A critical evaluation of diagnostic tools in abdominal surgery

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General introduction and thesis outline

GENERAL INTRODUCTION AND THESIS OUTLINE

For many decades, the use of diagnostic tools in medical care has been based on a one-size-fits-all approach, applying standardised care to patients with the same diseases. Recently, the concept of precision medicine has emerged, which aims to tailor medical decisions, practices and interventions to the individual patient based on their predicted risk or response of disease. The work in this thesis discusses two contrasting concepts of risk-stratified use of diagnostic tools in patients who underwent abdominal surgery, which will be introduced and elucidated below.

Part I: Intensified use of diagnostic tools in high-risk patients

Colorectal cancer is the third most common cancer and second leading cause of cancer-related mortality worldwide.[1] In the Netherlands, nearly 15,000 patients are newly diagnosed every year.[2] Over the past decades, the introduction of the screening program and improved treatment strategies have resulted in a reduced number of recurrences and improved survival rates.[3-7] After completion of curative intent treatment, it is common clinical practice to follow patients for several years, aiming to improve survival by detecting recurrence or second primary cancer in a curable stage. Despite this widespread practice, the exact content and intensity of follow-up regimens are highly controversial. **Chapter 1** provides an overview of recommendations and evidence on follow-up after curative intent treatment of non-metastatic colorectal cancer as described in national and international guidelines. We aimed to determine consensus and controversy on this topic in relation to existing and emerging evidence.

Recent meta-analyses of randomised clinical trials comparing different follow-up strategies could not demonstrate a significant survival benefit of intensive follow-up.[8,9] However, the data suggests that there might be a small risk reduction in mortality, and definitive conclusions cannot be drawn based on the presently available data. This may be the result of a dilution effect due to the high number of low-risk patients included in these studies. Intensive follow-up may improve survival in patients who are at high risk of developing recurrence. Besides the liver and lungs, a common site of recurrence in patients with colorectal cancer is the peritoneum. Several studies have identified locally advanced disease (T4) as an independent risk factor for the development of metachronous peritoneal metastases (PM), with reported incidences of up to 30%.[10,11] Peritoneal dissemination was formerly considered a terminal condition with a median survival ranging from five months if untreated to 24 months with modern systemic therapy regimens with or without biological agents.[12-16] Currently, the only curative treatment option consists of cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Both the effectiveness and morbidity of CRS/HIPEC highly depend on the extent of peritoneal disease, which is regularly assessed with the peritoneal cancer index

(PCI).[17-25] This therapy is therefore restricted to patients in good clinical condition with a relatively limited extent of peritoneal disease, and with no or limited extra-peritoneal metastatic localisations. Unfortunately, due to low sensitivity of imaging modalities and the absence of early symptoms, PM are often detected in a relatively late stage, and only approximately a quarter of these patients are eligible to undergo CRS/HIPEC.

Between April 2015 and February 2017, the COLOPEC multicentre, randomised controlled trial (NCT02231086) investigated the effect of HIPEC in the adjuvant setting on the development of PM in patients with T4 or perforated colon cancer.[26] Before the primary endpoint was reached, the COLOPEC trial revealed that PM were already detected in 9 of 100 patients (9%) in the experimental arm during the surgical re-exploration right prior to the planned adjuvant HIPEC procedure, which was performed within only two months after primary resection. Eight of these nine patients (89%) were treated with CRS/HIPEC. This finding led to the hypothesis that early detection of PM may improve survival by increasing the proportion of patients eligible for curative intent treatment. A new diagnostic strategy aiming at detection of PM in a curable stage is investigated in the COLOPEC 2 trial, of which the study protocol is described in **chapter 2**. The objective of this multicentre, randomised clinical trial is to determine the value of a more intensive follow-up regimen including one or two diagnostic laparoscopies for early detection of occult PM in patients with histopathologically proven T4 (pT4) colon cancer.

