISCUSSION

This systematic review of 44 studies shows that impairment in geriatric domains is common among older patients with a haematological malignancy, even in patients with a good performance status. Most relevant is frailty (assessed with a frailty screening tool

or by summarising the geriatric assessment), which showed an association with mortality, treatment-related toxicity and treatment non-completion. Other relevant geriatric impairments were IADL functioning, nutritional status and polypharmacy. Impaired physical capacity was mainly associated with health care utilisation.

However, these data should be interpreted with care. The included studies are heterogeneous in study population, design, treatment regimens, content of geriatric assessment and reported outcomes. Various haematological malignancies can have a very different disease course and intensity of treatment; and geriatric impairments that were associated with outcome in one setting may not retain their predictive value in another disease entity. In addition, the content of geriatric assessments including the definition of frailty (assessed by summarising the geriatric assessment), was not consistent. Moreover, geriatric impairments were mainly assessed with screening tools (for example MMSE for cognition), and it should be realized that those results are not the same as an actual diagnosis made by a comprehensive geriatric assessment. Due to this heterogeneity, a meta-analysis or a meaningful subgroup analysis (for example, by type of malignancy) could not be performed; and interpretation and extrapolation of results should be done with caution. Another limitation of this review is the selection procedure of the literature. We decided to only select studies for which full text is available and select studies that performed a geriatric assessment with validated tools which exists of at least more than two geriatric domains. Studies which focus on a single impairment and their relation to outcome were not included, meaning some information on individual associations may have been missed.

Despite of these limitations, this review provides a thorough update and overview of all currently available evidence on the relevance of a geriatric assessment for older patients with a haematological malignancy. At the time of previous systematic review of Hamaker et al.,[17] the evidence was limited due to a lack of published studies. In the last five years, the number of publications concerning the association of geriatric assessment with outcomes in patients with haematological malignancies has highly increased, allowing for a useful update on the available data.

Performing a geriatric assessment could have an additive value to clinical judgement, treatment allocation and the implementation of non-oncological interventions. In daily practice, oncologists are able to detect obviously frail patients by clinical judgement. However, estimating the reserve capacity and resilience of the remaining older patients by clinical judgement is difficult, as demonstrated by the discrepancy between performance status and geriatric assessment. In addition, it can be challenging to distinguish whether the detected vulnerabilities are disease-related or patient related. This may require a more thorough evaluation of the patient's overall health status, including consultation of a geriatrician.

The impact of performing a geriatric assessments on treatment allocation has already been demonstrated in older patients with solid malignancies.[73,74] In a systematic review, the oncologic treatment plan was altered in 28% of patients after geriatric assessment, primarily

resulting in a less intensive treatment option. This review showed that using a geriatric assessment to guide treatment decisions appeared to have a positive effect on clinical outcome, showing less treatment-related toxicity and complications, and increased treatment completion.[75] For example, in patients with cognitive impairments, the treatment decision making process should be performed carefully due to a higher risk of chemotherapy-related progression of cognitive dysfunction, treatment non-compliance and death.[52,71]

In order to tailor cancer treatment to individual needs, it can be interesting to attach patient reported outcome measures (PROMS) in the treatment decision making process. These PROMS, such as physical functioning and quality of life during and after treatment were hardly assessed in the included studies, while quality of life can be of primary importance to many older patients.[76] Therefore, it is highly relevant that future studies address the association between geriatric impairments and PROMS.[77]

In addition to clinical judgment and treatment allocation, a geriatric assessment can be used to introduce non-oncological interventions before and during treatment in hopes of increasing the patient's health status, resilience and treatment tolerance. However, the evidence concerning the effectiveness of such non-oncological interventions is limited. Previous research suggests that perhaps physiotherapy [78,79] as well as nutritional counselling [80–82] can improve survival, physical functioning and quality of life. Moreover, non-oncological interventions in older patients undergoing chemotherapy, can improve treatment completion and treatment modifications.[83] The process in which patient's condition will be enhanced before starting treatment, is called prehabilitation. Although promising results of the first studies which assess the effectiveness of prehabilitation in patients with solid malignancies,[84,85] the level of evidence is weak, making it too early to draw definitive conclusions. Currently, according to clinicaltrials.gov (search February 5th 2020), there are 29 on-going trials in which the effect of non-oncological interventions on clinical outcome measures in older cancer patients is assessed; six out of these 29 trials focus on haematological malignancies.[86] Based on these numbers, further data will follow in the coming years.

In conclusion, this review demonstrates the relevance of performing a geriatric assessment in older patients with a haematological malignancy. Although the results should be interpreted and extrapolated carefully, our review shows that even in patients with a good performance status, a geriatric assessment can detect geriatric impairments that might be predictive for mortality. Moreover, geriatric impairments seem to be associated with a higher risk of treatment-related toxicity, treatment non-completion and using health care services. Future research is needed to extend these findings with a focus on reserve capacity, resilience, quality of life and the effectiveness of non-oncological interventions.

Table 1. Characteristics of studies on the association between the geriatric assessment and outcome measures.

Publication		Study population					GA		Outcome measures		
Author	Year	Patient population	Type of malignancy	Number of patients	Me(di)an age*	Treatment	Number of domains assessed	Summarised GA score	Prevalence geriatric conditions	Survival	Other
Aguiar[19]	2020	65+	MDS	79	77 (70-84)	No disease modifying therapy	3		+		
Corsetti[20]	2013	65+ or unfit for aggressive CT	AML; RAEB	31	72 (55-84)	CT	2	+	+	+	
Deschler[21]	2013	60+	AML; MDS	195	71 (60-87)	BSC; CT	5		+	+	
Holmes[22]	2014	60+	AML; MDS	50	65 (60-73)	HSCT	8	+	+		
Klepin[23]	2013	60+	AML	74	68 (65-74)	CT	5		+	+	
Klepin[24]	2020	60+	AML (FLT3)	40	68 (61-83)	CT	7		+	+	
Molga[25,26]	2020	65+	AML;MDS	98	77 (66-95)	BSC;CT	7		+	+	Treatment completion
Umit[27]	2018	no age limit	AML	372	63 (19-97)	CT	4		+	+	
Goede[28]	2016	no age limit	CLL	75	75 (48-87)	CT	3		+	+	Toxicity
Molica[29]	2019	65+	CLL	108	71 (65-90)	CT	2	+	+	+	Toxicity
Ribi[30]	2017	no age limit	B cell lymphoma	41	75 (40-94)	various	4	+	+	+	
Merli[31]	2020	65+ and unfit	DLBCL	33	82 (68-89)	CT	2		+		
Ong[32]	2019	60+	DLBCL	205	73 (60-97)	CT	2	+	+	+	Health care utilisation, toxicity, treatment completion
Spina[33]	2012	70+	DLBCL	100	75 (70-89)	CT	4	+	+	+	Toxicity
Tucci[34]	2009	65+	DLBCL	84	73 (66-89)	CT	1	+	+	+	Toxicity

Publication		Study population					GA		Outcome measures		
Author	Year	Patient population	Type of malignancy	Number of patients	Me(di)an age*	Treatment	Number of domains assessed	Summarised GA score	Prevalence geriatric conditions	Survival	Other
Tucci[35]	2015	69+	DLBCL	173	77	various	2	+	+	+	
Aaldriks[36]	2015	70+	NHL	44	78 (70-86)	CT	3		+	+	Treatment completion
Naito[37]	2016	65+	NHL	93	77 (65-90)	various	5		+	+	Toxicity
Park[38]	2015	65+	NHL	70	74 (65-92)	CT	4		+	+	Treatment completion
Siegel[39]	2006	60+	NHL	25	70 (60-85)	?	3		+		
Soubeyran[40]	2011	70+ , unfit for aggressive CT	NHL	32	79 (70-92)	CT	4		+	+	
Winkelmann[41]	2011	18+	NHL	143	63 (18-88)	CT	2		+	+	
Okuyama[42]	2015	65+	Lymphoma, MM	106	74 (65-90)	CT	5	+	+		
Engelhardt[43]	2016	no age limit	MM	125	63 (56-71)	CT	2		+	+	
Gavriatopoulou[44]	2019	80+	MM	110	83 (80-92)	CT	3		+	+	
Palumbo[45]	2015	70+	MM	869	74 (70-78)	CT	2	+	+	+	Toxicity, Treatment completion
Rosko[46]	2019	18+	MM, amyloidosis	100	59 (36-75)	HSCT	6		+		Health care utilisation
Wildes[47]	2019	65+	MM	40	71 (66-76)	BSC;HSCT	5		+		
Zhong[48]	2017	no age limit	MM	628	58 (52-66)	CT	2	+	+	+	Toxicity
Buckstein[49]	2016	65+	various	445	71 (65-79)	CT	3		+	+	
Deschler[50]	2018	60+	various	106	66 (60-78)	HSCT	5		+	+	

Publication		Study population					GA		Outcome measures		
Author	Year	Patient population	Type of malignancy	Number of patients	Me(di)an age*	Treatment	Number of domains assessed	Summarised GA score	Prevalence geriatric conditions	Survival	Other
Derman[51]	2019	60+	various	192	>67 (60-83)	HSCT	5		+		
Dubruille[52]	2015	65+	various	90	74 (65-89)	CT	8	+	+	+	
Dumontier[53]	2019	75+	various	464	80 (76-84)	BSC;CT	3		+	+	Health care utilisation
Hamaker[54]	2016	65+	various	157	78 (67-99)	various	7	+	+	+	
Huang[55]	2020	50+	various	148	62 (50-76)	HSCT	6		+	+	Health care utilisation, toxicity
Lin[56]	2020	60+	various	457	66 (60-79)	HSCT	5		+	+	
Liu[57]	2019	75+	various	448	80 (76-84)	BSC;CT	2	+	+	+	Health care utilisation
Muffly[58]	2014	50+	various	203	58 (54-63)	HSCT	3	+	+	+	
Nawas[59]	2019	50+	various	184	61 (50-75)	HSCT	5		+	+	Health care utilisation, toxicity
Rodrigues[60]	2020	60+	various	40	68 (60-76)	HSCT	6	+	+		
Rollot-Trad[61]	2008	75+, geriatric department	various	54	86 (75-99)	various	4		+	+	
Silay[62]	2015	65+	various	61	69	?	7		+		Health care utilisation
Velghe[63]	2014	70+	various	50	76 (70-87)	various	6	+	+		

* Reported as mean (± SD) or median (range or IQR)
ADL, activities of daily living; AML, acute myeloid leukaemia; BSC, best supportive care; CT, chemotherapy; CLL chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FLT3, FMS like tyrosine Kinase-3; GA, geriatric assessment; IADL, instrumental activities of daily living; IQR, interquartile range; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PS, WHO performance status; RAEB, refractory anaemia with excess of blasts; SD, standard deviation; HSCT, haematopoetic stemcell transplantation.

Table 2. Comparison of impaired performance status with impairments in geriatric domains

Author	Year	Type of malignancy	N	Me(di)an age*	Poor PS	ADL	IADL	Cognition	Mood	Physical capacity	Nutritional status	Social support	Poly-pharmacy	Frailty screening tool	Summarised GA score
Aguiar[19]	2020	MDS	76	77 (70-84)	-	-	-	-	-	80 %	-	-	61 %	38 %	-
Corsetti[20]	2013	AML; RAEB	31	72 (55-84)	38 %	17 %	59 %	-	-	-	-	-	-	-	54 %
Deschler[21]	2013	AML; MDS	195	71 (60-87)	47 %	34 %	31 %	9 %	14 %	55 %	-	-	-	-	-
Holmes[22]	2014	AML; MDS	50	65 (60-73)	12 %	16 %	-	16 %	10 %	18 %	36 %	54 %	> 28 %	-	66 %
Klepin[22]	2013	AML	74	68 (65-74)	22 %	50 %	41 %	29 %	40 %	50 %	-	-	-	-	-
Klepin[24]	2020	AML (FLT3)	40	68 (61-83)	?	?	?	?	?	56 %	-	?	36 %	-	-
Molga[25,26]	2020	AML;MDS	98	77 (66-95)	28 %	29 %	34%	11 %	32 %	31 %	27%	-	-	68%	-
Umit[27]	2018	AML	372	63 (19-97)	91 %	-	80 %	14 %	79 %	-	-	-	-	70 %	-
Goede[28]	2016	CLL	75	75 (48-87)	?	-	19 %	29 %	-	48 %	-	-	-	-	-
Molica[29]	2019	CLL	108	71 (65-90)	?	16 %	19 %	-	-	-	-	-	-	-	10 %
Ribi[30]	2017	B cell lymphoma	41	75 (40-94)	15 %	-	-	27 %	20 %	-	73 %	7 %	-	-	39 %
Merli[31]	2020	DLBCL	33	85 (68-89)	6 %	18 %	3 %	-	-	-	-	-	-	-	-
Ong[32]	2019	DLBCL	205	73 (60-97)	7 %	7 %	36 %	-	-	-	-	-	-	-	38 %
Spina[33]	2012	DLBCL	100	75 (70-89)	26 %	27 %	31 %	?	?	-	-	-	-	-	13 %
Tucci[34]	2009	DLBCL	84	73 (66-89)	?	12 %	-	-	-	-	-	-	-	-	50 %
Tucci[34]	2015	DLBCL	173	77	?	>4 %; <54 %	>9 %; <54 %	-	-	-	-	-	-	-	38 %
Aaldriks[36]	2015	NHL	44	78 (70-86)	6 %	-	-	5 %	-	-	34 %	-	-	43 %	-
Naito[37]	2016	NHL	93	77 (65-90)	22 %	28 %	27 %	4 %	15 %	-	51 %	-	-	-	-
Park[38]	2015	NHL	70	74 (65-92)	39 %	-	-	37 %	21 %	-	36 %	-	-	47 %	-
Siegel[39]	2006	NHL	25	70 (60-85)	12 %	-	-	0 %	16 %	12 %	-	-	-	-	-
Soubeyran[40]	2011	NHL	32	79 (70-92)	41 %	59 %	81 %	38 %	94 %	-	-	-	-	-	-

Author	Year	Type of malignancy	N	Me(di)an age*	Poor PS	ADL	IADL	Cognition	Mood	Physical capacity	Nutritional status	Social support	Poly-pharmacy	Frailty screening tool	Summarised GA score
Winkelmann[41]	2011	NHL	143	63 (18-88)	16 %	18 %	21 %	-	-	-	-	-	-	-	-
Okuyama[42]	2015	Lymphoma, MM	106	74(65-90)	29 %	33 %	45 %	23 %	30 %	-	-	-	17 %	-	50 %
Engelhardt[43]	2016	MM	125	63 (56-71)	28 %	48 %	85 %	-	-	-	-	-	-	-	-
Gavriatopoulou[44]	2019	MM	110	83 (80-92)	>60%	18 %	42 %	-	-	-	-	-	-	73 %	-
Palumbo[45]	2015	MM	869	74 (70-78)	21 %	14 %	18 %	-	-	-	-	-	-	-	30 %
Rosko[46]	2019	MM, amyloidosis	100	59 (36-75)	48 %	?	?	?	19 %	7 %	-	?	-	-	-
Wildes[47]	2019	MM	40	71 (66-76)	40 %	-	63 %	10 %	?	40 %	-	-	77 %	-	-
Zhong[48]	2017	MM	628	58 (52-66)	?	67 %	55 %	-	-	-	-	-	-	-	64 %
Buckstein[49]	2016	various	445	71 (65-79)	7 %	-	45 %	-	-	39 %	-	-	-	25 %	-
Deschler[50]	2018	various	106	66 (60-78)	60 %	9 %	31 %	12 %	-	3 %	76 %	-	-	-	-
Derman[51]	2019	various	192	>67(60-83)	< 50%	-	40 %	7 %	22 %	-	-	?	54 %	-	-
Dubruille[52]	2015	various	90	74 (65-89)	32 %	11 %	39 %	31 %	25 %	4 %	44 %	-	50 %	72 %	80 %
Dumontier[53]	2019	various	464	80 (76-84)	?	11%	27%	?	-	-	-	-	-	-	-
Hamaker[54]	2016	various	157	78 (67-99)	42 %	22 %	47 %	18 %	29 %	30 %	-	20 %	66 %	-	71 %
Huang[55]	2020	various	148	62 (50-76)	28 %	-	39 %	1 %	44 %	8%	-	?	50 %	-	-
Lin[56]	2020	various	57	66 (60-79)	<47 %	4 %	11 %	44 %	18 %	-	-	-	50 %	-	-
Liu[57]	2019	various	448	80 (76-84)	47 %	-	-	18 %	-	56 %	-	-	-	-	53 %
Muffly[58]	2014	various	203	58 (54-63)	29 %	7 %	40 %	-	-	24 %	-	-	-	-	25 %
Nawas[59]	2019	various	184	61 (50-75)	1 %	-	36 %	3 %	35 %	15 %	-	?	-	-	-
Rodrigues[60]	2020	various	40	68 (60-76)	75 %	-	10 %	21 %	18 %	16 %	43 %	-	80 %	-	19 %
Rollot-Trad[61]	2008	various	54	86 (75-99)	56 %	39 %	51 %	27 %	-	-	-	-	39 %	-	-

Author	Year	Type of malignancy	N	Me(di)an age*	Poor PS	ADL	IADL	Cognition	Mood	Physical capacity	Nutritional status	Social support	Poly-pharmacy	Frailty screening tool	Summarised GA score
Silay[62]	2015	various	61	69	?	21 %	26 %	26 %	34 %	16 %	27 %	-	51 %	-	-
Velghe[63]	2014	various	50	76 (70-87)	?	24 %	38 %	4 %	30 %	-	82 %	-	-	76 %	88 %

* Reported as mean (± SD) or median (range or IQR)
? Although geriatric condition was assessed, the proportion of patients with geriatric impairments could not be extracted from the published data.
ADL, activities of daily living; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FLT3, FMS like tyrosine Kinase-3; GA, geriatric assessment; IADL, instrumental activities of daily living; IQR, interquartile range; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PS, WHO performance status; RAEB, refractory anaemia with excess of blasts; SD, standard deviation.

Table 3. The association of geriatric assessment, age, performance status, comorbidity with mortality.

Publication				Results of uni/multivariate analysis													
Author	Year	Number of patients	Type of malignancy	Age	PS	Comorbidity	ADL	IADL	Cognition	Mood	Physical capacity	Nutritional status	Social support	Polypharmacy	Frailty screening tool	Summarised	GA score
Corsetti[20]	2011	31	AML/RAEB					-								-	
Deschler[21]	2013	195	AML/MDS	- -	+ +	+ +	+ +	- -	- -	-	- -						
Klepin[23]	2013	74	AML	- -	- -	- -	- -	- -	+ +	- -	+ +						
Klepin[24]	2020	40	AML (FLT3)		-	-	-	-	-	-	-		-	-			
Molga [25]	2020	98	AML/MDS		- -	+ +	+ +	+ +	- -	- -	- -	- -					
Umit[27]	2018	372	AML	+	+										+		
Goede[28]	2016	75	CLL	- -		-		-	- -		- -						
Molica[29]	2019	108	CLL	+ +	+	+ +	+ +	+								+ +	
Ribi[30]	2017	41	B cell lymphoma			-			-	-		+	-			+	
Ong[32]	2019	205	DLBCL													+ +	
Spina[33]	2012	100	DLBCL				- -	- -								+ +	
Tucci[34]	2009	84	DLBCL													+	
Tucci[35]	2015	173	DLBCL	+		+	+	+								+ +	
Aaldriks[36]	2015	44	NHL									-			+ +		
Naito[37]	2016	93	NHL	-	-	+ +	-	+	+ +	-		-					
Park[38]	2015	70	NHL		- -				-	-		+ +			-		
Soubeyran[40]	2011	32	NHL				+	+	+	+							
Winkelmann[41]	2011	143	NHL	- -	- -	- -	- -	+ +									
Engelhardt[43]	2016	125	MM	+		+ +									+ +		

Publication				Results of uni/multivariate analysis													
Author	Year	Number of patients	Type of malignancy	Age	PS	Comorbidity	ADL	IADL	Cognition	Mood	Physical capacity	Nutritional status	Social support	Polypharmacy	Frailty screening tool	Summarised	GA score
Gavriatopoulou[44]	2019	110	MM												- -		
Palumbo [45]	2015	869	MM	+ +		- -	+ +	+ +									
Zhong[48]	2017	628	MM	- -		- -	- -	- -								-	
Buckstein[49]	2016	445	various	+	+	+ +		+			+				+ +		
Deschler[50]	2018	106	various	+ +	+ +	-		-			+	-					
Dubruille [52]	2015	90	various	+ +	- -	-			+ +		-	-		-	-	-	
Dumontier[53]	2019	452	various	- -		- -	- -	+ +									
Hamaker[54]	2016	157	various	- -	- -	- -										+ +	
Huang[55]	2020	148	various		-			+ +	-								
Lin[56]	2020	457	various	+	+ +	- -		+ +									
Liu[57]	2019	448	various	+ +					+ +		+ +						
Muffly[58]	2014	203	various	+ +	-	+ +	-	+ +			+ +						
Nawas[59]	2019	184	various		- -			+ +					+				
Rollot-Trad[61]	2008	54	various	- -	- -		- -	- -	- -								
Proportion of studies with a significant association in univariate analysis				79%	63%	64%	67%	74%	55%	14%	63%	33%	33 %	0 %	71%	67%	
Proportion of studies with a significant association in multivariate analysis				43%	27%	47%	40%	62%	50%	0%	50%	50%	NA	NA	75%	100%	

+ association in univariate analysis. - no association in univariate analysis. ++ association in multivariate analysis. - - no association in multivariate analysis. NA not applicable. ADL, activities of daily living; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FLT3, FMS-like tyrosine kinase-3; GA, geriatric assessment; IADL, instrumental activities of daily living; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RAEB, refractory anaemia with excess of blasts.

REFERENCES

1. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: A report from the Haematological Malignancy Research Network. Br J Cancer. 2011;105:1684–92.
2. Institute NC. Cancer Stat Facts [Internet]. [cited 2019 Jul 21]. Available from: https://seer.cancer.gov
3. Bron D, Ades L, Fulop T, Goede V, Stauder R. Aging and blood disorders: New perspectives, new challenges. Haematologica. 2015;100:415–7.
4. Warren JL, Harlan LC, Stevens J, Little RF, Abel GA. Multiple myeloma treatment transformed: A population-based study of changes in initial management approaches in the United States. J Clin Oncol. 2013;31(16):1984–9.
5. Abel GA, Koreth J. Optimal positioning of hematopoietic stem cell transplantation for older patients with myelodysplastic syndromes. Curr Opin Hematol. 2013;20:150–156.
6. McClune BL, Weisdorf DJ, Pedersen TL, Da Silva GT, Tallman MS, Sierra J, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol. 2010;28:1878–1867.
7. 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.
8. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, 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):241–25.
9. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. Nurs Outlook. 2010;58(2):76–86.
10. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older Adults: Evidence for a Phenotype. Journals Gerontol Ser A Biol Sci Med Sci. 2001;56A(3):146–56.
11. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;8(1):323–36.
12. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;(173):489–95.
13. 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.
14. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32(24):2595–601.
15. 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;10(6):847–58.
16. Goede V, Stauder R. Multidisciplinary care in the hematology clinic: Implementation of geriatric oncology. J Geriatr Oncol. 2019;10(3):497–503.
17. Hamaker ME, Prins MC, Stauder R. The relevance of a geriatric assessment for elderly patients with a haematological malignancy - A systematic review. Leuk Res. 2014;(38):275–83.
18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute. Ottawa Ottawa Hosp Res Institute. 2012.
19. Aguiar APN, Mendonça P da S, Ribeiro-Júnior HL, Borges D de P, Sampaio HA de C, Martins MRA, et al. Myelodysplastic syndromes: An analysis of non-hematological prognostic factors and its relationship to age. J Geriatr Oncol. 2020;(11):125–7.
20. Corsetti MT, Salvi F, Perticone S, Baraldi A, De Paoli L, Gatto S, et al. Hematologic improvement and response in elderly AML/RAEB patients treated with valproic acid and low-dose Ara-C. Leuk Res. 2011;35(8):991–7.
21. Deschler B, Ihorst G, Platzbecker U, Germing U, März E, De Figuerido M, et al. Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. Haematologica. 2013;98(2):208–16.
22. Holmes H, 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.
23. Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood. 2013;121(21):4287–94.
24. Klepin HD, Ritchie E, Major-Elechi B, Le-Rademacher J, Seisler D, Storrick L, et al. Geriatric assessment among older adults receiving intensive therapy for acute myeloid leukemia: Report of CALGB 361006 (Alliance). J Geriatr Oncol. 2020;(11):107–13.
25. Molga A, Wall M, Chhetri R, Wee LY, Singhal D, Edwards S, et al. Comprehensive geriatric assessment predicts azacitidine treatment duration and survival in older patients with myelodysplastic syndromes. J Geriatr Oncol. 2020;(11):114–20.
26. Molga A, Wall M, Wee LYA, Chhetri R, Singhal D, Singhal N, et al. Screening for deficits using the G8 and VES-13 in older patients with Myelodysplastic syndromes. J Geriatr Oncol. 2020;(11):128–30.
27. Umit EG, Baysal M, Demir AM. Frailty in patients with acute myeloid leukaemia, conceptual misapprehension of chronological age. Eur J Cancer Care (Engl). 2018;27(2):1–8.
28. Goede V, Bahlo J, Chataline V, Eichhorst B, Dürig J, Stilgenbauer S, et al. Evaluation of geriatric assessment in patients with chronic lymphocytic leukemia: Results of the CLL9 trial of the German CLL study group. Leuk Lymphoma. 2016;57(4):789–96.
29. Molica S, Giannarelli D, Levato L, Mirabelli R, Levato D, Lentini M, et al. A simple score based on geriatric assessment predicts survival in elderly newly diagnosed chronic lymphocytic leukemia patients. Leuk Lymphoma. 2019;60(3):845–7.
30. Ribi K, Rondeau S, Hitz F, Mey U, Enoiu M, Pabst T, et al. Cancer-specific geriatric assessment and quality of life: important factors in caring for older patients with aggressive B-cell lymphoma. Support Care Cancer. 2017;25(9):2833–42.
31. Merli F, Cavallo F, Salvi F, Tucci A, Musuraca G, Nassi L, et al. Obinutuzumab and miniCHOP for unfit patients with diffuse large B-cell lymphoma. A phase II study by Fondazione Italiana Linfomi. J Geriatr Oncol. 2020;(11):37–40.
32. Ong DM, Ashby M, Grigg A, Gard G, Ng ZY, Huang H, et al. Comprehensive geriatric assessment is useful in an elderly Australian population with diffuse large B-cell lymphoma receiving rituximab-chemotherapy combinations. Br J Haematol. 2019;(187):73–81.
33. Spina M, Balzarotti M, Uziel L, Ferreri AJM, Fratino L, Magagnoli M, et al. Modulated Chemotherapy According to Modified Comprehensive Geriatric Assessment in 100 Consecutive Elderly Patients with Diffuse Large B-Cell Lymphoma. Oncologist. 2012;17(6):838–46.
34. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer. 2009;115(19):4547–53.
35. Tucci A, Martelli M, Rigacci L, Riccomagno P, Cabras MG, Salvi F, et al. Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: A prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL). Leuk Lymphoma. 2015;56(4):921–6.
36. Aaldriks A, Giltay E, Nortier J, Van der Geest LGM, Tanis BC, Ypma P, et al. Prognostic significance of geriatric assessment in combination with laboratory parameters in elderly patients with aggressive non-Hodgkin lymphoma. Leuk Lymphoma. 2015;56(4):927–35.
37. Naito Y, Sasaki H, Takamatsu Y, Kiyomi F, Tamura K. Retrospective Analysis of Treatment Outcomes and Geriatric Assessment in Elderly Malignant Lymphoma Patients. J Clin Exp Hematop. 2016;56(1):43–9.
38. Park S, Hong J, Hwang I, Ahn JY, Cho EY, Park J, et al. Comprehensive geriatric assessment in elderly patients with newly diagnosed aggressive non-Hodgkin lymphoma treated with multi-agent chemotherapy. J Geriatr Oncol. 2015;6(6):470–8.
39. Siegel AB, Lachs M, Coleman M, Leonard JP. Lymphoma in elderly patients: Novel functional assessment techniques provide better discrimination among patients than traditional performance status measures. Clin Lymphoma Myeloma. 2006;7(1):65–9.
40. Soubeyran P, Khaled H, MacKenzie M, Debois M, Fortpied C, de Bock R, et al. Diffuse large B-cell and peripheral T-cell non-Hodgkin's lymphoma in the frail elderly. A phase II EORTC trial with a progressive and cautious treatment emphasizing geriatric assessment. J Geriatr Oncol. 2011;2(1):36–44.
41. Winkelmann N, Petersen I, Kiehntopf M, Fricke HJ,

Hochhaus A, Wedding U. Results of comprehensive geriatric assessment effect survival in patients with malignant lymphoma. J Cancer Res Clin Oncol. 2011;137(4):733–8.
42. Okuyama T, Sugano K, Iida S, Ishida T, Kusumoto S, Akechi T. Screening performance for frailty among older patients with cancer: A cross-sectional observational study of two approaches. JNCCN J Natl Compr Cancer Netw. 2015;13(12):1525–31.
43. Engelhardt M, Dold SM, Ihorst G, Zober A, Möller M, Reinhardt H, et al. Geriatric assessment in multiple myeloma patients: Validation of the international Myeloma Working Group (IMWG) score and comparison with other common comorbidity scores. Haematologica. 2016;101(9):1110–9.
44. Gavriatopoulou M, Fotiou D, Koloventzou U, Roussou M, Migkou M, Ntanasis-Stathopoulos I, et al. Vulnerability variables among octogenerian myeloma patients: a single-center analysis of 110 patients. Leuk Lymphoma. 2019;60(3):619–28.
45. Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. Blood. 2015;125(13):2068–74.
46. Rosko AE, Huang Y, Benson DM, Efebera YA, Hofmeister C, Jaglowski S, et al. Use of a comprehensive frailty assessment to predict morbidity in patients with multiple myeloma undergoing transplant. J Geriatr Oncol. 2019;10(3):479–85.
47. Wildes TM, Tuchman SA, Klepin HD, Mikhael J, Trinkaus K, Stockerl-Goldstein K, et al. Geriatric Assessment in Older Adults with Multiple Myeloma. J Am Geriatr Soc. 2019;67(5):987–91.
48. Zhong YP, Zhang YZ, Liao AJ, Li SX, Tian C, Lu J. Geriatric assessment to predict survival and risk of serious adverse events in elderly newly diagnosed multiple myeloma patients: A multicenter study in China. Chin Med J (Engl). 2017;130(2):130–4.
49. Buckstein R, Wells RA, Zhu N, Leitch HA, Nevill TJ, Yee KWL, et al. Patient-related factors independently impact overall survival in patients with myelodysplastic syndromes: an MDS-CAN prospective study. Br J Haematol. 2016;174(1):88–101.
50. Deschler B, Ihorst G, Schnitzler S, Bertz H, Finke J. Geriatric assessment and quality of life in older patients considered for allogeneic hematopoietic cell transplantation: A prospective risk factor and serial assessment analysis article. Bone Marrow Transplant. 2018;53(5):565–75.
51. Derman BA, Kordas K, Ridgeway J, Chow S, Dale W, Lee SM, et al. Results from a multidisciplinary clinic guided by geriatric assessment before stem cell transplantation in older adults. Blood Adv. 2019;3(22):3488–98.
52. 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.
53. DuMontier C, Liu MA, Murillo A, Hshieh T, Javedan H, Soiffer R, et al. Function, Survival, and Care Utilization Among Older Adults With Hematologic Malignancies. J Am Geriatr Soc. 2019;(67):889–97.
54. Hamaker ME, Augschoell J, Stauder R. Clinical judgement and geriatric assessment for predicting prognosis and chemotherapy completion in older patients with a hematological malignancy. Leuk Lymphoma. 2016;57(11):2560–7.
55. Huang LW, Sheng Y, Andreadis C, Logan AC, Mannis GN, Smith CC, et al. Functional Status as Measured by Geriatric Assessment Predicts Inferior Survival in Older Allogeneic Hematopoietic Cell Transplantation Recipients: Functional Status Predicts Post-AlloHCT Survival. Biol Blood Marrow Transplant. 2020;(26):189–96.
56. Lin RJ, Elko TA, Devlin SM, Shahrokni A, Jakubowski AA, Dahi PB, et al. Impact of geriatric vulnerabilities on allogeneic hematopoietic cell transplantation outcomes in older patients with hematologic malignancies. Bone Marrow Transplant. 2020;(55):157–64.
57. Liu MA, DuMontier C, Murillo A, Hshieh TT, Bean JF, Soiffer RJ, et al. Gait speed, grip strength, and clinical outcomes in older patients with hematologic malignancies. Blood. 2019;134(4):374–82.
58. Muffly LS, Kocherginsky M, Stock W, Chu Q, Bishop MR, Godley LA, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. Haematologica. 2014;99(8):1373–9.
59. Nawas MT, Andreadis C, Martin TG, Wolf JL, Ai WZ, Kaplan LD, et al. Limitation in Patient-Reported Function Is Associated with Inferior Survival in Older Adults Undergoing Autologous Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2019;25(6):1218–24.
60. Rodrigues M, de Souza PMR, de Oliveira Muniz Koch L, Hamerschlak N. The use of comprehensive geriatric assessment in older patients before

allologeneic hematopoietic stem cell transplantation: A cross-sectional study. J Geriatr Oncol. 2020;(11):100–6.
61. Rollot-Trad F, Lahjibi H, Lazarovici C, Bauer C, Saint-Jean O, Gisselbrecht M. Haematological malignancies in older adults: experience in a geriatric acute care department. Rev Med Interne. 2008;29:541–9.
62. Silay K, Akinci S, Silay YS, Guney T, Ulas A, Akinci MB, et al. Hospitalization risk according to geriatric assessment and laboratory parameters in elderly hematologic cancer patients. Asian Pacific J Cancer Prev. 2015;16(2):1783–6.
63. 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.
64. Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Ellis LR, et al. The feasibility of inpatient geriatric assessment for older adults receiving induction chemotherapy for acute myelogenous leukemia. J Am Geriatr Soc. 2011;59(10):1837–46.
65. Klepin HD, Tooze JA, Pardee TS, Ellis LR, Berenzon D, Mihalko SL, et al. Effect of Intensive Chemotherapy on Physical, Cognitive, and Emotional Health of Older Adults with Acute Myeloid Leukemia. J Am Geriatr Soc. 2016;64(10):1988–95.
66. Isaacs A, Fiala M, Tuchman S, Wildes TM. A comparison of three different approaches to defining frailty in older patients with multiple myeloma. J Geriatr Oncol. 2019;In press.
67. 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.
68. Hofer F, Koinig KA, Nagl L, Borjan B, Stauder R. Fatigue at baseline is associated with geriatric impairments and represents an adverse prognostic factor in older patients with a hematological malignancy. Ann Hematol. 2018;97(11):2235–43.
69. Lin RJ, Shahrokni A, Dahi PB, Jakubowski AA, Devlin SM, Maloy MA, et al. Pretransplant comprehensive geriatric assessment in hematopoietic cell transplantation: a single center experience. Bone Marrow Transplant. 2018;53:1184–7.
70. Lin RJ, Dahi PB, Shahrokni A, Sarraf S, Korc-Grodzicki B, Devlin SM, et al. Feasibility of a patient-reported, electronic geriatric assessment tool in hematopoietic cell transplantation–a single institution pilot study. Leuk Lymphoma. 2019;60(13):3308–11.
71. Hshieh TT, Jung WF, Grande LJ, Chen J, Stone RM, Soiffer RJ, et al. Prevalence of cognitive impairment and association with survival among older patients with hematologic cancers. JAMA Oncol. 2018;4(5):686–93.
72. Muffly LS, Boulukos M, Swanson K, Kocherginsky M, Cerro P del, Schroeder L, et al. Pilot Study of Comprehensive Geriatric Assessment (CGA) in Allogeneic Transplant: CGA Captures a High Prevalence of Vulnerabilities in Older Transplant Recipients. Biol Blood Marrow Transplant. 2013;19(3):429–34.
73. Corre R, Greillier L, Le Caër H, Audigier-Valette C, Baize N, Bérard H, et al. Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non-small cell lung cancer: The Phase III randomized ESOGIA-GFPC-GECP 08-02 Study. J Clin Oncol. 2016;34(13):1476–83.
74. Kirkhus L, Benth JŠ, Rostoft S, Grønberg BH, Hjermstad MJ, Selbæk G, et al. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. Br J Cancer. 2017;117(4):470–7.
75. Hamaker ME, te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients – A systematic review. J Geriatr Oncol. 2018;9(5):430–40.
76. Van Leeuwen KM, Van Loon MS, Van Nes FA, Bosmans JE, De Veti HCW, Ket JCF, et al. What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):1–39.
77. Stauder R, Lambert J, Desruol-Allardin S, Savre I, Gaugler L, Stojkov I, Siebert U C-SH. Patient-reported outcome measures in studies of myelodysplastic syndromes and acute myeloid leukemia: Literature review and landscape analysis. Eur J Haematol. 2020;(00):1–12.
78. Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. Supervised exercise reduces cancer-related fatigue: A systematic review. J Physiother. 2015;61:3–9.
79. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev. 2017;52:91–104.
80. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutri-

tional interventions in malnourished patients with cancer: A systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(5):371–85.
81. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet. 2019;393(2312–2321).
82. Caillet P, Liuu E, Raynaud Simon A, Bonnefoy M, Guerin O, Berrut G, et al. Association between cachexia, chemotherapy and outcomes in older cancer patients: A systematic review. Clin Nutr. 2017;36:1473–82.
83. Kalsi T, Babic-Illman G, Ross PJ, Maisey NR, Hughes S, Fields P, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer. 2015;112:1435–44.
84. Bruns ERJ, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. Color Dis. 2016;18(8):267–77.
85. Driessen EJ, Peeters ME, Bongers BC, Maas HA, Bootsma GP, van Meeteren NL, et al. Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: A systematic review. Crit Rev Oncol Hematol. 2017;114:63–76.
86. ClinicalTrials.gov. U.S. National Library of Medicine [Internet]. [cited 2020 Feb 5]. Available from: https://clinicaltrials.gov/

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

Selection	1. Representativeness of the exposed cohort	+ Truly representative of the average older patient with a haematological malignancy
		+ In studies using a geriatric assessment to select patients for inclusion: if no other issues resulting in potential inclusion bias were encountered
		+/- Selected group of patients with a haematological malignancy and specific treatment
		- Mixed cohort of younger and older patients where me(di)an age is less than 68 years old or more than one third is < 65 years old.
		? No description of the derivation of the cohort
	2. Ascertainment of exposure (Geriatric Assessment)	+ Clearly described and using validated assessment tools
		- Using non-validated assessment tools for > 40% of investigated geriatric domains
		? No description
	3. Demonstration that outcomes of interest were not present at start of study	+ Yes
		- No
		na Not applicable in studies addressing the prevalence of geriatric impairments or using the geriatric assessment for patient selection or treatment assignment.
Outcome	1. Assessment of outcome (treatment alterations)	+ Clear description of method of assessment
		? No or unclear description of method of assessment
		na Not applicable in studies addressing the prevalence of geriatric impairments or using the geriatric assessment for patient selection or treatment assignment.
	2. Was follow-up long enough for outcome to occur?*	+ Yes
		- No
		? No statement
		na Not applicable in studies addressing the prevalence of geriatric impairments or using the geriatric assessment for patient selection or treatment assignment.
	3. Adequacy of follow-up of cohorts	+ 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
		na Not applicable in studies addressing the prevalence of geriatric impairments or using the geriatric assessment for patient selection or treatment assignment.

