Preoperative risk assessment of adverse outcomes in onco-geriatric surgical patients

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Colofon

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Introduction and outline of the thesis

Introduction and outline of the thesis

Worldwide, the burden of cancer increases. In 2015 there were 17.5 million incident cancer cases, compared with 14.9 million in 2013 and 8.5 million in 1990[1, 2]. A total of 16% to 35.6% of the increase in incident cancer cases can be attributed to population aging. Moreover, most solid tumours occur in the elderly population[1, 3]. As surgery plays an important role in the multimodality treatment of solid tumours, surgeons are being confronted with more and more onco-geriatric patients.

The heterogeneity of the onco-geriatric population poses a big challenge for clinicians when dealing with this growing number of patients, as it makes the decision-making process more complex. On the one hand, this challenge comes to expression by onco-geriatric patients receiving substandard treatment[4, 5], likely due to the assumption that increasing age itself is associated with reduced fitness for treatment and the complexity of predicting a geriatric patient's response to treatment[6-9]. On the other hand, the risk of overtreatment exists, with increased risks of adverse outcomes and impaired quality of life. In order to allocate appropriate treatments to patients, it is necessary to identify which of the onco-geriatric patients are fit and which are vulnerable or frail. Fit onco-geriatric patients are thought to be able to withstand major stressors like cancer surgery, possibly comparable to their younger counterparts. Frailty is, although not unambiguously defined in literature, 'a loss of resources in several domains of functioning' and results in increased vulnerability to stressors. Therefore, frail patients are at increased risk of adverse postoperative outcomes[10].

The Geriatric Assessment (GA) was originally developed by geriatricians to handle complex health care issues in frail elderly in a multidimensional and interdisciplinary manner[11, 12]. It comprises the evaluation of multiple domains, most commonly physical, functional, psychological and socio-environmental[11, 12]. Geriatric oncology adopted the GA, with the aim of identifying multidomain impairments that 1) were previously unrecognized and might influence the treatment plan, 2) are associated with an increased risk of adverse posttreatment outcomes and 3) might be amenable to a targeted intervention[13, 14].

Performing a full GA in every onco-geriatric patient is not feasible in a busy surgeon's practice, nor necessary, as the majority of patients is fit for surgery[11, 15]. Consensus as to what constitutes a complete GA and what are items or screening tools that can reliably assess the domains included is lacking, which hampers implementation in clinical practice[16, 17]. This is partly due

to discrepancies in outcomes between studies and the great variety regarding the population under study, the domains included, and the methods used to assess those domains[16, 17]. To provide a complete overview of the evidence available to date on the predictive value of separate GA domains and the different tools to assess them, regarding adverse postoperative outcomes in onco-geriatric patients, a systematic review of systematic reviews was performed **(chapter 2)**. The goal of this systematic review was to provide for scientifically substantiated recommendations to facilitate the implementation of a preoperative GA in daily clinical practice.

To easily identify which patients are at risk for adverse outcomes and who thus might benefit from further assessment, time-saving screening tools need to be investigated[18]. For this reason, the Preoperative Risk Estimation for Onco-geriatric Patients (PREOP)-study was designed by members of the surgical taskforce of the International Society of Geriatric Oncology (SIOG). Patients of 70 years of age or older, undergoing elective surgery for a solid tumour, were included in this prospective multicentre cohort study. The PREOP-study investigated the predictive ability of a set of screening tools regarding 30-day postoperative outcomes. The first analysis focused on the predictive value of the Timed Up and Go (TUG) regarding the risk of adverse outcomes up to 30-days postoperatively and compared it to the predictive ability of the well-known American Society of Anaesthesiologists (ASA)-classification, that is readily available for all surgical patients **(chapter 3)**. The TUG is an easy to administer tool that was developed with the purpose of identifying frail elderly by quantifying functional mobility[19]. Repeatedly, the TUG was found to be able to identify the level of physical disability in community dwelling elderly and to predict adverse outcomes in patients undergoing surgery and receiving chemotherapy[20-29]. Data on the predictive value of the TUG in the onco-geriatric surgical population were lacking until now.

The second analysis of the PREOP-study compared the geriatric screening tools, that touch on all domains that generally compose a GA, regarding their ability to predict the risk of major 30-day complications **(chapter 4)**. This analysis enhances comparability between different screening tools and GA domains and with other studies that might focus on only a few of the domains. Subsequently a preoperative risk score was developed, to stratify patients according to their risk of major 30-day complications.

Next, we looked into further detail at preoperative nutritional status in the same population **(chapter 5)**. Though infrequently included in a GA[16, 30], this domain is often affected in

onco-geriatric patients (32% to 64.2% at nutritional risk or malnourished)[31-33]. It is likely that nutritional impairment is a multifactorial problem in onco-geriatric patients, caused by cancer and its treatment, as well as factors associated with increasing age. For example, nutritional impairment is more prevalent in patients with advanced disease and intra-abdominal tumours[34-37]. Furthermore, the infamous side-effects of chemotherapy and radiotherapy, such as nausea, vomiting and mucositis, can increase the risk of nutritional impairment even further[35, 37]. Finally, other geriatric domains, including mood, functional status, polypharmacy and socio-environmental factors, are presumably associated with an impaired nutritional status as well[35, 38]. In **chapter 5** we analysed the associations between preoperative nutritional impairment, impairments in other geriatric domains and the risk of adverse postoperative outcomes in onco-geriatric surgical patients, as this might lead to targeted interventions to optimise patients for surgery and tailored treatment that hopefully will improve postoperative outcomes[39].

Finally, we completed the PREOP-study by addressing long-term outcomes in onco-geriatric surgical patients **(chapter 6)**. Data on long-term outcome measures in onco-geriatric surgical patients are scarce and seem under-exposed, whilst the life expectancy of elderly might be higher than one often thinks: life expectancy at 70 years of age is approximately 14 to 17 years, and octogenarians have a life expectancy of 8 to 10 years[40, 41]. Moreover, elderly rate maintaining their preoperative level of functioning as one of the most important outcomes, emphasizing the importance of knowing the long-term risk of institutionalisation[42]. This final chapter provides data on survival up to five years postoperatively and the impact on postoperative living situation up to two years postoperatively. Furthermore, the predictive ability of the PREOP risk score regarding these outcomes is analysed.

With this thesis, we aim to raise awareness to the fact that the onco-geriatric patient population is not simply an older version of its younger counterpart. The heterogeneity of this population complicates the decision-making process and emphasizes the need for tailored treatment. The PREOP-study eventually aimed to support these processes. The general discussion and my stand upon future perspectives, can be read in **chapter 7**.

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1

2

Delivering tailored surgery to older cancer patients: preoperative geriatric assessment domains and screening tools – A systematic review of systematic reviews

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Abstract

The onco-geriatric population is increasing, and thus more and more elderly will require surgery; an important treatment modality for many cancer types. This population's heterogeneity demands preoperative risk stratification, which has led to the introduction of Geriatric Assessment (GA) and associated screening tools in surgical oncology.

Many reviews have investigated the use of GA in onco-geriatric patients. Discrepancies in outcomes between studies currently hamper the implementation of a preoperative GA in clinical practice. A systematic review of systematic reviews was performed in order to investigate assessment tools of the most commonly included GA domains and their predictive ability regarding the adverse postoperative outcomes.

All domains – except polypharmacy – were, to a varying degree, associated with different adverse postoperative outcomes. Functional status, comorbidity and frailty were assessed most frequently and were most often significant. The association between domain impairments and adverse postoperative outcomes appeared to be greatly influenced by the study population characteristics and selection bias, as well as the type of assessment tool used due to possible ceiling effects and its sensitivity to detect domain impairments.

Frailty seems to be the most important predictor, which underpins the importance of an integrated approach. As it is unlikely that one universal GA will fit all, feasibility, based on the time, expertise, and resources available in daily clinical practice as well as the patient population to hand, should be taken into consideration, when tailoring the 'optimal GA'.

Introduction

Worldwide, the burden of cancer increases. In 2013 there were 14.9 million incident cancer cases, compared with 8.5 million in 1990[1]. A total of 35.6% of the absolute increase in incident cancer cases in this period could be attributed to aging, demonstrating the fact that cancer is mainly a disease of the elderly[1].

Surgery is an important part of the multimodality treatment of solid tumours. A recent questionnaire among surgical oncologists shows that chronological age alone is not perceived to be a valid reason to decline surgery to elderly anymore[2]. However, the ability to withstand major stressors like surgery varies greatly in the onco-geriatric population. Whilst elderly considered fit for surgery, might do as well as younger patients, vulnerable or frail patients are at an increased risk of adverse postoperative outcomes[3-6].

The heterogeneity of the onco-geriatric population underpins the need for preoperative assessment for this population in order to provide tailored treatment and improve postoperative outcomes[7]. Some clinicians involved in the care for onco-geriatric patients have adopted the geriatric assessment (GA) as a way to detect geriatric domain impairments, and identify those patients at an increased risk for adverse outcomes who might benefit from a geriatric intervention[8].

However, the domains included in a GA vary greatly between studies of onco-geriatric patients, and there is still no consensus regarding which items or screening tools should be used to assess those domains[9, 10]. Furthermore, performing a full GA in all onco-geriatric surgical patients is too time-consuming for clinical practice and also unnecessary, because the majority of these patients can be considered fit for surgery[11]. For these reasons, researchers have focused on the predictive ability and clinical value of separate domains of a GA and related easy-to-administer screening tools to select those patients for whom a full GA might be indicated. Discrepancies in outcomes between these studies currently hamper the implementation of a preoperative geriatric assessment in clinical practice[9]. The aim of the current systematic review was to compose a complete overview of the most commonly included domains of a GA and its predictive abilities regarding adverse postoperative outcomes in onco-geriatric patients, in order to provide scientifically substantiated recommendations for daily clinical practice. For that, a systematic review of systematic reviews was performed.

Methods

Search strategy and study selection

A search strategy for Medline and Embase was formulated, with assistance of a university librarian (supplementary file A). Subsequently, duplicates were removed, and all titles and abstracts were screened independently by two researchers (MGH and MK). For including the following, pre-specified eligibility criteria were used:

- Systematic review: reviews were defined as systematic if they included explicit inclusion criteria for studies.
- The review contained studies specifically focusing on older patients (mean age ≥ 60).
- The review contained studies on cancer patients undergoing surgery. At least one of the studies had to contain patients undergoing surgery for solid tumours.
- Predictors of adverse outcomes after cancer treatment were investigated. At least other outcomes than mortality had to be investigated.
- The above-mentioned predictors were (parts of) a GA or screening tools assessing GA domains.

In case of doubt, articles were included so the full text could be assessed and in case of discrepancy, an independent third party, BLvL, made the final decision to either include or exclude an article. The full texts of the remaining articles were also assessed independently by MGH and MK, using the same eligibility criteria, and again BLvL was consulted in case of discrepancies. When full-text articles could not be retrieved online or via a national university library exchange database, authors were contacted. Excluded were those publications that only reported descriptive results.

Data extraction

To assess the quality of the systematic reviews, the AMSTAR tool – 'a measurement tool to assess the methodological quality of systematic reviews'– was used[12, 13]. The quality of the systematic reviews was assessed independently by MGH and MK.

Data on the following, pre-specified GA domains were collected, as these are most often reported as being part of a comprehensive GA: functional status, nutritional status, cognition, social support, mood & emotional status, comorbidity, polypharmacy and frailty. Endpoints of interest were postoperative complications, discharge to a non-home institution and mortality. Initially, data were collected via systematic reviews, but if necessary, the original studies were read for further information and clarification, to allow for maximal transparency.

In order to clarify any uncertainties regarding study design of the original studies, types of patients included, or results of the studies, authors of the original studies were contacted where relevant. Results from adequate univariate and/or multivariate analyses were retrieved. Whenever available, negative results were reported as well. In case the systematic reviews reported different results originating from the same original studies (e.g. when multiple multivariable models were reported in the original studies), at least the most complete model for that domain was used or multiple models were used in case univariate models and/or models adjusted for confounders that were not other GA domains and/or multivariable models that included other GA domains were reported. Data extraction was performed in independently by MGH and MK, using self-designed and piloted forms.

Per GA domain the type of assessments used and their associations with the different outcomes were described and displayed in forest plots. These forest plots also displayed the percentage of onco-geriatric surgical patients (column 'population'). The remaining patients either were non-oncological elderly surgical patients (a) or non-surgical elderly cancer patients (b). No meta-analyses were performed due to the heterogeneity between studies.

Results

Included studies

The literature search performed at May 20th 2015 yielded 3,792 records (figure 1[14]). After removal of duplicates and screening of titles and abstracts, 90 full-text articles were selected and assessed for eligibility for the current systematic review. A total of nine systematic reviews were finally identified and most were of good quality (supplementary file B). The nine systematic reviews reported data on 20 different articles describing 17 different cohorts including onco-geriatric surgical patients.

Functional status

The functional status of a patient can be considered an essential element of a GA, as functional impairments are associated with other GA domain impairments and it influences the degree of autonomy of elderly patients[40, 41]. Nevertheless, a recent questionnaire among surgeons on preoperative assessments in elderly cancer patients, revealed that only a minority of surgeons performed functional assessments in these patients (Activities of Daily Living (ADL) or Instrumental ADL (IADL): 8%, Timed up and Go: 8%)[2].

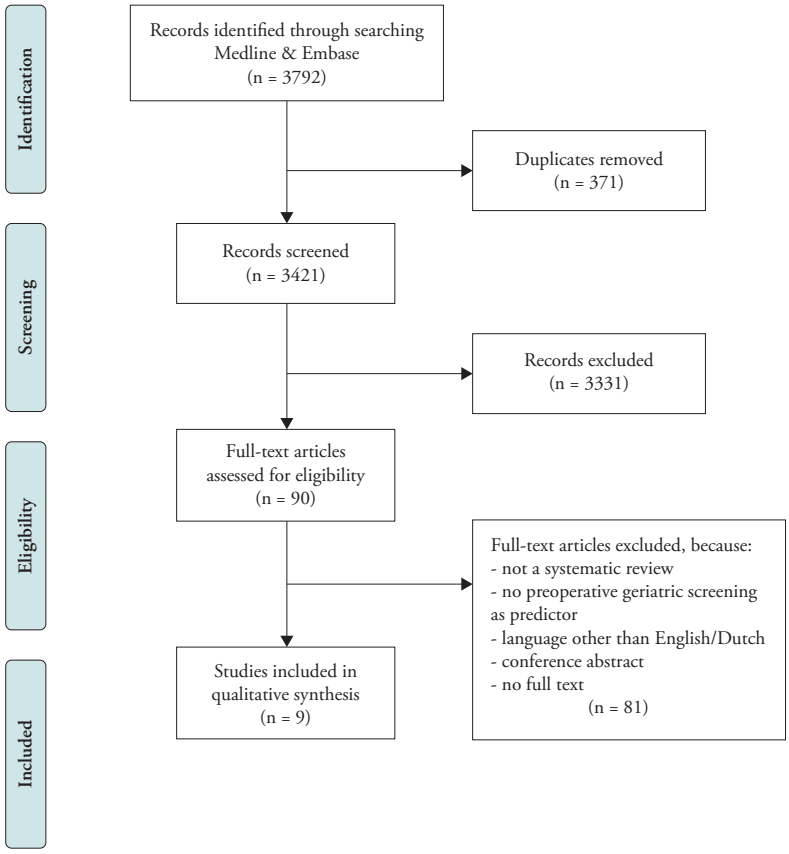
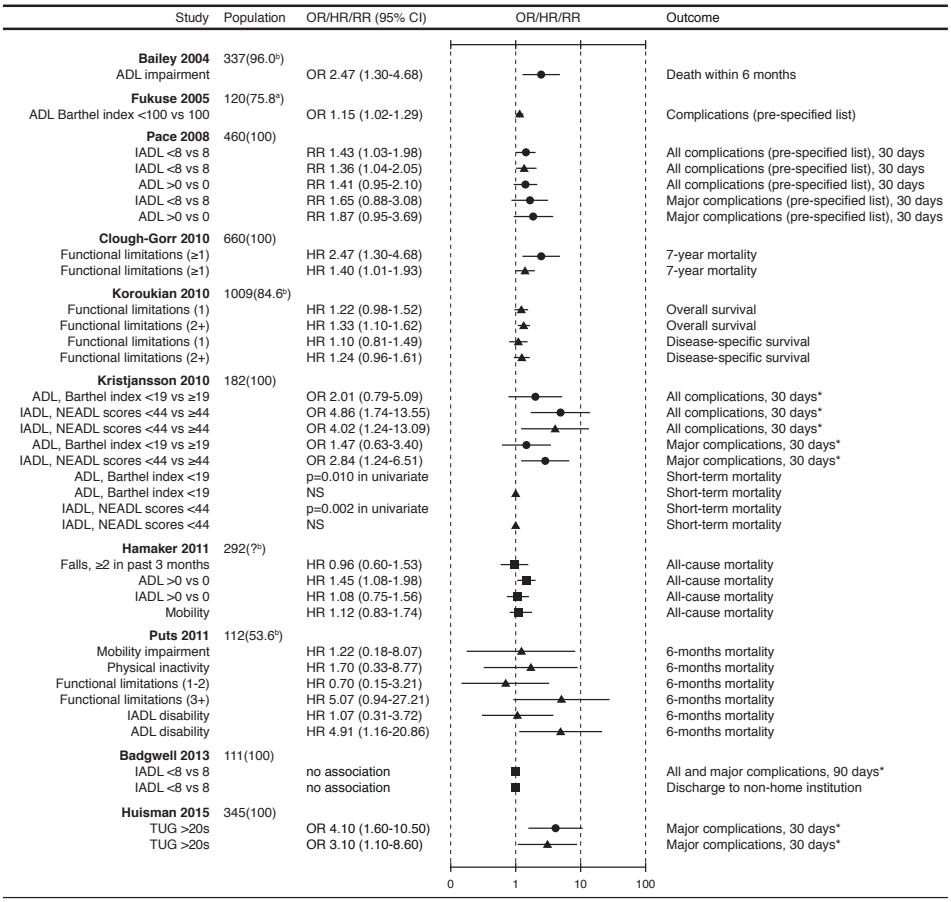


Figure 1 | PRISMA flow diagram

Functional status can be assessed in numerous ways. ADL and IADL as measurements for functional status were used most frequently, both in the current review (ADL in 7/10 studies, including the study from Koroukian et al. in which functional limitations was defined as ADL impairments, and IADL in 5/10 studies), as well as in the systematic review from Puts et al. (ADL in 93% of studies and IADL in 89% of all studies)[9].

The prevalence of ADL and IADL impairments ranged from 7.5% to 38.1% and from 12% to 76.9%, respectively[26, 28, 31]. In most onco-geriatric cohorts, both ADL and IADL impairments were not predictive of adverse postoperative outcomes (figure 2a). Four studies investigated ADL and/or IADL in relation to postoperative complications[16, 26, 28, 30]: ADL was never predictive of postoperative complications and for IADL conflicting results were observed. Impairments in ADL were predictive of mortality in four out of five studies among

a)



▲ In a multivariable model, i.e. with other geriatric domains
● In a model adjusted for confounders
■ In a univariate model
* According to modified Clavien-Dindo classification

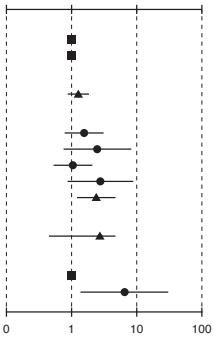
[a] 100% minus the reported percentage are non-oncological elderly surgical patients

[b] 100% minus the reported percentage are non-surgical elderly cancer patients

Figure 2 | Associations between geriatric domain impairments and adverse outcomes in original studies including onco-geriatric surgical patients for geriatric domains AeH. A: Functional status. B: Nutritional status. C: Cognition. D: Social support. E: Mood. F: Comorbidity. G: Polypharmacy. H: Frailty.

b)

Study	Population	OR/HR/RR (95% CI)	Outcome
Fukuse 2005	125(75.8[a])		
BMI <18.5 or >25		p=0.168	Complications (pre-specified list)
MMC female <17 / male <19 [c]		p=0.42	Complications (pre-specified list)
Clough-Gorr 2010	660(100)		
BMI>30		HR 1.27 (0.89-1.81)	7-year mortality
Kristjansson 2010	182(100)		
MNA, at risk		OR 1.56 (0.80-3.03)	All complications, 30 days*
MNA, malnourished		OR 2.49 (0.77-8.06)	All complications, 30 days*
MNA, at risk		OR 1.05 (0.54-2.04)	Major complications, 30 days*
MNA, malnourished		OR 2.77 (0.89-8.65)	Major complications, 30 days*
MNA at risk/malnourished		HR 2.39 (1.24-4.61)	Short-term mortality
Puts 2011	112(53.6[b])		
Poor nutritional status [d]		HR 2.73 (0.46-16.94)	6-months mortality
Badgwell 2013	111(100)		
Weight loss >10 % within 6 months		no association	All and major complications, 90 days*
Weight loss >10 % within 6 months		OR 6.50 (1.40-29.80)	Discharge to non-home institution



▲ In a multivariable model, i.e. with other geriatric domains
● In a model adjusted for confounders
■ In a univariate model
* According to modified Clavien-Dindo classification

[a] 100% minus the reported percentage are non-oncological elderly surgical patients

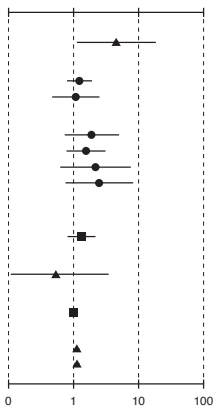
[b] 100% minus the reported percentage are non-surgical elderly cancer patients

[c] mid-arm muscle circumference

[d] BMI<22 or weight loss >3kg in 3 months or lack of appetite (quite a bit or very much)

c)

Study	Population	OR/HR/RR (95% CI)	Outcome
Fukuse 2005	120(75.8[a])		
MMSE <24		OR 4.55 (1.15-18.05)	Complications (pre-specified list)
Pace 2008	460(100)		
MMSE <24		RR 1.23 (0.81-1.88)	All complications (pre-specified list), 30 days
MMSE <24		RR 1.08 (0.48-2.44)	Major complications (pre-specified list), 30 days
Kristjansson 2010	182(100)		
MMSE intermediate 24-26		OR 1.90 (0.75-4.90)	Severe complications, 30 days*
MMSE intermediate 24-26		OR 1.56 (0.80-3.03)	All complications, 30 days*
MMSE cognitive dysfunction <24		OR 2.18 (0.64-7.41)	Severe complications, 30 days*
MMSE cognitive dysfunction <24		OR 2.49 (0.77-8.06)	All complications, 30 days*
MMSE		p=0.257	Overall survival
Hamaker 2011	292(?[b])		
Global cognitive impairment ≥3.9 [c]		HR 1.33 (0.83-2.13)	All-cause mortality
Puts 2011	112(53.6[b])		
Cognitive impairment [d]		HR 0.54 (0.09-3.39)	6-month mortality
Badgwell 2013	111(100)		
Mini-cog		no association	All and major complications, 90 days*
Giantin 2013	160(29.0[b])		
MMSE		HR 1.13 (1.04-1.22)	6-months survival
MMSE		HR 1.13 (1.05-1.21)	12-months survival



▲ In a multivariable model, i.e. with other geriatric domains
● In a model adjusted for confounders
■ In a univariate model
* According to modified Clavien-Dindo classification

[a] 100% minus the reported percentage are non-oncological elderly surgical patients

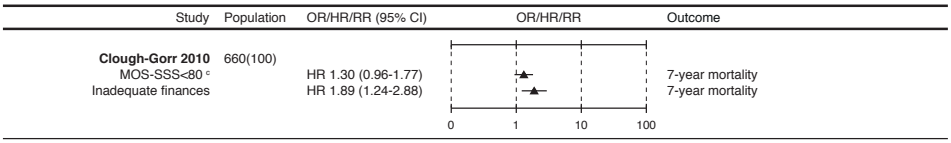
[b] 100% minus the reported percentage are non-surgical elderly cancer patients

[c] IQCODE short form

[d] MMSE + Montreal Cognition Assessment (MOCA): MoCA only when MMSE >25. Cognitive impairment if score ≤26 on either scale.

