University of Groningen

The inflammatory response in surgical oncology: potential sequelae in elderly patients

Plas, Matthijs

DOI:
[10.33612/diss.159657966](https://doi.org/10.33612/diss.159657966)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Plas, M. (2021). *The inflammatory response in surgical oncology: potential sequelae in elderly patients*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.159657966>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

The inflammatory response in surgical oncology: potential sequelae in elderly patients

Matthijs Plas

Colofon

Layout & cover design

Rianne Paardekooper - Post

Printed by

Gildeprint, Enschede

www.gildeprint.nl

Sponsors

Financial support for printing of this thesis was obtained by kind contributions from the University of Groningen, University Medical Center Groningen, Graduate School of Medical Sciences.

ISBN: 978-94-641-9108-0

© Copyright Matthijs Plas 2021, Groningen, The Netherlands

The copyright of the articles that have been published has been transferred to the respective journals. No parts of this thesis may be reproduced or transmitted in any form or by any means without prior permission of the copyright owner.

rijksuniversiteit
 groningen

The inflammatory response in surgical oncology: potential sequelae in elderly patients

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 10 maart 2021 om 14.30 uur

door

Matthijs Plas

geboren op 25 oktober 1991
te Assen

Promotores

Prof. dr. B.L. van Leeuwen

Prof. dr. G.H. de Bock

Prof. dr. A.R. Absalom

Beoordelingscommissie

Prof. dr. J.P.P.M. de Vries

Prof. dr. M.M.R.F. Struys

Prof. dr. M.H. Emmelot-Vonk

Paranimfen

Maureen Kanter

Wiggert van Ginkel

Table

of contents

Chapter 1 p 8

Introduction and outline
of the thesis

Part 1 The inflammatory response to surgery

Chapter 2 p 22

The systemic impact of the surgical
procedure in elderly oncological patients.

Eur J Surg Oncol. 2019 Aug;45(8):1403-1409

Chapter 3 p 42

The association between the
inflammatory response to surgery and
postoperative complications in older
patients with cancer; a prospective
prognostic factor study.

J Geriatr Oncol. 2020 Jun;11(5):873-879

Chapter 4 p 68

Enteral nutrition during major
surgery: how to proceed after
SANICS II.

Lancet Gastroenterol Hepatol. 2018 Jul;3(7):454

Part 2 Postoperative neurocognitive disorders

Chapter 5 p 76

Cognitive decline after major oncological surgery in the elderly.

Eur J Cancer. 2017 Nov;86:394-402

Chapter 6 p 98

Incidence and predictors of postoperative delirium after cytoreduction surgery-hyperthermic intraperitoneal chemotherapy.

J Surg Oncol. 2018 Feb;117(2):260-268 / *J Surg Oncol.* 2018

Mar;117(4):808

Chapter 7 p 124

The association of preoperative anxiety and depression with neurocognitive disorder following oncological surgery.

J Surg Oncol. 2020 Mar;121(4):676-687 / *J Surg Oncol.* 2020

Sep;122(3):564-565

Chapter 8 p 158

Summary and general discussion

Appendices p 174

Chapter 1

Introduction and outline
of the thesis

Cancer incidence and the ageing of society

Cancer is, after cardiovascular disease, the second main cause of death worldwide.¹ Over the last decades the incidence of cancer has increased, with numbers reported from 14 million new cancer cases in 2012 to an expected number of 24 million in 2035.² Prostate and breast cancer, both solid tumours, are the most reported types of cancer in developed countries for men and women respectively.³ Population ageing has substantially contributed to the rising number of new cancer cases and most solid tumours occur in the older population.^{4,5} Some of the same biologic mechanisms that regulate ageing also may be involved in the pathogenesis of cancer.⁶ As a result, the burden of this disease is now falling mainly on the elderly and by 2035 it is expected that older adults will represent 60% of all new diagnosed cancers.^{7,8} The number of people aged 65 years and older is expected to increase even further and to double in the next two decades, a forecast not restricted to first world countries.⁹

Surgical cancer treatment

In general, a solid tumour is considered as local disease that may, or may not, spread. Surgery to treat cancer removes the tumour and adjacent healthy tissue to prevent the spread of the tumour.¹⁰ Removing the tumour means removing the disease. When solid tumours are diagnosed at early stages, surgical resection provides locoregional control, and is often curative as a sole treatment or combined with other modalities.¹¹ In addition to locoregional control, cancer surgery can be helpful in treatment of metastatic disease and can be a valuable palliative treatment aimed at improving or preserving quality of life.¹²

Risk for postoperative adverse outcomes in elderly oncological patients

Postoperative complications

Surgical procedures are mainly performed with the aim to restore health, however the elderly have proven prone to develop postoperative complications with all of its consequences.^{13,14} Due to the ageing of society and increasing cancer incidence with ageing, surgery for elderly patients has, and will, become more and more common. Furthermore, the advances in anaesthetic and surgical techniques have also led to increasing rates of surgery among older patients. Nowadays, age alone is not a reason to decline surgical treatment, as it is seen as variation in a biological process rather than a pathologic condition.¹⁵ Although elderly patients diagnosed with cancer may benefit from surgical treatment, they are more susceptible for adverse events than the young.¹⁶ When postoperative complications occur in elderly patients, they are more likely to lead to adverse outcomes such as disability, loss of independence, diminished quality of life, high health care costs, and death.^{17,18} In the elderly, deterioration may occur in physical functioning, but also cognitive functioning may be affected in the postoperative course.¹⁹

Postoperative neurocognitive disorder

Incomplete physical and psychological recovery from surgery leads to impaired functioning.²⁰ Adverse outcomes on the level of cognitive functioning following surgery, especially, have an impact on the ability to sustain a manageable and worthwhile life.²¹ From the point of view of older patients, cognitive disturbances are among the most harmful postoperative complications that can occur. For elderly patients, these complications often mean the end of an independent life.²² Cognitive functioning may be impaired on the short-term, as for example in postoperative delirium, but also on the long-term as in postoperative cognitive decline.²³ Both impairments, explained as postoperative neurocognitive disorder, have a substantial effect on morbidity and mortality.²⁴

Postoperative delirium

Postoperative delirium is an acute confusion disorder characterized by an altered level of consciousness, inattention, and disorganized thinking.²⁵ The sometimes subtle change in cognition or perceptual disturbance, develops over a short period of time (hours to days) and may fluctuate over the course of a day.²⁶ Delirium can be

classified into three subtypes, namely, hyperactive, hypoactive, or mixed.²⁷ Delirium remains frequently unrecognized and is still poorly understood even though it was first described over 2500 years ago. Delirium is especially common in people aged 65 years or older, costly and sometimes even fatal.²⁸

Postoperative cognitive decline

In addition, older patients are vulnerable to memory disturbances and other types of cognitive impairment after surgical procedures. Following surgery, a substantial proportion of elderly patients will experience cognitive decline, especially in memory and executive functioning when compared to pre-operative levels of cognition.^{29,30} Postoperative cognitive decline is defined as a new cognitive impairment arising after a surgical procedure. For diagnosing postoperative cognitive decline, both pre- and postoperative testing of cognitive performance are necessary. The manifestations are subtle and diverse, depending on the cognitive domains that are affected.³¹ The most commonly seen problems are memory impairment and impaired performance on intellectual tasks. Cognitive decline can be observed in the first few days to weeks after surgery and persists for several months to years thereafter.^{32,33} Postoperative cognitive decline has been associated with poor short- and long-term outcomes, including decreased quality of life, increased disability, increased mortality and greater utilization of social and financial assistance.^{34,35}

Proposed mechanism

During the last decades, the role of a physiologic response in the development of postoperative complications (including cognitive impairment) has been suggested. The proposed underlying mechanism involves reactions of the immune system.

The immune system is primarily involved in surveillance of bodily tissues and protection from infectious agents and various forms of injury. During surgery tissue damage is inflicted, leading to the activation of the immune system. A tightly balanced reaction from the immune system is vital for recovery from trauma and surgery.³⁶ However, a severe and prolonged inflammatory response might be detrimental and might be associated with postoperative complications. The activation of the immune system leads to a process called inflammation, which is usually a discrete local event

and is intended to be protective.³⁷ Following surgery the tightly regulated immune response can expand beyond the local environment and can become systemic, as inflammatory mediators spread throughout the body.³⁸ So, the surgery-induced tissue damage can lead to the release of systemic (pro- and anti-) inflammatory mediators (see Figure 1).

The immune system contains a series of feedback loops to restore homeostasis. Dependent on the balance of pro-inflammatory and anti-inflammatory mediators, the response might return to baseline or progress to persistent inflammation or immunosuppression which might predispose patients to a complicated postoperative course.^{39,40}

Figure 1. This figure depicts the role of a physiologic response in the development of postoperative complications (including cognitive impairment). During surgery, tissue damage is inflicted, leading to the activation of the immune system (1). The tightly regulated immune response can expand beyond the local environment and can become systemic, as inflammatory mediators spread throughout the body (2). The systemic inflammatory mediators pass the blood–brain barrier and activate the microglia cells, a process called neuroinflammation (3).

Once the systemic inflammatory mediators pass the blood–brain barrier, they can

exert innumerable effects on the central nervous system, primarily through the activation of microglia. Microglia are the immune cells of the brain and the activation of the intrinsic immune system of the brain is a process called neuroinflammation. Neuroinflammation is the state in which microglia cells are activated and release inflammatory mediators in the brain.⁴¹ Evidence is accumulating that neuroinflammation leads to neuronal dysfunction and even neuronal death. Hypothetically, this process plays a crucial role in the development of cognitive impairment following cancer surgery.⁴² The blood–brain barrier acts in the maintenance and regulation of the adult neural stem cell population. And therefore the blood–brain barrier has a key role in processes involving neurodegeneration and cognitive impairment.⁴³ During the process of ageing, the blood–brain barrier is disrupted and the permeability changes.⁴⁴ It is described that the blood–brain barrier in elderly is more “leaky” and so more vulnerable to inflammatory mediator crossing. Knowledge on pathophysiology however is limited and research on cognitive dysfunction following cancer surgery is still in its early stages. For normal cognitive functioning, low levels of immune activation are essential, yet it has been acknowledged that chronic or exacerbated inflammation can adversely affect cognitive performance.⁴⁵

Aim

Although substantial progress has been made in recognizing and treating postoperative complications to improve the postoperative care, it remains unclear why and how especially the elderly are prone for the development of adverse outcomes and how the immune system plays a role. In order to better select the right treatment for the right patient and to develop strategies to better prevent and/or treat postoperative complications in elderly oncological patients, it is crucial to have a thorough understanding of the underlying mechanisms and its sequelae. Therefore the aim of this thesis is to study the negative sequelae of the inflammatory response, and the inflammatory response itself, to surgery in (elderly) oncological patients with special interest in cognitive functioning.

Outline

In **Part I** of the thesis the systemic inflammatory response that develops after surgery in elderly oncological patients and the association with the postoperative course is described. In **Chapter 2**, the association between a range of pre- and perioperative factors and the extent of the inflammatory response is explored and patients at risk of a greater inflammatory response following surgery are identified. In **Chapter 3**, associations of short-term changes in plasma levels of inflammatory biomarkers and subsequent postoperative complications are investigated in elderly patients undergoing surgery as part of oncological treatment. In **Chapter 4** a double-blind, randomized controlled trial of the effect of perioperative lipid-enriched enteral nutrition versus standard care is evaluated and thoughts on target populations for immunomodulating interventions are discussed.

In **Part II** of the thesis, focus lays on impairment of cognitive functioning in patients undergoing surgery as part of oncological treatment. Incidences and risk factors for postoperative delirium and postoperative cognitive dysfunction are investigated and an association with the inflammatory response following surgery is explored. In **Chapter 5**, the incidence of cognitive decline 3 months after surgery is subject of investigation. Potential patient-, disease- and surgery-related risk factors for postoperative cognitive decline in onco-geriatric patients are studied. In **Chapter 6**, the incidence of and risk factors for postoperative delirium after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) are investigated. CRS-HIPEC is a complex, time-consuming surgical procedure suspect for an exacerbated inflammatory response. **Chapter 7** investigates the incidence of cognitive decline 3 months after surgery among young and older patients undergoing surgery for cancer, and evaluates the role of preoperative (symptoms of) anxiety and depression. At last, in **Chapter 8** a general discussion and suggestions for the direction of future research are described.

References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: A systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1736-1788.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in europe: Estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403.
3. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2018.
4. Niccoli T, Partridge L. Ageing as a risk factor for disease. *Curr Biol*. 2012;22(17):R741-52.
5. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, et al. The global burden of cancer 2013. *JAMA Oncol*. 2015;1(4):505-527.
6. Finkel T, Serrano M, Blasco MA. The common biology of cancer and ageing. *Nature*. 2007;448(7155):767-774.
7. Pilleron S, Sarfati D, Janssen-Heijnen M, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. *Int J Cancer*. 2019;144(1):49-58.
8. Lunenfeld B, Stratton P. The clinical consequences of an ageing world and preventive strategies. *Best Pract Res Clin Obstet Gynaecol*. 2013;27(5):643-659.
9. United nations, department of economic and social affairs, population division. world population prospects, the 2015 revision. .
10. Wyld L, Audisio RA, Poston GJ. The evolution of cancer surgery and future perspectives. *Nat Rev Clin Oncol*. 2015;12(2):115-124.
11. Sullivan R, Alatisio OI, Anderson BO, et al. Global cancer surgery: Delivering safe, affordable, and timely cancer surgery. *Lancet Oncol*. 2015;16(11):1193-1224.
12. Miner TJ, Brennan MF, Jaques DP. A prospective, symptom related, outcomes analysis of 1022 palliative procedures for advanced cancer. *Ann Surg*. 2004;240(4):719-26; discussion 726-7.
13. Huisman MG, Audisio RA, Ugolini G, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: A multicenter prospective cohort study. *Eur J Surg Oncol*. 2015;41(7):844-851.
14. Ellison EC, Pawlik TM, Way DP, Satiaini B, Williams TE. The impact of the aging population and incidence of cancer on future projections of general surgical

workforce needs. *Surgery*. 2017.

15. Yang R, Wolfson M, Lewis MC. Unique aspects of the elderly surgical population: An anesthesiologist's perspective. *Geriatr Orthop Surg Rehabil*. 2011;2(2):56-64.

16. Bentrem DJ, Cohen ME, Hynes DM, Ko CY, Bilimoria KY. Identification of specific quality improvement opportunities for the elderly undergoing gastrointestinal surgery. *Arch Surg*. 2009;144(11):1013-1020.

17. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: Morbidity and mortality from major noncardiac surgery. *J Am Geriatr Soc*. 2005;53(3):424-429.

18. Lawrence VA, Hazuda HP, Cornell JE, et al. Functional independence after major abdominal surgery in the elderly. *J Am Coll Surg*. 2004;199(5):762-772.

19. Monk TG, Price CC. Postoperative cognitive disorders. *Curr Opin Crit Care*. 2011;17(4):376-381.

20. McKenna RJ S. Clinical aspects of cancer in the elderly. treatment decisions, treatment choices, and follow-up. *Cancer*. 1994;74(7 Suppl):2107-2117.

21. Borges J, Moreira J, Moreira A, Santos A, Abelha FJ. Impact of postoperative cognitive decline in quality of life: A prospective study. *Rev Bras Anesthesiol*. 2017;67(4):362-369.

22. Muller A, Lachmann G, Wolf A, Morgeli R, Weiss B, Spies C. Peri- and postoperative cognitive and consecutive functional problems of elderly patients. *Curr Opin Crit Care*. 2016;22(4):406-411.

23. Rudolph JL, Marcantonio ER, Culley DJ, et al. Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia*. 2008;63(9):941-947.

24. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth*. 2018;121(5):1005-1012.

25. Cerejeira J, Mukaetova-Ladinska EB. A clinical update on delirium: From early recognition to effective management. *Nurs Res Pract*. 2011;2011:875196.

26. Cole MG. Delirium in elderly patients. *Am J Geriatr Psychiatry*. 2004;12(1):7-21.

27. Flynn Makic MB. Preventing delirium in postoperative patients. *J Perianesth Nurs*. 2013;28(6):404-408.

28. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-922.

29. Hovens IB, Schoemaker RG, van der Zee EA, Heineman E, Izaks GJ, van Leeuwen BL. Thinking through postoperative cognitive dysfunction: How to bridge the gap between clinical and pre-clinical perspectives. *Brain Behav Immun*. 2012;26(7):1169-

1179.

30. Price CC, Garvan CW, Monk TG. Type and severity of cognitive decline in older adults after noncardiac surgery. *Anesthesiology*. 2008;108(1):8-17.

31. Rundshagen I. Postoperative cognitive dysfunction. *Dtsch Arztebl Int*. 2014;111(8):119-125.

32. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. international study of post-operative cognitive dysfunction. *Lancet*. 1998;351(9106):857-861.

33. Johnson T, Monk T, Rasmussen LS, et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology*. 2002;96(6):1351-1357.

34. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology*. 2009;110(3):548-555.

35. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*. 2008;108(1):18-30.

36. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;454(7203):428-435.

37. Medzhitov R. Inflammation 2010: New adventures of an old flame. *Cell*. 2010;140(6):771-776.

38. Giannoudis PV, Dinopoulos H, Chalidis B, Hall GM. Surgical stress response. *Injury*. 2006;37 Suppl 5:S3-9.

39. Lord JM, Midwinter MJ, Chen YF, et al. The systemic immune response to trauma: An overview of pathophysiology and treatment. *Lancet*. 2014;384(9952):1455-1465.

40. Dabrowska AM, Slotwinski R. The immune response to surgery and infection. *Cent Eur J Immunol*. 2014;39(4):532-537.

41. Karlidag R, Unal S, Sezer OH, et al. The role of oxidative stress in postoperative delirium. *Gen Hosp Psychiatry*. 2006;28(5):418-423.

42. Peng L, Xu L, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): A meta-analysis. *PLoS One*. 2013;8(11):e79624.

43. Delaney C, Campbell M. The blood brain barrier: Insights from development and ageing. *Tissue Barriers*. 2017;5(4):e1373897.

44. Erdo F, Denes L, de Lange E. Age-associated physiological and pathological changes at the blood-brain barrier: A review. *J Cereb Blood Flow Metab*. 2017;37(1):4-24.

45. Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain Behav Immun*. 2011;25(2):181-213.

Part 1

The inflammatory response to surgery

Chapter 2

The systemic impact of a surgical procedure in older oncological patients

M. Plas
J. J. de Haan
H. van der Wal-Huisman
A. Rutgers
A.R. Absalom
G.H. de Bock
B.L. van Leeuwen

Eur J Surg Oncol. 2019 Aug;45(8):1403-1409

Abstract

Background : An excessive inflammatory response accounts partially for the increased morbidity and mortality seen in elderly surgical patients. The aim of this study was to investigate the association between a range of pre- and peroperative factors and the extent of the inflammatory response, and to identify patients at risk of a greater inflammatory response following surgery.

Methods : Patients 65 years and older undergoing a surgical procedure for a solid malignant tumour were prospectively included in an observational cohort study. Inflammatory markers were measured in plasma samples pre- and postoperatively: C-reactive protein (CRP), Interleukin-1 beta (IL-1 β), IL-6, IL-10, IL-12, and Tumour necrosis factor alpha (TNF- α). Preoperative and postoperative inflammatory factor assay results were compared, and associations between inflammatory markers and pre- and peroperative factors were explored using multivariate linear regression analysis.

Results : Between July 2010 and April 2014, plasma samples of 224 patients were obtained. Median age was 72 (65-89) years and 108 (48.2%) patients were male. The predominant diagnosis was carcinoma, 156 (69.6%). Anaesthesia duration was associated with increase in CRP, IL-1 β and IL-6; intracavitary surgery with increase in IL-6; blood loss with decrease in CRP and IL-1 β ; total fluid volume administered with a decrease in IL-1 β and disease stage was associated with increase in IL-6.

Conclusion : The perioperative inflammatory response is related more to surgical characteristics rather than to preoperative factors (with the exception of disease stage). Elderly oncological patients undergoing longer lasting, intracavitary surgical procedures for more advanced disease stages develop the most intense inflammatory response.

Introduction

Over the next decades the global burden of cancer will increase, with over 20 million new cancer cases expected annually as early as 2025.¹ The majority of new patients with cancer are elderly.² Due to the combination of a growing cancer incidence, ageing of the population, and surgery continuing to be the principle treatment for many solid tumors, the number of elderly patients undergoing surgery as part of cancer treatment is expected to increase strongly. With advancing age, the immune system declines in reliability and efficiency, leading to greater susceptibility to a pathological course of an inflammatory response. This process is called “inflammaging”.³⁻⁵ In a surgical setting, where tissue barriers are breached, tissue damage activates the immune system leading to a systemic inflammatory response.^{6,7} Although intended to be protective by eliminating invading pathogens and repairing damaged tissue, an excessive inflammatory response can cause collateral tissue damage and lead to pathology.⁸ The systemic inflammatory response can be investigated straight-forward by assaying circulatory inflammatory markers, such as cytokines and other proteins.⁹ Tumour necrosis factor-alpha (TNF- α) is one of the first detectable cytokines during an immune response, regulating the release of both pro- and anti-inflammatory mediators.¹⁰ Important pro-inflammatory cytokines are Interleukin-1 beta (IL-1 β), crucial for host-defense responses to infection and injury, and Interleukin-6 (IL-6) that is a prognostic factor for postoperative outcome in trauma patients.^{11,12} Interleukin-10 (IL-10) is a strong anti-inflammatory cytokine in the acute phase that suppresses the release of Interleukin-12 (IL-12) that is crucial in preserving a responsive immune system in the postoperative period. In clinical practice, C-reactive protein (CRP), an acute phase protein produced by the liver in response to IL-6, is a standard clinical marker of inflammation.¹³ Postoperative complications in elderly patients are associated with higher morbidity and mortality rates and can affect quality of life.^{14,15} An excessive inflammatory response following surgery may account partially for the increased morbidity and mortality seen in elderly surgical patients. Nowadays, frailty, comprehensive geriatric assessments, pre- and rehabilitation programs, and multidisciplinary collaborations are getting attention in the elderly, all aimed to improve the postoperative outcome. However, there is still a lack of knowledge concerning the differences in physiological response to the surgical procedure itself in the elderly. The aim of the current study, a prospective cohort study of elderly patients undergoing oncological surgery, was to investigate pre- and peroperative factors associated with the extent of the inflammatory

response, and to identify those patients at risk of a greater inflammatory response following surgery.

Methods

The PICNIC cohort

The data used for this study is a sub-set of data gathered during the prospective observational study, 'PICNIC' (Postoperative Cognitive dysfunction In elderly Cancer patients), conducted from July 2010 until April 2014 at the University Medical Center Groningen (UMCG, Groningen, the Netherlands).^{16,17} This study was approved by the Medical Ethical Committee of the UMCG, and registered in the Dutch Clinical Trial Database (trial number NL31486.042.10). Patients aged 65 years and over, admitted to the UMCG for an elective surgical resection of a solid tumour (including gynaecological tract, digestive tract, soft tissue) were recruited. Written informed consent was obtained from all participants according to local regulations and data collection was conducted according to the declaration of Helsinki. Exclusion criteria of the 'PICNIC' study included: any physical condition potentially impeding compliance with the study, such as a severe visual or auditory impairment or a recent history of stroke (or other preoperative cognitive deficits) and insufficient understanding of the Dutch language. Of 307 patients included in the 'PICNIC' study, 14 patients were incorrectly included and 19 patients withdrew consent, so that data from 274 patients were available for analysis.

Blood plasma sampling and biochemical analyses

Blood samples were collected preoperatively, before induction of anaesthesia (T0) and at wound closure at the end of surgery (T1). The collection of blood was combined with blood withdrawals for standard care via (venous) lines placed for the surgical procedure. After blood samples were centrifuged at 2600 G for 10 min, plasma was aspirated and stored at -80°C. For the current study, only patients (n = 224) with blood plasma sampled at both sampling moments were included. The surgery-evoked inflammatory response was evaluated by calculating the changes in plasma inflammatory markers. The following biomarkers were assessed for the current analysis; CRP, IL-1 β , IL-6, IL-10, IL-12 and TNF- α . Analyses were performed in batches by Haemoscan[®] (Groningen) using sandwich ELISA technique for

interleukins, developed by BioLegend (San Diego, CA) and high sensitivity ELISA (Dakopatts, Glostrup, Denmark) for CRP.

Outcomes and determinants

Primary outcomes were plasma level alterations of inflammatory markers CRP, IL-1 β , IL-6, IL-10, IL-12 and TNF- α during surgical procedures. As a measure of the surgery-evoked inflammatory response, preoperative results of the inflammatory factor assays were subtracted from the postoperative outcomes (Δ CRP, Δ IL-1 β , Δ IL-6, Δ IL-10, Δ IL-12 and Δ TNF- α). Secondary outcomes were the preoperative plasma levels of the assessed inflammatory markers CRP, IL-1 β , IL-6, IL-10, IL-12 and TNF- α . Determinants considered were: age, gender, BMI, smoking state, comorbidities according to the Charlson Comorbidity Index (CCI), diabetes, COPD, hypertension, renal failure, cardiac problems, neo-adjuvant treatment, disease stage, immunosuppressive use, surgery duration, intracavitary surgery, blood loss, red blood cell (RBC) transfusion and epidural use.

Definitions and data collection

All clinical data such as age, gender, BMI, tumour type, disease stage, CCI, comorbidities, neo-adjuvant treatment and the surgical characteristics were prospectively collected. Steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and/or biologicals were considered immunomodulating drugs and as such registered in our dataset. Data about immunomodulating medication use and smoking were collected retrospectively by reviewing the electronic medical record (EMR). Smoking status was classified as: non-smoker, smoker and ex-smoker. Propofol administration during the maintenance phase of anaesthesia was defined as intravenous anaesthesia, whereas use of iso-, sevo- or desflurane maintenance was defined as inhalational anaesthesia. A surgical procedure in the thoracic or abdominal cavity was defined as intracavitary surgery.

Data analysis and statistics

Continuous data are presented as median and range, as the data were non-normally distributed. Categorical data are presented as number and percentages. Differences of the plasma levels of the inflammatory markers between sampling moments were explored to investigate the inflammatory response to the surgical procedure, by performing a Wilcoxon signed rank test. Logarithmic transformation was applied on the inflammatory response data (for the perioperative inflammatory response after subtraction), to reduce skewness and to approach normal distribution. Linear regression analyses were performed to evaluate which determinants were associated with the primary (surgery-evoked inflammatory response) and secondary (preoperative plasma levels of inflammatory markers) outcomes. All determinants were included in univariate analysis. If determinants were found significant ($p < 0.1$) in univariate analyses, multivariate linear regression analyses was performed. Step-by-step elimination of the least significant variable with backward selection was used for developing a multivariate model including only statistical significant variables. Post-hoc testing was executed according to the Bonferroni correction method to correct for multiple testing in univariate analyses.¹⁸ Results from linear regression analyses (B and 95% CI's) are represented in 10log scale. P -values < 0.05 were considered to be statistically significant for multivariate testing. Data analyses were performed using IBM SPSS Statistics version 23 (IBM Corporation, Armonk, NY) and GraphPad Prism version 5.04 (GraphPad Software, San Diego, CA).

Results

The demographic, tumour and surgical characteristics of 224 patients, included in the current analysis, are shown in Table 1. The median age of those included was 72 (65-89) years and 108 (48.2%) patients were male. Median score for the Charlson Comorbidity Index (CCI) was 3 (2-9). Hypertension was the most frequently noted comorbidity, in 76 (34.1%) patients of the study population. Of those included, 19 (8.5%) patients used immunomodulating medication. Histological diagnosis was carcinoma in 156 (69.6%) patients, sarcoma in 29 (12.9%) patients and melanoma in 25 (11.2%) patients. Most patients (176 (78.9%)) did not receive neo-adjuvant therapy (chemotherapy, radiation therapy or a combination) as part of their cancer treatment. All disease stages (I, II, III and IV) were represented in this cohort and

Table 1
Patient, tumour and surgical characteristics

Patient and tumour characteristics	Included in current analysis (n=224)
Age (years)	72 (65-89)
Gender	
<i>Female</i>	116 (51.8%)
<i>Male</i>	108 (48.2%)
BMI	26.3 (18.7-39.5)
Smoking	
<i>No</i>	164 (83.7%)
<i>Yes</i>	21 (10.7%)
<i>Former</i>	11 (5.6%)
Charlson Comorbidity Index (CCI)	3 (2-9)
<i>Diabetes</i>	46 (20.6%)
<i>COPD</i>	24 (10.7%)
<i>Hypertension</i>	76 (34.1%)
<i>Renal failure</i>	7 (3.1%)
<i>Cardiac problems</i>	32 (14.3%)
Immunomodulating drug use	19 (8.5%)
Tumour type	
<i>Carcinoma</i>	156 (69.6%)
<i>Sarcoma</i>	29 (12.9%)
<i>Melanoma</i>	25 (11.2%)
<i>Other malignancy</i>	3 (1.3%)
<i>No malignancy</i>	11 (4.9%)
Neo-adjuvant treatment	
<i>None</i>	176 (78.9%)
<i>Chemotherapy</i>	21 (9.4%)
<i>Radiation</i>	8 (3.6%)
<i>Combination</i>	18 (8.1%)
Disease Stage	
<i>Benign</i>	11 (4.9%)
<i>I</i>	54 (24.1%)
<i>II</i>	55 (24.6%)
<i>III</i>	60 (26.8%)
<i>IV</i>	44 (19.6%)
Surgical characteristics	
Intracavitary surgery	
<i>No (Skin / Extremities / Neck)</i>	71 (31.7%)
<i>Yes (Abdomen / Thorax)</i>	153 (68.3%)
Anaesthesia type	
<i>Intravenous</i>	145 (70%)
<i>Inhalational</i>	62 (30%)
Blood loss (ml)	150 (0-8300)
RBC 's transfusion (#)	0 (0-10)
Anaesthesia duration (min)	199.5 (40-1132)
Total transfusion (ml)	2000 (0-16000)
Epidural	113 (50.4%)
Median (range) & number (%)	

in 11 (5.0%) patients histological examination did not show malignant disease postoperatively. One hundred and fifty three (68.3%) patients underwent surgery in the thoracic or abdominal cavity.

Inflammatory marker plasma levels

The plasma concentrations of inflammatory markers CRP, IL-1 β , IL-6, IL-10, IL-12 and TNF- α are shown in Table 2. Preoperative plasma concentrations, those at wound closure and the perioperative change are presented. A significant difference for plasma levels between sampling moments was seen for the inflammatory markers CRP, IL-1 β , IL-6 and IL-10 (Fig. 1).

Fig. 1. This figure depicts plasma levels (median and interquartile range) of different inflammatory markers preoperatively (T0) and at wound closure (T1). The shown inflammatory markers showed a significant change between sampling moments.

Factors associated with baseline plasma concentrations

Univariate linear regression analyses showed that patient and tumour characteristics, including comorbidities and neo-adjuvant treatment, were not significantly associated with baseline plasma concentrations of the inflammatory markers (supplemental Table).

Table 2
Peroperative plasma cytokine levels (n=224)

Marker	Baseline (T0)	Wound closure (T1)	Δ (T1-T0)	p-value*
CRP	5.7 (0-204)	5.0 (0-189)	-0.6 (-117-143)	< 0.001
IL-1 β	0.0 (0-33)	0.6 (0-33)	0.4 (-23-14)	< 0.001
IL-6	0.0 (0-652)	88.6 (0-2386)	73.2 (-13-2386)	< 0.001
IL-10	13.0 (0-1565)	56.0 (0-1648)	34.5 (-544-1378)	< 0.001
IL-12	0.0 (0-1746)	0.0 (0-1437)	0.0 (-309-73)	0.743
TNF- α	0.0 (0-1056)	0.0 (0-1156)	0.0 (-147-910)	0.151

*Variable is denoted as median (range). *Differences between the two blood plasma samples were tested with the Wilcoxon signed rank test. A p-value of < 0.05 was considered significant.*

Factors associated with perioperative change in plasma concentrations

Chemoradiation as neo-adjuvant treatment was associated with a perioperative increase in plasma concentrations of IL-6 in univariate analyses (Table 3). Major surgery was found to be associated with perioperative increase in IL-6 and IL-10, whereas intracavitary surgery was only associated with perioperative increase in IL-6. Blood loss and the number of RBC's transfused were associated with perioperative decreases in CRP and IL-1 β , and an increase in IL-6. Anaesthesia duration was associated with the perioperative increase in IL-6 and IL-10. Total fluid transfusion was associated with the perioperative decrease in CRP and IL-1 β , and increase in IL-6, and IL-10. Lastly, epidural use was associated with the perioperative increase in IL-6. No other patients or tumour characteristics were found to be associated with changes in the inflammatory markers (Table 3).