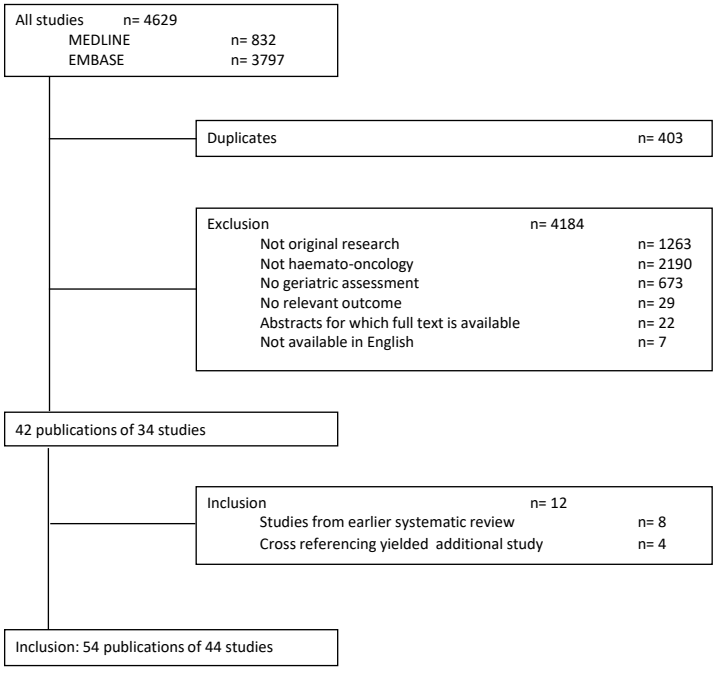
Appendix 1b. Quality assessment of included studies.

Publication		Selection			Outcome		
Author	Year	Representiveness of exposed cohort	Ascertainment of exposure (GA)	Outcome not present at start of study	Assessment of outcome	Sufficient duration of follow up	Adequacy of follow-up
Aaldriks[36]	2015	+	+	+	+	+	+
Aguiar[19]	2020	+	+	na	na	na	na
Buckstein[49]	2016	+	+	+	+	+	+
Corsetti[20]	2011	+/-	+	+	+	+	+
Deschler[21]	2013	+	+	+	+	+	+
Deschler[50]	2018	-	+	+	+	+	+
Derman[51]	2019	+/-	+	na	na	na	na
Dubruille[52]	2015	+	+	+	+	+	+
Dumontier[53]	2019	+	+	+	+	+	+
Engelhardt[43]	2016	-	+	+	+	+	+
Gavriatopoulou[44]	2019	+	+	+	+	+	+
Goede[28]	2016	+	+	+	+	+	+
Hamaker[54,67,68]	2016	+	+	+	+	+	+
Holmes[22]	2014	-	+	na	na	na	na
Huang[55]	2020	+/-	+	+	+	+	+
Klepin[23,64,65]	2016	+/-	+	+	+	+	+
Klepin [24]	2020	+/-	+	+	+	+	-
Lin[56,69,70]	2020	+/-	+	+	+	+	?
Liu[57,71]	2019	+	+	+	+	+	?
Merli[31]	2020	+/-	+	na	na	na	na
Molga[25,26]	2020	+	+	+	+	+	+
Molica[29]	2019	+	+	+	+	+	+
Muffly[58,72]	2014	-	+	+	+	+	+
Naito[37]	2016	+	+	+	+	+	+
Nawas[59]	2019	-	+	+	+	+	+
Okuyama[42]	2015	+	+	na	na	na	na
Ong[32]	2019	+	+	+	+	+	?
Palumbo[45]	2015	+	+	+	+	+	+
Park[38]	2015	+	+	+	+	+	+
Ribi[30]	2017	+	+	+	+	+	-
Rodrigues[60]	2020	+/-	+	na	na	na	na
Rollot-Trad[61]	2008	+	+	+	+	+	+

Publication		Selection			Outcome		
Author	Year	Representiveness of exposed cohort	Ascertainment of exposure (GA)	Outcome not present at start of study	Assessment of outcome	Sufficient duration of follow up	Adequacy of follow-up
Rosko[46]	2019	-	+	+	+	+	-
Siegel[39]	2006	+	+	na	na	na	na
Silay[62]	2015	+	+	+	+	+	?
Soubeyran[40]	2011	+	+	+	+	+	+
Spina[33]	2012	+	+	+	+	+	?
Tucci[34]	2009	+	+	+	+	+	+
Tucci[35]	2015	+	+	+	+	+	+
Umit[27]	2018	-	+	+	+	+	?
Velghe[63]	2014	+	+	na	na	na	na
Wildes[47,66]	2019	+	+	na	na	na	na
Winkelmann[41]	2011	-	+	+	+	+	+
Zhong[48]	2017	-	+	+	+	+	+

na, not applicable

Appendix 1c. Search results and study selection.



CHAPTER
3

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 ≥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 ≥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 ≥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 over 70 years of age.[1] Due to the ongoing ageing 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.[2,3] Finally, older patients and those with comorbidity are significantly under-represented in clinical trials.[4] 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 ageing processes across multiple organ systems.[5] While frailty is age-related, it does not necessarily coincidence 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.[6] 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.[7]

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 Diakonessenhuis Utrecht and the Haga hospital, The Hague. Between July 2018 and October 2019, all consecutive patients with cancer aged ≥70 years due 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 haematology 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 enrolment.

Data collection

For each patient, baseline demographic data were collected from the medical file by the primary investigator and during the GA including age at treatment, sex, educational level, living situation, comorbidity according to the Charlson Comorbidity Index (CCI, the items on tumour 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 specialised 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),[8] instrumental ADL (Lawton and Brody),[9] nutrition (mini nutritional assessment short-form, MNA-SF),[10] mobility (4-meter walking test and falls in the previous 6 months), cognition, polypharmacy (≥5 drugs) and mood. Cognition was assessed with the 6-item cognitive impairment test (6-CIT)[11] and the clock drawing test and was considered impaired if one of the two was or both were abnormal.[12] Mood was assessed with the patient health questionnaire-2 (PHQ-2)[13] and, in case of an abnormal score, the geriatric depression scale-15 (GDS-15)[14] 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.

Table 1. Content of geriatric assessment.

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

[a] Impairment: proportion of patients who scored below/above the cut-off value.
[b] Mobility was impaired if either the 4 meter walking test was < 0.8 m/s or there was ≥ 1 fall in the past 6 months.
[c] Cognition was impaired if either the 6-CIT or the Clock drawing test was abnormal.
[d] 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.

Clinical judgment

Prior to the start of chemotherapy, the patient, cancer specialist (oncologist/haematologist) 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, where 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

Sociodemographics 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.[15] 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.[16] 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 with palliative intent (66%) and had an ECOG PS of 0 or 1 (88%). One-third had a CCI-score of ≥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 impairments.

Table 2. Patient characteristics, N (%).

Characteristics	Total (n = 55)	
Age, median (range)	74	(70 – 95)
Sex		
Female	22	(40)
Male	33	(60)
Educational level[a]		
High	26	(47)
Medium	21	(38)
Low	8	(15)
Missing	0	
Marital status[b]		
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[c]	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	

[a] Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.
[b] Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited.
[c] 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.

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 ≤5 (Table 3). For example, patients with ≥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.

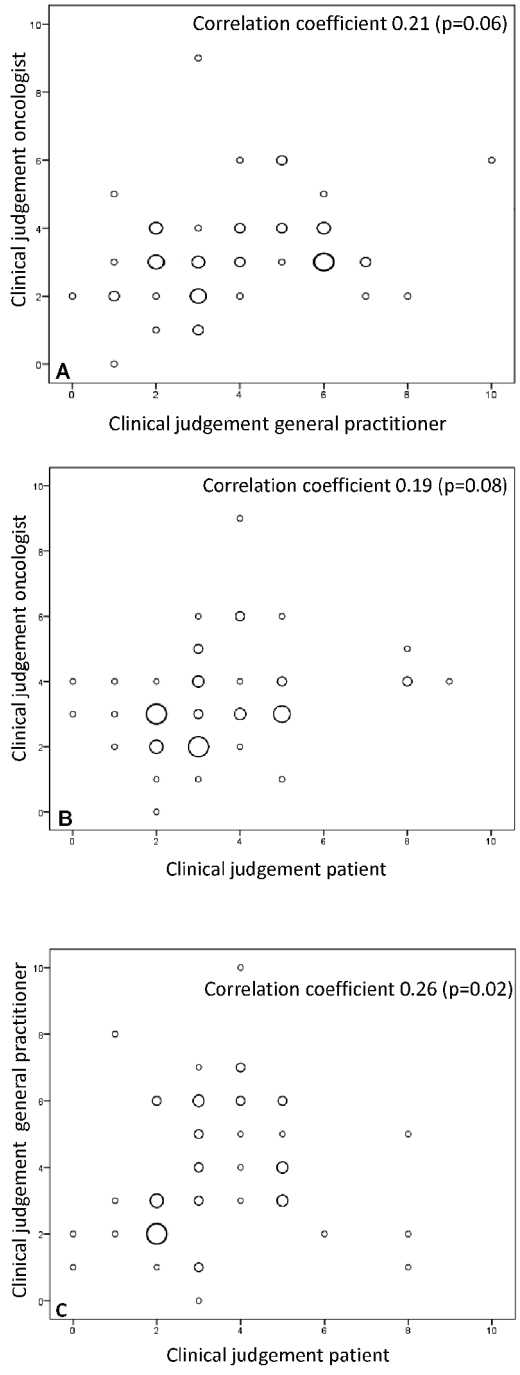
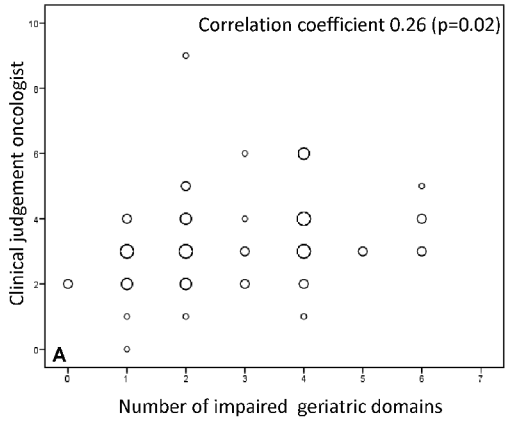
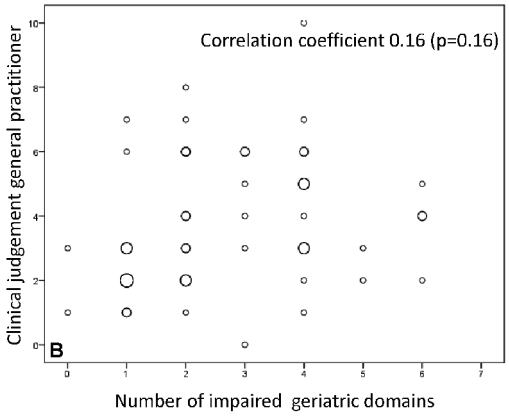


Figure 1. Correlations between clinical judgment scores of the cancer specialist and the general practitioner (1A), the cancer specialist and the patient (1B) and the general practitioner and the patient (1C).

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.





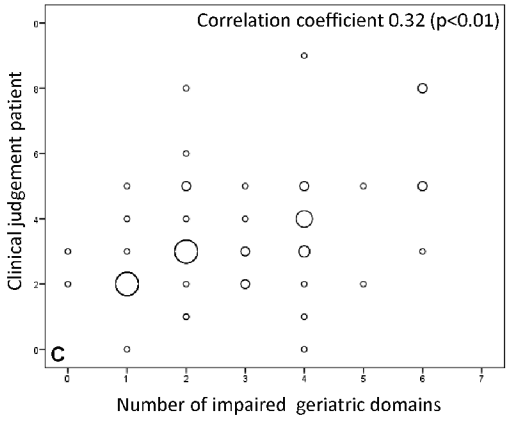


Figure 2. Correlations between clinical judgment score of the cancer specialist and geriatric assessment (2A), of the general practitioner and geriatric assessment (2B) and of the patient and geriatric assessment (2C).

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 patients 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 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 ageing 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.[17,18] Unfortunately, we could not analyse 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.[19–22] Only two studies specifically asked cancer specialists to rate their patients' frailty, using a classification of fit, vulnerable or frail.[19,20] One of these studies found that agreement between cancer specialist's clinical judgment and GA was only fair[19] and the other found poor sensitivity for clinical judgment compared to GA.[20] The other two studies assessed frailty indirectly, according to whether patients received standard or adapted treatment.[21,22] In agreement with our results, they found that GA identified more frail patients than clinical judgment.[19–22] Some studies also found that GA impairment was independently associated with poorer survival, while clinical judgment was not.[19,21] Two additional studies found that the oncologist's clinical judgment was also not predictive of chemotherapy toxicity.[23,24]

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).[25] 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.[25]

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.[26] 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.[25]

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 emphasise cancer-related factors such as tumour type and disease stage as well as ECOG

PS.[19] 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 ≥5. The fact that 76% of our patients had ≥2 impaired geriatric domains leads to the question 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 of 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 respectively 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,[27] GA systematically assesses all these different domains and often finds impairments that would have been missed with regular assessment.[20,28] 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.[29] 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 testing clinical judgment of multiple assessors. In addition, our GA included the main recommended domains and these domains were assessed with validated tests.[29,30] 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. Firstly, 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.[5] However, in the Netherlands people

are used to express feelings or thoughts intuitively on such a scale since their childhood. All hospitals use this method to evaluate a patient's pain intensity. Furthermore, our method has been used in one prior study that demonstrated that this scale has good diagnostic accuracy to assess frailty.[25] 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.

In 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. Accessed april 1, 2017.
2. Galvin A, Helmer C, Coureau G, Amadeo B, Rainfray M, Soubeyran P, et al. Determinants of functional decline in older adults experiencing cancer (the INCAPAC study). J Geriatr Oncol. 2019;10(6):913–20.
3. Kent EE, Ambs A, Mitchell SA, Clauser SB, Smith AW, Hays RD. Health-related quality of life in older adult survivors of selected cancers: Data from the SEER-MHOS linkage. Cancer. 2015;121(5):758–65.
4. 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 Oct;19(10):1069–75.
5. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013 Jun;14(6):392–7.
6. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: A systematic review. Ann Oncol. 2015;26:1091–1101.
7. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, 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):241–25.
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. 1963 Sep;185:914–9.
9. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179–86.
10. Rubenstein LZ, Harker JO, Salvà 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. 2001;56:M366–72.
11. Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. Int J Geriatr Psychiatry. 1999 Nov;14(11):936–40.
12. Wolf-Klein GP, Silverstone FA, Levy AP, Brod MS, Breuer J. Screening for Alzheimer's Disease by Clock Drawing. J Am Geriatr Soc. 1989;37:730–4.
13. Kroenke K, Spitzer RL, Williams JBW. The patient health questionnaire-2: Validity of a two-item depression screener. Med Care. 2003;(41):1284–92.
14. Sheikh J, Yesavage J. Geriatric Depression Scale (GDS). Recent evidence and development of a shorter version. Clin Gerontol a Guid to Assess Interv. 1986;165-73.
15. Arndt S, Turvey C, Andreasen NC. Correlating and predicting psychiatric symptom ratings: Spearmans r versus Kendalls tau correlation. J Psychiatr Res. 1999 Mar;33(2):97–104.
16. Hinkle D, Wiersma W, Jurs S. Applied Statistics for the Behavioral Sciences. 5th ed. Bo. Houghton Mifflin, editor. 2003.
17. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol. 2002 Jan;20(2):494–502.
18. Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. J Clin Oncol. 2016 Jul;34(20):2366–71.
19. Kirkhus L, Šaltyte Benth J, Rostoft S, Grønberg BH, Hjermstad MJ, Selbæk G, et al. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. Br J Cancer. 2017 Aug;117(4):470–7.
20. Wedding U, Ködding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol. 2007;64:1–9.
21. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer. 2009;115(19):4547–53.
22. Hamaker ME, Augschoell J, Stauder R. Clinical judgement and geriatric assessment for predicting prognosis and chemotherapy completion in older patients with a hematological malignancy. Leuk Lymphoma. 2016;57(11):2560–7.
23. Alibhai SMH, 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. 2017 Jan;8(1):31–6.
24. Moth EB, Kiely BE, Stefanic N, Naganathan V, Martin A, Grimison P, 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. 2019 Mar;10(2):202–9.
25. Sutorius FL, Hoogendijk EO, Prins BAH, van Hout HPJ. Comparison of 10 single and stepped methods to identify frail older persons in primary care: diagnostic and prognostic accuracy. BMC Fam Pract. 2016 Dec;17(1):102.
26. Loh KP, Duberstein P, Zittel J, Lei L, Culakova E, Xu H, et al. Relationships of self-perceived age with geriatric assessment domains in older adults with cancer. J Geriatr Oncol. 2020;11(6):1006-1010.
27. 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;10(6):847–58.
28. Extermann M. A comprehensive geriatric intervention detects multiple problems in older breast cancer patients. Crit Rev Oncol Hematol. 2004 Jan;49(1):69–75.
29. 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.
30. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32(24):2595–601.

CHAPTER
4

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

Objective

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.[1–3] 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.[4,5] 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.[6] 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.[7] 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.[8] 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).[7]

The G8 was the first such screening tool specifically designed for older patients with cancer.[9] 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[10]; 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 ≤ 14. The G8 is easy and quick to administer (median time five minutes) and its diagnostic accuracy has been validated in large independent cohorts.[11,12] Two systematic reviews concluded that the G8 was one of the most robust screening tools currently available.[13,14]

Although originally designed to identify those potentially frail older patients who may benefit from GA,[9,11] the association of the G8 with clinical outcomes such as treatment complications, physical functioning after treatment and survival has also been studied.[12,15] A review published in 2015 reported on the results of four studies relating the G8 to clinical outcomes.[14] 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.

Table 1. The original G8 screening tool.

	G8 items	Possible answers (score)
1	Food intake *(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 *(Weight loss during the last 3 months)*	0: weight loss > 3kg 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 or depression 2: no psychological problems
5	Body Mass Index (kg/m^2)	0: BMI <19 1: BMI=19 to BMI <21 2: BMI=21 to BMI <23 3: BMI=23 and >23
6	Medication *(Takes more than 3 prescription drugs per day)*	0: yes 1: no
7	Health status *(In comparison to other people of the same age, how does the patient consider his/her health status)*	0: not as good 0,5: does not know 1: as good 2: better
8	Age (years)	0: >85 1: 80-85 2: <80
	Total score	0-17

Scores ≤ 14: potentially frail.

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 20th 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,[16] 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 (IvW) 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 (IvW 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-Ottowa 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.[17] Cross-referencing yielded one additional study.[18] Ultimately, 54 publications from 46 studies were included for this review,[9,11,12,18-68] of which 18 were conference abstracts.[18,19,21,22,26,27,36,37,40,42,44,46,49,53,54,56,59,63]

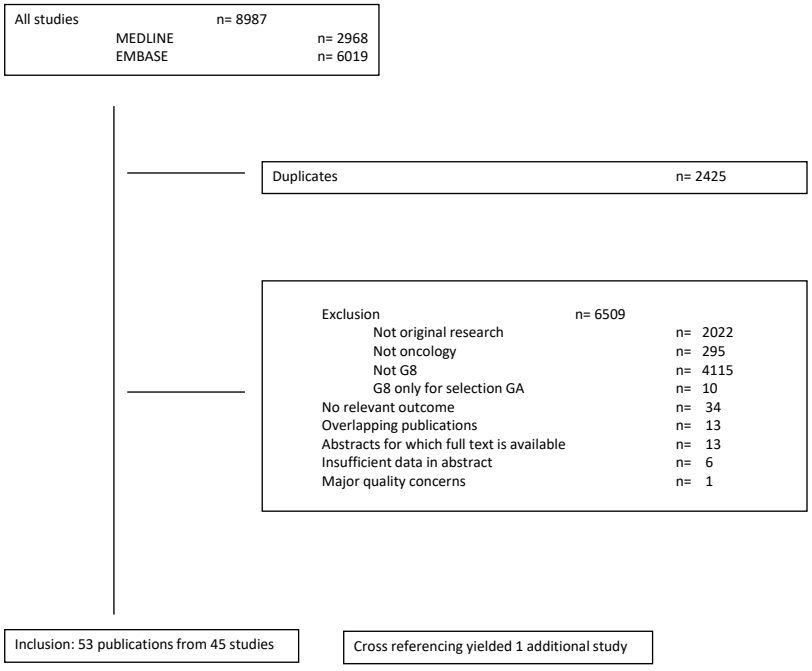

Figure 1. Search results and study selection.
GA, geriatric assessment.

The characteristics of these 46 studies are summarised in Table 2. The first publications were from 2012[9,18,33,55] and the majority of studies (74%) were published in the past four years. Median sample size was 143 patients (range 27-1435) and me(di)an age of the included patients ranged from 65 to 82 years. Study populations were heterogeneous, with

43% focusing on patients with various cancer types.[9,11,12,18–21,25,30,32,36–39,41,42,47,51,55,57,59,62,64,65] Two studies specifically mentioned they also included hospitalized patients,[26,44,45] while one study included hospitalized patients only.[33,34] Seventeen studies evaluated patients receiving various treatment regimens,[11,12,19,22,23,25,26,29,31,37,38,42,44,45,48–50,52,53,57] eleven focused on patients receiving chemotherapy,[9,18,20,21,27,28,30,33,34,36,43,66,67] five on radio(chemo)therapy,[24,47,51,54–56] six on surgery,[35,40,41,46,58,59,61] one on targeted therapy[32] and one on allogeneic stem-cell transplantation.[39] For five studies, the treatment was unknown.[60,62–65]

For outcomes, 19 studies addressed the comparison of the diagnostic accuracy of the G8 compared to GA.[9,11,12,22,34,37–39,41,43,44,50,51,53,55,60,64,65,67] 24 studies described the association of the G8 with survival,[11,12,20,22,24–26,28,31,34,39,42,48,49,52,54,56,57,60,19,61,63,66,67] 17 studies reported on the association of the G8 with course of treatment,[18–20,23,29,30,33,35,36,40,46,47,49,52,56,58,59,61] and four studies addressed the association between the G8 and patient-centred outcomes.[12,27,29,42,54] 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[44,53,68] and one publication addressed the prognostic value of one of the modified G8 versions.[45]

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.[18,38] In another study the description of the method of geriatric evaluation was insufficient with a high risk of bias as a consequence.[50] Duration of follow-up was not mentioned in fifteen publications.[18,19,21,25,28,30,32,36,47,49,52,58,59,62,63] Five publications had loss to follow-up rates over 10%,[12,27,29,42,54] while another 22 publications did not provide sufficient information to assess adequacy of follow-up.[18,19,21,24,25,28,30–33,36,37,46,48,49,52,56–60,62]

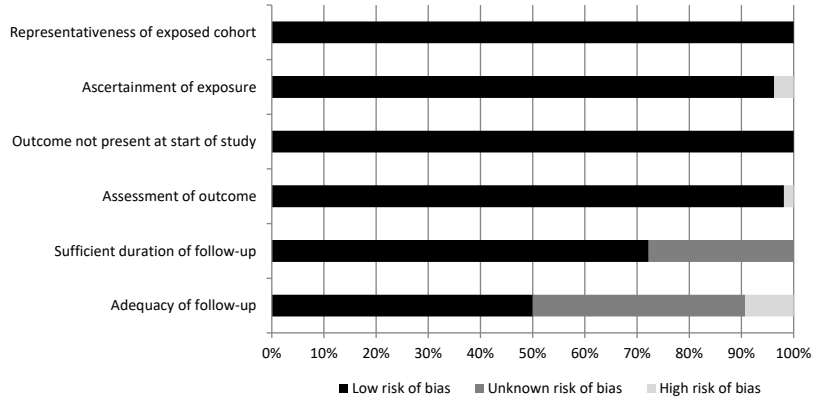

Figure 2. Outcome of the quality assessment. Details are reported in Appendix 1a (quality assessment questionnaire) and 1b (assessment per study).

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 [16,20,26,30,32,34,37,40,45,48,54,57,63,66] and seven performed multivariate analysis but did not report for which covariates they adjusted.[12,19,21,24,25,28,31] For another two studies it was unclear whether they performed univariate or multivariate analysis[59,62] and one study only did an univariate analysis.[61]

Diagnostic accuracy of the original G8 versus GA

For the 19 studies assessing the G8 in relation to GA,[9,11,12,22,34,37–39,41,43,44,50,51,53,55,60,64,65,67] 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),[9,11,12,28,31–33,35,37,38,45,47,50,55,58,59,62,64] and seventeen out of 19 studies (89%) assessed mood[9,11,12,28,31–33,35,37,38,47,50,55,58,59,62,64] and nutrition.[9,11,12,28,31–33,35,37,38,47,50,55,58,59,62,64] Cognition (n= 16, 84%),[9,11,12,28,31–33,35,37,38,47,50,55,58,62,64] mobility and/or falls (n= 15, 79%)[9,11,28,31–33,35,37,38,45,47,50,58,59,62,64] and comorbidity (n= 14, 74%)[9,11,12,28,33,35,38,47,50,55,58,59,62,64] were also commonly included while polypharmacy (n= 6, 32%),[9,11,12,28,33,35,38,47,50,55,58,59,62,64] social support (n= 6, 32%)[12,22,37,39,51,67] and fatigue (n= 1, 5%)[34] were less frequently included.

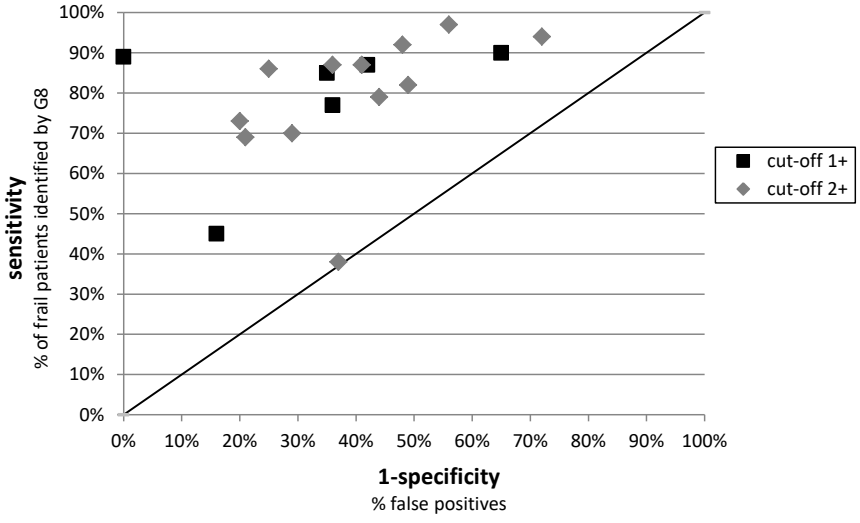

Figure 3. Sensitivity and 1-specificity of the original G8 for frailty on geriatric assessment (GA) based on the presence of one or more (cut-off 1+) or two or more (cut-off 2+) geriatric conditions on GA for the different studies.

Frailty based on GA was defined as the presence of one or more geriatric conditions in six studies[9,11,44,51,53,64] and two or more in twelve studies.[12,22,34,37–39,41,43,50,55,60,67] For one study,[65] 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 ≥1, the prevalence of frailty ranged from 31% to 94%, and in studies using a cut-off of ≥2, the range was 32% to 80%.

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 ≥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 ≥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).[11,12,19–21,24–26,28,30–32,34,37,40,45,48,54,57,59,61–63,66] An association between the G8 and survival was found in four out of eight studies addressing patients receiving chemotherapy and/or radiotherapy (50%)[20,21,24,28,30,34,54,66] and none of the three studies on surgery.[40,58,61] Eleven out of thirteen studies in patients receiving varying treatments found an association between frailty on the G8 and survival (85%).[11,12,19,25,26,31,32,37,45,48,57,62,63] 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 [18,19,23,29,30,33,35,36,40,46,47,56,58,61] and six of these found that a low G8 score was associated with the occurrence of toxicity or treatment-related complications (43%).[18,36,40,46,56,58] 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.[20] 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.[18,47,56] 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.[35,40,58,61] Four studies reported on treatment completion[19,30,47,52] 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,[40,49,59,61] only one study[40] (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)[12,27,29,42] and quality of life (n= 1).[54] Three studies found that a G8 score ≤ 14 was independently associated with either functional decline[12,27,42] or lower QoL (75%)[48] while the fourth study did not find an association.[29]

Performance of modified G8 versions

Two modified G8 versions were evaluated in three studies to assess its diagnostic performance compared to GA.[44,53,68] 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.[44] This modified G8, with a cut-off of ≥ 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.[53] In addition, an impaired score on this modified G8 was independently associated with poorer 1- and 3-years survival.[45]

The second modified G8 replaced the item on neuropsychological problems in the original G8 by a 4-item iADL score.[68] This modified G8 used the same cut-off value for potential frailty as the original G8 (≤ 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.[69] 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.[13,14] 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%[13] and 86%,[14] and specificity of 61%[13] and 60%[14] 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.[44,53,68] 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.[45]

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.

In 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.

Table 2. Included studies.

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 (me(di)an, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Agemi[19]	2015	A	Lung cancer	All patients aged ≥ 70 years candidate for oncological treatment	Various	101	81	79 (70-95)	82		X	X	
Aparicio[20]	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[21]	2016	A	Acute myeloid leukemia	Consecutive, newly diagnosed referrals aged > 60 years	CT	69	?	?	?		X		
Baitar[22,23]	2013	F	Various cancer types	Age ≥ 65 years, newly diagnosed cancer or recurrent disease	Various	170	54	77 (66-97)	76	X		X	
	2014	F											
Bellera[9,27]	2012	F	Various cancer types	Patients aged ≥ 70 years scheduled to receive first-line chemotherapy	CT	339	59	77 (70-99)	82	X			X
	2015	A											
Bonomo[24]	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[25]	2013	A	Various cancer types	Unelected outpatients aged > 70 years	Various	530	50	?	69		X		
Boulahssass[26]	2018	F	Various cancer types	Consecutive patients aged > 70 years, outpatient or hospitalised	Various	1050	40	82 (70-100)	86		X		
Cvetkovic[28]	2017	A	Indolent B-cell lymphoma	Consecutive patients aged ≥ 65 years fulfilling criteria for treatment	CT	89	51	75 (65-88)	?		X		
Decoster[29]	2017	F	Colorectal cancer	Age ≥ 70 years, newly diagnosed cancer or cancer progression/relapse	Various	193	62	77 (70-89)	?			X	X
Decoster[30]	2018	F	Metastatic colorectal cancer	Age ≥ 70 years, suitable for first-line chemotherapy	CT	248	62	77 (69-91)	81		X	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 (me(di)an, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Denewet[31]	2016	F	Various cancer types	Age ≥ 70 years with new cancer diagnosis or disease progression	Various	205	53	79 (70-93)	86		X		
Dimopoulos[32]	2016	A	Multiple myeloma	Consecutive, unselected patients aged > 65 years	TT	144	55	76 (66-92)	?		X		
Dubruille[33,34]	2012	F	Haematological cancers	Consecutive, inpatients aged ≥ 65 years, fit enough for chemotherapy	CT	90	57	74 (65-89)	72	X	X	X	
	2015	A											
Fagard[35]	2017	F	Colorectal cancer	Patients aged ≥ 70 years planned for surgery	Surgery	190	55	77 (70-97)	61			X	
Gangopadhyay[36]	2018	F	Various cancer types	Patients aged > 65 years who completed CTR	CTR	219	42	78 (65-89)	?			X	
Hamaker[37]	2014	F	Haematological cancers	Consecutive, newly diagnosed patients aged ≥ 67 years	Various	108	53	78 (67-99)	61	X	X		
Hentschel[38]	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[39]	2014	F	Haematological cancers	Patients eligible for allo-HCT aged ≥ 60 years	allo-HCT	50	70	65 (60-73)	56	X			
Kaibori[40]	2016	F	Hepatocellular carcinoma	Consecutive patients scheduled for liver resection aged ≥ 70 years	Surgery	71	73	77 (70-89)	55		X	X	
Kenig[41]	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[12,42]	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
		A											
Kim[43]	2017	A	Various cancer types	Patients receiving first-line chemotherapy aged ≥ 70 years	CT	301	?	75 (70-93)	88	X			
Martinez-Tapia[44,45]	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											

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 (me(di)an, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Matsushita[46]	2018	A	High-risk prostate cancer	Patients aged ≥ 75 years	Surgery	41	100	77 (IQR 76-79)	39			X	
Middelburg[47]	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[48]	2013	A	Various cancer types	Patients aged ≥ 70 years	Various	202	62	80	?		X		
Neve[49]	2016	F	Head and neck cancer	Aged ≥ 65 years with a primary malignancy	Various	35	63	74 (65-93)	49			X	
Ogawa[50]	2015	A	Lung cancer	Patients with various stages of lung cancer prior to treatment	Various	154	69	> 70 years	60	X			
Osborne[51]	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[52]	2016	A	Breast cancer	Consecutive patients aged ≥ 70 years	Various	92	1	78 (70-94)	?			X	
Pamoukdjian[53]	2017	F	Various cancer types	Consecutive outpatients aged ≥ 65 years	Various	252	45	81 (SD 6)	88	X			
Pottel[54,55]	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
	2012	F											
Runzer-Colmenares[56]	2017	F	Various cancer types	Older patients receiving RT with curative treatment intent	RT	181	100	78 (SD 5)	20			X	
Schulkes[57]	2017	F	Lung cancer	All patients aged ≥ 70 years	Various	142	62	77 (73-82)	70		X		
Silvestri[58,59]	2018	A	Kidney cancer	Patients aged ≥ 70 years prior to surgery	Surgery	162	46	77 (SD 6)	60		X	X	
Smets[60]	2014	F	Various cancer types	Patients aged ≥ 70 years, recently diagnosed with a solid tumor	?	108	35	76 (70-88)	60	X			
Soubeyran[11,68]	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											

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 (me(di)an, range)	% impaired according to G8	Comparison with GA	Survival	Course of treatment	Patient-centred outcomes
Souwer[61]	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[62]	2015	A	Haematological cancers	At initial diagnosis, age cut-off unclear	?	64	56	79	?		X		
Stokoe[18]	2012	A	Various cancer types	Patients aged ≥ 65 years	CT	165	?	71 (65-84)	?			X	
Takahashi[63]	2017	F	Various cancer types	Patients aged ≥ 70 years	?	264	66	75 (70-91)	83		X		
Velghe[64]	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[65]	2016	A	Various cancer types	All patients aged ≥ 70 years	?	50	?	?	41	X			
Wildiers[6]	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[67]	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.

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[65]	6	mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	?	41	31	74	74	86	56
Bellera[9]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	339	1+	82	94	85	65	97	21
Martinez-Tapia[44]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	729	1+	81	87	87	58	93	41
Osborne[51]	5	ADL, iADL, mobility/falls, social support, polypharmacy	156	1+	23	31	45	84	55	78
Pamoukdjian[53]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	252	1+	88	94	90	35	95	19
Soubeyran[11]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	1435	1+	68	80	77	64	90	40
Velghe[64]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	1+	76	88	89	100	100	55
Baitar[22]	8	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, comorbidity	170	2+	76	64	92	52	78	78
Dubruille[34]	9	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity, polypharmacy, fatigue	90	2+	72	80	79	56	88	40
Hamaker[37]	8	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, polypharmacy	108	2+	61	70	69	79	89	50
Hentschel[38]	6	cognition, mood, iADL, nutrition, mobility/falls, polypharmacy	63	2+	75	36	38	63	37	64
Holmes[39]	9	cognition, mood, ADL, iADL, nutrition, mobility/falls, social support, comorbidity, polypharmacy	50	2+	56	66	70	71	83	55
Kenig[41]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	135	2+	85	73	97	44	83	84
Kenis[12]	7	cognition, mood, ADL, iADL, nutrition, social support, comorbidity	937	2+	74	74	87	59	86	61
Kim[43]	6	cognition, mood, ADL, iADL, nutrition, mobility/falls	301	2+	88	73	94	28	79	60
Ogawa[50]	?	Unclear	154	2+	60	32	82	51	44	86
Pottel[55]	7	cognition, mood, ADL, iADL, nutrition, mobility/falls, comorbidity	50	2+	67	69	86	75	88	71
Smets[60]	6	cognition, mood, ADL, iADL, nutrition, comorbidity	108	2+	60	48	87	64	69	84
Yokom[67]	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.

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(di)an Follow-up	Toxicity or complications	Survival	Comparison of survival frail vs fit*
Aydin[21]	Acute myeloid leukemia	CT	85	?		+/++	
Cvetkovic[28]	Indolent B-cell lymphoma	CT	89	?		+/++	
Decoster[30]	Metastatic colorectal cancer	CT	252	2-3 months	+/--	+/--	PFS 8.7 vs 11.4 months
Dubruille[34]	Haematological cancers	CT	90	?	-	-	
Stokoe[18]	Various cancer types	CT	165	?	+		
Aparicio[20]	Metastatic colorectal cancer	CT (± TT)	102	20.4 months		-	
Wildiers[66]	Metastatic breast cancer	CT (± HT)	80	20.7 months		+/++	6-month OS 88% vs 100% 12-month OS 67% vs 100%
Baitar[23]	Various cancer types	CT or CRT	85	1 month	-/--		
Gangopadhyay[36]	Various cancer types	CRT	219	?	+/++		
Bonomo[24]	Head and neck cancer	RT	37	13 months		+/--	
Runzer-Colmenares[56]	Various cancer types	RT	181	10.2 months	+/++		
Middelburg[47]	Various cancer types	RT or CRT	409	?	+/--		
Pottel[54]	Head and neck cancer	RT or CRT	100	?		+/++	36-month OS 36% vs 70%
Fagard[35]	Colorectal cancer	Surgery	190	?	+/--		
Kaibori[40]	Hepatocellular carcinoma	Surgery	71	> 6 months after hepatectomy	+/++	-	
Matsushita[46]	High-risk prostate cancer	Surgery	41	?	+/++		
Silvestri[58,59]	Kidney cancer	Surgery	162	40.6 months	+	-	
Souwer[61]	Colorectal cancer	Surgery	139	At least 6 months	-	-	1-month OS 96% vs 96% 6-month OS 94% vs 96%
Dimopoulos[32]	Multiple myeloma	TT	144	?		+/++	

Stauder[62]	Haematological cancers	?	64	?		+	
Takahashi[63]	Various cancer types	?	264	?		+/++	Median OS 10.7 vs 25.6 months
Agemi[19]	Lung cancer	Various	101	?	-	+/++	
Bononi[25]	Various cancer types	Various	530	?		+/++	
Boulahssass[26]	Various cancer types	Various	1050	3.3 months		+/--	
Decoster[29]	Colorectal cancer	Various	193	2-3 months	-/--		
Denewet[31]	Various cancer types	Various	205	?		+/++	
Hamaker[37]	Haematological cancers	Various	108	33.6 months		+/++	12-month OS 36% vs 88%†
Kenis[12]	Various cancer types	Various	937	19 months		+/++	OS at 20 months ≈ 60% vs 90%‡
Martinez-Tapia[45]	Various cancer types	Various	1333	26.5 months		+/++	Median OS 13.1 vs 76 months
Molina-Garrido[48]	Various cancer types	Various	202	7.2 months		?/--	
Schulkes[57]	Lung cancer	Various	142	16.1 months		+/++	12-month OS 46% vs 79%
Soubeyran[11]	Various cancer types	Various	1167	12.4 months		+/++	

* 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 = overal survival; PFS = progression-free survival; RT = radiotherapy; TT = targeted therapy.