To identify patients at high risk of developing metachronous PM, a thorough understanding of the process of peritoneal dissemination is required. It is often hypothesised that the development of PM is a multistep process, starting with the detachment of cancer cells from the primary tumour. The exfoliated cells then need to gain motility and evade apoptosis, followed by migration and adherence to the peritoneal lining to ultimately invade the peritoneum. Finally, the malignant cells have to survive in the new tumour microenvironment and form PM.[27] To gain insight in the molecular mechanisms driving the formation of PM, in vivo models mimicking (part of) the peritoneal dissemination process are required. One complicating factor is the high heterogeneity that is observed among colorectal cancer patients, both in tendency to form PM, as in extensiveness and preferred localisation in case PM evolve. In **chapter 3**, an experimental mouse model reflecting this interpatient heterogeneity was created to further unravel the pathophysiological mechanisms of the metastatic cascade that result in PM. Using 15 well-characterised human colorectal cancer cell lines in combination with the lentiviral gene ontology (LeGO) labelling method, we aimed to identify subgroups with differential ability and patterns of peritoneal outgrowth, as well as to investigate clonal dynamics in the formation of PM.[28,29]

As in the COLOPEC 2 trial, other ongoing trials focusing on early detection or prevention of outgrowth of PM often include patients with locally advanced colon cancer.[26,30,31] Approximately 10-15% of patients with colon cancer has T4 disease at the time of diagnosis.[32-34] As new diagnostic and therapeutic strategies are often costly and invasive, identification of risk factors for metachronous PM within this heterogeneous T4 subpopulation has become increasingly important. This would enable tailoring of these strategies to the patients at highest risk, and thereby reducing costs and overtreatment. According to the 8th edition of the TNM classification, T4 is defined as a tumour penetrating all layers of the bowel wall. This includes the T4a category, referring to tumours penetrating the visceral peritoneum, and the T4b category defined as tumours directly invading other organs or structures.[35] Previously published studies investigating risk factors for peritoneal recurrence found PM to be more common in patients with pT4a colon cancer as compared to patients with pT4b colon cancer, although small sample sizes impeded statistical significance.[10,36-38] In **chapter 4**, we assessed the impact of pT4a versus pT4b subcategory on the risk of developing metachronous PM and other oncological outcomes in an international, multicentre study including 852 patients.

Part II: Reduced use of diagnostic tools in low-risk patients

Appendectomy and cholecystectomy for presumed benign diseases (i.e. appendicitis, cholecystitis, and gallstone disease) are among the most common procedures in surgical practice. In the Netherlands, approximately 16,000 appendectomies and 22,500 cholecystectomies are performed every year. Since the American College of Surgeons stated in 1926 that all tissues removed at operations should be examined by a pathologist, all appendiceal and gallbladder specimens are routinely submitted for histopathological examination.[39] The main purpose of this policy is to obtain a definitive diagnosis and to avoid the risk of missing unexpected pathology with clinical consequences for the patient. The increasing burden on pathology departments and high healthcare costs, combined with the rarity of unforeseen clinically relevant findings in appendectomy and cholecystectomy specimens, has fuelled an ongoing discussion regarding the necessity of this routine policy for several decades.

Selective histopathological examination encompasses that surgeons perform a macroscopic assessment of the appendix or gallbladder and select specimens that require further evaluation by a pathologist. Such a strategy would likely reduce costs and diminish the workload of pathologists, but also induces a risk of diagnoses being missed with potential disadvantageous consequences for the patient. However, it is hypothesised that tumours not detected during macroscopic assessment are of early stage. These missed tumours are likely to be clinically inconsequential, as the performed appendectomy or cholecystectomy already suffices.[40-47] During the past few years, numerous studies have summarised the histopathological findings

found in appendiceal and gallbladder specimens examined in their pathology unit. **Chapter 5** consists of a systematic review and meta-analysis of studies reporting on histopathological findings in appendices removed for suspected appendicitis. We aimed to determine whether routine histopathological examination following appendectomy is still necessary by investigating the incidence of aberrant findings, the ability of surgeons to identify unexpected pathology intraoperatively, and the impact of unexpected pathology on postoperative management. In **chapter 6**, a similar systematic review and meta-analysis provides an overview of recent literature regarding the incidence and clinical consequences of incidental gallbladder malignancies.