Table 3
Univariate linear regression analyses of the peroperative inflammatory response(Δ cytokine blood plasma levels) (n=224) (10Logaritmic transformation)

Patient and tumour variables	CRP	IL-1 β	IL-6	IL-10
	B (95%CI)	B (95%CI)	B (95%CI)	B (95%CI)
Age	0.001 (-0.003-0.01)	0.002 (-0.001-0.01)	-0.01 (-0.02-0.01)	0.00 (-0.004-0.01)
Gender	0.03 (-0.01-0.07)	0.02 (-0.02-0.06)	0.10 (-0.09-0.30)	-0.01 (-0.07-0.04)
BMI	0.00 (-0.001-0.001)	0.00 (-0.001-0.001)	-0.002 (-0.01-0.002)	0.00 (-0.001-0.001)
Smoking				
No	1	1	1	1
Yes	0.03 (-0.04-0.10)	0.02 (-0.04-0.09)	0.14 (-0.20-0.47)	0.01 (-0.08-0.11)
Former	0.01 (-0.09-0.10)	0.004 (-0.08-0.09)	0.34 (-0.11-0.79)	0.03 (-0.10-0.15)
Charlson Comorbidity Index	0.004 (-0.01-0.02)	0.01 (-0.01-0.02)	-0.003 (-0.06-0.06)	0.01 (-0.01-0.02)
Diabetes	0.01 (-0.05-0.06)	0.02 (-0.03-0.06)	0.07 (-0.17-0.31)	0.02 (-0.05-0.08)
COPD	0.01 (-0.06-0.08)	0.01 (-0.05-0.07)	-0.02 (-0.33-0.29)	0.01 (-0.08-0.09)
Hypertension	0.01 (-0.04-0.05)	0.02 (-0.02-0.06)	0.18 (-0.02-0.39)	0.04 (-0.02-0.10)
Renal failure	0.02 (-0.11-0.15)	0.003 (-0.11-0.11)	0.19 (-0.36-0.75)	0.04 (-0.12-0.20)
Cardiac problems	0.02 (-0.04-0.08)	0.01 (-0.04-0.06)	-0.29 (-0.56-0.01)	-0.03 (-0.11-0.05)
Neo-adjuvant treatment				
None	1	1	1	1
Chemotherapy	0.03 (-0.05-0.10)	0.01 (-0.06-0.07)	0.18 (-0.14-0.50)	0.03 (-0.06-0.13)
Radiation	0.02 (-0.01-0.13)	0.01 (-0.09-0.11)	0.17 (-0.33-0.67)	0.07 (-0.08-0.22)
Chemoradiation	-0.01 (-0.09-0.07)	0.01 (-0.06-0.08)	0.80 (0.46-1.15)	0.08 (-0.03-0.18)
Disease stage				
Benign, I & II	1	1	1	1
III & IV	0.02 (-0.03-0.06)	0.02 (-0.01-0.06)	0.23 (0.04-0.42)	-0.01 (-0.07-0.05)
Immunosuppressive use	0.01 (-0.06-0.09)	0.01 (-0.06-0.08)	-0.08 (-0.42-0.27)	0.01 (-0.09-0.10)
Surgical variables				
Intracavitary surgery	-0.02 (-0.07-0.02)	-0.01 (-0.05-0.03)	0.87 (0.69-1.04)	0.05 (-0.01-0.11)
Blood loss (liters)	-0.15 (-0.16-0.13)	-0.11 (-0.13-0.09)	0.35 (0.24-0.46)	0.04 (0.01-0.07)
RBC's transfusion	-0.11 (-0.13-0.10)	-0.10 (-0.11-0.08)	0.17 (0.07-0.27)	0.02 (-0.01-0.05)
Anaesthesia duration (hours)	-0.003 (-0.01-0.004)	-0.003 (-0.01-0.004)	0.19 (0.17-0.22)	0.02 (0.01-0.03)
Total transfusion (liters)	-0.03 (-0.04-0.02)	-0.03 (-0.04-0.02)	0.22 (0.19-0.26)	0.03 (0.01-0.04)
Epidural	-0.01 (-0.06-0.03)	-0.02 (-0.06-0.02)	0.60 (0.43-0.78)	0.07 (0.02-0.13)
Anaesthesia type				
Intravenous	1	1	1	1
Inhalational	0.03 (-0.02-0.08)	0.02 (-0.03-0.06)	0.13 (-0.09-0.34)	0.03 (-0.04-0.09)

Multivariate linear regression analysis showed that different surgical characteristics, and disease stage, were associated with the perioperative changes of the inflammatory markers CRP, IL-1 β and IL-6 (Table 4). Anaesthesia duration was associated with increase in CRP, IL-1 β and IL-6; intracavitary surgery was associated with increase in IL-6; blood loss was associated with decrease in CRP and IL-1 β ; total fluid transfusion was associated with IL-1 β and disease stage was associated with increase in IL-6. Multivariate modelling for IL-10 did not reveal independent associations. Multivariate modelling for the perioperative inflammatory response of IL-12 and TNF- α was not performed as these markers did not show a significant perioperative response as shown in Table 2.

Table 4

Multivariate linear regression analyses of the perioperative inflammatory response (Δ cytokine plasma levels) (n=224) (10Logaritmic transformation)

Variable	CRP B (95%CI)	IL-1 β B (95%CI)	IL-6 B (95%CI)
Anaesthesia duration (hours)	0.02 (0.01-0.02)	0.03 (0.02-0.03)	0.16 (0.14-0.18)
Intracavitary surgery			0.47 (0.33-0.62)
Blood loss (liter)	-0.17 (-0.19--0.15)	-0.14 (-0.17--0.12)	
Total transfusion (liter)		-0.02 (-0.03--0.003)	
Disease stage			
Benign, I & II			1
III & IV			0.14 (0.01-0.26)
	R ² 0.615	R ² 0.605	R ² 0.607

Discussion

Surgery in elderly oncological patients leads to the release of pro- and anti-inflammatory cytokines as part of immune system activation. This study shows that surgical characteristics rather than preoperative factors, like demographic and patient characteristics (with the exception of disease stage), determine the extent of the perioperative inflammatory response. Patients undergoing longer surgical procedures, intracavitary surgery or with more progressive disease, show the greatest inflammatory response to surgery. This is especially marked for IL-6.

The remodeling of the immune system in elderly as a result of life-long antigenic burden, is known as inflammaging.⁵ The process of inflammaging leads to systemic priming of immune cells preoperatively and therefore cytokine response to inflammatory stimuli might be more pronounced.^{3,19} In the current study, however, advancing age was not found to be an independent factor associated with a greater perioperative inflammatory response. The effect of ageing on the perioperative inflammatory response might be better demonstrated when comparing young patients with elderly, rather than searching for differences in those of 65 years and over. Literature is inconclusive about the influence of age on the cytokine response.²⁰ In a study comparing elderly patients with younger patients undergoing abdominal surgery, elderly patients (age 75-90 years) showed an increased and delayed IL-6 response to surgical trauma compared to young adults (age 36-60 years).²¹ Furthermore, in patients undergoing total hip arthroplasty, those over 65 years of age showed higher levels of IL-6 following surgery compared with middle-aged (40-65 years) patients.²²

Tissue damage (through trauma or surgery) leads to the activation of the immune system followed by cytokine release.^{23,24} In our study, intracavitary surgery was independently associated with the extent of the surgery-evoked inflammatory response.⁹ It is known that plasma levels of IL-6 reflect the extent of operative trauma. Our current findings show that intracavitary surgery leads to a more pronounced IL-6 response, likely because more tissue is damaged compared to more superficial procedures (thyroid, skin, breast and extremities). Studies have reported that laparoscopic interventions or minimally invasive procedures are associated with a tempered perioperative inflammatory response compared to open procedures, which inflict more tissue damage.²⁵⁻²⁷

The observed associations between anaesthesia duration and the magnitude of the inflammatory response does not necessarily reflect a causal relationship. As more extensive surgical procedures require a longer anaesthesia duration, it is plausible that extensive surgery causes a greater extent of surgical tissue trauma and thereby causes higher plasma levels of IL-6 following surgery. The exposure to anesthetic drugs can even reduce the inflammatory response to surgery; compared to inhalational drugs (sevoflurane), intravenous drugs (propofol) reduce the response and expression of IL-6.²⁸ Interestingly, literature shows that the choice of anesthetic drug may even influence long-term cancer outcome, with the suggestion

that propofol has beneficial anti-inflammatory effects during surgery, which improve survival.²⁹

Patients with disease stages III & IV showed a greater inflammatory response to surgery. It is plausible to assume that in these patients, more affected tissue had to be resected during the surgical procedure and more tissue is exposed to injurious stimuli. In our study patients with disease stages III & IV seemed to have longer surgical procedures when compared to patients with benign, stage I or stage II disease however differences in duration of surgery were not significant. Circulating levels of inflammatory cytokines (IL-6) have previously been associated with disease stage of oncological patients.³⁰ Increased blood loss was found to be associated with a less pronounced perioperative inflammatory response for plasma levels of CRP and IL-1 β . The observed finding for these two markers might be due to dilution of blood plasma as a result of the combination of blood loss and increased perioperative fluid transfusion to maintain cardiac output. However, this finding was not observed for the other inflammatory markers. Interestingly, a study comparing goal-directed fluid therapy to limitless administration of intravenous fluid during surgery, found a significant difference in plasma levels of IL-6.³¹ The findings suggested that unrestrained administration of intravenous fluid during surgery induces a more excessive inflammatory response.³²

In accordance with other studies, no difference in plasma levels of IL-12 and TNF- α between both sampling moments was observed in the current study. TNF- α is a known mediator of the perioperative inflammatory response, and is described in literature as a rapid response to acute injury. The combination of a median anaesthesia duration of 199.5 minutes in our study and a half-life of TNF- α less than 20 minutes, might have resulted in a failure to detect elevated plasma levels of TNF- α as result of the blood sampling interval.⁹ Due to variation in the duration of surgical procedures in the current analysis, the plasma sample moment at wound closure might be taken before, during or after the peak response of the analysed markers. Previous research reports that injury in humans leads to a diminished capacity to produce IL-12, similar to our finding that perioperative increase in IL-12 plasma levels was not observed.³³⁻³⁵ In a study investigating changes in plasma cytokines in response to musculoskeletal surgical trauma, a significant decrease for IL-12 plasma levels was observed at the end of surgery and subsequent period.³⁶ As marker of the inflammatory response, IL-10 is reserved a unique position. Although considered

an anti-inflammatory cytokine, IL-10 possesses pro-inflammatory properties and has the ability to differently affect the function of several immune cells.^{37,38} It is notable that elevation of different cytokines can indicate different etiologies of the inflammatory response. The elevation of one inflammatory cytokine may be induced by an entirely separate mechanism when compared to another, which might explain the current findings.

Evaluation of the study

The strength of the current study is the size of the study population. As far as we know, the current cohort is the largest cohort in which the surgery-evoked inflammatory response has been explored in an elderly oncological population. A weakness is the limited number of blood sampling points. Addition of more plasma sampling moments during the surgical procedure and in the postoperative course would have facilitated the production of a time-response curve per inflammatory marker, and a better assessment of the relationship between the inflammatory response following surgery and postoperative recovery in elderly. The influence of the perioperative inflammatory response on postoperative outcomes is clinically relevant information and is of surplus value to report in future projects. The optimal selection of the inflammatory markers is subject to debate. The inflammatory markers assessed in the current study were chosen based on pathway, mechanism and hypothesis. We intently did not use multiplex assays which simultaneously measure multiple markers as this could lead to incidental findings, not easily related to the assumed mechanism.

Future perspectives and clinical implications

The consequences of the perioperative inflammatory response have not been examined in this study. It is important to keep in mind that IL-6 is part of a greater, complex network so that current conclusions are limited to the associations found in the current study. Further investigation of the effects of IL-6 on postoperative recovery is required. This may lead to the development of potential interventions to interfere with this intricate mechanism (such as perioperative tocilizumab treatment for blocking IL-6 receptors), improving perioperative care and outcome for the elderly surgical oncological patient. It also underlines the potential benefit of minimally invasive procedures in this patient category, which likely benefits those at risk for an excessive inflammatory response, as cytokine release might be less pronounced. In gastric cancer patients, minimally invasive procedures attenuated

the inflammatory response and older gastric cancer patients demonstrated better postoperative outcomes compared to those undergoing open surgery.^{39,40} This underscores the importance of exploring the effect of minimally invasive surgery (MIS) in all older surgically treated oncological patients. Furthermore, it would be of interest to explore the inflammatory response in younger patients and compare results and postoperative outcomes with the elderly. Attention to optimise patients preoperatively (including prehabilitation) is important but should not replace further research for solutions to decrease the systemic inflammatory impact of the surgical procedure itself in elderly.

Conclusion

In conclusion, this prospective study showed the activation of the immune system in response to surgery in elderly by comparing preoperative and postoperative plasma levels of different inflammatory markers. A perioperative inflammatory response was observed for CRP, IL-1 β , IL-6 and IL-10. The perioperative inflammatory response is influenced by surgical characteristics rather than by preoperative factors, including neo-adjuvant treatment and comorbidities but with the exception of disease stage. Elderly oncological patients undergoing longer lasting, intracavitary surgical procedures for more advanced stage of disease, seem to develop the greatest inflammatory response, represented by increased plasma levels of IL-6. The effect of this surgery-evoked inflammatory response on postoperative outcome in this population still has to be determined.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-86.
2. Berger NA, Savvides P, Koroukian SM, et al. Cancer in the elderly. *Trans Am Clin Climatol Assoc*. 2006;117:147-55; discussion 155-6.
3. Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev*. 2007;128(1):92-105.
4. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. *Transpl Int*. 2009;22(11):1041-1050.
5. Franceschi C, Bonafe M, Valensin S, et al. Inflamm-aging. an evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:244-254.
6. Stoecklein VM, Osuka A, Lederer JA. Trauma equals danger--damage control by the immune system. *J Leukoc Biol*. 2012;92(3):539-551.
7. Kirchhoff P, Clavien PA, Hahnloser D. Complications in colorectal surgery: Risk factors and preventive strategies. *Patient Saf Surg*. 2010;4(1):5-9493-4-5.
8. Alazawi W, Pirmadjid N, Lahiri R, Bhattacharya S. Inflammatory and immune responses to surgery and their clinical impact. *Ann Surg*. 2016;264(1):73-80.
9. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery*. 2000;127(2):117-126.
10. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: A marker for prognosis and future therapeutic options. *J Infect Dis*. 2000;181(1):176-180.
11. Lopez-Castejon G, Brough D. Understanding the mechanism of IL-1beta secretion. *Cytokine Growth Factor Rev*. 2011;22(4):189-195.
12. Jawa RS, Anillo S, Huntoon K, Baumann H, Kulaylat M. Analytic review: Interleukin-6 in surgery, trauma, and critical care: Part I: Basic science. *J Intensive Care Med*. 2011;26(1):3-12.
13. Black S, Kushner I, Samols D. C-reactive protein. *J Biol Chem*. 2004;279(47):48487-48490.
14. Lawrence VA, Hazuda HP, Cornell JE, et al. Functional independence after major abdominal surgery in the elderly. *J Am Coll Surg*. 2004;199(5):762-772.
15. Alves A, Panis Y, Mathieu P, et al. Postoperative mortality and morbidity in french patients undergoing colorectal surgery: Results of a prospective multicenter study. *Arch Surg*. 2005;140(3):278-83, discussion 284.
16. Plas M, Rotteveel E, Izaks GJ, et al. Cognitive decline after major oncological

surgery in the elderly. *Eur J Cancer*. 2017;86:394-402.

17. Weerink LBM, van Leeuwen BL, Gernaat SAM, et al. Vitamin status and the development of postoperative cognitive decline in elderly surgical oncologic patients. *Ann Surg Oncol*. 2017.

18. Streiner DL, Norman GR. Correction for multiple testing: Is there a resolution? *Chest*. 2011;140(1):16-18.

19. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol*. 2004;39(5):687-699.

20. Miki C, Kusunoki M, Inoue Y, et al. Remodeling of the immunoinflammatory network system in elderly cancer patients: Implications of inflamm-aging and tumor-specific hyperinflammation. *Surg Today*. 2008;38(10):873-878.

21. Kudoh A, Katagai H, Takazawa T, Matsuki A. Plasma proinflammatory cytokine response to surgical stress in elderly patients. *Cytokine*. 2001;15(5):270-273.

22. Zhong J, Si HB, Zeng Y, et al. Comparison of cortisol and inflammatory response between aged and middle-aged patients undergoing total hip arthroplasty: A prospective observational study. *BMC Musculoskelet Disord*. 2017;18(1):541-017-1900-y.

23. Hazeldine J, Naumann DN, Toman E, et al. Prehospital immune responses and development of multiple organ dysfunction syndrome following traumatic injury: A prospective cohort study. *PLoS Med*. 2017;14(7):e1002338.

24. Kohl BA, Deutschman CS. The inflammatory response to surgery and trauma. *Curr Opin Crit Care*. 2006;12(4):325-332.

25. Harmon GD, Senagore AJ, Kilbride MJ, Warzynski MJ. Interleukin-6 response to laparoscopic and open colectomy. *Dis Colon Rectum*. 1994;37(8):754-759.

26. Veenhof AA, Sietses C, von Blomberg BM, et al. The surgical stress response and postoperative immune function after laparoscopic or conventional total mesorectal excision in rectal cancer: A randomized trial. *Int J Colorectal Dis*. 2011;26(1):53-59.

27. Linzer P, Filip M, Jurek P, Salek T, Gajdos M, Jarkovsky J. Comparison of biochemical response between the minimally invasive and standard open posterior lumbar interbody fusion. *Neurol Neurochir Pol*. 2016;50(1):16-23.

28. Tian HT, Duan XH, Yang YF, Wang Y, Bai QL, Zhang X. Effects of propofol or sevoflurane anesthesia on the perioperative inflammatory response, pulmonary function and cognitive function in patients receiving lung cancer resection. *Eur Rev Med Pharmacol Sci*. 2017;21(23):5515-5522.

29. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol*. 2017.

30. Chung YC, Chang YF. Serum interleukin-6 levels reflect the disease status of colorectal cancer. *J Surg Oncol*. 2003;83(4):222-226.
31. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg*. 2006;93(9):1069-1076.
32. Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting-a clinical review. *J Intensive Care*. 2016;4:27-016-0154-3. eCollection 2016.
33. Goebel A, Kavanagh E, Lyons A, et al. Injury induces deficient interleukin-12 production, but interleukin-12 therapy after injury restores resistance to infection. *Ann Surg*. 2000;231(2):253-261.
34. O'Sullivan ST, Lederer JA, Horgan AF, Chin DH, Mannick JA, Rodrick ML. Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. *Ann Surg*. 1995;222(4):482-90; discussion 490-2.
35. Hensler T, Heidecke CD, Hecker H, et al. Increased susceptibility to postoperative sepsis in patients with impaired monocyte IL-12 production. *J Immunol*. 1998;161(5):2655-2659.
36. Reikeras O, Borgen P, Reseland JE, Lyngstadaas SP. Changes in serum cytokines in response to musculoskeletal surgical trauma. *BMC Res Notes*. 2014;7:128-0500-7-128.
37. Mocellin S, Marincola FM, Young HA. Interleukin-10 and the immune response against cancer: A counterpoint. *J Leukoc Biol*. 2005;78(5):1043-1051.
38. Mocellin S, Marincola F, Rossi CR, Nitti D, Lise M. The multifaceted relationship between IL-10 and adaptive immunity: Putting together the pieces of a puzzle. *Cytokine Growth Factor Rev*. 2004;15(1):61-76.
39. Okholm C, Goetze JP, Svendsen LB, Achiam MP. Inflammatory response in laparoscopic vs. open surgery for gastric cancer. *Scand J Gastroenterol*. 2014;49(9):1027-1034.
40. Kwon IG, Cho I, Guner A, Kim HI, Noh SH, Hyung WJ. Minimally invasive surgery as a treatment option for gastric cancer in the elderly: Comparison with open surgery for patients 80 years and older. *Surg Endosc*. 2015;29(8):2321-2330.

Chapter 3

The association between the inflammatory response to surgery and postoperative complications in older patients with cancer; a prospective prognostic factor study

M. Plas
A. Rutgers
H. van der Wal-Huisman
J. J. de Haan
A.R. Absalom
G.H. de Bock
B.L. van Leeuwen

Abstract

Background : Accurate prognostic biomarkers would substantially improve surgical planning and decisions making yet no studies have been reported exploring the inflammatory response in surgically treated older patients with cancer. The aim of this study was to explore inflammatory biomarkers as potential prognostic factors for postoperative complications within 30 days in older patients with cancer.

Methods : Patients 65 years and older undergoing surgery for removal of a solid malignant tumour were included in an observational cohort study. All complications occurring up to 30 days postoperatively were documented prospectively. Inflammatory markers were measured in plasma samples pre- and postoperatively: C-reactive protein (CRP), Interleukin-1 beta (IL-1 β), IL-6, IL-10, IL-12, and Tumour necrosis factor-alpha (TNF- α). Associations between inflammatory markers and postoperative complications were explored using logistic regression analysis.

Results : Between July 2010 and April 2014, plasma samples of 224 patients were collected. Median age was 72 (65-89) years and 116 (51.8%) patients were female. Approximately half of the patients developed postoperative complications (49.6%) of whom 62 patients (55.9%) developed >1 complication. An independent prognostic effect was observed for the inflammatory biomarkers IL-6 and IL-10 for the occurrence of postoperative complications.

Conclusion : The perioperative inflammatory response is associated with complications, independently from patient and surgical factors which are also associated with outcome. Research is warranted towards further exploration of the perioperative inflammatory response with the aim to improve perioperative care and outcome, and might help to improve surgical planning and decision making for older patients with cancer.

Introduction

Although older patients diagnosed with cancer may benefit from surgical treatment, they are more susceptible to the complications of surgery and anesthesia than younger patients.¹ The frequency of postoperative complications in older patients undergoing elective surgery for solid tumour removal is relatively high, with incidences reported of >50% during the first 30 days postoperatively.^{2,3} When postoperative complications occur in older patients, they are more likely to lead to adverse outcomes such as disability, loss of independence, diminished quality of life, high health care costs, and death.^{4,5} Having prognostic factors established and available to assist with prognosis would be helpful in treatment planning and decision-making in older patients with cancer.⁶

Multiple patient-related factors as well as the severity of the surgical procedure itself are associated with adverse postoperative outcomes.⁷ Literature shows that pre-existing comorbidities and sex-related differences are associated with outcome in different surgical populations, and that frail patients have a significantly higher morbidity after elective surgical procedures compared to fit patients.⁸⁻¹⁰ It is likely that the immune system has a role in the pathogenesis of postoperative complications but few inflammatory biomarkers are established to further estimate the risk of postoperative complications across populations.¹¹ Tissue damage inflicted during surgery induces a systemic inflammatory response which is coordinated by the immune system and mediated by endogenous mediators such as C-reactive protein (CRP), Interleukin-1 β (IL-1 β), IL-6, IL-10, IL-12 and Tumour necrosis factor-alpha (TNF- α).¹² CRP is an acute phase protein and is used as a marker for tissue damage and inflammation.¹³ IL-1 β , IL-6, IL-10 and IL-12 are inflammatory cytokines, which can exert anti- and/or pro-inflammatory effects and are often used as marker for the inflammatory response to trauma.^{14,15} TNF- α is an early mediator in the immune response after injury.^{16,17} This systemic inflammatory response is thought to play a role in the development of postoperative complications, particularly in those of an inflammatory nature (e.g., delirium, surgical site infection, pneumonia, urinary tract infection, etc.).¹⁸⁻²¹ These inflammatory biomarkers might be useful as prognostic factors for the occurrence of postoperative complications.

Accurate prognostic inflammatory biomarkers would substantially improve surgical

planning and decision making yet no studies have been reported exploring the inflammatory response in surgically treated older patients with cancer. Therefore, in this exploratory prognostic factor study we aimed to explore inflammatory biomarkers as potential prognostic factors for postoperative complications within 30 days, in a well-defined prospective cohort consisting of consecutively recruited older patients undergoing surgery as part of oncological treatment.

Methods

The PICNIC Cohort

This prospective clinical study to investigate associations of inflammatory biomarkers and postoperative (inflammatory) complications in older patients with cancer is a sub-study of the observational study 'PICNIC' (Postoperative Cognitive dysfunction In elderly Cancer patients), conducted at the University Medical Center Groningen (UMCG, Groningen, the Netherlands).^{7,22,23} The study was registered on the Dutch Clinical Trial Database (trial number NL31486.042.10) and approved by the Medical Ethical Committee of the UMCG. The aim of 'PICNIC' was to identify predictors of postoperative outcome in older patients with cancer, with special focus on physical and cognitive functioning. Written informed consent was obtained from every patient enrolled in the study. Patients were enrolled in the study from July 2010 until April 2014.

Patients and clinical data collection

Patients aged 65 years and over referred to the UMCG for an elective resection of a solid tumour were considered eligible and were recruited for participation. Any physical condition potentially hindering compliance with the study protocol, such as (but not restricted to) severe visual or auditory impairment or a recent history of stroke or pre-existing cognitive impairment and insufficient understanding of Dutch language, were exclusion criteria of the 'PICNIC' study. Preoperatively the Mini-Mental State Examination (MMSE) was assessed for all patients for systematic screening for pre-existing cognitive impairment. Data collection was conducted following the Declaration of Helsinki. Privacy was guaranteed by using coded data

in the analysis. Patient characteristics such as age, sex, BMI, tumour type, disease stage, comorbidities according to the Charlson Comorbidity Index (CCI), frailty according to the Groningen Frailty Indicator (GFI), neo-adjuvant treatment and the surgical characteristics were prospectively collected during the study period.

Postoperative complications

All complications occurring up to 30 days postoperatively were documented prospectively in the Case Report Form (CRF) using clear pre-defined criteria (Clavien-Dindo Classification).²⁴ A subsequent search of the UMCG complication registry confirmed that all complications captured by the registry were also captured by our study. To guarantee the quality and validity of the registration, further actions were undertaken as careful monitoring is necessary.²⁵ In 2018, the patient records of all patients in whom complications were recorded, were reviewed. Discharge letters from the Electronic Medical Record (EMR) system, and all hardcopy patient files relevant to the hospital admission for the surgical procedure were reviewed by a research physician. All sections of the hardcopy patient files were examined page by page, including but not restricted to nursing-, consultant-, and progress notes. As traditional classification of complications by severity (Clavien-Dindo Classification) is not the most appropriate when exploring inflammatory biomarkers as potential prognostic factors for the postoperative course in a theory driven approach in the current study, postoperative complications were categorized as either non-inflammatory or inflammatory in nature retrospectively. Complications in which the immune system was thought to have played a role were considered inflammatory complications. In doubtful cases, the complication was discussed within the study group, and the complication was then defined as inflammatory or non-inflammatory according to the consensus opinion. Complications were considered inflammatory when diagnostic tests confirmed the occurrence of an infection (by cultures, radiographic findings or laboratory results) or when therapy was initiated by clinical suspicion of an infection. If complications were not considered as infectious, but with an assumed role of the immune system, they were assigned to the inflammatory subgroup. Examples include postoperative ileus, postoperative delirium and anastomotic leakage.²⁶⁻²⁸ Postoperative delirium was considered an inflammatory complication as several cytokines are involved in the occurrence of delirium postoperatively.²⁹ If a patient had multiple complications, of which at least one was of an inflammatory nature, then the patient was assigned to the inflammatory complication group.

Sampling and biochemical analyses

Blood samples were collected at two moments: 1) preoperatively before anaesthesia induction (T0), and 2) at wound closure (T1). After blood samples were centrifuged at 2600 G for 10 minutes, plasma was aliquotted and stored at -80°C. For current analysis, only patients with blood plasma collected at both sampling moments were included (Figure 1). The following inflammatory biomarkers were determined in plasma: C-reactive protein (CRP) (Lower limit of detection (LLD): 0.001 ug/ml), Interleukin-1 β (IL-1 β) (LLD: 1,27 pg/ml), IL-6 (LLD: 0,00 pg/ml), IL-10 (LLD: 3,28 pg/ml), IL-12 (LLD: 5,07 pg/ml), and Tumour necrosis factor-alpha (TNF- α) (LLD: 6,49 pg/ml). Analyses were performed in batches (measured in singular) by Haemoscan® (Groningen) using sandwich ELISA technique for interleukins, developed by BioLegend (San Diego, CA) and high sensitivity CRP ELISA (Dakopatts, Glostrup, Denmark) for CRP. As a measure of the inflammatory response following surgery, postoperative levels (T1) of the inflammatory biomarkers (CRP, IL-1 β , IL-6, IL-10, IL-12 and TNF- α) were used for analyses and adjusted for preoperative levels (T0). Preoperative blood samples were collected in the morning on the day of surgery.

Outcomes

Primary outcome of the current study was the association between inflammatory biomarkers (CRP, IL-1 β , IL-6, IL-10, IL-12 and TNF- α) and the occurrence of complications and inflammatory complications within 30 days postoperatively. Secondary outcomes were to explore inflammatory biomarkers as potential prognostic factors for postoperative complications while controlling for known confounders.

Statistical analyses

Characteristics (preoperative, surgical and biomarker) of all patients, patients developing complications, patients developing inflammatory complications and patients without complications were described. Median and interquartile range of postoperative levels (T1) of inflammatory markers were presented. The occurrence of each postoperative complication (non-inflammatory and inflammatory) was reported per complication (number and percentage) (see supplemental Table 2). Univariable and multivariable logistic regression analyses were used to: 1) explore associations between the inflammatory biomarkers and complications (yes vs. no) within 30 days postoperatively, 2) explore associations between the inflammatory biomarkers and inflammatory complications (yes vs. no) within 30 days postoperatively. Odds

ratios (ORs) and 95% confidence intervals (CIs) were estimated. A theory driven approach for exploratory factor analysis was used for forward selection of variables. First, a null-model was developed with factors associated with postoperative complications based on literature and theory. The included variables were: sex (female or male), GFI (score), CCI (score) and type/intensity of surgery (superficial or intra-abdominal/thoracic). To elucidate a potential independent prognostic effect for each inflammatory biomarker, multivariable regressions analyses was used, while controlling for confounders.³⁰ Logarithmic transformation was applied on inflammatory biomarker data (for preoperative levels (T0) and postoperative levels (T1)) to approach normal distribution by reducing skewness. *P*-values <0.05 were considered to be statistically significant. Inflammatory biomarkers found associated with outcome in univariable analyses were used in multivariable analyses. Statistical analyses were performed using IBM SPSS software, version 23.0 (IBM Corporation, Armonk, NY). Figures were designed with GraphPad Prism version 7.02 (GraphPad Software, San Diego, CA) and Adobe Illustrator, CS6 (Adobe Systems Incorporated, San Jose, CA).

Results

Of the 307 patients included in the 'PICNIC' study, 14 (4.6%) were incorrectly included, and 19 (6.2%) withdrew their consent before the start of the surgical procedure. Subsequently, 50 patients of the 274 included in the 'PICNIC' study were excluded from the current analysis due to incomplete blood plasma sampling. Data of the remaining 224 patients (73%) are presented in the current analysis (Figure 1).

Characteristics of the included patients

Patient and surgical characteristics are shown for all patients (n=224), for patients with complications (n=110) and for patients with an inflammatory complication (n=62) in Table 1. The patients from the 'PICNIC' study excluded due to incomplete blood plasma sampling did not differ from the included patients in characteristics (in patient nor surgical characteristics), which is shown in supplemental Table 1.