Figure 2 | (continued)

d)



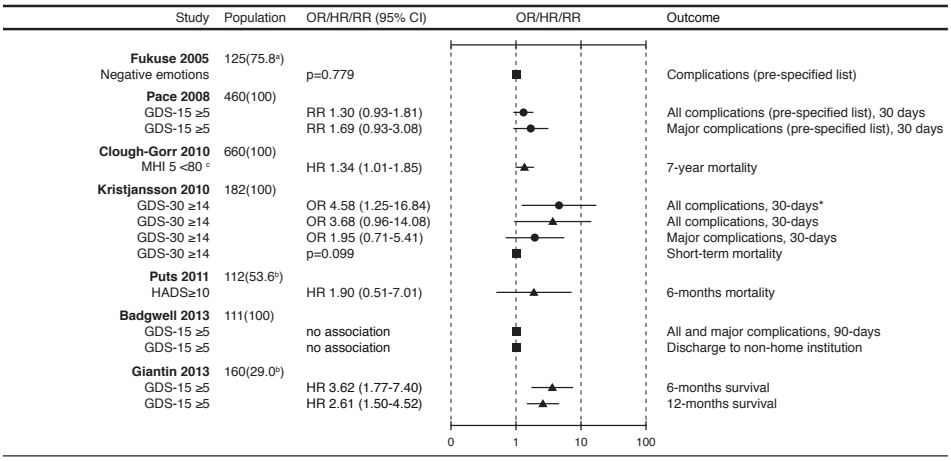
▲ In a multivariable model, i.e. with other geriatric domains
● In a model adjusted for confounders
■ In a univariate model

[a] 100% minus the reported percentage are non-oncological elderly surgical patients

[b] 100% minus the reported percentage are non-surgical elderly cancer patients

[c] 8 items from the 19-item Medical Outcomes Study Social Support Scale

e)



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● In a model adjusted for confounders
■ In a univariate model
* According to modified Clavien-Dindo classification

[a] 100% minus the reported percentage are non-oncological elderly surgical patients

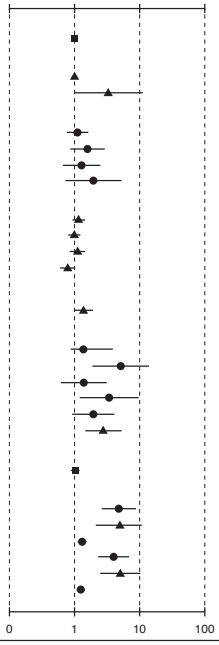
[b] 100% minus the reported percentage are non-surgical elderly cancer patients

[c] Five-item Mental Health Index on a 0-100 scale

Figure 2 | (continued)

f)

Study	Population	OR/HR/RR (95% CI)	Outcome
Fukuse 2005	125(75.8[a])		
Comorbidities, pre-specified		p=0.069	Complications (pre-specified list)
Bo 2007	294(52.4[a])		
CIRS (SI+CI) [c,d]		no association	1-month survival
CIRS (SI) [e]		OR 3.31 (1.01-10.89)	1-month survival
Pace 2008			
SIC (1) [f]		OR 1.11 (0.78-1.59)	All complications (pre-specified list), 30 days
SIC (2+)		OR 1.58 (0.88-2.85)	All complications (pre-specified list), 30 days
SIC (1)		OR 1.29 (0.68-2.44)	Major complications (pre-specified list), 30 days
SIC (2+)		OR 1.95 (0.74-5.18)	Major complications (pre-specified list), 30 days
Koroukian 2009	1009(84.6[b])		
1 comorbidity		HR 1.16 (0.95-1.42)	Overall survival
2+ comorbidity		HR 0.99 (0.82-1.20)	Overall survival
1 comorbidity		HR 1.11 (0.86-1.43)	Disease-specific survival
2+ comorbidity		HR 0.78 (0.61-1.00)	Disease-specific survival
Clough-Gorr 2010	660(100)		
CCI ≥1 [g]		HR 1.38 (1.01-1.88)	7-year mortality
Kristjansson 2010	182(100)		
CIRS, moderate		OR 1.83 (0.89-3.79)	All complications, 30 days*
CIRS, severe		OR 5.13 (1.92-13.66)	All complications, 30-days*
CIRS, moderate		OR 1.39 (0.63-3.05)	Major complications, 30-days*
CIRS, severe		OR 3.41 (1.23-9.44)	Major complications, 30-days*
CIRS, severe		HR 1.94 (0.94-4.01)	Early mortality
CIRS, severe		HR 2.78 (1.50-5.17)	Early mortality
Hamaker 2011	292(?[b])		
CCI [g]		HR 1.03 (0.90-1.17)	All-cause mortality
Giantin 2013	160(28.8[b])		
CIRS (SI) [c,d]		HR 4.80 (2.68-8.61)	6-months survival
CIRS (SI)		HR 5.01 (2.17-10.55)	6-months survival
CIRS (CI)		HR 1.31 (1.14-1.50)	6-months survival
CIRS (SI)		HR 3.98 (2.36-6.73)	12-months survival
CIRS (SI)		HR 5.06 (2.54-10.07)	12-months survival
CIRS (CI)		HR 1.25 (1.11-1.41)	12-months survival



▲ In a multivariable model, i.e. with other geriatric domains
● In a model adjusted for confounders
■ In a univariate model
* According to modified Clavien-Dindo classification

[a] 100% minus the reported percentage are non-oncological elderly surgical patients

[b] 100% minus the reported percentage are non-surgical elderly cancer patients

[c] Cumulative Index Rating Scale for Geriatrics, Comorbidity Index

[d] Cumulative Index Rating Scale for Geriatrics, Severity Index

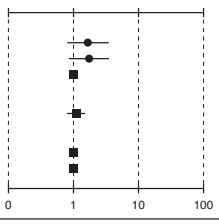
[e] in sub-group analysis of patients undergoing urgent surgery

[f] Satariano's Index of Comorbidities

[g] Charlson Comorbidity Index

g)

Study	Population	OR/HR/RR (95% CI)	Outcome
Kristjansson 2010	182(100)		
Polypharmacy ≥5		OR 1.67 (0.82-3.42)	All complications, 30 days*
Polypharmacy ≥5		OR 1.73 (0.87-3.44)	Major complications, 30 days*
Polypharmacy ≥5		p=0.495	Overall survival
Hamaker 2011	292(?[b])		
Polypharmacy ≥5		HR 1.10 (0.81-1.48)	All cause mortality
Badgwell 2013	111(100)		
Polypharmacy >5		no association	All and major complications, 90 days*
Polypharmacy >5		no association	Discharge to non-home institution



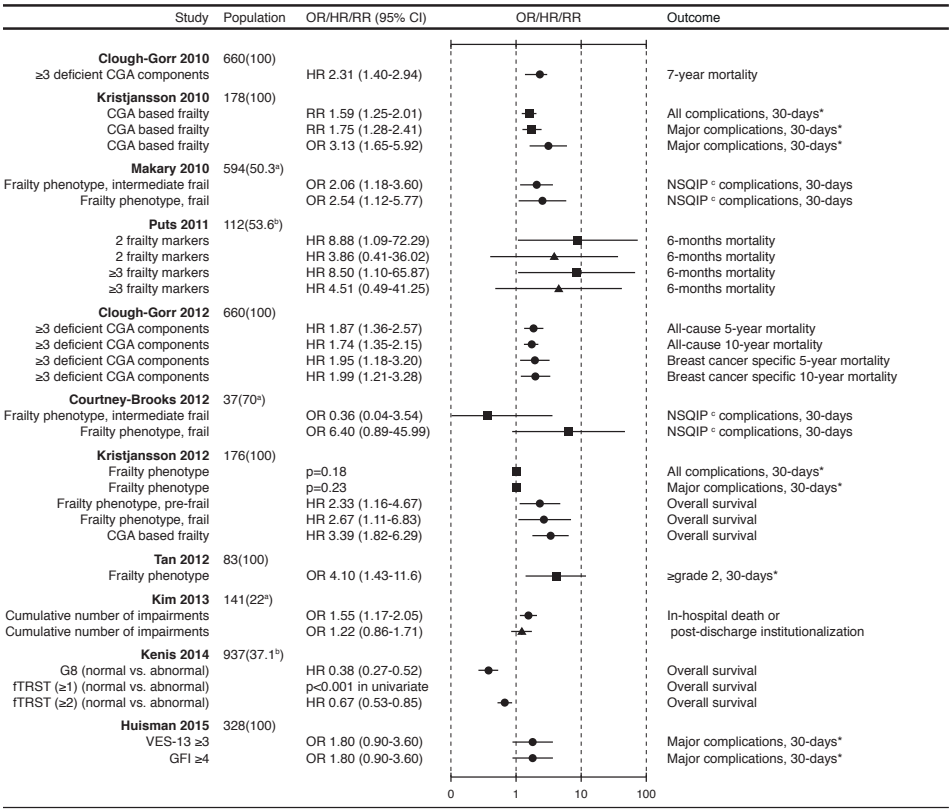
▲ In a multivariable model, i.e. with other geriatric domains
● In a model adjusted for confounders
■ In a univariate model
* According to modified Clavien-Dindo classification

[a] 100% minus the reported percentage are non-oncological elderly surgical patients

[b] 100% minus the reported percentage are non-surgical elderly cancer patients

Figure 2 | (continued)

h)



▲ In a multivariable model, i.e. with other geriatric domains
● In a model adjusted for confounders
■ In a univariate model
* According to modified Clavien-Dindo classification

[a] 100% minus the reported percentage are non-oncological elderly surgical patients

[b] 100% minus the reported percentage are non-surgical elderly cancer patients

[c] American College of Surgeons National Surgical Quality Improvement Program

Figure 2 | (continued)

onco-geriatric studies including patients undergoing surgery[30, 31, 35, 37, 38]. However, in one of these studies the presence of ≥2 functional limitations was only predictive of overall survival and not of disease-specific survival[37]. IADL was not predictive of mortality in either of the three studies[30, 31, 35], nor of discharge to a non-home institution[28]. The fact that ADL was not a predictor for postoperative complications and mortality in the solely surgical onco-geriatric cohorts, but that it was a predictor for mortality in cohorts in which 46.4% and 46.9% of patients received non-surgical cancer treatment[35] or supportive care[31], respectively, can be explained by the populations under study. Patients who are considered for elective

surgery must have a certain level of fitness, which includes the ability to perform the most basic activities, such as getting dressed, and going to the toilet, independently. Whereas the treatment goals for onco-geriatric patients undergoing non-surgical treatment may vary widely and might impact the prevalence of ADL impairments and its association with mortality.

Fall risk is frequently recorded by the number of falls, with or without injury, in a certain time period[15]. It is often integrated into the assessment of the presence of geriatric syndromes, such as depression, dementia, delirium, fatigue, frailty and osteoporosis[39]. One systematic review reported results on fall risk as a separate item and included one study that met our inclusion criteria[29]. No association between ≥2 falls in the past three months and all-cause mortality was found[31].

The fact that faster gait speed was associated with improved survival rates in elderly endorses the importance of this easy-to-administer parameter as part of a preoperative assessment[42]. However, in the current review, conflicting results were found regarding the association between functional status, as measured by physical inactivity, gait speed or presence of mobility impairments, and adverse outcomes. The Timed Up and Go (TUG) assesses a patient's mobility, coordination and muscle strength. More than 20 seconds to complete the TUG was an independent predictor for the occurrence of major postoperative complications[5]. Furthermore, ≥1 functional limitation on the 10-item physical function index of the Medical Outcomes Study Short Form-36, was a predictor of 7-year mortality[34]. However, a gait speed slower than 1m/s over a distance of 4 meters and physical inactivity, defined as no exercise or exercise less than weekly or once or twice weekly but less than vigorous walking, were not predictive of 6-months mortality[35]. Requiring help or the use of a walking aid for mobility was also not predictive of all-cause mortality[31]. The heterogeneity of assessments that are herein clustered as functional status measurements, as well as regarding the endpoints under study, makes it difficult to compare the results and thus explain the differences that are found.

Nutritional status

Nutritional status is frequently impaired in onco-geriatric patients, with reported prevalences of 32%-45.5%[5, 43, 44]. Known risk factors for an impaired nutritional status in cancer patients include advanced age, advanced disease, intra-abdominal tumours and a decreased performance status[45-47]. In elderly patients, nutritional status can be impaired due to physiological, social or economic reasons (e.g. poor dentition, disease, depression, insufficient resources or ADL/IADL impairments)[48].

Nutritional status can be assessed by several short screening tools, most of which include current body weight, presence and amount of unintentional weight loss and whether dietary intake has decreased recently[49]. Commonly used and validated screening tools to identify patients at increased nutritional risk are the Mini Nutritional Assessment (MNA) or MNA short form (MNA-sf), the Nutritional Risk Screening (NRS 2002) and the Malnutrition Universal Screening tool (MUST)[49].

In the systematic reviews from Hamaker et al and Puts et al., nutritional status was assessed in 24% and 54% of included studies, respectively[9, 29]. The MNA (including MNA-sf) and body mass index (BMI) were used for nutritional assessment most frequently (MNA: 6 out of 9 and 16 out of 40 studies, respectively. BMI: 15 out of 40 studies). Five original studies including onco-geriatric surgical patients were identified that assessed nutritional status in relation to adverse outcomes (figure 2b)[26, 28, 30, 34, 35]. In these studies, an impaired nutritional status did not predict postoperative complications. Furthermore, it did not predict 6-months nor 7-year mortality in two cohorts in which both surgical and non-surgical oncological treatments were combined. Weight loss >10% within 6 months and an increased risk according to the MNA were predictors of discharge to non-home institutions and short-term mortality in onco-geriatric patients undergoing abdominal surgery. This is consistent with the systematic review from Ramjaun et al., where nutritional status consistently predicted mortality across multiple studies on onco-geriatric non-surgical patients[39].

Cognition

Cognitive impairment frequently goes unnoticed in the elderly population. In a community-dwelling cohort with multimorbidity, 16% was found to have low cognitive functioning suggesting dementia, of which 89% did not have a previous diagnosis of dementia[50], and of 114 patients aged ≥60 who underwent acute or elective vascular surgery, 60.5% presented with previously undiagnosed cognitive impairments[51].

Cognition is represented in GAs both as a separate, stand-alone GA domain and as one of the items that are clustered together to form the domain of geriatric syndromes, where dementia or cognitive impairment is considered a key element. The mini-mental state examination (MMSE)[52], a quick and easily administered screening instrument for cognition, is used most frequently to assess cognition as part of a GA, but additional screening instruments, for instance the letter fluency test[53], frontal assessment battery[54] and clock drawing test[55] are also used. Sometimes screening instruments are used that are more receptive to very

mild forms of cognitive impairment, such as the MoCA[35]. Moreover, the IQCODE is a screening instrument that takes a patient's proxy as its source of information about changes in a patient's behaviour[31].

Seven original studies were identified that investigated cognition in relation to outcome (figure 2c). Four of these investigated mortality in relation to cognition, but in only one of these, impaired cognition was found to be related to increased 6 and 12 months' mortality[20, 30, 31, 35]. Out of four studies that investigated postoperative complications in relation to cognition, an association between impaired cognition and increased risk for complications was found in just one of these studies, in a multivariable model[16, 26, 28, 30].

Social support

The presence of a network that can provide for emotional, physical and informational support has a positive influence on quality of life in cancer patients[56]. Out of the nine systematic reviews, four reported data on social support as a separate item (i.e. not as part of a frailty assessment)[9, 10, 15, 25]. These reviews identified one prospective study on 660 older breast cancer survivors in which 'inadequate finances' was an independent predictor for a higher 7-year mortality risk, and in which the Medical Outcome Study - Social Support Survey score (MOS-SSS) was not (figure 2d)[34].

The evidence of the use of social support assessments as part of a preoperative assessment is limited. However, it is likely that the lack of social support increases the risk for adverse outcomes such as prolonged length of hospital stay and discharge to a non-home institution[57].

Mood & emotional status

Depressive symptoms are common amongst both the elderly and cancer patients[58, 59]. In addition, both groups are also at an increased risk of experiencing other symptoms associated with low mood, such as anxiety and loneliness[58, 60, 61]. Mood and emotional status, with depression in particular, are thought to have a profound influence on both mortality and post-treatment complications in an onco-geriatric population. Mood in an onco-geriatric patient population can be assessed by a symptomatic assessment carried out by an experienced psychiatrist or geriatrician, but there are also numerous screening tools, which are more commonly used as part of a GA. The one most used in GAs, is the Geriatric Depression Scale (GDS), of which the most frequently used subtype is a 15-item yes/no questionnaire[62]. Other mood and depression screening tools include the Hospital Anxiety and Depression

Scale (HADS), the positive and negative affect schedule (PANAS) and the Center for Epidemiological Studies Depression Scale (CES-D), none of which have been developed specifically for an onco-geriatric population.

The systematic review by Ramjaun et al. reported that depression was associated with increased mortality[39]. In the systematic review by Hamaker et al., mood was assessed in 25 of the 37 studies, but unambiguous evidence for an association between depression and adverse outcomes was not found[29]. For the current systematic review, seven original studies were identified that investigated an onco-geriatric surgical population, using four different tools (figure 2e). One study reported a significant increase in 6 and 12 months' mortality for patients with a positive GDS score, and a second reported an increased hazard ratio for 7-year mortality in relation to a positive Mental Health Index test score[20, 34]. Both results were derived from multivariable regression models, adjusted for other geriatric domains. An association between a positive GDS score and the occurrence of any postoperative complications in a for confounders adjusted model was found, but this association did not retain in a multivariable model with other GA domains, nor was a positive GDS score significantly associated with the occurrence of major complications and short-term mortality[30]. The remaining four studies that reported on mood and adverse postoperative outcomes did not find an association at all[16, 26, 28, 35].

A positive depression score could be related to adverse outcomes and mortality, although only the minority of the original studies investigating depression in an onco-geriatric surgical patient population reported a significant association. Of the screening tools available, the GDS is by far the most widely used, possibly because it was designed and validated specifically for an elderly population.

Comorbidity

In a GA, comorbidities are mostly assessed either by the Charlson Comorbidity Index (CCI) or by the Cumulative Index Rating Scale for Geriatrics (CIRS) comorbidity index (CI) and CIRS severity index (SI). The CCI predicts the risk of mortality for a patient based on the presence of several comorbid conditions and weights these using a three-point system for severity[63]. The CIRS weights the severity of all patient's comorbid conditions by assessing to what extent conditions are interfering with daily life at the moment of completing the questionnaire, as a proxy for how severe these conditions are at that particular moment[64]. This test, as a result, takes longer to complete than the CCI, because a more elaborate interview with a patient is required.

Eight original studies were identified via the systematic reviews that investigated an onco-geriatric surgical population (figure 2f). Six of those took mortality as an outcome, two of which did not find significant associations[31, 37]. Two studies found CIRS SI, CIRS CI or a CCI≥1 as predictors of 6 months, 12 months and 7-year mortality[20, 34]. In one study, the CIRS SI was only a predictor of 1-month survival in a sub-group analysis of patients who underwent emergency surgery, but not in the complete cohort[19]. One study found no significant association between CIRS and early mortality in a for confounders adjusted model which included ECOG performance status, but when ECOG performance status was replaced by nutritional status, the presence of severe comorbidity was a predictor of early mortality[30].

Three studies looked at the association between comorbidities and postoperative complications, two of which did not find an association[16, 26]. These two studies used indices of comorbidities that were neither developed for an onco-geriatric population nor validated. One study found a significant association between severe comorbidities and any or major 30-day complications, but not for moderate comorbidities and these outcomes[30].

The current results provide some evidence that the CIRS is a good screening tool in onco-geriatric surgical patients and might be preferable over the CCI. This is in line with the results from Hamaker et al., who identified 16 studies in which comorbidities were assessed in relation to mortality[29]. Of these, 5 used the CIRS to assess comorbidities, of which 4 found an association. The CCI was used in 5 studies and an association with mortality was identified in only one of these. Therefore, the CIRS might be considered a more sensitive screening instrument that can predict the risk for adverse outcomes in onco-geriatric patients than the CCI, and might be advised for clinical practice despite its longer time to complete.

Polypharmacy

Polypharmacy is common among onco-geriatric patients, both because this patient population frequently presents with multiple comorbidities requiring pharmacotherapy, and because patients sometimes require chemotherapy and various supporting medications as part of their oncological treatment[65]. The prevalence of polypharmacy, defined as the use of a large number of medications, varies greatly, because of the varying patient population under study and because of the differing cut-off points used to describe the presence of polypharmacy. In two cohorts of onco-geriatric patients undergoing abdominal surgery, the prevalence varied from 6.2% (≥8 drugs per day) to 48% (>5 drugs per day)[6, 28].

Studies investigating the use of a GA in onco-geriatric patients frequently integrated polypharmacy assessments in other parts of a geriatric assessment or in a screening tool[22, 32, 39]. As a consequence, only few data are available specifically on the predictive ability of polypharmacy in onco-geriatric surgical patients. Three original studies investigated the association between polypharmacy (>5 or ≥5 drugs per day) and postoperative complications, discharge to a non-home institution or mortality and none of them found significant associations (figure 2g)[28, 30, 31].

The high prevalence of polypharmacy on one side and the negative results regarding its predictive ability of adverse outcomes on the other side, makes the value of polypharmacy as part of a preoperative GA doubtful. The main point of discussion is whether polypharmacy should be taken as a proxy for frailty, and can thus be part of an integrated assessment, or whether there should there be a more in-depth evaluation or different definition of polypharmacy. Perhaps the presence of inappropriate medication use, or an analysis of the types of medications used including their potential interactions should be evaluated, rather than only taking the summative score of the total number of drugs used by a patient[65].

Frailty

Although there is no one clear-cut definition of frailty that is used in clinical practice, the term captures the natural, highly individual, age-related decline in health and the resulting vulnerability that is associated with this[66]. Its prevalence in the general population aged 65 years and over is estimated at 10%, increasing to 26-45% in the population aged 85 years and over[67, 68]. Within an onco-geriatric population the prevalence of frailty is much higher. It is estimated at 42% (range 6-86%) by Handforth et al., based on a systematic review on the prevalence and outcomes of frailty in older cancer patients including 22 studies of patients with a median age of 70 or over[32]. Moreover, an additional 43% (range 13-79%) of this population is classified as 'pre-frail', a term used to denote that, although the frailty cut-off point has not yet been reached, a patient is showing physical and/ or mental decline and is likely to become officially frail in future. The median patient population considered to be fit within the onco-geriatric patients is estimated at 32% (range 11-78%)[32].

There are multiple ways to assess frailty. Various frailty screening tools are used as part of a GA, such as the Groningen Frailty Index (GFI), the phenotype of frailty as described by Fried, Vulnerable Elderly Survey (VES-13), Triage Risk Screening Tool (TRST) and the Geriatric 8 (G8). In addition to this, frailty is sometimes assessed indirectly as a composite

GA score, either by taking a certain cut-off score above which a patient is considered frail, or by assessing the cumulative number of certain GA domain impairments. In both approaches, a consensus for a cut-off point for frailty or for the GA domains that should be assessed as part of a frailty assessment is lacking. The prevalence of frailty is higher when the GA is used as a measure for frailty than when a screening tool such as the Fried Frailty Criteria is applied[32].

A total of eleven original articles describing nine studies on onco-geriatric surgical patients were investigated in the included systematic reviews. Several instruments were used to identify frailty: frailty as assessed by a number of GA domains[18, 21, 34, 35], a CGA based frailty[6], the frailty phenotype as defined by Fried[17, 23, 27, 33], GFI[5], VES-13[5], G8 and fTRST[24]. Several studies distinguished a frail, a non-frail and a third, intermediate or pre-frail, patient group.

Of the six studies investigating mortality in relation to frailty in five cohorts, four concluded that there was an unambiguously significant association between frailty and mortality[21, 23, 24, 34]. One of these studies found this association using both a CGA based frailty, as well as the frailty phenotype[23]. One study looked at in-hospital death in combination with discharge to a non-home institution and found a significant association in a model adjusted for confounders, but not in a multivariable model[18]. The sixth study found significant associations in univariate models, but not in the multivariable models[35].

The association between frailty and postoperative complications, which was analysed in six original articles, was less clear-cut: in only three studies – using the frailty phenotype in two studies and a CGA based definition in a third – an association was found[6, 17, 27]. In the same cohort, in which CGA based frailty was predictive of complications, the frailty phenotype was not[23], whilst both were predictive of mortality in this cohort. One of the studies that did not identify an association, included only 37 patients, so its sample size may have been too small to study this relation[33]. VES-13 and GFI were not associated with major 30-day morbidity[5].

These results confirm that the presence of multiple domain impairments in onco-geriatric patients, as depicted by CGA based frailty measurements, results in an increased risk for adverse outcomes following treatment. Screening tools, such as GFI and VES-13, that aim to cover multiple domains, might not be sensitive enough to detect impairments in these domains.

Discussion

Recently, many reviews have been published on the ability of separate GA domains and associated screening tools to predict adverse post-treatment outcomes in onco-geriatric patients[9, 10, 15, 22, 25, 29, 32, 36, 39]. Whilst these reviews all share the same subject, they included different original studies. Often, the reviews refrained from giving recommendations for daily clinical practice due to the findings of conflicting results derived from heterogeneous studies and often it was concluded that additional studies are required. The current systematic review aimed to provide a complete overview of the evidence available to date regarding the predictive ability of GA domain assessments and screening tools regarding adverse postoperative outcomes.

Most GA domain assessment tools or screening tools were predictive of at least one of the outcomes that were investigated as endpoints in the current systematic review. The predictive ability of a certain GA domain appears to depend largely on the characteristics of the population under study and on the type of assessment or screening tool used. First, although surgery is often the only potentially curative treatment for solid malignancies, patients considered unfit for surgery may sometimes receive less burdensome, albeit non-potentially curative treatments to improve their survival or lessen their symptom burden. Alternatively, they may receive supportive care only. Consequently, patients that are treated surgically for solid malignancies tend to be fitter than those undergoing alternative treatment modalities. As a result of this, a ceiling effect for several assessment tools, such as the ADL, might be present in the 100% surgical cohorts.

On top of that, the patient population included in the original studies can be considered a selected population because a treatment decision had been made prior to inclusion, making fitness for treatment a prerequisite. It is therefore possible that the characteristics of the patients who were deemed suitable for a certain anti-cancer treatment and thus for inclusion in a study may also have influenced the association between GA domain impairments and post-treatment outcomes.

Second, the type of assessment or screening tool used might have influenced the results as well. This appears to be the case, for instance, for the comorbidity domain, where mainly CIRS is significantly associated with the risk for adverse outcomes, more so than alternative screening tools. Furthermore, it should be noted that most tools were not designed to predict adverse

outcomes. As different studies with varying study populations used different assessment tools, the magnitude of the influence of either of these two factors (study population and type of assessment tool) cannot be estimated or disentangled rightly.

Next to the variability in assessment or screening tools used within each geriatric domain, the domains making up a complete GA differ greatly, too. The most commonly included domains in a GA were functional status, comorbidity and frailty, which were all frequently associated with adverse outcomes in the current review. The results regarding frailty, and its high prevalence, underpin the importance of an integrated approach for onco-geriatric surgical patients, as it merely showed that the presence of multiple domain impairments put these patients at increased risk for adverse postoperative outcomes. Nutritional status was included in only a few studies, the majority of which did not find significant associations. This contrasts several other studies in which an impaired nutritional status was found to be a risk factor for adverse postoperative outcomes[5, 69, 70]. Furthermore, nutritional interventions have been shown to improve postoperative outcomes in malnourished patients[71]. Other domains that might be amenable to preoperative optimization, and might thus be useful to assess as part of a GA are functional status and mood[72]. It is reasonable to assume that by improving cardiovascular as well as muscular functioning, and by reducing anxiety levels, patients' resilience for a surgical procedure will increase. Finally, even though impaired cognition was not an evident predictor of adverse outcome in the current review, this domain is of relevance as it plays an important role in the decision-making process for patients when discussing their treatment options. A patient whose cognition is impaired, will experience difficulty overseeing his treatment options – including the option to forego aggressive treatment in favour of remaining independent, for instance – and cannot therefore truly engage in a shared decision-making process regarding his treatment[73].

A strength of the current study is its systematic methodology regarding the literature search and the subsequent steps involving independent selection of relevant articles, quality assessment and extraction of data. Furthermore, it provides for a comprehensive overview of the evidence available to date, which is emphasized by the fact that the included systematic reviews all included different original studies that were of relevance for our research question.

