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

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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 – 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. Functional impairment influences the degree of autonomy of elderly patients and preoperative optimization of this domain might improve outcomes. This latter can apply to the domains of nutritional status and mood as well. 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.

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 patients7. 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.

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. 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. 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. 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. Functional deterioration after surgery in onco-geriatric patients is prevalent and sometimes permanent, especially when functional impairments are present preoperatively. 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. As a result, inclusion rates can fall short, leading to logistical problems and reduced quality of the resulting evidence. 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. 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. 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.

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. 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. Finally, studies have indicated that an inflammatory response to surgery plays a central role in the development of postoperative complications.

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.
References