The postoperative course

Of the 224 older patients with cancer included in the current analysis, 110 (49.1%) developed complications postoperatively, among whom, 62 (56.4%) developed more than one complication. In total 252 complications occurred, of which 145 (57.5%) were non-inflammatory and 107 (42.4%) were considered inflammatory complications. Detailed description of the nature of the complications in the study population is shown in supplemental Table 2.

Inflammatory biomarker analysis

Postoperative plasma concentrations of inflammatory biomarkers for all patients, patients with complications, patients with inflammatory complications and patients without complications are shown in Table 1, preoperative plasma concentrations are not shown. The inflammatory biomarkers IL-12 and TNF- α did not show a peroperative change in plasma levels (most values remained under the detection limit) and were not used for further analysis.

Fig. 1. Study flowchart.
Flowchart diagram from included and excluded patients in the current study.

Table 1.

Characteristics of all patients, patients developing complications and patients developing inflammatory complications N(%), unless specified otherwise

	All patients (n=224)	Patients with at least one complication (n=110)	Patients with at least one inflammatory complication (n=62)	Patients without complications (n=114)
Age (years) ^a	72 (68-78)	72 (68-78)	72 (68-79)	72 (68-78)
Sex				
Female	116 (51.8%)	45 (40.9%)	22 (35.5%)	71 (62.3%)
Male	108 (48.2%)	65 (59.1%)	40 (64.5%)	43 (37.7%)
GFI ^a	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)
CCI ^a	3 (2-5)	4 (1-4)	4 (3-6)	3 (2-4)
Neo-adjuvant treat- ment				
None	177 (79%)	82 (74.5%)	46 (74.2%)	95 (83.3%)
Chemotherapy	21 (9.4%)	8 (7.3%)	2 (3.2%)	13 (11.4%)
Radiation	8 (3.6%)	5 (4.5%)	3 (4.8%)	3 (2.6%)
Chemoradiation	18 (8%)	15 (13.6%)	11 (17.7%)	3 (2.6%)
Disease stage				
Benign, I and II	118 (53.4%)	59 (53.6%)	32 (51.6%)	59 (52.7%)
III and IV	103 (46.6%)	51 (46.4%)	30 (48.4%)	53 (47.3%)
Anaesthesia duration (min.) ^a	199.5 (121-339)	282 (154.75- 437.5)	319 (174-464.25)	150 (98.75- 227.75)
Type of surgery				
Superficial	71 (31.7%)	23 (20.9%)	14 (22.6%)	48 (42.1%)
Intra-abdominal/ thoracic	153 (68.3%)	87 (79.1%)	48 (77.4%)	66 (57.9%)
Blood loss (liters) ^a	0.15 (0.03-0.475)	0.3 (0.1-0.65)	0.3 (0.1-0.8)	0.1 (0-3)
RBC's transfusions ^a	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Total transfusions (liters) ^a	2 (1-3.5)	3 (2-4.5)	3.5 (1.75-5)	1.6 (1-3)
Epidural	113 (50.4%)	63 (57.3%)	34 (54.8%)	50 (43.9%)
Biomarkers				
T1 – CRPa	5.03 (2.10-9.95)	7.95 (3.7-12.24)	7.54 (3.53-11.91)	3.92 (1.14-6.57)
T1 – IL-1β ^a	0.55 (0.34-0.86)	0.57 (0.36-0.87)	0.57 (0.36-0.91)	0.54 (0.32-0.82)
T1 – IL-6 ^a	88.57 (0-344.82)	228.16 (23.68- 549.21)	309.79 (21.34- 588.81)	0 (0-161.17)
T1 – IL-10 ^a	56 (18-132.5)	95.5 (37.25- 189.75)	107 (29-235.5)	32.5 (13-83.5)
T1 – IL-12 ^a	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
T1 – TNF-α ^a	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

^a Data shown as median (interquartile range). Postoperative values (T1) of the inflammatory biomarkers are shown as a measure of the inflammatory response following surgery. *GFI* Groningen Frailty Indicator, *CCI* Charlson Comorbidity Index, *RBC* Red blood cell, *CRP* C-reactive protein, *IL* interleukin, *TNF-α* tumour necrosis factor α .

Table 2.

Factors associated with postoperative complications and with inflammatory complications, univariable logistic regression analysis.

	Complications (yes vs no) (<i>n</i> =110 vs <i>n</i> =114)	Inflammatory complications ^b (yes vs no) (<i>n</i> =62 vs <i>n</i> =162)
	OR (CI)	OR (CI)
Biomarkers ^a		
CRP	3.88 (1.30-11.61) *	2.28 (0.78-6.67)
IL-1β	0.71 (0.18-2.77)	0.88 (0.20-3.95)
IL-6	2.03 (1.58-2.62) ***	1.80 (1.36-2.39) ***
IL-10	2.27 (1.44-3.57) ***	2.08 (1.25-3.45) **
IL-12	2.11 (0.71-6.20)	1.64 (0.57-4.73)
TNF-α	1.36 (0.71-2.61)	0.85 (0.40-1.81)
Age (years)	1.02 (0.98-1.07)	1.03 (0.98-1.08)
Sex		
Female	1	1
Male	2.4 (1.40-4.08) **	2.5 (1.37-4.61) **
GFI	0.93 (0.80-1.09)	1.003 (0.85-1.19)
CCI	1.29 (1.09-1.53) **	1.38 (1.17-1.65) **
Neo-adjuvant treatment		
None	1	1
Chemotherapy	0.71 (0.28-1.81)	0.30 (0.07-1.34)
Radiation	1.93 (0.45-8.33)	1.71 (0.39-7.43)
Chemoradiation	5.79 (1.62-20.72) **	4.48 (1.64-12.23) **
Disease stage		
Benign, I and II	1	1
III and IV	0.96 (0.57-1.63)	1.09 (0.61-1.96)
Anaesthesia duration (minutes)		
<180	1	1
≥180	3.45 (1.98-6.0) ***	3.55 (1.84-6.85) ***
Type of surgery		
Superficial	1	1
Intra-abdominal/thoracic	2.75 (1.52-4.97) **	1.86 (0.95-3.66)
Blood loss (liters)	2.05 (1.08-3.90) *	2.01 (1.15-3.52) *
RBC's transfusions	1.25 (0.87-1.79)	1.21 (0.90-1.61)
Total transfusions (liters)	1.61 (1.34-1.95) ***	1.39 (1.18-1.64) ***
Epidural	1.69 (0.99-2.87)	1.26 (0.70-2.27)

* $p < .05$, ** $p < .01$, *** $p < .001$ (bold values are considered significant). OR odds ratio, CI 95% confidence interval, GFI Groningen Frailty Indicator, CCI Charlson Comorbidity Index, CRP C-reactive protein, IL interleukin, TNF-α tumour necrosis factor-α. ^a Plasma levels of the inflammatory biomarkers were divided by a factor 100 to improve readability of OR's and 95%CI's. Postoperative values (T1) of the inflammatory biomarkers are used and corrected for preoperative values (T0) after 10Log transformation. ^b Patients with inflammatory complications versus patients without complications and non-inflammatory complications.

Table 3a.

Factors associated with postoperative complications, multivariable logistic regression analysis. A theory driven approach.

	Complications (yes vs no) (n=110 vs n=114) OR (CI)	Complications (yes vs no) (n=110 vs n=114) OR (CI)	Complications (yes vs no) (n=110 vs n=114) OR (CI)	Complications (yes vs no) (n=110 vs n=114) OR (CI)
Sex				
Female	1	1	1	1
Male	2.36 (1.23-4.52) **	2.44 (1.23-4.85) *	2.42 (1.25-4.71) **	2.30 (1.18-4.47) *
GFI	0.96 (0.80-1.14)	0.97 (0.81-1.17)	0.96 (0.81-1.15)	0.94 (0.78-1.12)
CCI	1.32 (1.06-1.64) *	1.28 (1.02-1.62) *	1.32 (1.06-1.66) *	1.32 (1.05-1.65) *
Type of surgery				
Superficial	1	1	1	1
Intra-abdominal/thoracic	3.49 (1.76-6.93) ***	1.44 (0.62-3.37)	2.50 (1.17-5.33) *	3.33 (1.64-6.78) **
IL-6 ^a	-	1.84 (1.32-2.57) ***	-	-
IL-10 ^a	-	-	1.73 (1.02-2.93) *	-
CRP ^a	-	-	-	1.95 (0.62-6.14)
R ²	0.20	0.29	0.22	0.23

* $p < .05$, ** $p < .01$, *** $p < .001$ (bold values are considered significant). OR odds ratio, CI 95% confidence interval, CCI Charlson Comorbidity Index, GFI Groningen Frailty Indicator, CRP C-reactive protein, IL interleukin, $TNF-\alpha$ tumour necrosis factor- α . ^a Plasma levels of the inflammatory biomarkers were divided by a factor 100 to improve readability of OR's and 95%CI's. Postoperative values (T1) of the inflammatory biomarkers are used and corrected for preoperative values (T0) after 10Log transformation.

Clinical and inflammatory factors associated with complications

Univariable logistic regression analyses showed that different inflammatory biomarkers (CRP, IL-6 and IL-10) were associated with the occurrence of postoperative complications (see Table 2). Clinical factors such as male sex, a higher CCI score, receiving neo-adjuvant chemoradiation and more extensive surgery (anaesthesia duration, type of surgery, amount of blood loss and amount of fluid transfusions) were associated with the occurrence of postoperative complications. For the occurrence of specific inflammatory complications, the inflammatory biomarkers IL-6 and IL-10 and clinical factors male sex, a higher CCI score and more extensive surgery, were found associated.

Multivariable logistic regression analysis showed that known clinical factors such as sex, comorbidities and extensive surgery were also in the current study associated with outcome, except frailty (see Table 3) and was considered as null-model. Multivariable models showed an independent prognostic effect for the inflammatory biomarkers IL-6 and IL-10 (adjusted for the confounders from the null-model) for the occurrence of postoperative complications (see Table 3a). When exploring an independent prognostic effect for the inflammatory biomarkers for the occurrence of inflammatory complications, only an effect was observed for IL-6 (adjusted for the confounders from the null-model) as shown in Table 3b.

Table 3b.
 Factors associated with inflammatory complications, multivariable logistic regression analysis. A theory driven approach.

	Inflammatory complications (yes vs no) (n=62 vs n=162) OR (CI)	Inflammatory complications (yes vs no) (n=62 vs n=162) OR (CI)	Inflammatory complications (yes vs no) (n=62 vs n=162) OR (CI)	Inflammatory complications (yes vs no) (n=62 vs n=162) OR (CI)
Sex				
Female	1	1	1	1
Male	1.95 (0.96-3.95)	1.80 (0.86-3.76)	2.02 (0.98-4.17)	1.90 (0.92-3.92)
GFI	1.02 (0.85-1.24)	1.06 (0.87-1.29)	1.05 (0.86-1.27)	1.01 (0.83-1.23)
CCI	1.34 (1.08-1.67) **	1.36 (1.08-1.73) *	1.36 (1.08-1.70) **	1.34 (1.07-1.68) *
Type of surgery				
Superficial	1	1	1	1
Intra-abdominal/thoracic	2.13 (0.99-4.60)	0.73 (0.26-2.01)	1.49 (0.63-3.55)	2.09 (0.93-4.71)
IL-6 ^a	-	2.04 (1.36-3.07) **	-	-
IL-10 ^a	-	-	1.75 (0.96-3.18)	-
CRP ^a	-	-	-	1.37 (0.44-4.25)
R ²	0.12	0.21	0.15	0.13

* $p < .05$, ** $p < .01$, *** $p < .001$ (bold values are considered significant). OR odds ratio, CI 95% confidence interval, CCI Charlson Comorbidity Index, GFI Groningen Frailty Indicator, CRP C-reactive protein, IL interleukin, TNF- α tumour necrosis factor- α . ^a Plasma levels of the inflammatory biomarkers were divided by a factor 100 to improve readability of OR's and 95%CI's. Postoperative values (T1) of the inflammatory biomarkers are used and corrected for preoperative values (T0) after 10Log transformation.

Discussion

The data we present here show that there is a prognostic factor association between the inflammatory biomarkers IL-6 and IL-10, and the occurrence postoperative complications in older patients with cancer. A total number of 252 complications were registered, of which 107 (42.3%) were considered to be immune system related. Male sex, the number of comorbidities and the extent of surgery were found associated with outcome in older patients with cancer undergoing surgery which lays in line with literature (the association was not observed for frailty).

Current findings in contrast to literature

Circulating IL-6 was first proposed as a useful marker for predicting postoperative complications more than 25 years ago.³¹ This cytokine is produced soon after surgical trauma and plasma levels increase in the period following surgery. The finding that plasma levels of IL-6 are associated with the occurrence of postoperative complications is consistent with published literature.³²⁻³⁴ Few studies have investigated the association between IL-6 and postoperative complications, although long-term changes of plasma levels of IL-6 (postoperative day 1) were associated with an increased risk of postoperative complications.³⁵ As a biomarker of the inflammatory response, IL-10 has an unusual position. Although considered an anti-inflammatory cytokine, it also possesses pro-inflammatory properties and has the ability to differently affect function of various immune cells.^{36,37} In the current study associations with patient, surgical and inflammatory mediators with the occurrence of postoperative complications were observed. We hypothesize that patient and surgical factors have an influence on the occurrence of postoperative complications, but also on the inflammatory response to surgery itself (see Figure 2). The number of patients experiencing postoperative complications in the current study is consistent with other studies reporting complication rates in older patients with cancer undergoing surgery.^{38,39}

Based on our data, older patients with cancer are predisposed by their comorbidities scored by the CCI for the development of complications in the postoperative course. The CCI was designed to quantify the risk of mortality over a one-year period after inpatient admission to the hospital by a weighted score computed by presence or absence of 19 comorbidities.⁴⁰ Given previous reports that found comorbidity as a predictor of outcomes in different surgical oncological populations, it is not

unexpected that comorbidities were found to be associated with postoperative complications in older patients.^{8,41,42} Our study underscores that older men are at increased risk compared to women for the development of complications.^{43,44} The distinction in complications rates might be a result of biologic sex-differences. However, other studies show conflicting results.^{9,43,45}

In literature frail patients are prone to postoperative complications when compared to fit patients.⁴⁶ In the current study an association of frailty with the occurrence of postoperative complications was not observed. The lack of association might be explained by the assessment of frailty as it remains controversial how to identify frailty.⁴⁷ In the current study the GFI was used for assessment of frailty.⁴⁸ Most patients were affected in GFI score as result of the oncological disease, however the study population was relatively fit. In literature 42% of older patients with cancer with any stage of solid or hematological malignancy are considered frail, in contrast to the 28.7% in our study (with a GFI score ≥ 4).⁴⁹ However, the lack of association might also be the result of selection bias, as it is likely that patients with the most worse health status are prone to drop out of the study during follow-up or even before surgery or were not eligible for surgical treatment in the first place.⁵⁰

Future perspectives and clinical implications

The possibilities for future research into the inflammatory response following surgery are twofold: 1) evaluating the prognostic value of inflammatory biomarker analysis for a complicated postoperative course and 2) identifying potential targets for preventive immunomodulating interventions. For example, a recent study in mice demonstrated that IL-6 is implicated in the pathophysiology of perioperative neurocognitive decline and that blockade of the IL6-receptor by tocilizumab attenuated neurocognitive decline.⁵¹ Especially in the oncological population, steps aiming at prevention and early detection of postoperative complications are important. The recovery from complications among older patients is unpredictable and variable, and complications can influence short- and long-term outcomes with even death as a possible result.⁵² In addition, adjuvant oncological treatment may be omitted in case of postoperative complications, also leading to decreased survival.^{53,54} In clinical practice, the inflammatory mediators IL-6 and IL-10 may provide early identification of patients with an increased risk of morbidity and thus, help to make decisions about additional monitoring and diagnostic procedures,

preventive measures and potentially the early treatment of postoperative complications. Predicting risk for adverse outcomes following oncological surgery in older patients will help with the implementation of both prophylactic measures and appropriate perioperative treatment plans. Before the above can be achieved, further exploration of the perioperative inflammatory response itself is necessary as the underlying mechanism is not fully understood yet.

Fig. 2. The inflammatory response to surgery

This figure depicts the found and hypothesized factors associated with the inflammatory response to surgery and factors associated with the occurrence of postoperative complications in older patients with cancer.

Evaluation of the study

The number of patients included in the current sub-study is a strength. The current cohort is the largest in which the perioperative changes in plasma levels of inflammatory biomarkers have been explored and associated with postoperative complications in older patients with cancer. To explore the effect of the surgical procedure on plasma levels of inflammatory markers, perioperative changes in plasma were estimated by drawing blood samples immediately before and after the surgical procedure. However, an extended sampling interval might have provided more insightful data on changes of plasma levels of inflammatory biomarkers on a longer term. It is plausible that in some patients blood samples were drawn in the ascending part of the inflammatory response curves. Increasing the diagnostic window of plasma sampling might be valuable for predicting complications.

Postoperative complication severity and subsequent consequences were not taken account of in the current study. The traditional classification of complications by severity (Clavien-Dindo) might not be the most appropriate when exploring an inflammatory phenomenon and associations with the postoperative course. We aimed to elucidating the inflammatory factors that influence postoperative morbidity rather than predict complication severity. In literature inflammatory complications are more frequently used as outcome in studies evaluating the prognostic value of inflammatory biomarkers.^{55,56} In addition, it is a well-known problem that complications are underreported. Underreporting usually occurs when complications are non-severe and not prospectively recorded, which might alter findings and conclusions.⁵⁷ The latter was overcome in our study by prospectively recording complications during the study period and by reviewing registrations after the study period.²⁵

The findings in the current study suggest that all postoperative complications have immune system involvement as inflammatory biomarkers were associated with postoperative complications overall (and not necessarily with inflammatory complications). Dividing complications in categories seemed redundant and the exact linkage between complications remains unclear. However, the results underscores the gap in knowledge considering the perioperative inflammatory response and the influence on the postoperative course.

Conclusions

Besides patient and surgical factors associated with adverse outcomes following oncological surgery in older patients, we also found an independent prognostic factor association with postoperative plasma levels of the inflammatory biomarkers IL-6 and IL-10. The inflammatory mediators are an interesting target for future preventive interventions which should interfere with the intricate inflammatory mechanism with the aim to improve perioperative care and outcome, and might help to improve surgical planning and decision making for older patients with cancer. Further research of the perioperative inflammatory response itself is fundamental as the underlying mechanism is not fully understood yet.

References

1. Bentrem DJ, Cohen ME, Hynes DM, Ko CY, Bilimoria KY. Identification of specific quality improvement opportunities for the elderly undergoing gastrointestinal surgery. *Arch Surg*. 2009;144(11):1013-1020.
2. Huisman MG, Audisio RA, Ugolini G, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: A multicenter prospective cohort study. *Eur J Surg Oncol*. 2015;41(7):844-851.
3. Ellison EC, Pawlik TM, Way DP, Satiaini B, Williams TE. The impact of the aging population and incidence of cancer on future projections of general surgical workforce needs. *Surgery*. 2017.
4. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: Morbidity and mortality from major noncardiac surgery. *J Am Geriatr Soc*. 2005;53(3):424-429.
5. Lawrence VA, Hazuda HP, Cornell JE, et al. Functional independence after major abdominal surgery in the elderly. *J Am Coll Surg*. 2004;199(5):762-772.
6. Couwenberg AM, de Beer FSA, Intven MPW, et al. The impact of postoperative complications on health-related quality of life in older patients with rectal cancer; a prospective cohort study. *J Geriatr Oncol*. 2018;9(2):102-109.
7. Plas M, de Haan JJ, van der Wal-Huisman H, et al. The systemic impact of a surgical procedure in older oncological patients. *Eur J Surg Oncol*. 2019.
8. Rouvelas I, Zeng W, Lindblad M, Viklund P, Ye W, Lagergren J. Survival after surgery for oesophageal cancer: A population-based study. *Lancet Oncol*. 2005;6(11):864-870.
9. Zhou C, Wu XR, Liu XH, et al. Male gender is associated with an increased risk of anastomotic leak in rectal cancer patients after total mesorectal excision. *Gastroenterol Rep (Oxf)*. 2018;6(2):137-143.
10. Tegels JJ, de Maat MF, Hulsewe KW, Hoofwijk AG, Stoot JH. Value of geriatric frailty and nutritional status assessment in predicting postoperative mortality in gastric cancer surgery. *J Gastrointest Surg*. 2014;18(3):439-45; discussion 445-6.
11. Watt DG, Horgan PG, McMillan DC. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: A systematic review. *Surgery*. 2015;157(2):362-380.
12. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery*. 2000;127(2):117-126.
13. Black S, Kushner I, Samols D. C-reactive protein. *J Biol Chem*. 2004;279(47):48487-

48490.

14. Marik PE, Flemmer M. The immune response to surgery and trauma: Implications for treatment. *J Trauma Acute Care Surg.* 2012;73(4):801-808.
15. Hensler T, Heidecke CD, Hecker H, et al. Increased susceptibility to postoperative sepsis in patients with impaired monocyte IL-12 production. *J Immunol.* 1998;161(5):2655-2659.
16. Tang GJ, Huang SL, Yien HW, et al. Tumor necrosis factor gene polymorphism and septic shock in surgical infection. *Crit Care Med.* 2000;28(8):2733-2736.
17. Bittar MN, Carey JA, Barnard JB, et al. Tumor necrosis factor alpha influences the inflammatory response after coronary surgery. *Ann Thorac Surg.* 2006;81(1):132-137.
18. Alazawi W, Pirmadjid N, Lahiri R, Bhattacharya S. Inflammatory and immune responses to surgery and their clinical impact. *Ann Surg.* 2016;264(1):73-80.
19. Rossaint J, Zarbock A. Perioperative inflammation and its modulation by anesthetics. *Anesth Analg.* 2017.
20. Kaufmann KB, Heinrich S, Staehle HF, Bogatyreva L, Buerkle H, Goebel U. Perioperative cytokine profile during lung surgery predicts patients at risk for postoperative complications-A prospective, clinical study. *PLoS One.* 2018;13(7):e0199807.
21. Kumar A, Torres ML, Cliby WA, et al. Inflammatory and nutritional serum markers as predictors of peri-operative morbidity and survival in ovarian cancer. *Anticancer Res.* 2017;37(7):3673-3677.
22. Plas M, Rotteveel E, Izaks GJ, et al. Cognitive decline after major oncological surgery in the elderly. *Eur J Cancer.* 2017;86:394-402.
23. Weerink LBM, van Leeuwen BL, Gernaat SAM, et al. Vitamin status and the development of postoperative cognitive decline in elderly surgical oncologic patients. *Ann Surg Oncol.* 2017.
24. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213.
25. Gunnarsson U, Seligsohn E, Jestin P, Pahlman L. Registration and validity of surgical complications in colorectal cancer surgery. *Br J Surg.* 2003;90(4):454-459.
26. Stakenborg N, Gomez-Pinilla PJ, Boeckstaens GE. Postoperative ileus: Pathophysiology, current therapeutic approaches. *Handb Exp Pharmacol.* 2017;239:39-57.
27. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and

cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One*. 2018;13(4):e0195659.

28. Su'a BU, Mikaere HL, Rahiri JL, Bissett IB, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. *Br J Surg*. 2017;104(5):503-512.

29. Vasunilashorn SM, Ngo L, Inouye SK, et al. Cytokines and postoperative delirium in older patients undergoing major elective surgery. *J Gerontol A Biol Sci Med Sci*. 2015;70(10):1289-1295.

30. Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis research strategy (PROGRESS) 2: Prognostic factor research. *PLoS Med*. 2013;10(2):e1001380.

31. Oka Y, Murata A, Nishijima J, et al. Circulating interleukin 6 as a useful marker for predicting postoperative complications. *Cytokine*. 1992;4(4):298-304.

32. Kimura F, Shimizu H, Yoshidome H, et al. Circulating cytokines, chemokines, and stress hormones are increased in patients with organ dysfunction following liver resection. *J Surg Res*. 2006;133(2):102-112.

33. Kimura F, Shimizu H, Yoshidome H, et al. Increased plasma levels of IL-6 and IL-8 are associated with surgical site infection after pancreaticoduodenectomy. *Pancreas*. 2006;32(2):178-185.

34. Musleh GS, Datta SS, Yonan NN, et al. Association of IL6 and IL10 with renal dysfunction and the use of haemofiltration during cardiopulmonary bypass. *Eur J Cardiothorac Surg*. 2009;35(3):511-514.

35. Rettig TC, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EM, Noordzij PG. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery. *Ann Surg*. 2016;263(6):1207-1212.

36. Mocellin S, Marincola F, Rossi CR, Nitti D, Lise M. The multifaceted relationship between IL-10 and adaptive immunity: Putting together the pieces of a puzzle. *Cytokine Growth Factor Rev*. 2004;15(1):61-76.

37. Mocellin S, Marincola FM, Young HA. Interleukin-10 and the immune response against cancer: A counterpoint. *J Leukoc Biol*. 2005;78(5):1043-1051.

38. Kristjansson SR, Nesbakken A, Jordhoy MS, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. *Crit Rev Oncol Hematol*. 2010;76(3):208-217.

39. Badgwell B, Stanley J, Chang GJ, et al. Comprehensive geriatric assessment of risk factors associated with adverse outcomes and resource utilization in cancer patients undergoing abdominal surgery. *J Surg Oncol*. 2013;108(3):182-186.

40. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis.* 1987;40(5):373-383.
41. Sanabria A, Carvalho AL, Melo RL, et al. Predictive factors for complications in elderly patients who underwent head and neck oncologic surgery. *Head Neck.* 2008;30(2):170-177.
42. Lagarde SM, Reitsma JB, Maris AK, et al. Preoperative prediction of the occurrence and severity of complications after esophagectomy for cancer with use of a nomogram. *Ann Thorac Surg.* 2008;85(6):1938-1945.
43. Kirchhoff P, Dincler S, Buchmann P. A multivariate analysis of potential risk factors for intra- and postoperative complications in 1316 elective laparoscopic colorectal procedures. *Ann Surg.* 2008;248(2):259-265.
44. Brooks Carthon JM, Jarrin O, Sloane D, Kutney-Lee A. Variations in postoperative complications according to race, ethnicity, and sex in older adults. *J Am Geriatr Soc.* 2013;61(9):1499-1507.
45. Offner PJ, Moore EE, Biffl WL. Male gender is a risk factor for major infections after surgery. *Arch Surg.* 1999;134(9):935-8; discussion 938-40.
46. Fagard K, Leonard S, Deschodt M, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. *J Geriatr Oncol.* 2016;7(6):479-491.
47. Bouillon K, Kivimaki M, Hamer M, et al. Measures of frailty in population-based studies: An overview. *BMC Geriatr.* 2013;13:64-2318-13-64.
48. Meulendijks FG, Hamaker ME, Boereboom FT, Kalf A, Vogtlander NP, van Munster BC. Groningen frailty indicator in older patients with end-stage renal disease. *Ren Fail.* 2015;37(9):1419-1424.
49. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: A systematic review. *Ann Oncol.* 2015;26(6):1091-1101.
50. Mody L, Miller DK, McGloin JM, et al. Recruitment and retention of older adults in aging research. *J Am Geriatr Soc.* 2008;56(12):2340-2348.
51. Hu J, Feng X, Valdearcos M, et al. Interleukin-6 is both necessary and sufficient to produce perioperative neurocognitive disorder in mice. *Br J Anaesth.* 2018;120(3):537-545.
52. Bellomo R, Goldsmith D, Russell S, Uchino S. Postoperative serious adverse events in a teaching hospital: A prospective study. *Med J Aust.* 2002;176(5):216-218.
53. Bos AC, van Erning FN, van Gestel YR, et al. Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. *Eur J Cancer.*

2015;51(17):2553-2561.

54. Etzioni DA, El-Khoueiry AB, Beart RW, Jr. Rates and predictors of chemotherapy use for stage III colon cancer: A systematic review. *Cancer*. 2008;113(12):3279-3289.

55. Welsch T, Frommhold K, Hinz U, et al. Persisting elevation of C-reactive protein after pancreatic resections can indicate developing inflammatory complications. *Surgery*. 2008;143(1):20-28.

56. Warschkow R, Steffen T, Beutner U, Muller SA, Schmied BM, Tarantino I. Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: A retrospective study of 1,187 patients. *Int J Colorectal Dis*. 2012;27(10):1377-1392-4. Epub 2011 Dec 22.

57. Feldman L, Barkun J, Barkun A, Sampalis J, Rosenberg L. Measuring postoperative complications in general surgery patients using an outcomes-based strategy: Comparison with complications presented at morbidity and mortality rounds. *Surgery*. 1997;122(4):711-9; discussion 719-20.

Supplemental Table 1.
Characteristics of all patients, patients developing complications and patients developing inflammatory complications N(%), unless specified otherwise

	Included patients (n=224)	Excluded patients due to incomplete sampling (n=50)	P-value
Age (years) ^a	72 (68-78)	70 (67-74)	0.064
Sex			0.426
Female	116 (51.8%)	29 (58%)	
Male	108 (48.2%)	21 (42%)	
GFI ^a	2 (1-4)	2 (1-3)	0.238
CCI ^a	3 (2-5)	3 (2-5)	0.917
Neo-adjuvant treatment			0.831
None	177 (79%)	37 (82.2%)	
Chemotherapy	21 (9.4%)	0 (0%)	
Radiation	8 (3.6%)	2 (4.4%)	
Chemoradiation	18 (8%)	6 (13.3%)	
Disease stage			0.400
Benign, I and II	118 (53.4%)	27 (60%)	
III and IV	103 (46.6%)	18 (40%)	
Anaesthesia duration (minutes) ^a	199.5 (121-339)	195 (127.5-355)	
Type of surgery			0.941
Superficial	71 (31.7%)	15 (30%)	0.669
Intra-abdominal/thoracic	153 (68.3%)	35 (70%)	
Blood loss (liters) ^a	0.15 (0.03-0.475)	0.15 (0.025-0.3)	0.442
RBC's transfusions ^a	0 (0-0)	0 (0-0)	0.642
Total transfusions (liters) ^a	2 (1-3.5)	2 (1-3.5)	0.398
Epidural	113 (50.4%)	21 (46.7%)	0.624

^a Data shown as median (interquartile range). CCI Charlson Comorbidity Index, GFI Groningen Frailty Indicator, RBC Red blood cell, CRP C-reactive protein, IL interleukin, TNF- α tumour necrosis factor- α . Group differences were explored using Mann-Whitney U and Pearson R testing.

Supplemental Table 2.
Description of the complications (non-inflammatory and inflammatory) in the postoperative period

Non - Inflammatory	Number (%)	Inflammatory	Number (%)
Cardiac	145 (57.5)	Delirium	107 (42.4)
Nutritional	18 (12.4)	Surgical site infection	29 (27.1)
Transfusion	17 (11.7)	Pneumonia	26 (24.3)
Electrolyte disturbances	15 (10.3)	Urinary tract infection	21 (19.6)
Fluid overload	14 (9.7)	Bloodstream infection	11 (10.2)
Chyle leakage	10 (6.9)	Postoperative ileus	8 (7.5)
Urologic	9 (6.2)	Anastomotic leakage	4 (3.7)
Pulmonary	8 (5.5)	Other	2 (1.9)
Re-bleeding	7 (4.8)		6 (5.6)
Neurologic	7 (4.8)		
Renal	6 (4.1)		
Platzbauch	3 (2.1)		
Medication	3 (2.1)		
Other	25 (17.2)		

Data per complication are shown, some patients developed > 1 complication.