A limitation is that, by using the methodology described in this systematic review, the most recent evidence from original studies could not be included. Another limitation of the predefined and systematic methodology is that the included systematic reviews were

considered a starting point for the data extraction and the original studies were checked for verification and complementing the data that were presented in the systematic reviews, if necessary. This allowed for maximal transparency and a systematic methodology, but might have led to the omission of some data of interest that were not presented in any of the systematic reviews. Another limitation is the rather low age cut-off that was used as an inclusion criterion. It allowed for the inclusion of relevant systematic reviews that did investigate GA-domains in the 'youngest old', but it makes it difficult to extrapolate the results to the 'oldest old'. Finally, not all studies contained 100% surgical patients as we included both studies that included surgical patients only, and studies with patients undergoing multimodality treatment, of which surgery had to be included. This approach was chosen as it comes close to the situation in daily practice and it allows for the maximum body of evidence, thereby warranting transparency by allowing the reader to interpret the strength of the results as the percentage of onco-geriatric surgical patients per study were displayed.

Based on the current evidence, it is not possible to reach a consensus as to what an optimal GA should look like. However, whether a consensus is actually necessary for delivering tailored surgery to onco-geriatric surgical patients is a matter for debate. The GA is not an aim in itself. Instead, firstly, it should lead to uncovering potential geriatric domain impairments that might benefit from optimization or so-called prehabilitation. Secondly, it should support the process of shared preoperative decision-making. Thirdly, it should help both the patient and the clinician to better anticipate the postoperative course. Feasibility, depending on the time, expertise and resources available in daily clinical practice, to either carry out comprehensive geriatric assessments or instead perform a set of quick and easily applied screening tools, need to be taken into consideration in each healthcare centre or department. Based on this systematic review, assessments of functional status and comorbidity are imperative as these pose increased risks for adverse outcomes. In addition, we would recommend a routine assessment of nutritional status and mood prior to surgery as preoperative optimization of these domains might improve outcomes.

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Conflicts of interest

None to declare.

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3

“Timed Up & Go”: a screening tool for predicting 30-day morbidity in onco-geriatric surgical patients?

Publication:

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Abstract

Objective: To determine the predictive value of the "Timed Up & Go" (TUG), a validated assessment tool, on a prospective cohort study and to compare these findings to the ASA classification, an instrument commonly used for quantifying patients' physical status and anaesthetic risk.

Background: In the onco-geriatric surgical population it is important to identify patients at increased risk of adverse postoperative outcome to minimize the risk of over- and under-treatment and improve outcome in this population.

Methods: 263 patients ≥70 years undergoing elective surgery for solid tumours were prospectively recruited. Primary endpoint was 30-day morbidity. Preoperatively TUG was administered, and ASA-classification was registered. Data were analysed using multivariable logistic regression analyses to estimate odds ratios (OR) and 95% confidence intervals (95%-CI). Absolute risks and area under the receiver operating characteristic curves (AUC's) were calculated.

Results: 164 (62.4%) patients (median age: 76) underwent major surgery. 50 (19.5%) patients experienced major complications. 50.0% of patients with high TUG and 24.8% of patients with ASA≥3 experienced major complications (absolute risks). TUG and ASA were independent predictors of the occurrence of major complications (TUG:OR 3.43; 95%-CI=1.13-10.36. ASA1 vs. 2:OR 5.67; 95%-CI=0.86-37.32. ASA1 vs. 3&4:OR 11.75; 95%-CI=1.62-85.11). AUC_{TUG} was 0.66 (95%-CI=0.57-0.75, $p<0.001$) and AUC_{ASA} was 0.58 (95%-CI=0.49-0.67, $p=0.09$).

Conclusions: Twice as many onco-geriatric patients at risk of postoperative complications, who might benefit from preoperative interventions, are identified using TUG than when using ASA.

Introduction

With the ageing of our society, the onco-geriatric surgical population is expected to increase. Currently 40% of all malignancies occur in patients over 70 years of age and the majority of patients undergoing surgery for a solid tumour are elderly[1-3]. Roughly 40% of this onco-geriatric surgical population can be considered to be frail[4, 5], which is defined as 'a loss of resources in several domains of functioning' resulting in increased vulnerability to stressors[6].

Frail onco-geriatric patients are at an increased risk of adverse outcome due to complications[7]. These patients need to be identified preoperatively to allow the effective implementation of preventive measures, to minimize the risk of over- and under-treatment and improve outcome in this population. The comprehensive geriatric assessment (CGA) has been introduced to identify frailty in geriatric oncolåogy[8, 9]. Unfortunately, CGA is time consuming and hence difficult to utilize in a busy clinical surgical practice. To easily identify which patients are at risk of postoperative complications and might benefit from further assessment and preoperative interventions[10, 11], time saving screening tools need to be investigated.

The American Society of Anaesthesiology classification (ASA) is a well-known classification that quantifies the preoperative physical status and gives an estimation of a patient's anaesthetic risk[12]. Studies show opposing results regarding the predictive value of high ASA-scores for postoperative morbidity and mortality[4, 13-16]. So far, the ASA-classification has not been proven predictive of postoperative outcome in onco-geriatric patients.

The "Timed Up and Go" (TUG) is a tool that has been made available for the purpose of identifying frail elderly by quantifying functional mobility[17]. It is an easy to administer measure of functional status. The TUG has extensively been studied in community dwelling elderly[18-22] and it was found to predict the risk of early death in onco-geriatric patients receiving chemotherapy[23]. The TUG was also investigated in cohorts of surgical patients. The TUG predicts long-term functional outcome in patients undergoing hip surgery[24, 25]. In patients undergoing major cardiovascular or abdominal surgery, the TUG successfully predicted discharge institutionalization and postoperative delirium[26, 27]. Data on the predictive value of the TUG in the onco-geriatric surgical population are lacking.
Our aim was to determine the predictive value of the TUG in a prospective cohort study and to compare this to the ASA-classification, a widely used instrument in the field of surgical oncology.

Methods

Ethics statement

Approval from the National Research Ethics Service Committee North West - Greater Manchester Central and the Medical Ethical Committee from Leiden University Medical Centre was obtained, and all included patients gave written informed consent. There was no financial incentive to the contributing centres for entering patients into the present study and no funding was acquired. PREOP is registered at the Dutch Trial register (Trial ID: NTR1567).

Design

A multicentre, prospective cohort study was designed to investigate Preoperative Risk Estimation for Onco-geriatric Patients (PREOP). The PREOP-study is an international study conducted to analyse several screening tools with regard to short term postoperative outcome. Recruitment took place in 6 different countries at 11 medical centres between September 2008 and January 2012. To reduce the possibility of selection bias and the influence of inter-centre variability, medical centres that included less than 10 patients were excluded from analysis. Centres participated actively during different periods of time, depending on the availability of research staff, explaining the relatively small number of included patients considering the long inclusion period.

Patients

A cohort of cancer patients aged ≥70 who were candidate for elective surgery under general anaesthesia, were invited to take part by the local coordinator. Patients requiring emergency surgical management (within 24 hours) were excluded from this study. This international study sample comprised a series of 302 patients. Medical centres that included less than 10 patients were excluded from analysis, which resulted in the analysis of 263 patients (table 1).

Endpoints

The primary endpoint was morbidity during the first 30 days after surgery. Morbidity was registered using the Clavien-Dindo classification, a scale ranking severity of complications from 'any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions' (grade one) to 'death of a patient' (grade five)[28]. Morbidity was dichotomized into minor (Clavien-Dindo grade one and two) and major complications (Clavien-Dindo grade three to five). Subsequently, a

Table 1 | Number of patients per center included in statistical analysis

Center	Number of patients
S. Orsola Malphighi Hospital, Bologna, Italy	119 (45.2%)
University Medical Center Groningen, Groningen, The Netherlands	45 (17.1%)
San Martino University Hospital, Genua, Italy	20 (7.6%)
Regional University Hospital of Patras, Patras, Greece	31 (11.8%)
The Highfield Hospital, Manchester, United Kingdom	19 (7.2%)
S. Maria Hospital, Perugia, Italy	15 (5.7%)
Clinical Center Nis, Nis, Serbia	14 (5.3%)
Total	263

dichotomous variable was created for morbidity during the first 30 days after surgery: "no/minor" versus "major" complications. Secondary endpoints were 30-day mortality, length of hospital stay, amount of days spent in the Intensive Care Unit (ICU) and the number of additional specialists involved in patient care. The secondary endpoints were dichotomized and cut off points were fixed at >7 days for length of stay after surgery, which was considered prolonged length of stay (LOS), >1 day admission at the ICU and >3 additional specialists involved in patient care.

Pre- and peri-operative data

Within two weeks prior to the surgical procedure, the TUG was administered as part of a larger test battery. TUG measures the time a person needs to get up out of a chair, walk three meters and return to the chair[17]. This is measured in seconds with a handheld stopwatch. Patients performed the TUG two times and for each patient, the mean of the two time measurements was calculated. Based on literature and the distribution of the mean values in the current study population, a score of less than or equal to 20 seconds on the TUG was considered a normal score[26]. The ASA-classification, ranging from 'a normal healthy patient' (ASA1) to 'moribund, i.e. not expected to survive 24h with or without surgery' (ASA5), was determined by an anaesthesiologist. The patients with score ASA 3 and ASA4 were combined for analysis.

Preoperative information regarding living situation, preoperative haemoglobin level, nutritional status and comorbidity was recorded.

Nutritional status was defined according to the following definitions[29]:

- Normal nutritional status.

- Mildly impaired nutritional status: >5% weight loss in 3 months or food intake less than 50-75% of their normal requirements in the past week.
- Moderately impaired nutritional status: >5% weight loss in 2 months or BMI 18.5-20.5 + poor overall condition or food intake 25-60% of their normal requirements in the past week.
- Severely impaired nutritional status: >5% weight loss in 1 month (>15% in 3 months) or BMI <18.5 + poor overall condition or food intake 0-25% of their normal requirements in the past week.

Perioperative data contained type of surgery (dichotomized into minor and major surgery), duration of anaesthesia and blood loss during surgery. At every participating centre data were collected by a research nurse.

Statistical analysis

In a univariable logistic regression the odds ratios (OR) and 95% confidence intervals (95%-CIs) were assessed for the presence of a major complication for each of the baseline characteristics including the TUG, ASA-score and TUG and ASA-score combined (TUG+ASA). When combining TUG and ASA-score, we divided this variable into three categories: 1) normal TUG and ASA1 or ASA2; 2) high TUG or ASA≥3; 3) high TUG and ASA≥3. We focused on the results on high TUG and ASA≥3 compared to both normal values. All ORs and 95%-CIs were adjusted for medical centre, as there were large differences between the participating centres regarding the number of patients included and the type of performed surgeries. To further adjust for contributing factors, all baseline characteristics were added to the centre-adjusted model, including TUG or ASA or TUG+ASA. A variable was selected for multivariable analysis when a significant OR with a minimal change of OR of 10% was observed in comparison with the centre-adjusted univariable model containing TUG, ASA or TUG+ASA. The same procedure was repeated for the secondary endpoints. Sensitivity and specificity of the TUG, ASA and TUG+ASA were calculated for the primary outcome measure. To make an accurate estimation of a patient's risk for a certain outcome, absolute risks were calculated[30]. The area under the receiver operating characteristic curves (AUCs) together with 95%-CIs were calculated for the TUG, ASA and TUG+ASA, if applicable. P-values < 0.05 were considered statistically significant. Data analysis was performed using IBM SPSS Statistics 20.0.

Results

Patient characteristics

The median age of this cohort was 76 years (range: 70-96) and 66.5% of patients were female (table 2). The majority of surgical procedures were laparotomies (n=156; 59.3%) and breast cancer surgeries (n=76; 28.9%) (table 2). Types of malignancies treated by means of a laparotomy were colorectal cancer (n=86), gastric cancer (n=21), pancreatic cancer (n=14), cholangio-, gallbladder- and papilla of Vater carcinoma (n=8), ovarian cancer (n=6), liver metastases of colon cancer (n=6), and other solid tumours (n= 14). One patient underwent a laparotomy for both colon and renal cell carcinoma. The majority of patients (62.4%) underwent major surgery. The median TUG in our sample was 11.3 seconds (Q_1-Q_3 8.2-16.5). A total of 220 patients (84.0%) completed the TUG within 20 seconds. The majority of patients were classified as ASA2 (n=121; 46.5%) and ASA3 (n=109; 41.9%). A total of 129 patients (49.8%) had both a normal TUG and ASA<3 (table 2).

Primary outcome measure

Complications occurred in 123 patients (46.8%) and of these patients, 50 patients developed major complications (table 3). Compared to women (12.7%), men (33.3%) were at higher risk of developing major complications postoperatively (OR 3.50; 95%-CI=1.67-7.34; p=0.001) (table 4), even when corrected for minor or major surgery (OR 2.29; 95%-CI=1.06-4.97; p=0.04).

The absolute risk for patients with high TUG to develop major complications was 50%, in contrast for patients with normal TUG which was 13.6% (table 4&5). Almost all patients that developed major complications and had a normal TUG underwent major surgery (n=26; 89.7%). After adjustment for nutritional status and minor or major surgery, patients with a high TUG had a 3.43 times higher risk of developing major complications within 30 days postoperatively as compared to patients with normal TUG (95%-CI=1.13-10.36; p=0.03) (table 5). Sensitivity of a high TUG was 42.0% and specificity was 89.8%. The AUC was 0.66 (95%-CI=0.57-0.75; p<0.001).

A total of 24.8% of patients classified as ASA3 or ASA4 developed major complications (table 4&5). From the patients classified as ASA1 or 2 who did develop major complications postoperatively, 19 (90.5%) underwent major surgery. Patients classified as ASA2 had a 5.67 times higher risk of experiencing major complications compared to patients labelled

Table 2 | Characteristics of 263 patients ≥70 years undergoing surgery for a solid tumor

Variable	Value[a]
Age (years)[b]	76 (73-81)
Gender	
Female	175 (66.5%)
Male	88 (33.5%)
Living situation	
Independent/family	258 (99.2%)
Residential care/nursing home	2 (0.8%)
Nutritional status	
Normal	171 (67.6%)
Mildly impaired	62 (24.5%)
Moderately & severely impaired	20 (7.9%)
Comorbidities (n)[b]	3 (2-4)
Hemoglobin level	
≥12g/dl	154 (62.9%)
<12g/dl	91 (37.1%)
Surgery	
Minor	99 (37.6%)
Breast cancer treatment (± lymph node)	76 (28.9%)
Excision malignancies of soft tissue, skin and/or lymph node	16 (6.1%)
Thyroidectomy	4 (1.5%)
Remaining	3 (1.1%)
Major	164 (62.4%)
Laparotomy	156 (59.3%)
Laparoscopic approach of G.I. or G.U. tumors	5 (1.9%)
Excision soft tissue sarcoma and vulvectomy	3 (1.1%)
Duration anesthesia (h)[b]	2.6 (1.5-4.0)
Blood loss during surgery (dl)[b]	1.0 (1.0-2.0)
TUG (s)[b]	11.3 (8.2-16.5)
TUG	
≤20.0 seconds	220 (84.0%)
>20.0 seconds	42 (16.0%)
ASA-score	
1	23 (8.8%)
2	121 (46.5%)
3	109 (41.9%)
4	7 (2.7%)

Table 2 | (continued)

Variable	Value[a]
TUG+ASA	
TUG≤20 + ASA<3	129 (49.8%)
TUG>20 + ASA≥3	26 (10.0%)

[a] Valid percentages were calculated when data were not available from all patients.

[b] Values are median and first and third quartiles.

Table 3 | Outcomes

Outcome measure	Patients (n=263)[a]
Complications	
No	140 (53.2%)
Any	123 (46.8%)
Major	50 (19.5%)
Mortality	
No	253 (96.6%)
Yes	9 (3.4%)
Readmission	
No	236 (91.8%)
Yes	21 (8.2%)
Length of stay >7 days	
No	128 (49.0%)
Yes	133 (51.0%)
Length of stay on ICU >1 day	
No	216 (82.4%)
Yes	46 (17.6%)
>3 additional specialists involved	
No	211 (82.7%)
Yes	44 (17.3%)

[a] Valid percentages were calculated when data were not available from all patients.

Table 4 | Univariable association between patient characteristics and no/minor and major complications

Variable	Major complication (n=263)[a]	Univariable OR (95% CI)[b]
TUG		
≤20.0 seconds	29 (13.6%)	1
>20.0 seconds	21 (50.0%)	4.86 (1.82-13.00)
ASA-score		P=0.001[c]
1	2 (9.1%)	1
2	19 (16.0%)	9.77 (1.58-60.61)
3&4	28 (24.8%)v	25.92 (3.97-169.47)
TUG+ASA		
TUG≤20 + ASA<3	12 (9.5%)	1
TUG>20 + ASA≥3	12 (46.2%)	9.06 (2.49-32.96)
Age (years)	78 (74-82)	1.05 (0.98-1.12)
Gender		
Female	22 (12.7%)	1
Male	28 (33.3%)	3.50 (1.67-7.34)
Living situation		
Independent/family	49 (19.4%)	[e]
Residential care/nursing home	0 (0%)	
Nutritional status		P<0.001c
Normal	18 (10.7%)	1
Mildly impaired	22 (36.7%)	4.55 (2.03-10.23)
Moderately & severely impaired	8 (42.1%)	5.00 (1.51-16.54)
Comorbidities (n)[d]	4 (3-6)	1.66 (1.34-2.05)
Hemoglobin level		
≥12g/dl	24 (16.0%)	1
<12g/dl	21 (23.6%)	1.21 (0.57-2.53)
Surgery		
Minor	4 (4.0%)	1
Major	46 (29.1%)	7.32 (2.38-22.49)
Duration anesthesia (h)[d]	3 (2.2-5.0)	1.27 (1.08-1.50)
Blood loss during surgery (dl)[d]	2.0 (1.0-3.0)	1.36 (1.10-1.69)

[a] Valid percentages were calculated when data were not available from all patients.

[b] Bold=statistically significant.

[c] Overall significance.

[d] Values are median and first and third quartiles.

[e] Due to small numbers of patients living residential care/nursing home, the living situation could not be included in the logistic regression.

Table 5 | Multivariable association of TUG and ASA with regard to major complications, prolonged LOS and >3 specialists involved in patient care

	Major complication		Stay >7 days		>3 specialists involved	
	%[a]	OR (95% CI)[b]	%[a]	OR (95% CI)[c]	%[a]	OR (95% CI)[c]
TUG		p=0.03		p=0.03		p=0.002
≤20.0s (n=214)	13.6%	1	47.3%	1	11.7%	1
>20.0s (n=42)	50.0%	3.43 (1.13-10.36)	70.0%	4.21 (1.14-15.58)	45.0%	5.39 (1.85-15.77)
ASA		p=0.04		Univariable OR NS		p=0.002
1 (n=22)	9.1%	1	65.2%		8.7%	1
2 (n=119)	16.0%	5.67 (0.86-37.32)	43.0%		7.7%	2.45 (0.35-17.46)
3&4 (n=113)	24.8%	11.75 (1.62-85.11)	55.3%		27.7%	14.23 (1.87-108.25)
TUG+ASA		p=0.03		p=0.04		p<0.001
TUG≤20 + ASA<3 (n=126)	9.5%	1	43.4%	1	4.8%	1
TUG>20 + ASA≥3 (n=26)	46.2%	5.34 (1.23-23.29)	66.7%	5.21 (1.10-24.73)	54.2%	29.56 (6.21-140.68)

[a] Absolute risks; Valid percentages were calculated when data were not available from all patients.

[b] Adjusted for center, minor/major surgery and nutritional status.

[c] Adjusted for center, gender, minor/major surgery and duration of anesthesia.

as ASA1 (95%-CI=0.86-37.32; p=0.07), when adjusted for nutritional status and minor or major surgery. Patients classified as ASA3 or ASA4 had a 11.75 times higher risk of major complications compared to patients classified as ASA1 (95%-CI=1.62-85.11; p=0.02) (table 5). Sensitivity of ASA≥3 was 57.1% and specificity was 58.5%. The AUC was 0.58 (95%-CI=0.49-0.67, p=0.09).

A total of 46.2% (n=12) of patients with both a high TUG and ASA≥3 developed major complications, compared to 9.5% (n=12) of patients with a normal TUG and ASA<3 (p<0.001) (table 4&5). Patients with both high TUG and ASA≥3 had a 5.34 times higher risk of developing major complications compared to patients with a normal TUG and ASA<3 (95%-CI=1.23-23.29; p=0.03), when adjusted for nutritional status and minor or major surgery (table 5). Sensitivity was 50.0% and specificity was 89.1%. The AUC was 0.70 (95%-CI=0.57-0.83; p=0.002).

Secondary outcome measures

30-day mortality

Nine patients died postoperatively (30-day mortality rate: 3.4%) (table 3), all these patients

developed major complications prior to death. Three patients died of a pulmonary embolism, three patients died of sepsis, two died of advanced neoplastic disease and one passed away after myocardial infarction. In a univariable logistic regression analysis the TUG and ASA were not predictive of 30-day mortality. The combined TUG and ASA variable was predictive of 30-day mortality in a univariable logistic regression analysis (OR 26.6; 95%-CI 1.79-396.59). Due to low numbers per cell, no multivariable logistic regression analysis was performed for mortality.

Length of stay

After surgery, 133 patients (51.0%) stayed over 7 days in hospital (table 3) and from these patients, 127 (95.5%) underwent major surgery. The absolute risk for patients with a high TUG to have a prolonged LOS was 70% (n=28), compared to 47.3% (n=104) for patients with a normal TUG. The contributing factors in the multivariable logistic regression model for the secondary endpoints were gender, minor or major surgery and duration of anaesthesia. In this multivariable logistic regression analysis, patients with a high TUG had a 4.21 times higher risk of prolonged LOS (95%-CI=1.14-15.58; p=0.03) (table 5). The AUC was 0.56 (95%-CI=0.49-0.63; p=0.10).

A total of 15 patients (65.2%) with ASA1 had a prolonged LOS and 13 of these patients (86.7%) underwent major surgery. A total of 43.0% (n=52) classified as ASA2 and 55.3% (n=63) classified as ASA3 or ASA4 had a prolonged LOS. The majority of these patients underwent major surgery (n=50 (96.2%) and n=61 (96.8%) respectively). Prolonged LOS could not be predicted by high ASA-classification in the univariable model (ASA1 vs. 2: OR 0.71; 95%-CI=0.24-2.10; p=0.54. ASA1 vs. 3&4: OR 1.53; 95%-CI=0.50-4.71; p=0.46) so no multivariable analysis was performed.

A total of 56 patients (43.4%) with a normal TUG and ASA<3 had a prolonged LOS, compared to 16 patients (66.7%) with both a high TUG and ASA≥3. The majority of these patients underwent major surgery as well (n=52 (92.9%) and n=14 (87.5%) respectively). In the multivariable logistic regression analysis, patients with both a high TUG and ASA≥3 had a 5.21 times higher risk of prolonged LOS (95%-CI=1.10-24.73) (table 5). The AUC was 0.58 (95%-CI=0.51-0.65; p=0.03).

Length of stay at Intensive Care Unit

A total of 46 patients (17.6%) required more than one day admission at the ICU (Q_3=1)

(table 3). All of these patients underwent major surgery. In a univariable logistic regression analysis it was found that neither TUG nor ASA, nor the combined TUG and ASA variable were predictive of a longer stay at the ICU (TUG p=0.08; ASA1 vs. 2 p=0.40; ASA1 vs. 3&4 p=0.05; TUG+ASA p=0.06). Therefore, no multivariable logistic regression analyses were performed.

Number of specialists involved

In 44 patients (17.3%), additional care from more than 3 specialists (Q_3=3) was required (table 3). Compared to patients with a normal TUG, relatively more patients with a high TUG needed care from more than 3 specialists (n=25 (11.7%) and n=18 (45.0%) respectively). The multivariable logistic regression analysis showed a 5.39 times higher chance to need care from more than 3 specialists in case of a high TUG (95%-CI=1.85-15.77; p=0.002) (table 5). The AUC was 0.66 (95%-CI=0.56-0.76; p=0.001).

Only 2 of the patients with ASA1 (8.7%) required care from more than 3 specialists, in patients with ASA2 this number was 9 (7.7%) and in patients classified as ASA3 or 4, this number was 31 (27.7%). Only patients classified as ASA3 or 4 were over 14 times more likely of requiring additional care from more than 3 specialists (ASA1 vs. 2: OR 2.45; 95%-CI=0.35-17.46; p=0.37. ASA1 vs. 3&4: OR 14.23; 95%-CI=1.87-108.25; p=0.01) (table 5). The AUC was 0.68 (95%-CI=0.59-0.76; p<0.001).

In 54.2% (n=13) of patients with both a high TUG and ASA≥3, care from more than 3 specialists was required. In patients with a normal TUG and ASA<3, this was 4.8% (n=6). Patients with both a high TUG and ASA≥3 were 29.56 times more likely of requiring additional care from more than 3 specialists (95%-CI=6.21-140.68; p<0.001). The AUC was 0.76 (95%-CI=0.68-0.84; p<0.001).

Discussion

The use of TUG and ASA as screening tools for short-term postoperative outcome in onco-geriatric surgical patients was investigated. Multivariable analysis showed a prognostic ability of TUG, ASA and TUG and ASA as a combined prognostic tool with regard to the occurrence of major complications within 30 days after surgery. Far more patients at risk of postoperative complications, who might benefit from preoperative interventions, were identified using the TUG than when using ASA: the absolute risk for patients with high TUG to develop major

complications was 50%, while the absolute risk for patients with ASA3 or 4 was 24.8%. The specificity of the TUG was high (89.8%), and the AUC_{TUG} was better than the AUC_{ASA}. The TUG and ASA as a combined variable showed no added value.

A considerable number of patients (n=123; 46.8%) experiencing complications within 30 days after surgery was recorded, of which 50 (40.7%) developed major complications. Other studies investigating onco-geriatric surgical patients have found a high incidence of postoperative morbidity as well[4, 14]. The high morbidity rates emphasize the importance of using preoperative screening tools to predict short-term postoperative outcome. Moreover, these results point out the urgent need for preoperative optimization of a substantial percentage of onco-geriatric patients.