Due to the lack of prospective studies confirming safety of a selective policy following appendectomy, it is still standard practice in the Netherlands to send all appendices for histopathological examination.[48] In contrast, based on two retrospective studies and a systematic review, the Dutch guideline for gallstone disease was updated in 2016 stating that histopathological examination of macroscopic normal gallbladders can be omitted.[44,47,49] However, results of a national survey recently showed that less than half of hospitals adopted this selective policy, and the need for more evidence on its safety was expressed.[50] Taken together, these observations encouraged us to conduct a nationwide prospective study to draw firm conclusions regarding oncological safety and potential cost savings of selective histopathological examination following appendectomy and cholecystectomy. In **chapter 7**, the study protocol and statistical analysis plan of the multicentre, prospective, cross-sectional FANCY study are presented. **Chapter 8** reports the clinical endpoints of the appendix part of the FANCY study, including 7339 appendectomised patients from 59 Dutch hospitals. **Chapter 9** describes the clinical outcomes of the gallbladder part of the FANCY study, in which a total of 42 Dutch hospitals took part resulting in the inclusion of 10,041 patients who underwent a cholecystectomy. Finally, **chapter 10** provides the results of the economic evaluation performed alongside the FANCY study.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018.
2. IKNL. Cijfers over kanker 2011-2019. Available at: www.iknl.nl/nkr-cijfers.
3. Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature. *Acta Oncol.* 2015;54(1):5-16.
4. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683-691.
5. de Neree Tot Babberich MPM, Vermeer NCA, Wouters M, et al. Postoperative outcomes of screen-detected vs non-screen-detected colorectal cancer in the Netherlands. *JAMA Surg.* 2018;153(12):e183567.
6. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(3):145-164.
7. Osterman E, Hammarström K, Imam I, Osterlund E, Sjöblom T, Glimelius B. Recurrence risk after radical colorectal cancer surgery - Less than before, but how high is it? *Cancers (Basel).* 2020;12(11).
8. Mokhles S, Macbeth F, Farewell V, et al. Meta-analysis of colorectal cancer follow-up after potentially curative resection. *Br J Surg.* 2016;103(10):1259-1268.
9. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev.* 2019;9(9):Cd002200.
10. Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg.* 2012;99(5):699-705.
11. van Gestel YR, Thomassen I, Lemmens VE, et al. Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. *Eur J Surg Oncol.* 2014;40(8):963-969.
12. Pelz JO, Chua TC, Esquivel J, et al. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer.* 2010;10:689.
13. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol.* 2009;27(5):681-685.
14. Chua TC, Morris DL, Saxena A, et al. Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: a multicenter study. *Ann Surg Oncol.* 2011;18(6):1560-1567.
15. Baratti D, Kusamura S, Pietrantonio F, Guaglio M, Niger M, Deraco M. Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review. *Crit Rev Oncol Hematol.* 2016;100:209-222.
16. Klaver YL, Simkens LH, Lemmens VE, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. *Eur J Surg Oncol.* 2012;38(7):617-623.
17. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol.* 2003;21(20):3737-3743.
18. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol.* 2010;28(1):63-68.
19. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer.* 2010;116(24):5608-5618.