Chapter 4

Enteral nutrition during surgery: how to proceed after SANICS II

M. Plas
B. L. van Leeuwen
J. J. de Haan

Dear editor,

We applaud Emmeline Peters and colleagues¹ for their well-powered, double-blind, randomised controlled trial (SANICS II) of the effect of perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery with primary anastomosis. The study¹ considered the risk of postoperative ileus as a primary outcome, in addition to anastomotic leakage and other clinical outcome parameters, including inflammation, as secondary outcomes. The nutritional intervention showed no advantage over standard care in terms of the primary or secondary outcomes. This absence of effect seemingly contrasts with much other published experimental and preclinical data, which have consistently shown anti-inflammatory and organ-preserving effects of enriched enteral nutrition compared with fasting.² Looking more closely at the patients and surgical procedures selected for SANICS II might explain why nutritional intervention did not benefit patients, and could provide perspectives for future studies. To show clear modulation of inflammation and organ function, a cohort must include patients with strong inflammatory responses and a high proportion of inflammatory complications. The characteristics of patients in the SANICS II trial suggest that the preconditions for development of a strong inflammatory response, which would allow for meaningful attenuation by the intervention, were not met. First, most patients in both study groups underwent laparoscopy. Laparoscopic or minimally invasive procedures induce a more moderate inflammatory response compared with open surgical procedures.³ Second, all patients were treated according to the enhanced recovery after surgery programme, which is associated with a decreased systemic inflammatory response in the postoperative period and a reduced number of complications.⁴ Indeed, the proportion of patients with inflammatory complications in SANICS II was low. As discussed by Peters and colleagues,¹ the large proportion of patients undergoing laparoscopy and implementation of the enhanced recovery after surgery protocol might have attenuated the inflammatory response to such an extent that nutritional intervention could not further improve clinical outcomes. Furthermore, the median duration of surgery was quite short: 145 min (IQR 119–185) in the intervention group and 150 min (120–185) in the control group. The duration of surgical procedures is correlated with the magnitude of the inflammatory response and the incidence of inflammatory complications.⁵ Finally, patients in the intervention group had a median age of 69 years, and thus represented a younger subgroup of elderly patients. With advancing age, the immune system declines

in efficiency, leading to a more pronounced cytokine response to surgery and a greater susceptibility to pathology following inflammatory events (a process termed inflammaging).^{6,7} The surgical stress response in the patients might have been too mild for enteral nutrition to have a beneficial effect. One possibility for future research is to explore nutritional intervention in surgical patients with more severe inflammatory responses and a higher incidence of postoperative complications, such as patients aged 75 years or older, with several comorbidities, who are scheduled for major oncological surgery without a prehabilitation or rehabilitation programme. The benefits of the enhanced recovery after surgery protocol should not be denied to patients; however, future studies could select patients who are elderly or who undergo open surgical procedures lasting more than 3 h. Although SANICS II showed that perioperative nutrition is not a beneficial intervention for all surgical patients, it should serve as a basis for further explorations regarding the applicability of enteral nutrition for improving outcomes of major surgery.

References

1. Peters EG, Smeets BJJ, Nors J, et al. Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): A multicentre, double-blind, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2018;3(4):242-251.
2. Lubbers T, Kox M, de Haan JJ, et al. Continuous administration of enteral lipid- and protein-rich nutrition limits inflammation in a human endotoxemia model. *Crit Care Med*. 2013;41(5):1258-1265.
3. Veenhof AA, Sietses C, von Blomberg BM, et al. The surgical stress response and postoperative immune function after laparoscopic or conventional total mesorectal excision in rectal cancer: A randomized trial. *Int J Colorectal Dis*. 2011;26(1):53-59.
4. Cabellos Olivares M, Labalde Martinez M, Torralba M, Rodriguez Fraile JR, Atance Martinez JC. C-reactive protein as a marker of the surgical stress reduction within an ERAS protocol (enhanced recovery after surgery) in colorectal surgery: A prospective cohort study. *J Surg Oncol*. 2018;117(4):717-724.
5. Procter LD, Davenport DL, Bernard AC, Zwischenberger JB. General surgical operative duration is associated with increased risk-adjusted infectious complication rates and length of hospital stay. *J Am Coll Surg*. 2010;210(1):60-5.e1-2.
6. Duggal NA, Upton J, Phillips AC, Sapey E, Lord JM. An age-related numerical and functional deficit in CD19(+) CD24(hi) CD38(hi) B cells is associated with an increase in systemic autoimmunity. *Aging Cell*. 2013;12(5):873-881.
7. Lord JM, Midwinter MJ, Chen YF, et al. The systemic immune response to trauma: An overview of pathophysiology and treatment. *Lancet*. 2014;384(9952):1455-1465.

Part 2

Postoperative neurocognitive disorders

Chapter 5

Cognitive decline after major oncological surgery in the elderly

M. Plas
E. Rotteveel,
G.J. Izaks
J.M. Spikman
H. van der Wal-Huisman
B. van Etten
A.R. Absalom
M.J.E. Mourits
G.H. de Bock
B.L. van Leeuwen

Abstract

Background : Elderly patients undergoing oncological surgery experience postoperative cognitive decline. The aims of this study were to examine the incidence of cognitive decline 3 months after surgery and identify potential patient-, disease- and surgery-related risk factors for postoperative cognitive decline in onco-geriatric patients.

Methods : A consecutive series of elderly patients (≥ 65 years) undergoing surgery for the removal of a solid tumour were included ($n = 307$). Cognitive performance was assessed pre-operatively and 3 months postoperatively. Postoperative decline was defined as a decline in scores of cognitive tests of $\geq 25\%$ on ≥ 2 of 5 tests.

Results : Of the patients who had completed the assessments, 117 (53%, 95% confidence interval [CI]: 47–60) had improved cognitive test scores, whereas 26 (12%, 95% CI: 7.6–16) showed cognitive decline at 3 months postoperatively. In patients aged >75 years, the incidence of overall cognitive decline 3 months postoperatively was 18% (95% CI: 9.3–27). In patients with lower pre-operative Mini-Mental State Examination (MMSE) score (≤ 26) the incidence was 37% (95% CI: 18–57), and in patients undergoing major surgery it was 18% (95% CI: 10.6–26). Of the cognitive domains, executive function was the most vulnerable to decline.

Conclusion : About half of the elderly patients show improvement in postoperative cognitive performance after oncological surgery, whereas 12% show cognitive decline. Advanced age, lower pre-operative MMSE score and major surgery are risk factors for cognitive decline at 3 months postoperatively and should be taken into account in the clinical decision-making progress. Research to develop interventions to preserve quality of life should focus on this high-risk subpopulation.

Introduction

Approximately 3.45 million people in Europe were diagnosed with cancer in 2012, of which more than half in patients were aged ≥ 65 years.^{1,2} As the population ages, and cancer is a disease of the elderly, the proportion of old and very old cancer patients increases.³ As surgery is the principle treatment for most solid tumours, the number of elderly patients undergoing surgery is expected to increase rapidly in the upcoming decades. A substantial proportion of these elderly patients will experience cognitive decline, especially in memory and executive functioning when compared to pre-operative levels of cognition.⁴⁻⁶

Cognitive decline can be observed in the first few days to weeks after surgery and persists for several months to years thereafter.⁷⁻⁹ Postoperative cognitive decline has been associated with poor short- and long-term outcomes, including decreased quality of life, increased disability, increased mortality and greater utilisation of social and financial assistance.^{10,11} Demographic factors as well as surgical characteristics might be associated with an increased risk of developing this complication.¹²⁻¹⁵ Nevertheless, knowledge of the incidence and predictors of postoperative cognitive decline is inconclusive. This study is, as far as we know, the first to include a consecutive series of surgical oncological patients aged ≥ 65 years with pre- and postoperative tests.

The aims of this study were to examine the incidence of cognitive decline 3 months after surgery and to identify potential patient, disease and surgery related risk factors for postoperative cognitive decline in onco-geriatric patients. Insight into the incidence and risk factors for cognitive decline after surgery in this specific population may provide focus points for clinical decision making and preventive interventions.

Methods

The 'PICNIC' (Postoperative Cognitive dysfunction In elderly Cancer patients) study was a prospective observational study conducted at the University Medical Center Groningen (UMCG, Groningen, the Netherlands). It was prospectively registered on the Dutch Clinical Trial Database (trial number NL31486.042.10), following approval

by the Medical Ethical Committee of the UMCG. Data collection was conducted according to the Declaration of Helsinki.

A consecutive series of patients aged ≥ 65 years, admitted to the UMCG for the surgical excision of a solid tumour (see Table 1), were included. Patients were enrolled between July 2010 and April 2014. The following exclusion criteria were included: any physical condition potentially impeding compliance with the study, such as a severe visual or auditory impairment or a recent history of stroke or pre-operative cognitive deficits and insufficient understanding of the Dutch language. All surgical procedures were elective and performed in optimal conditions by an experienced surgical team, as the UMCG is a tertiary referral centre. Written informed consent was obtained from all participating patients, and patients' identity was protected by coding data.

Cognitive domains

Neuropsychological tests to determine performance in three cognitive domains (memory, executive function and information processing speed) were conducted at baseline (approximately 2 weeks before surgery) and 3 months postoperatively.

Memory

Memory was assessed using the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT).¹⁶ Performance on the RAVLT was expressed as the total number of words (maximum of 75) correctly remembered during the five immediate recall trials (lowest score, 0; highest score, 75) and the total number of words (maximum of 15) remembered at the delayed recall trial (lowest score, 0; highest score, 15).

Information processing speed

The Trail Making Test part A (TMT-A) was used to measure information processing speed.¹⁷ The number of seconds it took to complete the TMT-A (lowest score, 0; highest score, 480) was used as outcome variable.

Executive function

The Ruff's Figural Fluency Test (RFFT) and the Trail Making Test part B (TMT-B) were used to measure executive functions (strategic reasoning, planning and the ability to ignore distracters).^{17,18} The total number of unique designs drawn in parts 1-5 (lowest score:0; highest score:175) of the RFFT and the number of seconds it took to complete the TMT-B (lowest score:0; highest score:480) were used as outcome variables.

Assessments

The Mini-Mental State Examination (MMSE) to assess overall cognitive function and the Groningen Frailty Indicator (GFI) to assess frailty were conducted at baseline.^{19,20} These tests and questionnaires were submitted in an ambulant setting and were conducted by a trained nurse or a psychology graduate student, preoperatively and 3 months postoperatively. Clinical data such as age, primary diagnosis and perioperative details, Charlson comorbidity index (CCI) (hypertension excluded), postoperative complications as scored by Clavien Dindo complication classification (postoperative delirium excluded), and indicators for socioeconomic status (SES) were prospectively collected.²¹

Definitions

Based on literature, postoperative cognitive decline was defined as a decline of $\geq 25\%$ at 3 months postoperatively, relative to the baseline score, in the scores of ≥ 2 tests performed as described above (the RAVLT immediate recall, the RAVLT delayed recall, the RFFT, the TMT-A and the TMT-B).²² For the specific cognitive domains, cognitive decline at 3 months was defined as a decline of $\geq 25\%$ in the test score on one test for that specific domain, compared with baseline. A surgical procedure with anaesthesia duration more than 210 min was defined as major surgery, and a procedure in the abdominal or thoracic cavity was defined as intracavitary surgery. For SES, postal codes were assigned to three categories.

Data analysis and statistics

Data are presented as median and interquartile range. To investigate whether included patients were representative of the study population, chi-square testing was performed. A Wilcoxon signed rank test was performed to compare cognitive assessment scores between both test moments. Univariate and multivariate logistic regression analyses were used to determine risk factors for postoperative cognitive decline 3 months postoperatively, overall and per cognitive domain. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. p -values < 0.05 were considered to be statistically significant. Data analysis was performed using IBM SPSS Statistics, version 23.

Results

Fig. 1 shows the flowchart of the inclusions. Of the 307 patients included in the trial, 14 patients (4.6%) were incorrect inclusions, and 19 patients (6.2%) withdrew their consent before the surgical procedure. In addition, 55 patients of the remaining 274 patients (20%) were excluded from the current analysis: eight patients (2.9%) had more than half of their baseline test data missing, five patients (1.6%) died before the 3 months follow-up, and 42 patients (14%) did not undergo the assessment 3 months postoperatively. The latter was mainly due to overall poor health status. Data of the remaining 219 patients (71%) were included in the current analysis (Fig. 1).

Fig. 1. Flowchart diagram from in- and excluded patients. Of the 307 included patients, 33 were excluded before surgery. Three months postoperatively 55 patients were excluded. The sample of current analysis included 219 patients.

There were no statistically significant differences between the 219 included patients and the 55 patients that were excluded from the current analysis regarding demographic, tumour and surgical characteristics (see table 1). Postoperatively, in 13 of 219 included patients, histological examination did not show malignant disease (in these cases the pathology showed pancreatic cysts in two (0.9%) patients, schwannoma in one (0.5%) patient, lipomas in three (1.4%) patients, fibro thecomas in two (0.9%) patients, tubulo villous adenomas in two (0.9%) patients and ovarian cysts in three (1.4%) patients).

Overall, there was statistically significant improvement comparing baseline scores to 3 months postoperatively (Table 2). Of the 219 patients included in the current analysis, 26 (12%, 95%CI:7.6-16) met the study criteria for overall cognitive decline 3 months postoperatively, whereas 117 (53%, 95%CI:47-60) patients had improved cognitive scores with a $\geq 25\%$ increase in score on ≥ 2 tests. In total, 45 (21%) patients showed decline in the executive function domain, 33 (15%) patients in the information processing domain and 29 (13%) patients in the memory domain (Fig. 2). As shown in Fig. 3, among patients aged >75 years, the incidence of overall cognitive decline was 18% (95%CI:9.3-27). Among all included patients with lower pre-operative MMSE score (≤ 26) the incidence was 37% (95%CI:18-56), in patients who underwent major surgery the incidence was 18% (95%CI:10.6-25) and in patients with intra-cavitary surgery the incidence of cognitive decline at 3 months was 14% (95%CI:8.5-19).

During admission, 23 (10.5%, 95%CI:6.4-14) patients were diagnosed and treated for postoperative delirium. Of these, 10 patients met the study criteria for postoperative cognitive decline 3 months postoperatively.

Univariate and multivariate predictors for overall cognitive decline at 3 months postoperatively are shown in Table 3. Lower pre-operative MMSE score (≤ 26) (OR 6.4, 95%CI:2.1-19), major surgery (OR 2.7, 95%CI:1.0-7.5) were independent risk factors for overall cognitive decline 3 months postoperatively, adjusted for postoperative delirium (OR 5.3, 95%CI 1.8-16).

Table 1.
Patient, tumour and surgical characteristics (n=274)

	Included in current analysis (n=219) n (%)	Age (median)	Excluded from cur- rent analysis ^a (n=55) n (%)	p ^{**}
Patient and tumour characteristics				
Age (years)				0.3
≤ 75	148 (68)	69	33 (60)	
> 75	71 (32)	79	22 (40)	
Gender				0.3
Female	112 (51)	72	32 (59)	
Male	107 (49)	70	22 (41)	
Living situation				0.7
Lives independently with others	154 (70)	70	36 (72)	
Lives alone	65 (30)	77	13 (26)	
Nursing home	-		1 (2)	
Educational level				0.3
Low	190 (87)	71	45 (82)	
High	29 (13)	70	10 (18)	
Socioeconomic status				0.2
Low	128 (60)	71	37 (70)	
Intermediate	61 (29)	70	9 (17)	
High	23 (11)	72	7 (13)	
Groningen Frailty Indicator (GFI)				0.09
≤ 3	143 (65)	70	29 (53)	
> 3	76 (35)	72	26 (47)	
Mini-Mental State Examination (MMSE)				0.5
≤ 26	24 (11)	75	8 (15)	
> 26	195 (89)	71	47 (85)	
Charlson comorbidity index (CCI)				0.9
≤ 2	87 (40)	71	20 (39)	
> 2	131 (60)	71	31 (61)	
Tumour type				0.3
Carcinoma	150 (69)	71	38 (78)	
Sarcoma	26 (12)	71	8 (16)	
Melanoma	25 (12)	71	2 (4)	
Other malignancy	3 (1)	78	-	
No malignancy	13 (6)	73	1 (2)	
Disease stage				0.2
Benign & I	67 (31)	71	13 (26)	
II	58 (27)	71	7 (14)	
III	51 (24)	71	14 (29)	
IV	40 (18)	69	15 (31)	
Surgical characteristics				
Major surgery				0.3
No	120 (55)	71.5	26 (47)	
Yes	99 (45)	70	29 (53)	

Table 1.
(continued)

Intracavitary surgery				1.0
No				
Skin / Extremities / Neck	77 (35)	71	19 (36)	
Yes				
Abdomen	127 (58)	71	31 (58)	
Thorax	15 (7)	70	3 (6)	
Postoperative course				
Postoperative delirium				0.7
No	196 (89)	71	43 (88)	
Yes	23 (11)	76	6 (12)	
Postoperative complications (without delirium)				0.6
Grade I	20 (9)	71.5	3 (6)	
Grade II	55 (25)	72	9 (18)	
Grade III	19 (9)	70	4 (8)	
Grade IV	8 (4)	68.5	4 (8)	
Re-operation within 30 days				1.0
No	201 (92)	71	45 (92)	
Yes	18 (8)	69.5	4 (8)	

^a Patients were excluded if they had more than 2 out of 5 of their baseline tests missing, withdrew their informed consent during follow-up, did not undergo the assessment 3 months postoperatively or died during follow-up. ** *p* values were derived from a Chi-Square test (<0.05 was considered significant).

Table 2.
Cognitive assessment scores per test part (n=219)

Domain	Baseline median [interquartile range]	3 months follow-up median [interquartile range]	<i>p</i> *
Memory			
RAVLT immediate recall	32 [25-39]	39 [32-47]	<0.001
RAVLT delayed recall	7 [4-9]	8 [5-10]	<0.001
Information processing speed			
TMT-A	48.9 [39.25-65.40]	45 [36.55-59.50]	0.001
Executive function			
RFFT	52 [40-64]	61 [48-79]	<0.001
TMT-B	118.6 [88.18-156.70]	110.6 [79.53-146.88]	0.008

RAVLT, Rey's Auditory Verbal Learning Test; TMT-A, Trail making Test part A; TMT-B, Trail making Test part B; RFFT, Ruff Figural Fluency Test. **p* values were derived from a Wilcoxon signed rank test paired (<0.05 was considered significant).

The overlap between affected cognitive domains in patients 3 months postoperatively is shown in Fig. 2, and risk factors for decline in these domains are shown in Table 4. Advanced age (>75 years) (OR 3.8, 95%CI:1.7-8.8) and higher CCI (> 2) (OR 2.7, 95%CI:1.0-7.0) were risk factors for decline in memory function. Intra-cavitary surgery (OR 2.9, 95%CI:1.2-6.8) and pre-operative lower MMSE score (≤ 26) (OR 4.5, 95%CI:1.8-11) were risk factors for decline in executive function. For the information processing, a lower pre-operative MMSE score (≤ 26) (OR 2.7, 95%CI:1.0-7.1) was a risk factor.

Fig. 2. This figure depicts the number and overlap of patients with an affected cognitive domain 3 months postoperatively. Decline in a cognitive domain was defined as a decline of $\geq 25\%$ on ≥ 1 tests in that specific domain.

Table 3.

Logistic regression analysis for cognitive decline 3 months postoperatively (n=219)

Risk factor	OR (95% CI)	Univariate <i>p</i>	OR (95% CI)	Multivariate <i>p</i>
Age (years)				
≤ 75	1			
> 75	2.3 (1.0-5.3)	0.046		
Educational level				
Low	1			
High	0.5 (0.1-2.2)	0.4		
Groningen Frailty Indicator (GFI)				
≤ 3	1			
> 3	1.0 (0.4-2.4)	1.0		
Mini-Mental State Examination (MMSE)				
> 26	1		1	
≤ 26	6.3 (2.4-17)	<0.001	6.4 (2.1-19)	0.001
Charlson comorbidity index (CCI)				
≤ 2	1			
> 2	1.0 (0.4-2.3)	1.0		
Major surgery				
No	1		1	
Yes	3.1 (1.3-7.5)	0.012	2.7 (1.0-7.5)	0.048
Intra-cavitary surgery				
No	1			
Yes	2.1 (0.8-5.9)	0.1		
Disease stage				
Benign & I	1			
II	2.2 (0.8-6.1)	0.1		
III	0.7 (0.2-2.6)	0.6		
IV	0.7 (0.2-2.9)	0.6		
Socioeconomic status				
Low	1			
Intermediate	1.1 (0.4-2.6)	0.9		
High	0.3 (0.0-2.5)	0.3		
Postoperative delirium				
No	1		1	
Yes	8.7 (3.3-23)	<0.001	5.3 (1.8-16)	0.002
Postoperative complications (without delirium)				
No	1			
Yes	1.7 (0.7-3.8)	0.2		
Re-operation within 30 d				
No	1			
Yes	0.9 (0.2-4.3)	0.9		

OR, odds ratio; CI, confidence interval. Bold values are considered statistically significant. Postoperative cognitive decline was defined as a decline of ≥25% on ≥2 out of 5 test parts compared to baseline. *p* values <0.05 were considered significant.

Table 4. Logistic regression analysis for decline per cognitive domain 3 months postoperatively (n=219)

Risk factor	Memory (n=29)			Executive function (n=45)			Information processing (n=33)		
	Univariate OR (95%CI)	<i>p</i>	Multivariate OR (95%CI)	Univariate OR (95%CI)	<i>p</i>	Multivariate OR (95%CI)	Univariate OR (95%CI)	<i>p</i>	Multivariate OR (95%CI)
Age (years)									
≤ 75	1		1	1		1	1		
> 75	3.6 (1.6-8.0)	0.002	3.8 (1.7-8.8)	1.7 (0.9-3.4)	0.1	1.1 (0.5-2.3)	1.1 (0.5-2.3)	0.9	
Educational level									
Low	1			1		1	1		
High	0.4 (0.1-2.0)	0.3		0.8 (0.3-2.2)	0.6	0.18 (0.0-1.3)	0.18 (0.0-1.3)	0.09	
Groningen Frailty Indicator (GFI)									
≤ 3	1			1		1	1		
> 3	1.4 (0.6-3.1)	0.4		0.9 (0.5-1.9)	0.8	1.5 (0.7-3.1)	1.5 (0.7-3.1)	0.3	
Mini-Mental State Examination (MMSE)									
> 26	1			1		1	1		1
≤ 26	3.2 (1.2-8.7)	0.019		4.0 (1.7-9.7)	0.002	4.5 (1.8-11.4)	2.7 (1.0-7.1)	0.047	2.7 (1.0-7.1)

Charlson comorbidity index (CCI)	≤ 2	1		1				1	
	> 2	2.7 (1.1-7.0)	0.038	1 (1.0-7.0)	2.7 0.046	0.8 (0.4-1.6)	0.6	1.6 (0.7-3.6)	0.2
Major surgery	No	1				1		1	
	Yes	1.4 (0.6-3.0)	0.5			1.5 (0.8-2.9)	0.2	1.2 (0.6-2.5)	0.7
Intra-cavitary surgery	No	1				1		1	
	Yes	1.9 (0.8-5.0)	0.2			2.6 (1.1-5.8)	0.025	2.9 (1.2-6.8)	0.7
Disease stage	Benign & I	1				1		1	
	II	1.0 (0.4-2.8)	0.9			2.1 (0.9-5.0)	0.09	1.9 (0.7-4.7)	0.2
	III	0.8 (0.3-2.2)	0.6			1.1 (0.4-2.9)	0.9	0.9 (0.3-2.6)	0.8
	IV	0.6 (0.2-2.2)	0.5			0.9 (0.3-2.7)	0.8	0.7 (0.2-2.5)	0.6
Socioeconomic status	Low	1				1		1	
	Intermediate	0.7 (0.3-1.8)	0.4			1.0 (0.5-2.2)	0.9	1.1 (0.5-2.6)	0.8
	High	0.2 (0.0-1.9)	0.2			0.8 (0.3-2.6)	0.7	0.9 (0.2-3.2)	0.8

OR, odds ratio; CI, confidence interval. Bold values are considered statistically significant. Decline in a cognitive domain was defined as a decline of ≥25% on ≥1 test in that specific domain. Predictors with a *p*-value of < 0.15 in univariate analysis were used in a multivariate model. A *p*-value of < 0.05 was considered significant.

Fig. 3. Incidence of overall cognitive decline and decline in cognitive domains in specific patient groups (n=219)

Discussion

In the present study, we found that although the group average scores in the cognitive tests improved significantly between baseline and 3 months after surgery, there was a subset of patients with a significant decline, with 12% (95%CI:7.6-16) of the patients showing evidence of cognitive decline. Advanced age (>75 years old), lower pre-operative MMSE score (≤ 26) and major surgery were risk factors for cognitive decline at 3 months postoperatively, when adjusting for postoperative delirium. The executive function domain was most vulnerable for decline. The incidence of postoperative cognitive decline was even higher in specific sub-groups of the study population. In patients with advanced age (>75 years) or those undergoing major surgery, 18% showed cognitive decline and in patients with lower pre-operative MMSE score (≤ 26) the incidence was 37%.

The learning effect

In general, it is well known that repetitive neuropsychological testing can result in a so-called test-retest effect, expressing the effects of learning from the previous test session.²³ In our population we found that there was an overall improvement in the test session after the first test session, which might be interpreted as a learning effect. However, it is more likely that patients had performed under their optimal cognitive level in the first test session, as a result of stress related to the fact that serious surgery had to take place.²⁴ So, better scores at 3 months postoperative might partly reflect the real cognitive levels of patients rather than a cognitive improvement. We deem it likely that a combination of a learning effect and reduced stress explains the results we found with regard to improved performance after surgery.²⁵ Of those included, 53% (95%CI 47-60) improved their cognitive test scores with $\geq 25\%$ on ≥ 2 tests. This finding makes a decline in cognitive test scores in the rest of the patients all the more striking.

Incidence of postoperative cognitive decline

The incidence of 12% (95%CI 7.6-16) postoperative cognitive decline shown in our elderly oncological population is in line with previous studies reporting an incidence of cognitive decline varying from 9.9% to 16% in older patients undergoing non-cardiac surgery at 3 months postoperatively.^{7,11,26} As described in our results, 14% of the included patients were not able to fulfil the cognitive assessment and questionnaires at 3 months follow-up. The latter was mainly due to self-reported overall health status. Possibly some patients refused to undergo follow-up testing

because they wished to conceal any form of cognitive impairment.¹³ Dropout in our study is comparable to other studies in the same research field.^{8,11} Due to dropout, the most strongly affected individuals may not have been taken into account in the evaluation of the incidence rates for cognitive decline across studies, and it might be that the true incidence of cognitive decline is even higher than the incidences we have reported.

Risk factors for overall cognitive decline

According to the literature, MMSE scores decline with age.²⁷ In our study lower pre-operative MMSE score was found to be predictive of the occurrence of cognitive decline after surgery. Lower pre-operative MMSE scores reflect pre-operative cognitive deficits, like mild cognitive impairment.²⁸ This suggests that when cognitive resilience is lower, patients are more susceptible to develop further cognitive deterioration after surgery.²⁹ Age itself was not found to be a risk factor for overall cognitive decline, but it was found to be predictive for decline in the memory domain, most possibly due to the relation of advanced age with lower preoperative MMSE scores.

It is considered that surgery-induced (neuro)inflammation plays a major role in the development of cognitive decline.³⁰ Surgery causes the release of cytokines through activation of the immune system in response to tissue damage.³¹ Patients with longer surgical procedures will most likely develop a more excessive cytokine release, making them prone to postoperative cognitive decline.^{31,32} This possibly explains why patients undergoing major surgery were at an increased risk of postoperative cognitive decline. Postoperative delirium was associated with postoperative cognitive decline. It is unclear whether this relation represents a continuum of disease between delirium and postoperative cognitive decline, as (neuro)inflammation plays a role in the development of both.³³ The proposed inflammatory mechanism might also apply to the earlier described cognitive improvement, where cancerous disease induces (neuro)inflammation which resolves after the surgical removal of the tumour.³⁴

Distinction of cognitive domains

In our study, the executive function domain was the most vulnerable for decline. Although executive function and memory domains are related, it is supported by literature from a neuroanatomical as well as an inflammatory perspective that these domains may not be affected equally in cognitive decline.^{25,26} Executive function is associated with the frontal cortex, subcortical nuclei and white matter tracts. Memory functions are associated with the medial temporal lobe, the thalamus and the basal forebrain.⁶ Age-related decline in executive functioning is related to concentrations of inflammatory markers, whereas decline in memory is not.³⁵ Neuroanatomical regions, and so cognitive domains, respond differently to the inflammatory response after surgery.⁵ A distinction between cognitive domains using different cognitive tests can increase insight into the involvement of inflammatory processes in postoperative cognitive impairment.

In our study, testing was performed several months after hospital admission, at the residence of the patients. The influence of stress on cognitive assessment was assumed to be less at this location and time since the operation.

There is a selection bias in patients' participation, with patients with a worse health status being more likely to decline to participate in a study.³⁶ The fact that this study was carried out in a tertiary referral centre, with specialised and centralised care, might augment this bias. As this study is observational, conclusions are limited to associations between risk factors and postoperative cognitive decline, and these associations do not imply causality.

Clinical implications and future perspectives

Clinicians should inform vulnerable patient groups, those with advanced age (>75 years old), lower preoperative MMSE score (≤ 26) and undergoing major surgery, of the possible adverse consequences of surgery on postoperative cognitive function. Research to develop preventive interventions to preserve quality of life should focus on this high-risk subpopulation. Then in the future, a more tailored approach can be offered to those at risk.³⁷

References

1. McKenna RJ S. Clinical aspects of cancer in the elderly. treatment decisions, treatment choices, and follow-up. *Cancer*. 1994;74(7 Suppl):2107-2117.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in europe: Estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403.
3. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, et al. The global burden of cancer 2013. *JAMA Oncol*. 2015;1(4):505-527.
4. Ramesh HS, Boase T, Audisio RA. Risk assessment for cancer surgery in elderly patients. *Clin Interv Aging*. 2006;1(3):221-227.
5. Hovens IB, Schoemaker RG, van der Zee EA, Heineman E, Izaks GJ, van Leeuwen BL. Thinking through postoperative cognitive dysfunction: How to bridge the gap between clinical and pre-clinical perspectives. *Brain Behav Immun*. 2012;26(7):1169-1179.
6. Price CC, Garvan CW, Monk TG. Type and severity of cognitive decline in older adults after noncardiac surgery. *Anesthesiology*. 2008;108(1):8-17.
7. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. international study of post-operative cognitive dysfunction. *Lancet*. 1998;351(9106):857-861.
8. Johnson T, Monk T, Rasmussen LS, et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology*. 2002;96(6):1351-1357.
9. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *Br J Anaesth*. 2009;103 Suppl 1:i41-46.
10. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology*. 2009;110(3):548-555.
11. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*. 2008;108(1):18-30.
12. Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. *Acta Anaesthesiol Scand*. 2010;54(8):951-956.
13. Rasmussen LS, Larsen K, Houx P, et al. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand*. 2001;45(3):275-289.
14. Valentin LS, Pietrobon R, Aguiar Junior W, et al. Definition and application of neuropsychological test battery to evaluate postoperative cognitive dysfunction. *Einstein (Sao Paulo)*. 2015;13(1):20-26.

15. Grape S, Ravussin P, Rossi A, Kern C, Steiner L. Postoperative cognitive dysfunction. *Trends in Anaesthesia and Critical Care*. 2012;2:411-416.
16. Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: Normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc*. 2005;11(3):290-302.
17. Reitan R, Wolfson D. The Halstead-Reitan neuropsychological test battery: Therapy and clinical interpretation. *Neuropsychological Press*. 1985.
18. Ruff R, Light R, Evans R. The ruff figural fluency test: A normative study with adults. *Developmental Neuropsychology*. 1987;3(1):37-51.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
20. Meulendijks FG, Hamaker ME, Boereboom FT, Kalf A, Vogtlander NP, van Munster BC. Groningen frailty indicator in older patients with end-stage renal disease. *Ren Fail*. 2015;37(9):1419-1424.
21. Aarts MJ, Koldewijn EL, Poortmans PM, Coebergh JW, Louwman M. The impact of socioeconomic status on prostate cancer treatment and survival in the southern netherlands. *Urology*. 2013;81(3):593-599.
22. Stump D, Newman S, Coker L, Phipps J, Miller C. Persistence of neuropsychological deficits following CABG. *Anesthesiology*. 1990;73(3).
23. Calamia M, Markon K, Tranel D. Scoring higher the second time around: Meta-analyses of practice effects in neuropsychological assessment. *Clin Neuropsychol*. 2012;26(4):543-570.
24. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med*. 2013;29(4):737-752.
25. Mandrick K, Peysakhovich V, Remy F, Lepron E, Causse M. Neural and psychophysiological correlates of human performance under stress and high mental workload. *Biol Psychol*. 2016;121(Pt A):62-73.
26. Shoair OA, Grasso li MP, Lahaye LA, Daniel R, Biddle CJ, Slattum PW. Incidence and risk factors for postoperative cognitive dysfunction in older adults undergoing major noncardiac surgery: A prospective study. *J Anaesthesiol Clin Pharmacol*. 2015;31(1):30-36.
27. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA*. 1993;269(18):2386-2391.