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/mdu210
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'Ardia 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, Higuet 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 impair-

ments 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 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-Poitrine 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 fraility 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-Poitrine 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.cllc.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. 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-Ottowa Scale.

Selection	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
Outcome	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* Health care utilisation: 30 days Physical functioning/quality of life: 3 months	+ yes - no ? not mentioned
	3. Adequacy of follow-up of cohorts†	+ 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
† 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[19]	+	+	+	+	?	?
Aparicio[20]	+	+	+	+	+	+
Aydin[21]	+	+	+	+	?	?
Baitar[22,23]	+	+	+	+	+	+
Bellera[9]	+	+	+	+	+	+
Bellera[27]	+	+	+	+	+	-
Bonomo[24]	+	+	+	+	+	?
Bononi[25]	+	+	+	+	?	?
Boulahssass[26]	+	+	+	+	+	+
Cvetkovic[28]	+	+	+	+	?	?
Decoster[29]	+	+	+	+	+	-
Decoster[30]	+	+	+	+	?	?
Denewet[31]	+	+	+	+	+	?
Dimopoulos[32]	+	+	+	+	?	?
Dubruille[34]	+	+	+	+	+	+
Dubruille[33]	+	+	+	+	+	?
Fagard[35]	+	+	+	+	+	+
Gangopadhyay[36]	+	+	+	+	?	?
Hamaker[37]	+	+	+	+	+	?
Hentschel[38]	+	-	+	+	+	+
Holmes[39]	+	+	+	+	+	+
Kaibori[40]	+	+	+	+	+	+
Kenig[41]	+	+	+	+	+	+
Kenis[12,42]	+	+	+	+	+	-
Kim[43]	+	+	+	+	+	+
Martinez-Tapia[44,45]	+	+	+	+	+	+
Matsushita[46]	+	+	+	+	+	?
Middelburg[47]	+	+	+	+	?	+
Molina-Garrido[48]	+	+	+	+	+	?
Neve[49]	+	+	+	+	?	?
Ogawa[50]	+	+	+	-	+	+
Osborne[51]	+	+	+	+	+	+
Osorio[52]	+	+	+	+	?	?
Pamoukdjian[53]	+	+	+	+	+	+
Pottel[54]	+	+	+	+	+	-

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
Pottel[55]	+	+	+	+	+	+
Runzer-Colmenares[56]	+	+	+	+	+	?
Schulkes[57]	+	+	+	+	+	?
Silvestri[58,59]	+	+	+	+	?	?
Smets[60]	+	+	+	+	+	?
Soubeyran[11,68]	+	+	+	+	+	+
Souwer[61]	+	+	+	+	+	+
Stauder[62]	+	+	+	+	?	?
Stokoe[18]	+	-	+	+	?	?
Takahashi[63]	+	+	+	+	?	+
Velghe[64]	+	+	+	+	+	+
Von Saint-George[65]	+	+	+	+	+	+
Wildiers[66]	+	+	+	+	+	+
Yokom[67]	+	+	+	+	+	+

CHAPTER
5

The G8 frailty screening tool and the decision-making process in older breast cancer patients

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ABSTRACT

Objective

To assess the decision-making process in fit and frail older breast cancer patients.

Methods

Breast cancer patients aged ≥70 years who completed the G8 frailty screening tool (G8) were included in this retrospective study. Socio-demographic and clinical characteristics were collected, as well as information from geriatric assessment (GA). Treatment decisions were compared to national guidelines.

Results

Of 177 patients, 85 patients were considered fit by the G8 (G8-fit) and 92 patients frail (G8-frail). All G8-fit and 53 G8-frail were proposed for surgery. GA was performed in 34 patients (9 G8-fit; 25 G8-frail) of whom 16 (2 G8-fit; 14 G8-frail) were considered frail (GA-frail). 28 out of these 34 patients were considered fit for surgery (including 11 GA-frail); their impairments were unlikely to interfere with surgery or life expectancy. Reasons for adjusting treatment were physical/cognitive condition and patient preference. Ultimately, 123 patients underwent surgery in accordance with guidelines (81 G8-fit; 42 G8-frail, $p<0.001$). Survival was reduced in G8-frail compared to G8-fit ($p=0.001$), but G8 lost its association with mortality in multivariable survival analysis. Among patients undergoing surgery, no difference in mortality was seen between G8-fit and G8-frail ($p=0.996$).

Conclusion

The G8 is associated with treatment decisions and did not affect survival in patients undergoing surgery. In the decision-making process, the G8 may help and estimates the need for adaptive care.

INTRODUCTION

As a result of ageing of the global population, older cancer patients are increasingly encountered in clinical oncology practice. The most frequently diagnosed form of cancer among older women worldwide is breast cancer.[1] In the Netherlands, approximately 15,000 patients are diagnosed with invasive breast cancer each year of whom 44% are aged 65 years or older at the time of diagnosis.[2]

The treatment decision-making process in older cancer patients can be challenging. Regularly, treatment guidelines are based on trials in which older patients are underrepresented.[3] The heterogeneity of the older population in terms of their comorbidities, physical and cognitive capacity and social support is an additional complicating factor. Geriatric impairments are common in this population and the accumulation of deficits across multiple organ systems leads to frailty, resulting in a decreased resistance to stressors and an increased risk of adverse health outcomes.

In accordance with guidelines, the standard treatment of primary localized breast cancer consists of surgery. However, in a majority of older breast cancer patients, tumours are hormone receptor sensitive in which case primary endocrine therapy might be an alternative.[4] During the past two decades in the Netherlands, omission of surgical treatment in older breast cancer patients increased, as well as the proportion of older patients who received primary endocrine therapy.[5,6] Although survival rates between these two treatment strategies are similar during the first years after diagnosis,[5] the harms and benefits of each treatment strategy should be evaluated before making a treatment decision.

In order to support the treatment decision-making process in older cancer patients, the geriatric 8 (G8) was introduced.[7,8] This frailty screening tool consists of eight items concerning multiple geriatric domains, including nutritional status, physical capacity, mood and polypharmacy. Scores range from 0 to 17, with scores ≤ 14 representing potential frailty. The G8 screening tool has been studied in a range of cancer types and is increasingly being used in cancer care and research. It is a useful diagnostic tool to identify older cancer patients who may benefit from a geriatric assessment and has prognostic relevance for survival and treatment related complications.[9]

In 2014, the Diakonessenhuis in Utrecht, the Netherlands started routine screening of all older, newly diagnosed breast cancer patients with the G8 frailty screening tool as part of the standard oncologic work-up, prior to treatment decision making. The aim of this study was to assess the decision-making process in fit and frail (based on the G8 frailty screening tool) older breast cancer patients.

METHODS

Study design and population

For this analysis, newly diagnosed breast cancer patients diagnosed in Diakonessenhuis Utrecht, a teaching hospital in the Netherlands, between 2014 and 2018 were selected from the administration data. Patients aged 70 years or older were considered eligible if they were newly diagnosed with a primary localized breast cancer, and underwent G8 screening at the time of diagnosis.

Localized breast cancer was defined as a tumour smaller then 50 mm in greatest dimension (T1 or T2), either no regional lymph node metastasis or ipsilateral axillary lymph node metastasis in level I or II only or unknown regional lymph node metastasis (N0 or N1 or Nx), and no evidence of distant metastasis (M0 or Mx).

The G8 frailty screening tool was completed by an oncology nurse for all included patients as a part of routine work-up. Generally, this tool was administered at the first visit to the outpatient clinic. Patients with a G8 score between 14.5-17 were considered fit and ≤14 as frail (Appendix).The score was included in the clinical data that was presented and discussed at the multidisciplinary tumour board meeting. A referral to the geriatrician for a geriatric assessment was only made if considered necessary by the treating physician or multidisciplinary team, irrespective of G8 score.

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.

Data collection

Patient, tumour and treatment characteristics were collected for all selected patients. For patient characteristics, this included: sex, age at time of diagnosis, WHO performance status and prior medical history (assessed by using Charlson Comorbidity Index (CCI)). Tumour characteristics included tumour type (ductal, lobular, other), TNM classification (AJCC 7th edition), Bloom-Richardson stage (BR), angio-invasion, hormone receptor status (oestrogen and progesteron) and human epidermal growth factor receptor 2 (HER2) status. Subsequently, the results of the G8 frailty screening tool were collected, as well as the initial treatment recommendations of the tumour board meetings.

If patients were referred to a geriatrician for a geriatric assessment, data on the reason for referral, the outcome of the evaluation (including patient's health status on the physical, psychological, functional and social domains) and treatment recommendations were collected from the medical records. Patients were considered frail if the geriatrician found two or more geriatric domains to be impaired or if at least one domain had severe impairment. For these patients, any changes in treatment plan based on the geriatric consultation were noted.

Final treatment decisions were compared with the national breast cancer guideline. At the

time of inclusion of patients, the guideline recommended surgical treatment for all older patients with early stage breast cancer, followed by radiotherapy if criteria were met. If tumours were hormone sensitive, hormonal therapy was recommended; and, in tumours with HER2-overexpression, adjuvant therapy with trastuzumab is only recommended in combination with chemotherapy. However, chemotherapy was only recommended if patients were younger than 70 years old.[10] Reasons to deviate from guideline-recommended treatment were collected from the clinical notes by one author (ES) and classified as physical/cognitive condition, patient preference or good response to neoadjuvant endocrine therapy. Data on survival were collected from the municipal database.

Outcome measures

Primary outcome was the proportion of fit and frail patients (based on the G8 frailty screening tool) treated in accordance with the national breast cancer treatment guideline. Secondary objectives included change of treatment plan after geriatric consultation and overall survival in fit and frail patients classified by treatment plan.

Statistical analysis

All analyses were performed in IBM SPSS Statistics 23. Clinical characteristics as well as treatment plans were presented as medians (range) or frequencies and proportions. For comparisons between fit and frail patients, a Pearson's chi-square test was used. To assess overall survival, Kaplan Meier method was used. Cox regression analysis was conducted to assess which characteristics were associated with survival, and included age, tumour stage, comorbidity as determined with the CCI and frailty based on G8. All variables were added into the regression analysis at once. P-values smaller than 0.05 were considered statistically significant.

RESULTS

Patients and tumour characteristics

Between 2014 and 2018, the G8 frailty screening tool was completed in 252 breast cancer patients. After exclusion of 35 patients with recurrent disease and 40 with locally advanced or metastatic breast cancer, 177 patients were included in this study (Figure 1). 98% of the patients were female with a median age of 79.6 years (range 70-96). In most patients the WHO performance status was not recorded. The majority had a tumour smaller than 2 cm (T1, 61%) and no lymph node involvement (N0, 68%). Further patients and tumour characteristics are detailed in Table 1.

G8 frailty screening tool and initial treatment proposal

Based on the G8 frailty screening tool, 85 patients (48%) were identified as fit and 92 (52%) as frail (Figure 1). The median G8 score for G8-fit patients was 15 (range 14.5-17), and for G8-frail patients 11.7 (range 4-14). G8-frail patients were significantly older than G8-fit patients ($p<0.001$) and had significantly more comorbidities ($p<0.001$). In addition, G8-frail

patients significantly more often had T2 disease (48% vs. 29%; p=0.012). No differences in hormone receptor status were seen (oestrogen positive 94% in G8-frail patients vs. 87% in G8-fit patients). Probably due to less surgical treatment among G8-frail patients, other tumour characteristics such as lymph node stage, BR grade and angio-invasion were more often unknown in G8-frail patients compared to G8-fit patients (Table 1).

All G8-fit patients were proposed for surgical treatment at the multidisciplinary tumour board. Of the 92 G8-frail patients, 53 (57%) were proposed for surgical treatment. In the remaining 39 patients, primary endocrine therapy was recommended, provided that patients had a hormone sensitive tumour (Figure 2).

Table 1. Baseline characteristics.

	All patients (n=177)	G8-fit (n=85)	G8-frail (n= 92)	P-value
Sex				1.0
Female	173 (98%)	83 (98%)	90 (98%)	
Male	4 (2%)	2 (2%)	2 (2%)	
Age at diagnosis (median, range)	79.6 (70.4-96.7)	76.9 (70.4-92.3)	84.2 (71.1-96.7)	< 0.001
CCI score (median, range)	1 (0-7)	0 (0-4)	1 (0-7)	< 0.001
Type of cancer				0.63
Ductal	148 (84%)	73 (86%)	75 (82%)	
Lobular	20 (11%)	11 (13%)	9 (10%)	
Other	9 (5%)	1 (1%)	8 (9%)	
T stage				0.012
T1	108 (61%)	60 (71%)	48 (52%)	
T2	69 (39%)	25 (29%)	44 (48%)	
N stage				0.15
N0	120 (68%)	59 (69%)	61 (66%)	
N1	35 (20%)	22 (26%)	13 (14%)	
Nx	22 (12%)	4 (5%)	17 (20%)	
Angio-invasion				1.0
Yes	6 (3%)	4 (5%)	2 (2%)	
No	109 (62%)	72 (85%)	37 (40%)	
Unknown	62 (35%)	9 (10%)	53 (58%)	
Hormone receptors				
Oestrogen				0.22
Positive	160 (90%)	74 (87%)	86 (94%)	
Negative	16 (9%)	10 (12%)	6 (6%)	
Unknown	1 (1%)	1 (1%)	0 (0%)	
Progesterone				0.46
Positive	123 (69%)	57 (67%)	66 (72%)	
Negative	53 (30%)	27 (32%)	26 (28%)	
Unknown	1 (1%)	1 (1%)	0 (0%)	
HER2 status				0.80
Positive	20 (11%)	9 (11%)	11 (12%)	
Negative	156 (88%)	75 (88%)	81 (88%)	
Unknown	1 (1%)	1 (1%)	0 (0%)	
BR§ grade				0.80
1	29 (16%)	19 (22%)	10 (11%)	
2	57 (32%)	41 (48%)	16 (17%)	
3	24 (14%)	16 (19%)	8 (9%)	
Unknown	67 (38%)	9 (11%)	58 (63%)	

§BR, Bloom-Richardson

Geriatric assessment

A geriatric assessment was performed in 34 patients; this included nine out of the 85 G8-fit patients (11%) and 25 of the 92 G8-frail patients (27%). Reasons for referral were often unknown but included age, comorbidity, evaluating vulnerability, evaluating cognitive and physical capacity and difficulties in the decision-making process. Geriatric assessment showed two or more impairments (GA-frail) in 47% of referrals (n=16, including 2 out of 9 G8-fit patients (22%), and 14 out of 25 G8-frail patients (56%)) (Figure 1). Most commonly diagnosed impairments were instrumental Activities of Daily Living (iADL) and physical functioning.

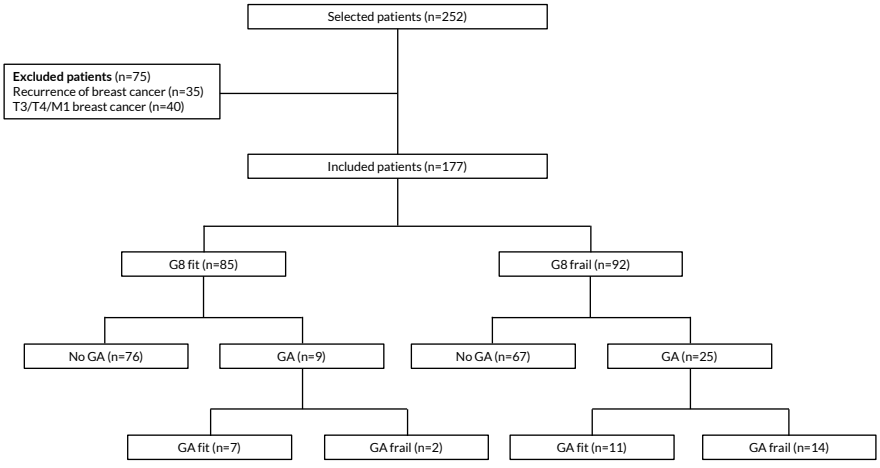

Figure 1. Patient selection and classification based on G8 screening tool. GA, geriatric assessment.

Treatment recommendations after geriatric assessment were surgical treatment for all nine G8-fit patients, including the two GA-frail patients, and for 19 out of 25 G8-frail patients (including nine GA-frail patients). For GA-frail patients recommended for surgical treatment, the primary reason for this recommendation was that the geriatric impairments were unlikely to interfere with surgery or did not significantly limit the patient's remaining life expectancy. Reasons for not recommending surgery were cognitive and/or physical condition.

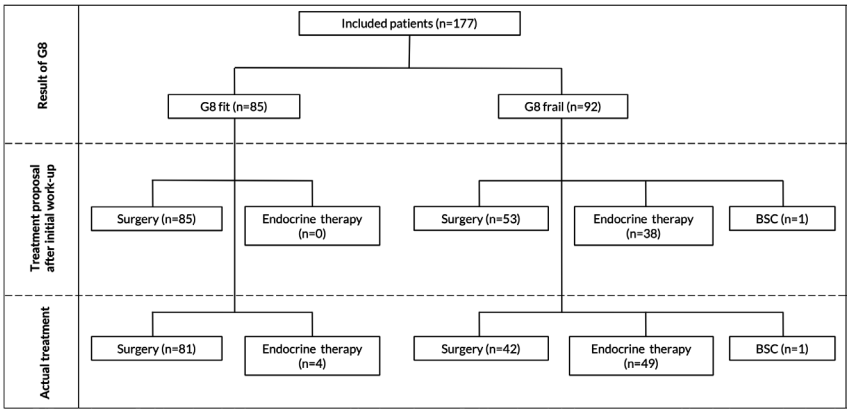

Figure 2. Results of G8, treatment proposal after initial work-up and actual treatment.

Final treatment plan and treatment adjustments

Ultimately, 123 patients (70%) underwent surgery in accordance with treatment guidelines; this was 81 out of 85 G8-fit (95%) and 42 out of 92 G8-frail patients (46%, p<0.001). One G8-frail patient received best supportive care only because of negative hormonal status and cognitive dysfunction. The remaining 53 patients (30%) received endocrine therapy of whom 44 patients received definitive endocrine therapy. Reasons to deviate from treatment guidelines were mostly physical/cognitive condition (n=17), patient preference (n=23; mainly based on shared decision making (n=21)). Nine patients received neoadjuvant endocrine therapy and showed tumour regression; therefore no surgical treatment was performed (Table 2). Of all patients, five G8-fit patients and one G8-frail patient received adjuvant chemotherapy. In a subgroup analysis of all G8-frail patients, the median G8 score was significantly higher in patients who received surgical treatment than patients who received non-standard treatment (median score of G8 13.5 (9.5-14) vs 10.6 (4-14); p<0.001).

Table 2. Treatment plan according to guidelines and treatment adjustments.

	Total (n =177)		G8-fit (n=85)		G8-frail (n=92)		P-value
Treatment plan according to guidelines							<0.001
Yes	109	(62%)	75	(88%)	34	(37%)	
No	68	(38%)	10	(12%)	58	(63%)	
No surgery	54	(30%)	4	(5%)	50	(54%)	
No or adjusted adjuvant therapy	14	(8 %)	6	(7%)	8	(9%)	
No surgery	54		4		50		0.371
Physical/cognitive condition	18	(33%)	-		18	(36%)	
Patient preference	23	(43%)	3	(75%)	20	(40%)	
Good response to neo-adjuvant endocrine therapy	9	(17%)	1	(25%)	8	(16%)	
Other	4	(7%)	-		4	(8%)	

Overall survival

One year follow-up was available for 168 out of 177 patients (95%) and three year follow-up for 156 patients (88%). One year after diagnosis, all 85 G8-fit patients (100%) and 83 out of 92 G8-frail patients (90%) were still alive (p=0.003). After three years, G8-fit patients had a reduced mortality compared to G8-frail patients (Figure 3A, 4.7% vs 18.5% p=0.001). In a multivariable analysis, increasing age (HR 3.53 95%CI 1.22-10.27) and increasing comorbidity burden (HR 2.72 95%CI 1.12-6.60) were the only factors associated with mortality, while tumour characteristics and G8 frailty status were not. In a subgroup analysis of patients undergoing surgery, G8-frailty status did not affect overall survival (Figure 3B, 4.9% vs 4.8% p=0.996). Among patients with a triple negative tumour (n=16), who were not suitable for systemic therapy, 15 patients received surgical treatment of whom 14 (93%) were still alive after three years (including 10 G8-fit and 4 G8-frail patients). Of all patients without surgical treatment (n=54), 16 patients died during three year follow up (all G8-frail patients).

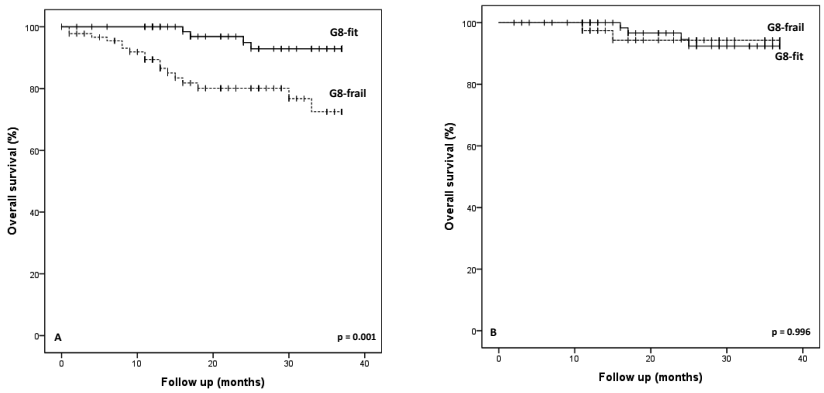

Figure 3. Three years overall survival based on G8 frailty screening tool. (A) Prognosis of all patients; (B) Prognosis in patients undergoing surgery.

DISCUSSION

This study assessed the treatment decision-making process in older patients with primary localized breast cancer and found that frailty, identified by G8 frailty screening tool, was associated with treatment decisions. All G8-fit patients and almost half of G8-frail patients were considered fit enough for surgical treatment and within three-year follow up, G8 frailty status did not affect overall survival in the group of patients undergoing surgery. Reasons for choosing primary endocrine therapy were mainly physical/cognitive condition and patient preference.

This analysis provides insight in the decision-making process in older breast cancer patients in our hospital. Although the G8 frailty screening tool is commonly used in oncology for identifying frailty,[9] this tool has scarcely been assessed in older breast cancer patients.[11,12] In particular, to the best of our knowledge, no prior studies have assessed the association between G8 frailty screening tool and the treatment decision-making process in older patients with primary localized breast cancer. Hence, these results can be of added value in clinical oncology practice.

This study has some limitations. Data on complications of surgical treatment, disease progression, recurrence of breast cancer and cause of death could not be completely retrieved, and therefore it is not possible to obtain a full picture of the course of treatment and disease for all patients. Another drawback includes the restricted knowledge of the exact role the G8 frailty screening tool played in the decision-making process. At that time, there was a particular need to identify frail patients, but a geriatric assessment for each patient was not yet feasible. Therefore, the G8 was introduced to detect potentially frail patients; but when G8 score was 14 or lower, patients were not automatically referred for further geriatric evaluation. And unfortunately, both in the multidisciplinary tumour board or outpatient clinic, it was not recorded if and how the G8 frailty status was taken into account

while making a treatment decision. Furthermore, this study is performed in a hospital where geriatric oncology is well embedded, with surgeons and oncologists who are well aware of the relevance of frailty in treatment decisions. Even though implementation of geriatric oncology is getting more attention across the globe, it still varies among different hospitals.[13–16] The results of this study therefore cannot simply be extrapolated to breast cancer patients in health care settings that are less geriatric oncology-minded.

The lack of association between G8 frailty status and mortality in the multivariable survival analysis might be explained by the fact that G8-frail patients had a higher CCI score and were older than G8-fit patients. Furthermore, this lack of association does not mean that considering a patient's frailty status in the treatment decision making process is not relevant. Frail older patients have less physiological reserve and are less resilient than fit older patients, making them more vulnerable to negative health outcomes.[17] The diagnosis of cancer and its treatment can negatively influence a patient's health status,[18] especially if they are frail, and this may result in a decline in physical functioning and/or quality of life.[19,20] At the same time, maintaining physical functioning and quality of life is at least as important as survival for most older patients.[21,22] Therefore, screening of frailty could provide awareness of frailty in the treatment decision making process and could, just like age and comorbidity, contribute to the actual treatment decision. In addition, frailty should be viewed within the context of the patient's priorities, the index disease and treatment options and has to be considered as a spectrum.[23,24] Thus, frailty identified by G8 frailty screening tool does not necessarily imply that older patients with early stage breast cancer are not suited for surgical treatment. Even if patients were assessed as frail after geriatric assessment, they were still frequently recommended for surgical treatment because of their estimated remaining life expectancy, especially when G8 score was 10 or higher. This appears to be an interesting cut-off value for future evaluation. Still, each time, the level of frailty and patient preferences must be carefully weighed against the efficacy and safety of a treatment. Hence, the G8 is not a simple 'go/no go tool' but rather should be an entry point for considering adaptive care, incorporating various disease and patient specific characteristics and preferences.

In some situations, omission of all breast cancer treatment may be the best option: for instance, in patients who are in the terminal phase of a comorbid illness, for whom the likely remaining life expectancy is so limited that the breast cancer itself becomes irrelevant. However, estimating life expectancy can be difficult, particularly in frail older patients who can remain in a state of poor physical or cognitive functioning for long time periods, even years.[25] Therefore, in most cases some kind of cancer treatment will be generally indicated. In accordance with the treatment guidelines, surgical treatment is still the cornerstone in older patients with primary localized breast cancer.[4] However, in a majority of older breast cancer patients, tumours are hormone receptor sensitive in which case primary endocrine therapy might be an alternative, provided that the estimated remaining life expectancy does not exceed the time period during which primary endocrine therapy can be expected to result in local regional tumour control.[4]

In order to detect competing causes of death, a mortality index such as the Lee index, can be used to predict four- and ten-year all-cause mortality using age, comorbidities and physical functioning measures.[26] To estimate the breast cancer specific mortality and assess the prognosis after surgical treatment and/or adjuvant therapy, the online PREDICT tool can be used.[27] This tool is recently validated in older breast cancer patients and can accurately predict five-year overall survival. However, it should still be considered that this tool does not incorporate patient characteristics such as comorbidities or functional status; in frail older patients, overall survival can be overestimated.[28,29] Hence, in patients with a high likelihood of surviving for longer than four years, the risk of failure of primary endocrine therapy with subsequent need of surgery at some point in their remaining life span becomes significant.[26,30] In this case, it might be preferable to perform the surgery up front, rather than wait a few years in which the patient will not only become older but also might incur more comorbid diseases.

Another important step in the decision making process is to assess the harms and benefits of surgical treatment versus primary endocrine therapy. Breast cancer surgery is classified as a low morbidity and low mortality procedure;[31] the risk of postoperative cognitive decline due to general anaesthesia with this kind of surgery is small.[32,33] Although these risks of surgical treatment often increase with age and comorbidities, the mortality risk in older breast cancer patients is mainly due to frailty rather than postoperative complications.[34]

With primary endocrine therapy, using multiple lines of treatment, evidence exists for disease control during an average of two to three years, although with a significant interindividual range.[30] At the same time, the impact of primary endocrine therapy should not be underestimated. It is a long-term treatment that requires adherence, which can be accompanied by adverse events.[35] Hospital visits are necessary to evaluate the effectiveness of endocrine therapy and for timely recognition of disease progression. All these aspects are associated with non-adherence[36,37] and might burden patient and their caregivers.[38] Furthermore, knowing that there is a risk of tumour grow without surgical treatment, might lead to distress in some patients. Especially in older patients, distress may interfere with their ability to cope effectively with cancer.[36]

In conclusion, the G8 frailty screening tool is associated with treatment choice in older patients with primary localized breast cancer; and G8 frailty status did not affect overall survival in the group of patients undergoing surgery. Therefore, the G8 may help in the treatment decision-making process and estimating the need for adaptive care. Still, depending on the frailty expertise within the breast cancer multidisciplinary team, G8-frail patients might warrant a referral to a geriatrician for further examination.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;(68):394–424.
2. Kankerregistratie N. Cijfers over kanker [Internet]. [cited 2019 Oct 2]. Available from: https://www.cijfersoverkanker.nl/
3. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: Known problem, little progress. J Clin Oncol. 2012;30(17):2036–8.
4. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: Updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13:148–60.
5. De Glas NA, Jonker JM, Bastiaannet E, De Craen AJM, Van De Velde CJH, Siesling S, et al. Impact of omission of surgery on survival of older patients with breast cancer. Br J Surg. 2014;101(11):1397–404.
6. Van De Water W, Bastiaannet E, Dekkers OM, De Craen AJM, Westendorp RGJ, Voogd AC, et al. Adherence to treatment guidelines and survival in patients with early-stage breast cancer by age at diagnosis. Br J Surg. 2012;(99):813–20.
7. 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):2166-2172.
8. 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.
9. 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;10(6):847–58.
10. Nederland I kankercentrum. Breast Cancer Dutch-Guideline Oncoline [Internet]. 2012. version 2. Available from: https://www.oncoline.nl/uploaded/docs/mammacarcinoom/Dutch Breast Cancer Guideline 2012.pdf
11. Dottorini L, Catena L, Sarno I, Di Menna G, Marte A, Novelli E, et al. The role of Geriatric screening tool (G8) in predicting side effect in older patients during therapy with aromatase inhibitor. Journal of Geriatric Oncology. 2019;10(2):356-358.
12. Osorio F, Urbano J, Barradas AR, Magalhaes A. Value of geriatric screening tools in the prediction of undertreatment in older patients with breast cancer. Eur J Cancer. 2016;57:S146–7.
13. Ghignone F, Van Leeuwen BL, Montroni I, Huisman MG, Somasundar P, Cheung KL, et al. The assessment and management of older cancer patients: A SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol. 2016;(42):297–302.
14. Baitar A, Kenis C, Moor R, Decoster L, Luce S, Bron D, et al. Implementation of geriatric assessment-based recommendations in older patients with cancer: A multicentre prospective study. J Geriatr Oncol. 2015;6(5):401–10.
15. Kenis C, Heeren P, Decoster L, Van Puyvelde K, Conings G, Cornelis F, et al. A Belgian survey on geriatric assessment in oncology focusing on large-scale implementation and related barriers and facilitators. J Nutr Heal Aging. 2016;20(1):60–70.
16. Jonker JM, Smorenburg CH, Schiphorst AH, van Rixtel B, Portielje JEA, Hamaker ME. Geriatric oncology in the Netherlands: A survey of medical oncology specialists and oncology nursing specialists. Eur J Cancer Care (Engl). 2014;23(6):803–10.
17. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older Adults: Evidence for a Phenotype. Journals Gerontol Ser A Biol Sci Med Sci. 2001;56A(3):146–56.
18. Huisingh-Scheetz M, Walston J. How should older adults with cancer be evaluated for frailty? J Geriatr Oncol. 2017;8:8–15.
19. Williams GR, Deal AM, Sanoff HK, Nyrop KA, Guerard EJ, Pergolotti M, et al. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer. 2019;27:2693–8.
20. Sehl M, Lu X, Silliman R, Ganz PA. Decline in physical functioning in first 2 years after breast cancer diagnosis predicts 10-year survival in older women. J Cancer Surviv. 2013;7(1):20–31.
21. Van Leeuwen KM, Van Loon MS, Van Nes FA, Bosmans JE, De Veti HCW, Ket JCF, et al. What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):1–39.
22. Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. J Natl Cancer

Inst. 1994;(86):1766–70.
23. Lang PO, Michel JP, Zekry D. Frailty syndrome: A transitional state in a dynamic process. Gerontology. 2009;55(5):539–49.
24. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. Nurs Outlook. 2010;58(2):76–86.
25. Thomas R, Pieri A, Cain H. A systematic review of generic and breast cancer specific life expectancy models in the elderly. Eur J Surg Oncol. 2017;(43):1816–27.
26. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. J Am Med Assoc. 2006;295(7):801–8.
27. Predict 2.1 [Internet]. [cited 2019 Dec 9]. Available from: https://breast.predict.nhs.uk/tool
28. De Glas NA, Bastiaannet E, Engels CC, De Craen AJM, Putter H, Van De Velde CJH, et al. Validity of the online PREDICT tool in older patients with breast cancer: A population-based study. Br J Cancer. 2016;114:395–400.
29. Candido dos Reis FJ, Wishart GC, Dicks EM, Greenberg D, Rashbass J, Schmidt MK, et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. Breast Cancer Res. 2017;19(58):1–3.
30. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. Br J Cancer. 2007;(96):1025–9.
31. Vitug AF, Newman LA. Complications in Breast Surgery. Surg Clin North Am. 2007;(87):431–51.
32. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet. 1998;(351):857-6.
33. Paredes S, Cortínez L, Contreras V, Silbert B. Post-operative cognitive dysfunction at 3 months in adults after non-cardiac surgery: a qualitative systematic review. Acta Anaesthesiol Scand. 2016;60(8):1043–58.
34. De Glas NA, Kiderlen M, Bastiaannet E, De Craen AJM, Portielje JEA, Liefers GJ. Chirurgische complicaties bij ouderen met borstkanker. Ned Tijdschr Geneeskd. 2013;157(38):A6525.
35. van de Water W, Bastiaannet E, Hille ETM, Meershoek-Klein Kranenbarg EM, Putter H, Seynaeve CM, et al. Age-Specific Nonpersistence of Endocrine Therapy in Postmenopausal Patients Diagnosed with Hormone Receptor-Positive Breast Cancer: A TEAM Study Analysis. Oncologist. 2012;(17):55–63.
36. Holland JC, Andersen B, Breitbart WS, Buchmann LO, Compas B, Deshields TL, et al. Distress Management: Clinical practice guidelines in oncology. JNCCN J Natl Compr Cancer Netw. 2013;11(2):190–207.
37. Lee SY, Seo JH. Current Strategies of Endocrine Therapy in Elderly Patients with Breast Cancer. Biomed Res Int. 2018; 6074808.
38. Jayani R, Hurria A. Caregivers of Older Adults With Cancer. Semin Oncol Nurs. 2012;28(4):221–5.

Appendix. G8 screening tool.

	G8 items	Possible answers (score)
1	Food intake *(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 *(Weight loss during the last 3 months)*	0: weight loss > 3kg 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 or depression 2: no psychological problems
5	Body Mass Index (kg/m^2)	0: BMI <19 1: BMI=19 to BMI <21 2: BMI=21 to BMI <23 3: BMI=23 and >23
6	Medication *(Takes more than 3 prescription drugs per day)*	0: yes 1: no
7	Health status *(In comparison to other people of the same age, how does the patient consider his/her health status)*	0: not as good 0,5: does not know 1: as good 2: better
8	Age (years)	0: >85 1: 80-85 2: <80
	Total score	0-17

Scores ≤ 14: potentially frail.

PART II

DECISION MAKING AND PATIENT RELATED OUTCOMES IN OLDER PATIENS WITH CANCER

CHAPTER
6

Treatment patterns and primary reasons for adjusted treatment in older and younger patients with stage II or III colorectal cancer

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ABSTRACT

Objective

This study aims to assess age-related treatment patterns and primary reasons for adjusted treatment in patients with colorectal cancer.

Methods

Patients with colorectal cancer stage II or III diagnosed between 2015 and 2018 in the Netherlands were eligible for this study. Data were provided by the Netherlands Cancer Registry and included socio-demographics, clinical characteristics, treatment patterns and primary reasons for adjusted treatment. Treatment patterns and reasons for adjusted treatment were analysed according to age groups.

Results

Of all 29,620 patients, 30% were aged <65 years (n=8,994), 34% between 65 and 75 years (n=10,173), 27% between 75 and 85 years (n=8,102) and 8% were ≥85 years (n=2,349). Irrespective of cancer location or stage, older patients received less frequently a combination of surgery and (neo)adjuvant therapy compared to younger patients (decreasing from 55% to 1% in colon cancer patients, and from 71% to 23% in rectal cancer patients aged <65 years and ≥85 years respectively). Omission of surgical treatment increased with age in both patients with colon cancer(ranging from 1% in patients aged <65 years to 16% in those ≥85 years) and rectal cancer (ranging from 12% in patients aged <65 years to 56% in those ≥85 years). The most common reasons for adjusted treatment were patient preference (27%) and functional status (20%), both reasons increased with advancing age.

Conclusion

Guideline non-adherence increased with advancing age and omission of standard treatment was mainly based on patient preference and functional status. These findings provides insight in the treatment decision-making process in patients with colorectal cancer. Future research is necessary to further assess patient's role in the treatment decision-making process.

INTRODUCTION

Colorectal cancer predominantly occurs in older patients. At diagnosis, the median age is 69 years and more than 30% of all patients are older than 75 years.[1,2] In 2018 in the Netherlands, more than 14,000 patients were diagnosed with colorectal cancer and due to the ageing of the population, the incidence of colorectal cancer worldwide is expected to rise over the coming decades.[1,2] According to the guidelines, colorectal cancer treatment mainly consists of surgical treatment, with additional (neo)adjuvant chemo(radio)therapy in case of higher recurrence risk. The choice of treatment depends on tumour characteristics, estimated life expectancy, patient's ability to tolerate cancer treatment and patient preferences.[3]

Older patients represent a heterogeneous population with large differences in physical and cognitive capacity and the presence of comorbidities. As a consequence, especially when older patients are frail, there is a higher risk for adverse events, complications, readmissions and treatment-related mortality.[4] Therefore, older patients with cancer are not always treated in accordance with guidelines. In the Netherlands, the proportion of patients with colorectal cancer treated in accordance with national guidelines varied between 53% and 90%;[5–10] and this proportion seems comparable with other countries.[11-21] Furthermore, guideline non-adherence increases with advancing age and this mainly concerns omission of adjuvant chemotherapy in colon cancer and (neo)adjuvant therapy in rectal cancer.[8-13;15-31]

An important question is whether treatment adjustments are justifiable adaptations based on the patient's health status or personal preferences, or perhaps should be considered as undertreatment. Many factors may influence the decision to withhold standard cancer treatment and the treatment decision can be based on patient-, tumour- or treatment-related characteristics.[32] Although little evidence is available in patients with colorectal cancer, previous studies demonstrated that older age and multiple comorbidities were the main reasons for omission of (neo)adjuvant therapy; a perceived minimal benefit or patient preference was less frequently mentioned.[10,25,26,28,33,34]

More research seems necessary to assess age-related differences in treatment patterns and improve insight in the treatment decision-making process. In 2015, the Dutch Cancer Institute began registering the primary reasons for treatment decisions in the National Cancer Registry. Based on these data, we conducted a nationwide population-based analysis to compare treatment patterns according to age and reasons for adjusted treatment in patients with stage II or III colorectal cancer.

METHODS

Patient selection

In the Netherlands, data on socio-demographic and clinical characteristics of patients with newly diagnosed malignancies are collected by the Netherlands Cancer Registry (NCR). The

NCR covers more than 95% of the Dutch population.[1,2] Patients are identified through the nationwide automated pathology archive and the hospital discharge register. Specially trained administrators collect patient, tumour and treatment characteristics from the patient's hospital files. In 2015, the NCR started registering the reasons for adjusting treatment and the degree of completion of planned oncological treatment.[1] For this analysis, all patients newly diagnosed patients with TNM stage II and III colorectal cancer between 2015 and 2018 were extracted from the NCR database. Patients were excluded if additional colorectal pathology was suspected based on available tumour- and treatment characteristics, for example patients who received a (sub)total (procto)colectomy.