In a prospective study among patients ≥75 years old undergoing major elective abdominal surgery, multivariable analysis of the predictive value of a high TUG (>20.0 seconds) for postoperative delirium showed a hazard ratio of 4.8. A total of 47.6% of patients with a high TUG suffered from postoperative delirium, compared to only 18.5% of patients with a normal TUG[26]. Robinson et al. found a 13 times higher risk of discharge to an institutional care facility, i.e. nursing home or rehabilitation centre, for geriatric surgical patients with a high TUG (≥15.0 seconds)[27]. In onco-geriatric patients undergoing chemotherapy, a TUG over 20 seconds was found to be a risk factor of death within six months[23]. These data show promising results regarding the use of the TUG as a screening tool in several sets of geriatric patients; to our knowledge this is the first study investigating on the predictive value of the TUG in an onco-geriatric surgical population.

The TUG is a well validated measure, which gives a reflection of a person's muscle strength, mobility and coordination. It is reproducible and proved to be predictive of outcome in the setting of the present large international cohort. However, the cut-off point for the TUG varies greatly between studies, making it difficult to compare outcome and stressing the importance of reporting the used cut-off point. The wide range in cut-off points could be depending on the characteristics of the studied population[18]. Factors as age, whether subjects are hospitalized or community-dwelling and off course the type of outcome measure, are all of influence on the appropriate cut-off point of the TUG score for specific cohorts. An established cut-off point cannot be generalized to an entire population, the lack of a uniform cut-off point for the TUG should therefore be accepted.

Data on ASA predicting the postoperative course have often been studied in colorectal

surgical patients, with conflicting results. In a set of colorectal cancer surgical patients, patients with ASA≥3 as a measure of comorbidity were at an increased risk of 30-day mortality and experiencing surgical complications[13]. In octogenarians undergoing colorectal cancer surgery, Tan et al. found patients classified as ASA≥3 being at increased risk of postoperative morbidity[15] and Heriot et al. identified high ASA as a risk factor of 30-day mortality. Patients classified as ASA3 had a 2.86 times higher risk of dying within the first 30 days after surgery and in patients classified as ASA4 or ASA5 this risk increased to 6.08[16]. In a similar population of elderly colorectal cancer patients, however, high ASA was not identified as a risk factor of postoperative complications[4]. This is in keeping with a broader population of onco-geriatric surgical patients, where high ASA was not found to be predictive of postoperative morbidity or mortality[14].

The discrepancy between these results could partly be explained by the interrater variability, which is a main disadvantage of the use of ASA as a screening tool[31] In the onco-geriatric surgical population, where the majority of patients is classified as ASA2 or ASA3 (table 2)[4], it is difficult to rely on ASA in order to make a distinction between patients at risk of postoperative complications and patients who are not. This suggests that ASA, which is the combination of comorbidity and the clinician's impression of a patient's functional status, might be not a valid measure to be a decisive screening tool in the onco-geriatric surgical population.

The risk of 30-day mortality could not be predicted by TUG nor ASA in the current cohort, which could be explained by lack of power as calculation of the sample size was based on 30-day morbidity. A limitation of the study was that PREOP did not focus on long-term outcome. It is known that postoperative complications increase long-term mortality rates in elderly patients undergoing major surgery[32], suggesting long-term mortality rates as a better outcome measure than short-term mortality[33]. Nevertheless, it endorses postoperative morbidity as an appropriate endpoint for the geriatric population. The association between postoperative morbidity and long-term mortality in the onco-geriatric population remains to be confirmed.

The current results show that the TUG is a more useful screening tool than ASA to identify those patients most at risk of adverse outcome. Providing extra preoperative care and prehabilitation to patients with a poor TUG performance may improve the performance on the TUG and thus improve postoperative outcome[34]. This is also emphasized by the ability of TUG to predict the extra need of healthcare postoperatively, shown by the prolonged

LOS and the increased number of specialists involved in patients with a high TUG. To optimize the process of screening for elderly at risk of major postoperative complications, more screening tools should be investigated and compared to the results of TUG and ASA. A recent suggestion is that a combination of screening tools, with different areas of attention, could provide a better predictive value regarding the risk of postoperative morbidity[35]. The final results of a comparison between other instruments aimed at predicting the risk of postoperative complications are awaited.

The PREOP-study is a large multicentre study, which is both a strength and a limitation. Some centres included few patients and patient selection as an explanation for these small number of patients is plausible. We intercepted this by excluding centres who included less than 10 patients. The possibly positive selection bias would, however, certainly not make our findings less likely. The great strength of our multicentre study is the broad generalizability of our results to the onco-geriatric surgical population.

The present analysis suggests that the routine use of the TUG as a screening tool in the onco-geriatric surgical population is of clinical relevance as it is capable of selecting the majority of patients at risk of postoperative complications. Efficiency entails providing the extra preoperative care to those who will benefit most and within this scope, the TUG could be of great importance.

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Remark regarding erratum

Unfortunately, during collection of the long-term follow-up data, we encountered an error. It appeared that from one medical centre, we received several case report forms (CRF's) twice in different batches. It concerned 17 out of 340 cases, which is 5%.

Earlier this was not noticed as the names of patients may not be entered into a database and the first batch was entered into the database by a different person than the second batch. Furthermore, as PREOP is a so called low risk study, the required percentage of CRF's that needed to be monitored was 10%. When monitoring 10% of the CRF's, we did not see this as well. We repeated the analyses with the corrected database.

Fortunately, our results altered slightly, and our conclusions did not change. An erratum was published in PLoS One, and this version is published in the current thesis as well.

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4

Screening for predictors of adverse outcome in onco-geriatric surgical patients

Publication:

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Abstract

Aims: The aim of this study was to investigate the predictive ability of screening tools regarding the occurrence of major postoperative complications in onco-geriatric surgical patients and to propose a scoring system.

Methods: 328 patients ≥70 years undergoing surgery for solid tumours were prospectively recruited. Preoperatively, twelve screening tools were administered. Primary endpoint was the incidence of major complications within 30 days. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated using logistic regression. A scoring system was derived from multivariate logistic regression analysis. The area under the receiver operating characteristic curve (AUC) was applied to evaluate model performance.

Results: At a median age of 76 years, 61 patients (18.6%) experienced major complications. In multivariate analysis, Timed Up and Go (TUG), ASA-classification and Nutritional Risk Screening (NRS) were predictors of major complications ($TUG_{>20}$ OR 3.1, 95%CI 1.1-8.6; $ASA_{\geq 3}$ OR 2.8, 95%CI 1.2-6.3; $NRS_{impaired}$ OR 3.3, 95%CI 1.6-6.8). The scoring system, including TUG, ASA, NRS, gender and type of surgery, showed good accuracy (AUC: 0.81, 95%CI 0.75-0.86). The negative predictive value with a cut-off point >8 was 93.8% and the positive predictive value was 40.3%.

Conclusions: A substantial number of patients experience major postoperative complications. TUG, ASA and NRS are screening tools predictive of the occurrence of major postoperative complications and, together with gender and type of surgery, compose a good scoring system.

Introduction

The International Agency for the Research on Cancer forecasts that the number of new cancer cases will increase from 12.4 million in 2008 to 20 or even 26 million in 2030[1]. The majority of cancer patients are over 64 years of age[2]. As surgery is still the most efficient treatment modality for many solid tumours, the share of onco-geriatric patients presenting for surgery will continue to increase. Though the majority of the onco-geriatric patients is fit for surgery and might have a better quality of life after surgery[3], a substantial part is at increased risk for adverse short-term postoperative outcomes, like complications and mortality[4, 5].

Next to the severity of the surgical procedure itself[6, 7], multiple patient related factors in the physical, mental and environmental domain are supposed to be associated with these adverse postoperative outcomes. Restricted basic or instrumental activities of daily living (ADL or IADL), decreased cognitive function, impaired mobility or nutritional status, fatigue and increased number of comorbidities are associated with adverse postoperative outcomes in elderly surgical patients in multiple prospective studies[5, 7-11]. To identify patients at risk for these adverse postoperative outcomes, impairments in the above mentioned domains can be identified through a standardized geriatric assessment (GA) as well as by the application of well-known and validated geriatric screening tools[4, 5, 7-14]. As a state of the art but time-consuming standardized GA is not indicated nor feasible for every onco-geriatric patient, frequently a selection of geriatric screening tools is preferred[12, 15].

Despite the increasing number of studies reporting on the use of screening tools in onco-geriatric surgical patients, a consensus has so far been lacking as to which tool best predicts postoperative outcomes[13-16]. This is mainly due to the lack of comparability between different studies, with a huge variation across the tools, the cohorts and the measure of the reported outcomes[13, 15]. The aim of the current study is to investigate the ability of well-known geriatric screening tools in predicting the occurrence of major postoperative complications in a relatively large cohort of onco-geriatric surgical patients and to propose a scoring system.

Patients and methods

Design

An international multicentre cohort study was designed to investigate screening tools for Preoperative Risk Estimation for Onco-geriatric Patients (PREOP) with regard to 30-day

postoperative outcomes. This study was approved by the appropriate ethics committees and is registered at the Dutch Trial register (Trial ID: NTR1567) and United Kingdom register (Research Ethics Committee reference: 10/H1008/59). All patients gave written informed consent in accord with the ethical standards of the local ethics committees.

Patients and centres

Cancer patients aged ≥70 years who were candidate for elective surgery for a solid tumour under general anaesthesia were invited to take part by the local coordinator. Patients requiring emergency surgical management and patients who were unable to give written informed consent, were not included in this study[17].

Recruitment took place in seven different countries at 14 medical centres between September 2008 and October 2012, where not all centres participated actively during the entire period. To reduce the possibility of selection bias and the influence of inter-centre variability, medical centres including less than ten patients were excluded from present analysis.

Screening tools

Within two weeks prior to surgery patients were tested with a battery of preoperative well-known screening tools by either a trained resident, nurse practitioner or medical student (table 1). As this took approximately 30 minutes, the patients were screened on the surgical ward, or at the preoperative assessment clinic. Functional status was assessed with the Timed Up and Go (TUG), ADL, IADL and the Eastern Cooperative Oncology Group Performance Status (ECOG PS). The Vulnerable Elders Survey (VES-13) incorporates age, self-rated health and functional limitations or disabilities to identify vulnerable elderly. The Groningen Frailty Index (GFI) is a multidimensional questionnaire assessing frailty in elderly. Cognitive function was assessed with the Mini Mental State Examination (MMSE). Mood and level of fatigue were assessed with the Geriatric Depression Scale (GDS) and Brief Fatigue Inventory (BFI) respectively. The American Society for Anaesthesiologist scale (ASA) was determined by the anaesthesiologist to quantify preoperative physical status and estimate the anaesthetic risk. Nutritional status was assessed with the Nutritional Risk Screening (NRS), which classifies patients as either with a normal nutritional status or with a mildly impaired nutritional status (weight loss greater than 5% in three months or a food intake below 50-75% of normal requirement in the preceding week), a moderately impaired nutritional status (weight loss greater than 5% in two months or a body mass index (BMI) between 18.5 and 20.5 kg/m^2 and impaired general condition or a food intake below 25-50% of normal requirement in

Table 1 | Components of PREOP

Test	Acronym	Purpose	Cut-off value for adverse results	Range of possible scores
Timed Up and Go18 [a]	TUG	a walking test to measure functional status	>20 seconds[b]	Not applicable
Vulnerable Elders Survey[19]	VES-13	a self-reported function-based screening tool to identify vulnerable elderly	≥3	0 - 10
Groningen Frailty Index[20]	GFI	to estimate frailty by a 15-item questionnaire	≥4	0 - 15
Activities of Daily Living[21]	ADL	depicts dependency regarding bathing, dressing, toileting, transfer, continence and feeding	>0	0 - 12
Instrumental Activities of Daily Living[22]	IADL	a questionnaire regarding 8 items needed to perform independently to maintain independence in the community	<8	0 - 8
Eastern Cooperative Oncology Group performance status[23]	ECOG PS	a physician's perspective of a patient's functional status; ranging from 0 to 4	>1	0 - 4
Mini Mental State Examination[24]	MMSE	a test consisting of 11 questions to assess cognitive function	≤26	0 - 30
Geriatric Depression Scale[25]	GDS	a 15-item self-rating depression screening scale for elderly populations	>5	0 - 15
Brief Fatigue Inventory[26]	BFI	a 9-item questionnaire to report on fatigue severity in cancer patients	>3	0 - 10
American Society for Anaesthesiologist scale[27] [c]	ASA	to quantify preoperative physical status and estimate anaesthetic risk	≥3	1 - 5
Nutritional Risk Screening[28]	NRS	nutritional status based on recent weight loss, overall condition and reduction of food intake	Impaired nutritional status was compared to normal nutritional status	Normal to severely impaired nutritional status

[a] Patients performed the TUG two times and for each patient, the mean of the two time measurements was calculated.

[b] Based on literature and the distribution of the mean values in the current study population, a score of less than or equal to 20 seconds on the TUG was considered a low score.[29]

[c] The ASA-classification was determined by an anaesthesiologist.

the preceding week) or a severely impaired nutritional status (weight loss greater than 5% in one month or a weight loss greater than 15% in three months or a BMI less than 18.5 kg/m^2 and an impaired general condition or a food intake below 25% of normal requirement in the preceding week).

Data collection and handling

Preoperative living situation, preoperative haemoglobin level and comorbidities were retrieved from the patients' files. Type and number of comorbidities were recorded, and a dichotomous variable was created based on the median number of comorbidities (>3). Data on tumour stage were retrieved from the pathologists' reports and patients' files. Surgical procedures were defined as minor surgery (e.g. procedures performed for tumours located at the extremities or superficially) and major surgery (e.g. procedures for intra-abdominal tumours).

Data were collected by local institutions and sent in batches to the coordinating centre (University Medical Centre Groningen, The Netherlands), where they were checked, cleaned and entered into an electronic database for statistical analysis.

Endpoint

The primary endpoint was the incidence of any major 30-day complications, according to the Clavien-Dindo classification (Clavien-Dindo grade ≥3)[30]. Major complications include complications requiring surgical, endoscopic or radiological intervention (grade three), life-threatening complications requiring Intensive Care management (grade four) and death of a patient (grade five). In most cases, delirium was considered a minor complication as treatment of delirium frequently involved pharmacological treatment only, which is classified as a grade 2 complication. During hospital admission complications were recorded prospectively. To complete the 30-days morbidity registration, patients' files were checked on the occurrence of complications. This endpoint was analysed as a dichotomous variable: major versus no/minor 30-day complications.

Power analysis

Based on the results of the PACE study, 30% postoperative morbidity in this study population was to be expected[7]. The hypothesis was that all tests had equal predictive value. A 10% difference in predictive value of the different questionnaires and tests was accepted. With an α of 0.05, a power of 0.7, and considering a drop-out rate of 10%, 326 patients needed to be recruited.

Statistical analysis

Baseline characteristics and outcomes were described as median and range or first and third quartiles for quantitative variables and absolute numbers and percentages for qualitative variables. The results on the geriatric screening tools were dichotomized based on predefined, literature-based cut-off points (table 1). To analyse the predictive ability of the geriatric screening tools with regard to any major 30-day complications, for every screening tool a for statistically significant confounders adjusted odds ratio (OR) and 95% confidence interval (95%-CI) was estimated using logistic regression analyses. To check for collinearity, the agreement between geriatric screening tools was considered (table 2). If >80% agreement between geriatric screening tools existed, one of the two geriatric screening tools was excluded from the multivariate logistic regression analysis. For major versus no/minor complications, backwards stepwise multivariate logistic regression analysis was performed to assess which combination of screening tools had the highest predictive ability. Based on the ORs in this model, a scoring system was composed. The receiver operating characteristic (ROC) and the area under the curve (AUC) were calculated to evaluate the model performance.

Missing values per geriatric screening tool ranged from 0.3% to 4.9%, and resulted in 13.7% missing cases in the multivariate analysis. As the missing values were missing at random or missing completely at random, multiple imputation was performed for the total scores on the questionnaires irrespective of whether values were missing at item- or variable level[31]. Multiple imputation was based on available results on the screening tools, age, gender, living situation, preoperative haemoglobin level, type of tumour, tumour stage, type of surgery and number of comorbidities. The reported results on the screening tools were pooled values, which were average values calculated from the five imputed datasets.

Data analysis was performed using IBM SPSS Statistics 22. P-values ≤ 0.05 were considered statistically significant.

Results

Patients

In total 362 patients were assessed in this study. Of these, 32 patients were excluded from analysis as they derived from one of the six medical centres that included <10 patients and two patients were excluded from analysis as they were diagnosed with a lymphoma. Data of 328 patients were analysed.

Table 2 | Agreement between geriatric screening tools[a]

Test[b]	TUG	VES-13	GFI	ADL	IADL	ECOG PS	MMSE	GDS	BFI	ASA	NRS	Comorbidities
TUG												
VES-13	73.2%											
GFI	59.1%	67.1%										
ADL	79.6%	70.4%	60.7%									
IADL	72.6%	78.7%	66.2%	73.2%								
ECOG PS	85.1%	72.0%	58.5%	79.9%	72.0%							
MMSE	67.4%	65.5%	59.1%	67.4%	68.3%	66.5%						
GDS	80.2%	73.8%	68.9%	74.7%	69.2%	77.1%	67.7%					
BFI	69.5%	72.0%	66.8%	64.3%	66.8%	70.4%	62.8%	72.3%				
ASA	59.8%	57.0%	55.5%	58.2%	57.9%	61.6%	56.4%	55.5%	60.1%			
NRS	66.5%	62.5%	62.5%	66.2%	63.1%	71.0%	60.1%	66.2%	59.1%	58.8%		
Comorbidities	69.5%	67.1%	61.0%	64.9%	63.7%	64.6%	59.8%	64.0%	64.9%	66.5%	61.3%	

[a] The agreement between the dichotomized results on the geriatric screening tools was considered.

[b] The meaning of the acronyms of the tests are shown in table 1.

Table 3 | Characteristics of 328 patients ≥70 years from eight medical centres undergoing surgery for a solid tumour

Variable		Value
Age, y[a]		76 (70-96)
Age categories	70-74	120 (36.6%)
	75-79	103 (31.4%)
	80-84	72 (22.0%)
	≥85	33 (10.1%)
Gender, female		203 (61.9%)
Living situation		
Independent/family		323 (99.4%)
Residential care/nursing home		2 (0.6%)
Comorbidities (n)[b]		3 (2-4)
Haemoglobin level		
≥12g/dl		198 (64.3%)
<12g/dl		110 (35.7%)
Surgery		
Minor		105 (32.0%)
Major		223 (68.0%)
Cancer site[c]		
Breast		80 (24.4%)
Colorectal		121 (36.9%)
Gastric		22 (6.7%)
Gynaecological		19 (5.8%)
Pancreas and biliary tract		34 (10.4%)
Remaining		12 (3.7%)
Renal and bladder		22 (6.7%)
Soft tissue and skin		18 (5.5%)
Tumour stage[d]		
Stage 0 or other benign diagnoses		19 (5.8%)
Stage 1		75 (22.9%)
Stage 2		83 (25.3%)
Stage 3		65 (19.8%)
Stage 4		53 (16.2%)
Unknown		33 (10.1%)

[a] Median age and range.

[b] Median and first and third quartiles.

[c] Two patients were operated on two different malignancies.

[d] The most common pre-malignant and benign diseases were situated in the pancreas (serous cystadenomas, n=2; cystic tumours, n=2; chronic inflammation, n=2), colon (dysplastic polyps, n=4) and breast (ductal carcinoma in situ, n=4).

The median age in this cohort was 76 years (table 3). Almost all patients were community-dwelling at the time of inclusion (n=323; 99.4%). The majority of patients underwent major surgery (n=223; 68.0%) and the most prevalent conditions were colorectal and breast cancer.

Major complications

Complications occurred in 167 patients (50.9%). A total of 61 patients (18.6%) experienced major complications within 30 days postoperatively. Of these, 56 (91.8%) underwent major surgery. Wound related complications and respiratory complications were the most frequent occurring major complications (n=31 and n=13 respectively). Mortality, classified as a grade five complication, occurred in 11 patients (3.4%).

ECOG PS and GDS were excluded from the multivariate logistic regression analysis, as the agreement between the dichotomized geriatric screening tool results was above 80% between the TUG and ECOG PS and GDS (table 2). In a multivariate logistic regression analysis corrected for gender and type of surgery, the TUG, ASA and NRS were predictors of major complications ($TUG_{>20}$ OR 3.1, 95% CI 1.1-8.6; $ASA_{\geq 3}$ OR 2.8, 95% CI 1.2-6.3; $NRS_{impaired}$ OR 3.3, 95% CI 1.6-6.8; $gender_{male}$ OR 3.0, 95% CI 1.4-6.4; type of $surgery_{major}$ OR 3.9, 95% CI 1.2-12.7) (table 4). In the complete case analysis (i.e. the original dataset without imputed values) similar ORs were found ($TUG_{>20}$ OR 2.9, 95% CI 1.0-8.1; $ASA_{\geq 3}$ OR 2.5, 95% CI 1.0-6.0; $NRS_{impaired}$ OR 3.1, 95% CI 1.5-6.7; $gender_{male}$ OR 3.0, 95% CI 1.4-6.7; type of $surgery_{major}$ OR 4.0, 95% CI 1.1-14.0). Age was not a predictor of major complications (OR 1.0; 95% CI 0.98-1.11). The absolute risks for major complications for the screening tools that were included in the multivariate logistic regression analysis were $47.2\%_{TUG>20}$ compared to $13.1\%_{TUG\leq 20}$, $24.5\%_{ASA\geq 3}$ compared to $13.8\%_{ASA<3}$ and $35.7\%_{impaired\ NRS}$ compared to $9.7\%_{normal\ NRS}$ (table 4).

The scoring system derived from the multivariate logistic regression analysis was as follows: gender + type of surgery + TUG + ASA + NRS. The weights of the individual risk score components are shown in table 5. The AUC for this individual risk score was 0.81, 95% CI 0.75-0.86. Based on the ROC a cut-off point was set at >8, with a sensitivity of 78.7% and a specificity of 73.4%. A total 36.3% of the patients (n=119) had a risk score >8, of which 48 experienced major complications (positive predictive value: 40.3%). The negative predictive value was 93.8%.

Table 4 | Geriatric screening tools as predictors of major complications within 30 days postoperatively (n=328)

Test		Major complications within 30 days N (%[a])	Adjusted OR (95%CI)[b]	Multivariate adjusted OR (95%CI)[b]
TUG	≤20.0 seconds	36 (13.1%)	1	1
	>20.0 seconds	25 (47.2%)	**4.1 (1.6-10.5)**	**3.1 (1.1-8.6)**
VES-13	<3	26 (13.1%)	1	
	≥3	35 (27.1%)	1.8 (0.9-3.6)	
GFI	<4	21 (12.9%)	1	
	≥4	40 (24.2%)	1.8 (0.9-3.6)	
ADL	0	32 (12.7%)	1	
	>0	29 (38.2%)	**3.4 (1.6-7.1)**	
IADL	8	24 (12.0%)	1	
	<8	37 (28.9%)	1.6 (0.8-3.2)	
ECOG PS	≤1	41 (14.9%)	1	
	>1	20 (37.7%)	**2.4 (1.1-5.2)**	
MMSE	>26	27 (13.3%)	1	
	≤26	34 (27.2%)	**2.2 (1.1-4.4)**	
GDS	≤5	31 (12.9%)	1	
	>5	30 (34.5%)	**2.4 (1.1-5.3)**	
BFI	≤3	24 (12.0%)	1	
	>3	37 (28.9%)	**2.6 (1.3-5.2)**	
ASA-score	<3	25 (13.8%)	1	1
	≥3	36 (24.5%)	**3.7 (1.7-8.1)**	**2.8 (1.2-6.3)**
NRS	Normal	21 (9.7%)	1	1
	Impaired	40 (35.7%)	**3.9 (1.9-7.9)**	**3.3 (1.6-6.8)**
Comorbidities	<4	27 (12.8%)	1	
	≥4	34 (29.1%)	**2.7 (1.3-5.4)**	

Bold statistically significant (p≤0.05).

[a] Absolute risk for major complications within 30 days.

[b] Corrected for centre, gender and type of surgery (minor/major).

Discussion

A total of 18.6% of the patients experienced major complications postoperatively. An individual risk score comprising the TUG, ASA, NRS, gender and type of surgery showed a good accuracy regarding the occurrence of major versus no/minor 30-day complications (AUC 0.81, 95% CI 0.75-0.86). The scoring system derived from the multivariate logistic regression analysis was as follows: gender + type of surgery + TUG + ASA + NRS (table 5). The optimal cut-off point of >8 resulted in a moderate positive predictive value (40.3%) and a good negative predictive value (93.8%), which is desirable for a screening method as there are few false negative cases.

The high number of patients experiencing adverse outcomes is consistent with other studies[4, 32], and emphasizes the need for preoperative screening for risk for adverse outcomes in onco-geriatric patients[12]. Especially as short-term complications increases the risk for long-term mortality[33].

The TUG gives an assessment of basic functional mobility, coordination and muscle strength in people who are able to walk on their own. In the current cohort, the TUG showed to be a good component to predict the risk for major complications, which underlines the importance of simple performance tests in the preoperative setting when it comes to risk stratification. This is in agreement with other studies finding gait speed as an important risk stratification method in the elderly[34, 35]. Similarly, in patients ≥75 years undergoing major abdominal surgery, $TUG_{>20}$ and $ASA_{\geq 3}$ have been shown to be independent risk factors for postoperative delirium (hazard $ratio_{TUG>20}$ (HZ) 4.8, 95% CI 1.5-15.6; $HZ_{ASA\geq 3}$ 3.3, 95% CI 1.2-9)[29]. In a cohort of mainly male patients ≥65 years undergoing major surgery (mainly abdominal and cardiac surgery), a $TUG_{>15}$ predicted postoperative complications, one-year mortality and discharge to an institutional care facility ($AUC_{complications}$ 0.78, 95% CI 0.67-0.88; $OR_{discharge\ institutionalization}$ 13.0, 95% CI 5.1-33.0)[5, 36, 37]. The TUG was analysed as a single screening tool[5], and as part of a multi domain assessment[36, 37]. A contrasting result was found in a retrospective cohort study among patients ≥65 years undergoing elective surgery (not only for oncological diagnoses): the TUG-score, analysed as a continuous measure, was not significantly different between the home discharge and the in-hospital death or post-discharge institutionalization groups (17.3 and 16.8 seconds respectively, p=0.588)[9]. Comparison with the above mentioned studies is difficult because of different study designs, cohort characteristics, and likely therefore varying cut-off points. The cut-off point in the

Table 5 | Scoring system for major 30-day postoperative complications

Gender	Female = 0
	Male = 3
Type of surgery	Minor = 0
	Major = 4
TUG	≤20 = 0
	>20 = 3
ASA	<3 = 0
	≥3 = 3
NRS	Normal = 0
	Impaired = 3

current study was based on the distribution of mean values in the current study, and on the study predicting postoperative delirium, as this cohort most resembled the PREOP cohort[29]. However, external validation of the $TUG_{>20}$ should be considered for future research.