28. Creavin ST, Wisniewski S, Noel-Storr AH, et al. Mini-mental state examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev*. 2016;(1):CD011145. doi(1):CD011145.
29. Stern Y. What is cognitive reserve? theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002;8(3):448-460.
30. Hovens IB, Schoemaker RG, van der Zee EA, Absalom AR, Heineman E, van Leeuwen BL. Postoperative cognitive dysfunction: Involvement of neuroinflammation and neuronal functioning. *Brain Behav Immun*. 2014;38:202-210.
31. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery*. 2000;127(2):117-126.
32. Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Pagel PS. Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. *J Anesth*. 2011;25(1):1-9.
33. Marcantonio ER. Postoperative delirium: A 76-year-old woman with delirium following surgery. *JAMA*. 2012;308(1):73-81.
34. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883-899.
35. Trompet S, de Craen AJ, Slagboom P, et al. Genetic variation in the interleukin-1 beta-converting enzyme associates with cognitive function. the PROSPER study. *Brain*. 2008;131(Pt 4):1069-1077.
36. Minder CE, Muller T, Gillmann G, Beck JC, Stuck AE. Subgroups of refusers in a disability prevention trial in older adults: Baseline and follow-up analysis. *Am J Public Health*. 2002;92(3):445-450.
37. Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN. Comprehensive geriatric assessment and its clinical impact in oncology. *Eur J Cancer*. 2007;43(15):2161-2169.

Chapter 6

Incidence and predictors of
postoperative delirium
after cytoreduction
surgery-hyperthermic
intraperitoneal
chemotherapy.

M. Plas
P.H.J. Hemmer
L.B. Been
R.J. van Ginkel
G.H. de Bock
B.L. van Leeuwen

Abstract

Background : Incidence of, and baseline characteristics associated with delirium in patients after cytoreduction surgery-hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), were subject of investigation.

Methods : The study was conducted among a consecutive series of prospectively included patients who underwent CRS-HIPEC at the University Medical Center Groningen, Groningen, the Netherlands, between February 2006 and January 2015. A chart-based instrument for delirium during hospitalization was used to identify patients with symptoms of delirium who were not diagnosed by a psychiatrist during admission. Uni- and multivariate logistic regression analyses were performed.

Results : Data of 136 patients were included in the analysis. Median age was 60 years (range: 18-76) and 50 (37%) patients were male. During hospitalization, 38 (28%) patients were diagnosed with delirium. Factors that differed significantly between the patients with and without delirium by univariate analysis were included in multivariate analysis. Multivariate analysis showed that after adjustment for age and complications other than delirium, having three or more organs resected and the CRP serum levels were independent predictors for delirium (OR: 3.97; 95% 1.24-12.76; OR: 1.01; 95% 1-1.01, respectively).

Conclusions : This report shows an incidence of 28% of delirium, occurring after CRS-HIPEC and suggests a role for systemic inflammation in the development of postoperative delirium.

Introduction

As systemic chemotherapy does not offer the possibility of cure in the treatment of peritoneal tumor dissemination in colorectal carcinoma, novel therapies have been developed. Cytoreduction surgery combined with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is now the recommended treatment option for many peritoneal surface malignancies.^{1,2} The purpose of cytoreduction is to obtain a macroscopically complete resection, followed by intraperitoneal hyperthermic chemotherapy to treat any microscopic residual disease.³ Current indications for CRS-HIPEC include non-invasive peritoneal carcinomatosis or sarcomatosis, peritoneal mesothelioma, perforated gastrointestinal cancers, gastrointestinal cancer adherent to adjacent organs, or structures and gastrointestinal cancer with positive peritoneal cytology.⁴ The advent of CRS-HIPEC has changed the treatment perspective toward a curative approach for selected patients with colorectal peritoneal malignancy, peritoneal mesothelioma, or pseudomyxoma peritonei, now increasingly considered to be a loco regional manifestation of disease rather than an end-stage terminal event.⁵

CRS-HIPEC is a complex and time-consuming procedure and the treatment can have a considerable effect on the patient's general condition. The effects can be on the respiratory, cardiovascular, electrolyte, and metabolic status, and lead to a high perioperative morbidity and prolonged hospitalization.^{6,7} Mental status may also be affected resulting in delirium, an acute confusion disorder characterized by an altered level of consciousness, inattention and disorganized thinking. This change in cognition or perceptual disturbance develops over a short period of time (hours to days) and may fluctuate over the course of a day. Delirium can be classified into three subtypes, namely hyperactive, hypoactive or mixed.⁸

Although the pathophysiology of delirium remains largely unknown, it is generally accepted that the etiology involves multiple factors of different significance.^{9,10} Consistent evidence is accumulating for the role of inflammatory processes arising due to surgical trauma and subsequent complications.¹¹ Research indicates that neuroinflammation plays a major role in the development of delirium.¹² It seems reasonable to expect that delirium is a frequent complication after CRS-HIPEC as this procedure is expected to cause a strong inflammatory response. However, few studies have reported on this specific postoperative complication. As delirium is

associated with increased morbidity and mortality, it is certainly a complication to be avoided or timely recognized.¹³ The purpose of this retrospective analysis is to identify the incidence of, and baseline characteristics associated with, delirium in a consecutive series of patients after CRS-HIPEC.

Methods

Patients and design

The study is a retrospective analysis of a consecutive series of prospectively included patients who underwent CRS-HIPEC surgery at the University Medical Center Groningen (UMCG), Groningen, the Netherlands, between February 2006 and January 2015. This study was approved by the local medical ethical committee and privacy was guaranteed by coding data. A prospective database was sustained, containing patient and tumor-specific data. Data included demographic characteristics, medical history, surgical procedure, diagnosis, and length of hospital stay.

Data acquisition

Data collected included body mass index (BMI), American Society of Anesthesiologists score (ASA), number of packed cells transfused, length of surgery, tumor type, peritoneal cancer index (PCI), number of organs resected during surgery and completeness of cytoreduction (CC) score. The blood serum levels of C-reactive protein (CRP) during hospitalization after the CRS-HIPEC were retrieved from the hospital's data center. To identify and rank the postoperative complications, the Clavien Dindo complication classification (CDCC) was used. The (age adjusted) Charlson comorbidity index (CCI), an index in which each medical condition is assigned a weighted score (range 0-19), was used to quantify the medical comorbidity. To see which patients developed a delirium or mental status change during admission, charts of all patients were reviewed.

Chart-based instrument for delirium during hospitalization

In certain patients, delirium was diagnosed by a psychiatrist or specialist in elderly medicine and registered as a postoperative complication during admission. To identify patients with symptoms of delirium during admission who were not conspicuous

during that time, the chart-based instrument for delirium during hospitalization was used retrospectively. The chart-based instrument was created with the goal of maximizing sensitivity for identification for delirium and prompts the chart abstractor to search for key terms of identification for delirium, particularly searching for any evidence of acute mental status change. The chart-based instrument is not recommended for individual patient care, but it is suitable for institutional reporting about delirium.^{14,15} All sections of the charts were searched, including but not restricted to progress notes, nursing notes, and consultant notes.

Data analysis and statistics

Patients, primary diagnosis, treatment and hospital stay were described as well as the incidence of delirium. The mean serum levels of CRP during admission in patients without delirium were compared to the last measured CRP serum level for patients with delirium before the onset of symptoms. To compare the patients with a delirium versus those without, and to search for characteristics, univariate and multivariate logistic regression analyses were performed to estimate ORs (odds ratios) and 95% CIs (confidence intervals). Two-sided testing was used, where a P -value <0.05 was considered to be statistically significant. All potential baseline characteristics were included in univariate analysis. Predictors with a P -value of <0.15 in univariate analysis were considered in a multivariate model. Step-by-step elimination of the least significant variable with backward selection was used for developing a multivariate model including only statistical significant variables. As age is a well-known factor being associated with delirium, age was forced into the model. To estimate associations between delirium and other complications (ORs and 95%CIs) logistic regression analyses were performed. To control for confounding with other complications than delirium, this variable was included in the multivariate regression models. Statistical analyses were performed using IBM SPSS software, version 23.0 (IBM Corporation, Armonk, NY).

Results

A total of 136 patients were included in the analysis. Median age of those undergoing CRS-HIPEC was 60 years (range: 18-76) and 50 (37%) patients were male (Table 1). The median BMI was 24 (range: 11.5-54.3). A majority of 104 (76.4%) patients were

diagnosed with a colorectal carcinoma as primary tumor. The surgical procedure of 68 (50%) patients lasted more than 9 h.. Twenty-seven (21%) patients needed 1-3 packed cells transfusions, 25 (19%) patients needed 3-6 packed cells transfusions and 8 (6%) patients more than 6 packed cells transfusions. Complete cytoreduction was achieved in 103 (77.4%) patients and Mitomycine C was used as HIPEC regimen in 128 (94.1%) patients. Median length of hospital stay was 16 days (range: 4-53) (Table 2). All patients received an epidural catheter containing levobupivacaine and sufentanil preoperatively, for postoperative analgesia.

The incidence of delirium

During hospitalization, 46 (34%) patients experienced mental status change, of which 38(28%)patientswerediagnosedwithdelirium.Otherpresentations,besidesdelirium, were mainly shortly disorganized thinking and hallucinations, with consciousness of the patient. Psychiatrists were consulted to evaluate the patients with delirium in 25 (65.8%) cases. The chart-based instrument for delirium during hospitalization identified two more patients who were suspicious for delirium. Haloperidol (an antipsychotic drug) was prescribed for 31 (88.6%) patients with delirium. Most patients developed delirium in the first seven days after surgery (see Figure 1).

Figure 1. Time of postoperative delirium onset shown for the first 15 days

Table 1.
Patient, tumor, and surgery characteristics (n=136)

	All patients	Non-delirious patients	Delirious patients
Demographic characteristics			
Number (n)	136	98	38
Age (years) median (range)	60 (18-76)	58 (26-74)	63 (18-76)
Male sex % (n)	37% (50)	37.8% (37)	34.2% (13)
BMI median (range)	24 (11.5-54.3)	24.2 (11.5-40.0)	24 (14.4-54.3)
ASA score median (range)	2 (0-3)	2 (0-3)	2 (0-3)
Age Adjusted Charlson Comorbidity (1) % (n)	7.4% (10)	5.1% (5)	13.2% (5)
Hypertension % (n)	21.3% (29)	15.3% (15)	36.8% (14)
Diabetes Mellitus II % (n)	2.2% (3)	2.0% (2)	2.6% (1)
Tumor and surgery characteristics			
Length of surgery (hours) % (n)			
≤ 9	50% (68)	58.2% (57)	28.9% (11)
> 9	50% (68)	41.8% (41)	71.1% (27)
Tumor type % (n)			
Colon/adeno/rectal carcinoma	76.5% (104)	76.5% (75)	76.3% (29)
Pseudomyxoma peritonei (Disseminated peritoneal adenomucinosis)	14.7% (20)	16.3% (16)	10.5% (4)
Pseudomyxoma peritonei (Peritoneal mucinous carcinomatosis)	2.9% (4)	3.1% (3)	2.6% (1)
Ovarian carcinoma	1.5% (2)	1.0% (1)	2.6% (1)
Intraperitoneal mesothelioma	3.7% (5)	3.1% (3)	5.3% (2)
Tubulo papillary mesothelioma	0.7% (1)	-	2.6% (1)
Peritoneal Cancer Index % (n)			
0-21	81.7% (58)	84.4% (38)	76.9% (20)
22-39	18.3% (13)	15.6 (7)	23.1% (6)

Table 1. (continued)
Patient, tumor, and surgery characteristics (n=136)

	All patients	Non-delirious patients	Delirious patients
Number of packed cells transfusions % (n)			
No packed cells transfusion	54.2% (71)	58.8% (55)	43.2% (16)
1-3 packed cells transfusions	20.6% (27)	19.1% (18)	24.3% (9)
3-6 packed cells transfusions	19.1% (25)	17.0% (16)	24.3% (9)
More than 6 packed cells transfusions	6.1% (8)	5.3% (5)	9.1% (3)
Number of organs resected % (n)			
0-2	30.1% (41)	37.8% (37)	10.5% (4)
3-7	69.9% (95)	62.2% (61)	89.5% (34)
HIPEC regimen mitomycine C	94.1% (128)	93.9% (92)	94.7% (36)
Completeness of cytoreduction score			
0	77.4% (103)	77.1% (74)	78.4% (29)
1	18.0% (24)	18.8% (18)	16.2% (6)
2	2.3% (3)	2.1% (2)	2.7% (1)
3	2.3% (3)	2.1% (2)	2.7% (1)

Postoperative complications

Postoperative complications were classified for the hospitalized postoperative period and are shown in Table 2. Complications rates were higher among the group of patients with postoperative delirium (86.8%) compared to those without (58.2%). Grade II complications were most frequently seen in both groups, followed by grade I complications in patients without delirium and grade III complications in patients with delirium. Sepsis occurred in 6 (15.8%) patients with delirium in contrast to 1 (1%) patient without delirium. Other reported infectious postoperative complications were line sepsis in 7 (5.1%) patients, wound infection in 5 (3.7%) patients and urinary tract infection in 10 (7.4%) patients. In the postoperative course, electrolyte derangement (hyponatremia or hypokalemia) was observed in 11 (8.1%) patients of which 1 (0.7%) patient had hyponatremia. The chance of postoperative delirium is five times greater in those patients with any other postoperative complication (OR: 4.75; 95% 1.71 – 13.20) and in patients with postoperative electrolyte derangements (OR: 5.31; 95% 1.46 – 19.35). In patients with sepsis the chance on postoperative delirium during admission is 18 times greater than in those without sepsis (OR: 18.19; 95% 2.11 – 156.82) (Table 3).

Table 2.
Postoperative patient characteristics (n=136)

Admission characteristics	All patients	Non-delirious patients	Delirious patients
Number (n)	136	98	38
Length of hospital stay (days) <i>median (range)</i>	16 (4–53)	15 (6–53)	21 (10–49)
Mental status change % (n)	33.8% (46)	8.2% (8)	100% (38)
Delirium	28% (38)	-	100% (38)
Other	6% (8)	8.2% (8)	-
C-reactive protein (mg/L) <i>median (range)</i>	85.5 (10–341)	78 (28–289)	109 (10–341)
Highest CRP during admission (mg/L)			
<150	39.8% (53)	44.8% (43)	27% (10)
>150	50.2% (80)	55.2% (53)	73% (27)
Highest CRP first 7 days post-operative (mg/L) <i>median (range)</i>	155 (44–364)	151 (44–364)	165 (52–341)
Clavien Dindo complication classification			
Grade I	19.1% (26)	20.4% (20)	15.8% (6)
Grade II	29.4% (40)	23.5% (23)	44.7% (17)
Grade III	13.2% (18)	10.2% (10)	21.1% (8)
Grade IV	2.9% (4)	3.1% (3)	2.6% (1)
Grade V	1.5% (2)	1.0% (1)	2.6% (1)

Table 3.

Associations between postoperative complications and delirium (n=136)

Variable	All patients	Non-delirious patients	Delirious patients	Odds ratio	95%CI	P
Postoperative complications (<i>without delirium</i>) % (n)	66.2% (90)	58.2% (57)	86.8% (33)	4.75	1.71–13.20	0.003
Electrolyte derangement	8.1% (11)	4.1% (4)	18.4% (7)	5.31	1.46–19.35	0.01
Sepsis	5.1% (7)	1.0% (1)	15.8% (6)	18.19	2.11–156.82	0.008
Line sepsis	2.2% (3)	2.0% (2)	2.6% (1)	1.30	0.11–14.74	0.83
Wound infection	3.7% (5)	3.1% (3)	5.3% (2)	1.76	0.28–10.97	0.55
Urinary tract infection	7.4% (10)	6.1% (6)	10.5% (4)	1.80	0.48–6.79	0.38

Bold values are considered significant. (P value <0.05).

C-reactive protein

Median CRP peak serum levels were 155 (44-364) mL/g during the first seven days after surgery and 180 (25-569) mL/g during admission. All patients showed an increase in CRP serum level in the postoperative period with a median of 78 (28-289) mL/g for the patients without delirium and a median of 109 (10-341) mL/g for those diagnosed with delirium.

Characteristics associated with delirium

Univariate logistic regression showed that the more organs were resected, the greater the chance of developing delirium after surgery (Table 4). More detailed analysis showed that the difference was significant between 0 and 2 organs resected versus 3-7 organs resected (OR: 5.16; 95% 1.69–15.70, $P = 0.004$). The length of the surgical procedure overall was longer for patients with delirium compared to the patients without delirium, where surgery lasting longer than 9 h was associated with an increased risk of developing a delirium (OR: 3.41; 95% 1.52–7.65, $P = 0.003$). Patients with delirium more often suffered from hypertension as a comorbid condition (OR: 3.23; 95% 1.37–7.62, $P = 0.007$). Serum levels of CRP, as described in methods, were higher in patients with postoperative delirium (OR: 1.01; 95% 1–1.01, $P = 0.01$). Multivariate logistic regressions showed that after adjustment for age and complications other than delirium, having three or more organs resected (OR: 3.97; 95% 1.24–12.76, $P = 0.02$) and a higher serum level of CRP (OR: 1.01; 95% 1–1.01, $P = 0.04$) were independent

significant predictors for postoperative delirium (Table 5), with age included in the model (OR: 1.61; 95% 0.64–4.05, $P = 0.31$). Even after exclusion of 7 (5.1%) patients that developed sepsis in the postoperative period (to avoid confounding) from additional regression analysis, the mentioned predictors were still significant in the multivariate model; after adjustment for age and complications other than delirium, having three or more organs resected (OR: 3.38; 95 % 1.04–11.01, $P = 0.04$) and a higher serum level of CRP (OR: 1.01; 95% 1.0–1.02, $P = 0.03$), with age included in the model (OR: 1.60; 95% 0.60–4.33, $P = 0.35$).

Table 4.
Predictors for the occurrence of a delirium after HIPEC, univariate logistic regression

Variable	Odds ratio	95%CI	P
Age (years)			
≤65	1		
>65	1.90	0.86 – 4.21	0.11
Sex			
Female	1		
Male	1.17	0.53 – 2.56	0.70
BMI	1.04	0.98 – 1.01	0.23
ASA score			0.73
1	1		
2	1.07	0.26 – 4.45	0.92
3	0.70	0.11 – 4.54	0.71
Age Adjusted Charlson Comorbidity	2.82	0.77 – 10.36	0.12
Hypertension			
No	1		
Yes	3.23	1.37 – 7.62	0.007
Diabetes Mellitus II			
No	1		
Yes	1.30	0.11 – 14.74	0.83
Length of surgery (h)			
≤9	1		
>9	3.41	1.52 – 7.65	0.003
Peritoneal Cancer Index			
≤21	1		
>22	1.63	0.48 – 5.50	0.43
Number of packed cells transfusions			0.28
No packed cells transfusion	1		
1-3 packed cells transfusions	1.72	0.65 – 4.56	0.28
3-6 packed cells transfusions	1.96	0.80 – 4.84	0.14
Number of organs resected			
≤2	1		
>3	5.16	1.69 – 15.70	0.004
Complete cytoreduction			
Yes	1		
No	0.93	0.37 – 2.32	0.87
C-reactive protein (mg/L)	1.01	1 – 1.01	0.01

Bold values are considered significant. (P value <0.05).

Table 5.
Predictors for the occurrence of a delirium after HIPEC, multivariate logistic regression

Variable	Odds ratio	All patients (n=136)		Odds ratio	Sepsis excluded (n=129)	
		95%CI	P		95%CI	P
Age (years)						
≤65	1			1		
>65	1.61	0.64 – 4.05	0.31	1.60	0.60 – 4.33	0.35
Number of organs resected						
≤2	1			1		
>3	3.97	1.24 – 12.76	0.02	3.38	1.04 – 11.01	0.04
C-Reactive Protein (mg/L)	1.01	1 – 1.01	0.04	1.01	1.0 – 1.02	0.03
Complications without delirium						
No	1			1		
Yes	3.82	1.19 – 12.30	0.03	3.22	0.99 – 10.51	0.05
Bold values are considered significant. (P value <0.05).						

Discussion

This report shows an incidence of 28% (95% CI 0.20–0.36) of postoperative delirium occurring after CRS-HIPEC. The main predictors for postoperative delirium were the number of organs resected during surgery and the serum level of CRP before the diagnosis of delirium. Age was not identified as independent predictor for postoperative delirium.

Incidence of postoperative delirium

In other studies the incidence of postoperative delirium varies among different surgical procedures with an incidence of 14.1% in elderly patients with colorectal cancer after surgery, 26.3% in patients after major head and neck surgery, and 50% in patients after esophagectomy.¹⁶⁻¹⁸ The incidence of delirium in this study is comparable with the incidence reported for major surgery in other fields. Due to the fluctuating course and the different subtypes of delirium, the diagnosis of delirium is estimated to be missed in 75% of cases according to literature.⁹ Therefore, it is plausible to assume that in reality the incidence of delirium after surgery is higher than noted in the previous studies. In particular, the hypoactive subtype of delirium

is hard to recognize by clinical staff, since the clinical features consist of fatigue and lack of activity, which can easily be mistaken for sleepiness.^{10,19}

Besides delirium, other mental status changes were found in our study, but did not reach the criteria according the DSM-IV for delirium. This could indicate that CRS-HIPEC has influence on mental status and emotions, but emotional functioning was not investigated in this study. A study which reported the recovery process of patients who underwent CRS-HIPEC, described that 49 of 76 (64%) patients suffered from anxiety, worry, feeling down or abandoned, and had hallucinations during the first 3 postoperative weeks.⁷

The inflammatory response

Surgical trauma is an initiator of an inflammatory response.¹¹ The data accumulated in the course of this study show an enormous rise of postoperative serum levels of CRP. This reflects the strong inflammatory response that occurs after the CRS-HIPEC procedure, as stated in earlier research.²⁰ The possibility of a link between CRP levels and delirium has been described, but published data are contradictory.²¹⁻²⁶ In our study, the extensive rise of CRP after CRS-HIPEC, indicating systemic inflammation, was seen and serum level of CRP was found as independent predictor for delirium.²⁷

Earlier research showed that a prolonged length of surgery was associated with a higher risk for postoperative delirium.²⁸⁻³¹ Our study showed similar results, in the group of patients with postoperative delirium, the length of surgery was longer than in the group of patients who did not experience postoperative delirium. This may be related to increased doses of anesthetic medicine and greater volumes of blood transfusion, with increased chance of hypo perfusion and systemic inflammatory response.³⁰ A relation between the increased systemic inflammatory response and prolonged length of surgery is important in sight of a possible association between the inflammatory response and postoperative delirium as earlier described. The increased length of surgery may predispose patients to delirium because of increased cytokines release.^{31,32}

An association between intraoperative blood loss and subsequent packed cells transfusions and the occurrence of delirium after surgery has been described in a few studies.^{32,33} Packed cells transfusion is described as a strong predictor for early postoperative delirium. Intraoperative transfusions of larger volumes of blood have

repeatedly been linked to postoperative delirium.³⁴ Although other studies have shown that patients who developed delirium had greater intraoperative blood loss and received more postoperative transfusions, this association was not found in our study.³⁵ It has been described that packed cells transfusion triggers an inflammatory response which has been shown to directly increase plasma concentrations of inflammatory mediators.³⁶ In our study, a difference in inflammatory response for CRP between the patients with delirium and without delirium was found.³⁴

Taken together, the findings in our study underscore the hypothesis of neuroinflammation as mechanism underlying the pathophysiology of delirium. Surgery initiates a systemic inflammatory response that can disrupt the function of multiple organs, including the brain.³⁷ The exaggerated neuro-inflammatory response may damage neurons, resulting in postoperative cognitive deterioration, like delirium.

Postoperative complications and delirium

The length of hospital stay of patients with postoperative delirium was longer than the length of hospital stay of patients who did not experience delirium. Prolonged hospital stay after postoperative delirium is frequently seen in other studies and is associated with an increase in postoperative complications.^{17,38,39} CRS-HIPEC comes with a high incidence of postoperative complications, also observed in our study.² Delirium and complications can co-exist, but the relation of delirium and other postoperative complications has not been well-examined. In the current study, the incidence rate of severe complications in patients with delirium was higher than in patients without delirium.

Age and comorbidities

Age was not an independent predictor for postoperative delirium, in contrast to literature where age > 70 years is described as a risk factor.⁴⁰ In our study few patients were aged 70 years or over, which might be an explanation for not reaching significance in multivariate analysis. As has been shown in other studies, in this study patients with delirium more often suffered from hypertension than the patients who did not develop a delirium.^{33,41} Hypertension possibly is a sign of increased vascular risk and may be indicative of vascular brain damage, making patients more vulnerable to conditions such as delirium.^{39,42} A similar effect of diabetes mellitus was not seen in the current study, probably due to the low incidence in the population.

Critical evaluation of the study

Although the present study provided novel information about postoperative delirium following CRS–HIPEC, there were a number of study limitations. First, an obvious limitation is the use of the chart-based method to identify patients with diagnosed and undiagnosed delirium, which mainly searches for hyperactive delirium.¹⁴ It might be possible that the hypoactive delirium was missed which may imply a higher incidence of delirium in reality, than found in our study. However, the chart-based method was used in addition to clinical diagnosis by a psychiatrist or specialist in elderly medicine. Second, for this study, we used a retrospective chart review, which is limited by the quality of the documentation in the charts. Third, more accurate data on opioid and/or narcotic use in the postoperative period than epidural use, were not available in this study. In a more ideal setting, a prospective analysis would overcome this weaknesses, and reliable data about the subtypes of delirium can be reported.

Unanswered questions and future research

Neuroinflammation is among the most popular hypothesized mechanism underlying the pathophysiology of delirium. Pro-inflammatory markers are associated with the development of delirium in relative healthy elderly.⁴³ However, the production of CRP, which is elevated in inflammation and infection, is under control of other cytokines. It may be that the levels of more specific cytokines are more closely related with the process of systemic inflammation, than CRP is. These cytokines could be more interesting for further research.³² Concerning the relation between postoperative complications and delirium, cause and effect remain unclear. Whether a postoperative delirium increases the risk for other postoperative complications or whether a postoperative delirium is a symptom of other complications which can occur after surgery, remains to be clarified and further research is needed.

Conclusions

In conclusion, this retrospective analysis shows an incidence of 28% of postoperative delirium, occurring after CRS–HIPEC. Surgery extensiveness and serum level of CRP were independent predictors for delirium postoperatively, when correcting for age and complications other than delirium. An extensive inflammatory response occurs after CRS–HIPEC, represented by elevated serum CRP levels. The process of systemic inflammation and the relation with levels of cytokines and delirium requires further research.

References

1. Elias D, Goere D, Dumont F, et al. Role of hyperthermic intraoperative peritoneal chemotherapy in the management of peritoneal metastases. *Eur J Cancer*. 2014;50(2):332-340.
2. van Oudheusden TR, Lemmens VE, Braam HJ, et al. Peritoneal metastases from small bowel cancer: Results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the netherlands. *Surgery*. 2015;157(6):1023-1027.
3. Kuijpers AM, Mirck B, Aalbers AG, et al. Cytoreduction and HIPEC in the netherlands: Nationwide long-term outcome following the dutch protocol. *Ann Surg Oncol*. 2013;20(13):4224-4230.
4. Ford J, Hanna M, Boston A, Berri R. Life after hyperthermic intraperitoneal chemotherapy; measuring quality of life and performance status after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. *Am J Surg*. 2016;211(3):546-550.
5. Shan LL, Saxena A, Shan BL, Morris DL. Quality of life after cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis: A systematic review and meta-analysis. *Surg Oncol*. 2014;23(4):199-210.
6. Tsilimparis N, Bockelmann C, Raue W, et al. Quality of life in patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: Is it worth the risk? *Ann Surg Oncol*. 2013;20(1):226-232.
7. Arakelian E, Gunningberg L, Larsson J, Norlen K, Mahteme H. Factors influencing early postoperative recovery after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol*. 2011;37(10):897-903.
8. Flynn Makic MB. Preventing delirium in postoperative patients. *J Perianesth Nurs*. 2013;28(6):404-408.
9. Trabold B, Metterlein T. Postoperative delirium: Risk factors, prevention, and treatment. *J Cardiothorac Vasc Anesth*. 2014;28(5):1352-1360.
10. Rudolph JL, Marcantonio ER. Review articles: Postoperative delirium: Acute change with long-term implications. *Anesth Analg*. 2011;112(5):1202-1211.
11. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery*. 2000;127(2):117-126.
12. Hovens IB, van Leeuwen BL, Nyakas C, Heineman E, van der Zee EA, Schoemaker RG. Postoperative cognitive dysfunction and microglial activation in associated brain regions in old rats. *Neurobiol Learn Mem*. 2015;118:74-79.
13. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in

mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291(14):1753-1762.

14. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST, Jr, Leslie DL, Agostini JV. A chart-based method for identification of delirium: Validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc*. 2005;53(2):312-318.

15. Saczynski JS, Kosar CM, Xu G, et al. A tale of two methods: Chart and interview methods for identifying delirium. *J Am Geriatr Soc*. 2014;62(3):518-524.

16. Yamagata K, Onizawa K, Yusa H, Wakatsuki T, Yanagawa T, Yoshida H. Risk factors for postoperative delirium in patients undergoing head and neck cancer surgery. *Int J Oral Maxillofac Surg*. 2005;34(1):33-36.

17. Takeuchi M, Takeuchi H, Fujisawa D, et al. Incidence and risk factors of postoperative delirium in patients with esophageal cancer. *Ann Surg Oncol*. 2012;19(12):3963-3970.

18. Tei M, Ikeda M, Haraguchi N, et al. Risk factors for postoperative delirium in elderly patients with colorectal cancer. *Surg Endosc*. 2010;24(9):2135-2139.

19. Steinmetz J, Rasmussen LS. Peri-operative cognitive dysfunction and protection. *Anaesthesia*. 2016;71 Suppl 1:58-63.

20. Muller H, Hahn M, Weller L, Simsa J. Strategies to reduce perioperative morbidity in cytoreductive surgery. *Hepatogastroenterology*. 2008;55(86-87):1523-1529.

21. Macdonald A, Adamis D, Treloar A, Martin F. C-reactive protein levels predict the incidence of delirium and recovery from it. *Age Ageing*. 2007;36(2):222-225.

22. Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. *J Gerontol A Biol Sci Med Sci*. 2007;62(4):420-426.

23. Pol RA, van Leeuwen BL, Izaks GJ, et al. C-reactive protein predicts postoperative delirium following vascular surgery. *Ann Vasc Surg*. 2014;28(8):1923-1930.

24. Girard TD, Ware LB, Bernard GR, et al. Associations of markers of inflammation and coagulation with delirium during critical illness. *Intensive Care Med*. 2012;38(12):1965-1973.

25. McGrane S, Girard TD, Thompson JL, et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. *Crit Care*. 2011;15(2):R78.

26. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive

dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Crit Care*. 2011;15(6):R297.

27. Zhang Z, Pan L, Deng H, Ni H, Xu X. Prediction of delirium in critically ill patients with elevated C-reactive protein. *J Crit Care*. 2014;29(1):88-92.

28. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. *Br J Anaesth*. 2015;115(3):418-426.

29. Mu DL, Wang DX, Li LH, et al. High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: A prospective cohort study. *Crit Care*. 2010;14(6):R238.

30. Zhang WY, Wu WL, Gu JJ, et al. Risk factors for postoperative delirium in patients after coronary artery bypass grafting: A prospective cohort study. *J Crit Care*. 2015;30(3):606-612.

31. Afonso A, Scurlock C, Reich D, et al. Predictive model for postoperative delirium in cardiac surgical patients. *Semin Cardiothorac Vasc Anesth*. 2010;14(3):212-217.