Data collection

Socio-demographic and clinical characteristics were collected from the registry data. These included age at diagnosis, socio-economic status and comorbidities. Socio-economic status was based on 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.[35] Comorbidities were classified according to the Charlson Comorbidity Index (CCI); however, data on comorbidities were not collected in all regions of the Netherlands.[36] Tumour characteristics included cancer type, disease stage and morphology. Rectosigmoid tumours were classified as colon cancer or rectal cancer based on their primary treatment decision. Those who received sigmoidresection or hemicolectomy and adjuvant chemotherapy if indicated were classified as colon cancer. Those who received low anterior resection or abdominoperineal resection and neo-adjuvant therapy if indicated, were classified as rectal cancer. For colon cancer, disease stage was based on pathological disease stage information, supplemented by clinical stage information if pathological stage was unavailable or unknown. For rectal cancer, as patients may receive neo-adjuvant therapy, disease stage was based on clinical disease stage information. Use of the multidisciplinary tumour board and reported initial treatment were collected. Reported initial treatment was classified as surgery only, surgery with (neo)adjuvant therapy, (chemo)radiotherapy only, or best supportive care. For patients receiving chemotherapy, type of chemotherapy was extracted.

Treatment patterns were compared with the national colorectal cancer guideline.[37] For patients with colon cancer, this guideline recommends surgical treatment for stage II or surgical treatment with adjuvant chemotherapy for stage III disease. Adjuvant chemotherapy may also be considered for patients with a high risk stage II colon carcinoma. Surgical treatment is also recommended for patients with stage II or III rectal cancer, and combined with neo-adjuvant (chemo)radiotherapy if criteria are met (Appendix). Not all criteria of high risk stage II colon carcinoma or criteria for neo-adjuvant therapy in patients with rectal cancer were available in the registry data. Therefore, adherence to guidelines could not be determined for all patients. Guideline non-adherence was classified by: no primary oncological treatment, no adjuvant therapy, no/partial neo-adjuvant therapy and no surgery after neo-adjuvant therapy. For patients receiving adjusted treatment, the primary reason for this treatment choice was extracted and classified by: age, comorbidity, functional status

(such as performance status or patient's condition), patient preference, minimal expected benefit, extensive disease, protocol of the hospital (such as 'watch and wait protocol' [38] or treatment decision made at the tumour board), died before surgery, complicated course after surgery, or other/unknown.

Statistical analyses

All analyses were performed separately for colon cancer and rectal cancer. Socio-demographics and clinical characteristics were presented as means (standard deviation (SD)) for normally distributed continuous variables, medians (range) for not-normally distributed variables or frequencies and proportions for categorical variables. For comparisons between patients with colon cancer and rectal cancer, Pearson's chi-square test was used for categorical variables. Depending on the distribution of the data, the independent samples T-test or Mann Whitney U test was used for continuous variables. To describe treatment patterns and reasons for adjusted treatment, patients were divided into four age-categories: <65 years, 65–75 years, 75–85 years, and ≥85 years. For comparisons between those four groups, Pearson's chi-square test was used for categorical variables. All analyses were executed using IBM SPSS Statistics version 23.0. A two-sided-p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Between 2015 and 2018, 30,436 patients were registered with colorectal cancer stage II or III in the Netherlands. Based on available tumour and treatment characteristics, 816 patients were suspected of having additional colorectal pathology and excluded. Thus, 29,620 patients were eligible for this study, of whom 20,444 patients were diagnosed with colon cancer and 9,176 patients were diagnosed with rectal cancer (Figure 1).

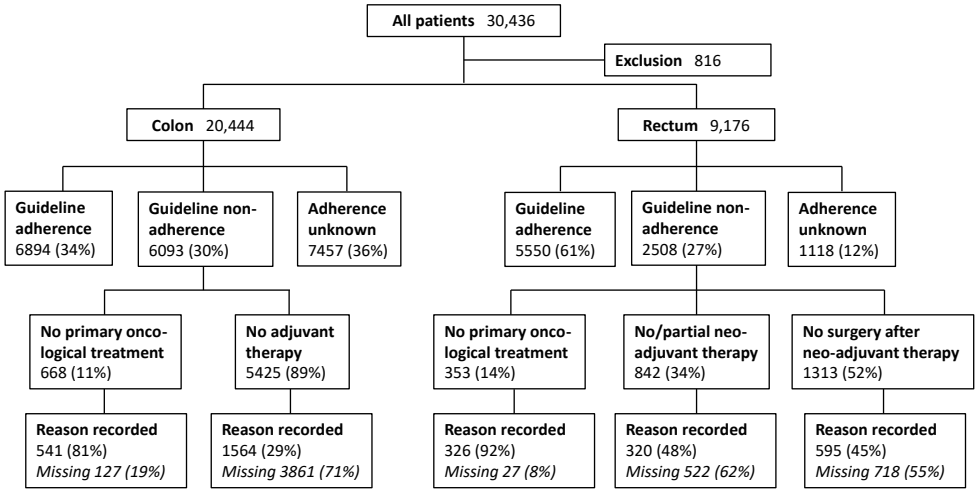

Figure 1. Treatment adherence and recorded reasons for adjusted treatment in patients with colon and rectal cancer.

Socio-demographics and clinical characteristics are summarized in Table 1. Median age at diagnosis was 71 years (interquartile range 62-78). Of these patients, 30% were aged <65 years (n=8,994), 34% between 65 and 74 years (n=10,173), 27% between 75 and 84 years(n=8,102) and 8% were ≥85 years (n= 2,349). Comorbidities were reported in 14,208 patients (48%) and most common comorbidities were diabetes mellitus (17%) and lung disease (11%). Comorbidities were more common in older patients (CCI ≥2: 7% of patients <65 versus 27% in those ≥85 years; p<0.001). For both cancer locations, stage II disease was more common in older patients (ranging from 37% in patients aged <65 to 54% in patients aged ≥85 years; p<0.001), whereas stage III disease was mainly diagnosed in younger patients (ranging from 64% in patients aged <65 years to 46% in patients aged ≥85 years; p<0.001). The likelihood of being discussed at the tumour board decreased with advancing age (79% of patients aged <65 versus 71% of patients aged ≥85 years, p<0.001).

Table 1. Socio-demographic and clinical characteristics of all patients.

	All patients (n= 29,620)		Colon cancer (n=20,444)		Rectal cancer (n=9,176)		P-value
Sex							<0.001
Men	16389	(55%)	10575	(52%)	5814	(63%)	
Women	13231	(45%)	9869	(48%)	3362	(37%)	
Missing	*0*						
Age (median , IQR)	71	(62-78)	71	(63-79)	68	(60-75)	<0.001
<65	8994	(30%)	5457	(27%)	3537	(39%)	<0.001
65-75	10173	(34%)	7118	(35%)	3055	(33%)	
75-85	8102	(27%)	6067	(30%)	2037	(22%)	
≥85	2349	(8%)	1802	(9%)	547	(6%)	
Missing	*0*						
Socio economic status							0.08
Low	9362	(32%)	6514	(32%)	2848	(31%)	
Medium	12102	(41%)	8265	(40%)	3837	(42%)	
High	8155	(28%)	5664	(28%)	2491	(27%)	
Missing	*1*		*1*		*0*		
CCI							<0.001
0	7388	(52%)	4889	(50%)	2499	(55%)	
1	4392	(31%)	3067	(32%)	1325	(29%)	
≥2	2428	(17%)	1742	(18%)	686	(15%)	
Missing	*15412*		*10746*		*4666*		
Type of comorbidity							
Heart disease	1137	(8%)	831	(9%)	306	(7%)	0.001
Peripheral vascular disease	836	(6%)	626	(7%)	210	(5%)	<0.001
Cerebrovascular disease	1237	(9%)	866	(9%)	371	(8%)	0.166
Neurologic disease	157	(1%)	110	(1%)	47	(1%)	0.625

	All patients (n= 29,620)		Colon cancer (n=20,444)		Rectal cancer (n=9,176)		P-value
Lung disease	1611	(11%)	1110	(11%)	501	(11%)	0.555
Connective tissue disease	364	(3%)	268	(3%)	96	(2%)	0.026
Gastrointestinal disease	416	(3%)	306	(3%)	110	(2%)	0.018
Diabetes Mellitus	2428	(17%)	1734	(18%)	694	(15%)	<0.001
Renal disease	482	(3%)	359	(4%)	123	(3%)	0.003
Tumour	1435	(10%)	990	(10%)	445	(10%)	0.530
Missing	*15412*		*10746*		*4666*		
Tumour type							<0.001*
Adenocarcinoma	28861	(97%)	19825	(97%)	9036	(98%)	
Other	411	(1%)	347	(2%)	64	(1%)	
Unknown	348	(1%)	272	(1%)	76	(1%)	
Missing	*0*						
Disease stage at diagnosis							<0.001
II	13394	(45%)	10585	(52%)	2809	(31%)	
III	16226	(55%)	9859	(48%)	6367	(69%)	
Missing	*0*						
MDT							0.002
Yes	23464	(79%)	16096	(79%)	7368	(80%)	
No	6156	(21%)	4348	(21%)	1808	(20%)	
Missing	*0*						

* statistical analysis performed without the category unknown. CCI: Charlson Comorbidity Index; MDT: multidisciplinary tumour board. IQR: interquartile range.

Treatment patterns in patients with colon cancer according to age

Treatment patterns in the 20,444 patients with colon cancer are shown in Figure 2A. Three percent (n=668) received no primary oncological treatment (314 patients with stage II and 354 patients with stage III). Omission of surgery increased steadily with age (ranging from 1% in patients aged <65 years to 16% in those ≥85 years; p<0.001) and with increasing comorbidity burden (ranging from 1% in patients with CCI 0 to 5% in patients with CCI ≥2; p<0.001). Of the remaining 19,776 patients treated surgically, 6,894 also received adjuvant chemotherapy: 6% of patients with stage II colon cancer and 63% for stage III. The reception of adjuvant chemotherapy in patients with stage III disease decreased with age, ranging from 55% of patients aged <65 to 1% of patients aged ≥85 years (p<0.001). Although chemotherapy mainly consisted of poly-drug therapy (79% of 6,894 patients who received chemotherapy), the proportion of patients with mono-drug therapy increased with advancing age, ranging from 5% in patients aged <65 years to 92% in patients aged ≥85 years (p<0.001).

Treatment patterns in patients with rectal cancer according to age

Treatment patterns in the 9,176 rectal cancer patients are shown in Figure 2B. Eighteen

percent (n=1666) received no surgical treatment (487 patients with stage II and 1,179 patients with stage III). Again, omission of surgery increased steadily with age (ranging from 12% in patients aged <65 years to 56% in those ≥85 years; p<0.001) and with increasing comorbidity burden (ranging from 14% in patients with CCI 0 to 26% in patients with CCI ≥2; p<0.001). Neo-adjuvant therapy prior to surgery was given to 34% of patients with stage II rectal cancer and 75% in stage III. Reception of neo-adjuvant therapy decreased with increasing age, ranging from 71% of patients aged <65 years to 23% of patients aged ≥85 years (p<0.001). Of all patients with stage II disease who received neo-adjuvant therapy, neo-adjuvant therapy consisted of chemoradiotherapy in 53%; 47% received radiotherapy. For stage III disease, this was 58% and 42% respectively. Irrespective of disease stage, the proportion of patients with neo-adjuvant chemoradiotherapy decreased with age (ranging from 66% in patients aged <65 years to 13% in patients aged ≥85 years; p<0.001) whereas the proportion of patients with neo-adjuvant radiotherapy increased with age (ranging from 34% in patients aged <65 years to 87% in patients aged ≥85 years; p<0.001).

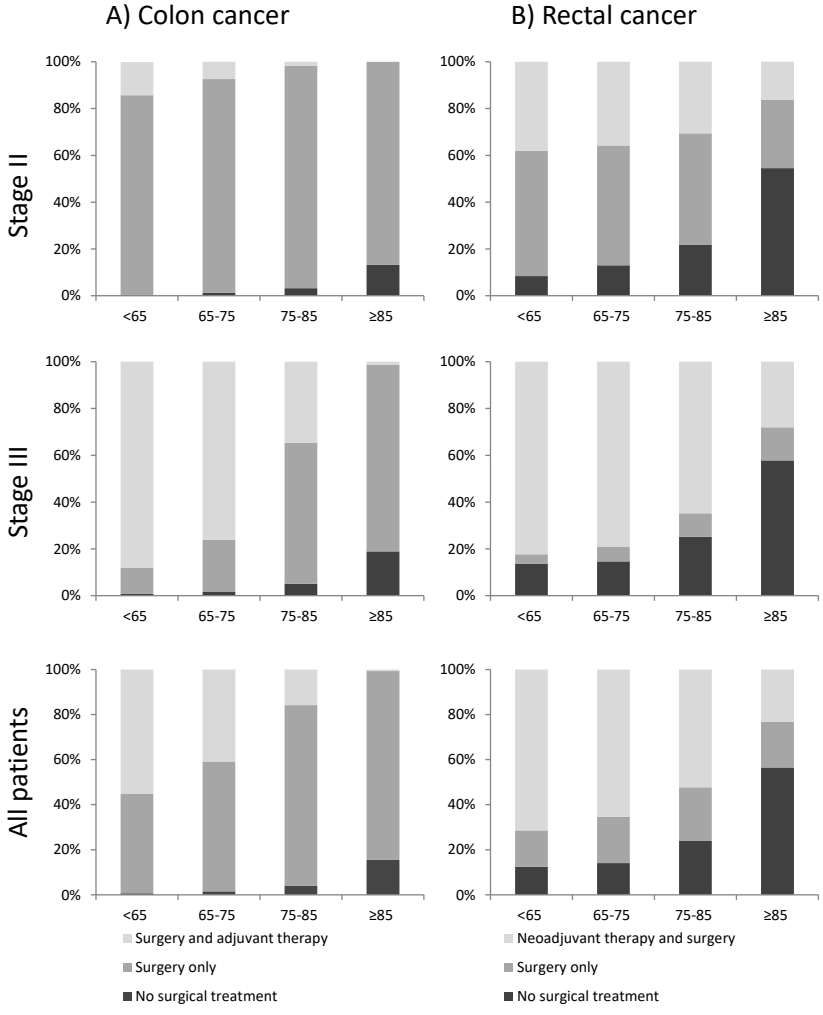

Figure 2. Type of treatment for patients with colon cancer(A) and rectal cancer(B).

Reasons for choosing adjusted treatment in both colon and rectal cancer

Based on what could be deduced from the registry data, 42% (n=12,444) of all patients were treated in accordance with the guideline and at least 29% (n=8,601) were not (Figure 1). In the remaining 29% (n=8,575), essential data were missing to determine whether or not there was an indication for additional therapy besides to surgical treatment. Guideline non-adherence increased with advancing age (ranging from 15% in patients aged <65 to 65% in patients aged ≥85 years; p<0.001) and with increasing comorbidity burden (ranging from 24% in patient with CCI 0 to 50% in patients with CCI ≥2; p<0.001).

Of the 8,601 patients receiving adjusted treatment, 1,021 patients received no primary oncological treatment whatsoever; 5,425 patients with colon cancer did not receive adjuvant therapy whilst this was required based on the guidelines, 842 patients with rectal cancer received no neo-adjuvant therapy or radiotherapy only despite guidelines recommending chemoradiotherapy, and 1,313 patients with rectal cancer did not proceed with surgery after neo-adjuvant therapy. Data on reasons for omission of treatment were available in 3,346 patients (39% of all patients receiving adjusted treatment; Figure 1).

Ultimately, reasons for omission of standard treatment were recorded in 3,346 out of 8,601 patients and are shown in Table 2. Reasons for omission of primary oncological treatment were recorded in 867 patients. The most common reported reasons were patient preference (39%) and functional status (29%) in both patients with colon and rectal cancer. Age was hardly mentioned as reason for omission of primary oncological treatment (3%).

Table 2A. Reported reasons for adjusted treatment in patients with colon cancer and rectal cancer according to adjusted treatment.

Reasons according to adjusted treatment	All patients	No primary oncological treatment	No adjuvant therapy	No/partial neo-adjuvant therapy	No surgery after neo-adjuvant therapy	P-value
N	3346	867	1564	320	595	
Age	9%	3%	15%	8%	3%	<0.001
Comorbidity	13%	16%	11%	16%	10%	
Functional status	20%	29%	18%	15%	16%	
Patient preference	27%	39%	27%	9%	20%	
Minimal expected benefit	3%	-	6%	1%	-	
Extensive disease	3%	7%	1%	1%	7%	
Protocol of the hospital	10%	-	3%	9%	41%	
Died before surgery	2%	5%	1%	-	1%	
Complicated course after surgery	1%	-	2%	-	-	
Other/unknown	12%	1%	16%	41%	2%	

For colon cancer, reasons for omission of adjuvant chemotherapy were recorded in 1,564 patients. Patient preference was most frequently mentioned (27%); this reason became less frequent with increasing age, ranging from 30% in patients aged <65 years to 8% in patients aged ≥85 years (p<0.001). In patients aged ≥85 years, age was the most commonly reported reason (50%) for omission of adjuvant chemotherapy.

For rectal cancer, reasons for omission of neo-adjuvant therapy or reduction of neo-adjuvant chemoradiotherapy to radiotherapy, were recorded in 320 patients. This adaption was mainly due to patient's comorbidity (16%) and functional status (15%). Reasons for omission of surgery after receiving neo-adjuvant therapy were recorded in 595 patients and primarily consisted of patient preference (20%) and functional status (16%), which both increased with advancing age (p<0.001). In 41% of the patients who did not receive surgery after neo-adjuvant therapy, their treatment choice was based on a watch and wait protocol of the hospital. Although not yet in accordance with the guideline, this policy has been increasingly routinely implemented over the years.

Overall, patient preference (27%) and functional status (20%) were the most commonly reported reasons for adjusted treatment, which both increased with advancing age (Table 2b). Age (9%) as reason for choosing adjusted treatment was less frequently mentioned, but increased with age, ranging from 0.2% in patients aged <65 years to 23% in patients aged ≥85 years. In 12% of the patients the reason for adjusted treatment was classified as other/unknown.

Table 2B. Reported reasons for adjusted treatment in patients with colon cancer and rectal cancer according to age.

Reasons according to age						
	All patients	<65 years	65-75 years	75-85 years	≥85 years	P-value
N	3346	468	860	1291	727	
Age	9%	-	1%	11%	23%	<0.001
Comorbidity	13%	8%	13%	16%	11%	
Functional status	20%	9%	18%	23%	23%	
Patient preference	27%	22%	27%	28%	29%	
Minimal expected benefit	3%	4%	4%	3%	-	
Extensive disease	3%	6%	3%	2%	4%	
Protocol of the hospital	10%	29%	14%	3%	1%	
Died before surgery	2%	1%	3%	2%	2%	
Complicated course after surgery	1%	1%	2%	1%	1%	
Other/unknown	12%	20%	15%	11%	6%	

DISCUSSION

This nationwide population-based study assessed age-related differences in treatment patterns and reasons for adjusted treatment in patients with stage II or III colorectal cancer and found that omission of surgical treatment and/or (neo)adjuvant therapy was more likely in older patients than younger patients. Furthermore, the intensity of (neo)adjuvant therapy tended to decrease with advancing age. Reported reasons for adjusted treatment were mainly based on patient preference or functional status, which both increased with advancing age.

While interpreting our results, several limitations need to be considered. First, we were not always able to determine whether patients were treated in accordance with the national guideline and it is likely that the proportion of guideline adherence has been underestimated. In patients with stage II colon cancer, it could not be assessed whether patients were diagnosed with high risk stage II disease and therefore, whether adjuvant chemotherapy was indicated. In rectal cancer patients, a few criteria needed to determine whether and which neo-adjuvant therapy was indicated were missing in the database. Another drawback of the study is that, especially in patients who received no (neo)adjuvant therapy or patients with rectal cancer who received no surgical treatment after neo-adjuvant therapy, reported reasons for adjusted treatment were often classified as 'other' without further specification. In addition, only one primary reason was extracted from medical files, whereas in daily practice the argumentation for omission of standard treatment often consists of a combination of reasons. Some nuances may thus have been lost.

Despite of these limitations, this is the first large nationwide population-based analysis in patients with colorectal cancer which assesses reasons behind age-related differences in treatment patterns. Compared to previous studies, the proportion of patients treated in accordance with the national guidelines appears to be smaller.[5-10] As stated before, this proportion is probably underestimated. Similar to what previous studies observed,[8-13;15-31] guideline non-adherence increased with advancing age. Although treating patients in accordance with the national guideline is considered to reflect good quality of care, guideline non-adherence does not necessarily mean that the quality of care is compromised. A deviation from standard treatment can be justified based on the patient's situation, where standard treatment may have been overtreatment; but adjusted treatment could also represent undertreatment. Therefore, knowing the reasons for deviating from guidelines is highly relevant.

Now that the Netherlands Cancer Registry has started recording the primary reasons for omission of standard treatment, it is possible to gain more insight in the treatment decision-making process. In contrast to previous small studies which demonstrated age and multiple comorbidities as reasons for omission of standard treatment,[10,25,26,28,33,34] age as a reason for adjusted treatment is reported in the minority of patients in our study. This is a positive trend which suggests that patients were assessed on more patient characteristics

than chronological age alone. Still, age as reason for adjusted treatment increased with advancing age and was especially observed in patients aged ≥85 years. Almost half of the patients aged ≥85 years and diagnosed with colon cancer for example, did not receive adjuvant chemotherapy based on age. This might be justifiable in light of remaining life expectancy, the limited survival benefit and increased toxicity risk of adjuvant chemotherapy in these patients. However, assessing patient's ability to tolerate cancer treatment can be challenging when knowledge concerning efficacy and safety of the standard cancer treatment or quality of life during and after treatment in older patients is limited. After all, older patients are frequently excluded from participation in clinical trials due to the heterogeneity of this population.[39] Nevertheless, it remains important to assess patient's biological age before making a treatment decision.[40]

During ageing, the chances of being diagnosed with one or more chronic diseases are increasing. Comorbidities might lead to a certain burden of disease which can interfere with daily activities. Therefore, it is relevant to consider patient's condition before making a treatment decision. Our results showed functional status as an important reason for adjusting treatment, but it was unknown how functional status was measured. The Karnofsky performance status or Eastern Cooperative Oncology Group performance status are standard measures for estimating patient's ability to tolerate cancer treatment. These two scores estimate whether a patient is able to perform daily activities without the help of others. However, performance status focuses only on patient's physical condition while patients can also be vulnerable on the cognitive, functional or social domain. In order to improve tailored care, especially in older patients, a geriatric evaluation can be of added value to determine unknown health impairments on all these domains and consider patient values and preferences.[41] A study by Jacobs et al. confirmed an increased use of some form of geriatric evaluation in the Netherlands in recent years.[42]

Over the years, patient preference appears to play an increasingly prominent role in the treatment decision-making process which has evolved to a more shared decision-making approach.[43] The results of our study reflect patient's involvement in the treatment decision-making process, given that patient preference is the most prevalent reason for choosing adjusted treatment, especially in older patients. Patient preference can be a justifiable reason for omission of standard treatment, provided certain conditions are met: a proper relationship between physician and patient, comprehensive information concerning diagnosis and treatment options, and clarity about patient's goals and priorities. Unfortunately, we could not ascertain why patients prefer an adjusted treatment. Regularly, older cancer patients indicate that survival benefit is secondary to quality of life;[44] and common concerns in older cancer patients are discomfort or side effects of cancer treatment, as well as transportation difficulties.[32] Although these assumptions are not always aligned with the expected medical reality, this can be a reason for declining cancer treatment.[45] Therefore, it is of primary importance to explore and integrate patient's priorities and assumptions in the treatment decision-making process. Observational cohort studies seem needed to assess age-related differences of patient's motivation in the treatment decision-making process.

The heterogeneity of the cancer population highlights the importance of discussing all patients at the tumour board. Unfortunately, our results showed a decrease of being discussed at the tumour board with advancing age. This might be explained by the fact that those diagnosed by the regular diagnostic route are automatically listed at the tumour board, while those with non-specific symptoms may be diagnosed in another way and may therefore not be discussed at a tumour board. Additionally, particular in older patients, treatment decisions are sometimes made in advance; patient preferences or clinical judgment may result in refraining cancer treatment. Nevertheless, in both cases, we still would recommend to discuss all patients at the tumour board as it may improve patient education and sometimes, less intensive treatment options might still be suitable.[46,47]

In conclusion, adjusted treatment increased with advancing age and is mainly based on patient preference and functional status in patients with stage II or III colorectal cancer. It highlights the beginning of incorporating care in which treatment decisions are based on biological age and in which patient preferences are considered.

REFERENCES

1. Integraal Kankercentrum Nederland (IKNL). Cijfers over Kanker [Internet]. [cited 2020 Jan 6]. Available from: https://www.iknl.nl/nkr-cijfers
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91.
3. Oncoline. Oncoline Colorectaalcarcinoom [Internet]. 2019 [cited 2020 Jan 6]. Available from: https://www.oncoline.nl/colorectaalcarcinoom
4. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. J Geriatr Oncol. 2016;7(6):479–91.
5. Keikes L, van Oijen MGH, Lemmens VEPP, Koopman M, Punt CJA. Evaluation of Guideline Adherence in Colorectal Cancer Treatment in The Netherlands: A Survey Among Medical Oncologists by the Dutch Colorectal Cancer Group. Clin Colorectal Cancer. 2018;17(1):58–64.
6. Heins MJ, De Jong JD, Spronk I, Ho VKY, Brink M, Korevaar JC. Adherence to cancer treatment guidelines: Influence of general and cancer-specific guideline characteristics. Eur J Public Health. 2017;27(4):616–20.
7. van Steenbergen LN, Rutten HJT, Creemers GJ, Pruijt JFM, Coebergh JWW, Lemmens VEPP. Large age and hospital-dependent variation in administration of adjuvant chemotherapy for stage III colon cancer in southern Netherlands. Ann Oncol. 2010;21(6):1273–8.
8. Van Gils CWM, Koopman M, Mol L, Redekop WK, Uyl-De Groot CA, Punt CJA. Adjuvant chemotherapy in stage III colon cancer: Guideline implementation, patterns of use and outcomes in daily practice in the Netherlands. Acta Oncol (Madr). 2012;51(1):57–64.
9. Van Leersum NJ, Snijders HS, Wouters MWJM, Henneman D, Marijnen CAM, Rutten HR, et al. Evaluating national practice of preoperative radiotherapy for rectal cancer based on clinical auditing. Eur J Surg Oncol. 2013;39(9):1000–6.
10. Schiphorst AHW, Verweij NM, Pronk A, Hamaker ME. Age-related guideline adherence and outcome in low rectal cancer. Dis Colon Rectum. 2014;57(8):967–75.
11. Abraham NS, Gossey JT, Davila JA, Al-Oudat S, Kramer JK. Receipt of recommended therapy by patients with advanced colorectal cancer. Am J Gastroenterol. 2006;101(6):1320–8.
12. Adelson P, Fusco K, Karapetis C, Wattchow D, Joshi R, Price T, et al. Use of guideline-recommended adjuvant therapies and survival outcomes for people with colorectal cancer at tertiary referral hospitals in South Australia. J Eval Clin Pract. 2018;24(1):134–44.
13. Schroen AT, Cress RD. Use of surgical procedures and adjuvant therapy in rectal cancer treatment: A population-based study. Ann Surg. 2001;234(5):641–51.
14. Beckmann KR, Bennett A, Young GP, Roder DM. Treatment patterns among colorectal cancer patients in South Australia: A demonstration of the utility of population-based data linkage. J Eval Clin Pract. 2014;20(4):467–77.
15. Bouvier AM, Minicozzi P, Grosclaude P, Bouvier V, Faivre J, Sant M. Patterns of adjuvant chemotherapy for stage II and III colon cancer in France and Italy. Dig Liver Dis. 2013;45(8):687–91.
16. Chagpar R, Xing Y, Chiang YJ, Feig BW, Chang GJ, You YN, et al. Adherence to stage-specific treatment guidelines for patients with colon cancer. J Clin Oncol. 2012;30(9):972–9.
17. Hines RB, Barrett A, Twumasi-Ankrah P, Broccoli D, Engelman KK, Baranda J, et al. Predictors of guideline treatment nonadherence and the impact on survival in patients with colorectal cancer. JNCCN J Natl Compr Cancer Netw. 2015;13(1):51–60.
18. Cree M, Tonita J, Turner D, Nugent Z, Alvi R, Barss R, et al. Comparison of treatment received versus long-standing guidelines for stage III colon and stage II/III rectal cancer patients diagnosed in Alberta, Saskatchewan, and Manitoba in 2004. Clin Colorectal Cancer. 2009;8(3):141–5.
19. Winget M, Hossain S, Yasui Y, Scarfe A. Characteristics of patients with stage III colon adenocarcinoma who fail to receive guideline-recommended treatment. Cancer. 2010;116(20):4849–56.
20. Dobie SA, Baldwin LM, Dominitz JA, Matthews B, Billingsley K, Barlow W. Completion of therapy by medicare patients with stage III colon cancer. J Natl Cancer Inst. 2006;98(9):610–9.
21. Midura EF, Jung AD, Daly MC, Hanseman DJ, Davis BR, Shah SA, et al. Cancer Center Volume and Type Impact Stage-Specific Utilization of Neoadjuvant Therapy in Rectal Cancer. Dig Dis Sci. 2017;62(8):1906–12.

22. Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. J Clin Oncol. 2002;20(5):1192–202.
23. Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. J Natl Cancer Inst. 2001;93(11):850–7.
24. Hamaker ME, te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients – A systematic review. J Geriatr Oncol. 2018;9(5):430–40.
25. Ko JJ, Kennecke HF, Lim HJ, Renouf DJ, Gill S, Woods R, et al. Reasons for underuse of adjuvant chemotherapy in elderly patients with stage III colon cancer. Clin Colorectal Cancer. 2016;15(2):179–85.
26. Mahoney T, Kuo YH, Topilow A, Davis JM. Stage III colon cancers: Why adjuvant chemotherapy is not offered to elderly patients. Arch Surg. 2000;135(2):182–5.
27. Eldin NS, Yasui Y, Scarfe A, Winget M. Adherence to treatment guidelines in stage ii/iii rectal cancer in Alberta, Canada. Clin Oncol. 2012;24(1):e9-17.
28. Ayanian JZ, Zaslavsky AM, Fuchs CS, Guadagnoli E, Creech CM, Cress RD, et al. Use of adjuvant chemotherapy and radiation therapy for colorectal cancer in a population-based cohort. J Clin Oncol. 2003;21(7):1293–300.
29. Ong S, Watters JM, Grunfeld E, O'Rourke K. Predictors of referral for adjuvant therapy for colorectal cancer. Can J Surg. 2005;48(3):225–9.
30. Bojer AS, Roikjær O. Elderly patients with colorectal cancer are oncologically undertreated. Eur J Surg Oncol. 2015;41(3):421–5.
31. Lemmens VEPP, Janssen-Heijnen MLG, Verheij CDGW, Houterman S, Repelaer Van Driel OJ, Coebergh JWW. Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. Br J Surg. 2005;92(5):615–23.
32. Puts MTE, Tapscott B, Fitch M, Howell D, Monette J, Wan-Chow-Wah D, et al. A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. Cancer Treat Rev. 2015;41(2):197–215.
33. Gilbar P, Lee A, Pokharel K. Why adjuvant chemotherapy for stage III colon cancer was not given: Reasons for non-recommendation by clinicians or patient refusal. J Oncol Pharm Pract. 2017;23(2):128–34.
34. Oliveria SA, Yood MU, Campbell UB, Yood SM, Stang P. Treatment and referral patterns for colorectal cancer. Med Care. 2004;42(9):901–6.
35. Environment NI for PH and the. Socio-economic status per postal code [Internet]. [cited 2020 Apr 6]. Available from: https://bronnen.zorggegevens.nl/Bron?naam=Sociaal-Economische-Status-per-postcodegebied
36. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40:373–383.
37. Federatie Medisch specialisten. Colorectal Cancer Dutch Guideline Oncoline version 3.0 [Internet]. 2014. Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/colorectaalcarcinoom.pdf
38. Beets GL, Figueiredo NL, Habr-Gama A, Van De Velde CJH. A new paradigm for rectal cancer: Organ preservation Introducing the International Watch & Wait Database (IWWD). Eur J Surg Oncol. 2015;41:1562–4.
39. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: Known problem, little progress. J Clin Oncol. 2012;30(17):2036–8.
40. Papamichael D, Hernandez P, Mistry R XE, C K. Adjuvant chemotherapy in patients with colorectal cancer. Is there a role in the older adult? Eur J Surg Oncol. 2020;46:363–8.
41. 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.
42. Jacobs A, van der Bol J, Tielemans L HM. Implementation of geriatric oncology in the Netherlands in the years 2013 to 2019. J Geriatr Oncol. 2020;20:S1879-4068.
43. Quill TE, Holloway RG. Evidence, preferences, recommendations - Finding the right balance in patient care. N Engl J Med. 2012;366(18):1653–5.
44. 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.
45. Rostoft, S; van den Bos FHM. Shared decision-making in older patients with cancer - What does the patient want? J Geriatr Oncol. 2020;In print.
46. Ryan J, Faragher I. Not all patients need to be discussed in a colorectal cancer MDT meeting. Color Dis. 2014;7:520–6.
47. Wood JJ, Metcalfe C, Paes A, Sylvester P, Durdey P,

Thomas MG, et al. An evaluation of treatment decisions at a colorectal cancer multi-disciplinary team. Color Dis. 2008;10:769–72.

Appendix. Summary of Dutch guideline for colorectal cancer stage II and III, version 3.0 (2014).

Primary treatment of patients with colon cancer

Stage II

Standard treatment consists of surgical resection of the tumour and adjuvant chemotherapy may be considered for patients with a high risk stage II colon carcinoma which is defined if at least 1 of the following characteristics is present: stage T4, <10 regional lymph nodes examined, presentation with obstruction or perforation, extramural vascular invasion, or poorly/undifferentiated tumors.

Stage III

Standard treatment consists of surgical resection with adjuvant chemotherapy.

Primary treatment of patients with rectal cancer

Standard treatment consists of at least surgical resection. The distance to the mesorectal fascia (MRF) of the primary rectal carcinoma is the leading factor in ascertaining the indication for neo-adjuvant therapy and not the distance of a possible pathological node to the MRF (Table 1). There is no indication for adjuvant chemotherapy with rectal carcinoma.

Table 1. Schematic display of the indication for neo-adjuvant treatment.

Tumour stage (MRI staged)	Neo-adjuvant treatment
$cT_{1-2}N_0$ or cT_3N_0 ≤5 mm extramural invasion; distance to the MRF >1 mm	None
$cT_{1-3}N_1$ or cT_3N_0 >5 mm extramural invasion; distance to the MRF >1 mm	5x5 Gy pre-operative radiotherapy
cT_4 of cT_3 with distance to the MRF ≤1 mm and/or cN_2 / extramesorectal pathological nodes (each N)	Chemoradiotherapy

CHAPTER
7

Study objectives in clinical trials in older patients with solid malignancies: do we measure what matters?

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ABSTRACT

Purpose

We set out to determine study objectives of clinical trials which included older patients with the four most common malignancies, to assess the extent to which the inclusion of patient related outcomes (PROs) has changed over the last fifteen years.

Methods

A search of the National Institutes of Health clinical trial registry was performed to identify currently recruiting or completed phase II or III clinical trials started between 2005 and 2020, which addressed chemotherapy or immunotherapy in patients aged >65 years with the four most common solid malignancies. Trial characteristics and study objectives were extracted from the registry website.

Results

Compared to disease- and treatment related outcomes, PROs were the least measured outcomes. Of the 1,663 trials, PROs were addressed in only 21% of all trials, in which quality of life as primary objective was found in less than 1% of all trials. Compared to all trials, trials exclusively for older patients addressed more often PROs (respectively, 30% vs 21%, $p < 0.001$). Over the last fifteen years, there was an incremental trend in the reporting of PROs from 17 to 24% of all trials ($p = 0.007$).

Conclusion

Despite a slight incremental trend over the past 15 years, PROs appear to be underrepresented in clinical trials which include patients with a solid malignancy. In order to provide physicians and older patients with cancer realistic information about the impact of chemo- or immunotherapy on quality of life or functioning, researchers should strongly consider including PROs in their future clinical trials.

INTRODUCTION

The proportion of older persons in the global population is rising. Particular in the western world, the proportion of patients aged 60 years or over will increase from 30% in 2020 up to 50% in 2050. In addition, survival beyond the age of 60 years is improving.[1] As a result, the incidence of diseases that are common among older patients, such as cancer, will also increase over the upcoming decades. Nowadays in the Netherlands, at least 70% of all patients with cancer is aged 60 years or older.[2]

Providing appropriate treatment for an older patient with cancer is challenging. On the one hand, older patients and especially those with comorbidities are frequently excluded from clinical trials.[3] However, the heterogeneity in physical and psychological condition, functioning and social context of older patients is significant. Therefore, evidence regarding efficacy and safety of cancer treatment for younger or fit patients with cancer may not be applicable to this older population. On the other hand, clinical trials have historically tended to focus on disease and treatment related outcomes, while older patients also want to be informed about the impact of cancer treatment on patient related outcomes (PROs) such as quality of life, functioning or health care utilization.[4] Previous research has shown that older patients are less willing to accept toxicity for additional survival benefit,[5] particularly when oncological treatment could potentially have a negative impact on functioning or quality of life.[6–8] Therefore, next to the importance of including disease and treatment related outcomes in clinical trials, this emphasizes the importance of including PROs in clinical trials in general and for older patients in particular.

PROs cover a range of health outcomes like symptoms, functional limitations, quality of life and patient satisfaction. These are generally measured with questionnaires, that collect information directly from the patient, without interpretation by others.[9] The recognition of their importance for both oncologic research as well as daily clinical practice is not new: in the last decade, multiple oncologic societies, scientific organisations and national health services have emphasized the need for gathering PROs evidence.[10–16] This becomes even more relevant in older patients.[17]

Last decade, our group conducted studies on the inclusion of PROs in poor prognosis malignancies,[18] lung cancer,[19] haematological malignancies,[20] and palliative chemotherapy[21] and found that these outcomes were rarely incorporated. Now, several years onward, we set out to assess trends in the choice of study objectives in trials started between 2005 and 2020, for four solid malignancies common in older patients.

METHODS

Data collection

We searched the United States National Institutes of Health clinical trial registry (www.

clinicaltrials.gov) for ongoing and completed clinical trials which focused on chemotherapy targeted therapy and/or immunotherapy in older patients with cancer. The search was performed on August 5th 2020, using the search terms "cancer", "chemotherapy", "immunotherapy" and "biologicals". The search was limited to trials started from 2005 onward, phase II and III, and open to patients aged >65 years. From this first selection based on search engine criteria, we selected trials with the four most prevalent cancer types in older patients: breast, colorectal, lung and prostate cancer. Based on protocol review, we excluded trials whose primary treatment of interest was not chemotherapy, targeted therapy or immunotherapy, or which focused on treatment of a specific symptom or side effects or diagnostic techniques.

For all included trials, the following data were extracted from the registry website by one author (ES): target disease entities, start year of the study, intervention, study phase, source of funding, age related inclusion criteria and primary and secondary study objectives.

Primary and secondary study objectives were classified based on phrasing as reported on clinical trial registry website and divided into ten categories: overall survival, progression-free survival, efficacy, toxicity, pharmacological parameters, biological outcome parameters, treatment completion, health care utilization, quality of life and functioning. All were grouped together in disease related outcomes, treatment related outcomes or PROs (Appendix).

Statistical analyses

Differences between categories were assessed by using a web-based chi-square calculator[22]. Comparisons were made for type of malignancy (breast cancer, colorectal cancer, lung cancer and prostate cancer) and trial characteristics (start of inclusion, type of intervention, study phase and source of funding). A p-value of <0.05 was considered significant.