An impaired nutritional status according to the NRS was observed in 34.1% of the patients. The high prevalence of malnutrition can be explained by the characteristics of the population under study, as the prevalence of malnutrition increases with age and is higher in cancer patients, especially when diagnosed with intra-abdominal tumours or advanced disease[38]. Nutritional status has been shown to be associated with in-hospital death or post-discharge institutionalization in a retrospective cohort study among patients ≥65 years undergoing elective surgery[9]. Prevalence of malnutrition, assessed with the Mini Nutritional Assessment (MNA), was 53.1% in the 'death or post-discharge institutionalization'-group versus 21.1% in the 'home discharge'-group. In patients ≥70 years undergoing surgery for colorectal cancer, the MNA was incorporated in a GA, based on which patients were classified as fit, intermediate or frail[4]. Frailty was an independent predictor of severe complications (OR 3.1; 95% CI 1.7-5.9). However, in the same cohort, a multivariate analysis of the separate screening tools did not identify the MNA as a predictor of severe complications[39]. Contrastingly, severe comorbidity and poor performance status were predictors of severe complications in the backwards stepwise logistic regression analysis.

The MNA has been validated in elderly and is frequently used to assess nutritional status in research studies[4, 9]. Comparing the NRS, used in the current study, to the more frequently

used MNA is not self-evident, because the NRS is probably less sensitive as it only includes questions regarding body mass index, amount of food intake and amount of weight loss. However, in patients ≥65 years undergoing major abdominal surgery, weight loss ≥10% as a measure of malnutrition is an independent predictor for prolonged hospital stay and discharge to a skilled nursing facility (OR 4.0; 95% CI 1.1-14.4 and OR 6.5; 95% CI 1.4-29.8 respectively), substantiating the current results and thus the use of NRS as a geriatric screening tool[32].

A strength of the PREOP-study is its prospective and comprehensive design. To our knowledge, the current study is the first to analyse all components recommended in a GA in one relatively large cohort of onco-geriatric surgical patients with varying malignancies[15]. This enhances comparability between the screening tools and between other studies including onco-geriatric surgical patients. Results are broadly generalizable to the onco-geriatric surgical population as the current study included patients with a wide range of malignancies. A large number of medical centres participated, which further enhances the generalisability of the results. The relatively long duration of this study is explained by the fact that centres did not participate actively during the entire study period and that only a few physicians per centre recruited patients. Although patients from low volume centres (<10) were excluded and centre was included as a confounding factor, selection bias remains a limitation of the current study as inclusion of a consecutive series of patients cannot be guaranteed. Furthermore, cultural differences could have influenced the reporting of results and answers to questionnaires. Considerations for future research include 1) reporting long-term results and patient reported outcome measures, such as quality of life and functional outcome; 2) investigating the effects of preoperative improvement of physical, functional and nutritional status on postoperative outcomes.

The results of the current study show that preoperative estimation of the risk for adverse postoperative outcomes is essential, as a substantial number of patients experience major postoperative complications. The TUG, ASA and NRS are simple and short screening tools that provide clinicians with accurate risk estimations. The scoring system can easily be implemented into daily practice as a screening measure, to support the judgment of the clinician. The high negative predictive value indicates that the scoring system can exclude the fit elderly from further evaluation, whilst a positive score might indicate that a more comprehensive assessment by a geriatrician or by means of a multidisciplinary meeting is indicated.

Conflict of interest statement

We have no conflicts of interests to declare.

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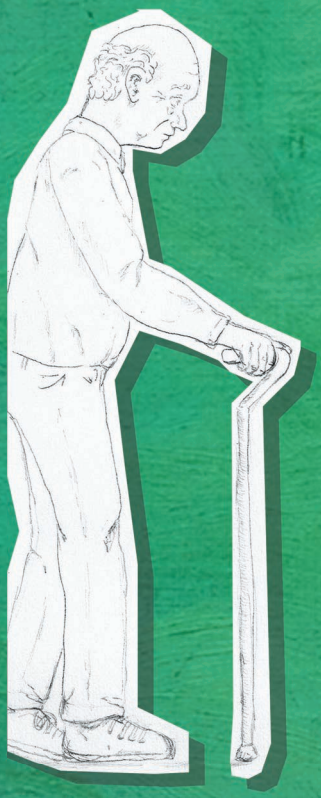

5

Poor nutritional status is associated with other geriatric domain impairments and adverse postoperative outcomes in onco-geriatric surgical patients

Publication:

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Abstract

Background: Nutritional status (NS), though frequently affected in onco-geriatric patients, is no standard part of a geriatric assessment. The aim of this study was to analyse the association between a preoperatively impaired NS and geriatric domain impairments and adverse postoperative outcomes in onco-geriatric surgical patients.

Methods: 309 patients ≥70 years undergoing surgery for solid tumours were prospectively recruited. Nine screening tools were preoperatively administered as part of a geriatric assessment. NS was based on BMI, weight loss and food intake. Odds ratio's (OR) and 95% confidence intervals (95%CI) were estimated using logistic regression analysis. The occurrence of 30-day adverse postoperative outcomes was recorded.

Results: At a median age of 76 years, 107 patients (34.6%) had an impaired NS. Decreased performance status and depression were associated with an impaired NS, when adjusted for tumour characteristics and comorbidities ($OR_{PS>1}$ 3.46; 95%CI 1.56-7.67. $OR_{GDS>5}$ 2.11; 95%CI 1.05-4.26). An impaired NS was an independent predictor for major complications (OR 3.3; 95%CI 1.6-6.8). Ten out of 11 patients who deceased had an impaired NS.

Conclusion: An impaired NS is prevalent in onco-geriatric patients considered to be fit for surgery. It is associated with decreased performance status and depression. An impaired NS is a predictor for adverse postoperative outcomes. NS should be incorporated in a geriatric assessment.

Introduction

Cancer is primarily a disease of the elderly. Currently, 50% of all malignancies are diagnosed in patients 65 years and older and it is predicted this percentage will increase to 70% by 2030[1]. Surgery plays an essential role in the treatment of solid tumours and it is therefore expected that increasing numbers of onco-geriatric patients will require surgery. Whilst fit onco-geriatric patients might recover from surgery as well as their younger counterparts, it is acknowledged that patients with geriatric domain impairments are at an increased risk of adverse postoperative outcomes, mortality and discharge to a non-home institution[2-5]. The preoperative identification of these impairments, utilizing screening elements of a Geriatric Assessment (GA), is essential in this heterogeneous population of onco-geriatric surgical patients.

Though not frequently included in a GA[6], nutritional status (NS) is one of the geriatric domains that is frequently impaired in onco-geriatric patients[7-9]. Recent studies on middle-aged and elderly cancer patients, reported high numbers of patients at nutritional risk or being malnourished (32% to 64.2%)[7-9]. These studies were performed amongst cohorts in which the majority of patients was diagnosed with advanced disease (80.6% stage III/IV and 46.3% with metastases, respectively)[7, 9] and frequently underwent chemotherapy with palliative intent (58.3%)[8]. Advanced disease is a known risk factor for malnutrition and many chemotherapeutic treatments are infamous for their side effects, such as nausea, vomiting and mucositis, increasing the risk for malnutrition even further[10, 11]. However, in recent *surgical* onco-geriatric cohorts with fewer patients with advanced disease, the prevalence of an impaired NS or risk thereof was also as high as 34.1% and 48%, respectively[12, 13].

As nutritional impairment is rather a multifactorial than an isolated problem, improving the understanding of geriatric domain impairments associated with malnourishment could lead to timely preventive measures[14]. For that, the aim of this study was to analyse the association between preoperatively impaired NS, the impairments in other geriatric domains, and the occurrence of adverse postoperative outcomes in onco-geriatric surgical patients.

Materials and methods

Design and cohort definition

Data were derived from the Preoperative Risk Estimation for Onco-geriatric Patients

(PREOP) study, an international prospective cohort study. The PREOP-study was approved by the appropriate ethics committees and was registered at the Dutch Trial register (Trial ID: NTR1567) and United Kingdom register (Research Ethics Committee reference: 10/H1008/59).

Data deriving from centres that included less than ten patients were excluded from analyses, to reduce the influence of selection bias. Of the 14 medical centres initially adhering to the project, eight were able to enrol ten or more patients in the present study. When peri- or postoperatively patients appeared to have a benign condition (n=19), they were excluded from further analyses as the association between cancer and NS is an important factor in the current analyses.

The detailed cohort definition and study protocol were published previously[12, 15]. In summary, patients aged 70 years and older, undergoing elective surgery for a solid tumour were included. Preoperatively, a battery of screening tools, assessing all domains recommended for a GA, was administered (Table 1).

Screening tools that assessed multiple geriatric domains were excluded from analyses, as these will not provide an answer to the research question of the current study. Complications up to 30 days after surgery were registered using the Clavien-Dindo classification. Major complications were defined as grade three to grade five, which were complications requiring surgical, endoscopic or radiological intervention (grade 3); life threatening complications requiring intensive care management (grade 4); and death of a patient (grade 5)[26].

Nutritional status

To determine the risk for an impaired NS, the nutritional risk screening (NRS) scale, based on the NRS-2002, was used[24]. Patients were stratified according to the following criteria:

- Normal NS
- Mildly impaired NS: weight loss greater than 5% in the previous three months or a food intake below 50-75% of normal requirement in the preceding week;
- Moderately impaired NS: weight loss greater than 5% in the previous two months or a body mass index (BMI) between 18.5 and 20.5 kg/m^2 and impaired general condition or a food intake below 25-50% of normal requirement in the preceding week;
- Severely impaired NS: weight loss greater than 5% in the previous month or a weight loss greater than 15% in three months or a BMI less than 18.5 kg/m^2 and an impaired general condition or a food intake below 25% of normal requirement in the preceding week.

Table 1 | Components of PREOP

Test	Acronym	Purpose	Cut-off value for adverse results	Range of possible scores
Timed Up and Go[16] [a]	TUG	A walking test to measure functional status	>20 seconds[b]	Not applicable
Activities of Daily Living[17]	ADL	Depicts dependency regarding bathing, dressing, toileting, transfer, continence and feeding	>0	0 - 12
Instrumental Activities of Daily Living[18]	IADL	A questionnaire regarding 8 items needed to perform independently to maintain independence in the community	<8	0 - 8
Eastern Cooperative Oncology Group performance status[19]	ECOG PS	A physician's perspective of a patient's functional status; ranging from 0 to 4	>1	0 - 4
Mini Mental State Examination[20]	MMSE	A test consisting of 11 questions to assess cognitive function	≤26	0 - 30
Geriatric Depression Scale[21]	GDS	A 15-item self-rating depression screening scale for elderly populations	>5	0 - 15
Brief Fatigue Inventory[22]	BFI	A 9-item questionnaire to report on fatigue severity in cancer patients	>3	0 - 10
American Society for Anaesthesiologist scale[23] [c]	ASA	To quantify preoperative physical status and estimate anaesthetic risk	≥3	1 - 5
Nutritional Risk Screening[24]	NS	Nutritional status based on recent weight loss, overall condition and reduction of food intake	Impaired nutritional status was compared to normal nutritional status	Normal to severely impaired nutritional status

[a] Patients performed the TUG two times and for each patient, the mean of the two time measurements was calculated; [b] based on literature and the distribution of the mean values in the current study population, a score of less than or equal to 20 seconds on the TUG was considered a low score[25]; [c] the ASA-classification was determined by an anaesthesiologist.

Statistical analysis

Results on the geriatric screening tools and the occurrence of major postoperative complications were analysed as dichotomized values, based on predefined, literature based cut-off points. Categorical data were described as frequencies and proportions, and continuous variables as median and interquartile range (i.q.r.).

For further analyses, NS was considered as a dependent variable. Logistic regression analysis was used to estimate odds ratio's (OR) and 95% confidence intervals (95% CI), which were at least adjusted for centre. Both complete cohort analyses as well as a sub-group analyses for patients with intra-abdominal tumours were performed. Firstly, the associations between

patients' demographics and disease characteristics and NS (impaired versus normal) were estimated. Subsequently, the associations between the geriatric screening tools and NS were estimated in a model adjusted for centre (model 1) and in a model adjusted for statistically significant confounders (model 2 for the complete cohort or model 3 for patients with intra-abdominal tumours).

The association between an impaired NS and other geriatric domain impairments as independent variables and the occurrence of major postoperative complications as a dependent variable, was estimated using backwards stepwise logistic regression analysis, whilst forcing statistically significant patients' and disease characteristics into the model[12]. The association between an impaired NS and 30-day mortality was evaluated using Fisher's exact test.

Missing values for the geriatric screening tools were addressed by multiple imputation, as the missing values were supposed to be missing (completely) at random. Multiple imputation was performed for the total scores on the questionnaires and was based on available results on the screening tools, age, gender, living situation, preoperative haemoglobin level, type of tumour, tumour stage, type of surgery and number of comorbidities[12, 27]. The reported results on the screening tools were pooled values, which were average values calculated from the five imputed datasets[12].

Missing values for tumour stage (n=32) were not addressed by multiple imputation, leading to multivariate logistic regression analyses of 277 cases for model 2. Sensitivity analyses were performed for model 1, to discover possible discrepancies between complete case analyses based on model 2 and analyses of the entire cohort.

Data analysis and multiple imputation were performed using IBM SPSS Statistics 23. P-values ≤ 0.05 were considered statistically significant.

Results

Baseline characteristics

Data of 309 patients deriving from eight medical centres were analysed. Baseline characteristics are shown in table 2. A total of 190 patients were female (61.5%) and the median age was 76 years (i.q.r.: 8). The vast majority of patients had an intra-abdominal tumour (n = 207; 67%). Patients were most frequently planned for colorectal and breast cancer surgery (n=117, 37.6%

Table 2 | Patients' characteristics

Variable	Value
Gender, female	190 (61.5)
Age	
70-74	110 (35.6)
75-79	99 (32.0)
80-84	69 (22.3)
≥85	31 (10.0)
Weight (kg)a	
Female	67 (15.6)
Male	73 (14.6)
BMI (kg/m2)a	
Female	26 (5.8)
Male	25 (3.9)
Living situation	
Independent/family	304 (99.3)
Residential care/nursing home	2 (0.7)
Comorbiditiesa	3 (2)
Cancer siteb	
Superficial	102 (33.0)
Intra-abdominal	207 (67.0)
Breast	77 (24.8)
Colorectal	117 (37.6)
Gastric and oesophageal	22 (7.1)
Gynaecological	18 (5.8)
Pancreas and biliary tract	29 (9.3)
Remaining	9 (2.9)
Renal and bladder	23 (7.4)
Soft tissue and skin	16 (5.1)
Tumour stage	
Stage 1	76 (24.6)
Stage 2	83 (26.9)
Stage 3	65 (21.0)
Stage 4	53 (17.2)
Unclassified/missing	32 (10.4)

Values in parentheses are percentages unless indicated otherwise;

a values are median (i.q.r.);

b one patient was operated on colon and renal cancer and one on melanoma skin cancer and breast cancer: for tumour staging and subsequent analyses the most severe disease was analysed;

kg = kilograms; BMI = Body Mass Index

and n=77, 24.8%, respectively). The 9 tumour sites that were classified as remaining, were thyroid (n=5), anus (n=3) and prostate (n=1). The pathologists' reports confirmed stage 1, 2, 3 and 4 disease in 76 (24.6%), 83 (26.9%), 65 (21%) and 53 (17.2%) patients, respectively.

Nutritional status

Table 3 shows the associations between the patients' demographics and disease characteristics and NS. A total of 202 (65.4%) patients were defined as having a normal NS, 81 (26.2%) had a mild nutritional impairment and 26 (8.4 %) had a moderate or severe nutritional impairment. Advanced age was overall not statistically significantly associated with the risk for an impaired NS, except for the group aged 80 to 84 years old (OR 2.2; 95% CI 1.1-4.5). A high number of comorbidities was associated with an impaired NS (OR 2.10; 95% CI 1.20-3.68). Patients with a tumour located in the pancreas, biliary tract, stomach, oesophagus, kidney, bladder, colon or rectum had the highest risks for an impaired NS. With increasing tumour stage, the risk for an impaired NS increased as well, whilst the 95% CI's did overlap (Stage 3: OR 2.1; 95% CI 1.1-3.9. Stage 4: OR 2.6; 95% CI 1.2-5.4). In a sub-group analysis on patients with intra-abdominal tumours, a high number of comorbidities and a tumour located in the pancreas or biliary tract were associated with an impaired NS ($OR_{Comorbidities \geq 4}$ 2.4; 95% CI 1.3-4.5. $OR_{pancreas\ and\ biliary\ tract}$ 3.1; 95% CI 1.1-8.4 with reference to colorectal cancer).

Geriatric domains associated with nutritional status

A total of 65.4% of the patients with an ECOG PS >1 had an impaired NS (Table 4). Furthermore, an impaired functional status or signs of depression were frequently accompanied by an impaired NS (51.9% of $TUG_{>20}$, 50.7% of $ADL_{>0}$ and 50.6% of $GDS_{>5}$). The majority of patients that did not have a geriatric domain impairment, had a normal NS as well (ranging from 68.9% for $TUG_{\leq 20}$ to 73.7% for $IADL_{8}$). The domains significantly associated with an impaired NS were ECOG PS ($OR_{PS>1}$ 3.5; 95% CI 1.6-7.7) and GDS ($OR_{GDS>5}$ 2.1; 95% CI 1.1-4.3), when adjusted for centre, age, comorbidities, tumour site and tumour stage (Table 4, model 2). In a sub-group analysis on patients with intra-abdominal tumours ADL ($OR_{ADL>0}$ 2.2; 95% CI 1.1-4.6), IADL ($OR_{<8}$ 2.8; 95% CI 1.5-5.5), ECOG PS ($OR_{ECOG\ PS>1}$ 3.4; 95% CI 1.4-8.0) and GDS ($OR_{GDS>5}$ 2.3; 95% CI 1.1-4.8) were significantly associated with an impaired NS, when adjusted for centre and comorbidities (Table 4, model 3).

Nutritional status and adverse postoperative outcomes

A total of 160 (51.8%) patients experienced at least one complication within 30 days after

Table 3 | Association between patients' characteristics and impaired nutritional status

Variable	Normal nutritional status	Impaired nutritional status	Adjusted OR[b, c]	Adjusted OR[b, d]
Gender				
Female	129 (67.9)	61 (32.1)	1	1
Male	73 (61.3)	46 (38.7)	1.14 (0.67-1.96)	0.74 (0.42-1.33)
Age				
70-74	80 (72.7)	30 (27.3)	1	1
75-79	64 (64.6)	35 (35.4)	1.27 (0.67-2.42)	1.48 (0.71-3.07)
80-84	41 (59.4)	28 (40.6)	**2.22 (1.10-4.48)**	1.97 (0.88-4.41)
≥85	18 (58.1)	13 (41.9)	2.29 (0.93-5.63)	3.13 (0.98-9.99)
Weight (kg)				
Female	68.1 (11.6)a	60.0 (19.1)a	**0.94 (0.91-0.97)**	**0.95 (0.92-0.99)**
Male	75.2 (12.1)a	70.4 (15.8)a	**0.94 (0.90-0.99)**	**0.93 (0.89-0.98)**
BMI(kg/m^2)				
Female	26.5 (5.3)a	23.6 (6.0)a	**0.85 (0.78-0.93)**	**0.90 (0.81-0.99)**
Male	25.4 (3.5)a	24.1 (5.2)a	**0.82 (0.71-0.96)**	**0.79 (0.67-0.93)**
Comorbidities				
<4	138 (70.1)	59 (29.9)	1	1
≥4	64 (57.1)	48 (42.9)	**2.10 (1.20-3.68)**	**2.39 (1.26-4.54)**
Tumour site				
Superficial	87 (85.3)	15 (14.7)	1	Not applicable
Intra-abdominal	115 (55.6)	92 (4.4)	**3.87 (1.98-7.57)**	
Breast	67 (88.2)	9 (11.8)	1	
Colorectal	72 (61.5)	45 (38.5)	**4.09 (1.74-9.59)**	1
Gastric and Oesophageal	10 (45.5)	12 (54.5)	**9.60 (2.96-31.13)**	2.33 (0.86-6.35)
Gynaecological	15 (83.3)	3 (16.7)	1.18 (0.24-5.81)	0.32 (0.06-1.75)
Pancreas and biliary tract	11 (37.9)	18 (62.1)	**12.27 (3.42-44.03)**	**3.07 (1.12-8.40)**
Remaining	3 (33.3)	6 (66.7)	**11.56 (2.02-66.21)**	4.37 (0.41-47.06)
Renal and bladder	12 (54.5)	10 (45.5)	**7.09 (1.86-27.09)**	1.65 (0.55-4.91)
Soft tissue and skin	13 (81.3)	3 (18.8)	1.76 (0.27-11.45)	Not performede
Tumour stage				
Stage 1 or 2	120 (75.5)	39 (24.5)	1	1
Stage 3	37 (56.9)	28 (43.1)	**2.05 (1.07-3.92)**	1.56 (0.73-3.37)
Stage 4	25 (47.2)	28 (52.8)	**2.58 (1.24-5.37)**	1.76 (0.81-3.83)

Values in parentheses in the second and third column are percentages unless indicated otherwise; values in parentheses in the final two columns are 95% CI; [a] values are median (i.q.r.); [b] adjusted for centre; [c] analysis of complete cohort; [d] sub-group analysis of patients with intra-abdominal tumours; [e] only one patient with an intra-abdominal soft tissue tumour; kg = kilograms; BMI = Body Mass Index; **Bold** = statistically significant (≤ 0.05)

Table 4 | Association between geriatric screening tools and impaired nutritional status

Geriatric screening tool[a]	Normal nutritional status	Impaired nutritional status	Adjusted OR model 1[b, d]	Adjusted OR model 1[c, d]	Adjusted OR model 2[b]	Adjusted OR model 3[c]
TUG						
≤20 s	177 (68.9)	80 (31.1)	1	1	1	1
>20 s	25 (48.1)	27 (51.9)	1.99 (0.89-4.49)	1.42 (0.53-3.78)	1.12 (0.41-3.09)	1.14 (0.41-3.18)
ADL						
0	168 (70.6)	70 (29.4)	1	1	1	1
>0	35 (49.3)	36 (50.7)	2.16 (1.17-3.99)	2.41 (1.17-4.95)	1.66 (0.84-3.28)	2.23 (1.07-4.63)
IADL						
8	137 (73.7)	49 (26.3)	1	1	1	1
<8	66 (53.7)	57 (46.3)	2.20 (1.29-3.75)	3.11 (1.63-5.92)	1.67 (0.88-3.16)	2.82 (1.46-5.45)
ECOG PS						
≤1	184 (71.6)	73 (28.4)	1	1	1	1
>1	18 (34.6)	34 (65.4)	4.41 (2.16-8.97)	3.68 (1.60-8.48)	3.46 (1.56-7.67)	3.38 (1.44-7.95)
MMSE						
>26	135 (70.3)	57 (29.7)	1	1	1	1
≤26	67 (57.3)	50 (42.7)	1.66 (0.98-2.80)	1.72 (0.93-3.16)	1.33 (0.72-2.45)	1.56 (0.84-2.91)
GDS						
≤5	160 (71.4)	64 (28.6)	1	1	1	1
>5	42 (49.4)	43 (50.6)	2.32 (1.25-4.30)	2.43 (1.16-5.10)	2.11 (1.05-4.26)	2.25 (1.06-4.77)
BFI						
≤3	128 (69.2)	57 (30.8)	1	1	1	1
>3	74 (59.7)	50 (40.3)	1.49 (0.87-2.56)	1.56 (0.83-2.93)	1.13 (0.61-2.12)	1.39 (0.73-2.66)
ASA-score						
<3	124 (71.7)	49 (28.3)	1	1	1	1
≥3	78 (57.4)	58 (42.6)	2.39 (1.39-4.12)	2.14 (1.13-4.04)	1.56 (0.81-2.99)	1.69 (0.86-3.35)

Values in parentheses in the second and third column are percentages; values in parentheses in the other columns are 95% CI; [a] acronyms of the screening tools are spelled out in table 1; model 1 is adjusted for centre.; model 2 is adjusted for centre, age (continuous), comorbidities (<4 or ≥4), tumour site (intra-abdominal versus superficial) and tumour stage (1-4); model 3 is adjusted for centre and comorbidities (<4 or ≥4); [b] analysis of complete cohort; [c] sub-group analysis of patients with intra-abdominal tumours; [d] sensitivity analyses were performed for model 1 with the complete cases of model 2 (minus 32 cases in which tumour stage was missing): n=277 for complete cohort and n=179 for sub-group analysis: similar results were found (data not shown); **Bold** = statistically significant (≤ 0.05)

surgery. Major complications occurred in 57 (18.4%) patients, including death in 11 patients (30-day mortality rate: 3.6%). Of the 11 patients who deceased within 30 days postoperatively, ten patients had an impaired NS (90.9%) (p<0.001). Of all patients with a normal NS,

Table 5 | Association between geriatric screening tools and major postoperative complications

Geriatric screening tool[a]	Adjusted OR[b]
NS	
Normal	1
Impaired	3.3 (1.6-6.8)
TUG	
≤20 s	1
>20 s	3.1 (1.1-8.6)
ASA-score	
<3	1
≥3	2.8 (1.2-6.3)

Values in parentheses are 95% CI; [a] acronyms of the screening tools are spelled out in table 1; [b] adjusted for centre, gender and type of surgery

90.6% did not experience any major postoperative complications. Of all patients with an impaired NS, 35.5% experienced major postoperative complications. The best combination of screening tools with regard to predicting the risk for major postoperative complications comprised an assessment of NS, TUG and ASA score (table 5), as was previously shown[12]. We therefore reinforce the statement that the assessment of NS preoperatively, allows a clear understanding of the operative risk.