32. Hasegawa T, Saito I, Takeda D, et al. Risk factors associated with postoperative delirium after surgery for oral cancer. *J Craniomaxillofac Surg*. 2015;43(7):1094-1098.

33. Schneider F, Bohner H, Habel U, et al. Risk factors for postoperative delirium in vascular surgery. *Gen Hosp Psychiatry*. 2002;24(1):28-34.

34. Behrends M, DePalma G, Sands L, Leung J. Association between intraoperative blood transfusions and early postoperative delirium in older adults. *J Am Geriatr Soc*. 2013;61(3):365-370.

35. Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. *Am J Med*. 1998;105(5):380-384.

36. Avall A, Hyllner M, Bengtson JP, Carlsson L, Bengtsson A. Postoperative inflammatory response after autologous and allogeneic blood transfusion. *Anesthesiology*. 1997;87(3):511-516.

37. Terrando N, Eriksson LI, Ryu JK, et al. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol*. 2011;70(6):986-995.

38. Raats JW, van Eijnden WA, Crolla RM, Steyerberg EW, van der Laan L. Risk factors and outcomes for postoperative delirium after major surgery in elderly patients. *PLoS One*. 2015;10(8):e0136071.

39. Olin K, Eriksdotter-Jonhagen M, Jansson A, Herrington MK, Kristiansson M, Permert J. Postoperative delirium in elderly patients after major abdominal surgery.

Br J Surg. 2005;92(12):1559-1564.

40. Bilotta F, Lauretta MP, Borozdina A, Mizikov VM, Rosa G. Postoperative delirium: Risk factors, diagnosis and perioperative care. *Minerva Anesthesiol.* 2013;79(9):1066-1076.

41. Chen CC, Lin MT, Liang JT, Chen CM, Yen CJ, Huang GH. Pre-surgical geriatric syndromes, frailty, and risks for postoperative delirium in older patients undergoing gastrointestinal surgery: Prevalence and red flags. *J Gastrointest Surg.* 2015;19(5):927-934.

42. Pinho C, Cruz S, Santos A, Abelha FJ. Postoperative delirium: Age and low functional reserve as independent risk factors. *J Clin Anesth.* 2016;33:507-513.

43. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: Diagnosis, prevention and treatment. *Nat Rev Neurol.* 2009;5(4):210-220.

Reply to comment on:

Incidence and predictors
of postoperative delirium
after cytoreduction
surgery-hyperthermic
intraperitoneal
chemotherapy

M. Plas

P.H.J. Hemmer

L.B. Been

R.J. van Ginkel

G.H. de Bock

B.L. van Leeuwen

Dear Editor,

We appreciate the interest in our work and the opportunity to respond to the comments and matters raised by Weng et al.¹ regarding our article on “Incidence and predictors of postoperative delirium after cytoreduction surgery-hyperthermic intraperitoneal chemotherapy.”² The study was conducted among a consecutive series of 136 prospectively included patients who underwent CRS-HIPEC at our hospital. Twenty-eight percent of our patients developed a postoperative delirium. Excluding patients with sepsis (n=7), having three or more organs resected and the CRP serum levels were the main predictors. Given the relatively small sample size, the confidence intervals were rather wide. Weng et al. questioned whether multicollinearity might be an alternative explanation for these wide confidence intervals.

However, as all variance inflation factors (data not reported) were close to one, this is not an explanation. We agree with the authors that in this study we did not focus on model performance by evaluation of the Area under the Curve (AUC), the Net Reclassification Improvement (NRI), the Integrated Discrimination Improvement (IDI) or due to our relatively small sample size by cross-validation or bootstrapping. Our main argument for this is that the main focus of this analysis was to evaluate factors associated with the occurrence of postoperative delirium and not to propose a predictive model.

As a consequence, our conclusion is that future research is needed to evaluate whether a postoperative delirium increases the risk for other postoperative complications or whether a postoperative delirium is a symptom of other complications which can occur after surgery.³

Acknowledgment

We thank Jing Du for helping with data analysis.

References

1. Weng J, Wu H, Wang Z. Incidence and predictors of postoperative delirium after cytoreduction surgery-hyperthermic intraperitoneal chemotherapy: Methodological issues. *J Surg Oncol*. 2018;117(4):807.
2. Plas M, Hemmer PHJ, Been LB, van Ginkel RJ, de Bock GH, van Leeuwen BL. Incidence and predictors of postoperative delirium after cytoreduction surgery-hyperthermic intraperitoneal chemotherapy. *J Surg Oncol*. 2018;117(2):260-268.
3. Olin K, Eriksdotter-Jonhagen M, Jansson A, Herrington MK, Kristiansson M, Permert J. Postoperative delirium in elderly patients after major abdominal surgery. *Br J Surg*. 2005;92(12):1559-1564.

Chapter 7

The association of preoperative anxiety and depression with neurocognitive disorder following oncological surgery

J. Du
M. Plas
A.R. Absalom
B.L. van Leeuwen
G.H. de Bock

Abstract

Background : The proposed underlying mechanisms of anxiety and depression, and of postoperative neurocognitive disorder (NCD), each include immune system involvement. Therefore, the aims of this study were to investigate the incidence of postoperative NCD 3 months after surgery among oncological patients undergoing surgery and to evaluate the role of preoperative anxiety and depression.

Method : A consecutive series of patients (age ≥ 18 years) undergoing surgery for the removal of solid tumors were included (n=218). Cognitive performance was assessed preoperatively and at 3 months postoperatively. Preoperative anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale.

Results : NCD affected 12.3% of elderly patients (age ≥ 70 years, n=57) at 3 months after surgery, with executive function mostly affected. By contrast, 8.4% of younger patients (age < 70 years, n=107) were affected, with information processing speed mostly affected. Low educational attainment was a risk factor (OR 6.0; 95% CI: 1.9–19.0) of overall NCD, whereas preoperative anxiety was associated with decline in the domain of executive function.

Conclusion : Postoperative NCD is a complication of oncological surgery for all adults instead of the elderly only. Preoperative anxiety was associated with an increased risk of executive function decline, and low educational attainment was a key factor for overall NCD.

Introduction

The ageing society has led to rapid increases in the number of patients with cancer across all ages.¹ The combination of the rise in cancer incidence, and surgery as one of the main treatments for solid tumors results in the forecast that the number of oncological patients eligible for surgery will also increase.² The treatment phase of oncological disease is accompanied by (symptoms of) anxiety and depression, where 19% and 12.9% of patients show signs of anxiety and depression.³ Undergoing surgery, fear of cancer recurrence and death, and the risk of potential adverse postoperative outcomes have influence on anxiety and depression and affect quality of life negatively.⁴ An adverse outcome after surgery considered particularly relevant in (but not restricted to) the elderly is postoperative cognitive decline.⁵ This deterioration in cognitive functioning following surgery has been termed as postoperative neurocognitive disorder (NCD) recently.⁶

Although it has been reported that postoperative NCD is a multifactorial phenomenon, there are few well-established risk factors.⁷ Accumulating evidence suggests that postoperative NCD might result from increased inflammatory activity.^{8,9} As both anxiety and depression are associated with increased inflammatory activity, preoperative symptoms might predispose patients for the development of postoperative NCD.^{10,11} In literature most studies focused on the elderly, but this subject would be interesting for both the young and the old, as younger patients tend to experience more anxiety and depression during cancer treatment but older patients are at increased risk for postoperative NCD by advancing age.^{12,13} Although definition, degree and duration of postoperative NCD are well explored, the influence of anxiety and depression on the development of postoperative NCD has not been investigated extensively.

We hypothesize that patients with (symptoms of) anxiety and depression have a higher risk for the development of postoperative NCD compared with patients without these symptoms. The aim of this study is to investigate the incidence of postoperative NCD 3 months after surgery among young and older patients undergoing surgery for cancer and to evaluate the role of preoperative (symptoms of) anxiety and depression.

Methods

Study design

This study is embedded in the prospective observational study 'PICNIC-B-HAPPY' (Predicting Postoperative Outcome in Elderly Surgical Cancer Patients: Biomarkers and Handgrip Strength as Predictors of Postoperative Outcome in the Elderly), conducted at the University Medical Center Groningen (UMCG, Groningen, The Netherlands) from August 2014 until March 2017. The study was registered on the Dutch Clinical Trial Database (trial number NL45602.042.14), following approval by the Medical Ethics Committee of the UMCG. A consecutive series of patients aged 18 years and over, admitted to the UMCG for surgical removal of a solid tumor (including gynecological tract, digestive tract, soft tissue) were invited to participate. Patients were excluded if surgery was scheduled in less than 24 hours after inclusion or if patients had any physical condition that could potentially impede compliance with the study, such as severe visual or auditory impairment, recent history of stroke or insufficient understanding of the Dutch language. Data collection was conducted in accordance with the Declaration of Helsinki.¹⁴ Written informed consent was obtained from all patients in accordance with local regulations, and patients' identities were anonymized by coding data before statistical analysis.

Outcomes

The primary study outcome was the incidence of postoperative NCD 3 months after surgery in young and older patients undergoing surgery for cancer. Secondary study outcomes were the prevalence of preoperative (symptoms of) anxiety and depression in young and older patients undergoing surgery for cancer and the associations between risk factors, including preoperative anxiety and depression, with postoperative NCD 3 months after surgery.

Definitions and data collection

Neuropsychological tests to determine performance in three cognitive domains (memory, executive function and information processing speed) were conducted at baseline (approximately 2 weeks before surgery) and 3 months after surgery. The Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) for immediate and delayed recall, the Trail Making Test part A (TMT-A) and B (TMT-B), and Ruff's Figural Fluency Test (RFFT) were used to determine neurocognitive performance in the domains of memory, executive function and information processing speed. The RAVLT was used as an indicator of memory and expressed as the total number of

words correctly remembered during the five immediate recall trials (lowest score, 0; highest score, 75) and the total number of words remembered at the delayed recall trial (lowest score, 0; highest score, 15).¹⁵ The TMT-A was used as an indicator of information processing speed and expressed as the number of seconds it took to complete the TMT-A (lowest score, 0; highest score, 480).¹⁶ Performance on executive function was expressed as total number of the number of seconds it took to complete the TMT-B (lowest score: 0; highest score: 480) and the unique designs drawn in parts 1-5 (lowest score: 0; highest score: 175) of the RFFT.^{5,16,17} A dedicated nurse and a medical or neuropsychology graduate student were trained on neuropsychological test administration and relevant interview techniques by a neuropsychologist. All measures were administered and scored in a standardized manner. Postoperative NCD was studied at overall and per cognitive domain. Overall postoperative NCD was defined as a $\geq 25\%$ decline in the performance scores compared with the baseline score, in at least two of the five tests.^{5,18} Whereas domain postoperative NCD was defined as a $\geq 25\%$ decline in the performance scores in a specific domain compared with the baseline score in that domain

Anxiety and depression symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) at baseline (approximately 2 weeks before surgery).¹⁹ The HADS is a 14-item screening tool that focuses on nonphysical symptoms of anxiety and depression, using 7 items for anxiety (HADS-A) and depression (HADS-D), respectively. Responses are rated from 0 to 3 points, total scores on HADS-A and HADS-D may range from 0 to 21 points. Optimal balance between sensitivity and specificity for HADS as screening instrument is achieved most frequently at a cut-off score of ≥ 8 for HADS-A and HADS-D. For both subscales sensitivities and specificities are approximately 0.80.²⁰

Patient, psychosocial, disease and treatment details were collected prospectively from baseline. Socioeconomic status (SES) was estimated for each patient, using an area-based measure (postal codes) provided by the Dutch governmental organization *Sociaal Cultureel Planbureau* that assigned an overall score for income level, degree of unemployment and percentage of low education level. Accordingly, postal codes were assigned to 3 SES categories: low (fourth and fifth quintile), intermediate (third quintile), and high (first and second quintile). Independence was assessed using the Instrumental Activities of Daily Living (IADL) scale, and frailty was assessed using the Groningen Frailty Index (GFI).^{21,22} Preoperative cognitive function was assessed using

the Mini-Mental State Examination (MMSE), whereas comorbidity was assessed using the Charlson Comorbidity Index (CCI).^{23,24} Tumor stage was assessed using the TNM classification system, and anesthetic risk was estimated 24 hours before surgery using the American Society for Anesthesiologist scale (ASA).²⁵

Educational attainment was categorized into primary school or below, and higher than primary school (In the Netherlands, most children finish primary school at the age of 12). Socioeconomic status was categorized into low, intermediate and high.²⁶ A surgical procedure with an anesthesia duration of >210 minutes was defined as major surgery.⁵ A history of chemotherapy or radiotherapy indicated either neoadjuvant or postoperative (within 3 months) therapy. Patients aged ≥ 70 years were considered as elderly and patients aged <70 years as young. Clinically relevant or literature-based cut-off scores were used to dichotomize the variables, as detailed in Appendix 1.

Data analysis and statistics

Patients with at least one complete cognitive test series (out of the maximum of five complete cognitive test series) were included in the analysis. A cognitive test series consists of baseline testing and testing at 3 months postoperatively. χ^2 tests were performed to assess whether there were differences between included and excluded patients. Cognitive assessment scores are presented as medians and interquartile ranges (IQRs). Wilcoxon-signed rank tests were used to assess changes in cognitive performance over time. Univariate and multivariate logistic regression analysis were performed to evaluate the associations between risk factors and NCD at 3 months after surgery. Variables with P -values of $<.15$ in univariate analyses were included in the multivariable analyses. Given the specific interest in the role of preoperative depression, HADS-D outcomes were retained in the multivariate models. A rule of at least five events per predictor variable in the multivariable analysis was applied.²⁷ Odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were estimated and are reported. P -values of $<.05$ were considered to indicate statistical significance. Data analysis was performed using IBM SPSS, Version 23 (IBM Corp, Armonk, NY) and and GraphPad Prism version 5.04 (GraphPad Software, San Diego, CA).

Results

Figure 1. Flowchart from in- and excluded patients. Of the 218 included patients, 22 were excluded before surgery. Three months postoperatively 32 patients were excluded. The sample of current analysis included 164 patients.

Figure 1 shows the flowchart of the patients included in the ‘PICNIC-B-HAPPY’ study. Of the 218 consecutive patients enrolled in the study, 3 patients (1.4%) were excluded as they did not undergo surgery at the UMCG, and a further 19 patients (8.7%) withdrew their consent before surgery. In addition, 32 of the remaining 196 patients (16.3%) were excluded from the analysis due to no complete cognitive assessment data or death 3 months after surgery. Poor health status was the main reason leading to incomplete cognitive assessment data, especially at 3 months after surgery as patients were unable to undergo or finish the formal assessments. Data for the remaining 164 patients (75.2%) were analyzed in the current study.

Table 1.
Patient, psychosocial, disease, and treatment details
(n = 218)

Risk factors	Included (n = 164)	Excluded* (n = 54)	p**
	% (n)	% (n)	
Patient and psychosocial characteristics			
Age (years)			
<70	65.2 (107)	58.1 (25)	.388
≥70	34.8 (57)	41.9 (18)	
Gender			
Female	46.3 (76)	34.9 (15)	.178
Male	53.7 (88)	65.1 (28)	
Educational level			
Primary school or lower	12.9 (21)	12.9 (4)	.998
Higher than primary school	87.1 (142)	87.1 (27)	
Social Economic Status ^a			
Low (7–10)	72.5 (116)	64.8 (35)	.284
Intermediate or high (1–6)	27.5 (44)	35.2 (19)	
Living situation			
Lives independently with others	76.7 (125)	74.3 (26)	.762
Lives alone	23.3 (38)	25.7 (9)	
Instrumental Activities of Daily Living ^b			
= 8	83.9 (135)	75.0 (21)	.255
<8	16.1 (26)	25.0 (7)	
Body Mass Index ^a			
Normal (<25)	36.3 (58)	21.4 (6)	.127
Overweight (≥25)	63.8 (102)	78.6 (22)	
Groningen Frailty Indicator			
<4	79.3 (130)	78.8 (26)	.951
≥4	20.7 (34)	21.2 (7)	
Mini-Mental State Examination			
≤26	6.1 (10)	12.9 (4)	.245
>26	93.9 (154)	87.1 (27)	
Charlson Comorbidity Index			
≤2	26.2 (43)	18.2 (6)	.330
>2	73.8 (121)	81.8 (27)	
Hospital Anxiety and Depression Scale-Anxiety ^c			
No (≤7)	84.6 (137)	77.4 (24)	.327
Mild or moderate (8–14)	15.4 (25)	22.6 (7)	
Hospital Anxiety and Depression Scale-Depression ^c			
No (≤7)	88.3 (143)	87.1 (27)	.769
Mild or moderate (8–14)	11.7 (19)	12.9 (4)	
Disease and treatment characteristics			
Tumor stage ^b			
Benign, 0, I , or II	43.8 (71)	35.3 (12)	.360
III or IV	56.2 (91)	64.7 (22)	

Table 1. (continued)
Patient, psychosocial, disease, and treatment details
(n = 218)

American Society of Anesthesiologists physical status classification			
<3	79.9 (131)	67.7 (21)	.135
≥3	20.1 (33)	32.3 (10)	
Invasive Surgery			
No	30.5 (50)	25.0 (8)	.534
Yes	69.5 (114)	75.0 (24)	
Major surgery			
No	40.9 (67)	53.3 (16)	.204
Yes	59.1 (97)	46.7 (14)	
History of chemo/radiotherapy			
No	54.8 (85)	41.9 (13)	.189
Yes	45.2 (70)	58.1 (18)	
Postoperative delirium			
No	94.5 (155)	92.6 (25)	.657
Yes	5.5 (9)	7.4 (2)	

**Patients were excluded if they had all the five tests incomplete or withdrew their informed consent. In the excluded group, basic characteristics were missing due to withdrawal of informed consent before the first assessment. **P values were derived from χ^2 tests or Fisher's exact tests. A surgical procedure with an anaesthesia duration of >210 min was defined as major surgery. ^a Four missing data. ^b Three missing data. ^c Two missing data.*

Patients included and excluded from the analysis were comparable in health status (Table 1). Of the 164 included patients, most had education to a level higher than primary school (87.1%), but also had low SES (72.5%) and high rates of comorbidities (73.8%). More than half of the included patients either had a body mass index exceeding 25 kg/m² (63.8%) or underwent invasive surgery (69.5%). To the elderly group, 57 patients were assigned with a median age of 75 years (IQR: 72.5–78.5) and 107 patients to the young group with a median age of 61 years (IQR: 52–67).

Preoperatively, 25 (15.4%) patients had mild or moderate signs of anxiety and 19 (11.7%) patients had mild or moderate signs of depression. In the elderly group 5 (9.0%) patients had mild or moderate signs of anxiety preoperatively compared with 20 (18.7%) patients in the younger group. Mild or moderate signs of depression preoperatively were seen in 7 (12.3%) patients in the elderly group in contrast to 12 (11.2%) patients in the younger group.

Table 2.
Cognitive assessment scores per test (n=164)

Domain	Baseline median (interquartile range)	3 mo follow- up median (interquartile range)	P
Memory			
RAVLT immediate recall	35.5 (26.0–44.0)	41.0 (33.0–52.0)	<.001
RAVLT delayed recall	7 (4–9)	9 (6–12)	<.001
Information processing speed			
TMT-A	39.1 (29.8–53.6)	36.8 (28.5–50.1)	.021
Executive function			
RFFT	65.0 (47.5–84.5)	78.0 (58.0–100.0)	<.001
TMT-B	92.7 (66.6–128.8)	80.0 (60.1–117.5)	.003

Abbreviations: RAVLT, Rey's Auditory Verbal Learning Test; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B; RFFT, Ruff's Figural Fluency Test. All P values were derived from Wilcoxon signed rank tests paired (P <.05 was considered significant).

Table 2 shows the results of the neuropsychological tests at baseline and at 3 months postoperatively. Overall, there was statistically significant improvement in cognitive function in 87 patients (53.0% [95%CI: 45.4–60.6]). However, 16 patients (9.8% [95%CI: 5.3–14.4]) suffered from postoperative NCD at 3 months (Figure 2), including 7 in the elderly group (12.3% [95%CI: 3.8–20.8]) and 9 in the young group (8.4% [95%CI: 3.1–13.7]). In the elderly group, 31.6% (95%CI: 19.5–43.7) encountered decline in the domain of executive function, while in the young group, 13.1% (95%CI: 6.7–19.5) experienced decline in the domain of information processing speed. Incidences of neurocognitive change (disorder and improvement) from baseline to 3 months postoperatively are shown in Appendix 2.

The results of logistic regression analysis for overall postoperative NCD are shown in Table 3. Low education attainment (OR 6.1 [95%CI: 1.4–26.0]) was identified as a risk factor, while tumor stage III/IV (OR 0.3 [95%CI: 0.1–0.9]) was identified as an apparent protective factor of postoperative NCD. Despite the expectations, a preoperative HADS-A or HADS-D score >7, was not associated with NCD 3 months after surgery.

The risk factors for postoperative NCD at the domain level are shown in Table 4. For the memory domain, an ASA score ≥ 3 (OR 3.7 [95%CI: 1.1–12.5]) was identified as a risk factor, while tumor stage III/IV (OR 0.3 [95%CI: 0.1–0.9]) was identified as an apparent protective factor. In the executive function domain, age ≥ 70 (OR 2.5 [95%CI: 1.1–6.1]), education to primary school level or below (OR 4.2 [95%CI:

1.5–12.3]), and HADS-A score >7 (OR 3.4 [95%CI: 1.1–10.9]) were risk factors, while major surgery (OR 0.3 [95%CI: 0.1–0.7]) was a protective factor. Again, a preoperative HADS-D score >7 was not associated with postoperative NCD in specific domains.

Figure 2. Cognitive decline at 3 months postoperatively. Data show the results of neurocognitive disorder overall and at the domain level as incidence (%) (95% confidence interval)

Table 3.
Logistic regression analysis for neurocognitive disorder
by 3 mo postoperatively (n=164)

Risk factors	Univariable (n = 16) OR (95%CI)	P	Multivariable (n = 16) OR (95%CI)	P
Patient and psychosocial characteristics				
Age (years)		.397		
<70	1			
≥70	1.6 (0.6–4.5)			
Gender		.754		
Female	1			
Male	1.2 (0.4–3.3)			
Educational level ^a		.003		.003
Primary school or lower	6.0 (1.9–19.0)		6.0 (1.8–20.1)	
Higher than primary school	1		1	
Social Economic Status ^d		.073*		
Low (7–10)	6.6 (0.8–51.3)			
Intermediate or high (1–6)	1			
Living situation		.059*		
Lives alone	2.8 (1.0–8.1)			
Lives independently with others	1			
Instrumental Activities of Daily Living ^c		.790		
= 8	1			
<8	0.8 (0.2–3.8)			
Body Mass Index ^d		.277		
Normal (<25)	1			
Overweight (≥25)	0.6 (0.2–1.6)			
Groningen Frailty Indicator		.875		
<4	1			
≥4	0.9 (0.2–3.4)			
Mini-Mental State Examination		.593		
≤26	1			
>26	1.8 (0.2–16.7)			
Charlson Comorbidity Index		.880		
≤2	1			
>2	1.1 (0.3–3.6)			
Hospital Anxiety and Depression Scale-Anxiety ^b		.262		
No (≤7)	1			
Mild or moderate (8–14)	2.0 (0.6–6.9)			
Hospital Anxiety and Depression Scale-Depression ^b		.891		.931
No (≤7)	1		1	
Mild or moderate (8–14)	1.1 (0.2–5.4)		1.1 (0.2–5.7)	
Disease and treatment characteristics				
Tumor stage ^b		.038		.041
Benign, 0, I, or II	1		1	
III or IV	0.3 (0.1–0.9)		0.3 (0.1–1.0)	

American Society of Anesthesiologists physical status classification		.567
<3	1	
≥3	0.6 (0.1–3.0)	
Invasive Surgery		.971
No	1	
Yes	1.0 (0.3–3.1)	
Major surgery		.796
No	1	
Yes	1.2 (0.4–3.3)	
History of chemo/radiotherapy ^e		.983
No	1	
Yes	1.0 (0.3–2.8)	
Postoperative delirium		n.a.
No	1	
Yes	n.a.	

Note: Neurocognitive disorder was defined as a score drop of ≥25% on ≥ 2 of 5 tests. Depression and factors with a P-value of < .15 in univariable analysis were included in the multivariable model. P values < .05 were considered significant. Bold values are considered statistically significant. Abbreviations: CI, confidence interval; OR, odds ratio.

*Variables that were non-significant in a multivariable model. ^a One missing data. ^b Two missing data. ^c Three missing data. ^d Four missing data. ^e Nine missing data.

Table 4.
Logistic regression analysis for neurocognitive disorder

Risk factors	Univariable		Memory (n = 19) Multivariable	
	OR (95%CI)	p	OR (95%CI)	p
Patient and psychosocial characteristics				
Age (years)				
<70	1			
≥70	1.2 (0.4–3.2)	.729		
Gender				
Female	1			
Male	1.3 (0.5–3.4)	.620		
Educational level ^a				
Primary school or lower	2.3 (0.7–8.0)	.180		
Higher than primary school	1			
Social Economic Status ^d				
Low (7–10)	3.5 (0.8–15.8)	.105*		
Intermediate or high (1–6)	1			
Living situation ^a				
Lives alone	1.3 (0.4–3.8)	.680		
Lives independently with others	1			
Instrumental Activities of Daily Living ^c				
= 8	1			
<8	1.0 (0.3–3.8)	.969		
Body Mass Index ^d				
Normal (<25)	1			
Overweight (≥25)	1.8 (0.6–5.3)	.281		
Groningen Frailty Indicator				
<4	1			
≥4	1.5 (0.5–4.4)	.506		
Mini-Mental State Examination				
≤26	1			
>26	1.5 (0.2–13.3)	.733		
Charlson Comorbidity Index				
≤2	1			
>2	3.4 (0.7–15.3)	.114*		
Hospital Anxiety and Depression Scale-Anxiety ^b				
No (≤7)	1			
Mild or moderate (8–14)	1.6 (0.5–5.2)	.468		
Hospital Anxiety and Depression Scale-Depression ^b				
No (≤7)	1		1	
Mild or moderate (8–14)	1.5 (0.4–5.9)	.538	1.5 (0.4–6.7)	.559
Disease and treatment characteristics				
Tumor stage ^b				
Benign, 0, I, or II	1		1	
III or IV	0.3 (0.1–0.9)	.027	0.3 (0.1–0.9)	.035

per domain at 3 mo postoperatively (n = 164)

Information processing speed (n = 26)				Executive Function (n = 33)			
Univariable		Multivariable		Univariable		Multivariable	
OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
1				1		1	
1.8 (0.8–4.2)	.179			2.8 (1.3–6.1)	.010	2.5 (1.1–6.1)	.037
1				1			
0.8 (0.4–1.9)	.680			1.4 (0.6–3.1)	.394		
0.9 (0.2–3.3)	.881			4.7 (1.8–12.3)	.002	4.2 (1.5–12.3)	.008
1				1		1	
1.0 (0.4–2.5)	.923			2.4 (0.9–6.7)	.091*		
1				1			
0.7 (0.3–2.1)	.568			2.3 (1.0–5.2)	.054*		
1				1			
1.0 (0.3–3.1)	.971			1.5 (0.6–4.1)	.378		
1				1			
0.5 (0.2–1.2)	.140*			0.7 (0.3–1.6)	.409		
1				1			
0.6 (0.2–2.0)	.447			1.9 (0.8–4.6)	.139*		
1				1			
0.6 (0.1–5.3)	.680			5.6 (1.4–22.3)	.014*		
1				1			
1.0 (0.4–2.5)	.962			1.8 (0.7–4.7)	0.236		
1				1		1	
1.0 (0.3–3.2)	.982			2.1 (0.8–5.4)	0.122	3.4 (1.1–10.9)	.035
1				1			
0.6 (0.1–2.7)	.483			2.0 (0.7–5.7)	0.203	1.2 (0.3–4.3)	.745
1				1			
0.8 (0.3–1.8)	.529			1.1 (0.5–2.4)	0.828		

Table 4. (continued)
Logistic regression analysis for neurocognitive disorder

Risk factors	Univariable		Memory (n = 19) Multivariable	
	OR (95%CI)	p	OR (95%CI)	p
American Society of Anesthesiologists physical status classification				
<3	1		1	
≥3	4.3 (1.5–11.9)	.006	4.1 (1.4–11.8)	.009
Invasive Surgery				
No	1			
Yes	2.7 (0.7–9.7)	.130*		
Major surgery				
No	1			
Yes	2.8 (0.9–9.0)	.077*		
History of chemo/radiotherapy ^a				
No	1			
Yes	1.8 (0.7–4.8)	.241		
Postoperative delirium				
No	1			
Yes	2.6 (0.5–13.8)	.271		

Note: Decline in a cognitive domain was defined as a decline of ≥25% on ≥1 test in that specific domain. Depression and factors with a P value of <.15 in the univariable analysis were included in a multivariable model. P values <.05 were considered significant. Bold values in the table indicate those considered statistically significant. Abbreviations: CI, confidence interval; OR, odds ratio.

*: These variables were non-significant in a multivariable model. a One missing data. b Two missing data. c Three missing dat. d Four missing data. e Nine missing data.

per domain at 3 mo postoperatively (n = 164)

Information processing speed (n = 26)				Executive Function (n = 33)			
Univariable		Multivariable		Univariable		Multivariable	
OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
1				1			
0.1 (0.02–1.0)	.055*			1.4 (0.6–3.5)	0.457		
1				1			
1.3 (0.5–3.2)	.635			1.0 (0.4–2.3)	0.959		
1				1		1	
1.4 (0.6–3.4)	.447			0.4 (0.2–0.8)	0.013	0.3 (0.1–0.7)	.008
1				1			
1.3 (0.6–3.0)	.532			0.9 (0.4–1.9)	0.719		
1				1			
0.64 (0.1–5.3)	.680			1.1 (0.2–5.7)	0.879		

Discussion

In this study, 12% of patients aged ≥ 70 experienced NCD at 3 months after surgery, compared with 8% of those in patients aged < 70 . Their affected domains were different in each group, with executive functioning most frequently affected in the elderly group (32%) and information processing speed most frequently affected in the young group (13%). Patients with lower educational attainment were at greater risk of postoperative NCD than those with higher educational attainment, whereas preoperative self-reported anxiety was associated with decline at executive function domain.

Incidence of postoperative NCD and the domains most commonly affected

The finding that 12% of patients experienced postoperative NCD in the elderly group is consistent with the results of previous studies in elderly populations, which have shown that the incidence of NCD varies from 9.9% to 16% after noncardiac surgery.^{5,28,29} Only two studies have investigated the incidence of NCD in young adults (age < 65 years), and these reported incidences of 5.7% and 6.4%.^{7,13} The slightly higher incidence in our study might reflect the slightly older population, the longer mean anaesthesia duration, and relatively invasive surgical procedures, which has been associated with a higher risk of NCD.^{7,13} Furthermore, the differences in neuropsychological tests, the definitions of NCD and the study populations themselves might have affected the incidence of postoperative NCD.

The domain most vulnerable to decline was executive function, while memory function was least affected. This is consistent with previous findings among elderly patients with cancer.⁵ This distinction between cognitive domains supports the hypothesis that specific brain areas might respond differently to the perioperative inflammatory response.³⁰ It was also notable that the incidence of decline in executive function was twice as high in the elderly group than in the young group. This might be due to the increased susceptibility and reactivity to inflammatory mediators of the areas associated with executive function in the aged brain, which in turn, exacerbated the neuroinflammatory response.^{31,32}

Preoperative (symptoms of) anxiety and depression

Preoperative anxiety was a risk factor of decline in executive function, controversially to what was hypothesized, preoperative depression was not associated with NCD 3 months after surgery in our adult population with cancer. It is possible that patients with symptoms of depression were less motivated to participate in the cognitive assessment in this study, thereby confounding the results. Supporting this theory, the incidence of self-reported depression was only 11.6%, which is much lower than the reported 27% in a meta-analysis of data for patients screened by self-report instruments during treatment for cancer.³³ The prevalence (15.2%) of anxiety in patients preoperatively in the current study lays in line with literature as on average 19% of patients show levels of anxiety in the clinical range during oncological treatment.³ However, younger patients experienced more (symptoms of) anxiety when compared with older patients. Studies point out that age is inversely related to emotional distress, and that younger patients tend to experience higher levels of anxiety due to a larger disruption of social and familial roles by diagnosis and treatment.³⁴ Besides, younger patients have more limited life experience to help them cope with such traumatic situations.