RESULTS

The search of the National Institutes of Health clinical trial registry yielded 28,097 trials. After exclusion of trials due to limitations applied in search engine or based on protocol review, 1,663 trials remained for inclusion in this overview (Figure 1).

Study characteristics of these selected trials are summarized in Table 1. The majority of trials addressed patients with lung cancer (40%), followed by breast cancer (29%), colorectal cancer (20%) and prostate cancer (11%). Chemotherapy was the primary focus in 31% of the trials and targeted therapy +/- chemotherapy was addressed in 54% of the trials. Immunotherapy +/- chemotherapy was addressed in 15% of the trials. Most trials were phase II (73%) and industry-sponsored (55%).

The great majority of studies were open to all adult patients, while 2.3% focused exclusively on older patients, using a lower age limit for inclusion of 60 years or older.

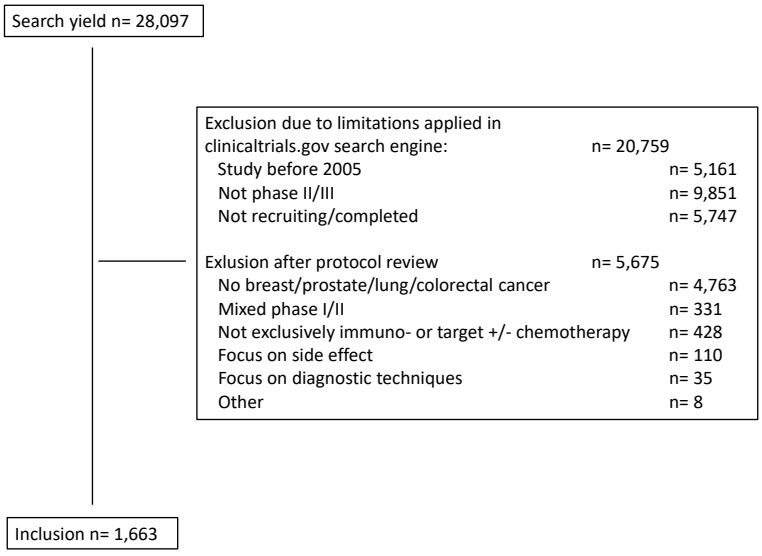

Figure 1. Search results and study selection.

Study objectives

Study objectives of included trials are shown in Table 2. Primary and secondary study objectives mainly consisted of disease related outcomes; progression free survival was the most frequently mentioned study objective (81%), followed by efficacy (77%) and overall survival (69%). Toxicity was the most frequently used treatment related outcome (61%), mainly addressed as secondary study objective.

PROs were included in 21% of all trials (14% in phase II, 38% of phase III trials, p<0.001); quality of life was most frequently addressed (13% in phase II and 36% in phase III trials, p<0.001). However, quality of life as primary study objective was found in less than 1% (n=9) of trials.

Compared to all included trials, trials exclusively for older patients (≥60 years) more often addressed PROs, (30% vs 21% in all trials, p<0.001); especially functioning was more often mentioned as study objective (21% vs 3% in all selected trials, p<0.001). No relevant differences were observed in PROs among the various cancer types (ranging from 18% in breast cancer to 23% in lung cancer, p=0.36), among the various interventions (varying between 19% in trials with chemotherapy only and 22% in trials with targeted therapy +/- chemotherapy, p =0.42). PROs tended to be more often included in industry sponsored trials (22% vs 18% in non-industry sponsored trials, p=0.05).

Incorporation of patient related outcomes over time

Overall, there was a slight increase in the inclusion of PROs from 17% between 2005-2009 up to 24% between 2015-2020 (p=0.007, Figure 2). This increase was also seen specifically in trials for breast cancer (increase from 12% to 24%, p=0.01) and colorectal cancer (12 to 25%, p=0.04), while the inclusion remained more or less stable for lung cancer (21% to

25%, p=0.37) and prostate cancer (23% to 20%, p=0.91). This increase was also seen in phase II trials, and industry sponsored trials (Figure 2). For trials assessing immunotherapy +/- chemotherapy, inclusion of patient related outcome measures fluctuated while trials assessing targeted therapy +/- chemotherapy and chemotherapy showed an increase of their focus on PROs over time. This increase was only significant for trials focused on chemotherapy only (14% to 25%, p=0.03).

Table 1. Schematic display of the indication for neo-adjuvant treatment.

	All trials (n=1663)	
Diagnosis		
Breast cancer	487	(29%)
Colorectal cancer	331	(20%)
Lung cancer	663	(40%)
Prostate cancer	182	(11%)
Start of inclusion		
2005-2009	638	(38%)
2010-2014	399	(24%)
2015-2020	626	(38%)
Intervention		
Chemotherapy only	517	(31%)
Targeted therapy +/- chemotherapy	896	(54%)
Immunotherapy +/- chemotherapy	250	(15%)
Phase		
II	1218	(73%)
III	445	(27%)
Sponsors[$]		
Industry	919	(55%)
NIH	226	(14%)
Other	551	(33%)
Lower age limit		
≤ 25	1610	(97%)
25-59	1	(0.1%)
60-69	5	(0.3%)
≥ 70	29	(2%)
None/unknown	18	(1%)
Upper age limit		
65-74	141	(8%)
75-84	202	(12%)
≥ 85	90	(6%)
Not specified	1230	(74%)

[$] Trials could have multiple sponsors. Abbreviations: NIH, National Institutes of Health

Table 2. Primary and secondary study objectives of all selected trials.

	All outcomes	Primary study objectives	Secondary study objectives
Disease related study objectives			
Overall survival	1146 (69%)	183 (11%)	963 (58%)
Progression free survival	1348 (81%)	695 (42%)	653 (39%)
Efficacy	1288 (77%)	696 (42%)	592 (36%)
Biological outcome parameters	264 (16%)	69 (4%)	195 (12%)
Treatment related study objectives			
Toxicity	1013 (61%)	144 (9%)	869 (52%)
Pharmacological parameters	114 (7%)	9 (0.5%)	105 (6%)
Treatment completion	43 (3%)	10 (1%)	33 (2%)
Patient related study objectives			
Health care utilization	26 (2%)	-	26 (2%)
Quality of life	318 (19%)	9 (0.5%)	309 (19%)
Functioning	47 (3%)	3 (0.2%)	44 (3%)

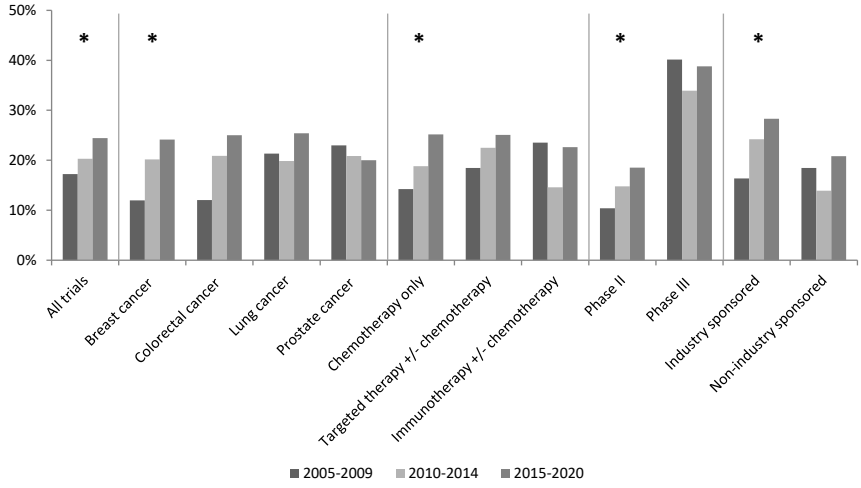

Figure 2. The proportion of trials with patient related outcomes and their changes over time, stratified by trial characteristics. * significant difference over time (p<0.05)

DISCUSSION

We evaluated trends over time in the choice of study objectives in phase II or III clinical trials for the four most prevalent solid malignancies in older patients, registered in the National Institutes of Health clinical trial registry. Although there was a slight increase of PROs over the last fifteen years, PROs were included in only a small portion of studies: only one out of five trials included any type of PRO in their study protocol.

This study has several limitations. Due to our search and selection strategy in only one database, the National Institutes of Health clinical trial registry, our overview does not include all clinical trials worldwide. However, the National Institutes of Health clinical trial registry is by far the largest registry and therefore, the results from our analysis are a good representation of current clinical trial practice. Another drawback of this study is that we limited our search to what was presented in the clinical trial registry regarding outcome measures. It is possible that other study objectives were formulated in the full study protocol.

Nevertheless, this overview reflects the study objectives in oncological trials and in contrast to previous research, we assessed how these study objectives have changed in the past fifteen years. When designing a clinical trial in which a new drug will be investigated, it makes sense to first focus on efficacy and safety before focussing on PROs. However, once these have been established, the impact of treatment on the quality of life and functioning of the patient also deserves to be investigated. It is difficult to label a treatment as successful, when its effectiveness in decreasing tumour burden comes at the cost of the patient's quality of life or their ability to carry out daily activities that matter to them. This becomes even more pertinent in older patients, who may lack the resilience to recover from this impact.[23]

Disappointingly, despite small increases, the proportion of studies including PROs in their study objectives remains limited. Thus, the endorsement of PROs by multiple oncologic societies, scientific organisations and national health services,[10–16] has not resulted in a significant change in the inclusion of PROs in current oncology research. We need to consider what factors hinder their incorporation in trial design.

Inclusion of PROs in clinical trials could be challenging due to the uncertainty about the quality and appropriate application of existing tools for assessing PROs.[24] This may discourage researchers from selecting them as a study objective in clinical trials. When choosing a patient related outcome measure, it is important that the instrument matches the research question and study population. Generic instruments measure a broad range of medical issues to provide comparisons with the norm population or between diseases; but these instruments may include aspects that are irrelevant for specific patient populations.[9] Therefore, it is preferable to use disease specific PROs that are intended to be used for a particular patient group. However, partly due to the limited number of well validated instruments, there is still no consensus on suitability of PROs in various study populations.[24]

In addition, as many of the commonly used instruments were originally developed for use in research, extrapolation of PROs to clinical practice may also be difficult. For example, the EORTC-QLQ-C30 questionnaire that assesses health related quality of life (HR-QoL), focuses on the level of experienced impairments and not on the impact of these impairments on experienced HR-QoL.[25] Furthermore, cut-off values of this questionnaire are not available and interpretation of the clinical relevance of changes in HR-QoL are mostly done by some rules of thumbs.[26] Finally, longitudinal reporting of PROs may be subject to the response shift phenomenon, which reflect patient's ability to adapt to new life circumstances, as well as recall

bias which refers to the potential risk of inaccurate recall to past events or experiences.[27] Both may influence patient's evaluation of HR-QoL after treatment. As a result of these disadvantages, the comparability of PROs in trials across health care institutions or between countries will remain difficult and the inclusion of PROs in trial design may remain limited as well.

On top of the aforementioned difficulties, researchers and physicians might not be sufficiently aware of the added value of measuring PROs in daily practice. Although it is stated that PROs are an umbrella term of evaluating symptoms, functional limitations, quality of life and patient satisfaction, at the outset of PROs in the early 1990's, it was often assumed that PROs were a measure of quality of life and therefore only of interest to patients.[9] In contrast, PROs could also provide insight in patient's tolerance to a treatment and can show the differences between patient's perspective and physician's perspective. These discrepancies are for example found in documenting toxicity: patients with ovarian cancer who received chemotherapy reported peripheral neuropathy twice as much as physicians did.[28] Hence, measuring PROs may improve patient education and should be as important as disease and treatment related outcomes.

Patients increasingly want to be informed about the impact of cancer treatment on daily life.[4] Therefore, we would like to encourage researchers and physicians to contribute in optimizing the quality and applicability of PROs, and include them in trial design. Several international organisations, such as International Consortium for Health Outcomes Measurement (IHCOM) and the Organisation for Economic Co-operation and Development (OECD), have already taken some initiatives to improve the standardisation and use of PROs in clinical trials worldwide.[29,30] In addition, the SPIRIT-PRO guidelines and CONSORT-PRO guidelines already provide recommendations for researchers to improve the use and report of PROs.[31,32] We need to start focussing on PROs as a standard outcome in clinical trials now, so in due time more information about the possible risk and benefits of systemic cancer therapy can be shared in the doctor's office. This can help physicians and patients in the treatment decision-making process.[33]

In conclusion, study objectives of currently ongoing clinical trials in the four most common solid malignancies in older patients included mainly disease and treatment related outcome measures. Although there has been a slight increase over the years, PROs were observed in less than a quarter of all selected trials. In order to provide physicians and older cancer patients with realistic information about the impact of systemic cancer therapy on quality of life or functioning, researchers should strongly consider including patient related study objectives in their clinical trials.

REFERENCES

1. Nations U. World Population Ageing 2019 [Internet]. 2019. Available from: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf
2. Integraal Kankercentrum Nederland (IKNL). Cijfers over Kanker [Internet]. [cited 2020 Jan 6]. Available from: https://www.iknl.nl/nkr-cijfers
3. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: Known problem, little progress. J Clin Oncol. 2012;30(17):2036–8.
4. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the Treatment Preferences of Seriously Ill Patients. N Engl J Med. 2002;346(14):1061–5.
5. Hurria A, Mohile SG, Dale W. Research Priorities in Geriatric Oncology: Addressing the Needs of an Aging Population. JNCCN J Natl Compr Cancer Netw. 2012;10(2):286–8.
6. Pallis AG, Ring A, Fortpied C, Penninckx B, van Nes MC, Wedding U, et al. Eortc workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. Ann Oncol. 2011;22(8):1922–6.
7. Van Leeuwen KM, Van Loon MS, Van Nes FA, Bosmans JE, De Veti HCW, Ket JCF, et al. What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):1–39.
8. Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. J Natl Cancer Inst. 1994;(86):1766–70.
9. McKenna SP. Measuring patient-reported outcomes: Moving beyond misplaced common sense to hard science. BMC Med. 2011;(9):86.
10. Schnipper LE, Davidson NE, Wollins DS, Blayney DW, Dicker AP, Ganz PA, et al. Updating the American society of clinical oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol. 2016;34(24):2925–34.
11. Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol. 2015;26:1547–73.
12. Agency EM. Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man: the use of patient-reported outcome (PRO) measures in oncology studies [Internet]. 2016 [cited 2020 Nov 23]. Available from: http://www.ema.europa.eu/docs/en_GB/document_ library/Other/2016/04/WC500205159.pdf
13. Food and Drug Administration. Guidance for Industry: patient-reported outcome measures: use in medical product development to support labelling claims. 2009.
14. Devlin NJ, Appleby J, Buxton M, Vallance-Owen A. Getting the most out of PROMS. Putting health outcomes at the heart of NHS decision making. Health Econ. 2010.
15. Kessel, P. van, Triemstra, M., Boer, D. de. Handreiking voor het meten van kwaliteit van zorg met Patient Reported Outcome Measures. NIVEL, 2014.
16. Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, et al. End points and trial design in geriatric oncology research: A joint European Organisation for Research and Treatment of Cancer-Alliance for clinical trials in oncology-international society of geriatric oncology position article. J Clin Oncol. 2013;31(29):3711–8.
17. Scotté F, Bossi P, Carola E, Cudennec T, Dielenseger P, Gomes F, et al. Addressing the quality of life needs of older patients with cancer: A SIOG consensus paper and practical guide. Annals of Oncology. 2018;29(8):1718-1726.
18. 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. 2017;26:65–71.
19. Schulkes KJG, Nguyen C, van den Bos F, Hamaker ME, van Elden LJR. Patient-Centered Outcome Measures in Lung Cancer Trials. Lung. 2016;194(4):647–52.
20. Hamaker ME, Stauder R, van Munster B. Ongoing clinical trials in elderly patients with a haematological malignancy: are we addressing the right outcome measures? J Geriatr Oncol. Ann Oncol. 2014 Mar;25(3):675-681.
21. van Bekkum ML, van Munster BC, Thunnissen PLM, Smorenburg CH, Hamaker ME. Current palliative chemotherapy trials in the elderly neglect patient-centred outcome measures. J Geriatr Oncol. J Geriatr Oncol. 2015;6(1):15-22.
22. Preacher K. Calculation for the chi-square test: an interactive calculation tool for chi-square tests of goodness of fit and independence [Computer software]. [Internet]. 2001. Available from: http://

quantpsy.org/chisq/chisq.htm
23. MacLeod S, Musich S, Hawkins K, Alsgaard K, Wicker ER. The impact of resilience among older adults. Geriatr Nurs (Minneap). 2016;37:266–72.
24. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Relat Outcome Meas. 2018;9:353–67.
25. Fayers P, Aaronson N, Bjordal K. EORTC QLQ-C30 scoring manual. Europen Organization for Research and Treatment of cancer. 2001.
26. Cocks K, King MT, Velikova G, St-James MM, 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. J Clin Oncol. 2011;29(1):89-96.
27. Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MAG, Fayers PM. The clinical significance of adaptation to changing health: A meta-analysis of response shift. Qual Life Res. 2006;15(9):1533–50.
28. Park SB, Kwok JB, Asher R, Lee CK, Beale P, Selle F, et al. Clinical and genetic predictors of paclitaxel neurotoxicity based on patient- versus clinicianreported incidence and severity of neurotoxicity in the ICON7 trial. Ann Oncol. 2017;28(2733–40).
29. OECD. Recommendations to OECD ministers of health from the high level reflection group on the future of health statistics [Internet]. 2017. Available from: https://www.oecd.org/els/health-systems/Recommendations-from-high-level-reflection-group-on-the-future-of-health-statistics.pdf
30. IHCOM. International Consortium for Health Outcomes Measurement [Internet]. [cited 2020 Nov 25]. Available from: https://www.ichom.org/
31. Calvert M, Brundage M, Jacobsen PB, Schünemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: Implications for clinical trials and practice. Health Qual Life Outcomes. 2013;11:184.
32. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols the spirit-pro extension. JAMA - J Am Med Assoc. 2018;319:483–94.
33. Field J, Holmes MM, Newell D. PROMs data: can it be used to make decisions for individual patients? A narrative review. Patient Relat Outcome Meas. 2019;10:233–41.

Appendix. Classification of study objectives.

	Study objective	Classification
Disease related outcomes	Overall survival Mortality at a particular time point during follow-up	Overall survival
	Progression-free survival Event-free survival Disease-free survival Time-to-progression Duration of response	Progression free survival
	Response rate Efficacy Time-to-response	Efficacy
	Laboratory parameters Genetic parameters Tumor biology	Biological parameters
Treatment related outcomes	Toxicity Safety Feasibility Maximum-tolerated dose	Toxicity
	Pharmacokinetics Pharmacodynamics	Pharmacological parameters
	Completion of planned treatment Achieved dose intensity Compliance to treatment	Treatment completion
Patient related outcomes	Health care utilization Health economics	Health care utilization
	Quality of life Symptom relief Patient satisfaction Patient reported outcomes	Quality of life
	Care dependence Institutionalization ECOG or WHO performance status Geriatric assessment G8 frailty screening tool	Functioning

Classification is based on phrasing as reported on clinical trial registry website. Abbreviations: ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization.

CHAPTER
8

The impact of surgery and adjuvant chemotherapy on health-related quality of life in patients with colon cancer: changes at group-level versus individual-level

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ABSTRACT

Objective

This study aims to evaluate changes in health-related quality of life (HR-QoL) one year after surgical treatment in patients with primary resectable colon cancer and to assess whether changes at group-level differ from changes at individual level. In addition, we assess which characteristics are associated with a decline of HR-QoL.

Methods

Patients with primary resectable colon cancer who received surgical treatment and adjuvant chemotherapy if indicated were selected from the Prospective Dutch ColoRectal Cancer cohort (PLCRC). HR-QoL was assessed using EORTC-QLQ-C30 questionnaire before surgery and twelve months post-surgery. Outcomes were assessed at group-level and individual-level. Logistic regression analysis was conducted to assess which socio-demographic and clinical characteristics were associated with a clinically relevant decline of HR-QoL at twelve months.

Results

Of all 324 patients, the baseline level of HR-QoL summary score was relatively high with a mean of 88.1 (SD 11.4). On group level, the change of HR-QoL at twelve months varied between -2% for cognitive functioning and +9% for emotional functioning. On individual level, 15% of all patients experienced a clinically relevant decline in HR-QoL summary score at twelve months. Older age, comorbidity burden or the reception of adjuvant chemotherapy were independently associated with a decline of HR-QoL in one of the functional subscales of EORTC-QLQ-C30 at twelve months.

Conclusion

Only trivial changes of HR-QoL were observed after colon cancer treatment on group level whereas on individual level at least one out of ten patients experienced a decline of HR-QoL twelve months post-surgery. It is important to consider individual differences while making a treatment decision.

INTRODUCTION

Colon cancer is a typical disease of the ageing population. The median age of patients at diagnosis is 67 years[1] and due to ageing of the population and the implementation of screening for colorectal cancer, the prevalence of colon cancer will increase.[2] This will present a challenge in the decision-making process.

Treatment for primary resectable colon cancer consists of surgery and adjuvant chemotherapy for high risk stage II and stage III patients as indicated by the national guideline.[3] Treatment recommendations are based on tumour characteristics and should be weighed against patient characteristics and preferences. Since the beginning of shared decision-making, it has become increasingly important to consider patient preferences. These preferences also concern the impact of colon cancer treatment on quality of life during and after treatment. Health related quality of life (HR-QoL) is defined as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns',[4] and is frequently divided in various domains such as physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning.[5] Particularly in older patients, the maintenance of quality of life may be just as important as survival benefit.[6] Therefore, it is important to consider quality of life in the treatment decision making process of patients with colon cancer.

Previous studies which assessed HR-QoL in colorectal cancer patients showed that the greatest decline in HR-QoL is expected within the first months after diagnosis and may gradually improve over time, although physical functioning and role functioning can remain affected in the longer-term.[7,8] In reported clinical studies, the impact of colon cancer treatment on HR-QoL is mainly expressed at group level in which longitudinal measurements of quality of life are commonly compared per group, based on patient or treatment characteristics. As a result, improvements or deteriorations of HR-QoL at an individual level may be lost, while particularly these individual differences are relevant to properly inform an individual patient about the impact of colorectal cancer treatment.[9]

Due to the heterogeneity of the population, it becomes increasingly relevant to estimate individual differences in HR-QoL and assess which patient characteristics are associated with a decline of HR-QoL during or after colorectal cancer treatment. Filling this knowledge gap may guide patients and physicians in the treatment decision-making process. Therefore, this study aims to evaluate changes in HR-QoL in patients with primary resectable colon cancer and address whether changes at group-level differ from changes at individual level. In addition, we assess which characteristics are associated with a decline of HR-QoL twelve months post-surgery.

METHODS

Patient selection

Data of the multicentre Prospective Dutch ColoRectal Cancer cohort (PLCRC) were requested.[10] This nationwide observational cohort study includes adults with histologically proven colorectal cancer and registers longitudinal clinical data; while striving to include patients at the time of diagnosis, participation in the cohort is also possible at later stages in the treatment trajectory. Of all approached patients, 90% consented to inclusion.[10] Socio-demographic and clinical characteristics of patients are collected by the Netherlands Cancer Registry (NCR) which now covers more than 95% of the Dutch population.[2] Specially trained administrators collect patient, tumour and treatment characteristics from the patients' hospital files. Patient reported outcomes such as quality of life were collected by using validated questionnaires. All patients provided informed consent between 2013 and 2019 and the PLCRC study has been approved by the medical ethical review committee.[10]

Patients with resectable primary colon cancer who received surgical treatment and adjuvant chemotherapy if indicated were selected. PLCRC includes patients with all stages of colorectal cancer in the course of their disease. As we set out to analyse the functional impact of cancer treatment over time, we only included patients who completed the first measurement prior to surgery, and who filled out a questionnaire at twelve months. Patients were excluded if primary irresectable tumours or additional colon pathology were suspected by the authors (ES, MH); this was based on available tumour- and treatment characteristics, for example patients who received neo-adjuvant therapy or a (sub)total colectomy were excluded.

Data collection

Socio-demographic and clinical characteristics were collected from the NCR. Socio-demographic characteristics included sex, age at diagnosis, education level, living situation and comorbidities. Comorbidities were classified according to the Charlson Comorbidity Index (CCI);[11] however, data on comorbidities were not collected in all hospitals and therefore, comorbidities were not available for all patients. Tumour characteristics consisted of tumour location and tumour stage according to guideline.[12] Tumour stage was based on pathological disease stage information, supplemented by clinical stage information if pathological stage was unavailable. Treatment characteristics included type of surgical treatment, ileo/colostomy and postoperative surgical complications such as anastomotic leakage and/or abscess.

HR-QoL was assessed prior to surgical treatment (T0) and twelve months (T12) after surgery, using the Dutch version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30). This questionnaire consists of thirty items concerning five functional subscales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), nine symptom subscales and global health status.[5] Data from EORTC QLQ-C30 questionnaires were transformed to a range of 0 to 100 in accordance with the EORTC QLQ-C30 manual; higher scores mean

better functioning and quality of life. For our analysis, the five functional subscales were used, in addition to a HR-QoL summary score, which is calculated based on the mean score of global health status and all functioning and symptom subscales.[13,14]

Clinically relevant differences (CRD) in HR-QoL were assessed using the published guideline for the EORTC QLQ-C30,[15] which categorises differences from trivial to large. We considered any difference in HR-QoL categorized as 'small' or higher as clinically relevant. For emotional functioning and summary score, there is no CRD available; therefore Norman's rule of thumb was used to assess clinical relevance. This rule states that a difference of half a standard deviation (SD) or more can be regarded clinically relevant.[16] On individual level, CRD were categorized as a clinically relevant improvement or clinically relevant decline in HR-QoL, whereas no CRD was categorized as stable HR-QoL twelve months post-surgery.

Statistical analyses

All analyses were performed in IBM SPSS Statistics 23. Socio-demographic characteristics and clinical characteristics as well as the outcomes of the EORTC QLQ-C30 were presented as means (SD) for normally distributed continuous variables, medians (range) for not-normally distributed variables or frequencies and proportions for categorical variables. Differences in mean changes in HR-QoL compared to baseline measurements were analysed with the paired T-test. In addition, mean change of average HR-QoL score at twelve months compared to baseline was calculated to assess impact of colon cancer treatment on HR-QoL at group level. At an individual level, we calculated proportion of individuals experiencing a clinically relevant decline of HR-QoL at twelve months.

Univariable and multivariable logistic regression analysis was conducted to assess which characteristics were associated with a decline of quality of life and included sex, age, living situation, education level, comorbidities and reception of adjuvant chemotherapy. For multivariable analysis, all variables were added into the regression analysis at once. P-values smaller than 0.05 were considered statistically significant.

RESULTS

Patient selection and baseline characteristics

Between 2013 and 2019, 1800 patients were selected from the PLCRC database. After exclusion of twelve patients suspected of having additional colon pathology, 1289 patients with a baseline measurement post-surgery and 175 patients with no baseline measurement or no follow-up measurement at twelve months, 324 patients were included in this analysis (Appendix).

Baseline measurement was completed 34 days prior to surgery (median, interquartile range 26-46 days); baseline characteristics are listed in Table 1. Mean age of all patients was 66.4 years (SD 9.2), 68% were men and comorbidities were present in 43% of all patients. The

majority of the patients lived together with a partner and/or children (81%). A right sided tumour (50%) was the most prevalent tumour location, followed by sigmoid tumours (39%). Surgical treatment mainly consisted of hemicolectomy (59%) or sigmoid resection (30%). Postoperative surgical complications such as anastomic leakage and/or abscess were present in 3% of the patients and 5% received an ileostomy or colostomy. Adjuvant chemotherapy was prescribed in 32% of all patients.

Table 1. Baseline characteristics of all included patients.

	All (n=324)
Age in years (mean ± SD)	66.4 ± 9.2
Sex	
Men	219 (68%)
Women	105 (32%)
CCI	
0	72 (58%)
1	39 (32%)
≥2	13 (11%)
Missing	*200*
Current living situation	
Living alone	57 (19%)
With partner and/or children	238 (81%)
Missing	*29*
Education level	
Low	106 (36%)
Middle	81 (28%)
High	105 (36%)
Missing	*32*
Tumour stage	
1	98 (30%)
2	113 (35%)
3	113 (35%)
HR-QoL baseline	
Summary score	88.1 ± 11.4
Global health status	78.1 ± 18.0
Physical functioning	90.0 ± 14.7
Role functioning	88.4 ± 19.6
Emotional functioning	83.3 ± 18.0
Cognitive functioning	90.0 ± 15.7
Social functioning	91.0 ± 16.3

At baseline, the mean HR-QoL summary score was 88.1 (SD 11.4). For the different subscales, baseline HR-QoL varied between 78.1 (SD 18.0) for global health status and 91.0 (SD 16.3) for social functioning (Table 1).

The impact of colon cancer treatment on quality of life at group level vs individual level

At group level, the mean change of HR-QoL compared to baseline is depicted in Figure 1, showing a statistically significant increase of HR-QoL summary score of 2.3 points above baseline level at twelve months ($p<0.001$); this change was of trivial clinical relevance. For the five functional subscales of the EORTC-QLQ-C30, changes varied between -1.9 points for cognitive functioning and +7.8 points for emotional functioning. Although changes for physical functioning, emotional functioning and cognitive functioning were statistically significant, none of the changes for the functional subscales were of clinical relevance. Based on the standard deviation (ranging from 11 to 21 points), a wide range in HR-QoL was observed.

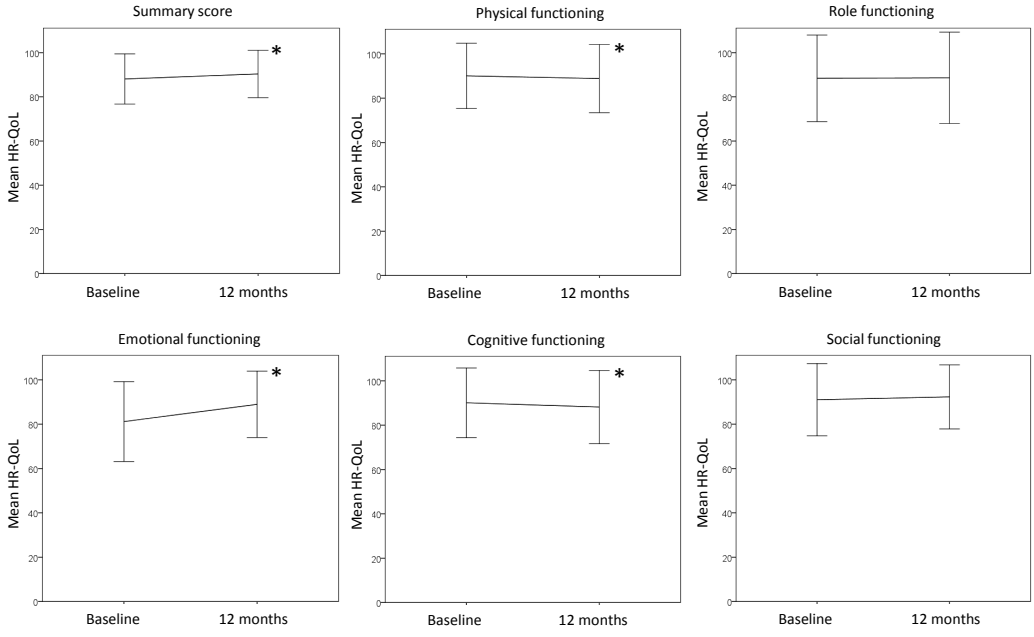


Figure 1. HR-QoL summary score and HR-QoL of the EORTC QLQ-C30 subscales at baseline and at twelve months follow up.
* significant difference compared to HR-QoL at baseline. Error bars: standard deviation.

At the individual level, HR-QoL remained stable or improved twelve months post-surgery for the majority of patients, but a clinically relevant decline in HR-QoL summary score was observed in 15% of all patients (Figure 2). Patients were particularly at risk of a clinically relevant decline of physical functioning (28%), cognitive functioning (26%) or global health status (25%). Reversely, a clinically relevant improvement in HR-QoL varied between 17% for cognitive functioning and 39% for global health status of all patients.

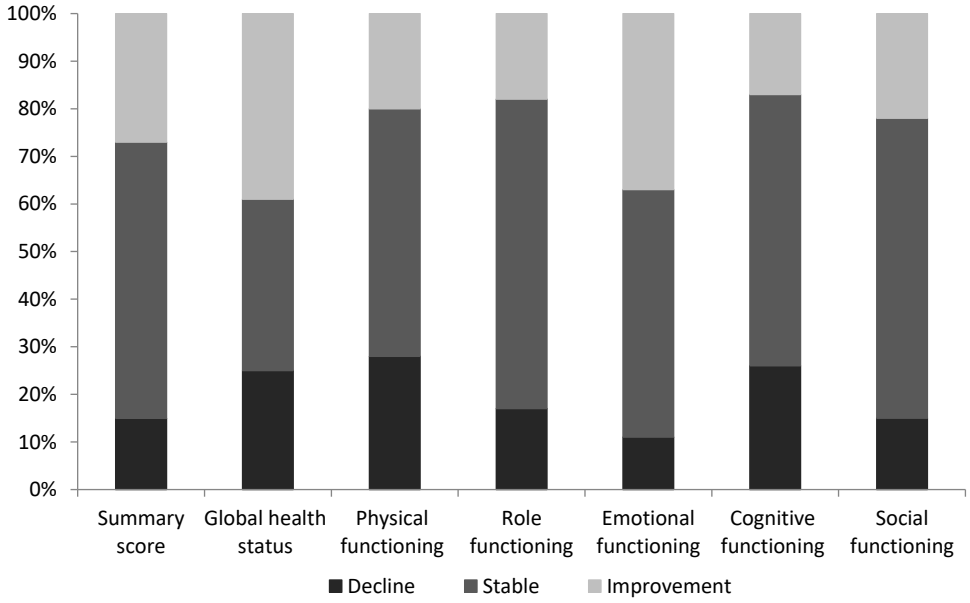


Figure 2. Clinically relevant differences of HR-QoL in individual patients twelve months after surgery.

Table 2. Comparison of changes in quality of life scores on group level vs. individual patient level.

	Change in average score at twelve months compared to baseline level (%)	Individuals experiencing clinically relevant decline at twelve months compared to baseline (%)	Individuals experiencing clinically relevant improvement at twelve months compared to baseline (%)
Summary score	+2.6%	15%	27%
Global health status	+4.7%	26%	39%
Physical functioning	-1.3%	28%	20%
Role functioning	+0.2%	17%	18%
Emotional functioning	+9%	11%	37%
Cognitive functioning	-2%	26%	17%
Social functioning	+1.4%	16%	22%

Thus, group descriptives such as mean change over time differ from clinically relevant changes on an individual level as shown in Table 2 which illustrates the impact of colon cancer treatment on HR-QoL at group level versus individual level side-by-side.

Characteristics associated with a clinically relevant decline of quality of life

To assess which socio-demographic and clinical characteristics were associated with experiencing a clinically relevant decline of HR-QoL at twelve months, a univariate logistic regression analysis was conducted including sex, age, living situation, education level, comorbidities and treatment type. At twelve months, none of these factors were associated with a decline in the HR-QoL summary score.

For the functional subscales, multivariable analyses showed that a clinically relevant decline of physical functioning was independently associated with older age (OR 2.7 95%CI 1.0-7.0). A clinically relevant decline of role functioning was associated with comorbidity burden (OR 9.2 95%CI 2.3-36.9). For cognitive functioning, the only factor independently associated with a clinically relevant decline was treatment with adjuvant chemotherapy (OR 3.5 95%CI 1.2-9.4). For global health status, emotional and social functioning, there were no significant associations at a multivariable level.

DISCUSSION

This study evaluates the changes in HR-QoL one year after surgical treatment in patients with primary resectable colon cancer, showing that changes of HR-QoL at group level differed from changes of HR-QoL at individual level. At group level, although sometimes statistically significant, no clinical relevant changes of HR-QoL summary score and the EORTC-QLQ-C30 subscales twelve months post-surgery were observed. Nevertheless, on individual level there is a risk of 15% to experience a clinically relevant decline in HR-QoL summary score one year post-surgery. For the five functional subscales of the EORTC-QLQ-C30, the risk of a clinically relevant decline in HR-QoL varied between 11% for emotional functioning up to 28% for physical functioning. Older patients were at risk of losing physical functioning, patients with at least one comorbidity were at risk of losing role functioning and those who received adjuvant chemotherapy were at risk of a decline of cognitive functioning twelve months post-surgery.

In the treatment decision-making process, patients need to be optimally informed about the efficacy, safety and impact of a treatment. In general, this information is based on data reflecting averages at a group level. However, these group averages cannot always be easily translated to an individual patient. Our findings illustrate that it might be challenging to properly inform an individual patient in the treatment decision-making process. Although at group level no clinically relevant changes in HR-QoL were observed, there was still a considerable chance of a clinically relevant difference of HR-QoL at an individual level. Two out of five patients experienced an improvement of their global health status one year post-surgery. After all, colon cancer treatment can reduce tumour-related complaints and therefore, patients could experience a clinically relevant improvement of HR-QoL one year post-surgery. Reversely, one out of three patients is at risk of a loss of physical functioning one year post-surgery. This discrepancy between changes of HR-QoL at group level versus individual level should be acknowledged by physicians and explained to patients in daily practice. Sharing this information should be just as important as highlighting the adverse events of chemotherapy such as heart failure or neurotoxicity.

Although our results show that there is a relevant discrepancy between changes in HR-QoL at group level versus individual level, research data are mainly presented at a group level. Hence, data from clinical trials cannot be easily extrapolated to individuals in the general

population. Also, hardly any consideration is given to the spread of a group average in research data, and many oncological trials which assess quality of life present their results as a single sentence statement.[17] Consequently, changes in HR-QoL at an individual level might be underestimated. Therefore, physicians need to be critical while interpreting these group averages of research data. Furthermore, future studies should more often consider presenting their data at an individual level in order to improve the knowledge about the impact of cancer treatment.

Additionally, it is of clinical importance to identify those patients who are at risk of a clinically relevant decline in HR-QoL one year post surgery. However, we found that different risk factors were relevant for each of the EORTC-QLQ-C30 functional subscales, without a common denominator. Similar to findings in previous studies,[7,18] we found that older patients are at risk of losing physical functioning which might be related to loss of reserve capacity with ageing. Although a previous study showed that a high comorbidity burden can cause a decline in various HR-QoL subscales,[19] in our study a high comorbidity burden was only a risk factor for a loss in role functioning. Finally, patients who received adjuvant chemotherapy were at risk of a clinically relevant decline of cognitive functioning, as has been described previously.[20–23] Still, no consistent independent predictor of a clinically relevant decline in HR-QoL was identified among the risk factors that were assessed. However, data on potential predictors of decline in HR-QoL, such as patient's functional status, cognitive status, complications or adverse events during treatment were lacking.[8] This highlights the importance of collecting patient characteristics in more detail and across a wide range of domains in future research, in order to optimize the recognition of those who might be at risk of a clinically relevant decline of HR-QoL one year post-surgery.

This study had some limitations. The PLCRC project was not developed with this specific research question in mind, but as general registry of colorectal cancer patients in the Netherlands that could be used to answer future research questions regarding all phases of the colorectal disease or treatment trajectory. For this reason, the cohort not only strives to include all patients with a new cancer diagnosis, but also allowed the recruitment of patients whose disease trajectory had already started prior to the start of the PLCRC project. This explains why we had to exclude a significant number of patients, as we were only interested in those with a baseline measurement taken before the surgery. A second limitation is that the PLCRC database contains only a limited amount of potential predictors of a clinically relevant HR-QoL decline and thus we were unable to perform more detailed prediction analysis. Finally, some selection bias could not be excluded. Colon cancer treatment, particular adjuvant chemotherapy, tends to be offered to relatively fit patients and those patients might be more resilient than frail patients. In addition, individuals who withdraw their cohort participation may have had more or worse symptoms which may affect their experience of HR-QoL and therefore, we may underestimate the risk of a clinically relevant decline of HR-QoL one year post-surgery.