20. Cavaliere F, De Simone M, Virzi S, et al. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. *Eur J Surg Oncol.* 2011;37(2):148-154.
21. Weber T, Roitman M, Link KH. Current status of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Clin Colorectal Cancer.* 2012;11(3):167-176.
22. Baratti D, Kusamura S, Iusco D, et al. Postoperative complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy affect long-term outcome of patients with peritoneal metastases from colorectal cancer: a two-center study of 101 patients. *Dis Colon Rectum.* 2014;57(7):858-868.
23. Nikolic S, Dzodic R, Zegarac M, et al. Survival prognostic factors in patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy: a single institution experience. *J BUON.* 2014;19(1):66-74.
24. Rivard JD, McConnell YJ, Temple WJ, Mack LA. Cytoreduction and heated intraperitoneal chemotherapy for colorectal cancer: are we excluding patients who may benefit? *J Surg Oncol.* 2014;109(2):104-109.
25. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res.* 1996;82:359-374.
26. Klaver CEL, Wisselink DD, Punt CJA, et al. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. *Lancet Gastroenterol Hepatol.* 2019;4(10):761-770.
27. de Cuba EM, Kwakman R, van Egmond M, et al. Understanding molecular mechanisms in peritoneal dissemination of colorectal cancer: future possibilities for personalised treatment by use of biomarkers. *Virchows Arch.* 2012;461(3):231-243.
28. Weber K, Thomaschewski M, Benten D, Fehse B. RGB marking with lentiviral vectors for multicolor clonal cell tracking. *Nat Protoc.* 2012;7(5):839-849.
29. van der Heijden M, Miedema DM, Waclaw B, et al. Spatiotemporal regulation of clonogenicity in colorectal cancer xenografts. *Proc Natl Acad Sci U S A.* 2019;116(13):6140-6145.
30. Arjona-Sánchez A, Barrios P, Boldo-Roda E, et al. HIPECT4: multicentre, randomized clinical trial to evaluate safety and efficacy of Hyperthermic intra-peritoneal chemotherapy (HIPEC) with Mitomycin C used during surgery for treatment of locally advanced colorectal carcinoma. *BMC Cancer.* 2018;18(1):183.
31. Surgery with HIPEC in treating patients with a high risk of developing colorectal peritoneal carcinomatosis. ClinicalTrialsgov; 2017 Number NCY02179489. Available at: https://clinicaltrialsgov/ct2/show/NCT02179489.
32. Segelman J, Akre O, Gustafsson UO, Bottai M, Martling A. Individualized prediction of risk of metachronous peritoneal carcinomatosis from colorectal cancer. *Colorectal Dis.* 2014;16(5):359-367.
33. Klaver CE, Gietelink L, Bemelman WA, et al. Locally advanced colon cancer: Evaluation of current clinical practice and treatment outcomes at the population level. *J Natl Compr Canc Netw.* 2017;15(2):181-190.
34. de Neree Tot Babberich MPM, Detering R, Dekker JWT, et al. Achievements in colorectal cancer care during 8 years of auditing in The Netherlands. *Eur J Surg Oncol.* 2018;44(9):1361-1370.
35. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual (8th edition).* 2017.
36. Hompes D, Tiek J, Wolthuis A, et al. HIPEC in T4a colon cancer: a defendable treatment to improve oncologic outcome? *Ann Oncol.* 2012;23(12):3123-3129.
37. van Santvoort HC, Braam HJ, Spekreijse KR, et al. Peritoneal carcinomatosis in t4 colorectal cancer: occurrence and risk factors. *Ann Surg Oncol.* 2014;21(5):1686-1691.
38. Segelman J, Akre O, Gustafsson UO, Bottai M, Martling A. External validation of models predicting the individual risk of metachronous peritoneal carcinomatosis from colon and rectal cancer. *Colorectal Dis.* 2016;18(4):378-385.
39. American College of Surgeons. A manual of hospital standardization. 1926. Available at: https://archive.org/details/HospitalStandarizationManual1926.

40. Matthyssens LE, Ziol M, Barrat C, Champault GG. Routine surgical pathology in general surgery. *Br J Surg.* 2006;93(3):362-368.
41. Alemayehu H, Snyder CL, St Peter SD, Ostlie DJ. Incidence and outcomes of unexpected pathology findings after appendectomy. *J Pediatr Surg.* 2014;49(9):1390-1393.
42. Jahan B, Najeeb S, Shaikh AW. Acute appendicitis, correlating histopathological findings with clinical-is histopathology needed for all? *Pakistan Journal of Medical and Health Sciences.* 2016;10(1):118-121.
43. Mittal R, Jesudason MR, Nayak S. Selective histopathology in cholecystectomy for gallstone disease. *Indian J Gastroenterol.* 2010;29(1):26-30.
44. van Vliet JL, van Gulik TM, Verbeek PC. Is it necessary to send gallbladder specimens for routine histopathological examination after cholecystectomy? The use of macroscopic examination. *Dig Surg.* 2013;30(4-6):472-475.
45. Emmett CD, Barrett P, Gilliam AD, Mitchell AI. Routine versus selective histological examination after cholecystectomy to exclude incidental gallbladder carcinoma. *Ann R Coll Surg Engl.* 2015;97(7):526-529.
46. Almuslamani AJ, Alsoude M, Alomari M, Mnazel T, Khasawana G. Histopathological examination on suspicious gallbladder specimens at Royal Medical Services Hospitals. *Rawal Medical Journal.* 2011;36(2):93-96.
47. Deng YL, Xiong XZ, Zhou Y, Shrestha A, Li FY, Cheng NS. Selective histology of cholecystectomy specimens - is it justified? *J Surg Res.* 2015;193(1):196-201.
48. Nederlandse Vereniging voor Heelkunde (NVvH). Evidence-based richtlijn, Acute appendicitis, 2019.
49. Swank HA, Mulder IM, Hop WC, van de Vijver MJ, Lange JF, Bemelman WA. Routine histopathology for carcinoma in cholecystectomy specimens not evidence based: a systematic review. *Surg Endosc.* 2013;27(12):4439-4448.
50. Corten B, Leclercq WKG, Dejong CH, Roumen RMH, Slooter GD. Selective histological examination after cholecystectomy: An analysis of current daily practice in the Netherlands. *World J Surg.* 2019.