Other risk factors

Educational attainment was found to be strongly associated with postoperative NCD. This is supported by a review that showed low educational attainment to be associated with an increased risk of NCD after surgery.⁷ It has been suggested that low education attainment itself might indicate lower cognitive reserves. That is, patients with high cognitive reserves may be better able to cope with disruptions by having more efficient and flexible cognitions than their peers with low reserves. Therefore, low education attainment might be a confounder rather than a risk factor of NCD.³⁵ This might be expected when comparing NCD with a control group (eg, based on a z-score cut-off of 1.96).^{13,28,36} However, in our study, cognitive function was compared before and after surgery in the same group, where education attainment was unchanged.

It was notable that advanced tumor stage was protective against overall NCD and a decline in the memory domain. This may be because patients with advanced tumors had been physically ill and worried about their diagnosis and the upcoming surgery, potentially resulting in a higher chance of missing data and a worse performance

on the preoperative neuropsychological tests.³⁷ Those who underwent successful surgery might then have benefitted from physical improvement and stress relief that improved their postoperative cognitive performance. Equally, those who had continuing illness after surgery may have been unable to complete the cognitive assessment, as was observed in the International Study of Postoperative Cognitive Dysfunction in which continuing ill health after surgery commonly led to study withdrawal.²⁸ Therefore, for patients with advanced tumors, improvements in cognitive performance scores might be expected in the research setting that are not seen in daily clinical practice.³⁸

Strengths and limitations

There are several strengths of this study. First, the cohort was prospectively designed, and a research team was trained to conduct the tests in a standardized manner to avoid subjective bias in the delivery of the neuropsychological tests. Second, patient needs were prioritized when conducting the study, aiming to achieve a consecutive series of patients and to minimize dropout. When an additional visit to the hospital was a burden, assessments were completed at patients' places of residence. Third, our deep investigation of NCD at the domain level in a wide age group, and not merely among the elderly, contributes to a greater understanding of the incidence of postoperative NCD and the domains of cognition that are affected. However, certain limitations of the present study should also be noted. The study was conducted in a tertiary referral center, which introduced selection bias. Patients referred to this hospital generally undergo more complex surgical procedures compared with the wider population who undergo surgery for cancer. In the study cohort, individuals with relatively worse health statuses also had a higher chance of being excluded. Meanwhile, patients with symptoms of depression were less motivated to participate which might limit the ability to assess the association between depression and postoperative NCD. There were 12% of the included patients unable to complete the follow-up cognitive assessments at 3 months, and this dropout rate is comparable to that in other studies on this topic.^{13,39} However, given that the excluded patients had a relatively worse health status and given that patients with impaired cognitive statuses are more likely to be lost to follow-up, there is good reason to believe that the true incidence of NCD was even higher than that reported. It should also be noted that the failure to include a healthy control group prevented from accounting for a learning effect and might blur the true effect of surgery on cognitive change over time. However, a learning effect should cause postoperative cognitive performance

to improve from baseline, reducing the chance of detecting NCD. This is yet another factor indicating that the true incidence of postoperative NCD could be even higher than we estimated.

Clinical implications and future perspectives

Clinicians and family members need to be aware of this increased vulnerability among patients with low educational attainment and preoperative anxiety symptoms and must be more vigilant for NCD in this population. Given that postoperative NCD also appears to occur at a high incidence among younger adult patients, researchers should investigate this phenomenon among patients of all ages in the future. A larger patient cohort from primary or secondary care will be needed to study the effect of psychosocial factors, specifically preoperative depression, on postoperative outcomes in the future. For a better understanding of pathophysiology, associations with inflammatory mediators, preoperative anxiety and depression and postoperative NCD should be explored, as the proposed underlying mechanisms involve the immune system.

Acknowledgments

We would like to thank all 218 participants, the participating nurses, the medical and psychological students who helped with data collection. We thank Dr Robert Sykes (www.doctored.org.uk) for providing editorial services in later drafts of this manuscript.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2):87-108.
2. Sullivan R, Alatise OI, Anderson BO, et al. Global cancer surgery: Delivering safe, affordable, and timely cancer surgery. *Lancet Oncol.* 2015;16(11):1193-1224.
3. Linden W, Vodermaier A, Mackenzie R, Greig D. Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. *J Affect Disord.* 2012;141(2-3):343-351.
4. Vyas A, Babcock Z, Kogut S. Impact of depression treatment on health-related quality of life among adults with cancer and depression: A population-level analysis. *J Cancer Surviv.* 2017;11(5):624-633.
5. Plas M, Rotteveel E, Izaks GJ, et al. Cognitive decline after major oncological surgery in the elderly. *Eur J Cancer.* 2017;86:394-402.
6. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth.* 2018;121(5):1005-1012.
7. Berger M, Nadler JW, Browndyke J, et al. Postoperative cognitive dysfunction: Minding the gaps in our knowledge of a common postoperative complication in the elderly. *Anesthesiol Clin.* 2015;33(3):517-550.
8. Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. *EBioMedicine.* 2018;37:547-556.
9. Peng L, Xu L, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): A meta-analysis. *PLoS One.* 2013;8(11):e79624.
10. Camacho A. Is anxious-depression an inflammatory state? *Med Hypotheses.* 2013;81(4):577-581.
11. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol.* 2008;26(6):971-982.
12. Jimenez-Fonseca P, Calderon C, Hernandez R, et al. Factors associated with anxiety and depression in cancer patients prior to initiating adjuvant therapy. *Clin Transl Oncol.* 2018;20(11):1408-1415.
13. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology.* 2008;108(1):18-30.
14. Goodyear MD, Krleza-Jeric K, Lemmens T. The declaration of helsinki. *BMJ.* 2007;335(7621):624-625.

15. Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: Normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc.* 2005;11(3):290-302.
16. Reitan R, Wolfson D. The Halstead-Reitan neuropsychological test battery: Therapy and clinical interpretation. *Neuropsychological Press.* 1985.
17. Ruff R, Light R, Evans R. The ruff figural fluency test: A normative study with adults. *Developmental Neuropsychology.* 1987;3(1):37-51.
18. Stump D, Newman S, Coker L, Phipps J, Miller C. Persistence of neuropsychological deficits following CABG. *Anesthesiology.* 1990;73(3).
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.
20. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. an updated literature review. *J Psychosom Res.* 2002;52(2):69-77.
21. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9(3):179-186.
22. Meulendijks FG, Hamaker ME, Boereboom FT, Kalf A, Vogtlander NP, van Munster BC. Groningen frailty indicator in older patients with end-stage renal disease. *Ren Fail.* 2015;37(9):1419-1424.
23. Folstein MF, Folstein SE, McHugh PR. «Mini-mental state». A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis.* 1987;40(5):373-383.
25. Daabiss M. American society of anaesthesiologists physical status classification. *Indian J Anaesth.* 2011;55(2):111-115.
26. Boslooper K, Hoogendoorn M, van Roon EN, et al. No outcome disparities in patients with diffuse large B-cell lymphoma and a low socioeconomic status. *Cancer Epidemiol.* 2017;48:110-116.
27. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol.* 2007;165(6):710-718.
28. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. international study of post-operative cognitive dysfunction. *Lancet.* 1998;351(9106):857-861.

29. Shoair OA, Grasso li MP, Lahaye LA, Daniel R, Biddle CJ, Slattum PW. Incidence and risk factors for postoperative cognitive dysfunction in older adults undergoing major noncardiac surgery: A prospective study. *J Anaesthesiol Clin Pharmacol*. 2015;31(1):30-36.
30. Hovens IB, Schoemaker RG, van der Zee EA, Heineman E, Izaks GJ, van Leeuwen BL. Thinking through postoperative cognitive dysfunction: How to bridge the gap between clinical and pre-clinical perspectives. *Brain Behav Immun*. 2012;26(7):1169-1179.
31. Price CC, Garvan CW, Monk TG. Type and severity of cognitive decline in older adults after noncardiac surgery. *Anesthesiology*. 2008;108(1):8-17.
32. Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. *Neuroimmunomodulation*. 2008;15(4-6):323-330.
33. Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: A meta-analysis of diagnostic interviews and self-report instruments. *Psychooncology*. 2014;23(2):121-130.
34. Carlson LE, Angen M, Cullum J, et al. High levels of untreated distress and fatigue in cancer patients. *Br J Cancer*. 2004;90(12):2297-2304.
35. Feinkohl I, Winterer G, Spies CD, Pischon T. Cognitive reserve and the risk of postoperative cognitive dysfunction. *Dtsch Arztebl Int*. 2017;114(7):110-117.
36. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology*. 2009;110(3):548-555.
37. O'Toole MS, Pedersen AD, Hougaard E, Rosenberg NK. Neuropsychological test performance in social anxiety disorder. *Nord J Psychiatry*. 2015;69(6):444-452.
38. O'Toole MS, Pedersen AD. A systematic review of neuropsychological performance in social anxiety disorder. *Nord J Psychiatry*. 2011;65(3):147-161.
39. Johnson T, Monk T, Rasmussen LS, et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology*. 2002;96(6):1351-1357.

Appendix 1:
Components of the PICNIC-B-HAPPY study

Test	Short name.	Purpose	Cut-off value for adverse results	Score Range
Socioeconomic Status	SES	A combined score estimated for each four-digit postal code area, based on income level, degree of unemployment and percentage of low education level by the "Social Cultureel Planbureau"	High (first and second quintile); Intermediate (third quintile); Low (fourth and fifth quintile)	
Groningen Frailty Indicator	GFI	A 15-item screening instrument measures the loss of functions and resources in 4 domains: physical, cognitive, social, and psychological to determine the level of frailty	≥4	0–15
Instrumental Activities of Daily Living	IADL	A questionnaire regarding 8 items needed to perform independently to maintain independence in the community	<8	0–8
Body mass index	BMI	A measure of body fat based on height and weight	≥25	N.A.
Hospital Anxiety and Depression Scale-Anxiety	HADS-A	A questionnaire using 7 items to identify anxiety	>7	0–21
Hospital Anxiety and Depression Scale-Depression	HADS-D	A questionnaire using 7 items to identify depression	>7	0–21
Mini Mental State Examination	MMSE	A test consisting of 11 questions to assess cognitive function	≤26	0–30
Charlson Comorbidity Index	CCI	A scale predicts the one-year mortality for a patient who may have a range of comorbid conditions	≥2	1,2,3 or 6 for each condition
American Society for Anesthesiologist scale	ASA	To quantify preoperative physical status and estimate anaesthetic risk	≥3	1–5
PICNIC-B-Happy study = Predicting postoperative outcome in elderly surgical cancer patients: Biomarkers and handgrip strength as predictors of postoperative outcome in the elderly.				

Appendix 2:

Incidence of neurocognitive change from baseline to 3 months postoperatively

	All (n = 158)		Elderly group (Age ≥65 y; n = 89)		Young group (Age <65 y; n = 69)	
	n	Incidence (%) (95%CI)	n	Incidence (%) (95%CI)	n	Incidence (%) (95%CI)
Neurocognitive disorder						
Overall	16	10.1 (5.9–15.9)	10	11.2 (5.5–19.7)	6	8.7 (3.3–18.0)
Memory	17	10.8 (6.4–16.7)	8	9.0 (4.0–16.9)	9	13.0 (6.1–23.3)
Information processing speed	26	16.5 (11.0–23.2)	15	16.9 (9.8–26.3)	11	15.9 (8.2–26.7)
Executive function	30	19.0 (13.2–26.0)	22	24.7 (16.2–35.0)	8	11.6 (5.1–21.6)
Neurocognitive improvement						
Overall	86	54.4 (46.3–62.4)	54	60.7 (49.8–70.9)	32	46.4 (34.3–58.8)
Memory	93	58.9 (50.8–66.6)	57	64.0 (53.2–73.9)	36	52.2 (39.8–64.4)
Information processing speed	35	22.2 (15.9–29.4)	18	20.2 (12.4–30.1)	17	24.6 (15.1–36.5)
Executive function	82	51.9 (43.8–59.9)	45	50.6 (39.8–61.3)	37	53.6 (41.2–65.7)

Postoperative neurocognitive disorder/improvement was defined as a postoperative disorder/improvement of ≥25% on ≥2 out of 5 tests compared with the preoperative baseline assessment. Disorder/improvement on a specific domain was defined as a decline/improvement of ≥25% on ≥1 test in that specific domain.

Dear Editor,

We appreciate the interest in our work and the opportunity to respond to the comments and matters raised by Xiao et al.¹ In this study, we evaluated the association between preoperative anxiety and depression with neurocognitive disorder following oncological surgery.² We defined neurocognitive disorder as a $\geq 25\%$ decline in the performance scores three months after surgery, compared with the baseline score (in at least two of the five cognitive performance tests). Xiao et al. are correct that the research criteria used in our study for postoperative neurocognitive disorder (NCD) are not the same as in the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) criteria. The possible contrast between research criteria and the DSM-5 is the requirement for a cognitive concern in the latter and evidence of functional ability.³ Applying the criteria of DSM-5 might miss high functioning individuals despite the presence of symptoms of cognitive dysfunction.

To adjust for potential confounders, we did a multivariable analysis. Next to preoperative factors (education, comorbidities etc.) it is known that surgical factors are of great importance in the development of postoperative NCD. In a previous study of our group, it has been shown that surgical procedures with an anesthesia duration of 210 minutes or more (major surgery) are predictive for cognitive decline at three months postoperatively.⁴ Furthermore, surgical procedures performed for tumors located intra-abdominally are strongly associated with adverse outcomes when compared to less invasive procedures.⁵ Therefore, these risk factors were used reflecting surgical intensity. Still, we agree that a widely used risk factor score reflecting surgical intensity is of surplus value, once validated in older patients with cancer.

The delirium observation screening scale (DOS) was used to screen for signs of postoperative delirium and patients with a score ≥ 3 until seven days after surgery were indicated as delirious. When a patient was indicated as delirious by this scale, the patient would be seen by a geriatrician or consultant psychiatrist to apply the DSM-5 criteria. Xiao et al. criticized that the criteria for postoperative delirium (POD) should meet the DSM-5 criteria. We feel that as signs of delirium fluctuate throughout the day, using the DSM-5 criteria and depending on the availability of a psychiatrist, delirium is underdiagnosed in clinical practice. The DOS was used as part of regular care in the surgical oncological ward in the UMCG, which holds

the advantage of broad coverage and early recognition of delirium. In the research setting, we aimed to evaluate whether this early recognized signs of delirium would be associated with postoperative cognitive decline.

Finally, Xiao et al, mentioned that postoperative factors were not included in the models for postoperative neurocognitive disorder (NCD) and therefore might have influenced results. Due to the sample size and statistical power considered choices for analysis were made and the focus of the current study was mainly on preoperative signs of anxiety and depressions and not necessarily on per- and postoperative factors. Besides, in a previous study of our group, we observed that POD was associated with postoperative NCD while other postoperative complications were not.⁴ Therefore the recognized signs of delirium after surgery was of higher interest. None of the patients in the current study experienced POD as well as postoperative NCD at three months after surgery, thus this factor was not included into the analysis.

In summary, it is our hope that further well-designed studies will be conducted to advance our knowledge on risk factors of postoperative NCD and to improve the cognitive outcome of oncological patients after surgical treatment.

References

1. Xiao G, Xue F, Liu S, Zou Y. Assessing associations of preoperative anxiety and depression with neurocognitive disorder after oncological surgery. *J Surg Oncol*. 2020.
2. Du J, Plas M, Absalom AR, van Leeuwen BL, de Bock GH. The association of preoperative anxiety and depression with neurocognitive disorder following oncological surgery. *J Surg Oncol*. 2020;121(4):676-687.
3. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth*. 2018;121(5):1005-1012.
4. Plas M, Rotteveel E, Izaks GJ, et al. Cognitive decline after major oncological surgery in the elderly. *Eur J Cancer*. 2017;86:394-402.
5. Huisman MG, Audisio RA, Ugolini G, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: A multicenter prospective cohort study. *Eur J Surg Oncol*. 2015;41(7):844-851.

Chapter 8

Summary and general
discussion

Summary

The aim of this thesis was to elucidate the inflammatory response to surgery and possible negative sequelae in (elderly) oncological patients, with special interest in cognitive functioning. For that, the prospective studies PICNIC and PICNIC-B-HAPPY, and a retrospective CRS-HIPEC study, were performed.

The perioperative inflammatory response is related to the postoperative morbidity seen in elderly patients. In **chapter 2** the association between a range of pre- and peroperative factors and the extent of the inflammatory response were investigated and patients at risk of a greater inflammatory response following surgery were identified in elderly oncological patients. Plasma samples of 224 patients 65 years and older, undergoing a surgical procedure for the removal of a solid malignant tumour were obtained. Median age was 72 (65-89) years and 108 (48.2%) patients were male. Anaesthesia duration was associated with an increase of plasma levels of CRP, IL-1 β and IL-6; intracavitary surgery with an increase in plasma levels of IL-6; blood loss with a decrease in plasma levels of CRP and IL-1 β ; total fluid volume administered with a decrease in plasma levels of IL-1 β and disease stage was associated with increase in plasma levels of IL-6. The perioperative inflammatory response is determined by surgical characteristics rather than by preoperative factors. Elderly oncological patients undergoing longer lasting, intracavitary surgical procedures for more advanced disease stages developed the most intense inflammatory response.

The perioperative inflammatory response is associated with complications, independent of patient and surgical factors which are also associated with outcome. Associations were observed for short-term changes for plasma levels of the inflammatory mediators IL-6 and IL-10 with postoperative complications (**chapter 3**). Data of the 224 elderly patients with complete plasma sampling of the 'PICNIC' study were used. All complications occurring up to 30 days postoperatively were documented prospectively and to improve the quality of the registration of postoperative complications, all complications were thoroughly reviewed using clear pre-defined criteria. In 2018, all data considering complications were re-analyzed by reviewing all related patients' records. The presented study in this thesis shows the association of inflammatory biomarkers with complications in the postoperative course in elderly oncological patients. Half of the patients

did not develop complications in the postoperative period, however 110 (49.6%) did of which 62 patients (55.9% of patients with complications) developed >1 complication. A total number of 252 complications was registered, of which 107 (42.3%) were considered to have immune system involvement. Besides patient and surgical factors associated with adverse outcomes following oncological surgery in older patients, an independent prognostic effect of postoperative plasma levels of the inflammatory biomarkers IL-6 and IL-10 was found.

Chapter 4 consists of a comment on a double-blind, randomized controlled trial of the effect of perioperative lipid-enriched enteral nutrition versus standard care. Thoughts on target populations for immunomodulating interventions are discussed. Based on data presented in chapter 2 and 3 it appears that to show clear modulation of inflammation and organ function, a cohort must include patients with strong inflammatory responses and a high proportion of inflammatory complications. An option for future research is to explore nutritional intervention in surgical patients with more severe inflammatory responses and a higher incidence of postoperative complications, such as patients aged 75 years or older, with several comorbidities, who are scheduled for major oncological surgery without a prehabilitation or rehabilitation program.

In **chapter 5** the incidence of cognitive decline 3 months after surgery was examined and potential patient-, disease- and surgery-related risk factors for postoperative cognitive decline in onco-geriatric patients were identified. A consecutive series of elderly patients (≥ 65 years) undergoing surgery for the removal of a solid tumour was included ($n=307$). Cognitive performance was assessed pre-operatively and 3 months postoperatively. Of the patients who had completed the assessments, 117 (53%, 95%CI 47-60) had improved cognitive test scores, whereas 26 (12%, 95% CI 7.6-16) showed cognitive decline at 3 months postoperatively. In patients aged >75 years, the incidence of overall cognitive decline 3 months postoperatively was 18% (95% CI 9.3-27). In patients with lower pre-operative Mini-Mental State Examination (MMSE) score (≤ 26) the incidence was 37% (95% CI 18-57), and in patients undergoing major surgery it was 18% (95% CI 10.6-26). Of the cognitive domains, executive function was the most vulnerable to decline. Advanced age, lower pre-operative MMSE score and major surgery are risk factors for cognitive decline at 3 months postoperatively and should be taken into account in the clinical decision-making progress.

A role of systemic inflammation in the development of postoperative delirium, a postoperative complication affecting cognition, was suggested in patients undergoing cytoreduction surgery-hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) (**chapter 6**). Incidence and baseline characteristics associated with postoperative delirium were subject of investigation in 136 patients, of which data were included in analysis. During hospitalization, 38 (28%) patients were diagnosed with delirium. Factors that differed significantly between the patients with and without delirium by univariate analysis were included in multivariate analysis. Multivariate analysis showed that after adjustment for age and complications other than delirium, having three or more organs resected and the CRP serum levels were independent predictors for delirium (OR: 4.0;95% CI 1.2-12.8; OR: 1.01;95% CI 1-1.01, respectively).

The proposed underlying mechanisms of anxiety and depression, and postoperative neurocognitive disorder (NCD) all have immune system involvement. Therefore, in **chapter 7** the incidence of postoperative NCD 3 months after surgery among oncological patients undergoing surgery and the role of preoperative anxiety and depression were investigated. Clinical and psychosocial factors were assessed preoperatively in 218 patients aged ≥ 18 years undergoing surgery to remove a solid tumor. Furthermore five neuropsychological tests in the domains of executive function, information processing speed and memory, before and at 3 months after surgery were performed. Neurocognitive disorder affected 12.3% of elderly patients (age ≥ 75 years, $n = 57$) at 3 months after surgery, with executive function mostly affected. By contrast, 8.4% of the younger patients (age < 70 years, $n = 107$) were affected, with information processing speed mostly affected. However, whereas preoperative depression was not a risk factor for cognitive decline, low educational attainment was a risk factor (OR: 6.0;95% CI 1.9–19.0). Preoperative anxiety was associated with decline in the domain of executive function. Postoperative NCD is a complication of oncological surgery for adults of all ages. Despite expectations, preoperative anxiety or depression were not associated with an increased risk of NCD, but low educational attainment was associated with postoperative NCD.

General discussion

This thesis shows that during solid tumour resection (surgery) the immune system is activated, leading to increased plasma levels of inflammatory mediators at wound closure. A balanced response of the immune system is necessary for recovery.^{1,2} A more outspoken inflammatory response following surgery is related to complications in the postoperative course.³ However, detailed knowledge about the immune system in patients undergoing surgery is too scarce to target the immune system for interventions.⁴ Questions concerning how the inflammatory response should and might be influenced and who will benefit from these immunomodulating interventions must be addressed.

Plasma levels of certain inflammatory mediators increase during surgery (**chapter 2**). However, the challenge is to deliver convincing evidence that increased perioperative plasma levels are related to the occurrence of postoperative complications (**chapter 3**). The development of complications is influenced by many factors which cannot all be attributed to the immune system. Studies successfully linking the perioperative inflammatory response to morbidity and mortality have been published, but the results are mixed.⁵⁻⁷ After cardiac surgery, the development of an inflammatory response and associations with increased risk for morbidity and mortality are confirmed.⁸ Data on an inflammatory response after surgery in older oncological patients are lacking, as this population is one of the least studied on this aspect.⁹ So far, substantiating the influence of the perioperative inflammatory response on outcomes has been more successful and well-explored in animal studies. Animal studies show that a greater inflammatory response following surgery influences outcomes negatively with examples like postoperative ileus, infections, anastomotic leakage and postoperative cognitive disorders.¹⁰⁻¹⁴ The lack of convincing evidence in our studies might be explained by the methods used for assessment of the perioperative inflammatory response. To explore the effect of the surgical procedure on plasma levels of inflammatory markers, perioperative changes in plasma were estimated by drawing blood samples immediately before and after the surgical procedure. The number of blood sampling points was limited. Addition of more plasma sampling moments during the surgical procedure and in the postoperative course (especially the postoperative days) would have facilitated the production of a time-response curve per inflammatory marker. Potentially leading to assessment of the relationship between the inflammatory response following surgery and postoperative recovery in elderly.¹⁵

In the first postoperative days, higher serum levels of the inflammatory mediator CRP were associated with the occurrence of postoperative delirium in patients undergoing CRS-HIPEC (**chapter 6**). This emphasizes the relevance of extending the monitoring of the inflammatory mediators into the period after wound closure. Besides, it motivates to further explore the pathophysiology of neuroinflammation and how undergoing surgery may lead to complications affecting cognition in patients.¹⁶

Figure 1. This figure depicts the inflammatory model of the pathophysiology of postoperative complications affecting cognition. ^aThe extent and magnitude of the systemic inflammatory response varies widely among individuals, possibly related to chronic activity of stress response system. ^bIt is unknown which specific cytokines or mediators cross the blood-brain barrier. ^cLikely risk factors for the long-term consequences of neuroinflammation include preexisting cognitive impairment, cerebrovascular disease, and severe illness. Figure from: JAMA. 2012 July 4; 308(1): 73–81. doi:10.1001/jama.2012.6857.

The immune system is complex and not completely assessed by determining six inflammatory mediators in plasma of elderly undergoing oncological surgery. The optimal selection of the inflammatory markers for analysis is subject to debate. The inflammatory markers assessed in the described studies in this thesis were chosen based on a proposed pathway, mechanism and hypothesis. When interpreting

studies, investigating inflammatory mediators independently, a degree of caution is advised.¹⁷ The identification of biomarkers capable to accurately predict complications during the early postoperative phase remains a clear unmet need. Inflammatory biomarkers are not routinely and widely used in clinical practice. CRP is an acute phase protein produced by the liver and is a standard clinical marker of inflammation.¹⁸ Other inflammatory biomarkers than CRP might facilitate prevention or earlier detection of postoperative complications. For example, plasma levels of IL-6 increase rapidly and peak 24 hours after surgery, whereas CRP peaks after 48 hours.¹⁹ Regrettably, assays of inflammatory markers are more expensive than CRP assays and ineffective use of diagnostics should be avoided. An ideal marker should be able to distinguish between the inflammatory response and infection allowing earlier identification of patients developing severe infectious complications. Our knowledge on perioperative inflammatory response assessment that evolved by conducting these studies is of great importance for future projects.

This thesis explored adverse outcomes following oncological surgical procedures with special interest in those affecting cognitive functioning (**chapter 5-7**). Concerning the relation between postoperative complications and delirium, cause and effect remain unclear. Whether a postoperative delirium increases the risk for other postoperative complications or if it is a symptom of other complications which can occur after surgery, remains to be clarified. In **chapter 5** postoperative delirium was associated with postoperative cognitive decline. It is unclear whether this relation represents a continuum of disease between delirium and postoperative cognitive decline, as neuroinflammation is suggested to play a role in the development of both.²⁰ In general, assessing postoperative cognitive decline is challenging due to differences in populations, terminology and assessment methods used.²¹ However, consensus is recently achieved in how to report cognitive impairment associated with anaesthesia and surgery.²²

Relevance of the findings

This thesis aimed to study the negative sequelae of the inflammatory response, and the inflammatory response itself, to surgery in elderly oncological patients with special interest in cognitive functioning. The postoperative period of elderly patients undergoing surgery in sight of oncological treatment was closely scrutinized and findings are diverse (see Figure 2). The perioperative inflammatory response was measured by assessing different inflammatory mediators and patients at risk for a greater inflammatory response were identified. In addition, the association between the inflammatory response and postoperative complications, and the association between the conditions (anxiety and depression) with the proposed shared pathophysiology, were investigated. At last, the occurrence of cognitive complications with delirium during hospital admission and cognitive decline 3 months postoperatively were explored. This thesis is a step further into the process to translate preclinical findings into clinical practice and is therefore highly relevant.

Figure 2. This figure depicts a schematic overview of the associations found in the current thesis. Different patient, as well as surgical factors are associated with the postoperative course, but also do influence each other. Conclusions are limited to associations between factor and event, and these associations do not necessarily imply causality.

Implications for future research

Although surgical procedures are aimed at improving health and well-being, approximately 50% of the older patients undergoing surgery experiences postoperative complications. Older patients are a heterogeneous group with regard to physical activity, comorbidities and self-support. They may be fit with active lifestyles or frail and not able to live independently.²³ As older patients may suffer from impaired cognitive functioning, reduced physiologic reserves or other diagnosis than cancer, it is challenging to make choices regarding treatment. In oncology a balance between treatment risk and the risk of oncological disease itself is essential. In the elderly, treatment aims may be different than in younger patients.²⁴ Therefore, tailored treatment becomes more and more accepted in oncology.²⁵

As more extended and invasive surgery is associated with a more outspoken inflammatory response to surgery and with postoperative complications (including postoperative cognitive decline), surgical technique is an interesting factor for potential interference.²⁶ Since minimally invasive surgery (MIS) may attenuate the inflammatory response, it has also been speculated that it may reduce the incidence of postoperative complications.²⁷ In sight of the knowledge that advanced age and major surgery are risk factors for cognitive decline, MIS is potentially favorable in the elderly (**chapter 5**). There is a new interest on the influence of the perioperative immune response on disease recurrence after surgery.^{28,29} Animal studies have shown that the inflammatory response to surgery can promote the outgrowth of tumour cells.³⁰ Therefore, the immune response of different surgical techniques may influence survival.³¹

Modulation of the immune system is suggested as one way of optimizing the postoperative course for surgical patients.³² The immune system eliminates threats that could hamper the body's capability to preserve homeostasis and during surgery homeostasis gets disrupted.³³ Immunomodulation may occur by boosting or by inhibiting the immune response. The role of excessive or deficient levels of inflammatory mediators in pathophysiology of complications will determine the direction of immunomodulation. Immunomodulation may be beneficial for prevention and treatment of postoperative adverse events, however improving postoperative outcomes in clinical practice by such interventions seems far away.³⁴ The findings in this thesis underscore the relevance of exploring such

immunomodulating preventive interventions. Modulation of the inflammatory response to surgery, requires a meticulous knowledge of the acute inflammatory response and its mechanisms.⁴ Tocilizumab, a humanized monoclonal antibody which binds to IL-6 receptors, might be a drug of interest.³⁵ It has been shown successful in attainment of postoperative cognitive functioning in animals.³⁶

Interference in neural signaling is an alternative way to modulate the immune response as the immune system and the autonomic nervous system bidirectionally communicate and share many mediators and receptors.^{37,38} The bidirectional communication network including the central nervous system, the autonomic nervous system, the enteric nervous system and the hypothalamic pituitary adrenal axis is called the gut-brain axis.³⁹ Administration of lipid-rich nutrition was previously shown to reduce the inflammatory response by activating the autonomic nervous system.⁴⁰ In experimental studies, enteral nutrition reduces postoperative ileus (a complication with proposed immune system involvement) by dampening the inflammatory response via a mechanism that involves activation of the autonomic nervous system.⁴¹ Lastly, immunonutrition has been suggested to enhance postoperative recovery by interfering with the immune response and might therefore be an interesting intervention for older patients undergoing surgery as part of oncological treatment.⁴²

In conclusion

Exploring the negative sequelae of surgery in elderly oncological patients might help to give insight into the consequences of the complex immune response to surgery. Identification of patients at increased risk of postoperative complications enables tailored treatment, ultimately leading to improved quality of care and improved postoperative outcomes in older oncological patients. Prevention of postoperative neurocognitive disorder will improve outcomes and preserve quality of life following surgery for the elderly. Nevertheless, before promising interventions may be developed, a deeper understanding of the proposed underlying inflammatory mechanism is essential. Finally, suggestions for future research include further investigation of the process of neuroinflammation, exploring the possibilities of immunomodulation in older surgical patients and monitoring the effect on postoperative outcome. This is no real ending, it is just the place where this thesis ends.