Nevertheless, our findings highlight the importance of analysing individual changes in HR-QoL to identify those who might be at risk of losing HR-QoL after colon cancer treatment. Recognizing these patients can contribute to a more individualized approach of colon cancer treatment. Reconsidering treatment proposals based on patient characteristics and preferences could lead to pre-emptive treatment adjustments. In addition, patients could receive extra support during treatment. For example, to reduce the risk of complications, adverse events or readmissions after surgical treatment, an enhanced recovery program can be established.[24,25] Another strategy to enhance patients' preoperative condition for improving postoperative outcome might be prehabilitation. Physical prehabilitation as well as nutritional prehabilitation may improve patients physical condition and recovery after surgery.[26,27] In addition, although evidence is limited, there might be a role for physical training in preventing cognitive impairment after cancer treatment.[28] Maintaining physical and cognitive functioning could have a positive impact of HR-QoL and may reduce the risk of a clinically relevant decline in HR-QoL post- surgery.[29]

In conclusion, only trivial changes of HR-QoL were observed after colon cancer treatment on group level whereas on individual level at least one out of ten patients can experience a decline of HR-QoL one year post surgery. Although no consistent risk factor for a clinically relevant decline of HR-QoL was found, it is important to consider individual differences while making a treatment decision.

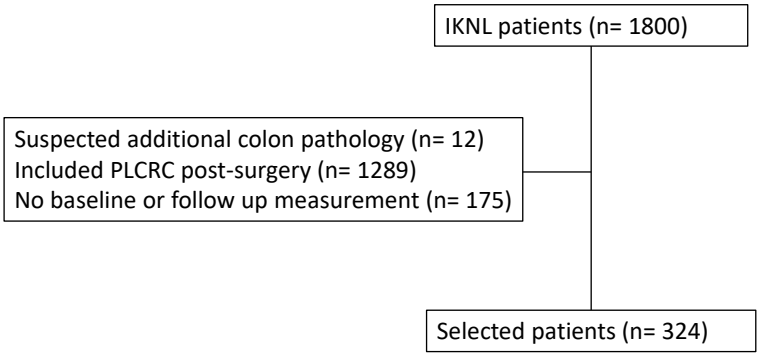
REFERENCES

1. Institute NC. Cancer Stat Facts [Internet]. [cited 2019 Jul 21]. Available from: https://seer.cancer.gov
2. Integraal Kankercentrum Nederland (IKNL). Cijfers over Kanker [Internet]. [cited 2020 Jan 6]. Available from: https://www.iknl.nl/nkr-cijfers
3. Federatie Medisch specialisten. Colorectal Cancer Dutch Guideline Oncoline version 3.0 [Internet]. 2014. Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/colorectaalcarcinoom.pdf
4. The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403–9.
5. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.
6. Mohile SG, Hurria A, Cohen HJ, Rowland JH, Leach CR, Arora NK, et al. Improving the quality of survivorship for older adults with cancer. Cancer. 2016;122:2459–68.
7. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SAC, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. J Geriatr Oncol. 2015;6:153–64.
8. Couwenberg AM, Burbach JPM, van Grevenstein WMU, Smits AB, Consten ECJ, Schiphorst AHW, et al. Effect of Neoadjuvant Therapy and Rectal Surgery on Health-related Quality of Life in Patients With Rectal Cancer During the First 2 Years After Diagnosis. Clin Colorectal Cancer. 2018;500–12.
9. Cella D, Bullinger M, Scott C, Barofsky I, Aaronson N, Berzon R, et al. Group vs individual approaches to understanding the clinical significance of differences or changes in quality of life. Mayo Clin Proc. 2002;77:384–92.
10. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, Dik VK, May AM, Meijer GA, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. Acta Oncol (Madr). 2016;55(11):1273–80.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40:373–383.
12. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL TA. AJCC Cancer Staging Manual 7th edition [Internet]. 2010. Available from: http://cancerstaging.org/references-tools/deskreferences/Documents/AJCC 7th Ed Cancer Staging Manual.pdf
13. Fayers P, Aaronson N, Bjordal K. EORTC QLQ-C30 scoring manual. Europen Organization for Research and Treatment of cancer. 2001.
14. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol. 2016;69:79-88.
15. Cocks K, King MT, Velikova G, St-James MM, 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.
16. Norman GR, Sloan JA, Wyrwich KW. Interpretation of Changes in Health-related Quality of Life. Med Care. 2003;41(5):582-92.
17. 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. 2017;26:65–71.
18. De Roo AC, Li Y, Abrahamse PH, Regenbogen SE, Suwanabol PA. Long-term Functional Decline After High-Risk Elective Colorectal Surgery in Older Adults. Dis Colon Rectum. 2020;63(1):75-83.
19. Cummings A, Grimmett C, Calman L, Patel M, Permyakova NV, Winter J, 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. 2018;27(10):2427-2435.
20. Vardy JL, Dhillon HM, Pond GR, Rourke SB, Bekele T, Renton C, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: A prospective, longitudinal, controlled study. J Clin Oncol. 2015;(33):4085–92.
21. Andreis F, Ferri M, Mazzocchi M, Meriggi F, Rizzi A, Rota L, et al. Lack of a chemobrain effect for adjuvant FOLFOX chemotherapy in colon cancer patients. A pilot study. Support Care Cancer. 2013;(21):583–90.
22. 22. Sales MVC, Suemoto CK, Apolinario D, Ser-

rao VT, Andrade CS, Conceição DM, et al. Effects of Adjuvant Chemotherapy on Cognitive Function of Patients With Early-stage Colorectal Cancer. Clin Colorectal Cancer. 2019;18(1):19–27.

23. Falleti MG, Sanfilippo A, Maruff P, Weih LA, Phillips KA. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: A meta-analysis of the current literature. Brain Cogn. 2005;(59):60–70.
24. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: A meta-analysis of randomized controlled trials. World J Surg. 2014;38:1531–41.
25. Slieker J, Frauche P, Jurt J, Addor V, Blanc C, Demartines N, et al. Enhanced recovery ERAS for elderly: a safe and beneficial pathway in colorectal surgery. Int J Colorectal Dis. 2017;32:215–21.
26. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N, et al. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. Gastroenterology. 2018;155(2):391-410.e4.
27. Bruns ERJ, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. Color Dis. 2016;18(8):267–77.
28. Campbell KL, Zadravec K, Bland KA, Chesley E, Wolf F, Janelsins MC. The Effect of Exercise on Cancer-Related Cognitive Impairment and Applications for Physical Therapy: Systematic Review of Randomized Controlled Trials. Physical Therapy. 2020;100(3):523-542.
29. Bours MJL, Linden BWA, Winkels RM, Duijnhoven FJ, Mols F, Roekel EH, et al. Candidate Predictors of Health-Related Quality of Life of Colorectal Cancer Survivors: A Systematic Review. Oncologist. 2016;21:433–52.

Appendix. Patient selection.



CHAPTER
9

Differences in the impact of surgery and adjuvant chemotherapy on resilience of health-related quality of life in patients with colon cancer

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ABSTRACT

Objective

This study aims to evaluate quality of life trajectory during the first year after surgical treatment in patients with resectable primary colon cancer.

Methods

Patients with resectable primary colon cancer diagnosed between 2013 and 2019 who received surgical treatment and adjuvant chemotherapy if indicated were selected from the Prospective Dutch ColoRectal Cancer cohort study (PLCRC). Health related quality of life (HR-QoL) was assessed using EORTC-QLQ-C30 questionnaire before surgery, and three and twelve months after surgery. HR-QoL scores varied between 0-100 and outcomes were compared according to age (<70 years, ≥70 years), comorbidity (yes, no) and treatment type (adjuvant chemotherapy, surgical treatment only). Based on the clinically relevant differences of HR-QoL over time, the extent of resilience of HR-QoL at twelve months post-surgery was calculated.

Results

For all 458 patients, the baseline level of HR-QoL summary score was relatively high with a mean of 87.9 (SD 11.5), and did not significantly differ between older and younger patients. The strongest decline of HR-QoL compared to baseline was observed at three months with a gradual recovery over time. Fourteen percent of all patients were non-resilient or showed a late decline at twelve months post-surgery. Compared to younger patients, older patients who received adjuvant chemotherapy were less resilient (respectively 53% and 32%, p=0.07) and at risk of a late decline in HR-QoL one year post-surgery (respectively 3% versus 16%, p=0.02). Comorbidity status had no significant impact on the HR-QoL trajectory.

Conclusion

Colon cancer treatment was associated with a decline in HR-QoL three months post-surgery, but most patients return to baseline level within twelve months. Although the minority were non-resilient or showed a late decline, it is important to recognize those patients who are at risk for a permanent loss of HR-QoL.

INTRODUCTION

Worldwide, colon cancer is the third most common cancer.[1] Although the incidence rate of colorectal cancer is falling last decade,[2] still approximately half of all patients with colon cancer are aged 70 years or older.[3] These older patients represent a heterogeneous population and are frequently excluded from clinical trial participation, specific treatment recommendations for older patients are often lacking. Also, older patients seem less willing to accept toxicity for additional survival benefit,[4] particularly when oncological treatment could potentially have a negative impact on functioning or quality of life.[5–7] Therefore, physicians will be confronted with an increasingly complex treatment decision-making process in older patients.

In the treatment decision-making process, tumour characteristics should be carefully weighed against patient characteristics and preferences. Nevertheless, treatment recommendations are mainly based on tumour characteristics and particularly in older patients, it can be difficult to consider whether standard colon cancer treatment – consisting of surgery and additional chemotherapy in high risk stage II or stage III disease[8] – will be the most appropriate treatment.

In order to improve the treatment decision-making process, more information about the impact of cancer treatment on daily life in older patients is needed. Previous research has shown that patients with colorectal cancer may experience a decline in quality of life within the first months after treatment, and this decline seems to be more pronounced in older or vulnerable patients.[9,10] Whether or not quality of life will recover over time, will depend on the patient's adaptive capacity.[11] This capacity to resist functional decline following a health stressor, or to subsequently recover physical and psychological health is called resilience.[12,13] In a previous study, we evaluated the changes in quality of life in colon cancer patients one year after cancer treatment. We demonstrated a relevant discrepancy between changes in quality of life at group level versus individual level. Only trivial changes of HR-QoL were observed after colon cancer treatment on group level whereas on individual level at least one out of ten patients can experience a decline of HR-QoL one year post surgery.[14] In the current analysis, we focus on changes in quality of life during the first year after colon cancer treatment including patient's resilience in quality of life. In addition, we assess whether these changes are related to age, comorbidity or treatment.

METHODS

Patient selection

Data of the multicentre "Prospective Dutch ColoRectal Cancer cohort" (PLCRC) were requested.[15] This nationwide observational cohort study includes adults with histologically proven colorectal cancer and registers longitudinal clinical data; while striving to include patients at the time of diagnosis, participation in the cohort is also possible at later stages in the treatment trajectory.

Of all approached patients, 90% consented to inclusion[15]. Socio-demographic and clinical characteristics of patients are collected by the Netherlands Cancer Registry (NCR) which now covers more than 95% of the Dutch population.[16] Patient, tumour and treatment characteristics were collected from the patient's hospital files, and longitudinal patient reported outcome measures such as quality of life by using validated questionnaires. All patients provided informed consent between 2013 and 2019 and the PLCRC study has been approved by the medical ethical review committee.[15]

Patients with resectable primary colon cancer who received surgical treatment and adjuvant chemotherapy if indicated were selected. The Dutch guideline recommend adjuvant chemotherapy for stage III disease and may also be considered for patients with a high risk stage II colon carcinoma. As we set out to analyse the impact of cancer treatment over time, we only included patients who completed the first measurement of HR-QoL prior to surgery, and who filled out a questionnaire at three or twelve months. Patients were excluded if primary irresectable tumour or additional colon pathology was suspected; this was based on available tumour- and treatment characteristics, for example patients who received neo-adjuvant therapy.

Data collection

Registered socio-demographic characteristics included sex, age at diagnosis, education level, living situation and comorbidities were collected. Comorbidities were classified according to the Charlson Comorbidity Index (CCI); however, data on comorbidities were not collected in all hospitals and therefore, comorbidities were only partly available.[17] Tumour characteristics consisted of tumour location and tumour stage according to the AJCC guideline.[18] Tumour stage was based on pathological disease stage information, supplemented by clinical stage information if pathological stage was unavailable. Treatment characteristics included type of surgical treatment, ileo/colostomy and postoperative surgical complications such as anastomic leakage and/or abscess. No data concerning type and completion of adjuvant chemotherapy regimen were available.

Health-related quality of life (HR-QoL) was assessed prior to surgical treatment (T0), and three (T3) and twelve months (T12) after surgery, using the Dutch version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30). This questionnaire consists of thirty items concerning five functional subscales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), nine symptom subscales and global health status.[19] The primary outcome for this analysis was the HR-QoL summary score , which is calculated based on the mean score of global health status and all functioning and symptom subscales.[20,21] In addition, results of the five functional subscales were used to address individual changes in these functional domains. Data from HR-QoL summary score as well as the functional subscales are presented on a range of 0 to 100 where higher scores signify better functioning and quality of life.[20]

Clinically relevant differences (CRD) in HR-QoL were assessed using a published guideline for the EORTC QLQ-C30, which categorises differences from trivial (difference of 0-6 points) to large (difference of at least 15 points).[22] We considered any difference in HR-QoL categorized as small, medium or large as clinically relevant. For emotional functioning and summary score, there is no CRD available; therefore Norman's rule of thumb was used to assess clinical relevance. This rule states that a difference of half a standard deviation (SD) or more can be regarded clinically relevant.[23] CRD in HR-QoL were classified as: stable, improvement, resilient, non-resilient, late decline. Patients who did not experience a CRD compared to baseline level were considered to have a stable level of HR-QoL. An improvement of HR-QoL was defined as a clinically relevant increase of HR-QoL. Resilience was defined as a recovery of HR-QoL to baseline level after a clinically relevant decline in HR-QoL at three months. Non resilience was defined as a clinically relevant decline in HR-QoL at three months that continued up to twelve months. Late decline was defined as a clinically relevant decline at twelve months without experiencing a clinically relevant decline in HR-QoL at three months.

Statistical analyses

All analyses were performed in IBM SPSS Statistics 23. Socio-demographic characteristics and clinical characteristics as well as the outcomes of the EORTC-QLQC30 were presented as means (SD) for normally distributed continuous variables, medians (range) for not-normally distributed variables or frequencies and proportions for categorical variables. Changes in quality of life over time were assessed according to age, comorbidities and type of treatment. For comparison between patients aged <70 years and ≥70 years, patients with or without comorbidities (CCI ≥1, CCI 0) and for comparison between treatment groups (adjuvant chemotherapy (yes, no)), Pearson's chi-square test or Fishers exact tests were used for categorical variables. Depending on distribution of data, independent samples T-tests or Mann Whitney U tests were used to test differences in continuous variables. Differences in mean changes in HR-QoL compared to baseline measurements were analysed with the paired T-test. P-values smaller than 0.05 were considered statistically significant.

RESULTS

Patient selection and baseline characteristics

Between 2013 and 2019, 1800 patients with a diagnosis of colon cancer were registered in the PLCRC database. Twelve patients suspected for additional colon pathology, 1289 patients who provided informed consent post-surgery and 41 patients without HR-QoL baseline measurement or follow-up measurement were excluded, resulting in 458 eligible patients for this analysis, of whom 40% (n=181) were aged 70 years and older (Appendix 1a). Baseline characteristics of all included patients and their HR-QoL level at baseline are presented in Table 1. Mean age of all patients was 66.4 years (SD 9.5) and 68% were men. Patients aged 70 years and older more often had a CCI of ≥2 compared to patients aged younger than 70 years (20% versus 6% respectively, p=0.001) and a low education level

(51% versus 29% in younger patients, p<0.001). Age groups were comparable in disease characteristics such as tumour stage and location (data not shown).

At baseline, the mean HR-QoL summary score was 87.9 (SD 11.5), which did not significantly differ between older and younger patients (Table 1). For the various functional subscales, mean baseline HR-QoL varied between 77.5 (SD 18.3) for global health status and 90.5 (SD 17.1) for social functioning. Compared to younger patients, baseline HR-QoL in older patients was significantly lower for physical functioning (mean 85.5 versus 92.8 respectively, p<0.001) and slightly higher for emotional functioning (mean 82.7 versus 80.7 respectively, p=0.07) and cognitive functioning (mean 91.7 versus 89.2, p=0.08).

Table 1. Baseline characteristics of all included patients, stratified by age.

	All (n=458)	<70y (n=277)	≥70y (n=181)	P-value
Age in years (mean ± SD)	66.4 ± 9.5	60.5 ± 6.9	75.4 ± 4.7	
Sex				
Men	310 (68%)	175 (63%)	135 (75%)	0.01
CCI				
0	133 (61%)	90 (70%)	43 (48%)	0.001
1	58 (27%)	30 (24%)	28 (32%)	
≥2	26 (12%)	8 (6%)	18 (20%)	
Missing	241	149	92	
Current living situation				
Living alone	73 (17%)	38 (15%)	35 (20%)	0.20
With partner and/or children	352 (83%)	212 (85%)	140 (80%)	
Missing	33	27	6	
Education level*				
Low	160 (38%)	73 (29%)	87 (51%)	<0.001
Middle	112 (26%)	76 (31%)	36 (21%)	
High	152 (36%)	103 (41%)	49 (29%)	
Missing	34	25	9	
Tumour stage#				
1	133 (29%)	89 (32%)	44 (24%)	0.18
2	163 (36%)	96 (35%)	67 (37%)	
3	162 (35%)	92 (33%)	70 (39%)	
HR-QoL baseline				
Summary score	87.9 ± 11.5	88.3 ± 11.1	87.3 ± 12.0	0.39
Global health status	77.5 ± 18.3	78.0 ± 17.2	76.6 ± 19.7	0.43
Physical functioning	89.9 ± 14.7	92.8 ± 12.6	85.5 ± 16.4	<0.001
Role functioning	88.3 ± 20.5	89.0 ± 19.9	87.0 ± 21.3	0.31
Emotional functioning	80.7 ± 18.4	79.5 ± 18.2	82.7 ± 18.5	0.07
Cognitive functioning	90.2 ± 15.6	89.2 ± 16.6	91.7 ± 13.8	0.08
Social functioning	90.5 ± 17.1	90.3 ± 16.9	90.8 ± 17.4	0.77

*Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less
tumour stage according to the AJCC guideline

Of all patients, surgical treatment mainly consisted of hemicolectomy (61%) or sigmoid resection (29%). Registered postoperative surgical complications were present in 2% of the patients and 6% received an ileostomy or colostomy. Adjuvant chemotherapy was prescribed more often to younger patients (37% versus 24% in older patients, p=0.006). The oldest patient who received adjuvant chemotherapy was 82 years old.

Quality of life over time

After three and twelve months, 436 and 324 patients completed the EORTC QLQ-C30 questionnaires respectively. The mean change of HR-QoL summary score compared to baseline is depicted in Figure 1, showing a significant decline (3.7 points, p<0.001) at three months with subsequent recovery and increasing to 2.3 points above baseline at twelve months (p<0.001). These changes at group level are not clinically relevant.

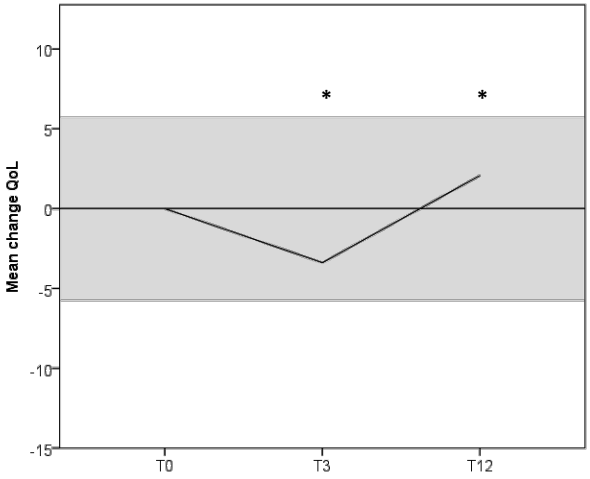


Figure 1. Mean change in HR-QoL summary score compared to baseline measurement during twelve months follow up of all patients. T0; prior to surgery; T3: three months after surgery; T12: twelve months after surgery. Changes within the gray zone are of no or trivial clinically relevance. * significant difference of HR-QoL compared to baseline level.

Figure 2 shows the course of HR-QoL summary score for individual patients who filled out EORTC-QLQ-C30 questionnaire at baseline, at three months and twelve months (n=305). At three months, 35% of all patients experienced a clinically relevant decline in HR-QoL summary score. The majority of those who experienced a decline (76%) demonstrated resilience. At twelve months, 14% of all patients still experienced loss in the HR-QoL summary score: 8% due to non-resilience and 6% due to late decline.

Course of quality of life according to treatment type, age and comorbidity

Details on the course of HR-QoL according to age and treatment type are shown in Figure 3. Compared to those who received surgical treatment only, patients who received adjuvant chemotherapy less often experienced a stable HR-QoL summary score during follow up (respectively 48% and 16%, p<0.001). However, irrespective of treatment type, the majority of both older and younger patients recovered to baseline level of HR-QoL summary score

at twelve months (in 83% and 87% respectively, p=0.79). Age-related differences were only observed in those who received adjuvant chemotherapy: older patients seemed to be less often resilient than younger patients (respectively 32% and 53%, p=0.07) and more often experienced a late decline in HR-QoL summary score (16% vs 3% in younger patients, p=0.02). Comorbidity status did not have a significant impact on the HR-QoL during the first year post surgery (data not shown).

For global health status and the five functional subscales, no age-related differences of the HR-QoL trajectory were observed when clinically relevant differences of HR-QoL were dichotomized in patients who experienced a stable or improved HR-QoL or were resilient, and those who experienced a late decline or were non resilient (Appendix 1b).

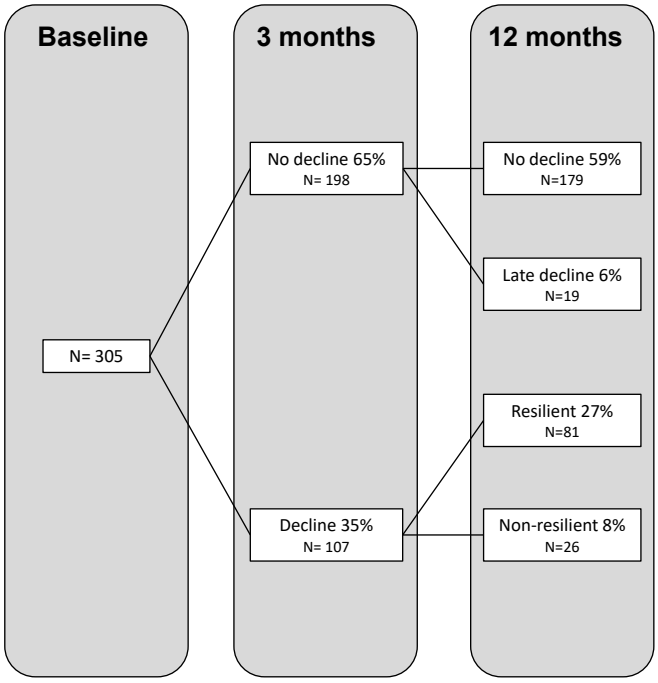


Figure 2. Resilience in all patients who filled out EORTC-QLQ-C30 questionnaire at baseline, at three and twelve months.

DISCUSSION

The current study assessed the changes in HR-QoL during the first year after surgical treatment in patients with primary resectable colon cancer. We found that after a small decline in HR-QoL summary score three months post-surgery, HR-QoL on average recovered to baseline level. Still, 14% of all patients were non-resilient or experienced a late decline in HR-QoL twelve months post-surgery. Age related differences were only observed in older patients who received adjuvant chemotherapy; those were less resilient and at risk of a late decline in HR-QoL one year after start of treatment.

Similar to previous studies, our findings appear to be comparable and also showed a temporary decline of HR-QoL during the first months after surgery with a likelihood of returning to baseline level of HR-QoL one year after treatment. Conflicting results were observed in studies evaluating age or type of treatment as predictor of HR-QoL in colorectal cancer survivors,[24] whereas our findings demonstrated a larger deterioration of HR-QoL in older patients who received adjuvant chemotherapy. In addition, previous studies showed the presence of comorbidities as a risk factor for a deterioration of HR-QoL after treatment;[24] as comorbidity status was missing in half of our study population, this could not be confirmed in our study. However, previous studies evaluating HR-QoL were mainly conducted in colorectal or rectal cancer only,[25] while our study focussed specifically on colon cancer. This could affect comparisons with these prior studies, as rectal surgery is quite different from colon surgery, and additional treatments (chemotherapy, radiotherapy) also differ.

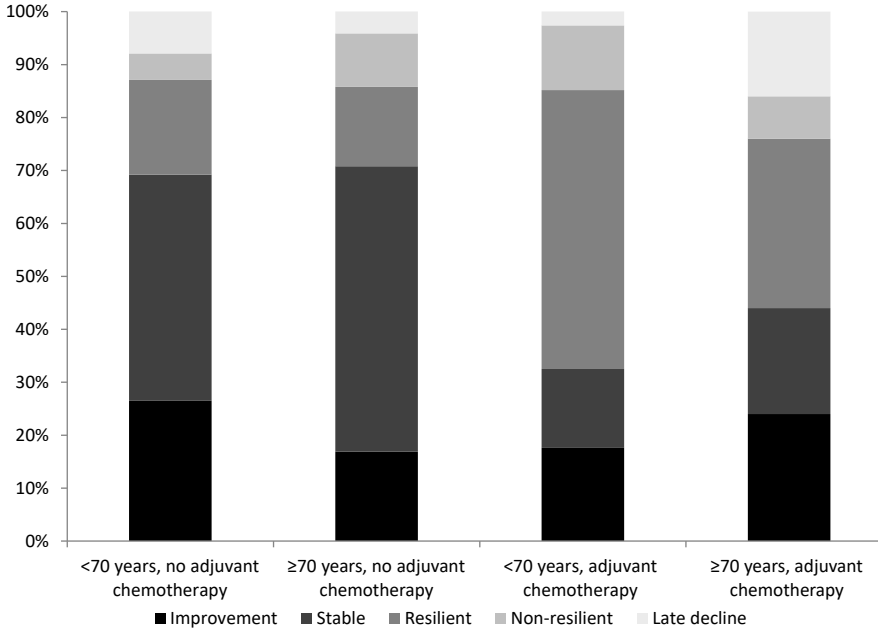


Figure 3. Clinically relevant differences of HR-QoL summary score at twelve months compared to baseline level, stratified by age and the reception of adjuvant chemotherapy.

Some limitations of this study should be considered. First, the PLCRC project was not developed with this specific research question in mind, but as general registry of colorectal cancer patients in the Netherlands that could be used to answer future research questions regarding all phases of the colorectal disease or treatment trajectory. For this reason, the cohort not only strives to include all patients with a new cancer diagnosis, but also allowed the recruitment of patients whose disease trajectory had already started prior to the start of the PLCRC project. This explains why we had to exclude a significant number of patients, as we were only interested in those with a baseline measurement taken before the surgery. Second, a certain selection bias cannot be excluded. Older patients may receive a less aggressive chemotherapy regimen compared to younger patients and it is possible that older patients were carefully selected pre-operatively. After all, omission of surgical treatment and

adjuvant chemotherapy in patients with colorectal cancer increases with advancing age.[14] Second, no data were available concerning patient's physical or cognitive status at baseline (e.g. WHO performance status or frailty level) and course of treatment (e.g. post-operative non-surgical complications or adverse events due to adjuvant chemotherapy). Although it could be expected that post-operative complications are associated with long-lasting negative impact on HR-QoL,[10] this lack of data prevented us from assessing these aspects associated with the course of HR-QoL. It would be of interest to include more patient characteristics and information about the course of treatment in future studies.

At the onset of the study, we hypothesized that irrespective of treatment type, older patients would be more affected by colon cancer treatment than younger patients, given their lower physiological reserves and increasing comorbidities. However, this was only observed in older patients who received adjuvant chemotherapy. There could be several reasons why we found relatively few age-related differences. First of all, it is possible that there are in fact only limited differences in the impact of colon cancer treatment, irrespective of age. Second, it could be that patient selection meant that those older patients whose low reserves or comorbidities were likely to negatively affect treatment outcome, did not undergo surgical resection. Finally, the lack of differences might reflect the dynamics of the definition of good quality of life as life progresses. On the one hand, younger patients could experience a greater impact of cancer diagnosis and its treatment due to higher work-related and social demands. On the other hand, the way people experience their quality of life could be affected by the response shift phenomenon in which people alter their internal standards, values and conceptualisation of HR-QoL when they experience changes in their health status.[26] In this situation, an inevitable decline in physical or cognitive functioning during ageing or disease, is not necessarily associated with a lower level of HR-QoL. Still, older patients who received adjuvant chemotherapy were more likely to be non-resilient or experience a late decline in HR-QoL one year post-surgery than their younger counterparts. This may suggest they had limited reserve capacity and highlights the importance of carefully selecting patients pre-operatively.

Our study provides insight in the risk of non-resilience or late decline of HR-QoL in patients with colon cancer specifically which may support patients and physicians in the treatment decision making process. In addition to information about the efficacy and safety of a treatment, there is an increasing interest in understanding the impact of cancer treatment on patient related outcomes such as quality of life.[27–29] Although a slight increase of measuring patient related outcomes in clinical oncological trials is observed, still limited evidence is available,[30] complicating the improvement of patient education.

Cancer treatment decisions are frequently based on national guidelines in which specific treatment recommendation for older patients are limited. In order to individualize cancer treatment, particularly in older patients or those with comorbidities, it is recommended to include patient's level of frailty.[31] Although frailty is considered a dynamic process, patient's frailty status has often been operationalized as a static measure which does not reflect

someone's adaptive capacity to a health stressor.[12] Therefore, it could be of interest to estimate patient's level of resilience pre-operatively, instead of a traditional frailty score. Strategies to assess patient's physical and psychological potential to recover after colon cancer treatment are needed. In our previous research we found no predictive markers for a persistent decline in HR-QoL at one year post-surgery.[14] It is known that resilience is associated with optimism, adaptive coping strategies, social support and being physically active and independent, whereas depression and hopelessness are associated with low resilience.[32] In the treatment decision making process, these characteristics could be discussed with patient, family and general practitioner or if necessary, geriatrician, in order to assess whether the HR-QoL trajectory of a patient with colon cancer could be at risk of non-resilience. Additionally, if we can create more insight into factors that may influence the HR-QoL trajectory of patients with colon cancer, future research may address whether interventions can enhance the degree of resilience.[32]

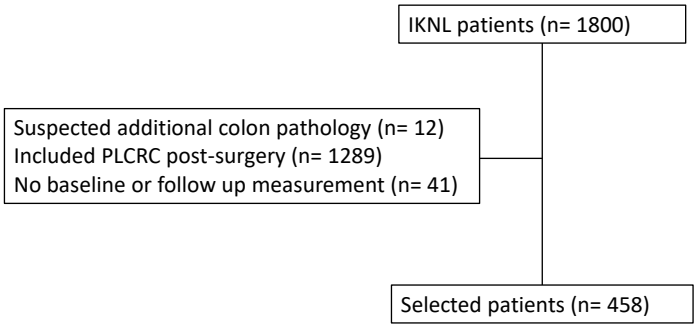
In conclusion, oncological treatment in patients with colon cancer is associated with a decline in HR-QoL at three months, but within twelve months, three quarter of those patients returned to baseline level. Still, particularly older patients who received adjuvant chemotherapy were at risk of non-resilience or a late decline in HR-QoL. These data could help in patients counselling regarding colon cancer treatment.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;(68):394–424.
2. Institute NC. Cancer Stat Facts [Internet]. [cited 2019 Jul 21]. Available from: https://seer.cancer.gov
3. Kankerregistratie N. Cijfers over kanker [Internet]. [cited 2019 Oct 2]. Available from: https://www.cijfersoverkanker.nl/
4. Hurria A, Mohile SG, Dale W. Research Priorities in Geriatric Oncology: Addressing the Needs of an Aging Population. JNCCN J Natl Compr Cancer Netw. 2012;10(2):286–8.
5. Pallis AG, Ring A, Fortpied C, Penninckx B, van Nes MC, Wedding U, et al. Eortc workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. Ann Oncol. 2011;22(8):1922–6.
6. Van Leeuwen KM, Van Loon MS, Van Nes FA, Bosmans JE, De Veti HCW, Ket JCF, et al. What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):1–39.
7. Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. J Natl Cancer Inst. 1994;86(23):1766–70.
8. Federatie Medisch specialisten. Colorectal Cancer Dutch Guideline Oncoline version 3.0 [Internet]. 2014. Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/colorectaalcarcinoom.pdf
9. Hamaker ME, Prins MC, Schiphorst AH, van Tuyl SAC, Pronk A, van den Bos F. Long-term changes in physical capacity after colorectal cancer treatment. J Geriatr Oncol. 2015;6:153–64.
10. Couwenberg AM, Burbach JPM, van Grevenstein WMU, Smits AB, Consten ECJ, Schiphorst AHW, et al. Effect of Neoadjuvant Therapy and Rectal Surgery on Health-related Quality of Life in Patients With Rectal Cancer During the First 2 Years After Diagnosis. Clin Colorectal Cancer. 2018;500–12.
11. Tamura S, Suzuki K, Ito Y, Fukawa A. Factors related to the resilience and mental health of adult cancer patients: a systematic review. Support Care Cancer. 2021;29(7):3471-3486
12. Gijzel SMW, Whitson HE, van de Leemput IA, Scheffer M, van Asselt D, Rector JL, et al. Resilience in Clinical Care: Getting a Grip on the Recovery Potential of Older Adults. J Am Geriatr Soc. 2019;67(12):2650–7.
13. Seiler A, Jenewein J. Resilience in cancer patients. Front Psychiatry. 2019;10(208).
14. E.R.M. Scheepers, G.R. Vink, A.H.W. Schiphorst, M.H. Emmelot-Vonk, L.H. van Huis-Tanja MEH. The impact of surgery and adjuvant chemotherapy on health-related quality of life in patients with colon cancer: changes at group-level versus individual-level. Submitted.
15. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, Dik VK, May AM, Meijer GA, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. Acta Oncol (Madr). 2016;55(11):1273–80.
16. Integraal Kankercentrum Nederland (IKNL). Cijfers over Kanker [Internet]. [cited 2020 Jan 6]. Available from: https://www.iknl.nl/nkr-cijfers
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40:373–383.
18. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL TA. AJCC Cancer Staging Manual 7th edition [Internet]. 2010. Available from: http://cancerstaging.org/references-tools/deskreferences/Documents/AJCC 7th Ed Cancer Staging Manual.pdf
19. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.
20. Fayers P, Aaronson N, Bjordal K. EORTC QLQ-C30 scoring manual. Europen Organization for Research and Treatment of cancer. 2001.
21. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol. 2016;69:79-88.
22. Cocks K, King MT, Velikova G, St-James MM, 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.
23. Norman GR, Sloan JA, Wyrwich KW. Interpretation of Changes in Health-related Quality of Life.

Med Care. 2003;41(5):582-92.
24. Bours MJL, Linden BWA, Winkels RM, Duijnhoven FJ, Mols F, Roekel EH, et al. Candidate Predictors of Health-Related Quality of Life of Colorectal Cancer Survivors: A Systematic Review. Oncologist. 2016;21:433–52.
25. Cabilan CJ, Hines S. The short-term impact of colorectal cancer treatment on physical activity, functional status and quality of life: A systematic review. JBI Database Syst Rev Implement Reports. 2017;15(2):517–66.
26. Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MAG, Fayers PM. The clinical significance of adaptation to changing health: A meta-analysis of response shift. Qual Life Res. 2006;15(9):1533–50.
27. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the Treatment Preferences of Seriously Ill Patients. N Engl J Med. 2002;346(14):1061–5.
28. Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, et al. End points and trial design in geriatric oncology research: A joint European Organisation for Research and Treatment of Cancer-Alliance for clinical trials in oncology-international society of geriatric oncology position article. J Clin Oncol. 2013;31(29):3711–8.
29. Schnipper LE, Davidson NE, Wollins DS, Blayney DW, Dicker AP, Ganz PA, et al. Updating the American society of clinical oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol. 2016;34(24):2925–34.
30. E.R.M. Scheepers, L. H. van Huis-Tanja, M. H. Emmelot-Vonk ME, Hamaker. Study objectives in clinical trials in older patients with solid malignancies: do we measure what matters? Qual Life Res. 2021;30(7):1833–9.
31. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, 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):241–25.
32. MacLeod S, Musich S, Hawkins K, Alsgaard K, Wicker ER. The impact of resilience among older adults. Geriatr Nurs (Minneap). 2016;37:266–72

Appendix 1a. Patient selection.



Appendix 1b. Clinically relevant differences of HR-QoL at twelve months compared to baseline level, stratified by age.

	Improvement/stable/resilience	Non resilience/late decline	P-value
Global health status **			0.93
<70 years	139 (74%)	48 (26%)	
≥ 70 years	82 (74%)	29 (26%)	
Total	221 (74%)	77 (26%)	
Physical functioning			0.29
<70 years	143 (75%)	48 (25%)	
≥ 70 years	79 (69%)	35 (31%)	
Total	222 (73%)	83 (27%)	
Role functioning*			0.45
<70 years	161 (85%)	29 (15%)	
≥ 70 years	92 (81%)	21 (19%)	
Total	253 (84%)	50 (16%)	
Emotional functioning*			0.98
<70 years	168 (88%)	22 (12%)	
≥ 70 years	100 (89%)	13 (11%)	
Total	268 (88%)	35 (12%)	
Cognitive functioning*			0.68
<70 years	142 (75%)	48 (25%)	
≥ 70 years	82 (73%)	31 (27%)	
Total	224 (74%)	79 (26%)	
Social functioning*			0.97
<70 years	160 (84%)	30 (16%)	
≥ 70 years	95 (84%)	18 (16%)	
Total	255 (84%)	48 (16%)	

CHAPTER
10

Perceived social support in patients with endometrial or ovarian cancer: a secondary analysis from the ROGY Care study

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ABSTRACT

Objective

Social support may reduce the amount of psychological distress and increase quality of life. This study assessed whether socio-demographic, personality, and clinical characteristics predict the level of perceived social support in patients with endometrial or ovarian cancer.

Methods

Patients with endometrial or ovarian cancer who participated in the ROGY Care study and completed the Multidimensional Scale of Perceived Social Support(MSPSS) 12 months after inclusion were eligible for this study (n=238). Logistic regression analysis was conducted to determine the predictive value of socio-demographic characteristics, personality and clinical characteristics after initial treatment on the perceived level of social support after 12 months.

Results

Of the 238 patients (mean age 64.8 ± 9.4 years), 139 patients had endometrial cancer (58%) and 99 patients had ovarian cancer (42%). One year after inclusion, the level of perceived social support was high in 79% of all patients (n=189). Patients experiencing low level of perceived social support (n=49) less often had a partner (69% versus 83% in patients with high level of perceived social support; p=0.029), had a higher education level (24% versus 15% respectively; p=0.013) and a distressed (type D) personality was more common (40% versus 16% respectively; p<0.001). In multivariable analysis, a type D personality, characterized by negative affect and social inhibition, was the only independent predictor of a low level of perceived social support (OR 2.96; 95% CI 1.37-6.37;p=0.006).