Discussion

Onco-geriatric patients undergoing elective surgery, can be considered a selected and thus relatively fit part of the onco-geriatric population[28]. Nevertheless, an impaired NS was frequently seen in this cohort of onco-geriatric surgical patients (34.6%). An impaired NS was associated with both tumour characteristics and an increased number of other comorbidities as well as decreased performance status, signs of depression and an impaired functional status. An impaired NS is an important predictor for major complications including death.

The prevalence of an impaired NS is comparable with several other cohorts of onco-geriatric patients, whilst a lower prevalence was to be expected as fewer patients (38.2%) were diagnosed with advanced disease[7-9]. This discrepancy between observed and expected values can be explained by either an underestimation of the prevalence of malnutrition in the other

cohorts, an overestimation in the current study or by the fact that the other cohorts concern selected patients as well, i.e. with no or few geriatric domain impairments. Bozzetti et al. assessed NS using the NRS-2002, which is similar to the nutritional screening in the current study and has proven to be suitable for use in hospitalized patients and, specifically, in cancer patients[7, 29]. The study by Aaldriks et al. administered the Mini Nutritional Assessment, which has been validated for elderly people, with a sensitivity of 96% and specificity of 98% in elderly patients (not specifically cancer patients), and was found to be able to detect a risk of malnutrition before changes in weight or albumin levels occurred[8, 30]. Thus underestimation of the prevalence of malnutrition in the other studies or an overestimation in the current study are unlikely.

It is likely that these cohorts of patients, undergoing active anti-cancer treatment or at least able to attend an ambulatory consultation, consist of selected and relatively fit patients as well. This hypothesis is substantiated by the higher prevalence of (risk of) malnutrition in another study of onco-geriatric patients by Paillaud et al. (64.2%)[9]. Participants of this study were patients that were referred to a geriatric oncology clinic, thus with a higher a priori chance of geriatric domain impairments. This was subsequently confirmed by, for example, a $PS_{>1}$ in 50.4% of patients, compared to 16.8% in the current cohort and 20% in the cohort from Bozzetti et al., and a $MMSE_{\leq 24}$ in 29.8%, compared to 9% in the cohort from Aaldriks et al. These results suggest that, maybe even stronger than disease characteristics, geriatric domain impairments are associated with NS. It should be emphasized that these prevalences of an impaired NS stem from cohorts in which a decision on treatment modality had already been made and thus, extrapolating results to all onco-geriatric patients in daily clinical practice should occur with caution.

The results of the current study show that in onco-geriatric patients, independent of tumour site and stage and comorbidities, impairments in the geriatric domains performance status, mood and functional status are associated with the risk of an impaired NS. The results maintained in a sub-group analysis on patients with intra-abdominal tumours, whom are at greatest risk for both an impaired NS[7, 9] and adverse outcomes after major surgery[12]. The results are comparable to results found in different studies including onco-geriatric patients or elderly hospitalized patients[9, 31-33]. Other associated geriatric domain impairments were cognitive and mobility impairments, which were assessed with the MMSE, TUG and risk of falls.

The importance of preoperative nutritional screening is emphasized by the fact that out of all geriatric screening tools, an impaired NS – combined with TUG-score and ASA status – was best in predicting the occurrence of major postoperative complications. On top of that, ten out of 11 patients who deceased within 30-days postoperatively, had an impaired NS. Similarly, in patients ≥65 years undergoing pancreaticoduodenectomy for benign disease, a 'Severe Nutritional Risk' was found to be a prognostic factor for long-term survival (adjusted hazard ratio 2.74; 95% CI 1.25-6.02)[34]. Furthermore, NS, assessed either by the MNA-score, recent weight loss, body mass index (BMI) or serum albumin levels, are known prognostic factors of survival and response to chemotherapy in cancer patients[5, 8, 35]. Data on the predictive ability of nutritional markers on postoperative outcomes in the elderly general surgery and hip surgery patient populations are scarce and nutritional markers are operationalized in several ways, according to a systematic review including 15 studies[36]. Serum albumin is a frequently investigated nutritional parameter (13 out of 15 studies) with – overall – positive results regarding its predictive ability of postoperative outcomes such as postoperative complications, mortality and length of hospital stay. However, serum albumin might be merely a marker of inflammatory metabolism rather than a pure representative of nutritional status in surgical patients[36]. Three included studies used a nutritional questionnaire, such as the MNA or the food frequency questionnaire. These were not associated with adverse postoperative outcomes. Out of 15 studies, one was comparable to the current study: a retrospective study on elderly gastrointestinal surgery patients, which found ≥10% weight loss in 6 months as a risk factor for postoperative morbidity. Despite promising results regarding weight loss, BMI and serum albumin levels, based on the current literature it can be concluded, that no consensus has been reached as to what an appropriate nutritional screening tool entails and what its' exact value is.

The use of nutritional interventions in order to improve these outcomes has not been clearly established yet[35, 37, 38]. A meta-analysis on the influence of nutritional support on adverse outcomes in cancer patients, showed no advantage for the intervention arms[37]. It was noted that the lack of effect might be attributed to poor study designs and heterogeneous patient populations. However, colorectal cancer patients subjected to a so-called trimodal prehabilitation program, consisting of nutritional counselling, protein supplementation, anxiety reduction exercises and physical exercise, showed improved functional outcome after surgery[39]. Furthermore, over the last several years, multiple studies suggested that enhanced recovery programs for elderly surgical patients were feasible and led to equally positive results as compared to their younger counterparts[40-42]. Unfortunately, elderly patients have high

variability within their own group and what was demonstrated for patients with colorectal cancer, was not repeated for elderly patients with gastric cancer[43]. These results endorse the importance of an integrated approach in cancer patients, assessing at least NS, performance status and mood. Furthermore, more than from a strict list of postoperative prescriptions within a protocol, selected elderly patients might benefit from controlled and tailored (p) rehabilitation programmes.

Due to the cross-sectional nature of the current analyses, no clear conclusions on possible causal relations regarding NS and impairments in other geriatric domains can be drawn. The association between an impaired NS, functional status and depression can go both ways and the influence of common risk factors, such as disease burden and social factors, cannot be ignored.

It can be hypothesized that the link between impaired NS, depression, functional impairment and adverse postoperative outcomes, is via inflammatory pathways. It is known that aging is accompanied by a low-grade inflammatory state and that increased levels of pro-inflammatory cytokines are associated with functional decline, multiple geriatric domain impairments, frailty and mortality in the elderly[44-46]. Furthermore, cancer patients, especially in an advanced stage, are at risk for cachexia. This is a complex and systemic syndrome characterized by loss of skeletal muscle mass (with or without loss of fat mass), often accompanied by reduced food intake and systemic inflammation and frequently leading to functional impairment[47]. Finally, bidirectional associations between diet and depression via inflammatory pathways, have been postulated. Diet can either promote or attenuate inflammatory effects, inflammation can induce 'sickness behaviour' including depressive symptoms in susceptible persons and depression can increase pro-inflammatory cytokine production[48, 49]. On top of that, depressed patients elicit higher inflammatory responses to physical and psychological stress[49], thus putting them at increased risk for adverse outcomes after a major stressor such as surgery. Future research should point out whether these hypotheses can be confirmed in an onco-geriatric population, in which multiple parameters (e.g. aging, tumour biology and cancer treatment effects) influence the inflammatory state[50].

The main strength of our study is its comprehensive and detailed assessment of patients' demographics, disease characteristics and geriatric domains in a cohort of onco-geriatric surgical patients, who were prospectively recruited in multiple centres from different countries. Previous studies have focused on impaired NS and its association with other geriatric domain

impairments in cohorts including many *non*-surgical patients with advanced disease and/or undergoing palliative treatment, whereas the current study focused on patients that were considered fit for surgery and were, moreover, less frequently diagnosed with advanced disease. These results should raise awareness amongst surgeons on NS being a multifactorial and prevalent issue in their patient population.

An impaired NS is frequently seen in onco-geriatric patients considered to be fit for surgery. The results of the current study confirm that an impaired NS is associated with functional impairments and possible depression in these patients. Moreover, our data substantiate that NS is an important risk factor for adverse postoperative outcomes. This emphasizes the importance of a geriatric assessment in onco-geriatric surgical patients and that a nutritional assessment should be an essential part of this. Identification of the patients with an impaired NS is of the utmost importance, especially as they might benefit from preventive strategies.

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Conflict of interest

All authors have no conflicts of interest to declare.

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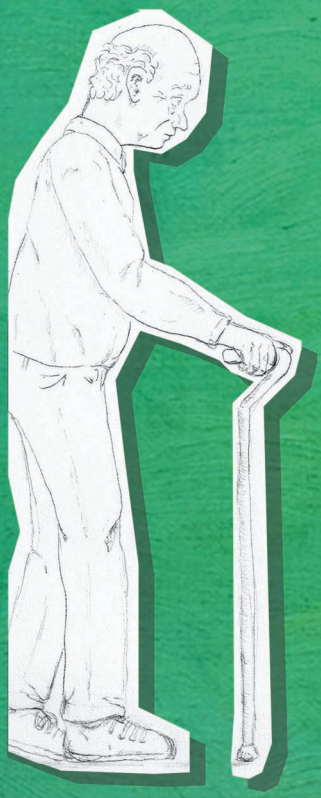

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Long-term survival and risk of institutionalization in onco-geriatric surgical patients: long-term results of the PREOP-study

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Abstract

Importance: Preoperative risk assessment with regards to adverse long-term outcomes is imperative for the shared decision-making process in the onco-geriatric surgical population.

Objective: To evaluate long-term survival and institutionalization in onco-geriatric surgical patients, and to analyze the association between the PREOP risk score and these outcomes.

Design: The PREOP-study (Preoperative Risk Estimation for Onco-geriatric Patients) is a prospective cohort study. Patient enrollment: September 2008 – October 2012. Collection of follow-up data: January 2015 – August 2016.

Setting: International multicenter study.

Participants: Patients aged ≥70, undergoing elective surgery for a solid tumor. Five centers (out of the original eight) participated in long-term follow-up, accounting for 249 patients (out of the original 328). Exclusion of patients with a primary benign diagnosis resulted in a cohort of 229 patients.

Exposure: The PREOP risk score, developed to predict the risk of major 30-day complications, comprised the Timed Up & Go test, the Nutritional Risk Screening, gender, type of surgery and ASA-classification. A score >8 is considered abnormal.

Main outcomes: The endpoints were long-term survival and institutionalization. The hypotheses were formulated a priori.

Results: A total of 149 woman and 80 men with a median age of 76 (IQR 8) were included. Survival at one, two and five years postoperatively was 84%, 77% and 56%, respectively. One-year survival was worse for patients with a PREOP risk score >8 as compared to ≤8 (70% versus 91%). Of the patients alive one year postoperatively, 43 (26%) were institutionalized. By two years postoperatively, almost half of the entire cohort (46%) were institutionalized or had died. A PREOP risk score >8 was associated with increased mortality (HR:2.6; 95%CI:1.7-4.0), irrespective of stage and age, but not with institutionalization ($OR_{1yr\ vs\ preop}$1.6; 95%CI:0.7-3.8; $OR_{2yr\ vs\ preop}$2.2; 95%CI:0.9-5.5).

Conclusions and Relevance: A high PREOP-score was associated with mortality, but not with staying independent. Although survival in onco-geriatric patients is acceptable, physical functioning might deteriorate. It is imperative to preoperatively discuss treatment goals and expectations.

Trial Registration: Dutch Trial register (Trial ID: NTR1567; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1567) and United Kingdom register (Research Ethics Committee reference: 10/H1008/59).

Introduction

The elderly population is growing worldwide and is expected to exceed 1 billion by 2020[1]. Solid tumors mainly affect patients aged 65 years and older and in the last few years, geriatric oncology leaders have attempted to spread the key concept that chronological age is not a contraindication per se to surgical treatments[2-5]. Nevertheless, onco-geriatric patients still often receive substandard treatment compared to their younger counterparts[6]. For example, it has been shown that elderly women affected by breast cancer are less often offered surgical treatment[7], as well as elderly affected by pancreatic cancer in the USA[8] or French women with an ovarian neoplasm[9].

It has been suggested that surgical oncologists probably deviate more often from standard treatment protocols in the geriatric population, because of the higher risk of a troublesome postoperative course and because of a lack of certainty about the gain obtainable from surgery, both in terms of survival and quality of life[10]. However, data as to why standard treatment of these geriatric patients was omitted, is lacking and therefore the question on whether this decision might be justified cannot be answered with certainty[7-9]. Moreover, most studies have their focus on short-term outcomes in onco-geriatric surgical patients, where most patients will die outside of the immediate postoperative period[11, 12]. Additionally, long-term loss of independence remains only partially explored in the elderly setting, as preservation of preoperative functional status has been found to be one of the most important patient-centered outcomes [13].

Outcome prediction in onco-geriatric surgical patients has become a research area of growing interest in the past few years. Several studies have evaluated the ability of time-saving and easy-to-administer geriatric screening tools to predict the risk for postoperative complications[14-16]. Recently, the PREOP-study, a multicenter prospective cohort study, identified the Timed Up & Go test and Nutritional Risk Screening – as part of a newly developed PREOP risk score – as easy and quick tools able to predict major 30-day postoperative complications in onco-geriatric surgical patients[17].

The primary aim of the current study was to provide data on long-term survival and institutionalization in onco-geriatric surgical patients as these data are scarce, whilst these long-term outcomes might be an important aspect to consider in the preoperative decision-making process. Furthermore, we hypothesized that geriatric domain impairments might be

associated with impaired long-term outcomes. For this, we analyzed the association between the PREOP risk score and long-term survival and institutionalization.

Methods

Study Design

The current study concerns the long-term follow-up of the PREOP-study (Preoperative Risk Estimation for Onco-geriatric Patients), a prospective international multicenter cohort study[17-19]. PREOP was designed by members of the surgical taskforce of the International Society of Geriatric Oncology (SIOG), to investigate the predictive ability of geriatric screening tools, assessing all domains recommended for a geriatric assessment, with regards to 30-day postoperative outcomes. Patients aged 70 years and older, undergoing elective surgery for a solid tumor, suspicious for malignancy, were included. Patient enrollment took place between September 2008 and October 2012. The PREOP-study was approved by the appropriate ethics committees and is registered at the Dutch Trial register (Trial ID: NTR1567) and United Kingdom register (Research Ethics Committee reference: 10/H1008/59). All patients gave written informed consent in accord with the ethical standards of the local ethics committees.

The previous analyses of the PREOP-study focused on the short-term outcomes[17-19], whereas analyses of long-term outcomes will be herein presented. For the latter, centers that participated in the PREOP-study were asked to additionally collect data on survival and on living situation up to two years postoperatively. These long-term follow-up data were collected between January 2015 and August 2016.

Patients

For the current study, patients were included if postoperative histology confirmed the malignant nature of the tumor, as the current analyses comprise long-term survival data which are influenced by the presence of a malignancy.

Endpoints

For the current study, the primary endpoint was long-term survival, expressed as postoperative survival at six months, and one, two and five years, respectively. The secondary endpoint was long-term institutionalization, expressed as the change in living situation at one year and two years postoperatively as compared to the preoperative living situation. Living situation was

defined according to the following categories: a) independent, b) assisted living, c) nursing home.

PREOP risk score

The PREOP risk score comprises five variables of which two are geriatric screening tools, knowing the Timed Up & Go and the Nutritional Risk Screening[17]. The Timed Up & Go comprises the time a patient needs to get up from a chair, walk 3 meters, turn around, walk back and sit down again[20]. The Nutritional Risk Screening is based on recent weight loss, overall condition and reduction of food intake[21]. Furthermore gender, type of surgery and ASA-classification (American Society for Anesthesiologists classification) are included in the PREOP risk score. The score is derived from multivariable logistic regression analysis with regards to the occurrence of major 30-day postoperative complications. To calculate the PREOP risk score, assess the patient on the several items and sum up the rates:

- Gender: female = 0, male = 3
- Type of surgery: minor = 0, major = 4
- Timed Up & Go: ≤20sec = 0, >20sec = 3
- ASA: <3 = 0, ≥3 = 3
- Nutritional Risk Screening: normal = 0, impaired = 3

Based on the area under the curve of the receiver operating characteristic, a cut-off point was set at >8. A high PREOP risk score corresponded with a higher risk of major complications. In agreement with the previous study, for the current analyses a high PREOP risk score (>8) was compared to a low PREOP risk score (≤8).

Statistical analysis

Descriptive data were provided as absolute numbers and proportions for categorical data. Overall survival, the primary endpoint, was analyzed by means of survival analyses. Median follow-up time was calculated by means of the Kaplan Meier estimate of potential follow-up method[22]. Kaplan Meier analyses were performed. Proportional hazards assumptions were evaluated graphically, using log minus log Cox regression curves. Cox regression was used to estimate hazard ratio's (HR) and 95% confidence intervals (95% CI), which were adjusted for center. In a multivariable Cox regression analysis, the HR for the PREOP risk score with regards to mortality was adjusted for cancer stage, age as a continuous variable and center.
Living situation at one year and two years postoperatively was compared to the preoperative living situation: patients who were institutionalized were compared to patients who did not

change their living situation or in whom it even improved, i.e. moving from a nursing facility to independent living. Logistic regression analysis was used to estimate odds ratio's (OR) and 95% CI's, which were adjusted for center.
For previous analyses missing values for the geriatric screening tools were handled by means of multiple imputation, after the assumptions for performing multiple imputation were checked and met[17, 19]. The PREOP risk scores were calculated based on these imputed datasets. For the current analyses, these PREOP risk scores were used as well.

Values were considered statistically significant at a p value ≤0.05. All statistical analyses were completed with IBM SPSS Statistics version 23.

Results

Description of cohort

Out of the eight medical centers that provided data of the 328 patients that were included in the original study, five agreed to collect long-term follow-up data which accounted for a total of 249 patients. Two of the remaining centers were not able to collect these data due to lack of manpower and one center did not respond to our invitation. Exclusion of patients with a primary benign diagnosis resulted in a cohort of 229 patients. Baseline variables of this cohort are described in Table 1. The characteristics of the patients included in this analysis are comparable to those of the original cohort (data not shown).

Survival

The survival at six months, one, two and five years postoperatively was 91%, 84%, 77% and 56%, respectively. The median follow-up time was 55 months (95%CI 54-56).

Overall survival per disease stage and PREOP risk score are shown in Table 2. Disease stage and age were statistically significant predictors for increased mortality ($HR_{stage\ 3}$ 3.1; 95% CI 1.8-5.3. $HR_{stage\ 4}$ 6.4; 95% CI 3.6-11.4 HR_{age} 1.1; 95% CI 1.0-1.1.). A high PREOP risk score was a statistically significant predictor for increased mortality ($HR_{PREOP>8}$ 3.1; 95% CI 2.0-4.7), even irrespective of disease stage and age ($HR_{PREOP>8}$ 2.6; 95% CI 1.7-4.0). This multivariable association persisted when the patients who did not survive the first postoperative year were excluded, as an attempt to eliminate the effect of the occurrence of postoperative complications on the association between the PREOP risk score and mortality ($HR_{PREOP>8}$ 2.5; 95% CI 1.5-4.4). The survival functions for the PREOP risk score per disease

Table 1 | Baseline variables of 229 onco-geriatric surgical patients

Variable	No. (%)
Gender	
Female	149 (65)
Male	80 (35)
Age	
70-74	83 (36)
75-79	71 (31)
80-84	52 (23)
≥85	23 (10)
Cancer site	
Breast	67 (29)
Colorectal	81 (35)
Gastric	15 (7)
Gynaecological	13 (6)
Hepatobiliary & pancreatic	23 (10)
Remaining	8 (3)
Renal & bladder	9 (4)
Soft tissue & skin	13 (6)
Stage	
I/II	132 (60)
III	47 (22)
IV	40 (18)
Type of surgery	
Minor	88 (38)
Major	141 (62)
PREOP risk score	
≤8	155 (68)
>8	74 (32)
Living situation preoperatively	
Independent	226 (99)
Dependent	2 (1)

Table 2 | Life table for disease stage and PREOP risk score

	6 months survival (SE)	1 year survival (SE)	2 years survival (SE)	5 years survival (SE)
Stage 1/2	96% (2)	95% (2)	91% (3)	73% (5)
Stage 3	91% (4)	77% (6)	75% (7)	44% (8)
Stage 4	78% (7)	58% (8)	38% (8)	11% (5)
PREOP risk score ≤8	95% (2)	91% (2)	87% (3)	68% (4)
PREOP risk score >8	84% (4)	70% (5)	56% (6)	30% (6)

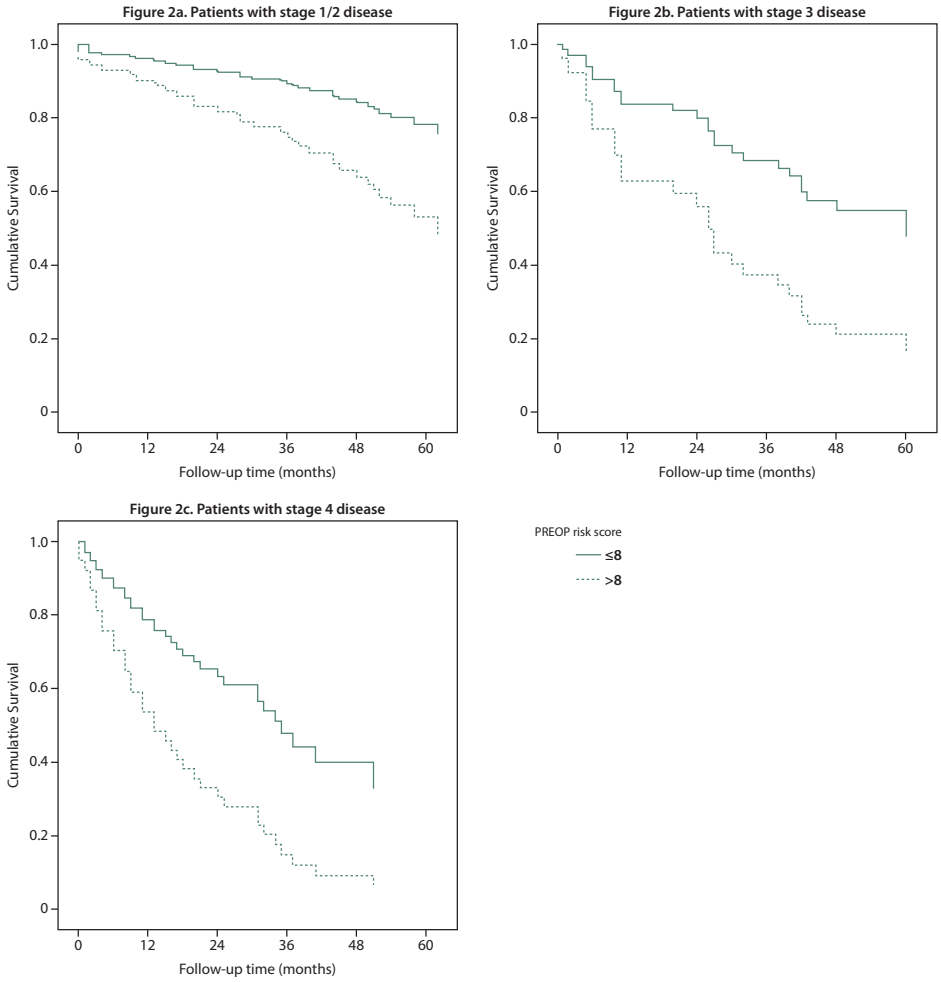

Figure 1 | Survival functions for the PREOP risk score per disease stage

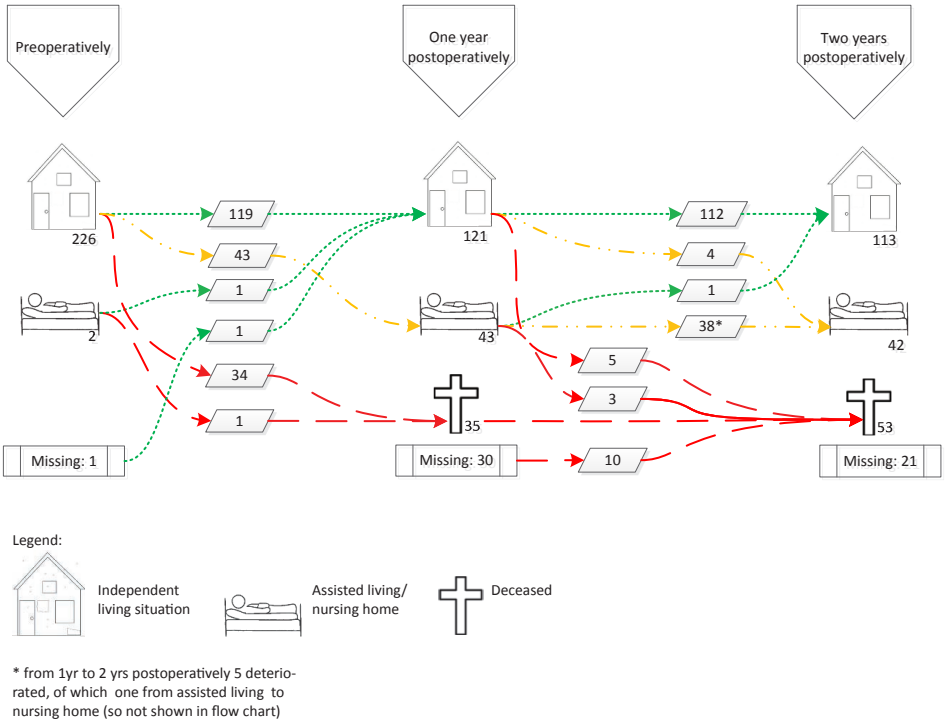

Figure 2 | Living situation preoperatively and at one and two years postoperatively

stage are shown in Figure 1. One-year survival was 70% (standard error (SE) 5%) for patients with a PREOP risk score >8, compared to 91% (SE 2%) for patients with a PREOP risk score ≤8.

Deterioration in living situation

Living situation at one and two years postoperatively are shown in Figure 2. During the first postoperative year, 43 patients (26%) were institutionalized. At two years postoperatively, this number was 42 (27%). When comparing the living situation of patients two years postoperatively to one year postoperatively, one patient improved (0.6%) and five deteriorated in living situation (3%). Out of the two patients that preoperatively lived in a nursing home, one returned to an independent living situation postoperatively and the other patient did not survive the first postoperative year.