References

1. Stoecklein VM, Osuka A, Lederer JA. Trauma equals danger--damage control by the immune system. *J Leukoc Biol.* 2012;92(3):539-551.
2. O'Dwyer MJ, Owen HC, Torrance HD. The perioperative immune response. *Curr Opin Crit Care.* 2015;21(4):336-342.
3. Mokart D, Capo C, Blache JL, et al. Early postoperative compensatory anti-inflammatory response syndrome is associated with septic complications after major surgical trauma in patients with cancer. *Br J Surg.* 2002;89(11):1450-1456.
4. Andersson R, Andersson B, Andersson E, Eckerwall G, Norden M, Tingstedt B. Immunomodulation in surgical practice. *HPB (Oxford).* 2006;8(2):116-123.
5. Nemeth E, Vig K, Racz K, et al. Influence of the postoperative inflammatory response on cognitive decline in elderly patients undergoing on-pump cardiac surgery: A controlled, prospective observational study. *BMC Anesthesiol.* 2017;17(1):113-017-0408-1.
6. McSorley ST, Watt DG, Horgan PG, McMillan DC. Postoperative systemic inflammatory response, complication severity, and survival following surgery for colorectal cancer. *Ann Surg Oncol.* 2016;23(9):2832-2840.
7. Kaufmann KB, Heinrich S, Staehle HF, Bogatyreva L, Buerkle H, Goebel U. Perioperative cytokine profile during lung surgery predicts patients at risk for postoperative complications-A prospective, clinical study. *PLoS One.* 2018;13(7):e0199807.
8. Brocca A, Virzi GM, de Cal M, Giavarina D, Carta M, Ronco C. Elevated levels of procalcitonin and interleukin-6 are linked with postoperative complications in cardiac surgery. *Scand J Surg.* 2017;106(4):318-324.
9. Hempenius L, Slaets JP, Boelens MA, et al. Inclusion of frail elderly patients in clinical trials: Solutions to the problems. *J Geriatr Oncol.* 2013;4(1):26-31.
10. Turler A, Moore BA, Pezzone MA, Overhaus M, Kalff JC, Bauer AJ. Colonic postoperative inflammatory ileus in the rat. *Ann Surg.* 2002;236(1):56-66.
11. Greca FH, Souza Filho ZA, Giovanini A, Camargo Junior CA, Rubin MR, Silva RF. Interleukin-6 (IL-6) influence on colonic anastomosis healing in rats. *Acta Cir Bras.* 2007;22(2):110-114.
12. Barrientos RM, Hein AM, Frank MG, Watkins LR, Maier SF. Intracisternal interleukin-1 receptor antagonist prevents postoperative cognitive decline and neuroinflammatory response in aged rats. *J Neurosci.* 2012;32(42):14641-14648.
13. Inoue K, Suzuki T, Igarashi T, et al. Deep anesthesia worsens outcome of rats with inflammatory responses. *Inflamm Res.* 2016;65(7):563-571.

14. Zhang H, Sun T, Liu Z, Zhang J, Wang X, Liu J. Systemic inflammatory responses and lung injury following hip fracture surgery increases susceptibility to infection in aged rats. *Mediators Inflamm.* 2013;2013:536435.
15. Rettig TC, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EM, Noordzij PG. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery. *Ann Surg.* 2016;263(6):1207-1212.
16. Forsberg A, Cervenka S, Jonsson Fagerlund M, et al. The immune response of the human brain to abdominal surgery. *Ann Neurol.* 2017;81(4):572-582.
17. Monastero RN, Pentyala S. Cytokines as biomarkers and their respective clinical cutoff levels. *Int J Inflamm.* 2017;2017:4309485.
18. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol.* 2018;9:754.
19. Sakamoto K, Arakawa H, Mita S, et al. Elevation of circulating interleukin 6 after surgery: Factors influencing the serum level. *Cytokine.* 1994;6(2):181-186.
20. Marcantonio ER. Postoperative delirium: A 76-year-old woman with delirium following surgery. *JAMA.* 2012;308(1):73-81.
21. Hovens IB, Schoemaker RG, van der Zee EA, Heineman E, Izaks GJ, van Leeuwen BL. Thinking through postoperative cognitive dysfunction: How to bridge the gap between clinical and pre-clinical perspectives. *Brain Behav Immun.* 2012;26(7):1169-1179.
22. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth.* 2018;121(5):1005-1012.
23. Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. *Ann Surg.* 2009;250(3):449-455.
24. Stepney R. Advances in caring for the older cancer patient: A report from the 2015 conference of the international society of geriatric oncology. *Cancer Biol Med.* 2016;13(1):150-155.
25. Renfro LA, An MW, Mandrekar SJ. Precision oncology: A new era of cancer clinical trials. *Cancer Lett.* 2017;387:121-126.
26. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery.* 2000;127(2):117-126.
27. Okholm C, Goetze JP, Svendsen LB, Achiam MP. Inflammatory response in laparoscopic vs. open surgery for gastric cancer. *Scand J Gastroenterol.* 2014;49(9):1027-1034.

28. Baum M, Demicheli R, Hrushesky W, Retsky M. Does surgery unfavourably perturb the “natural history” of early breast cancer by accelerating the appearance of distant metastases? *Eur J Cancer*. 2005;41(4):508-515.
29. Gottschalk A, Sharma S, Ford J, Durieux ME, Tiouririne M. Review article: The role of the perioperative period in recurrence after cancer surgery. *Anesth Analg*. 2010;110(6):1636-1643.
30. Krall JA, Reinhardt F, Mercury OA, et al. The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy. *Sci Transl Med*. 2018;10(436):10.1126/scitranslmed.aan3464.
31. Dolan RD, Lim J, McSorley ST, Horgan PG, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis. *Sci Rep*. 2017;7(1):16717-017-16955-5.
32. Gaudilliere B, Fragiadakis GK, Bruggner RV, et al. Clinical recovery from surgery correlates with single-cell immune signatures. *Sci Transl Med*. 2014;6(255):255ra131.
33. Kyrou I, Tsigos C. Stress hormones: Physiological stress and regulation of metabolism. *Curr Opin Pharmacol*. 2009;9(6):787-793.
34. Nader ND. Immunomodulation mechanisms in disease and in the surgical patient. *Immunol Invest*. 2017;46(8):765-768.
35. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy*. 2016;8(8):959-970.
36. Hu J, Feng X, Valdearcos M, et al. Interleukin-6 is both necessary and sufficient to produce perioperative neurocognitive disorder in mice. *Br J Anaesth*. 2018;120(3):537-545.
37. Shepherd AJ, Downing JE, Miyan JA. Without nerves, immunology remains incomplete -in vivo veritas. *Immunology*. 2005;116(2):145-163.
38. Kumar V, Sharma A. Is neuroimmunomodulation a future therapeutic approach for sepsis? *Int Immunopharmacol*. 2010;10(1):9-17.
39. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*. 2015;28(2):203-209.
40. Lubbers T, Kox M, de Haan JJ, et al. Continuous administration of enteral lipid- and protein-rich nutrition limits inflammation in a human endotoxemia model. *Crit Care Med*. 2013;41(5):1258-1265.
41. Lubbers T, Luyer MD, de Haan JJ, Hadfoune M, Buurman WA, Greve JW. Lipid-rich enteral nutrition reduces postoperative ileus in rats via activation of cholecystokinin-receptors. *Ann Surg*. 2009;249(3):481-487.
42. Cerantola Y, Hubner M, Grass F, Demartines N, Schafer M. Immunonutrition in gastrointestinal surgery. *Br J Surg*. 2011;98(1):37-48.

Appendices

Nederlandse samenvatting

Dutch summary

Dankwoord

Acknowledgements

Curriculum Vitae

Nederlandse samenvatting (Summary in Dutch)

De stijgende incidentie van kanker en de vergrijzing

Jaarlijks krijgen ongeveer 116.000 mensen in Nederland kanker. Kanker is een aandoening die met name op hogere leeftijd voorkomt. Meer dan de helft van alle patiënten is ouder dan 65 jaar op het moment dat de diagnose wordt gesteld. Mede door de naoorlogse geboortegolf, is het aantal 65-plussers fors toegenomen. Onder andere door de toename van deze groep en gezien het feit dat de ouderen in Nederland ook steeds ouder worden, stijgt het aantal mensen met kanker.

Chirurgische behandeling van solide tumoren

Er zijn vele soorten kanker en de ziekte kan zich presenteren op verschillende manieren. Wanneer door verkeerde celdeling een gezwel (tumor) ontstaat in vast weefsel zoals organen, huid, botten of slijmvliezen, noemt men dit een solide tumor. Het zijn de meest voorkomende tumoren. Wanneer de ziekte onbehandeld blijft, kan dit ernstige gevolgen hebben voor de gezondheid en kan men aan de ziekte overlijden. Er zijn verschillende behandelingen mogelijk, vaak bestaand uit een combinatie van chirurgie, radiotherapie en chemotherapie. Van de behandeling van solide tumoren is chirurgie een essentieel onderdeel. Door de stijging van de incidentie van solide tumoren op oudere leeftijd die gepaard gaat met vergrijzing, komt het steeds vaker voor dat oudere patiënten worden geopereerd. Leeftijd is tegenwoordig geen reden meer om iemand niet te opereren. Dit komt onder andere door de ontwikkelingen in de techniek van de anesthesie en chirurgie.

Risico op complicaties na chirurgie in (oudere) patiënten met kanker

Het ondergaan van een operatie is niet zonder risico's. Zowel na (postoperatief) als tijdens de operatie kunnen complicaties optreden, ongeacht de leeftijd van de patiënt. Voorbeelden van postoperatieve complicaties zijn: een wondinfectie, een longontsteking of bijvoorbeeld een urineweginfectie. In het algemeen lopen ouderen meer risico op deze complicaties en andere problemen na de operatie. Oudere patiënten hebben over het algemeen een trager herstel en een hoger risico op een verminderde kwaliteit van leven na de operatie. Soms worden patiënten na een operatie niet meer 'de oude'. Dit is soms een gevolg van cognitieve problemen. Deze

problemen bestaan bijvoorbeeld uit geheugenproblemen, concentratieproblemen of een verminderd vermogen om te plannen en informatie te verwerken. Dit disfunctioneren van het cognitieve vermogen na een operatie (postoperatieve cognitieve disfunctie (POCD)) heeft grote invloed op het leven van patiënten en kan ouderen na operaties afhankelijk van anderen maken. Ook kan het er toe leiden dat zij gebonden zijn aan huis. En dat terwijl het vermogen om zelfstandig te functioneren onmisbaar is voor de kwaliteit van leven voor patiënten met kanker. Daarnaast kunnen zich ook problemen met het bewustzijn voordoen tijdens de ziekenhuisopname, zoals plotselinge verwardheid na de operatie, oftewel een delier. Een postoperatief delier wordt gekenmerkt door een acute, fluctuerende verandering in het bewustzijn. Behalve dat een delier erg vervelend is voor de patiënt zelf, leidt een delier ook vaak tot langere ziekenhuisopname en wordt het herstel na de operatie negatief beïnvloedt. Dit probleem treft met name oudere patiënten.

Het onderliggend mechanisme

Sinds een aantal jaar denkt men dat een fysiologische reactie aan de basis ligt van het ontstaan van postoperatieve complicaties. Schade aan weefsels is een onvermijdelijk gevolg van operaties. De respons van het lichaam op weefsel schade is een zogeheten ontstekingsreactie. Tijdens een operatie vindt altijd een ontstekingsreactie plaats. Dit is een normale reactie waarmee wondgenezing en het herstel van het lichaam in gang worden gezet. Het immuunsysteem produceert ontstekingsfactoren die dienen als signaalstoffen om dit proces te coördineren. De ontstekingsfactoren komen in de bloedbaan terecht en worden door het hele lichaam verspreid (Figuur 1), ook naar de hersenen, waar ze de immuuncellen van de hersenen (microglia) activeren. De microglia produceren vervolgens na deze activatie, zelf ook ontstekingsfactoren in de hersenen. Dit proces wordt neuroinflammatie genoemd. Deze op herstel gerichte reactie kan ook nadelige gevolgen hebben voor het herstel, met name wanneer deze reactie (te) groot is of (te) lang duurt. Eerder onderzoek heeft aangetoond dat veroudering gepaard gaat met veranderingen in het immuunsysteem en de bijbehorende ontstekingsreactie. Deze veranderde ontstekingsreactie zou kunnen verklaren waarom juist ouderen kwetsbaar zijn voor cognitieve disfunctie, andere complicaties na een operatie en neuroinflammatie. Kortom, een in principe beschermende en functionele reactie van het immuunsysteem kan potentieel schadelijke gevolgen in de periode na de operatie.

Figuur 1. Deze figuur is een vereenvoudigde weergave van de ontstekingsreactie die ontstaat bij operaties. Tijdens een operatie vindt altijd een ontstekingsreactie plaats, als gevolg van de weefselschade van de operatie (1). De ontstekingsfactoren komen in de bloedbaan terecht en worden door het hele lichaam verspreid (2). Deze ontstekingsreactie kan zich uitbreiden naar alle organen, waaronder de hersenen, waar ze de immuuncellen van de hersenen (microglia) activeren (3).

Doel van het proefschrift

Het doel van dit proefschrift is de ontstekingsreactie die ontstaat bij operaties, te onderzoeken en de mogelijke gevolgen hiervan in kaart te brengen voor met name oudere patiënten met kanker. Speciale aandacht gaat uit naar de gevolgen voor het cognitief functioneren in de periode na een operatie, zowel in het ziekenhuis als thuis. Om deze doelen te bereiken werden de PICNIC-studie, PICNIC-B-HAPPY-studie en een CRS-HIPEC-studie uitgevoerd.

De bevindingen van dit proefschrift

Zoals hiervoor beschreven is de ontstekingsreactie mogelijk betrokken bij de ontwikkeling van postoperatieve complicaties die gezien worden bij met name oudere patiënten. Om te onderzoeken welke factoren van invloed zijn op de ontstekingsreactie, werd in **hoofdstuk 2** de associatie onderzocht tussen preoperatieve en chirurgische factoren en de uitgebreidheid van de ontstekingsreactie die ontstaat bij operaties in oudere patiënten met kanker. Ook werd gekeken welke patiënten risico liepen op het ontwikkelen van een grotere ontstekingsreactie. Plasma monsters (extracties van gecentrifugeerd bloed) van 224 patiënten met een leeftijd van 65 jaar en ouder werden verzameld. Alle patiënten ondergingen een chirurgische procedure voor het verwijderen van een solide tumor in het kader van de behandeling van kanker. Concluderend wordt de ontstekingsreactie met name door chirurgische factoren en niet door preoperatieve factoren (met de uitzondering van het stadium van de ziekte) bepaald. Oudere patiënten met kanker die langere operaties ondergaan in de buik en/of borstholte met een verder gevorderd ziektestadium ontwikkelen de meest uitgesproken ontstekingsreactie tijdens de operatie.

In **hoofdstuk 3** werd de invloed van de ontstekingsreactie tijdens een operatie, op het ontstaan van complicaties na de operatie onderzocht. Gegevens van 224 patiënten uit de PICNIC-studie werden gebruikt. Tijdens de studie werden de postoperatieve complicaties geregistreerd. In 2018 werden alle gegevens nogmaals gecontroleerd door de patiëntendossiers op te vragen en de complicatieregistraties na te lopen. Ongeveer de helft van de patiënten kreeg geen complicatie in de periode na de operatie, echter 110 patiënten kregen wel een complicatie waarvan er 62 patiënten meer dan één complicatie ontwikkelden. Naast patiënt- en chirurgische factoren die van invloed waren op het krijgen van complicaties, werd een verband gevonden met een stijging van de bepaalde ontstekingsfactoren tijdens de operatie. Desalniettemin leek de invloed van de stijging van de ontstekingsfactoren tijdens de operatie beperkt, met name wanneer de metingen gecorrigeerd werden voor de duur van de operatie. Mogelijk is de volledige ontstekingsreactie die tijdens een operatie ontstaat niet gemeten doordat de bloedmonsters (te) kort na de operatie werden afgenomen.

Onderzoek bij zowel proefdieren als gezonde proefpersonen heeft laten zien dat geringe hoeveelheden verrijkte voeding een ontstekingsreactie zoals die ontstaat

tijdens een operatie, kan remmen. Speciale voeding, toegediend vlak voordat een ontstekingsreactie ontstaat, remt het immuunsysteem en daarmee de ontstekingsreactie. In **hoofdstuk 4** worden de bevindingen van een onderzoek van een andere onderzoeksgroep naar de invloed van verrijkte voeding uiteengezet. Gebaseerd op de bevindingen uit **hoofdstuk 2 en 3** lijkt het zo te zijn dat wanneer men een effect wil aantonen van het beïnvloeden van de ontstekingsreactie, een dergelijke studie verricht dient te worden bij patiënten die een hevige ontstekingsreactie ontwikkelen en patiënten die veelal te maken krijgen met complicaties. Het advies wordt gegeven toekomstig onderzoek met verrijkte voeding te verrichten bij patiënten van 75 jaar en ouder, met meerdere comorbiditeiten, die een grote oncologische operatie dienen te ondergaan. Het eerste gedeelte van het proefschrift (**hoofdstuk 2-4**) laat zien dat bij operaties waarbij solide tumoren worden verwijderd, het immuunsysteem wordt geactiveerd, wat leidt tot een stijging van ontstekingsfactoren in het bloed. Het is nog onduidelijk of een stijging van deze factoren een direct verband heeft met het optreden van complicaties na een operatie. Er zijn studies die een direct verband beschrijven. Echter deze studies zijn meestal uitgevoerd bij cardiologische patiënten en niet bij oudere patiënten met kanker. In het eerste deel van dit proefschrift waren zes ontstekingsfactoren geanalyseerd met als doel om het patroon van de ontstekingsreactie in kaart te brengen. Een punt van discussie blijft welke ontstekingsfactoren de reactie van immuunsysteem op de juiste manier weergeven en op welk tijdstip deze factoren het beste gemeten kunnen worden. Het analyseren van andere ontstekingsfactoren of andere meetmomenten zouden kunnen helpen bij het beter in kaart brengen van de reactie van het immuunsysteem op operaties. Dit geldt ook voor een eventuele samenhang van ontstekingsfactoren met complicaties na een operatie.

In het tweede deel van dit proefschrift (**hoofdstuk 5-7**) is gekeken naar het effect van oncologische operaties op het cognitief functioneren.

In **hoofdstuk 5** werd de incidentie van cognitieve achteruitgang drie maanden na de operatie onderzocht bij oudere patiënten met kanker. Ook werden verschillende risicofactoren onderzocht. Een groep van 307 oudere patiënten (65 jaar en ouder) participeerde in de studie en allen werden geopereerd om een solide tumor te verwijderen. Het cognitief functioneren werd voor de operatie en drie maanden daarna in kaart gebracht door middel van cognitieve testen. Van alle patiënten die de cognitieve testen volbrachten, verbeterden 117 (53%) patiënten hun cognitieve

test scores, waar 26 (12%) patiënten een duidelijke achteruitgang van het cognitief functioneren lieten zien drie maanden na de operatie. In specifieke patiëntgroepen bleek het percentage patiënten met achteruitgang van cognitieve test scores nog hoger te zijn. Dit betrof de patiënten met een leeftijd van boven de 75 jaar, patiënten met een lagere score op de Mini-Mental State Examination (MMSE) voor de operatie en patiënten die langere operaties ondergingen. Het is belangrijk rekening te houden met deze risicofactoren tijdens de besluitvorming rondom een operatie.

Wanneer na een operatie een delier optreedt is er sprake van acute verwardheid en soms wisselende oriëntatie. Bij patiënten die een zogeheten HIPEC-procedure ondergingen werd in **hoofdstuk 6** onderzocht of deze verwardheid gerelateerd kon worden aan de ontstekingsreactie rondom een operatie. HIPEC staat voor Hypertherme Intraperitoneale Chemotherapie, een procedure waarbij alle zichtbare tumor verwijderd wordt en de eventuele achtergebleven niet-zichtbare kankercellen worden behandeld door de buikholte te spoelen met verwarmde chemotherapie. De incidentie van het delier en risicofactoren werd onderzocht bij 136 patiënten. Tijdens de ziekenhuisopname kregen 38 (28%) patiënten de diagnose postoperatief delier. Statistische analyse liet zien dat (na het corrigeren voor leeftijd en andere postoperatieve complicaties) het aantal organen dat verwijderd werd tijdens de operatie en serum waarden van de ontstekingsfactor CRP voorspellers zijn voor het krijgen van een delier. De relatie tussen de ontstekingsreactie en het ontstaan van een postoperatief delier dient echter nog verder onderzocht te worden.

Een systemische ontstekingsreactie zou ten grondslag kunnen liggen aan zowel symptomen van angst en depressie, als postoperatieve neurocognitieve stoornissen. Daarom werd in **hoofdstuk 7** de relatie onderzocht tussen symptomen van angst en depressie voor de operatie met neurocognitieve stoornissen na de operatie. Verschillende factoren werden onderzocht voor 218 patiënten van 18 jaar en ouder die een operatie ondergingen voor de verwijdering van een solide tumor (PICNIC-B-HAPPY-studie). Symptomen van angst en depressie voor de operatie werden (in tegenstelling tot de verwachting) niet geassocieerd met de cognitieve problemen na de operatie. Wat wel bleek was dat het niet gevolgd hebben van voortgezet onderwijs (onderwijs na de basisschool) een risico factor is voor het ontwikkelen van cognitieve problemen na de operatie.

De relatie tussen postoperatieve complicaties en het postoperatief delier is nog niet opgehelderd. Of een delier het risico op het krijgen van andere complicaties verhoogt of dat een delier een uiting is van andere complicaties blijft een vraag die onbeantwoord is. Wat is oorzaak en wat is gevolg? Het onderzoek naar cognitieve complicaties zoals het postoperatief delier en POCD blijft een uitdaging omdat het diagnosticeren van dergelijke problemen niet eenvoudig is. Daarbij wordt onderzoek verricht in verschillende populaties, wordt verschillende terminologie gehanteerd en verschillende onderzoeksmethoden gebruikt waardoor resultaten niet altijd met elkaar te vergelijken zijn.

Het toekomstperspectief

Ondanks dat operaties erop gericht zijn om gezondheid te behouden danwel te herstellen gaan ze soms gepaard met problemen. Rondom 50% van de oudere patiënten ontwikkelt een complicatie na een operatie. Bij ouderen is het (mede hierdoor) een uitdaging keuzes te maken ten aanzien van de behandeling van de ziekte. Daarbij spelen verschillende comorbiditeiten, verminderde fysiologische reserves en mogelijke cognitieve beperkingen passend bij de leeftijd ook een rol. In de oncologie is het opmaken van de balans, tussen risico's van behandeling en risico's van de ziekte zelf, essentieel. Hierdoor kan het zijn dat bij oudere patiënten de behandeldoelen en daarmee behandelkeuzes anders zijn dan bij jongere patiënten. Behandeling op maat krijgt hierdoor meer en meer aandacht binnen de oncologie.

Gezien complicaties na een operatie frequent gezien worden, behoeft het de aandacht te proberen deze problemen te voorkomen. Uitgebreide en meer invasieve operaties (zoals in de buik- en/of borstholte) zijn geassocieerd met een hevigere ontstekingsreactie. Gezien de gedachte dat deze ontstekingsreactie invloed heeft op het krijgen van complicaties of niet, is de manier van opereren (oftewel chirurgische techniek) wellicht een manier op de postoperatieve uitkomsten te verbeteren. Minder invasieve operatietechnieken zouden uitkomst kunnen bieden voor oudere patiënten met de hypothese dat dit tot een minder hevige ontstekingsreactie leidt en mogelijk minder complicaties.

Een mogelijke manier om complicaties te voorkomen is het moduleren (sturen) van de ontstekingsreactie. Immunomodulatie kan plaatsvinden door de ontstekingsreactie te activeren dan wel te remmen om zo het overschot (of tekort) van ontstekingsfactoren te compenseren. Op deze manier kan de door de operatie

verstoorde balans weer hersteld worden. In dierstudies is het op deze manier gelukt op met bepaalde medicatie (zoals tocilizumab) de ontstekingsreactie te beïnvloeden waarna de uitkomsten na een operatie werden verbeterd doordat complicaties werden voorkomen. Ook wordt er onderzoek gedaan naar het toedienen van speciale soorten voeding (vet verrijkte sondevoeding) rondom operaties bij patiënten. Het toedienen van voeding bij patiënt tijdens de operatie heeft mogelijk een gunstig effect op de ontstekingsreactie, deze verloopt hierdoor minder hevig. In theorie heeft dit een gunstig effect op de postoperatieve uitkomsten maar dat zal de praktijk nog moeten uitwijzen.

Idealiter is het in de toekomst mogelijk om voor of tijdens een operatie bij een kwetsbare patiënt maatregelen te kunnen treffen die voorkomen dat een te hevige ontstekingsreactie optreedt, met alle gevolgen van dien. Als het lukt een effectieve preventieve behandeling te vinden, leidt dit mogelijk tot een verbeterde kwaliteit van leven en minder functieverlies in de tijd na de operatie en voor hen die de ziekte overleven. Juist nu behandelingen intensiever zijn, wordt de balans tussen langer leven en kwaliteit van leven voor patiënten steeds belangrijker.

Conclusie

Inzichten in de potentiële negatieve gevolgen van operaties bij oudere patiënten met kanker dragen bij aan het ontrafelen van de complexe ontstekingsreactie. Identificatie van patiënten met een verhoogd risico op complicaties na een operatie, maakt het mogelijk zorg op maat te leveren. Uiteindelijk zou dit kunnen leiden tot een verbetering van de kwaliteit van zorg en een verbetering van de postoperatieve uitkomsten in oudere patiënten. Het voorkomen van postoperatieve neurocognitieve stoornissen (zoals het delier en POCD) is belangrijk omdat het vermogen om zelfstandig te functioneren onmisbaar is voor de kwaliteit van leven. Echter voordat veelbelovende interventies ontwikkeld kunnen worden, is meer kennis nodig van de ontstekingsreactie en het immuunsysteem zelf. In een maatschappij waarbij iedereen, of zijn omgeving, getroffen kan worden door kanker, verdient dit onderwerp de aandacht. Het is belangrijk om onderzoek mogelijk te maken naar de gevolgen van zowel de ziekte, als de daarmee gepaard gaande behandeling.

Dankwoord - Acknowledgements

Dit proefschrift zoals het hier voor u ligt zou niet tot stand zijn gekomen zonder de steun en inzet van een groot aantal mensen. Er zijn een aantal mensen die een speciale dank verdienen: voor jullie is dit dankwoord. De waarde die ik hecht aan de steun die ik kreeg van jullie kan ik niet in woorden uitdrukken maar bij deze een poging.

Beste Prof. B.L. van Leeuwen. Beste Barbara, het begon allemaal in december 2014. Ik was de coassistent die een incisie mocht zetten op OK, onder begeleiding van Lukas en jou. Jullie overwogen hierna een psycholoog te bellen voor mentale ondersteuning. Dit was een typerend begin voor alles wat volgde. Wij zijn verschillend in karakter, maar hebben dezelfde humor en dat heeft veel goeds gebracht! Samen met Truuske hebben we ons gestort op het opschrijven van PICNIC en dat is gelukt. Ik wil je graag bedanken voor je relativeringsvermogen en het feit dat je me altijd weer wist te motiveren, niet alleen met betrekking tot dit onderzoek, maar ook daarbuiten. In een tijd waarin veel is veranderd, was de wetenschap altijd een stabiele factor.

Beste Prof. G.H. de Bock. Beste Truuske, een duwtje in de goede richting, een spontane ingeving en eerlijk advies. Zo viel het puzzelstukje altijd op zijn plek (steeds weer opnieuw). Het vertrouwen dat ik van je kreeg, heeft me over de tijd doen realiseren dat ook ik de wetenschap kan uitoefenen. Boven alle kennis en vaardigheden die ik van je heb mogen leren, waardeer ik de gesprekken die we samen met Barbara hadden over wat belangrijk is in het leven. Ik ben blij dat we elkaar hebben leren kennen. We vormen een dynamisch drietal. Verschillend, maar aanvullend. Truuske, wanneer je de afgelopen jaren zei dat het goed was, was dat het ook echt.

Beste Prof. A.R. Absalom. Beste Tony, jij wist mij altijd weer te enthousiasmeren over de data. De bijeenkomsten leidden tot nieuwe inzichten en daardoor ook tot nieuwe energie! Door je feedback was ik in staat de puntjes op de i te zetten. De samenwerking met Barbara, Truuske en jou, allen vanuit een andere discipline is hetgeen waar ik veel van heb geleerd. Dank voor je visie! En zeker niet te vergeten het aanbrengen van nuance in de tekst.

Hooggeleerde leden van de leescommissie, Prof. dr. M.H. Emmelot-Vonk, Prof. dr. M.M.R.F. Struys en Prof. dr. J.P.P.M. de Vries, hartelijk dank voor de tijd en bereidwilligheid om de wetenschappelijke waarde van dit proefschrift te beoordelen.

Naast mijn promotoren wil ik graag alle andere auteurs bedanken die hebben meegewerkt hebben aan het tot stand komen van dit proefschrift. Het was prettig samenwerken! In het bijzonder Jacco de Haan en Bram Rutgers, bedankt voor de fijne samenwerking en de waardevolle inzichten in de discipline overstijgende materie. Jing Du, thank you for joining the team, your trust and your great analytic capabilities. Our collaboration was 'amazing'.

Al mijn onderzoeksvrienden van de chirurgie! In wisselende samenstellingen, in een tijd van komen en van gaan, zowel in 'T Hok' als op 'The Office', mocht ik jullie directe collega zijn en vriend worden. Suzanne, Maureen, Jara, Leonie, Jelena, Eric, Arne, Marc, Otis, Rob, Lisanne en Gepke, dankjulliewel! Qua carrière scheiden de paden, maar de vriendschap blijft. De avonturen in de Uurwerker, Chupitos, 9^{de} Cirkel, de IMONO en in Boedapest moeten natuurlijk herbeleefd worden.

Hanneke, wat begon als begeleiding bij mijn scriptie bij PICNIC, veranderde in een heel fijne samenwerking! We zaten veelal in hetzelfde schuitje met dezelfde academische frustratie, de deur stond altijd open voor zoveel meer dan de wetenschap. Dankje!

To all the colleagues of the Oncological Epidemiology Unit and The Screening and Diagnostic in Oncology Journal Club members, thank you for all the valuable meetings and the discussions. In the beginning I felt as the not-knowing outsider but I learnt a lot and that feeling disappeared.

Uiteraard ook alle waardering en dank voor mijn collega's van zowel de afdeling Chirurgie als Epidemiologie van UMCG. Petra en Clara, jullie zijn goud waard. Met jullie is alles te bespreken! Maarten en Karin, bedankt dat ik parttime jullie kamergenoot mocht zijn bij de Epidemiologie. De regels zo ver buigen totdat ze net niet breken, is het leukste!

Curriculum Vitae

Matthijs Plas werd geboren op 25 oktober 1991 te Assen, waarna hij opgroeide als middelste kind van Henry en Adrie Plas in Bovensmilde samen met zijn zus Christine en broertje Sander. Zijn middelbare schooltijd bracht hij door op de Christelijke Scholengemeenschap Vincent van Gogh te Assen waar hij in 2010 zijn gymnasium diploma behaalde.

In september 2010 begon hij aan zijn studie Geneeskunde aan de Rijksuniversiteit van Groningen. Na de Minor Neurowetenschappen en het coschap Chirurgie was de belangstelling voor de wetenschap gewekt. Tijdens zijn verdere studie werd de basis gelegd voor zijn promotietraject bij de afdelingen Chirurgische Oncologie, Epidemiologie en Anesthesiologie van het Universitair Medisch Centrum Groningen, onder begeleiding van prof. dr. B.L. van Leeuwen, prof. dr. G.H. de Bock en prof. dr. A.R. Absalom.

Met omzwervingen naar Almelo en Emmen, maar met Groningen als wetenschappelijke basis, behaalde Matthijs zijn artsexamen in december 2017 om vervolgens zijn promotietraject af te ronden werkzaam als arts-onderzoeker bij de afdelingen Chirurgische Oncologie en Epidemiologie van het Universitair Medisch Centrum Groningen. In het voorjaar van 2021 bood hij zijn proefschrift getiteld "The inflammatory response in surgical oncology: potential sequelae in elderly patients" aan ter verkrijging van de doctorsgraad.

Op dit moment is Matthijs werkzaam in het Medisch Centrum Leeuwarden en bezig met zijn specialisatie bij de interne geneeskunde.