Conclusions

In patients with endometrial or ovarian cancer, the level of perceived social support is mainly associated with a distressed (type D) personality. Those patients can be at risk of experiencing less social support. Future research is needed to assess whether they might benefit from additional support during cancer diagnosis and treatment.

INTRODUCTION

Gynaecological cancers account for almost 15% of all reported cancer cases in females worldwide of which 70% can be attributed to endometrial and ovarian cancer in industrialized countries.[1] Endometrial cancer has a more favourable prognosis than ovarian cancer, with a five year survival of 80% and 38% respectively.[2] Women diagnosed with gynaecological cancer often experience treatment-related side effects.[3] These side effects can lead to psychological distress and decreased quality of life.[4,5]

Social support appears to be an important protective factor that may reduce the amount of distress and increase quality of life.[6,7] Social support refers to the psychological and material resources provided by one's social network (e.g. partner, family, friends or health care professionals), intended to benefit the ability to cope with stress.[8] Social support includes instrumental support (provision of material aid), informational support (provision of relevant information) and emotional support (provision of empathy, caring, trust). According to the socio-emotional selectivity theory, the need for social support may vary throughout life.[9,10]

Although the relation between social support and the level of distress is not completely understood, it is known that distress will activate the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA)-axis or changes in behaviour.[6,11] Social support is suggested to be an important stress resilience factor: interpersonal relationships may influence patient's thoughts and behaviour which can reduce the level of distress.[12] As a result, patients could be less prone for physical and psychiatric disorders, such as cardiovascular disease, depression and anxiety.[6]

Nearly half of patients with gynaecological cancer report an unmet need for support.[3,13] However, knowledge about potential predictors of perceived social support is limited. Previous studies in various cancer types, demonstrated that patients without a partner[14,15] and patients with a lower education level[15–17] or socio-economic status[15,16] perceive a lower level of social support. Furthermore, personality traits such as low levels of extraversion, or openness, and high level of neuroticism are risk factors of a less perceived social support.[18] Patients with a distressed (type D) personality, who typically experience negative emotions and avoid social interactions may be at risk of experiencing less social support.[19,20] The role of age in the level of perceived social support revealed conflicting data,[15,16,21] some reported a higher unmet need for support in younger[21] or older gynaecological cancer patients,[16] whereas some did not find an association with age.[15]

In order to better meet the individual needs of patients after initial treatment of gynaecological cancer and during survivorship, awareness of patient's perceived social support and factors that affect it could be helpful. Therefore, the aim of the current study is to assess whether socio-demographic, personality and clinical characteristics predict the level of perceived social support in patients with endometrial or ovarian cancer. We hypothesized that older age, type D personality and intensity of treatment would be mainly associated with the level

of perceived social support.

METHODS

Study design and population

This study is a secondary analysis of the ROGY Care trial; a trial that referred to the 'Registrationsystem Oncological GYnecology', a web-based patient registration system used by gynaecologists in the South of the Netherlands since 2006. This prospective cluster randomized controlled trial was conducted between 2011 and 2016 in twelve hospitals in the South of the Netherlands, and addressed the effects of providing a Survivorship Care plan (SCP) to improve information provision and post-treatment care. Usual care was compared with 'SCP care' in which information about the tumor stage and treatment was personally discussed with the patient and a document was provided.[22]

As the SCP is a form of informational support, we presumed that the intervention did not affect the level of perceived social support as this intervention focuses on emotional support. Therefore, data of both trial arms were combined for this observational study. Adult patients (≥18 years), diagnosed with endometrial or ovarian cancer and receiving cancer treatment with curative intent were eligible for this study. Patients who were not treated with curable intent or were not able to complete a questionnaire in Dutch were excluded. After initial treatment and after 6, 12, 18 and 24 months of follow up, data concerning patient reported outcomes were collected.[22–24] However, perceived social support was only measured at 12 months. Therefore, for the current study, we used socio-demographic characteristics, type D personality, clinical characteristics at baseline and the level of perceived social support at 12 months. All patients provided informed consent prior to enrollment and this study was approved by the medical research ethics committees of the participating hospitals and executed in accordance with the Declaration of Helsinki (2008).[22]

Measures

Socio-demographic variables were obtained from the questionnaire and included age at diagnosis, self-reported comorbidities (assessed by the adapted Self-administered Comorbidity Questionnaire[25]), partner status (yes, no) and educational level (low (no primary school), intermediate (lower general secondary education/vocational training), high (high vocational training/university). The validity and reliability of the adapted Self-administered Comorbidity Questionnaire was satisfactory (Cronbach's Alpha 0.75, test-retest correlations 0.94).[25,26] Clinical variables were derived from the Netherlands Cancer Registry (NCR), and included cancer type, FIGO stage and type of treatment. Type D personality was assessed by the DS14 at baseline.[27] This questionnaire consists of a negative affectivity scale and a social inhibition scale which both contains seven items with statements that people often use to describe themselves. Answers were rated on a scale from zero to four, where zero indicated 'false' and four indicated 'true'. Only if both scales are positive (score ≥10), a type D personality was qualified. The internal consistency and reliability of negative affectivity

scale and social inhibition scale were satisfactory (Cronbach's Alpha of respectively 0.86 and 0.88; test-retest correlations of respectively 0.72 and 0.82).[27] One year after inclusion the perceived social support was measured with the Multidimensional Scale of Perceived Social Support (MSPSS).[28] This questionnaire contains twelve items in which the perceived social support of significant other, family and friends was measured. Answers were rated on a scale from one to seven, where one indicated 'very strongly disagree' and seven indicated a 'very strongly agree' (Appendix 1a). Higher scores indicate higher level of social support. The outcome of the MSPSS was composed by the mean of the given answers on the total scale or subscale (significant other, family, friends).[28] Only patients who completed at least 50% of the questions of each subscale (2 out of 4 questions) were included in this analysis. Internal consistency of the domain scales in our sample (Cronbach Alpha's, significant other=0.935; family=0.944; friends=0.959; total score=0.959) and test-retest correlations of the original study in undergraduates and of the Dutch version of MSPSS in cardiac patients was satisfactory.[28,29] For the purpose of this study, the MSPSS scores were dichotomized into a low level and high level of perceived social support. Based on the answer options, a score between 1 and 5 ('very strongly disagree' to 'neutral') was considered as low level of perceived social support and a score of 5 or more 'mildly agree' to 'very strongly agree') was considered as a high level of social support.[30]

Predictors of social support

In order to assess the predictors of perceived social support, a prediction model was developed. A priori, due to contradictory results of previous studies,[15,16,21] we were interested in the effect of ageing on the level of perceived social support. Therefore, age was classified in two groups: <70 years and ≥70 years. Furthermore, we presumed that the intensity of treatment, rather than the type of cancer, may affect the level of perceived social support. Due to adverse events and frequent hospital visits, a treatment with chemo- and/or radiotherapy was seen as the most intensive treatment. Therefore, type of treatment was classified as chemo- and/or radiotherapy (yes, no). Additional predictors were selected based on results of univariate analysis.

Statistical analyses

Socio-demographics characteristics, personality and clinical characteristics as well as the outcomes of the MSPSS were presented as means (standard deviation(SD)) for normally distributed continuous variables, medians ((interquartile)range) for not-normally distributed variables or frequencies and proportions for categorical variables. For comparisons between the low and high social support group, Pearson's chi-square or Fisher exact test was used for categorical variables. Depending on the distribution of the data, the independent samples T-test or Mann Whitney U test was used for continuous variables.

A prediction model was developed to determine the predictive value of socio-demographic characteristics, type D personality and clinical characteristics on the level of perceived social support. Variables that significantly differed between low and high social support groups (partner status, education level, type D personality) and a-priori selected variables (age, type of treatment) were entered into a logistic regression analysis in order to assess

baseline predictors of perceived social support. To assess perceived social support in more detail the independent samples T-test was used to analyse each subscale of social support in relation to the potential predictors. All analyses were performed in SPSS Statistics version 23.0. P-values smaller than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

From 2011 to 2016, 544 patients were invited to participate in the ROGY Care study. Twelve months after inclusion, 238 patients returned the MSPSS questionnaire and these MSPSS responders were eligible for the present study (Figure 1). In comparison to non-responders and patients lost to follow up, responders at 12 months were younger (68.8 and 70.2 versus 64.8 years respectively; p<0.001). In comparison to patients lost to follow up, responders at 12 months more often had a partner (66% versus 80% respectively; p=0.002) and a higher educational level (12% versus 17% respectively; p <0.001; Appendix 1b). Characteristics of MSPSS responders are shown in Table 1. Their mean age was 64.8 years (± 9.4 years), the majority had endometrial cancer(58%) and nearly all patients received surgical treatment (98%).

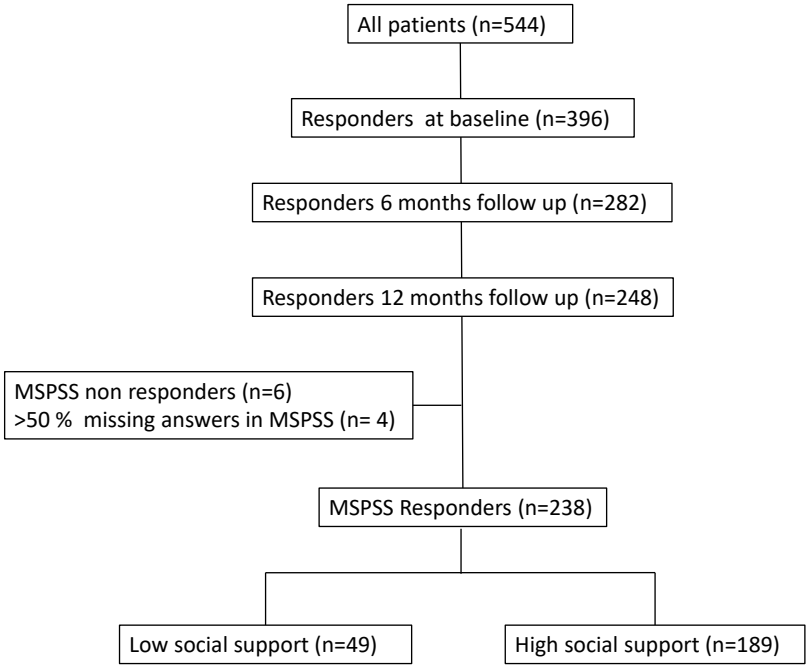

Figure 1. Selection of patients included in the ROGY Care study.

Level of perceived social support and its predictors

One year after inclusion, the level of perceived social support of all MSPSS responders was high with a MSPSS score of 5.8 (SD 1.3). Among the different subscales, the level of perceived

social support from significant other, family and friends was 6.0 (SD 1.4), 5.8 (SD 1.5) and 5.6 (SD 1.4), respectively.

The socio-demographic and clinical characteristics which were associated with the level of perceived social support are summarized in Table 1. Patients experiencing low level of social support less often had a partner (69% versus 83% in patients with high level of perceived social support; p=0.029), had a higher education level (24% versus 15%; p=0.013) and more frequently had a type D personality (40% versus 16%; p<0.001) (Table 1).

Table 1. Socio-demographic characteristics, personality and clinical characteristics by perceived level of social support.

	All responders at 12 months (n=238)		Low level of social support (n=49)		High level of social support (n= 189)		P-value
	N	%/SD	N	%/SD	N	%/SD	
Patient characteristics							
Age at time of diagnosis							
Mean ± SD	64.8	± 9.4	62.2	± 8.8	64.1	± 9.6	0.47
<70	175	73%	34	69%	141	75%	0.46
≥70	63	27%	15	31%	48	25%	
Missing	0		0		0		
Comorbidities							
None	62	28%	8	17%	54	31%	0.20
1	62	28%	14	31%	48	27%	
2 or more	99	44%	24	52%	75	42%	
Missing	15		3		12		
Partner							0.03
No	47	20%	15	31%	32	17%	
Yes	188	80%	33	69%	155	83%	
Missing	3		1		2		
Education level							0.01
Low	28	12%	-		28	15%	
Intermediate	166	71%	35	76%	131	70%	
High	40	17%	11	24%	29	15%	
Missing	4		3		1		
Personality type D							<0.001
No	184	79%	28	60%	156	84%	
Yes	49	21%	19	40%	30	16%	
Missing	5		2		3		

	All responders at 12 months (n=238)		Low level of social support (n=49)		High level of social support (n= 189)		P-value
	N	%/SD	N	%/SD	N	%/SD	
Disease characteristics							
Type of Cancer							0.52
Endometrial cancer	139	58%	31	63%	108	57%	
Ovarian cancer	99	42%	18	37%	81	43%	
Missing	0		0		0		
FIGO stage							0.14
I	153	69%	38	81%	115	66%	
II	12	5%	-		12	7%	
III	42	19%	7	15%	35	20%	
IV	15	7%	2	4%	13	8%	
Missing	16		2		14		
Treatment							
Chemo and/or radiotherapy							0.09
No	114	48%	29	59%	85	46%	
Yes	122	52%	20	41%	102	55%	

SD: standard deviation. Low education level: no primary school; intermediate education level: lower general secondary education/ vocational training; high vocational training/university. P value <0.05 was considered statistically significant .

Type D personality as a predictor of social support

Due to the sample size, a maximum of five baseline characteristics could be selected to assess predictors of social support.[31] Socio-demographic characteristics, personality and clinical variables that were significantly associated with social support in the univariate analysis (partner status, education level, type D personality) and the a priori selected characteristics (age, type of treatment) were entered in a logistic regression analysis. Type D personality was the only factor which was independently associated with a low level of social support (OR 2.96; 95% CI 1.37-6.37; p=0.006) (Table 2).

Table 2. Multivariable logistic regression analysis of socio-demographic characteristics, personality and clinical characteristics as predictors of low level of perceived social support.

Variables	Categories	Odds Ratio	CI 95%	P-value
Age	≥ 70y vs <70y	0.90	0.38-2.1	0.814
Partner	yes vs no	0.51	0.22-1.18	0.116
Education level	high vs low/intermediate	1.91	0.82-4.44	0.132
Personality type D	yes vs no	2.96	1.37-6.37	0.006
Chemo- and/or radiotherapy	yes vs no	0.68	0.38-1.36	0.275

Reference category for the equations is 'high social support'. CI: confidence interval.
Low education level: no primary school; intermediate education level: lower general secondary education/vocational training; high vocational training/university. P value <0.05 was considered statistically significant.

Level of perceived social support from significant other, family and friends

To assess perceived social support in more detail, each subscale of social support was analysed in relation to the potential predictors. These results are summarized in Figure 2. Although no difference was shown in the total MSPSS score, older patients perceived less social support from friends compared to younger patients (5.2 (SD 1.5) versus 5.7 (SD 1.4); p=0.02). Patients without a partner experienced less social support from significant other compared to patients with a partner (5.4 (SD 1.9) versus 6.2 (SD 1.1); p=0.006). The difference in the level of perceived social support between patients with and without personality type D was reflected in every subscale of social support (significant other p=0.002; family p=0.002; friends p=0.003). Furthermore, both subscales of type D personality (negative affect and social inhibition) were significantly associated with all subscales of social support (data not shown). Patients who received only surgical treatment experienced less social support from family and friends compared to patients who received surgical treatment with additional chemo- and/or radiotherapy (family p=0.04; friends p=0.04). No significant differences of the MSPSS subscales were noted between groups based on education level.

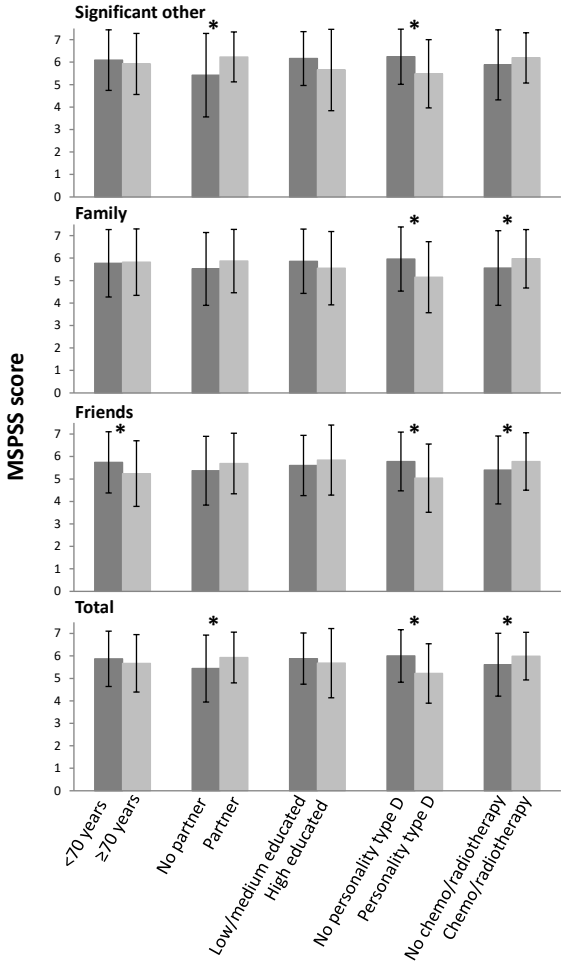

Figure 2. MSPSS scores (subscales and total score) of all responders, stratified by potential predictors of social support.
A higher MSPSS score indicated more social support. Error bars: standard deviation; *significant difference (p<0.05).

DISCUSSION

In the current study, the majority of the patients with endometrial or ovarian cancer experienced a high level of social support. Although we expected that also age and type of treatment could have an impact on the perceived level of social support, our results demonstrate that only type D personality was an independent predictor of the level of perceived social support.

Previous studies have reported that an unmet support need in gynaecological cancer patients is common.[3,13] However, in our study, the perceived level of social support was relatively high and appears to be sufficient for the majority of the patients. This finding could be partially explained by the fact that the MSPSS questionnaire focused on emotional support only, whereas unmet needs could also include instrumental support or informational support.[8] Secondly, the MSPSS questionnaire focused on the satisfaction with social support and its availability when needed; it did not assess the received level of social support that referred to specific supportive actions offered by others. Hence, even if the received level of social support is limited, the level of perceived social support might be experienced as being sufficient.

Regardless, the level of perceived social support in this study was comparable to three studies that also used the MSPSS questionnaire in patients with gynaecological cancer.[16,32,33] In contrast to our findings, these studies showed that the level of perceived social support from family was higher than perceived social support from a significant other.[16,32,33] However, these studies were performed in Turkey[16,33] and China[32] and could therefore be influenced by cultural differences in the perception and reception of family support. Although inter-individual differences should be considered, Western Europe appears to prioritize individual independence, whereas Eastern Europe and East Asia are more typically characterized as family-centred cultures with a subsequent higher level of family support.[34,35]

Prior research showed that patients without a partner[14,15] and patients with a lower education level[15–17] or socio-economic status[15,16] were at risk for a lower level of social support. These results could not be confirmed in our study. Inevitably, patients without a partner experienced less social support from a significant other. However, the total level of social support was still relatively high. A similar effect was found in older patients who perceived less social support from friends; they still experienced the total level of social support as relatively high. This suggests that the source of social support might be less relevant than the perception of social support itself. However, this finding might also be explained by the sample size of our study population and potential selection bias. After all, in contrast to what was seen in earlier studies, no difference was found in social support based on education level in our study.

This study showed type D personality as the only characteristic which was predictive for the level of perceived social support. This may be explained by a tendency for people with type D personality to avoid social contacts because of fear of disapproval.[27] Hence, a low

level of perceived social support in patients with type D personality may due to less social contacts. In addition, low level of perceived social support may also be due to their increased experience of negative emotions and their concerns during illness, with beliefs that illness had more serious consequences.[20] A previous study showed an association between type D personality and increased use of health care due to worse illness perceptions.[36]

To the best of our knowledge, our study is the first that assessed the association between type D personality and the level of perceived social support in patients with endometrial or ovarian cancer. Thus far, there is limited evidence of the association between a distressed personality and social support in cancer patients. A study in colorectal cancer patients showed that type D personality is associated with psychological distress[20] and need of supportive care,[37] but the association between type D personality and perceived social support was not assessed. The effect of personality type D on perceived social support was demonstrated in healthy individuals with neurotic personality traits, which is common in those with a type D personality, and patients with chronic illness; they were more likely to report a lower level of social support.[19]

This study had some limitations. Only 60% of all responders at baseline completed the MSPSS questionnaire at twelve months, and responders were younger, more often had a partner and a higher education level. Second, the prevalence of type D personality in the general population is higher than demonstrated in this study.[38] These differences may influence the level of perceived social support and our findings may not be generalizable to all patients with endometrial or ovarian cancer. Furthermore, since this study was powered for the primary analysis of the ROGY Care trial, the statistical power of a full regression model may be insufficient. Therefore, a limited regression model could be used with a maximum of five potential predictors[31] and some effects may have been missed.

Despite of these limitations, this study provides insight in predictors of social support which can be relevant in daily clinical practice in order to recognize patients who are at risk of insufficient perceived social support. First, based on our results, it could be of interest to pay attention to patient's personality after a cancer diagnosis. Gloom, anxiety, reticence, lack of self-assurance or neuroticism are characteristics of patients that may all fit with a distressed personality.[18] Second, it seems important to notice that the level of perceived social support may be relative to its need. While the received level of social support in older patients may be lower compared to younger patients, the perceived level of social support can still be sufficient.[39] This may reflect patients' ability to adapt to new life circumstances without losing their satisfaction with social support. This 'response shift' refers to changes in internal standards or values which can affect the evaluation of patient reported outcomes. It is a common phenomenon in the way people experience quality of life, but the contribution of perceived social support to response shift among cancer patients is still unknown.[39] Social support may also change over time due to the socio-emotional selectivity theory which assumes that during ageing, but also during illness, people proactively limit their contact to those who are emotionally close, particularly in case of shortened life expectancy.[9,10] Future

studies may assess the potential discrepancy between received and perceived social support, the predictors of received social support and the association of these two aspects of social support with clinical health outcomes.

Hence, exploring a patient's personality and desire for social support can help to detect patients who may be in need for extra support during cancer diagnosis and treatment. However, the effectiveness of psychosocial interventions in patients with type D personality is still unclear. In patients with cancer, several interventions such as psychotherapy and psycho-education showed promising positive effects on psychological distress and quality of life.[40,41] However, evidence is based on heterogeneous studies of limited quality and effects on perceived social support were not explored. Furthermore, these interventions might have a different effect on distressed patients due to their characteristics of social inhibition. It is, therefore, relevant that future studies address the effectiveness of psychosocial interventions in (gynaecological) cancer patients, particularly in those who are vulnerable.

In conclusion, the level of perceived social support in patients with endometrial or ovarian cancer is mainly predicted by a type D personality. Particularly these distressed patients, characterized by negativity and social inhibition, are at risk of a lower level of perceived social support. Interventions to enhance social support in these patients requires further research.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;(68):394–424.
2. Integraal Kankercentrum Nederland (IKNL). Cijfers over Kanker [Internet]. [cited 2020 Jan 6]. Available from: https://www.iknl.nl/nkr-cijfers
3. Beesley VL, Alemayehu C, Webb PM. A systematic literature review of the prevalence of and risk factors for supportive care needs among women with gynaecological cancer and their caregivers. Supportive Care in Cancer. 2018;26(3):701-710.
4. Sekse RJT, Dunberger G, Olesen ML, Østerbye M, Seibæk L. Lived experiences and quality of life after gynaecological cancer—An integrative review. J Clin Nurs. 2019;(28):1393–421.
5. Hsieh CC, Chen CA, Hsiao FH, Shun SC. The correlations of sexual activity, sleep problems, emotional distress, attachment styles with quality of life: Comparison between gynaecological cancer survivors and noncancer women. J Clin Nurs. 2014;(23):985–94.
6. Ozbay F, Fitterling H, Charney D, Southwick S. Social support and resilience to stress across the life span: A neurobiologic framework. Curr Psychiatry Rep. 2008;304–10.
7. Dumitrache CG, Rubio L, Rubio-Herrera R. Perceived health status and life satisfaction in old age, and the moderating role of social support. Aging Ment Heal. 2017;21(7):751–757.
8. Cohen S. Social relationships and health. Am Psychol. 2004;676–84.
9. Carstensen LL, Isaacowitz DM, Charles ST. Taking time seriously: A theory of socioemotional selectivity. Am Psychol. 1999;54:165–81.
10. Pinquart M, Silbereisen RK. Socioemotional selectivity in cancer patients. Psychol Aging. 2006;21(2):419–23.
11. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. Brain Behav Immun. 2013;(30):S41–7.
12. Bandura A. Social foundations of thought and action: A social cognitive theory. Social foundations of thought and action: A social cognitive theory. Englewood Cliffs, NJ, US: Prentice-Hall, Inc; 1986. xiii, 617–xiii, 617. (Prentice-Hall series in social learning theory.).
13. Faller H, Brähler E, Härter M, Keller M, Schulz H, Wegscheider K, et al. Unmet needs for information and psychosocial support in relation to quality of life and emotional distress: A comparison between gynecological and breast cancer patients. Patient Educ Couns. 2017;(100):1934–42.
14. Grav S, Romild U, Hellzèn O, Stordal E. Association of personality, neighbourhood, and civic participation with the level of perceived social support: The HUNT study, a cross-sectional survey. Scand J Public Health. 2013;41:579–86.
15. Forsythe LP, Alfano CM, Kent EE, Weaver KE, Bellizzi K, Arora N, et al. Social support, self-efficacy for decision-making, and follow-up care use in long-term cancer survivors. Psychooncology. 2014;(23):788–96.
16. Yilmaz SD, Bal MD, Beji NK, Arvas M. Ways of coping with stress and perceived social support in gynecologic cancer patients. Cancer Nurs. 2015;38(2):E57–62.
17. Drageset S, Lindstrøm TC. Coping with a possible breast cancer diagnosis: Demographic factors and social support. J Adv Nurs. 2005;51(3):217–26.
18. Swickert RJ, Hittner JB, Foster A. Big Five traits interact to predict perceived social support. Pers Individ Dif. 2010;48:736–41.
19. Horwood S, Anglim J, Tooley G. Statistically modelling the relationships between Type D personality and social support, health behaviors and symptom severity in chronic illness groups. Psychol Heal. 2016;31(9):1047–63.
20. Mols F, Denollet J, Kaptein AA, Reemst PHM, Thong MSY. The association between Type D personality and illness perceptions in colorectal cancer survivors: A study from the population-based PROFILES registry. J Psychosom Res. 2012;73(3):232–9.
21. Bergerot CD, Clark KL, Obenchain R, Philip EJ, Loscalzo M. Breast and gynecological cancer patients' risk factors associated with biopsychosocial problem-related distress. Psychooncology. 2018;(27):1013–20.
22. van de Poll-Franse L V., Nicolaije KAH, Vos MC, Pijnenborg JMA, Boll D, Husson O, 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. 2011;12(256).
23. Nicolaije KAH, Ezendam NPM, Vos MC, Pijnenborg JMA, Boll D, Boss EA, et al. Impact of an automat-

ically generated cancer survivorship care plan on patient-reported outcomes in routine clinical practice: Longitudinal outcomes of a pragmatic, cluster randomized trial. J Clin Oncol. 2015;33(31):3550–9.
24. de Rooij BH, Ezendam NPM, Nicolaije KAH, Caroline Vos M, Pijnenborg JMA, Boll D, 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. 2017;145(2):319–28.
25. 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):156–63.
26. Erdem D, Gezer H, Acer Kasman S DM. Reliability and Validity of the Self-Administered Comorbidity Questionnaire in Psoriatic Arthritis [abstract]. Arthritis Rheumatol [Internet]. 2019;71(suppl 10). Available from: https://acrabstracts.org/abstract/reliability-and-validity-of-the-self-administered-comorbidity-questionnaire-in-psoriatic-arthritis/
27. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and type D personality. Psychosom Med. 2005;67(1):89–97.
28. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. J Pers Assess. 1988;52:30–41.
29. Pedersen SS, Spinder H, Erdman RAM, Denollet J. Poor perceived social support in implantable cardioverter defibrillator (ICD) patients and their partners: Cross-validation of the multidimensional scale of perceived social support. Psychosomatics. 2009;50(5):461–7.
30. Zimet GD. Multidimensional scale of perceived social support [Internet]. [cited 2020 Feb 27]. Available from: https://gzimet.wixsite.com/mspss
31. Harrell FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med. 1984;3(2):143–52.
32. Wen Q, Shao Z, Zhang P, Zhu T, Li D, Wang S. Mental distress, quality of life and social support in recurrent ovarian cancer patients during active chemotherapy. Eur J Obstet Gynecol Reprod Biol. 2017;(216):85–91.
33. Pinar G, Okdem S, Buyukgonenc L, Ayhan A. The relationship between social support and the level of anxiety, depression, and quality of life of Turkish women with gynecologic cancer. Cancer Nurs. 2012;35(229):235.
34. Campos B, Kim HS. Incorporating the cultural diversity of family and close relationships into the study of health. Am Psychol. 2017;72(0):543–54.
35. de Jong Gierveld J, Tesch-Römer C. Loneliness in old age in Eastern and Western European societies: Theoretical perspectives. Eur J Ageing. 2012;9(4):285–95.
36. Mols F, Oerlemans S, Denollet J, Roukema JA, van de Poll-Franse L V. Type D personality is associated with increased comorbidity burden and health care utilization among 3080 cancer survivors. Gen Hosp Psychiatry. 2012;34(4):352–9.
37. Shun SC, Yeh KH, Liang JT, Huang J, Chen SC, Lin BR, et al. Unmet supportive care needs of patients with colorectal cancer: Significant differences by type D personality. Oncol Nurs Forum. 2014;41(1):3–11.
38. Mols F, Denollet J. Type D personality in the general population: A systematic review of health status, mechanisms of disease, and work-related problems. Health Qual Life Outcomes. 2010;8(9):1–10.
39. Ilie G, Bradfield J, Moodie L, Lawen T, Ilie A, Lawen Z, et al. The role of response-shift in studies assessing quality of life outcomes among cancer patients: A systematic review. Front Oncol. 2019;9:1–25.
40. Faller H, Schuler M, Richard M, Heckl U, Weis J, Kuffner R. Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: Systematic review and meta-analysis. J Clin Oncol. 2013;31(6):782–93.
41. Kalter J, Verdonck-de Leeuw IM, Sweegers MG, Aaronson NK, Jacobsen PB, Newton RU, et al. Effects and moderators of psychosocial interventions on quality of life, and emotional and social function in patients with cancer: An individual patient data meta-analysis of 22 RCTs. Psychooncology. 2018;27:1150–61.

Appendix 1a. Multidimensional Scale of Perceived Social Support (MSPSS).

	MSPSS						
Significant other							
1. There is a special person who is around when I am in need	1	2	3	4	5	6	7
2. There is a special person with whom I can share joys and sorrows	1	2	3	4	5	6	7
3. I have a special person who is a real source of comfort to me	1	2	3	4	5	6	7
4. There is a special person in my life who cares about my feelings	1	2	3	4	5	6	7
Family							
5. My family really tries to help me.	1	2	3	4	5	6	7
6. I get the emotional help & support I need from my family	1	2	3	4	5	6	7
7. I can talk about my problems with my family	1	2	3	4	5	6	7
8. My family is willing to help me make decisions	1	2	3	4	5	6	7
Friends							
9. My friends really try to help me	1	2	3	4	5	6	7
10. I can count on my friends when things go wrong	1	2	3	4	5	6	7
11. I have friends with whom I can share my joys and sorrows	1	2	3	4	5	6	7
12. I can talk about my problems with my friends	1	2	3	4	5	6	7

Circle the "1" if you very strongly disagree, Circle the "2" if you Strongly Disagree, Circle the "3" if you Mildly Disagree, Circle the "4" if you are Neutral, Circle the "5" if you Mildly Agree, Circle the "6" if you Strongly Agree, Circle the "7" if you Very Strongly Agree.

Appendix 1b. Baseline characteristics of all patients included in the Rogy Care trial.

	All patients (n=544)		Non responders (n=148)		Lost to follow-up (n= 158)		MSPSS responders (n=238)		P-value
	N	%/SD	N	%/SD	N	%/SD	N	%/SD	
Patient characteristics									
Age at time of diagnosis									
Mean ± SD	66.4	± 10.6	68.8	± 11.4	70.2	± 11.1	64.8	± 9.4	<0.001
<70	336	62%	83	56%	78	49%	175	73%	<0.001
>=70	206	38%	63	43%	80	51%	63	27%	
Missing	2		2		0		0		
Comorbidities									
None	97	26%	-		35	24%	62	28%	0.53 *
1	110	30%	-		48	33%	62	28%	
2 or more	163	44%	1	100%	63	43%	99	44%	
Missing	174		147		12		15		
Partner									0.002 *
Yes	292	74%	1	100%	103	66%	188	80%	
No	100	26%	-		53	34%	47	20%	
Missing	152		147		2		3		

	All patients (n=544)		Non responders (n=148)		Lost to follow-up (n= 158)		MSPSS responders (n=238)		P-value
	N	%/SD	N	%/SD	N	%/SD	N	%/SD	
Education level									<0.001 *
Low	74	19%	-		46	30%	28	12%	
Intermediate	256	66%	1	100%	89	58%	166	71%	
High	59	15%	-		19	12%	40	17%	
Missing	155		147		4		4		
Personality type D									<0.001
No	374	82%	71	100%	119	79%	184	79%	
Yes	80	18%	-		31	21%	49	21%	
Missing	90		77		8		5		
Disease characteristics									
Type of Cancer									
Endometrial	296	55%	75	52%	82	52%	139	58%	0.29
Ovarian	246	45%	71	48%	76	48%	99	42%	
Missing	2		2		0		0		
Tumour Stage									0.008
I	293	59%	62	48%	78	55%	153	69%	
II	36	7%	14	11%	10	7%	12	5%	
III	119	24%	39	26%	38	27%	42	19%	
IV	45	9%	14	11%	16	11%	15	7%	
Missing	51		19		16		16		
Treatment									
Chemo and/or radiotherapy									0.02
Yes	313	58%	91	63%	100	64%	122	52%	
No	224	42%	53	37%	57	36%	114	48%	
Missing	7		4		1		2		

* compared between lost to follow up and MSPSS responders. SD: standard deviation. Low education level: no primary school; intermediate education level: lower general secondary education/vocational training; high vocational training/university. P-value <0.05 was considered statistically significant

PART III

GENERAL DISCUSSION AND SUMMARY

CHAPTER
11

General discussion

GENERAL DISCUSSION

In geriatric oncology, it remains challenging to improve tailor-made cancer care. With the results of the research presented in this thesis we have tried to clarify several issues concerning the treatment decision-making process in older patients with cancer. Part I focuses on various methods to assess the level of frailty in older patients with cancer. Part II describes current treatment patterns and elaborates on the impact of cancer treatment on patient related outcomes (PROs). Here the results of the studies of this thesis are discussed and placed in a wider perspective. In addition, directions for future research will be given.

Evolution of treatment decision-making process and its challenges

In the past, treatment decisions in healthcare were regularly based on the paternalistic model in which moral principles of benefit and doing no harm to the patient took centre stage. Physicians imposed the best treatment on patients according to their own judgment. During the last decades of the 20th century, the concept of shared decision making arose. This concept includes a comparable moral principle; however, patients' characteristics and preferences play a more central role in the decision-making process. Four steps are roughly distinguished: 1) the physician informs the patient that a decision is to be made and highlights the involvement of patient's opinion. 2) the physician explains the course of disease and the various treatment options, pros and cons included; it is important to realise and explain that the various treatment options can be equivalent to each other. 3) patient's health goals and preferences are discussed. 4) physician and patient balance the various treatment options and a final treatment decision is taken.[1]

Although the various steps of shared decision-making process are clear, going through these steps and making a final treatment decision in older patients with cancer is still challenging. Due to the lack of evidence concerning the course of treatment, risk of adverse outcomes and its impact on daily life in this specific patient group, it is challenging to inform these patients appropriately.

As ageing is an individualized process, older patients remain a heterogeneous patient group with large differences in physical, psychological and functional health status; and they often have different preferences and health goals than their younger counterparts. In addition, older patients with cancer are underrepresented in clinical oncological trials and evidence concerning the course of disease after treatment and its impact on daily life for this specific patient group is limited available. National guidelines scarcely include specific treatment recommendations for this older population. It is incorrect to assume that the available evidence of their younger counterparts will automatically be suitable for the older population. Hence, in older patients with cancer, proposing an individualized cancer treatment in which a balance is found between under- and overtreatment is a challenge.

Objectifying the heterogeneity of older patients with cancer and assessing their ability to tolerate cancer treatment will make it possible to improve patient education during the

treatment decision-making process and shared decision making. The following additional steps in the decision-making process are needed:

1. Evaluating patient's level of vitality and ability to tolerate treatment
2. Collecting reliable and relevant evidence which can be extrapolated to an individual level
3. Creating awareness of frailty and discuss this aspect during multidisciplinary team meetings
4. Assessing whether a patient could qualify for non-oncological interventions to improve their resilience and treatment tolerance

Evaluating patient's level of vitality and ability to tolerate treatment

In geriatric medicine, patient's vitality is quantified by assessing the level of frailty. Frailty reflects the cumulative decline of physiological systems during lifetime and is defined as a state of vulnerability to poor resolution of homeostasis after a stressor event which increases the risk of adverse outcomes.[2] In geriatric oncology, it is estimated that more than half of cancer patients aged 70 years or older are (pre)frail.[3] Compared to fit patients, frail patients are almost twice as likely to die within five years after cancer treatment and their risk of treatment intolerance within 30 days is three to four times higher.[3,4] In addition, frail patients are at risk of a decline in physical functioning and quality of life within one year after cancer treatment.[3,4] It is therefore important to assess the level of frailty in older patients with cancer.[5]

In daily practice, the most common method to assess the level of frailty is by using physician's clinical judgment. Apart from disease characteristics, a physician can easily focus on clinical warning signs of frailty by a thorough observation during the first visit. How does the patient walk into the doctor's office? Does the patient know why he/she is visiting a physician? Does the patient need help from a caregiver during the conversation and physical examination? Although clinical judgment is always available and requires no additional investments in time or resources, navigating solely on clinical judgment for identification of potentially frail patients could result in missing patients with relevant geriatric impairments (**Chapter 3**). In current practice, the WHO performance status is often used by physicians in order to support their clinical judgment. However, on that basis, geriatric impairments in patients with a haematological malignancy can be missed (**Chapter 2**). This highlights the importance of improving the clinical judgment of physicians and supporting them with valuable tools in order to estimate patient's tolerability to cancer treatment.

The accepted gold standard for assessing the level of frailty is a comprehensive geriatric assessment. This multidisciplinary diagnostic treatment process evaluates physical, psychosocial and functional domains of an older patient. In addition, a comprehensive geriatric assessment includes patient's preferences and health goals. Altogether, an integral care plan for an individual patient can be drawn up and used for intervention and follow-up.[6] However, in daily oncological practice and research, comprehensive geriatric assessment is often replaced by a more limited geriatric assessment. This assessment, which

can be performed by others than a geriatrician, consists of multiple questionnaires which address the various geriatric domains. However, these validated tools can still miss geriatric impairments, do not consider the index disease or patient's preferences and health goals, and lack an individualised integral care plan. Nevertheless, in solid malignancies[7] as well as in haematological malignancies (**Chapter 2**), a geriatric assessment can identify geriatric impairments which are frequently undetected with a standard oncologic evaluation.