Table 3 | Preoperative variables' associations with deterioration of living situation at one year postoperatively[a]

	Independent living situation, No. (%)	Institutionalized, No. (%)	OR (95%CI)[b]
Age			
70-74	46 (38)	12 (28)	1
75-79	40 (33)	10 (23)	1.7 (0.5-5.6)
80-84	27 (22)	15 (35)	**5.0 (1.5-16.2)**
≥85	8 (7)	6 (14)	**6.1 (1.5-25.5)**
Gender			
Female	81 (67)	32 (74)	1
Male	40 (33)	11 (26)	0.7 (0.3-1.8)
Disease stage			
1/2	85 (73)	28 (65)	1
3	21 (18)	8 (19)	0.9 (0.3-2.7)
4	10 (9)	7 (16)	3.6 (0.7-17.5)
Type of surgery			
Minor	61 (50)	19 (44)	1
Major	60 (50)	24 (56)	1.1 (0.5-2.6)
PREOP risk score[c]			
≤8	93 (77)	30 (70)	1
>8	28 (23)	13 (30)	1.6 (0.7-3.8)
Nutritional Risk Screening			
Normal	92 (76)	32 (74)	1
Impaired	29 (24)	11 (26)	1.1 (0.4-2.9)
Timed Up and Go			
≤20	112 (93)	33 (77)	1
>20	9 (7)	10 (23)	**4.5 (1.5-13.4)**
ASA			
<3	71 (59)	16 (37)	1
≥3	50 (41)	27 (63)	**3.3 (1.4-7.9)**

[a] As the deterioration in living situation occurred mainly during the first postoperative year, results with regard to this endpoint were shown.

[b] Univariable odds ratio's, adjusted for center.

[c] PREOP risk score includes: gender, type of surgery, Timed Up & Go, ASA and Nutritional Risk Screening

A PREOP risk score >8 was not statistically significantly associated with a higher risk for institutionalization one year and two years postoperatively (1 yr. vs. preoperatively: OR 1.6; 95% CI 0.7-3.8; 2 yr. vs. preoperatively: OR 2.2; 95% CI 0.9-5.5), whilst age, ASA-classification and Timed Up & Go – components of the PREOP risk score – were (Table 3). The proportion of patients living independently at home was not statistically significantly different between patients with a high and low PREOP risk score (1yr: 68% compared to 76%, p=0.36; 2yrs: 63% compared to 76%, p=0.13).

Discussion

The overall survival rates at six months and one, two and five years postoperatively were 91%, 84%, 77% and 56%, respectively. One-year survival rates were 70% and 91% for patients with a PREOP risk score >8 and ≤8, respectively. Given the patients that were alive one year postoperatively, more than one in every four was institutionalized. By two years postoperatively, almost half of the entire cohort (46%) were institutionalized or had passed away. The PREOP risk score was associated with survival, irrespective of disease stage and age, but not with the risk of institutionalization.

Short term and long-term survival rates in our study were comparable to those of geriatric patients in other cohorts[11, 23-26]. A study by Ommundsen and colleagues is one of few that focused on long-term survival in geriatric colorectal cancer patients, with a five-year survival rate of 48%[23]. Similar to our study, the presence of frailty was accompanied by decreased survival rates, independent of disease stage: five-year survival rates were 24% and 66% in frail and non-frail patients, respectively, where we found 70% and 91% at one year postoperatively.

The PREOP risk score was associated with long-term survival. In the study by Ommundsen, individual geriatric assessment parameters predictive of long-term survival were nutritional status, instrumental activities of daily living and comorbidities, independent of disease stage[23]. In a systematic review conflicting results were found regarding the prediction of survival[33]. In the majority of studies, frailty – according to different definitions – and comorbidity are statistically significantly associated with survival, whilst functional status and nutritional status are mostly not. The presence of frailty – whether identified by an official assessment or established by clinical judgment – might be an explanation for the share of geriatric patients that have been classified as being undertreated as compared to their younger counterparts, in other studies[7-9].

A deterioration in living situation can be considered a proxy for functional status[27], as an increased level of dependency in the activities of daily living and instrumental activities of daily living might eventually lead to institutionalization. By two years postoperatively, in the current study, one in five of all patients was institutionalized, a quarter had died, and roughly half were living independently at home. A postoperative deterioration in functional status is frequently observed, with the prevalence varying from 3% to 69%, depending on the population under study and the type and timing of the endpoint[28-31]. Although a partial recovery is observed during the postoperative course, overall scores of functional status assessments at one year postoperatively infrequently return to their preoperative value[29]. This deterioration occurs predominantly in geriatric patients[31, 32], and especially in the frail[32]. These results point out that geriatric patients are at risk of permanent, or at least long-term, functional decline after surgery.

The fact that the PREOP risk score was not associated with the risk for institutionalization, might be due to a lack of power. Similarly, in the study by Rönning et al., frailty indicators were not predictive of functional decline, which might have been due to a lack of power as well[31]. Another possible explanation for the lack of an association between the PREOP risk score and long-term institutionalization, can be that the PREOP risk score was designed to predict clinical outcomes, whereas risk of institutionalization is also determined by multiple non-clinical factors (i.e. presence of family, financial situation). In our international cohort, cultural differences for example might have also influenced the destination of patients with functional decline[38]. Finally, over a two years' time period, other factors than the index surgery, such as comorbidities or (treatment of) recurrence of disease, might have contributed to functional decline, subsequently leading to institutionalization.

In contrast, we did observe an association between a high Timed Up & Go score and long-term institutionalization. Other studies also found that impaired preoperative functional status and the occurrence of postoperative complications are associated with postoperative functional decline[30, 32]. Functional decline can be seen as a result of a protracted postoperative course in patients with reduced physiological reserves at the start of their treatment. The positive effects of prehabilitation on postoperative outcomes in different studies imply that patients might be able to improve their PREOP risk score and reduce their risk of adverse outcomes[35-37].

The current study has a few limitations. First, there is the lost to follow-up, as over time a number of patients died and thus the sample size decreased, which is inherent to this age-group. This lost to follow-up limited the number of variables that could be included in the statistical models and it also did not allow for the presentation of stratified analyses per cancer site. In addition, there were three centers that did contribute to the short-term outcome, but not to the long-term outcome. This was due to logistical instead of patient-related reasons.

As long-term institutionalization is a quite crude measure for functional decline, the magnitude of this problem is likely underestimated by our results as it only includes the patients that deteriorated the most. Nevertheless, the prevalence emphasizes the importance of this outcome measure in the onco-geriatric patient population and, to our knowledge, the current study is the first to provide data on impact of surgery on long-term institutionalization in this population. Finally, external validation of the PREOP risk score is needed, in order to determine the generalizability of this screening tool.

The current study aimed to provide data on long-term outcome in onco-geriatric surgical patients, in order to support the shared decision-making process in daily clinical practice. We want to emphasize that increasing age itself should not be a factor that withholds surgeons from performing surgery with curative intent on the geriatric patient population, as our data showed that survival rates were rather good, and the majority of patients was able to stay independently at home, even after undergoing invasive cancer treatments. Patients with a PREOP risk score ≤8 have a high chance of an uncomplicated course up to two years postoperatively, whereas attention is needed when patients score poorly as their postoperative course is not well anticipated. Furthermore, we point out that, although we might be able to cure our patients, that does not necessarily imply that our patients will return to their preoperative level of functioning. Awareness of this fact, both by physicians as well as by patients, is of the utmost importance. It is imperative to preoperatively discuss treatment goals and expectations, and verify their feasibility by comparing it to a risk assessment for this individual patient based upon objective parameters.

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7

Summary and general discussion

Summary of main findings

The aim of this thesis was to provide data on predicting the risk for adverse postoperative outcomes in onco-geriatric patients, in order to raise more awareness to the different approaches that this growing group of patients needs, and to provide scientifically substantiated recommendations for daily clinical practice. For that, a systematic review of systematic reviews as well as the PREOP-study were performed.

The systematic review on the predictive ability of the most commonly included domains in a GA regarding adverse postoperative outcomes in onco-geriatric surgical patients **(chapter 2),** confirmed the heterogeneity that exists not only in the patient population at hand, regarding their level of fitness, but also in the studies itself. Differences in study populations, domains included in the study and in tools used to assess those domains make comparisons between studies difficult and a formal meta-analysis impossible. Nevertheless, this systematic review aimed to present all data available in a transparent and systematic manner. By presenting the different univariable and multivariable models, the negative results if present, and the percentage of onco-geriatric surgical patients per cohort, we allow the reader to evaluate the strength of the evidence themselves. The GA domains under investigation were all, but polypharmacy, predictive of at least one of the evaluated endpoints. The presence of frailty – defined by either a composite GA score, a cumulative number of GA impairments or by Fried's frailty phenotype[1] – was frequently associated with the occurrence of adverse outcomes, which denotes that the presence of multiple impairments poses patients at an increased risk. Furthermore, comorbidity as measured with the Cumulative Illness Rating Scale, was frequently associated with survival. For functional status, conflicting results were found, but its assessment is nevertheless advised as it is often associated with impairments in other domains[2, 3]. Functional impairment influences the degree of autonomy of elderly patients and preoperative optimization of this domain might improve outcomes[4]. This latter can apply to the domains of nutritional status and mood as well[4, 5]. In addition, the assessment of cognitive status is recommended, not necessarily in relation to the risk of adverse outcomes, but more in the light of estimating a person's ability to oversee his or her treatment options and its accompanying consequences regarding complications, functional outcomes and mortality[6].

The effectiveness of two screening tools, the Timed Up and GO (TUG) and the American Society of Anaesthesiologists (ASA)-classification, in predicting adverse postoperative

outcomes in onco-geriatric patients was described in **chapter 3**. The majority of the 263 patients, with a median age of 76 years, underwent major surgery (n=164, 62%). Almost half of the cohort experienced complications (n=123, 47%), of which 50 were classified as major complications according to the Clavien-Dindo classification, including death in 9 patients[7]. A prolonged length of stay was frequently observed (51%), and in 17% of the patients more than 3 specialists were involved in postoperative care. A TUG >20 seconds was predictive of these endpoints in multivariable analysis. ASA ≥3 was predictive of the occurrence of major complications and the need for more than 3 specialists. The TUG had better positive predictive value and higher specificity than the ASA-classification. The TUG and ASA-classification combined as a composite score, was predictive of all endpoints, but it showed no real added value as compared to the TUG alone.

In **chapter 4** all geriatric screening tools included in the PREOP-study, were analysed regarding the predictive ability of major 30-day complications. For this analysis, data of 328 patients (62% female) with a median age of 76 years were analysed, of which 223 (68%) underwent major surgery. Colorectal and breast cancer were most prevalent (37% and 25%, respectively) and 36% was diagnosed with stage 3 or stage 4 disease. Complications were observed in more than half of all patients (n=167, 51%) and 61 patients (19%) experienced major complications, of which 11 died. The PREOP risk score was based on multivariable logistic regression analysis and comprised gender, type of surgery, TUG, ASA-classification and the Nutritional Risk Screening (NRS). Male gender, a TUG of >20 seconds, an ASA-classification ≥3 and an impaired nutritional status according to the NRS are all worth three points and undergoing major surgery is worth four points, with zero being the reference value. The sum of these points constitutes the PREOP risk score. The area under de receiver operating characteristic curve (AUC ROC) was 0.81 (95%CI 0.75-0.86) and based on the ROC a cut-off point for the score was set at 8. The negative predictive value (no complications in patients with a PREOP ≤8) was 94%, which endorses its value as a screening tool. Implementation of the score in clinical practice can follow upon external validation.

As an attempt to better understand the multifactorial aetiology of an impaired nutritional status in onco-geriatric patients, as measured by the NRS, the associations between impairments in this domain and other geriatric domain impairments were investigated **(chapter 5)**. Whilst the patients in this cohort were all considered fit for surgery, an impaired nutritional status was still observed in 35% of the 309 patients. Advanced stage, intra-abdominal tumours and an increased number of comorbidities were associated with an increased risk of an impaired

nutritional status. A decreased performance status, signs of depression and an impaired functional status (according to the ADL and IADL tools) were the geriatric domains that were statistically significantly associated with the risk of an impaired nutritional status. In patients with a normal nutritional status, only 9% experienced major complications, compared to 36% of the patients with an impaired nutritional status. Ten out of the eleven patients that died, had an impaired nutritional status.

Long-term survival in the PREOP-cohort was rather good and comparable to survival rates in other geriatric cohorts **(chapter 6)**[8-12]. One- and five-year survival were 84% and 56%, respectively. The patients in the current cohort are a selected part of the onco-geriatric population, as a treatment decision, i.e. to perform surgery, had already been made and these patients were thus considered fit for surgery. Extrapolating the results to the entire onco-geriatric population should therefore happen with care. Nevertheless, a survival difference between patients with a PREOP risk score >8 and a PREOP risk score <8 was observed: 70% as compared to 91% one-year survival. This score was associated with survival, independent of disease stage and age. Of the patients alive one year postoperatively, 43 (26%) were institutionalized. At two years postoperatively only 54% was living independently. The PREOP risk score was not associated with risk of institutionalisation.

General discussion

Implications for clinical practice

The main findings of this thesis emphasize the importance of the implementation of preoperative GA in daily clinical practice, as a tool for risk estimation. An important part of the cohort did well after surgery, according to our endpoints included, and this corroborates that (potentially) curative treatment should not be withheld solely based on increasing age. Concurrently, reminding ourselves that the PREOP-study cohort comprises a selected cohort. Undertreatment of onco-geriatric patients based on age was suspected by several studies, that found geriatric patients were less often treated according to oncology treatment guidelines as compared to non-geriatric patients[13-16]. On the other hand, however, approximately one in five patients in the PREOP-study suffered from major complications, i.e. complications that required surgical, endoscopic or radiological interventions or admission to the Intensive Care Unit, or that even led to death. Preoperative determination of an increased risk for major adverse outcomes might presumably lead to conscious disregard of standard treatment protocols, with the aim of providing the best possible care for this individual patient. For

example, by primarily deciding for an ostomy instead of a primary anastomosis, to avoid complications such as anastomotic leakage or faecal incontinence. Patient tailored treatment deviating from guidelines will lead to better outcome and cannot simply be classified as undertreatment.

Following the results of the systematic review, it can be concluded that a preoperative risk-estimation of adverse postoperative outcomes can be performed in different ways and by assessing different geriatric domains. The PREOP-study identified functional status, nutritional status and ASA-classification as factors associated with adverse postoperative outcomes, such as complications and mortality. However, Dutch population-based studies identified comorbidity as an important factor related to adverse outcomes and possibly to undertreatment as well[17-20]. Geriatric patients with more comorbidities, especially cardiovascular disease, diabetes and COPD, were treated less aggressively for certain types of cancer, and their survival rates were frequently worse as compared to those of geriatric patients with less or no comorbidity[17-20]. An advantage of these population-based studies, as compared to observational studies, is the absence of selection bias. A disadvantage is that it lacks individual patient data, such as information regarding the presence of GA-domain impairments, the severity of present comorbidities and the reasons as to why certain treatment guidelines were disregarded.

Tailored treatment is nowadays widely accepted in oncology and the pre-treatment work-up is expanded with often expensive tests to allow for this[21, 22]. Preoperative risk screening in onco-geriatric patients fits very well in this diagnostic work-up and is easily performed and in-expensive. The preoperative assessment could have different implications, such as – indeed – making the decision not to forego with standard treatment or, on the contrary, to support the presumption that a patient is fit for surgery. Furthermore, patients at an increased risk, selected to undergo surgery, might benefit from further comprehensive assessments. Involvement of a geriatrician might be warranted for 1) performing these assessments, 2) proposing targets for preoperative optimisation, 3) implementation and follow-up of the effect of preoperative optimization strategies, and/or 4) performing a more consulting role regarding the different treatment options in the light of his or her geriatric expertise. This involvement could take shape in an interdisciplinary meeting specifically for geriatric oncology patients[23]. For these reasons, the collaboration with geriatricians should become more acknowledged in the management of onco-geriatric surgical patients.

Next to the collaboration with geriatricians, the importance of consultation of the general practitioner (GP) should be stressed. The GP often has a long-standing relation with the patient and its family, especially if the patient already presents with substantial comorbidity or frailty. Information regarding these matters, as well as the opinion of the GP on certain social or medical issues are of great value. Whilst participation in interdisciplinary meetings might be unfeasible due to logistical reasons, their input could be collected beforehand via teleconsultation using structured templates[24].

Implications for education

Performing preoperative risk assessments, being able to advise patients on their treatment options, engaging in interdisciplinary discussions on (onco-)geriatric patients and anticipating the postoperative course, requires adequate training on these matters and makes integration of geriatrics into the surgical training programme a precondition[25]. A way to achieve this, could be by means of combined education sessions with residents in geriatrics and surgery. The above-mentioned topics can be taught by experts in both geriatrics as well as in 'geriatric surgery', and the residents could team up and discuss cases and exchange points of view on topics such as shared-decision making, geriatric assessment and advanced care planning. In addition, mutual learning programmes might lead to better interdisciplinary collaboration and efficient utilisation of each other's expertise.

Communication is another competency that needs to be addressed, as conversations with geriatric patients often require a different approach: treatment goals and options can differ, and a more prominent role for advanced care planning may be required[25]. Elderly patients value preservation of functional status and prolongation of life, when it is accompanied with at least a certain level of quality of life, often as the most important outcomes[26, 27]. In the PREOP-study, more than a quarter of the patients still alive at one and two years postoperatively were institutionalised **(chapter 6)**. The absence of caregivers at home and an impaired level of functioning, are important risk factors for institutionalisation[28]. Functional deterioration after surgery in onco-geriatric patients is prevalent and sometimes permanent, especially when functional impairments are present preoperatively[29-32]. It can be assumed that postoperative institutionalisation, accompanied by a deterioration of functional status, leads to loss of quality of life. The possibility of these outcomes and the risks thereof need to be discussed and taken into consideration when a treatment plan is made. When a patient is frail, at increased risk for adverse outcomes, or is hesitant to undergo major surgery, it can be decided upon to not forego with surgical treatment. In that case, additional advanced care planning is essential.

Implications for future research

Several questions and remarks have arisen after performing the studies and writing this thesis, that could be subject to future studies. Examples include adding Patient Reported Outcome Measures (PROMs) as an endpoint to clinical studies in order to facilitate tailored treatment, investigating the effect of prehabilitation on postoperative outcomes and investigating the possible underlying construct of preoperative geriatric domain impairments and the accompanying risk of adverse postoperative outcomes in onco-geriatric patients.

Patient Reported Outcome Measures

In addition to the typical clinical outcome parameters, such as postoperative complications and survival, future studies should incorporate patient reported outcome measures (PROMs) more often. Examples of PROMs are health related quality of life, physical functioning and symptom severity. A major challenge when it comes to assessing PROMs, is to apply valid tools. In other words: does the tool measure what you aim to measure? Other challenges, that specifically go for the (frail) elderly study population, include minimizing the risk of participating in a study being too burdensome and assuring that the population of interest can understand and fill in the instrument[33]. As a result, inclusion rates can fall short, leading to logistical problems and reduced quality of the resulting evidence[33]. By joining forces, for example by the international collaboration of SIOG and its taskforces, inclusion rates can be improved, and the strength of the resulting evidence can be increased.

Incorporating PROMs in clinical research, as an endpoint, is useful and important as patients value these endpoints most[26, 27]. On top of that, more knowledge on long-term functional outcomes and health related quality of life in onco-geriatric patients might facilitate the preoperative shared decision-making process, it improves the ability to anticipate the needs of this growing group of patients, and this also allows for more efficient allocation of resources such as postoperative counselling and referral to rehabilitation facilities. The incorporation of PROMs in clinical research and everyday care will be yet another step towards providing tailored treatment in onco-geriatric surgical patients.

Prehabilitation

Improving a patient's resilience to a surgical stressor, by means of improving physical fitness and nutritional status, and by attempting to reduce stress levels, sounds apparent. Allocating interventions to those who are expected to benefit most, is efficient and would imply that the onco-geriatric population with multidomain impairments, is *the* population of interest.

Authors of a recently published RCT claimed to be the first to provide for robust evidence on the effectiveness of prehabilitation in patients at increased risk for adverse outcomes (>70 years of age and/or classified as ASA III/IV) undergoing major abdominal surgery[34]. The patients in the intervention group were subjected to a prehabilitation program that consisted of a motivational interview, promotion of regular physical activity and a supervised high-intensity endurance training. A positive effect on the number of complications was found in the intervention group, as compared to the control group (31% versus 62%, respectively).
Additionally, when designing prehabilitation studies for onco-geriatric surgical patients, optimising not only the functional domain, but also nutritional status and mood might be key to improving outcome in this high-risk population[chapter 5, 4].

The inflammatory response as possible underlying construct to preoperative geriatric domain impairments and adverse postoperative outcomes

Next to intervening on the presumed causal relationship between preoperative impairments of the functional and nutritional domains and adverse postoperative outcomes by means of prehabilitation, it is interesting to explore what might be (part of) the underlying construct of the association between geriatric domain impairments and adverse outcomes in onco-geriatric surgical patients. As already postulated in **chapter 5**, the covering link might be that of inflammatory responses. First, aging is associated with a low-grade inflammatory state, and pro-inflammatory cytokines appear to be increased in patients with geriatric domain impairments, which are again associated with increased mortality[35-37]. Cancer can be associated with systemic inflammation in the light of cancer cachexia, which is defined as 'a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass, that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment', which is associated with increased risk of mortality as well[38]. Finally, studies have indicated that an inflammatory response to surgery plays a central role in the development of postoperative complications[39, 40].

In conclusion

Preoperative geriatric assessment and identification of patients at increased risk of adverse outcomes enable tailored treatment, ultimately leading to improved quality of care and better postoperative outcomes in onco-geriatric surgical patients. For this, collaboration with geriatricians and patients' GP's should be encouraged and courses on 'geriatrics in surgery' should be evolved and implemented in the surgical training programme. Finally, suggestions for future research include the assessment of PROMs to enhance tailored treatment, further

exploring the effect of multimodal prehabilitation in onco-geriatric patients at increased risk of adverse postoperative outcomes, and investigating inflammation and the operative inflammatory response as the possible underlying construct.

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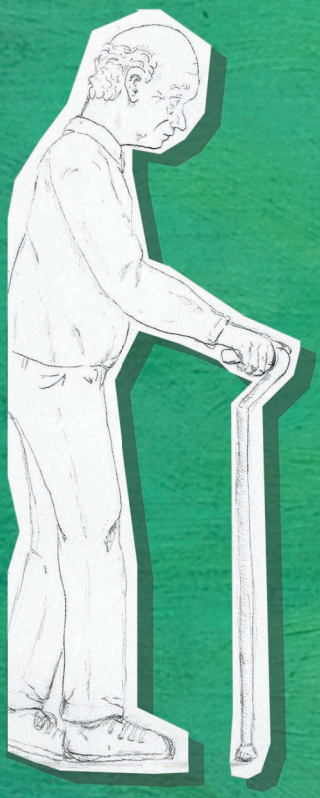

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Nederlandstalige samenvatting (Summary in Dutch)

Samenvatting

Oudere patiënten met kanker, ook wel onco-geriatrische patiënten genoemd, lopen grotere risico's op ongunstige uitkomsten na een operatie. In vergelijking met jongere patiënten, die vaak fitter zijn en sneller herstellen, hebben deze oudere patiënten meer kans op postoperatieve complicaties, inclusief mortaliteit, en verlies van functie en zelfstandigheid. Het doel van dit proefschrift is om risico's op ongunstige uitkomsten van de operatie bij deze patiënten te identificeren. Op deze manier wordt een bijdrage geleverd aan de bewustwording dat deze groep onco-geriatrische patiënten mogelijk een andere benadering nodig heeft dan jongere patiënten. Verder voorziet het in wetenschappelijk onderbouwde adviezen voor de zogeheten preoperatieve geriatrische screening in de dagelijkse klinische praktijk.

Om deze doelen te bereiken, werd een systematische review van uitgebrachte studies geschreven en werd de PREOP-studie uitgevoerd. PREOP staat voor Preoperative Risk Estimation for Onco-geriatric Patients. Met deze studie onderzochten we het voorspellend vermogen van verschillende geriatrische screeningsinstrumenten ten aanzien van ongunstige postoperatieve uitkomsten. Met deze geriatrische screeningsinstrumenten werden verschillende onderdelen – ook wel domeinen genoemd – beoordeeld, die vaak in een geriatrisch assessment (GA) voorkomen. Het GA is, kort gezegd, een uitgebreid onderzoek dat verschillende domeinen en beperkingen daarin in kaart brengt bij oudere patiënten. Het GA omvat meestal de domeinen functionele status (hoe functioneert iemand), voedingsstatus, cognitie (vermogen om informatie te verwerken), sociale steun, stemming, comorbiditeit (de aanwezigheid van andere aandoeningen naast de ziekte waaraan de patiënt geopereerd wordt) en polyfarmacie (meervoudig medicijnengebruik). Voor deze studie werden patiënten van 70 jaar en ouder geïncludeerd, die electief werden geopereerd vanwege een voor maligniteit verdachte solide tumor. De postoperatieve eindpunten waren ongunstige uitkomsten op de korte en lange termijn.

De systematische review was gericht op studies waarin onderzoek is gedaan onder onco-geriatrische patiënten, naar het voorspellend vermogen van beperkingen in verschillende GA-domeinen ten aanzien van ongunstige uitkomsten na een operatie **(hoofdstuk 2)**. Deze review bevestigde dat er niet alleen sprake is van heterogeniteit binnen de onco-geriatrische chirurgische studiepopulatie wat betreft mate van fitheid van deze patiënten, maar dat er ook grote verschillen zijn tussen de studies. Die verschillen hebben betrekking op studiepopulaties, bestudeerde domeinen en de instrumenten die zijn gebruikt om de domeinen te beoordelen.

Dit maakt het lastig om studies te vergelijken en dit stond een formele meta-analyse in de weg. Deze review was erop gericht om alle beschikbare data op een transparante en systematische manier te presenteren, zodat de lezer zelf de mogelijkheid krijgt om de bewijskracht te bepalen. De onderzochte GA domeinen waren allemaal, op polyfarmacie na, voorspellend voor minstens één van de onderzochte postoperatieve uitkomsten. De aanwezigheid van 'frailty' ofwel kwetsbaarheid – gedefinieerd als een samengestelde GA score, het cumulatieve aantal GA beperkingen, of als 'Fried's frailty phenotype'[1] – werd frequent in verband gebracht met ongunstige uitkomsten na de operatie. Dat geeft aan dat meerdere beperkingen bij een patiënt leiden tot een hoger operatierisico. Comorbiditeit, indien vastgesteld met 'the Cumulative Illness Rating Scale', werd frequent geassocieerd met overleving. Voor functionele status, als GA domein, werden tegenstrijdige resultaten gevonden. Desondanks adviseren we inclusie van dit domein, omdat het vaak in verband is gebracht met beperkingen in andere domeinen[2,3].