Although a geriatric assessment has been acknowledged as the recommended approach to identify frailty, not all older patients with cancer require a geriatric assessment. Therefore, a two-step approach, starting with a screening tool to identify those who will benefit from a geriatric assessment, has been recommended by the International Society of Geriatric Oncology (SIOG).[8] The Geriatric 8 (G8), a frailty screening tool specifically designed for older patients with cancer,[9] is not only able to detect potentially frail patients but it may also have prognostic value to adverse events and mortality (**Chapter 4**). It is desirable that this robust and frequently studied frailty screening tool in oncology is used in cancer patients aged 70 years and older to create awareness of assessing frailty and identify potentially frail patients who may benefit from a geriatric assessment.[10,11] Ultimately, performing a geriatric assessment can contribute to assess patient's tolerability to cancer treatment and can help to prevent under- or overtreatment.

It also has to be realised that frailty reflects a spectrum and should be viewed within the context of the index disease, treatment options and patient's priorities. Identifying frailty does not necessarily imply that those patients are not suited for cancer treatment. In early breast cancer patients for example, even if patients were assessed as frail by G8 screening tool or geriatric assessment, they were still frequently recommended for regular surgical treatment without affecting overall survival (**Chapter 5**). Hence, the estimated remaining life expectancy of frail patients can exceed the expected cancer specific mortality.

Just as frailty does not necessarily means someone is unsuited for cancer treatment, it is also incorrect to assume that all fit older patients can undergo standard cancer treatment. Frequently, physicians observe an unexpected course of disease or treatment in patients who were considered fit. Examples are an unforeseen inability to tolerate cancer treatment or worsening of functioning after treatment. Hence, the level of frailty is not always in proportion to the risk of adverse health outcomes after cancer treatment. Therefore, identifying the level of frailty should be an entry point for a careful consideration whether adaptive cancer care is needed.

Currently, patient's frailty status is often operationalized as a static measure which reflect to a lesser extent someone's ability to recover after cancer treatment.[12] This recovery potential, also called someone's resilience, is a rising concept in geriatric medicine. It is defined as patient's ability to resist functional decline or recover physical and psychological health following a health stressor.[12,13] Research in which resilience has been addressed in older cancer patients is scarce. Previous studies in non-cancer patients demonstrated that

resilience is associated with optimism, adaptive coping strategies, social support and being physically active and independent, whereas depression and hopelessness are associated with a lower level of resilience.[14] Our research, which focused on resilience of health related quality of life in patients with colon cancer, did not show a predictive marker for the level of quality of life one year post surgery (**Chapter 8**). However, among those who received adjuvant chemotherapy, older patients were less resilient than their younger counterparts (**Chapter 9**). In order to collect more evidence concerning resilience in patients with cancer, longitudinal studies with multiple measurements around a stressor need to be performed.[12] Until then, physicians are recommended to explicitly ask for patient's recovery trajectory after a previous (surgical) treatment.

Collecting reliable and relevant evidence which can be extrapolated to an individual level

Whereas the cancer population continues ageing, the knowledge concerning the course of disease in older patients with cancer, as well as their risk of treatment related toxicity, complications, mortality and their ability to recover, lagged behind. Clinical oncological trials are frequently designed as a randomized controlled trial to assess the efficacy of new treatment options and offer the highest level of evidence. In daily practice, the provided evidence cannot easily be extrapolated to an older individual with cancer.

First, the corresponding eligibility criteria of these trials are often restrictive and mainly focused on age,[15] comorbidities and organ specific functioning.[16,17] Consequently, only fit older patients can participate in these trials. Second, the collected baseline characteristics in oncological trials mainly consist of sex, age, performance status, and comorbidity status whereas these patient characteristics are not a complete reflection of an older individual and their potential physical or psychosocial vulnerabilities. Due to a lack of patient centred characteristics, it is not possible to assess whether these physical or psychosocial vulnerabilities could be predictive of the course of disease, adverse treatment events and recovery potential. On top of that, not all relevant health outcomes for older patients are assessed in oncological trials. When designing a clinical trial in which a new drug will be investigated, it makes sense to first focus on efficacy and safety. However, patients increasingly want to be informed about the impact of cancer treatment on daily life.[18] Especially for most older patients with cancer, maintaining physical functioning and quality of life is at least as important as survival benefit.[19,20] Still, only the minority of clinical oncological trials for older patients include PROs such as quality of life, functioning and health care utilisation (**Chapter 7**); and reporting these data in a full text publication is often limited to a single sentence statement.[21] A final aspect which can make it difficult to extrapolate research data of oncological trials to an older individual is that research data are often presented at a group level. The absence of changes at group level over time does not necessarily mean that there are no changes at an individual level. This aspect was observed in colon cancer patients and their health related quality of life trajectory after surgical treatment. While only trivial changes of health related quality of life were observed after colon cancer treatment on group level, at least one out of ten patients still experienced a decline of quality of life one year post-surgery (**Chapter 8**). Hence, changes at an individual level might be underestimated.

In order to improve the available knowledge in geriatric oncology, several changes in the study design of clinical oncological trials are needed. Next to broadening the inclusion criteria of oncological trials in order to let (pre)frail older patients participate, it will be of added value to collect patient characteristics in more detail. For example, by collecting characteristics concerning patient's personality, it was observed that a type D personality, which is characterized by negativity and social inhibition, was associated with a lower level of perceived social support in patients with endometrial or ovarian cancer (**Chapter 10**). Furthermore, relevant health outcomes at multiple time points need to be assessed; PROs are as important as disease or treatment related outcomes. Lastly, these outcomes need to be analysed at a group level and at an individual level.

As a result of these proposed changes in clinical oncological trials design, it will not always be possible to design a randomized controlled trial in order to pursue a high level of evidence. However, other study designs such as a (prospective) cohort study can reliable reflect the effect of interventions in day-to-day practice. An alternative study design is an extended trial in which a cohort of older patients is added to the superior treatment arm of a randomized controlled trial.[22]

A final remark concerning study objectives in clinical trials has to be made. In addition to efficacy and safety of cancer treatment it is desirable to assess PROs. Those outcomes are directly obtained from the patient by questionnaires and include signs and symptoms that cannot be observed by others, such as quality of life or daily functioning.[23] Particular for older patients with cancer, the impact of cancer treatment on these PROs might be just as important as survival benefit. However, these PROs provide evidence which may sometimes be difficult to interpret and extrapolate into daily practice. The generally patient related outcome measurements will not always match the research question and study population. As generic measurements may include aspects that are irrelevant for specific patient populations, it is preferable to use disease specific instruments. However, those are often incompletely validated which makes it challenging to choose the right measurement for answering the research question.[23,24] In addition, the questionnaires are not always provided with cut-off values and rules of thumb are frequently necessary to interpret the results in a clinically relevant way.[25] Finally, the response shift phenomenon, which reflects patient's ability to adapt to new life circumstances, as well as recall bias which refers to the potential risk of inaccurate recall to past events or experiences,[26] need to be considered while interpreting any longitudinal results. Nevertheless, in order to answer patient's questions in daily practice, it is important to implement patient reported outcome measures in geriatric cancer care. In the Netherlands, the TOPIC-SF has been selected as a suitable PRO measure to assess health outcomes in older hospitalized patients. [27,28] Nowadays, the TOPIC-SF will be slowly implemented and future clinical trials are still needed to assess the level of health gain by using the TOPIC-SF in older patients. Despite this encouraging initiative, it is also recommended to further optimize the quality of PRO measurements in future research.[29–32]

Creating awareness of frailty and discussing this aspect during multidisciplinary team meetings

Although some challenges still lie ahead, it appears that over the years some progress has been made in the treatment decision-making process for older patients with cancer. In the Netherlands, there is an increase of performing a geriatric evaluation from 56% in 2013 to 98% in 2019.[33] In addition, treatment adjustments in patients with colorectal cancer are more often based on functional status and patient preferences (**Chapter 6**). In order to provide a tailor-made and patient-focused cancer care for our rapidly growing older population, this positive trend in which treatment decisions are not only based on chronological age alone and patient's involvement is considered more important, should be preserved. Therefore, physicians need to be aware of the prevalence of frailty among older patients with cancer and they need to be educated about the various methods to assess the level of frailty.

Originally, multidisciplinary team (MDT) meetings were launched due to the involvement of a growing number of physicians in cancer care. The core function of these meetings was to group these physicians and determine patient's treatment plan. Since the introduction of MDT meetings, particular in complex cases, associations with clinical outcomes for cancer patients in terms of better survival, reduction of waiting time from diagnosis to treatment and improvement of quality of life have been demonstrated.[34,35] However, those meetings are mainly disease-oriented and patient-centred information is often lacking. Particular in the heterogeneous older population, patient-centred information should be at least as important as disease-oriented information. Furthermore, often no geriatrician is currently present at a MDT meeting whereas a geriatrician eminently can focus on this patient centred information such as frailty, resilience and patient's preferences. In order to achieve a more individualized treatment decision-making process, it would be valuable to discuss these aspects structurally in a MDT meeting, preferably in presence of a geriatrician trained in oncology. If multiple geriatric impairments appear to be present, a comprehensive geriatric assessment should be performed before making a treatment decision.

Assessing whether a patient could qualify for non-oncological interventions

Reconsidering the level of frailty, including the level of resilience, could lead to a better prediction of the remaining life expectancy and a patient's tolerability for cancer treatment which may lead to pre-emptive treatment adjustments. However, next to treatment adjustments, it is also interesting to consider whether an individual could benefit from extra support during treatment. Examples of non-oncological interventions are pre-, peri- or post-rehabilitation, respectively optimizing patient's condition prior to, during or after treatment. Those interventions consist mostly of physical exercise, psychological support, nutritional interventions, optimizing comorbidities and reducing of polypharmacy which ideally improve patient's condition prior to and during treatment, improve the recovery trajectory after cancer treatment and the long-term prognosis. In this way, patient's level of resilience could be enhanced.

Various rehabilitation programmes are developed. The most well-known multidisciplinary

rehabilitation program to reduce patient's level of distress to surgery is the Enhanced Recovery After Surgery (ERAS) program.[36] This multimodal perioperative care program is associated with a reduction of complications, adverse events or readmissions after surgical treatment, especially in colorectal surgery;[37,38] and therefore, it is incorporated in the Dutch national guideline for colorectal cancer treatment.[39]

In order to reduce the risk of functional decline after cancer treatment, it could be worthwhile to invest in optimizing patient's condition before starting treatment. During recent years, an increasing amount of research is conducted to assess the effectiveness of prehabilitation. Among these studies, mainly performed in patients who received cancer surgery, it is observed that physical exercise might have a beneficial effect on functional capacity, postoperative complications, length of hospital stay and quality of life.[40,41] Nutritional interventions and psychological interventions are less addressed. Nutritional support may lead to a decrease in post-operative complications[42] and psychological support may have a beneficial effect on PROs such as symptom release and quality of life.[43] However, the conducted studies are heterogeneous in study population, interventions, outcome measures and quality which make it hard to compare them. Only few focus on older patients with cancer and the majority of these older patients were relatively fit.[40,42,44] In addition to this paucity of evidence of prehabilitation, the effectiveness may also depend on compliance rate and the interval between diagnosis and treatment.[45] Still, a multimodal prehabilitation program, possibly combined with rehabilitation[46] or geriatric co-management[47] during treatment might be promising. Nevertheless, larger trials in which vulnerable older patients with cancer can participate will be valuable. These trials should also focus on compliance, cost-effectiveness and be extended to trials in which patients receive chemotherapy, targeted therapy or immunotherapy.

In conclusion, treatment decision making in geriatric oncology remains challenging. However, by gathering more knowledge on the course of disease in older patients with cancer, structurally assessing their level of frailty, patient preferences and health goals, physicians might be able to improve the treatment decision-making process. Future research, especially focussing on the impact of cancer treatment on PROs, (p)rehabilitation and resilience may further individualize treatment decisions in older patients with cancer.

REFERENCES

1. Stiggelbout AM, Pieterse AH, De Haes JCJM. Shared decision making: Concepts, evidence, and practice. Patient Educ Couns. 2015;1172–9.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752–762.
3. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: A systematic review. Ann Oncol. 2015;26:1091–1101.
4. Kirkhus L, Šaltyte Benth J, Grønberg BH, Hjermstad MJ, Rostoft S, Harneshaug M, 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. 2019;33:312–22.
5. 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.
6. Parker SG, Mccue P, Phelps K, Mccleod A, Arora S, Nockels K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. Age Ageing. 2018;47(1):149–55.
7. Hamaker ME, te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients – A systematic review. J Geriatr Oncol. 2018;9(5):430–40.
8. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, 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):241–25.
9. 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.
10. 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;26:288–300.
11. 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:e437–44.
12. Gijzel SMW, Whitson HE, van de Leemput IA, Scheffer M, van Asselt D, Rector JL, et al. Resilience in Clinical Care: Getting a Grip on the Recovery Potential of Older Adults. J Am Geriatr Soc. 2019;67(12):2650–7.
13. 13. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: Systematic review and development of an emerging construct. Journals Gerontol - Ser A Biol Sci Med Sci. 2016;71(4):489–95.
14. MacLeod S, Musich S, Hawkins K, Alsgaard K, Wicker ER. The impact of resilience among older adults. Geriatr Nurs (Minneap). 2016;37:266–72.
15. 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.
16. Canouï-Poitrine F, Lièvre A, Dayde F, Lopez-Trabada-Ataz D, Baumgaertner I, Dubreuil O, et al. Inclusion of Older Patients with Cancer in Clinical Trials: The SAGE Prospective Multicenter Cohort Survey. Oncologist. 2019;24(12):e1351–e1359.
17. Srikanthan A, Vera-Badillo F, Ethier J, Goldstein R, Templeton AJ, Ocana A, et al. Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies. Cancer Treat Rev. 2016;43:67–73.
18. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the Treatment Preferences of Seriously Ill Patients. N Engl J Med. 2002;346(14):1061–5.
19. Yellen SB, Cella DF, Leslie WT. Age and clinical decision making in oncology patients. J Natl Cancer Inst. 1994;86(23):1766–70.
20. Van Leeuwen KM, Van Loon MS, Van Nes FA, Bosmans JE, De Veti HCW, Ket JCF, et al. What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):1–39.
21. 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. 2017;26:65–71.
22. Soto-Perez-De-Celis E, Lichtman SM. Con-

siderations for clinical trial design in older adults with cancer. Expert Opin Investig Drugs. 2017;26(10):1099–102.
23. McKenna SP. Measuring patient-reported outcomes: Moving beyond misplaced common sense to hard science. BMC Med. 2011;9(86).
24. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Relat Outcome Meas. 2018;9:353–67.
25. Cocks K, King MT, Velikova G, St-James MM, 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.
26. Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MAG, Fayers PM. The clinical significance of adaptation to changing health: A meta-analysis of response shift. Qual Life Res. 2006;15(9):1533–50.
27. Hems M, Harkes M, Moret-Hartman M, Melis RJF, Schoon Y. Eerste ervaringen met patiënt gerapporteerde uitkomstmaten in de geriatrie. Tijdschr Gerontol Geriatr. 2017;48:287–96.
28. Harkes M, van Campen J, Habets H, Lamemrs R, Lan T, Schoon Y, et al. Patient Reported Outcome Measures in de geriatrie - adviesrapport. 2019.
29. OECD. Recommendations to OECD ministers of health from the high level reflection group on the future of health statistics [Internet]. 2017. Available from: https://www.oecd.org/els/health-systems/Recommendations-from-high-level-reflection-group-on-the-future-of-health-statistics.pdf
30. IHCOM. International Consortium for Health Outcomes Measurement [Internet]. [cited 2020 Nov 25]. Available from: https://www.ichom.org/
31. Calvert M, Brundage M, Jacobsen PB, Schünemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: Implications for clinical trials and practice. Health Qual Life Outcomes. 2013;11:184.
32. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols the spirit-pro extension. JAMA - J Am Med Assoc. 2018;319:483–94.
33. Jacobs A, van der Bol J, Tielemans L HM. Implementation of geriatric oncology in the Netherlands in the years 2013 to 2019. J Geriatr Oncol. 2020;20:S1879-4068.
34. Borras JM, Albreht T, Audisio R, Briers E, Casali P, Esperou H, et al. Policy statement on multidisciplinary cancer care. Eur J Cancer. 2014;50(3):475–80.
35. Winters D, Soukop T, Green JS., Sevdalis N, Lamb BW. The Cancer Multidisciplinary Team Meeting: in need of change? History, challenges and future perspective. BJU Int. 2021;2021;128(3):271-279.
36. Ljungqvist O, Young-Fadok T, Demartines N. The History of Enhanced Recovery after Surgery and the ERAS Society. J Laparoendosc Adv Surg Tech. 2017;27:860–2.
37. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M. Enhanced recovery program in colorectal surgery: A meta-analysis of randomized controlled trials. World J Surg. 2014;38:1531–41.
38. Slieker J, Frauche P, Jurt J, Addor V, Blanc C, Demartines N, et al. Enhanced recovery ERAS for elderly: a safe and beneficial pathway in colorectal surgery. Int J Colorectal Dis. 2017;32:215–21.
39. NVVH. Colorectaal Carcinoom [Internet]. 2019 [cited 2021 Jun 4]. Available from: https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crc.html
40. Forbes CC, Swan F, Greenley SL, Lind M, Johnson MJ. Physical activity and nutrition interventions for older adults with cancer: a systematic review. J Cancer Surviv. 2020;14(5):689–71.
41. Steffens D, Beckenkamp PR, Young J, Solomon M, da Silva TM, Hancock MJ. Is preoperative physical activity level of patients undergoing cancer surgery associated with postoperative outcomes? A systematic review and meta-analysis. Eur J Surg Oncol. 2019;45(4):510–8.
42. Hamaker ME, Oosterlaan F, van Huis LH, Thielen N, Vondeling A, van den Bos F. Nutritional status and interventions for patients with cancer – A systematic review. J Geriatr Oncol. 2021;12(1):6–21.
43. Tsimopoulou I, Pasquali S, Howard R, Desai A, Gourevitch D, Tolosa I, et al. Psychological Prehabilitation Before Cancer Surgery: A Systematic Review. Ann Surg Oncol. 2015;22(13):4117–23.
44. Bruns ERJ, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. Color Dis. 2016;18(8):267–77.
45. Molenaar CJL, Janssen L, van der Peet DL, Winter DC, Roumen RMH, Slooter GD. Conflicting Guidelines: A Systematic Review on the Proper Interval

for Colorectal Cancer Treatment. World J Surg. 2021;45(7):2235–50.
46. Faithfull S, Turner L, Poole K, Joy M, Manders R, Weprin J, et al. Prehabilitation for adults diagnosed with cancer: A systematic review of long-term physical function, nutrition and patient-reported outcomes. Eur J Cancer Care (Engl). 2019;28(4):e13023.
47. Kim SJ. Geriatric co-management is associated with reduced 90-day postoperative mortality among patients aged 75+ with cancer. J Geriatr Oncol. 2019;10:S3-4.

CHAPTER
12

Summary

SUMMARY

The treatment decision-making process may be difficult in older patients with cancer. Treatment decisions are mainly based on national guidelines which contain limited recommendations concerning treatment decisions in older patients with cancer. Older patients less often participate in scientific research and comprise a heterogeneous population which varies widely in comorbidities, physical and cognitive condition, functioning in daily life and treatment goals. Therefore, the treatment decision-making process in older patients with cancer requires an individualized approach. As the number of older patients with cancer is growing worldwide, physicians will increasingly face this challenge.

In this thesis, we wanted to increase the level of evidence concerning treatment decision-making process in older patients with cancer. To this end, different ways to assess the level of frailty in older patients with cancer were evaluated (**Part I**). Thereafter, the current treatment decisions in older patients with colorectal cancer were demonstrated. Finally, we evaluated to what extent patientrelated outcomes are included in clinical oncological trials and assessed the impact of cancer treatment on patient related outcomes such as quality of life or social support (**Part II**).

In **Part I**, we focused on assessing the level of frailty in older patients with cancer. We have studied three methods to assess the level of frailty: the geriatric assessment, the G8 frailty screening tool and physician's clinical judgment. In order to estimate the level of frailty in older patients, a comprehensive geriatric assessment is considered as the 'golden standard'. The impact of performing a geriatric assessment on treatment allocation has already been demonstrated in older patients with solid malignancies. In those patients, performing a geriatric assessment has a positive effect on clinical outcomes such as toxicity, treatment-related complications and treatment completion. However, limited evidence is available for patients with a haematological malignancy and therefore, we have studied this in **Chapter 2**. This systematic review summarized all available evidence on the value of performing a geriatric assessment in older patients with a haematological malignancy. A geriatric assessment was shown to be able to detect geriatric impairments, even in patients with a good WHO performance status. In addition, geriatric impairments were associated with a greater risk of toxicity, treatment non-completion and hospitalisation. Before starting treatment in older patients with haematological malignancies a geriatric assessment should be considered.

Chapter 3 assessed the level of frailty based on clinical judgment. Correlations between clinical judgment for frailty of the cancer specialist, the general practitioner and patients themselves were assessed in patients undergoing geriatric assessment, including the G8 frailty screening tool. These correlations were poor; despite the presence of multiple geriatric impairments, patients were frequently assessed as fit by the oncologist, general practitioner and patients themselves. 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. Performing a geriatric evaluation may be of added value in tailoring cancer treatment.

Because not all older patients with cancer need a geriatric assessment before making a treatment decision, the International Organization of Geriatric Oncology (SIOG) recommends screening for frailty first. The G8 frailty screening tool has been recommended as the screening tool of choice by the SIOG. In **Chapter 4**, we performed a systematic review to provide insight into the diagnostic value of the G8 and assessed to what extent the G8 is associated with clinical outcome measures. Based on all available evidence, the G8 can be used to identify potentially frail patients who may benefit from a geriatric assessment. In addition, this review showed that a low G8 score (potentially frail) is associated with mortality and treatment-related complications. Therefore, the G8 may help physicians make informed treatment decisions.

Limited evidence is available to what extent the G8 frailty screening tool is associated with treatment decisions in older cancer patients. Therefore, in **Chapter 5** we assessed this association in older patients with breast cancer. Compared to 'G8 fit' patients, patients considered as 'G8 frail' were more likely to receive non-standard treatment in which surgery was omitted. However, of all patients who received surgery, no difference was observed in risk of mortality between those who were considered as 'G8 fit' or 'G8 frail'. These findings suggest that, depending on the geriatric expertise within the multidisciplinary team, the G8-frail patients might warrant a referral to a geriatrician for further examination to prevent undertreatment.

In **Part II** of this thesis, we focused on current cancer treatment decision for older cancer patients and patient related outcomes. **Chapter 6** demonstrated the current treatment decisions in patients with colorectal cancer. Data from a large nationwide cohort study showed that guideline non-adherence increased with advancing age. Omission of standard treatment was mainly based on patient preference and functional status whereas in the past chronological age and comorbidity status were most mentioned reasons for guideline non-adherence. This implies a positive trend in tailoring cancer care.

We also studied the impact of cancer treatment on patient related outcomes such as quality of life, functioning or health care utilisation. Compared to younger patients, treatment goals in older patients may differ. Although survival benefit remains an important clinical outcome for older patients, the maintenance of self-care capacity, independently functioning in daily life and quality of life can be just as important. **Chapter 7** listed the frequency of measuring patient related outcomes in clinical trials which included older patients with the four most common malignancies. Although the importance of these clinical outcomes is being emphasized by several international organizations, only a small increase has been observed over the years: a quarter of the currently ongoing trials collected patient related outcomes.

In **Chapter 8** and **Chapter 9** we focused on the health related quality of life (HR-QoL)

trajectory in patients with colon cancer who received surgical treatment and adjuvant chemotherapy if necessary. At group level, only trivial changes of HR-QoL were observed after colon cancer treatment, whereas on individual level at least one out of ten patients experienced a decline of HR-QoL twelve months post-surgery. No predictive marker for a persistent decline in HR-QoL at one year post-surgery was found (**Chapter 8**). In contrast, the level of resilience lagged most in older patients who received adjuvant chemotherapy (**Chapter 9**). These findings suggest the importance of an individualized approach in the cancer treatment decision-making process.

Experiencing a sufficient level of social support may contribute to a good level of quality of life. In **Chapter 10** we studied predictive markers that may have an impact on the perceived level of social support in patients with ovarian cancer. Particular patients with a type D personality, characterized by a negative affect and social inhibition, more often experience a limited degree of social support.

The results of this thesis and their implications for clinical practice and future research are discussed in **Chapter 11**.

In summary, the results of the studies performed in this thesis show that estimating frailty based on clinical judgment and/or WHO performance status is suboptimal. Adding a geriatric evaluation can identify potentially frail patients who are at risk for mortality and toxicity, treatment non completion and health care utilization. Although biological age and patient preferences are more often considered in the treatment decision-making process, performing a geriatric evaluation in those who are potentially frail can be helpful in order to tailor cancer treatment. After all, many individual differences in quality of life after cancer treatment are observed. Those patient related outcomes should be more often included as study objective in future clinical trials to improve the decision-making process in older patients with cancer.

CHAPTER
13

Summary in Dutch
samenvatting in het Nederlands

SAMENVATTING IN HET NEDERLANDS

De besluitvorming omtrent de behandeling bij oudere patiënten met kanker kan complex zijn. Behandelkeuzes worden veelal gemaakt met behulp van landelijke richtlijnen. Echter bevatten deze richtlijnen beperkte informatie over de oncologische besluitvorming bij de oudere patiënt. Oudere patiënten nemen veelal niet deel aan wetenschappelijke studies waardoor het verkrijgen van nieuwe informatie over deze groep patiënten achterblijft. Daarnaast betreft het een heterogene groep patiënten; zowel de fysieke en cognitieve conditie als het functioneren in het dagelijks leven lopen sterk uiteen. Bovendien hebben zij verschillende behandelwensen waarbij, naast overlevingswinst, patiëntgerichte uitkomsten, zoals onafhankelijkheid en kwaliteit van leven, eveneens een belangrijke rol spelen bij het maken van een behandelkeuze. De behandelkeuze bij de oudere patiënt met kanker vraagt derhalve om een geïndividualiseerde benadering. Met het toenemend aantal ouderen met kanker in de Nederlands samenleving komen artsen steeds vaker voor deze uitdagende oncologische besluitvorming te staan.

Met dit proefschrift willen we de kennis vergroten omtrent het besluitvormingsproces bij oudere patiënten met kanker. In eerste instantie staan we stil bij de verschillende manieren om kwetsbaarheid in te schatten bij ouderen met kanker (**Deel I**). Vervolgens beschrijven we de huidige behandelkeuzes voor patiënten met darmkanker. Tot slot evalueren we in hoeverre patiëntgerichte uitkomsten worden geïncludeerd in klinische oncologische studies en bestuderen we de invloed van een oncologische behandeling op patiëntgerichte uitkomsten zoals kwaliteit van leven en sociale steun (**Deel II**).

In **Deel I** ligt de nadruk op het inschatten van kwetsbaarheid van de oudere patiënt met kanker. De verschillende methodes die we in dit proefschrift hebben bestudeerd zijn het geriatrisch assessment, het screeningsinstrument G8 en de klinische blik.

Bij patiënten met een solide maligniteit blijkt het uitvoeren van een geriatrisch assessment ter bevordering van de oncologische besluitvorming een positief effect te hebben op klinische uitkomsten zoals toxiciteit, behandeling gerelateerde complicaties en het voltooien van de behandeling. In hoeverre dit ook van toepassing is voor patiënten met een hematologische maligniteit is onvoldoende bekend en dit hebben we bestudeerd in **Hoofdstuk 2**. In deze systematische review hebben we al het beschikbare bewijs voor het gebruik van een geriatrisch assessment van deze patiëntengroep samengevat. Met het uitvoeren van een geriatrisch assessment blijkt dat stoornissen in één van de geriatrische domeinen beter naar voren komen dan met de gebruikelijke inschatting van de conditie van de patiënt, middels bijvoorbeeld een WHO-performance status. Daarnaast zijn stoornissen in geriatrische domeinen geassocieerd met het beloop van de behandeling waarbij er een groter risico is op toxiciteit, het niet voltooien van de behandeling en het gebruik van de gezondheidszorg. Nog voordat een behandeling bij oudere patiënten met een hematologische maligniteit wordt gestart moet een geriatrisch assessment overwogen worden.

Het inschatten van de mate van kwetsbaarheid bij oudere patiënten met kanker met behulp van de klinische blik werd onderzocht in **Hoofdstuk 3**. De correlatie tussen de klinische blik van de oncoloog, de huisarts en patiënten zelf werd met elkaar vergeleken en we vergeleken de klinische blik met het geriatrisch assessment. Deze correlaties waren slecht; ondanks dat patiënten veelal meerdere stoornissen in geriatrische domeinen hadden, werden patiënten regelmatig als fit ingeschat door de oncoloog, de huisarts en de patiënten zelf. Dit laat zien dat patiënten met relevante stoornissen in één van de geriatrische domeinen gemist kunnen worden wanneer vertrouwd wordt op de klinische blik. Om een op maat gemaakte behandeling voor oudere patiënten met kanker op te stellen kan het toevoegen van een geriatrische evaluatie aan de klinische blik van meerwaarde zijn.

Omdat een geriatrisch assessment niet bij alle oudere patiënten met kanker noodzakelijk is, adviseert de Internationale Vereniging voor Geriatrische Oncologie (SIOG) om eerst te screenen op kwetsbaarheid. De G8 is volgens de SIOG het screeningsinstrument van eerste keus om de kwetsbaarheid van een oudere patiënt met kanker in te schatten. In **Hoofdstuk 4** hebben we een systematische review uitgevoerd om inzicht te geven in de diagnostische waarde van de G8. Daarnaast bestudeerden we in hoeverre de G8 geassocieerd is met klinische uitkomstmaten. Wij concluderen dat de G8 kan worden toegepast als eerste stap om in te schatten welke patiënten potentieel kwetsbaar zijn en een uitgebreid geriatrisch assessment nodig hebben. Daarnaast is een lage G8 score (potentieel kwetsbaar) geassocieerd met een hoger risico op overlijden of behandeling gerelateerde complicaties. De G8 kan derhalve artsen ondersteunen bij de oncologische besluitvorming.

In hoeverre het inschatten van kwetsbaarheid met de G8 daadwerkelijk geassocieerd is met de behandelkeuze in oudere patiënten met kanker is onvoldoende bekend. In **Hoofdstuk 5** hebben we deze associatie onderzocht in oudere patiënten met borstkanker. In vergelijking met G8 -fitte patiënten, ontvingen patiënten die als G8-kwetsbaar werden beschouwd vaker een niet-standaard behandeling waarbij de borstoperatie achterwege werd gelaten. Echter, van de patiënten die een operatie ondergingen, is het risico op overlijden na de operatie vergelijkbaar tussen fitte en kwetsbare patiënten. Dit impliceert dat, afhankelijk van de geriatrische expertise binnen het multidisciplinaire team, een verwijzing naar de geriater voor verdere geriatrische evaluatie te rechtvaardigen is bij patiënten met borstkanker die als G8-kwetsbaar worden beschouwd om onderbehandeling te voorkomen.

In **Deel II** van dit proefschrift ligt de focus op huidige oncologische besluitvorming in oudere patiënten met kanker en patiëntgerichte uitkomsten. **Hoofdstuk 6** beschrijft de huidige behandelkeuzes van patiënten met darmkanker in de klinische praktijk. Data van een groot landelijk cohortonderzoek laten zien dat, naarmate de leeftijd vordert, de kans groter is dat wordt afgezien van een standaard behandeling. Redenen voor een niet-standaard behandeling waren voornamelijk gebaseerd op de functionele status van de patiënt en zijn/haar wensen met betrekking tot de behandeling. In tegenstelling tot het verleden waarbij de chronologische leeftijd en co-morbiditeit vaak werden benoemd als reden om af te zien van een behandeling volgens de richtlijn, lijkt de behandelkeuze nu vaker gebaseerd op de

biologische leeftijd en wensen van de patiënt. Dit suggereert dat behandelkeuzes meer op het individu worden afgestemd.

We bestudeerden tevens de invloed van een oncologische behandeling op patiëntgerichte uitkomsten zoals kwaliteit van leven, dagelijks functioneren of het gebruik van de gezondheidszorg. Behandelvoorkeuren van oudere patiënten met kanker kunnen verschillen ten opzichte van jongere patiënten. Hoewel overlevingswinst ook voor ouderen een belangrijke uitkomstmaat blijft, vinden zij het eveneens belangrijk, of zelfs belangrijker, om onafhankelijk te kunnen blijven functioneren in het dagelijks leven en kwaliteit van leven te behouden. In **Hoofdstuk 7** hebben we op een rij gezet hoe vaak patiëntgerichte uitkomsten worden gemeten in klinisch oncologisch onderzoek. Ondanks dat het belang van deze uitkomstmaten door meerdere internationale organisaties wordt benadrukt, is er over de jaren heen enkel een kleine stijging zichtbaar waarbij slechts in een kwart van de uitgevoerde studies patiëntgerichte uitkomstmaten worden gemeten.

In **Hoofdstuk 8** en **Hoofdstuk 9** bestudeerden we het beloop van kwaliteit van leven van patiënten die wegens darmkanker een operatie hadden ondergaan en eventueel aanvullende chemotherapie hadden gekregen. Ondanks dat er één jaar na de oncologische behandeling op groepsniveau geen klinisch relevant verschil in kwaliteit van leven werd gezien, werden op individueel niveau grote verschillen waargenomen waarbij tenminste één op de tien patiënten een klinisch relevante daling van kwaliteit van leven ervaarden. Er werden geen risicofactoren gevonden voor het ervaren van een klinisch relevant verschil in kwaliteit van leven één jaar na de behandeling (**Hoofdstuk 8**). Toch bleef de mate van veerkracht het meeste achter bij oudere patiënten die aanvullende chemotherapie hadden ontvangen (**Hoofdstuk 9**). Deze resultaten laten het belang zien van een geïndividualiseerde benadering tijdens het oncologische besluitvormingsproces.

Het ervaren van sociale steun is een belangrijk onderdeel voor het ervaren van voldoende kwaliteit van leven. In **Hoofdstuk 10** gaan we op zoek naar factoren die van invloed zijn op het ervaren van sociale steun in patiënten met baarmoeder- en eierstokkanker. Voornamelijk patiënten met een type D-persoonlijkheid, gekarakteriseerd door een negatief affect en sociale inhibitie, ervaren vaker een beperkte mate van sociale steun.

In **Hoofdstuk 11** worden alle resultaten van dit proefschrift en hun toepassingen voor de dagelijkse klinische praktijk bediscussieerd. Tevens bespreken we enkele suggesties voor toekomstig onderzoek.

Samenvattend blijkt uit de resultaten van de verrichte studies in dit proefschrift dat het inschatten van kwetsbaarheid op basis van de klinische blik en/of de WHO-performance status suboptimaal is. Het toevoegen van een geriatrische evaluatie kan potentieel kwetsbare patiënten identificeren die een hoger risico hebben op overlijden, toxiciteit, het niet voltooien van de behandeling of die vaker gebruik maken van de gezondheidszorg. Ondanks dat er steeds vaker wordt afgezien van een behandeling volgens de richtlijn op basis van de

biologische leeftijd van de patiënt en zijn/haar behandelwensen, blijven de gegevens van een geriatrische evaluatie belangrijk in het besluitvormingsproces om een geïndividualiseerde behandeling op te kunnen stellen. Er worden immers veel individuele verschillen in kwaliteit van leven na een oncologische behandeling waargenomen. Derhalve zou het de moeite waard zijn om patiëntgerichte uitkomsten vaker te bestuderen in toekomstig wetenschappelijk onderzoek om zo het besluitvormingsproces bij oudere patiënten met kanker te verbeteren.

APPENDICES

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LIST OF PUBLICATIONS

Geriatric assessment in older patients with a hematologic malignancy: a systematic review.
Scheepers ERM, Vondeling AM, Thielen N, van der Griend R, Stauder R, Hamaker ME.
Haematologica 2020 Jun;105(6):1484-1493.

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 Sep;11(7):1138–1144.

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 ERM**, van Huis-Tanja L, Emmelot-Vonk MH, Bellera C, Soubeyran P, Hamaker ME.
J Geriatr Oncol. 2019;10(6):847-858.

The G8 frailty screening tool and the decision-making process in older breast cancer patients.
Scheepers ERM, van der Molen LF, van den Bos F, Burgmans JP, van Huis-Tanja LH, Hamaker ME.
Eur J Cancer Care (Engl). 2021;30(1):e13357.

Treatment patterns and primary reasons for adjusted treatment in older and younger patients with stage II or III colorectal cancer.
Scheepers ERM, Schiphorst AH, van Huis-Tanja LH, Emmelot-Vonk MH, Hamaker ME.
Eur J Surg Oncol. 2021; 47(7):1675-1682.

Study objectives in clinical trials in older patients with solid malignancies: do we measure what matters?
Scheepers ERM, van Huis-Tanja LH, Emmelot-Vonk MH, Hamaker ME.
Qual Life Res. 2021;30(7):1833-1839.

The impact of surgery and adjuvant chemotherapy on health-related quality of life in patients with colon cancer: changes at group-level versus individual-level.
Scheepers ERM, Vink GR, Schiphorst AHW, Emmelot-Vonk MH, van Huis-Tanja LH, Hamaker ME.
Submitted

Differences in the impact of surgery and adjuvant chemotherapy on resilience of health-related quality of life in patients with colon cancer.
Scheepers ERM, Vink GR, Schiphorst AHW, Emmelot-Vonk MH, van Huis-Tanja LH, Hamaker ME.
Submitted

Perceived social support in patients with endometrial or ovarian cancer: a secondary analysis from the ROGY care study.
Scheepers ERM, de Rooij BH, Pijnenborg JMA, van Huis-Tanja LH, Ezendam NPM, Hamaker ME.
Gynecol Oncol. 2021;160(3):811-816.

Azacitidine might be beneficial in a subgroup of older AML patients compared to intensive chemotherapy: A single centre retrospective study of 227 consecutive patients.
Van Der Helm LH*, **Scheepers ERM***, Veeger NJ, Daenen SMGJ, Mulder AB, Van Den Berg E, Vellenga E, Huls G.
J Hematol Oncol. 2013;16(6):29.
* authors contributed equally

A man with backache and a genital skin lesion.
Scheepers ERM, Flinterman AE, Thielen N.
Ned Tijdschr Geneeskd. 2019;19(163):D3381.

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CURRICULUM VITAE

Ellen Scheepers was born in Zutphen, the Netherlands, on 20th of February in 1990. She grew up in Steenderen and in 2008, she graduated from the Atheneum Isendoorn College in Warnsveld. Afterwards, she moved to Groningen to study Life Science & Technology and Pharmacy at the University of Groningen; she successfully finished both propaedeutic exams. During this year she became interested in scientific research. After successfully finishing the selection procedure, she studied Medicine between 2009 and 2015. She followed her clerkships in Groningen, Enschede and Malawi. She combined her studies with the extracurricular Honours program in which she published her first scientific article. During her job at the Department of Internal Medicine and Geriatric Medicine in the Deventer Hospital, she became interested in Geriatric Medicine. In 2017 she started as a resident in Geriatric Medicine in the Diakonessenhuis Utrecht. There she met Dr. Marije Hamaker and they started a collaboration; a new research project was born. After finishing the first two years of her residency, in October 2019 she started with her PhD program under supervision of Dr. Marije Hamaker, Dr. Lieke van Huis and Prof.dr. Marielle Emmelot-Vonk. In January 2021 she continued her residency Geriatric Medicine at the Catharina Hospital in Eindhoven. From 2018 until 2021, she was an active board member of the jNVKG (Nederlands Vereniging voor Klinische Geriatrie junior). She lives in Waalre, together with her partner Jorden and adorable daughter Lotta.