Beperkingen in functionele status beïnvloeden de mate van autonomie van oudere patiënten. Optimalisering van deze status vóór de operatie zou kunnen leiden tot betere postoperatieve uitkomsten[4]. Dit laatste kan ook van toepassing zijn op de domeinen voedingsstatus en stemming[4,5]. In aanvulling op de reeds genoemde domeinen, adviseren we ook de cognitieve status van de patiënt te beoordelen. Niet zozeer omdat deze status van invloed zou zijn op mogelijke ongunstige uitkomsten, maar meer omdat een patiënt met goed functionerende cognitieve functies beter in staat is de behandelopties te overzien[6]. En daarmee ook mogelijke complicaties, functionele uitkomsten en mortaliteit.

De effectiviteit van 2 geriatrische screeningsinstrumenten, de Timed Up and Go (TUG) en de American Society of Anaesthesiologists (ASA)-classificatie, in het voorspellen van ongunstige postoperatieve uitkomsten in onco-geriatrische patiënten is beschreven in **hoofdstuk 3**. De TUG is een makkelijk uit te voeren screeningsinstrument dat wat zegt over iemands spierkracht en loopsnelheid[1]. Bij de TUG wordt de tijd gemeten die iemand nodig heeft om op te staan uit een stoel, drie meter te lopen, om te draaien, terug te lopen en weer te gaan zitten. De ASA-classificatie is een veel gebruikte perioperatieve maat voor de algehele gezondheidstoestand van een patiënt, met een range van 1 (een gezonde patiënt, behoudens de te opereren afwijkingen) tot 5 (er is sprake van een afwijking waaraan de patiënt zonder operatie waarschijnlijk binnen 24 uur zal overlijden)[2].

De meerderheid van de 263 geïncludeerde patiënten, met een mediane leeftijd van 76 jaar, onderging een zware operatie, zoals bijvoorbeeld een buikoperatie (n=164, 62%). Bijna de

helft van het cohort ontwikkelde complicaties (n=123, 47%), waarvan 50 ernstig volgens de Clavien-Dindo classificatie[7]. Van deze 50 overleden er 9 binnen 30 dagen na de operatie. Er was vaak sprake van een verlengde opnameduur (51%), en bij 17% van de patiënten waren postoperatief meer dan 3 specialismen in consult.

Een TUG van >20 seconden was voorspellend voor deze eindpunten in multivariabele analyses. ASA ≥3 was voorspellend voor het optreden van ernstige complicaties en voor de noodzaak tot betrokkenheid van meer dan 3 specialismen. De TUG had een betere voorspellende waarde en hogere specificiteit dan de ASA-classificatie. De TUG en ASA-classificatie als gecombineerde score, was voorspellend voor alle eindpunten, maar had geen toegevoegde waarde ten opzichte van de TUG alleen.

In **hoofdstuk 4** zijn alle geriatrische screeningsinstrumenten, die geïncludeerd waren in de PREOP-studie, geanalyseerd met betrekking tot hun voorspellende waarde van ernstige complicaties binnen 30 dagen na de operatie. Op basis daarvan werd de PREOP-risicoscore ontwikkeld. Hiervoor werden data geanalyseerd van 328 patiënten, met een mediane leeftijd van 76, waarvan 62% vrouw. Totaal ondergingen 223 (68%) zware operaties. Colorectaal carcinoom en borstkanker kwamen het meest voor (respectievelijk 37% en 25%), en bij 36% was sprake van gevorderde ziekte (stadium 3 of 4). Van complicaties was sprake in meer dan de helft van de gevallen (n=167, 51%), en 61 patiënten (19%) ontwikkelden ernstige complicaties, waarvan 11 patiënten zijn overleden.

De PREOP-risicoscore is gebaseerd op multivariabele logistische regressie en omvat geslacht, type operatie, TUG, ASA-classificatie en voedingsstatus volgens de Nutritional Risk Screening (NRS). Aan mannelijk geslacht, een TUG van >20 seconden, ASA ≥3 en een verminderde voedingsstatus worden ieder drie punten toegekend, waarbij nul de referentiewaarde is. Het ondergaan van een zware operatie is 4 punten waard, tegenover 0 punten voor een minder zware operatie, zoals bijvoorbeeld een ingreep in verband met borstkanker. Het totaal aantal punten (maximaal 16) is de PREOP-risicoscore.

De accuratesse van de score werd getest door het meten van de oppervlakte onder de 'receiver operating characteristic' curve (ROC). Deze was goed, met een oppervlakte onder de curve van 0.81 (95% betrouwbaarheidsinterval 0.75-0.86). Op basis van de ROC werd het afkappunt voor een hoge, dan wel lage PREOP-risicoscore gesteld op 8. De negatief voorspellende waarde was 94% (het percentage patiënten zonder complicaties onder de patiënten met een PREOP-risicoscore ≤8). Dit onderstreept de waarde van deze score als screeningsinstrument, omdat

je daarvoor zo min mogelijk vals negatieve uitslagen wilt hebben. De reproduceerbaarheid van de PREOP-risicoscore in andere populaties (externe validatie) is nog een belangrijke stap alvorens we de score in de praktijk kunnen implementeren.

In **hoofdstuk 5** werd dieper ingegaan op de preoperatieve voedingsstatus van de onco-geriatrische patiënten. Daarbij werden verbanden tussen een verminderde voedingstoestand en beperkingen in andere GA domeinen onderzocht. Wat opviel was dat wel 35% van de 309 patiënten een verminderde voedingstoestand had, terwijl het cohort bestond uit patiënten die geopereerd waren en dus 'fit for surgery' werden geacht.

Gevorderde ziekte (stadium 3 of 4), intra-abdominale tumoren en de aanwezigheid van meer comorbiditeit waren geassocieerd met een hoger risico op een verminderde voedingstoestand. Een verminderde performance status, tekenen van depressie en een verminderde functionele status (gemeten met de 'Activities of Daily Living' en 'Instrumental Activities of Daily Living' screeningsinstrumenten) waren de geriatrische domeinen die statistisch significant geassocieerd waren met het risico op een verminderde voedingstoestand.

Van de patiënten met een normale voedingstoestand, ontwikkelde slechts 9% ernstige complicaties, vergeleken met 36% van de patiënten met een verminderde voedingstoestand. Tien van de elf patiënten die zijn overleden, hadden een verminderde voedingstoestand.

In **hoofdstuk 6** werd de langetermijnoverleving van het PREOP-cohort in kaart gebracht. Deze was redelijk goed en vergelijkbaar met de overleving van onco-geriatrische chirurgische patiënten in andere cohorten[8-12]. De één- en vijfjaarsoverleving waren respectievelijk 84% en 56%. Hierbij is het belangrijk dat we ons realiseren dat het PREOP-cohort een geselecteerde groep was onder de onco-geriatrische patiënten. Deze patiënten werden fit genoeg bevonden om een operatie te ondergaan en deel te nemen aan het onderzoek. Men moet dus voorzichtig zijn met het extrapoleren van de hier gepresenteerde resultaten naar de gehele onco-geriatrische patiëntenpopulatie. Desalniettemin was er wel sprake van een statistisch significant verschil in overleving tussen patiënten met een PREOP-risicoscore >8 en die met een score ≤8: 70% versus 91% één-jaarsoverleving. De PREOP-risicoscore was geassocieerd met overleving, onafhankelijk van het ziektestadium en van leeftijd.

Van de patiënten die na één jaar nog in leven waren, waren er 43 (26%) opgenomen in een verpleeg- of verzorgingstehuis. Twee jaar na de operatie woonde slechts 54% van het totale

initiële cohort nog in hun eigen huis. De rest van de patiënten was overleden of woonde inmiddels in een verpleeg- of verzorgingstehuis. De PREOP-risicoscore was niet geassocieerd met het risico op opname in een verpleeg- of verzorgingstehuis.

Discussie

Implicaties voor de dagelijkse praktijk

De bevindingen van dit proefschrift onderstrepen het belang van de implementatie van een preoperatief geriatrisch assessment in de dagelijkse praktijk, als een manier om preoperatief het risico op ongunstige postoperatieve uitkomsten in te schatten. Een groot deel van het cohort verging het na de operatie goed, volgens de door ons geïncludeerde eindpunten. Dit bevestigt dat we de oudere patiënten (potentieel) curatieve behandelingen niet moeten onthouden op basis van hogere leeftijd alleen. Hierbij moeten we ons er tegelijkertijd bewust van zijn dat de PREOP-studie bestaat uit een geselecteerde groep patiënten, namelijk die patiënten die goed genoeg zijn om aan een onderzoek mee te doen en bij wie al was besloten tot een operatie.

Uit verschillende studies is de suggestie gerezen dat er sprake is van onderbehandeling van onco-geriatrische patiënten die mogelijk samenhangt met leeftijdsdiscriminatie. Deze studies stelden vast dat geriatrische patiënten minder vaak worden behandeld volgens de geldende oncologische behandelrichtlijnen dan jongere patiënten[13-16]. Echter, aan de andere kant stelden we in de PREOP-studie vast dat ongeveer één op de vijf patiënten ernstige complicaties ontwikkelde. Dit waren complicaties waarvoor chirurgische, endoscopische of radiologische interventies nodig waren, waarvoor patiënten opgenomen dienden te worden op de intensive care of waaraan zij zelfs kwamen te overlijden.

Wanneer preoperatief een verhoogd risico op ernstige postoperatieve complicaties wordt vastgesteld, kan dat een reden zijn om bewust van een richtlijn af te wijken, met juist als doel de best mogelijke zorg te bieden aan de individuele patiënt. Een voorbeeld hiervan is om er primair voor te kiezen een stoma aan te leggen in plaats van een anastomose te maken, teneinde complicaties zoals naadlekkage of fecale incontinentie te vermijden. Zorg op maat, en daarbij mogelijk afwijken van geldende behandelrichtlijnen leidt tot betere uitkomsten en kan niet zonder meer geclassificeerd worden als onderbehandeling.

Zoals beschreven in de systematische review, kan een preoperatieve risico-inventarisatie

verschillende vormen aannemen en verschillende onderdelen bevatten. Met de PREOP-studie werden de functionele status, voedingstoestand en ASA-classificatie geïdentificeerd als factoren die geassocieerd zijn met ongunstige postoperatieve uitkomsten, zoals complicaties en overleving. Echter, uit Nederlandse population-based studies bleek dat aanwezigheid van comorbiditeit in belangrijke mate geassocieerd is met ongunstige uitkomsten en mogelijk met het risico op onderbehandeling[17-20]. Oudere patiënten met meer comorbiditeit, met name cardiovasculaire aandoeningen, diabetes en COPD, werden in geval van sommige soorten kanker minder agressief behandeld en hun overleving was vaak slechter dan dat van oudere patiënten zonder comorbiditeit[17-20]. Een voordeel van deze studies, ten opzichte van observationele studies, is dat er geen sprake is van selectie-bias. Een nadeel is dat het geen individuele patiënt data bevat, waaronder bijvoorbeeld informatie over de aanwezigheid van beperkingen in verschillende GA-domeinen, de ernst van de comorbiditeit en de reden om af te wijken van een reguliere behandelrichtlijn.

Zorg op maat – ofwel 'tailored treatment' – is tegenwoordig een breed geaccepteerd begrip in de oncologie en de work-up van oncologische patiënten omvat tegenwoordig vaak kostbare testen om dit te faciliteren[21,22]. Preoperatieve risico-inventarisatie bij onco-geriatrische patiënten draagt bij aan het bieden van zorg op maat en is bovendien makkelijk uitvoerbaar en goedkoop. Zo'n risico-inventarisatie kan verschillende gevolgen hebben. Het kan de inschatting van de arts ondersteunen: ofwel dat een patiënt 'fit for surgery' is, ofwel dat dit niet het geval is, waardoor men kan besluiten om van de standaardbehandeling af te wijken. Verder kunnen patiënten, bij wie een verhoogd risico op ongunstige postoperatieve uitkomsten is vastgesteld, baat hebben bij een meer uitgebreide GA. Daarbij kan de betrokkenheid van een geriater of specialist ouderengeneeskunde van belang zijn om meerdere redenen, zoals 1) uitvoeren van deze uitgebreide assessments, 2) voorstellen van domeinen die preoperatief geoptimaliseerd kunnen worden, 3) implementeren en follow-up van preoperatieve optimalisatie strategieën, en/of 4) adviezen geven vanuit zijn of haar specifieke expertise ten aanzien van de geschiktheid van de verschillende behandelopties. Deze betrokkenheid kan bewerkstelligd worden door middel van multidisciplinaire besprekingen specifiek gericht op de onco-geriatrische patiënten[23]. Een goede samenwerking tussen chirurgen en geriaters of specialisten ouderengeneeskunde is om deze redenen zeer belangrijk wanneer het gaat om de zorg voor onco-geriatrische patiënten en derhalve moet dit in ziekenhuizen gefaciliteerd worden.

Naast de samenwerking met geriaters of specialisten ouderengeneeskunde, moet het belang

van de rol van de huisarts benadrukt worden. De huisarts heeft vaak al een langer bestaande behandelrelatie met de patiënt en zijn of haar familie, vooral wanneer het een kwetsbare patiënt of een patiënt met veel comorbiditeit betreft. Informatie omtrent deze zaken, maar ook de mening van de huisarts wat betreft bepaalde sociale en medische factoren kunnen zeer waardevol zijn. Deelname van huisartsen aan multidisciplinaire besprekingen zal logistiek niet haalbaar zijn, maar hun input zou bijvoorbeeld gerealiseerd kunnen worden middels teleconsultatie, waarbij gebruik kan worden gemaakt van gestructureerde templates[24].

Implicaties voor onderwijs

Uitvoeren van preoperatieve risico-inventarisaties, patiënten adviseren ten aanzien van hun behandelopties, deelnemen aan multidisciplinaire discussies over (onco-)geriatrische patiënten en anticiperen op het postoperatieve beloop, vereisen adequate training. Integratie van geriatrie in het chirurgische curriculum is daarvoor een belangrijke randvoorwaarde[25]. Een manier om dit te bereiken is door gemeenschappelijk onderwijs voor arts-assistenten geriatrie/ouderengeneeskunde en chirurgie te organiseren. Dit onderwijs kan bestaan uit lezingen over de bovengenoemde onderwerpen door geriaters of chirurgen met 'de geriatrische patiënt' als aandachtsgebied. Verder kunnen arts-assistenten gezamenlijk casuïstiek bespreken en gezichtspunten delen ten aanzien van gezamenlijke besluitvorming (d.w.z. in samenspraak met de patiënt), het geriatrisch assessment en bespreken van de gewenste zorg in de fase van levenseinde, ofwel advanced care planning. Volgen van gezamenlijk onderwijs kan bovendien leiden tot betere interdisciplinaire samenwerking en efficiënter gebruik van elkaars expertise. Communicatie en gespreksvoering zijn competenties die ook speciale aandacht verdienen in het licht van het onderwerp van dit proefschrift, aangezien gesprekken met geriatrische patiënten vaak een andere benadering vereisen: behandeldoelen en -opties kunnen anders zijn, en er kan sprake zijn van een prominentere rol voor advanced care planning[25]. Verder moet men in het oog houden wat belangrijke eindpunten zijn die men na moet of kan streven. Zo waarderen geriatrische patiënten behoud van functionele status en levensverlenging, wanneer het gepaard gaat met een zekere kwaliteit van leven, als belangrijkste uitkomsten[26, 27].

Meer dan een kwart van de patiënten in de PREOP-studie die na één en twee jaar postoperatief nog in leven waren, woonden niet meer thuis, maar in een instelling **(hoofdstuk 6)**. Als er geen mantelzorg is en de patiënt beperkt is in zijn of haar functioneren, is de kans reëel dat hij of zij wordt opgenomen in een verpleeg- of verzorgingstehuis[28]. Postoperatieve achteruitgang in functionele status bij onco-geriatrische patiënten komt frequent voor en is soms van blijvende aard, met name wanneer er preoperatief al sprake was van beperkingen

in functionele status[29-32]. De kans is zeer reëel dat een geriatrische patiënt postoperatief achteruitgaat in zijn of haar functionele status, of zelfs opgenomen moet worden in een verpleeg- of verzorgingstehuis. En dit geldt zeker als de patiënt is geclassificeerd als kwetsbaar. Bovendien kan beide leiden tot verlies van kwaliteit van leven. Derhalve dient preoperatief de kans op ongunstige postoperatieve uitkomsten ingeschat te worden. Dit risico moet meegenomen worden bij het opstellen van het behandelplan en dient met de patiënt en zijn of haar familie besproken te worden. Wanneer een patiënt zeer kwetsbaar is, een verhoogd risico heeft op postoperatieve complicaties op de korte en lange termijn, of zelf twijfelt of hij of zij een grote operatie wil ondergaan, kan gezamenlijk besloten worden om niet te opereren. In dat geval is advanced care planning essentieel.

Implicaties voor toekomstig onderzoek

Door de studies die hebben geleid tot dit proefschrift zijn er verschillende nieuwe vraagstukken ontstaan die onderwerp kunnen zijn van vervolgstudies. Voorbeeld hiervan is de implementatie van zogeheten 'Patient Reported Outcome Measures' (PROMs) als eindpunten in klinische studies. Ook het effect van prehabilitatie (bepaalde factoren, zoals voedingsstatus of conditie, voorafgaand aan de operatie optimaliseren) op postoperatieve uitkomsten bij onco-geriatrische patiënten, kan een onderwerp zijn voor een vervolgstudie. Wat ook geldt voor het analyseren van wat mogelijk het onderliggende mechanisme kan zijn van preoperatieve beperkingen in de geriatrische domeinen en het daarmee gepaard gaande risico op ongunstige postoperatieve uitkomsten voor onco-geriatrische patiënten.

Patient Reported Outcome Measures

In aanvulling op de veel gebruikte klinische uitkomsten, zoals postoperatieve complicaties en overleving, zouden PROMs vaker opgenomen moeten worden als eindpunt in klinische studies. Voorbeelden van door patiënt gerapporteerde uitkomsten zijn gezondheid gerelateerde kwaliteit van leven, functioneren en symptomen. Een belangrijk aandachtspunt hierbij: hoe vind je valide meetinstrumenten die precies meten wat je beoogt vast te stellen? Een andere uitdaging, met name wanneer de studiepopulatie (kwetsbare) ouderen bevat, is het beperken van de last voor de patiënt die deelname aan een studie met zich mee kan brengen[33]. Ook is het belangrijk dat de studiepopulatie het meetinstrument begrijpt en gemakkelijk kan invullen[33]. Wanneer deze uitdagingen niet worden geadresseerd, kan dat ertoe leiden dat de inclusie van patiënten moeizaam gaat, waardoor er mogelijk onvoldoende patiënten geïncludeerd worden en de kwaliteit van het onderzoek achteruit gaat[33]. Door krachten te bundelen, bijvoorbeeld via internationale organisaties zoals SIOG (International Society of Geriatric Oncology),

kunnen grotere studiepopulaties en multicenter studies gerealiseerd worden, wat de kwaliteit van het resulterende bewijs ten goede komt.

Implementeren van PROMs als eindpunt in klinische studies is om meerdere redenen belangrijk. In de eerste plaats omdat patiënten zelf deze eindpunten het meest waardvol achten[26, 27]. Bovendien kan meer kennis over lange-termijn uitkomsten wat betreft functionele status en kwaliteit van leven het preoperatieve proces van gezamenlijke besluitvorming faciliteren. Verder kan het ervoor zorgen dat we beter kunnen anticiperen op de postoperatieve zorgbehoeftes van deze groeiende groep patiënten, wat er tot slot ook toe kan leiden dat eventuele extra postoperatieve begeleiding en revalidatiemogelijkheden efficiënt ingezet kunnen worden bij de patiënten die dat het meest nodig hebben. Kortom, de implementatie van PROMs in klinisch onderzoek én in de dagelijkse klinische praktijk is een belangrijke stap in het proces richting individuele zorg op maat voor de onco-geriatrische chirurgische patiënt.

Prehabilitatie

Prehabilitatie is preoperatief optimaliseren van de patiënt op verschillende domeinen, zodat het lichaam zich mogelijk beter kan verweren tegen grote stressoren zoals een operatie, met als uiteindelijk doel het verbeteren van de postoperatieve resultaten. Preoperatief verbeteren van de functionele status en voedingstoestand en reductie van stress-levels zijn interventies die worden onderzocht in verschillende prehabilitatie studies[4, 34]. Inzetten van deze interventies bij patiënten bij wie deze domeinen het meest frequent aangedaan zijn en die dus mogelijk ook het meest van deze interventies kunnen profiteren, is efficiënt. Dit impliceert dat de onco-geriatrische patiëntenpopulatie, met frequent beperkingen in meerdere domeinen, een belangrijke doelgroep is voor prehabilitatie studies.

Auteurs van een recent gepubliceerde gerandomiseerde studie claimen het eerste robuuste bewijs te hebben geleverd dat prehabilitatie bij patiënten met een verhoogd risico op ongunstige postoperatieve uitkomsten (>70 jaar en/of ASA III/IV) die een grote buikoperatie ondergaan, effectief is[34]. De patiënten in de interventiegroep werden onderworpen aan een prehabilitatie programma bestaande uit motiverende gespreksvoering, het bevorderen van reguliere fysieke activiteiten en gesuperviseerde high-intensity training. Er was een positief effect van dit prehabilitatie programma op het aantal postoperatieve complicaties: 31% van de patiënten in de interventiegroep ontwikkelde complicaties, tegenover 62% in de controlegroep.

De resultaten uit deze studie stemmen hoopvol wat betreft het effect van prehabilitatie op postoperatieve uitkomsten bij onco-geriatrische patiënten. Echter, in aanvulling op verbetering van de functionele status, zijn de geriatrische domeinen voedingsstatus en stemming mogelijk ook essentiële factoren die – indien geoptimaliseerd – kunnen bijdragen aan betere postoperatieve uitkomsten in deze hoog-risico populatie[hoofdstuk 5, 4].

De inflammatoire reactie als potentieel onderliggend mechanisme voor de relatie tussen beperkingen in geriatrische domeinen en ongunstige postoperatieve uitkomsten

Bij prehabilitatie studies wordt gekeken naar het effect van het verbeteren van de preoperatieve status van de patiënt op de postoperatieve uitkomsten. In het verlengde hiervan is het interessant te onderzoeken wat het mechanisme is dat hieraan ten grondslag zou kunnen liggen. Zoals reeds geopperd in **hoofdstuk 5**, zou een inflammatoire respons de link kunnen zijn. Ten eerste is veroudering geassocieerd met een staat van laaggradige inflammatie, en pro-inflammatoire cytokines lijken verhoogd te zijn in patiënten die beperkingen hebben in meerdere geriatrische domeinen, wat bovendien weer geassocieerd is met een verhoogd risico op mortaliteit[35-37]. Ten tweede kunnen patiënten met kanker lijden aan cachexie, wat ook geassocieerd is met systemische inflammatie en een verhoogd risico op mortaliteit[34]. Cachexie wordt gedefinieerd als een multifactorieel syndroom wat gekarakteriseerd wordt door een persisterend verlies van skeletspiermassa, wat niet omkeerbaar is middels voedingsadviezen, en bovendien leidt tot achteruitgang van functionele status[38]. Tot slot hebben studies uitgewezen dat een inflammatoire respons op een operatie een centrale rol speelt in het ontwikkelen van postoperatieve complicaties[39, 40].

Concluderend

Uitvoeren van een preoperatief geriatrisch assessment en identificeren van patiënten met een verhoogd risico op ongunstige postoperatieve uitkomsten, faciliteren het bieden van zorg op maat, gericht op de individuele patiënt. Dit leidt uiteindelijk tot efficiënt ingerichte en verbeterde kwaliteit van zorg en idealiter ook tot betere postoperatieve uitkomsten bij onco-geriatrische chirurgische patiënten. Om dit te bereiken moet de samenwerking met geriaters en huisartsen aangemoedigd worden en moet geriatrie in de chirurgische opleiding geïmplementeerd worden. Eén van de suggesties voor toekomstig onderzoek is de implementatie van PROMs als eindpunten in klinisch onderzoek. Verder kan men onderzoeken wat het effect van prehabilitatie is op onco-geriatrische patiënten met een verhoogd risico op ongunstige postoperatieve uitkomsten. De laatste suggestie is het analyseren van de inflammatoire respons als mogelijk onderliggend mechanisme van de associatie tussen beperkingen in geriatrische domeinen en ongunstige postoperatieve uitkomsten.

Referenties

Zie hoofdstuk 7.

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Curriculum vitae and list of publications

Curriculum vitae

Monique Huisman was born on March 9th, 1989 in Zwolle. After graduating from high school in Meppel in 2006, and following one year of studying psychology, she studied medicine at the University of Groningen. In 2010 she started her masters with a scientific internship at the PICNIC study, a study led by dr. Barbara van Leeuwen on postoperative cognitive decline in elderly cancer patients. Following this internship, Monique began to work on the PREOP study, under the supervision of prof. Truuske de Bock, dr. Barbara van Leeuwen and prof. Riccardo Audisio. In 2012 this resulted in the start of a formal MD/PhD-program provided by the Junior Scientific Masterclass, University Medical Center Groningen, University of Groningen. After graduating medicine cum laude in 2013, she worked as a clinical investigator for two years straight. During this period, she followed a training program to become a clinical epidemiologist. Furthermore, she received a grant of €10.000 from the Van der Meer – Boerema foundation. Part of this grant was used as a travel grant in order to work at the McGill Nutritional and Performance Laboratory in Montréal, Canada.

In December 2015 Monique acquired experience in clinical practice as an intern at the department of surgery at the Martini Hospital in Groningen. In September 2016, her surgical residency program took off at the University Medical Center Groningen, under the supervision of prof. dr. Heineman and dr. Van Ginkel. Currently, Monique has proceeded her training at Ziekenhuisgroep Twente in Almelo and Hengelo under the supervision of dr. Lutke Holzik.

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